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The Molecular Modeling Workbook for ORGANIC CHEMISTRY

Warren J. Hehre

Wavefunction, Inc.

18401 Von Karman Ave., Suite 370

Irvine, CA 92612

Alan J. Shusterman

Department of Chemistry

Reed College

3203 S. E. Woodstock Blvd.

Portland, OR 97202

Janet E. Nelson

Wavefunction, Inc.

18401 Von Karman Ave., Suite 370

Irvine, CA 92612



Wavefunction, Inc.

18401 Von Karman Ave., Suite 370

Irvine, CA 92612

Acknowledgments

Many people have contributed their experience and their wisdom to this workbook. Special thanks goes to Bernard Deppmeier, Andy Driessen, Tim Hume and Jeffrey Johnson at Wavefunction for their development of SPARTAN View, to Robert Topper (Cooper Union) and Jurgen Schnitker (Wavefunction) for their careful reading of the entire manuscript and to Patrick McDougal (Reed College) for suggesting several problems. As always, Pamela Ohsan is thanked for turning our “sloppy manuscript” into a finished book.

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ISBN 1-890661-06-6

Printed in the United States of America

Molecular Modeling in Organic Chemistry

Why is it important to introduce molecular modeling in the beginning organic chemistry course? With so many new concepts already essential to understanding organic chemistry, and with the mass of unfamiliar material already heaped upon the student, how can introduction of yet another dimension to the subject be justified? And, isn't modeling supposed to be grounded in quantum mechanics, the rudiments of which haven't even yet been presented to the student? Wouldn't it really be better to postpone consideration of molecular modeling until the basics are in place? We think not. Molecular modeling allows the student to think more clearly about issues which are fundamental to the study of organic chemistry – structure, stability and reactivity – than would be possible without the use of a computer.

In order to fully appreciate the widespread application that molecular modeling can find in beginning organic chemistry, it is important to appreciate the fundamental relationship between molecular structure and chemical, physical and biological properties. So-called structure-property relationships are explored in nearly every college chemistry course, whether introductory or advanced. Students are first taught about the structures of molecules, and are then taught how to relate structure to molecular properties.

The widespread use of this teaching technique, and the critical and central role of structural concepts in chemistry, suggests that the depiction and manipulation of structural models is a highly developed science. Unfortunately, this is not the case. The two-dimensional line figures, introduced more than a century ago to draw molecular structures, are still routinely used in education and research. Although easy for an expert to understand and produce, such drawings do not look at all like the molecules they are supposed to depict. In fact, learning how to interpret and create simple line drawings is one of the largest hurdles that students face, and is one of the principal reasons why many students find organic chemistry difficult.

Using computers to display molecular structure is an attractive alternative to traditional line drawings for several reasons. First, the model displayed on a computer screen “looks” and “behaves” more like a “real molecule” than a drawing does. The computer model can be viewed from different angles, and different display formats can be used to show atomic positions, atomic volumes, and other features of interest. Second, the computer can produce a good model even when the student does not know how to make an accurate drawing. Thus, the student, working with a computer, can explore “new areas of chemistry”

where his or her knowledge of structure may be limited. Third, many molecules commonly encountered in beginning organic chemistry cannot be represented accurately, if at all, by simple drawings. These include molecules in which the charge is delocalized, many unstable molecules and, perhaps most important, reaction transition states. Computer models treat such species no differently than they handle structures which are well represented by conventional drawings. Fourth, molecular modeling can also be used to predict and display a variety of chemical and physical properties such as energy, dipole moment, and so on. Thus, the computer can be more than a simple structure display tool; it can also provide a means for visualizing, investigating and studying a multitude of chemical phenomena. These many advantages imply that the classroom use of computer modeling can be of enormous benefit in teaching about molecular structure and molecular properties.

We contend therefore that introduction of molecular modeling very early into the curriculum need not complicate or confuse the learning of organic chemistry, but rather assist the student in visualizing the structures of organic molecules and in learning the intimate connections between molecular structure and molecular properties.

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To the Student

The world of science is a deliciously excruciating blend of the general and the specific. There are general laws and rules of broad application ($E=mc^2$, opposite charges attract), but the precise way in which these laws combine in any particular instance always depends on the specifics of the situation.

Nowhere is this conflict more evident than in organic chemistry. To take one example, organic chemists describe the oxygen-hydrogen (OH) bond as a “polar covalent bond.” This description is valid for virtually every “OH” - containing molecule in existence, and it turns out that many “OH” molecules share common characteristics that can be attributed to this peculiar bond. The generalities tend to fall apart, though, when applied to specific molecules. Methanol, $\text{CH}_3\text{--OH}$, and octanol, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{--OH}$, both contain a polar covalent OH bond, but while this bond can make any number of methanol molecules dissolve in water, octanol is insoluble.

Chemists also routinely encounter situations where a general rule can produce a variety of consequences. Consider the “rule” that carbon atoms always form four bonds to neighboring atoms. This rule is obeyed by literally millions of different chemicals, but it can still have surprising consequences. For decades chemists thought that pure carbon, C_n , could only satisfy the “four bond” rule in two ways: by forming a rigid three-dimensional network (diamond) or by forming flat layered sheets (graphite). Recently, however, it was discovered that other forms with unusual structures were possible, and these too satisfied the four bond rule (see **Chapter 12, Problem 6**).

What this adds up to is simply the fact that your study of organic chemistry must integrate the general with the specific. You must not only learn general patterns but also how to apply them to specific molecules, and you must also learn the behavior of specific molecules in order to see where patterns come from. These skills can be learned in a variety of ways, but one of the most effective learning techniques is to study models of molecules that duplicate their size, shape, stability, and other chemically important properties. That is where this workbook comes in.

This workbook contains over 200 problems that will allow you to build and refine your understanding of chemistry from the molecule’s “eye view”. This is achieved by basing every problem on a set of molecular models that you view and manipulate on your own personal computer. We believe that this combination of problems+models will improve your understanding of molecular structure and the relationship between molecular structure and other properties. More importantly, we believe that when you do the problems in this workbook you will gain a much better grasp of the **conceptual** basis of organic chemistry, and that this will make the rest of your study of organic chemistry more satisfactory and ultimately more successful.

The use of the workbook is very simple. Begin by loading the software and models onto

your computer (see instructions on CDROM). Then read the tutorial describing the use of the SPARTANView program (this is the program used to access all of the models), and perform the instructions on your computer **as you read**. This last point needs to be emphasized. The tutorial and the problems can only be completed by working at your computer.

The next step is to learn some chemistry. Depending on your background, you may need to read some or all of the essays that describe how to work with modeling data (this information quickly becomes second-nature, especially if you make working these problems part of your regular study routine). Then tackle the problems beginning with Chapter 1.

The problems are collected in 21 chapters that correspond in an obvious way to the chapters found in any contemporary organic chemistry textbook. The problems inside each chapter are organized so that they are best worked in sequence from first to last, but, depending on your background, you can attempt any problem you like.

None of the problems are of the “flash card” variety. Be prepared to **look** at molecules, to move them, to measure them, to animate them, to find regions that are electron poor or electron rich, and most of all, to think about their chemistry. We guarantee that, after this, you will never look at molecules the same way again!

To the Teacher

Molecular modeling is a major new learning activity, and there are substantial obstacles that must be overcome before it can be used to best effect. Training is required so that teachers can decide what aspects of modeling will prove most useful, and students can make most effective use of their time. Funds need to be raised for the purchase of computer hardware and software.

This workbook allows teachers to offer a modeling-intensive organic chemistry course while bypassing, or at least simplifying, these issues. The workbook comes complete with over one thousand models on CD-ROM. These span all of the topics routinely encountered in a two-semester science majors course. The CD-ROM also contains the SPARTANView program needed to view and query the models. SPARTANView operates on Mac and PC compatible personal computers, and students can master its use after just a few minutes of training. Therefore, the complete workbook package lets students (and teachers) focus on the most important job: learning organic chemistry.

SPARTANView and the model archive can be used separately from the workbook, thereby promoting a much wider range of model-based instruction. Many of the models in the archive have been chosen because of their utility as visual aids in chemistry lectures. A teacher with access to computer projection hardware can use SPARTANView and the models supplied to enhance virtually any lecture with easily manipulated, three-dimensional molecular models and animations. Using SPARTAN, teachers can also create their own models, and present them in class using SPARTANView. This is discussed in **Appendix C**. Teacher-generated models can also be transferred electronically to students so that they can be studied at the students' convenience. Thus, this workbook and its CD-ROM are the “starter kit” for introducing molecular modeling into the organic curriculum.

The workbook itself consists of three sections: a tutorial describing the use of SpartanView, several essays describing how to work with molecular modeling data, and 21 chapters incorporating over 200 organic chemistry problems to be solved using molecular models. The chapters are organized along the same lines as contemporary elementary organic chemistry textbooks, making it easy to find problems for virtually any topic. Solutions are not provided in the workbook, but rather are available on a separate CD-ROM.

The sequence of problems inside each chapter is designed to follow, as much as possible, the logical development of the subject material. A student will normally find that the most straightforward way to do the problems in a chapter is to begin with the first one and continue straight through to the last. The problems are sufficiently independent, however, so that any individual problem can be worked without reference to other problems.

Each problem is presented on a single page. This comprises background chemistry, experimental observations, and a series of questions to be answered. The margin contains additional useful material including color graphics of selected models and reference data. The questions are similar to, and complement those, found in contemporary organic chemistry textbooks. Thus, depending on the subject material, a student might be asked to draw Lewis structures that describe a molecule's structure, predict or interpret some aspect of molecular structure, identify a reactive site within a molecule, or to compare and rank molecules by their reactivity. The one thing that all of the questions have in common is that they can only be answered by examining the models that are provided. Therefore, problem-solving is tightly integrated with structure visualization. Students must look at and manipulate molecules in ways that they will not do otherwise.

Of course, the fact that every problem presents molecular models raises natural questions about the accuracy and meaning of these models. Molecular models are not derived from experiments, but rather from computer calculations. Thus, there will be some differences between modeling data and experimental data, and one must occasionally interpret these data in different ways.

Nearly all of the models used in the workbook were calculated with SPARTAN using standard *ab initio* methods and the 3-21G basis set. This level of theory is of "intermediate" reliability. Details are provided in **Appendix B**.

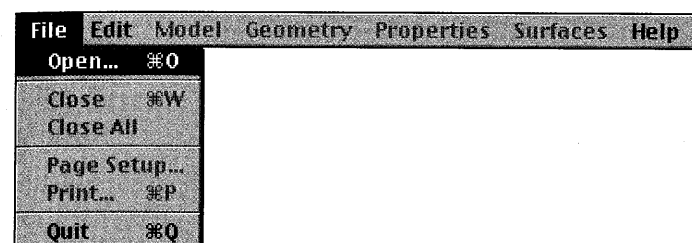
The reliability and meaning of model energies requires special consideration. Model energies give the best results when used to compare molecules that contain the same number and type of chemical bonds, e.g., conformational isomers or the reactants and products in certain types of reactions. Even then, energy differences obtained from models may differ substantially from the free energy differences (ΔG) measured in solution that organic chemists are accustomed to. The total energies provided in this workbook are closely related to experimental enthalpies (ΔH). These provide an excellent starting point for describing gas-phase chemistry, but in order to convert them into accurate solution-phase ΔG values, corrections for interactions with solvent and for entropy would need to be made. This lies outside the scope of an elementary organic chemistry course. Therefore, we have limited energy calculations to situations where gas-phase energies provide useful qualitative (and often quantitative) estimates of solution-phase chemistry, and the data should be interpreted in this light.

How to Use SPARTANView

This section serves as a practical introduction to the SPARTANView program for Power Mac's and PC's (Windows 95/NT). It will show you how to: 1) view and manipulate molecules on screen, 2) measure bond distances, angles and dihedral angles, 3) display energies, dipole moments, atomic charges and frequencies and 4) display graphical surfaces and maps.

File Menu: Opening, Closing and Manipulating Molecules

The **File** menu accesses the molecule archive.



Enter the folder "**Tutorial**" and **Open "Tutorial A"**. This brings all the molecules discussed in the first part of this section onto the screen. All molecules can be removed by selecting **Close All**. Individual molecules may be removed by first selecting them (see below) and then selecting **Close**.

The mouse, together with one or more keys, is used both to select and manipulate (translate, rotate and scale) molecules. Available functions are listed at the right and also in **Manipulating Molecules (Help menu)**.

Identify *ethane* on the screen, and *click* on it (left mouse button on the PC) to make it the selected molecule. Practice rotating and translating ethane. Select a different molecule, and then rotate and translate it.

MAC

Select	click on object
Rotate	move mouse with button depressed
Translate	press option key and move mouse with button depressed
Scale	press option key and ⌘ together and move mouse with button depressed

PC

Select	click (left mouse button) on object
Rotate	move mouse with left button depressed
Translate	move mouse with right button depressed
Scale	press shift key and move mouse with right button depressed

Model Menu: Viewing Molecules with Different Models

Return to ethane (*click* on it) and then, one after the other, select **Wire**, **Ball and Wire**, **Tube**, **Ball and Spoke**, or **Space Filling** from the **Model** menu to view ethane with a variety of different models.



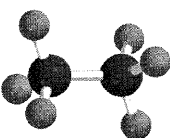
Wire



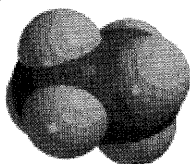
Ball and Wire



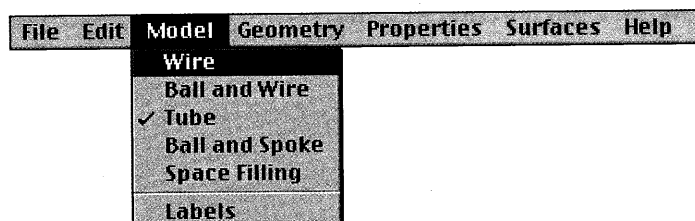
Tube



Ball and Spoke



Space Filling



Use the **3** key to toggle between stereo 3-D and regular display. To view in 3-D you will need to wear the red/blue glasses provided with SPARTANView.

All five models for ethane show roughly the same information. The **Wire** model looks like a line formula in your chemistry textbook, except that all atoms, not just carbons, are found at the end of a line or at the intersection of lines. (The only exception occurs where three atoms lie on a line. Here, a **Wire** model will not show the exact position of the center atom.) The **Wire** model uses color to distinguish different atoms, and one, two and three lines to indicate single, double and triple bonds, respectively.

The **Ball and Wire** model is identical to the **Wire** model, except that atom positions are represented by small spheres. This makes it possible to identify all atom locations in all molecules. The **Tube** model is identical to the **Wire** model, except that bonds, whether single, double or triple, are represented by single colored tubes. The tubes are useful because they better convey the three-dimensional shape of a molecule. The **Ball and Spoke** model is a variation on the **Tube** model; atom positions are represented by colored spheres, making it possible to see all atom locations in all molecules.

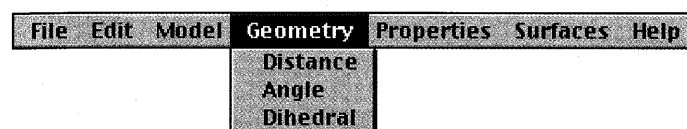
The most novel model is the **Space-Filling** model. No bonds are shown. Rather, each atom is displayed as a colored sphere that represents the atom's approximate size, and the complete model indicates the molecule's

approximate size. The existence (or absence) of bonds can be inferred from the amount of overlap between neighboring atomic spheres. If two spheres substantially overlap, then the atoms are almost certainly bonded, and conversely, if two spheres hardly overlap, then the atoms are not bonded. Intermediate overlaps suggest "weak bonding", for example, hydrogen bonding.

Atoms are colored according to type (see table at right). Atoms may also be labelled by selecting **Labels** (labels may be "turned off" by selecting **Labels** a second time). Only wire and ball-and-wire models may be labelled.

Geometry Menu: Measuring Molecular Geometries

Distances, angles, and dihedral angles can easily be measured with SPARTANView using **Distance**, **Angle**, and **Dihedral**, respectively, from the **Geometry** menu.



- A. Distance:** This measures the distance between two atoms. First select *propene* from the molecules on screen, and then select **Distance** from the **Geometry** menu. *Click* on a bond or on any two atoms (the atoms do not need to be bonded). The distance (in Ångstroms) will be displayed at the bottom of the screen. Repeat the process as necessary, and *click* on **Done** when finished.
- B. Angle:** This measures the angle around a central atom. Select *ammonia* from the molecules on screen, and then select **Angle**. *Click* first on H, then on N, then on another H, or on two NH bonds. The angle (in degrees) will be displayed at the bottom of the screen. Repeat the process as necessary, and *click* on **Done** when finished.
- C. Dihedral:** This measures the angle formed by two intersecting planes, the first plane containing the first three atoms and the second plane containing the last three atoms. Select *hydrogen peroxide* from the molecules on screen, and then select **Dihedral**. *Click*

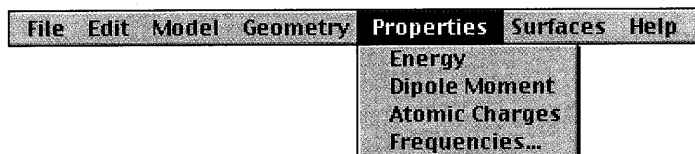
Atom Colors

Hydrogen	white
Lithium	tan
Beryllium	green
Boron	tan
Carbon	black
Nitrogen	blue-gray
Oxygen	red
Fluorine	green
Aluminum	violet
Sodium	yellow
Silicon	grey
Phosphorous	tan
Sulfur	sky blue
Chlorine	tan
Potassium	orange
Bromine	orange
Iron	green
Iodine	tan

on the four atoms in the sequence H O O H (or the three bonds in sequence H–O O–O O–H). The dihedral angle (in degrees) will be displayed at the bottom of the screen. Repeat the process as necessary, and *click* on **Done** when finished.

Properties Menu: Displaying Molecular Properties

Energies, dipole moments, atomic charges and frequencies are available under the **Properties** menu.



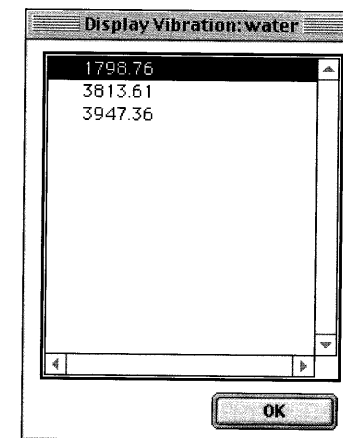
- A. **Energy:** Select *acetic acid* from the molecules on screen, and then select **Energy** from the **Properties** menu. The energy of acetic acid (in atomic units or au) is displayed at the bottom of the screen. *Click* on **Done**.
- B. **Dipole Moment:** To display the dipole moment of acetic acid, select **Dipole Moment**. The magnitude of the dipole moment (in debyes) is displayed at the bottom of the screen and the dipole moment vector “+—”, where “+” to “—” refer to the positive and negative ends of the dipole moment, respectively, is attached to the model on screen. *Click* on **Done**.

The dipole moment vector will not be displayed if the magnitude of the dipole moment is zero. Also, only dipole moments for neutral molecules are displayed.

- C. **Atomic Charges:** To display atomic charges for acetic acid, select **Atomic Charges**. *Click* on an atom. The charge on that atom is displayed at the bottom of the screen. A positive number indicates a deficiency of electrons and a negative number, an excess of electrons. Repeat the process as necessary for different atoms, and *click* on **Done** when finished.
- D. **Frequencies:** Molecules vibrate (stretch, bend, twist) even if they are cooled to 0 K. This is the basis of infrared/Raman spectroscopy, where absorption of energy occurs when the frequency of molecular

motions matches the frequency of the light. Infrared/Raman spectroscopy is very important in organic chemistry as different functional groups vibrate at different and characteristic frequencies.

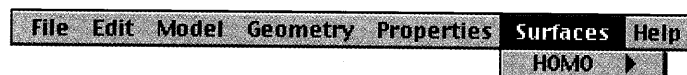
Select *water* from the molecules on screen and display it as a ball-and-spoke model (**Ball and Spoke** from the **Model** menu). To animate a vibration, select **Frequencies**, *double click* on its frequency (in cm^{-1}) in the dialog which results, and then *click* on **OK**. You can select another frequency by reentering the dialog, *double clicking* on another frequency and *clicking* on **OK**. You can turn off the animation by reentering the dialog, *double clicking* on the selected frequency and *clicking* on **OK**.



Surfaces Menu: Displaying Graphical Surfaces

Electron densities, bond densities, and spin densities, as well as particular molecular orbitals may be displayed as graphical surfaces. In addition, the value of the electrostatic potential or the absolute value of a particular molecular orbital may be mapped onto an electron density surface. These maps provide information about the environment around the accessible surface of a molecule. Electrostatic potential maps show overall charge distribution, while orbital maps reveal likely sites for electrophilic and/or nucleophilic attack. Surface displays may be combined with any type of model display.

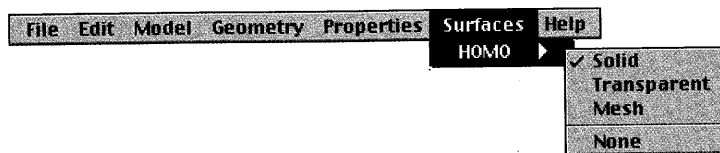
Surfaces and maps are accessible from the **Surfaces** menu.



If surfaces are available, this menu will contain one or more entries describing the surfaces, e.g., HOMO referring to the highest-occupied molecular orbital.

Select *ethene* from the molecules on screen. Select **Surfaces** and then **Solid** under the **HOMO** sub-menu which appears.

While SPARTANView allows you to display two (or more) surfaces or maps at one time, this can lead to confusion and is not advised. Be certain to “turn off” one surface before displaying another surface.



This will result in the display of ethene's highest-occupied molecular orbital as a solid. It is a π orbital, equally concentrated above and below the plane of the molecule. The colors ("red" and "blue") give the sign of the orbital.

Select **benzene** from the molecules on screen, and select **Surfaces. Potential Map** refers to an electrostatic potential map. Select **Transparent** to present it as a transparent (actually translucent) solid. This will allow you to see the molecular skeleton underneath. The surface is colored "red" in the π system (indicating negative potential and the fact that this region is attracted to a positive charge), and "blue" in the σ system (indicating positive potential and the fact that this region is repelled by a positive charge).

Finally, select **acetone** from the molecules on screen. Here, both the LUMO and the LUMO map are available under the **Surfaces** menu. First, select **LUMO** and display it as a **Solid**. It describes a π -type antibonding (π^*) orbital concentrated primarily on the carbonyl carbon and oxygen. Next, "turn off" this surface (select **None** under the **LUMO** sub-menu), and then select **LUMO Map** under the **Surfaces** menu. Display the map as a transparent solid. Note the "blue" spot (maximum value of the LUMO) directly over the carbonyl carbon. This reveals the most likely site for nucleophilic attack.

Select **Close All** (**File** menu) to remove all molecules from the screen.

Collections of Molecules

SPARTANVIEW is able to handle collections of molecules. The most common use will be to provide animated displays of molecules, e.g., undergoing conformational change or chemical reaction. A more mundane use will simply be to present molecule data in a compact manner, as only one molecule at a time from the collection may be displayed on screen. Molecules in collections may not

have frequency data, nor may they have surfaces.

Open "Tutorial B" from the "Tutorial" folder (**File** menu). This brings all the molecules discussed in the second part of this section onto the screen.

Select **bromide+tert-butyl chloride** from the molecules on screen. This provides a series of "frames" describing the S_N2 displacement of chloride in *tert*-butyl chloride by bromide. A bar appears at the bottom of the screen.



You can step forward or backward through the individual frames by *clicking* on ► and ◀, respectively, at the right of the bar, or animate the sequence of frames by *clicking* on ► at the left of the bar. The animation can be "turned off" by *clicking* on || (which replaces ►) at the left of the bar. Finally, different frames may be manually selected using the slider. Practice these functions and pay particular attention to the changes in geometry which occur during the S_N2 displacement reaction. Experiment with different model types to get the clearest picture.

Select **Energy** (**Properties** menu). Notice that it updates automatically as you go from one frame to another. This allows you to easily construct reaction energy diagrams (energy vs. frame number or vs. a specific geometrical parameter). Make such a plot for this S_N2 reaction. Note, that the reaction as written is thermodynamically favorable, i.e., it is exothermic. Note also, that only a relatively small energy barrier needs to be surmounted.

Next, select **phenylacetylene** from among the molecules on screen. This provides a small selection of 4-substituted phenylacetylenes. The only difference in the appearance of the display is that in this case, the name of the molecule in the collection (**H**, **Me**, **OMe**, **Cl** and **NO2**) appears in place of the "Frame: i" (i is the number of the frame in the overall sequence) to the right of the bar at the bottom of the screen.

Examine dipole moments by selecting **Dipole Moment** (**Properties** menu). As with the energy, this display remains as you step through the different members in the collection.

Edit Menu: Copying Graphics and Data

Copy under the **Edit** menu is used for copying graphics and data onto the clipboard. This can later be imported into such programs as Microsoft Word and Excel. There are two modes of operation:

Where **Distance**, **Angle** or **Dihedral** (**Geometry** menu) or **Energy**, **Dipole Moment** or **Atomic Charges** (**Properties** menu) have been selected, **Copy** copies the selected quantity, in addition to the name of the molecule, to the clipboard. (For molecule collections, quantities for all members together with member names are copied to the clipboard.) Otherwise, **Copy** copies the contents of the screen (minus the background) to the clipboard.

Select **Close All** from the **File** menu to remove all the molecules from the screen.

You are now ready to proceed with the problems in this workbook. To bring all the models required for a particular problem onto the screen, you first need to enter the proper chapter folder ("**Chapter1**", "**Chapter2**", ...) and then select the appropriate problem, e.g., "**05 Formal Charges**" from "**Chapter 1**". A few problems require two screens of models, e.g., "**07 Regiochem of Additions**" from **Chapter 7**. Here the first screen is labeled "**A**" and the second "**B**", e.g., "**07 Regiochem of Additions A**".

How to Use Energies to Calculate Thermodynamic and Kinetic Data

In addition to molecular geometry, the most important quantity to come out of molecular modeling is the energy. Energy can be used to reveal which of several isomers is most stable, to determine whether a particular chemical reaction will have a thermodynamic driving force (an "exothermic" reaction) or be thermodynamically uphill (an "endothermic" reaction), and to ascertain how fast a reaction is likely to proceed. Other molecular properties, such as the dipole moment, are also important, but the energy plays a special role.

There are many ways to express the energy of a molecule. Most common to organic chemists is as a **heat of formation**, ΔH_f . This is the heat of a hypothetical chemical reaction that creates a molecule from so-called "standard states" of each of its constituent elements. For example, ΔH_f for methane would be the energy required to create CH_4 from graphite and H_2 , the "standard states" of carbon and hydrogen, respectively.

An alternative, **total energy**, will be used throughout this workbook. The total energy is the heat of a hypothetical reaction that creates a molecule from a collection of separated nuclei and electrons. Like the heat of formation, total energy cannot be measured directly, and is used solely to provide a standard method for expressing and comparing energies.

Total energies are always negative numbers and, in comparison with the energies of chemical bonds, are very large. They are generally expressed in "so-called" **atomic units** or **au**, but may be converted to other units as desired:

$$1 \text{ au} = 627.5 \text{ kcal/mol} = 2625 \text{ kJ/mol}$$

Total energies (like heats of formation) may be used to calculate energies of **balanced** chemical reactions (reactants \rightarrow products):

$$\Delta E(\text{reaction}) = E_{\text{product1}} + E_{\text{product2}} + \dots - E_{\text{reactant1}} - E_{\text{reactant2}} - \dots$$

A negative ΔE indicates an exothermic (thermodynamically favorable) reaction, while a positive ΔE an endothermic (thermodynamically unfavorable) reaction.

Comparison of isomer stability involves chemical reaction in which the "reactant" is one isomer and the "product" is another isomer (isomer1 \rightarrow isomer2).

$$\Delta E(\text{isomer}) = E_{\text{isomer2}} - E_{\text{isomer1}}$$

A negative ΔE means that isomer2 is more stable than isomer1, and vice-versa.

Total energies may also be used to calculate activation energies, ΔE^\ddagger .

$$\Delta E^\ddagger = E_{\text{transition state}} - E_{\text{reactant1}} - E_{\text{reactant2}} - \dots$$

Here, $E_{\text{transition state}}$ is the total energy of the transition state.

Although there are many situations where one needs only to know whether a reaction is exothermic or endothermic, or if one reaction is more exothermic than another, there are situations where one needs to convert energies into other data.

Equilibrium concentrations of reactants and products can be calculated from the equilibrium constant, K_{eq} , which is related to the free energy of reaction, ΔG_{rxn} :

$$K_{\text{eq}} = \exp(-\Delta G_{\text{rxn}}/RT)$$

Here R is the gas constant and T is the temperature (in K). At room temperature (298K) and for ΔG_{rxn} in au, this is given by:

$$K_{\text{eq}} = \exp(-1060 \Delta G_{\text{rxn}})$$

ΔG_{rxn} has two components, the enthalpy of reaction, ΔH_{rxn} , and the entropy of reaction, ΔS_{rxn} . These are defined by the following formulas:

$$\Delta G_{\text{rxn}} = \Delta H_{\text{rxn}} - T\Delta S_{\text{rxn}}$$

$$\Delta H_{\text{rxn}} \approx \Delta E_{\text{rxn}} = E_{\text{product1}} + E_{\text{product2}} + \dots - E_{\text{reactant1}} - E_{\text{reactant2}} - \dots$$

$$\Delta S_{\text{rxn}} = S_{\text{product1}} + S_{\text{product2}} + \dots - S_{\text{reactant1}} - S_{\text{reactant2}} - \dots$$

Although ΔG_{rxn} depends on both enthalpy and entropy, there are many reactions for which the entropy contribution is small, and can be neglected. Thus, if $\Delta H_{\text{rxn}} \approx \Delta E_{\text{rxn}}$, we can estimate equilibrium constants for such reactions by the following equation:

$$K_{\text{eq}} \approx \exp(-\Delta E_{\text{rxn}}/RT) \approx \exp(-1060 \Delta E_{\text{rxn}})$$

Reaction rate constants, k_{rxn} , are also related to free energies. As before, if entropy contributions can be neglected, the rate constant can be obtained directly from the activation energy, ΔE^\ddagger , by:

$$k_{\text{rxn}} \approx (k_B T/h) [\exp(-\Delta E^\ddagger/RT)]$$

Here k_B and h are the Boltzmann and Planck constants, respectively. At room temperature and for ΔE^\ddagger in au, k_{rxn} is given by:

$$k_{\text{rxn}} = 6.2 \times 10^{12} \exp(-1060 \Delta E^\ddagger)$$

Another way to describe reaction rates is by half-life, $t_{1/2}$, the amount of time it takes for the reactant concentration to drop to one half of its original value. When the reaction follows a first-order rate law, $\text{rate} = -k_{\text{rxn}}[\text{reactant}]$, $t_{1/2}$ is given by:

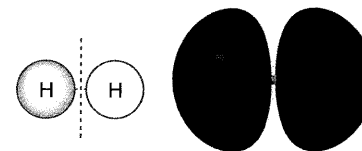
$$t_{1/2} = \ln 2/k_{\text{rxn}} = 0.69/k_{\text{rxn}}$$

Molecular Orbitals. Quantum Mechanics in Pictures

Chemists have developed a number of methods for describing electrons in molecules. Lewis structures are the most familiar. These drawings assign electrons either to single atoms (lone pairs) or pairs of atoms (bonds). You are probably also familiar with atomic orbitals. These are mathematical solutions to the quantum mechanical equations that describe electron motion inside atoms. The orbitals resemble waves in that they typically have large positive magnitudes in some regions of space (a “crest”), have large negative magnitudes in others (a “trough”), and pass through zero, or vanish, somewhere in between (“go through a node”).

A convenient “orbital” method for describing electron motion in molecules is the method of molecular orbitals. Molecular orbitals are defined and calculated in the same way as atomic orbitals and they display similar wave-like properties. The main difference between molecular and atomic orbitals is that molecular orbitals are not confined to a single atom. The “crests” and “troughs” in an atomic orbital are confined to a region close to the atomic nucleus (typically within 1-2 Å). The electrons in a molecule, on the other hand, do not “stick” to a single atom, and are free to move all around the molecule. Consequently, the “crests” and “troughs” in a molecular orbital are usually spread over several atoms.

Orbital Surfaces. Molecular orbitals provide important clues about chemical reactivity, but before we can use this information we first need to understand what molecular orbitals look like. The following figure shows two representations, a drawing and a computer-generated picture, of a relatively high-energy, unoccupied molecular orbital of hydrogen molecule, H_2 .



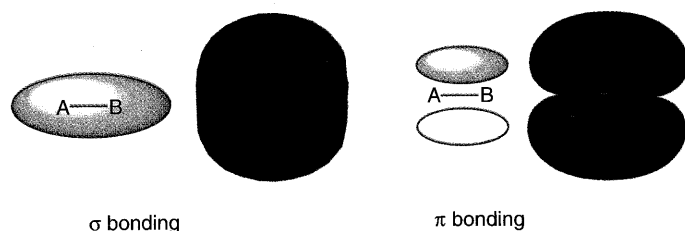
The drawing shows the molecule with the orbital drawing, two circles and a dashed line, superimposed on it. The circles identify regions of space where the orbital takes on a significant value, either positive (shaded circle) or negative (unshaded circle). The dashed line identifies an orbital node, locations where the orbital’s value is exactly zero. The drawing is useful, but it is also limited. We only obtain information about the orbital in two dimensions, and we only learn the location of “significant” regions and not how the orbital builds and decays inside and outside of these regions.

The computer-generated picture depicts the same orbital as an “orbital surface”. The

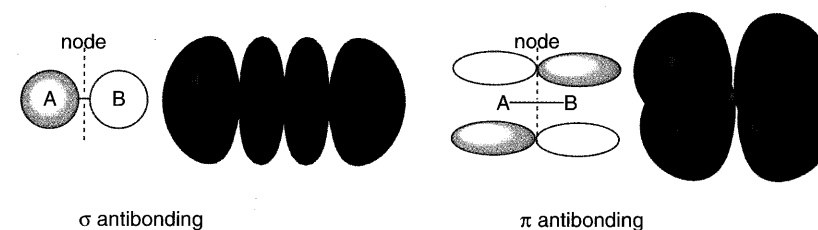
surface is mathematically accurate in that it is derived from an authentic (but approximate) calculated solution to the quantum mechanical equations of electron motion. Equally important, the picture is three-dimensional. It can be manipulated using a computer, and can be looked at from a variety of different perspectives. Note that what we call an “orbital surface” actually consists of two distinct surfaces represented by different colors. The surfaces have the same meaning as the two circles in the orbital drawing. They identify regions where the orbital takes on a significant value, either positive (blue) or negative (red). The orbital node is not shown, but we can guess that it lies midway between the two surfaces (this follows from the fact that the orbital’s value can only change from positive to negative by passing through zero).

Orbital Shapes and Chemical Bonds. Although molecular orbitals and Lewis structures are both used to describe electron distributions in molecules, they are used for different purposes. Lewis structures are used to count the number of bonding and nonbonding electrons around each atom. Molecular orbitals are not useful as counting tools, but orbital shapes and orbital energies are useful tools for describing chemical bonding and reactivity. This section describes a number of common orbital shapes and illustrates how they may be used to interpret chemical bonding and reactivity.

Molecular orbital surfaces can extend over varying numbers of atoms. If the orbital surface (or surfaces) is confined to a single atom, the orbital is regarded as nonbonding. If the orbital contains a surface that extends over the bonding region between two neighboring atoms, the orbital is regarded as bonding with respect to these atoms. Adding electrons to this orbital will strengthen the bond between these atoms and cause them to draw closer together, while removing electrons will have the opposite effect. The following pictures show drawings and orbital surfaces for two different kinds of bonding orbitals. The drawing and surface on the left correspond to a σ bond while the drawing and surface on the right correspond to a π bond.



It is also possible for an orbital to contain a node that divides the bonding region into separate “atomic” regions. This orbital is regarded as antibonding with respect to these atoms. Adding electrons to an antibonding orbital weakens the bond and drives the atoms apart, while removing electrons from the orbital has the opposite effect. The following pictures show drawings and orbital surfaces for two different kinds of antibonding orbitals. As above, the left and right-hand sides correspond to σ and π type arrangements, respectively.



Notice that bonds can be strengthened in two different ways, by adding electrons to bonding orbitals, and by removing electrons from antibonding orbitals. The converse also holds.

Singlet Methylene, CH_2 . Because most molecules contain many atoms, most molecular orbitals are delocalized. Large, delocalized orbitals have complicated shapes and contain multiple interactions that may be bonding, nonbonding, antibonding, or any mixture of all three. Nevertheless, these shapes can still be broken down into two-atom interactions and analyzed using the principles outlined above. This process is illustrated for a triatomic molecule, “singlet” methylene, CH_2 . (“Singlet” refers to the fact that the eight electrons in this highly reactive molecule are organized into four pairs, and that each pair of electrons occupies a different molecular orbital.)

The lowest energy molecular orbital of singlet methylene looks like a $1s$ atomic orbital on carbon. The electrons occupying this orbital restrict their motion to the immediate region of the carbon nucleus and do not significantly affect bonding. Because of this restriction, and because the orbital’s energy is very low (-11 au), this orbital is referred to as a “core” orbital and its electrons are referred to as “core” electrons.

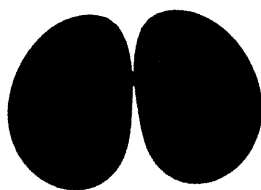


The next higher energy orbital is much higher in energy (-0.9 au) and it is completely delocalized. The orbital surface consists of a single surface that encompasses all three atoms. This means that this orbital is simultaneously (σ) bonding with respect to each CH atom pair.

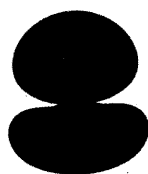


The next higher energy orbital (-0.6 au) is depicted by two surfaces, a positive (blue) surface that encloses one CH bonding region and a negative (red) surface that encloses the other CH bonding region. Since each surface encloses a bonding region, this orbital is simultaneously (σ) bonding with respect to each CH atom pair, and this reinforces the

bonding character of the previous orbital. (The node that separates the two surfaces passes through the carbon nucleus, but not through either of the CH bonding regions, so it does not affect bonding.)



The highest-occupied molecular orbital is called the HOMO (-0.4 au). The HOMO is depicted by two orbital surfaces. One surface extends into carbon's "nonbonding" region opposite the two hydrogens. The other surface encompasses the two CH bonding regions. Although it is hard to track the exact path of the orbital node in this picture, it happens to pass almost exactly through the carbon. This means that this particular orbital possesses bonding as well as nonbonding character. It turns out that the nonbonding character of the orbital is much more important.



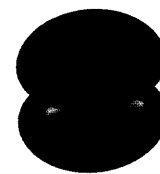
HOMO of CH_2

The above analysis shows that while the occupied orbitals of singlet methylene are spread over several atoms or "delocalized", they are comprehensible. The orbitals divide into two groups, a single low-energy "core" orbital and three higher-energy "valence" orbitals. The latter consist of two CH bonding orbitals and a nonbonding orbital on carbon. There is no one-to-one correspondence between these orbitals and the Lewis structure. The bonding orbitals are not associated with particular bonds, and the nonbonding orbital contains bonding interactions as well.

Singlet methylene also possesses unoccupied molecular orbitals. The unoccupied orbitals have higher (more positive) energies than the occupied orbitals, and these orbitals, because they are unoccupied, do not describe the electron distribution in singlet methylene. Nevertheless, the shapes of unoccupied orbitals, in particular, the few lowest energy unoccupied orbitals, are worth considering because they provide valuable insight into the methylene's chemical reactivity.

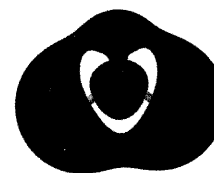
The lowest-unoccupied molecular orbital is called the LUMO ($+0.1$ au). The LUMO has nonbonding character, and looks like a $2p$ atomic orbital on carbon. If this molecule

were to accept electrons, the "extra" electrons would occupy this carbon nonbonding orbital; carbon would become more electron-rich, but the CH bonds would not be much affected.



LUMO of CH_2

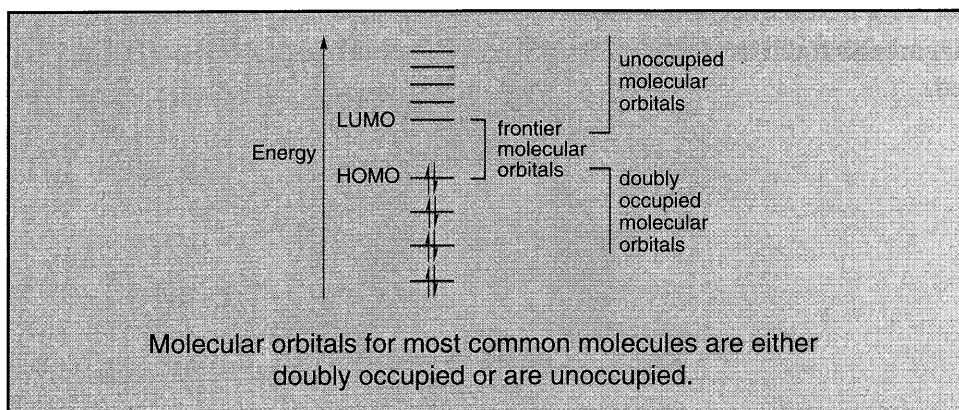
The next higher-energy unoccupied orbital ($+0.3$ au) has a more complicated shape. It is depicted by two surfaces, and the node separating these surfaces is seen to divide the two CH bonding regions into "atomic" regions. In other words, this orbital is CH antibonding. The node does not divide the region between the two hydrogens, so this orbital is weakly HH bonding (the bonding effect is weak because the atoms are far apart).



Frontier Orbitals and Chemical Reactivity. Chemical reactions typically involve movement of electrons from an "electron donor" (base, nucleophile, reducing agent) to an "electron acceptor" (acid, electrophile, oxidizing agent). This electron movement between molecules can also be thought of as electron movement between molecular orbitals, and the properties of these "electron donor" and "electron acceptor" orbitals provide considerable insight into chemical reactivity.

The first step in constructing a "molecular orbital" picture of a chemical reaction is to decide which orbitals are most likely to serve as the "electron donor" and "electron acceptor" orbitals. It should be obvious that the "electron donor" orbital must be drawn from the set of occupied orbitals, and the "electron acceptor" orbital must be an unoccupied orbital, but there are many orbitals in each set to choose from.

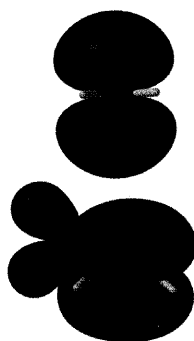
Orbital energy is usually the deciding factor. The chemical reactions that we observe are the ones that proceed quickly, and such reactions typically have small energy barriers. Therefore, chemical reactivity should be associated with the donor-acceptor orbital combination that requires the smallest energy input for electron movement. The best combination is typically the one involving the HOMO as the donor orbital and the LUMO as the acceptor orbital. The HOMO and LUMO are collectively referred to as the "frontier orbitals", and most chemical reactions involve electron movement between them.



One very important question for chemists is the problem of chemical selectivity. In an experiment where more than one combination of reagents can react, which combination will react first? The answer can often be found by examining frontier orbital energies. Consider a set of electron-donor reagents, where chemical reaction requires electron donation from the donor's HOMO. It is reasonable to expect that the donor with the highest energy HOMO will give up its electrons most easily and be the most reactive. Electron-acceptor reagents should follow the opposite pattern. The reagent with the lowest energy LUMO should be able to accept electrons most easily and be the most reactive. And, if we have a mixture of several donor and acceptor reagents, the fastest chemical reaction should involve the reagent combination that has the smallest HOMO – LUMO energy gap.

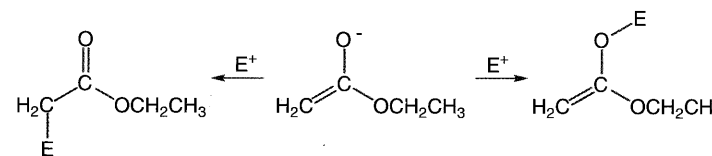
Another selectivity question arises when molecules contain multiple reactive sites. If the relevant frontier orbital is delocalized over all of these sites, then the orbital's energy is useless as a guide to "site selectivity". In this case, only the orbital's shape is important.

For electron movement to occur, the donor and acceptor molecules must approach so that the donor HOMO and acceptor LUMO can interact. For example, the LUMO of singlet methylene is a 2p atomic orbital on carbon that is perpendicular to the molecular plane. Donors must approach methylene in a way that allows interaction of the donor HOMO with the 2p orbital.

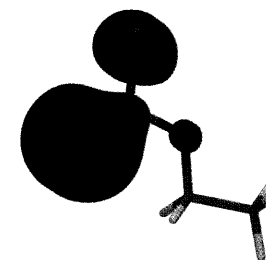


LUMO of methylene (top) approaching HOMO of donor molecule (bottom)

Delocalized frontier orbitals provide a different kind of problem. The ester enolate shown below might react with electrophiles at two different sites.

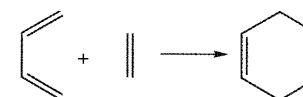


Because the anion acts as an electron donor, we can find clues to its reactivity preferences by examining the shape of its HOMO. The HOMO is delocalized over several sites, but the largest contribution to the HOMO clearly comes from the terminal carbon atom. Therefore, we expect electron movement and bond formation to occur at this carbon, and lead to the product shown on the left.

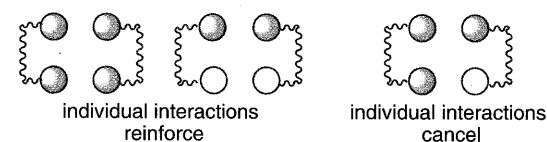


HOMO of ester enolate

In certain cases, multiple frontier orbital interactions must be considered. This is particularly true of "cycloaddition" reactions, such as the Diels-Alder reaction between 1,3-butadiene and ethene.

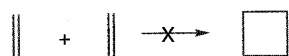


The key feature of this reaction is that the reactants combine in a way that allows two bonds to form simultaneously. This implies two different sites of satisfactory frontier orbital interaction (the two new bonds that form are sufficiently far apart that they do not interact with each other during the reaction). If we focus exclusively on the interactions of the terminal carbons in each molecule, then several different frontier orbital combinations can be imagined.



In all three frontier orbital combinations shown above, the “upper” orbital components are the same sign, and their overlap is positive. In the two cases on the left, the lower orbital components also lead to positive overlap. Thus, the upper and lower interactions reinforce, and the total frontier orbital interaction is non-zero. Electron movement (chemical reaction) can occur. The right-most case is different. Here the lower orbital components lead to negative overlap (the orbitals have opposite signs at the interacting sites), and the total overlap is zero. No electron movement and no chemical reaction can occur in this case.

As it happens, the frontier orbital interactions in the Diels-Alder cycloaddition shown above are like those found in the middle drawing, i.e., the upper and lower interactions reinforce and the reaction proceeds. The cycloaddition of two ethene molecules (shown below), however, involves a frontier orbital interaction like the one on the right, so this reaction does not occur.



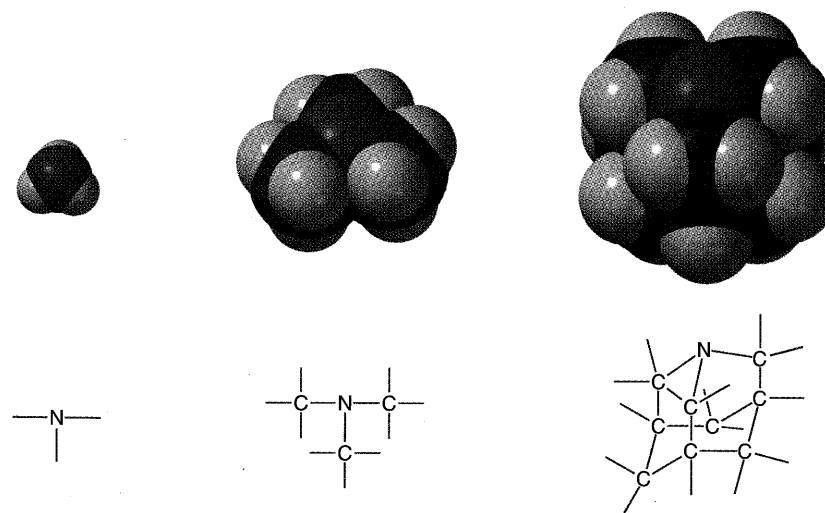
The importance of orbital overlap in determining why certain chemical reactions proceed easily while other “similar reactions” do not go at all was first advanced by Woodward and Hoffmann, and collectively their ideas are now known as the Woodward-Hoffmann rules. Applications of these ideas can be found in **Chapter 21**.

Electron Densities and the Sizes and Shapes of Molecules

How “big” is an atom or a molecule? It should be fairly obvious that atoms and molecules do take up a definite amount of space. A gas can be compressed into a smaller volume but only so far. Liquids and solids cannot be easily compressed. While the individual molecules in a gas are widely separated and can be pushed into a much smaller volume, the molecules in a liquid or a solid are already close together and cannot be “squeezed” much further. The “bottom line” is that atoms and molecules require a certain amount of space. But how much?

Space-Filling Models. For most of this century, chemists have tried to answer the “size” question by using a special set of molecular models known as “space-filling” or “CPK” models. The space-filling model of an atom is simply a sphere of fixed radius. A different radius is used for each element, and the radii are chosen to reproduce certain experimental observations, such as the compressibility of a gas, or the spacing between atoms in a crystal.

Space-filling models of molecules consist of a set of interpenetrating atomic spheres. Interpenetrating spheres are required because the chemical bonds that hold the molecule together cause the atoms to move very close together. Interestingly, “interpenetration” can be used as a criterion for chemical bonding. If two atomic spheres in a space-filling model strongly interpenetrate then the atoms must be bonded. Otherwise the atoms are not bonded.

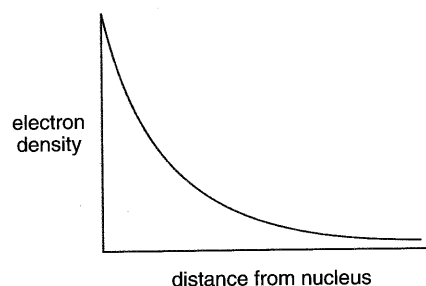


space-filling models of ammonia (left), trimethylamine (center) and quinuclidine (right)

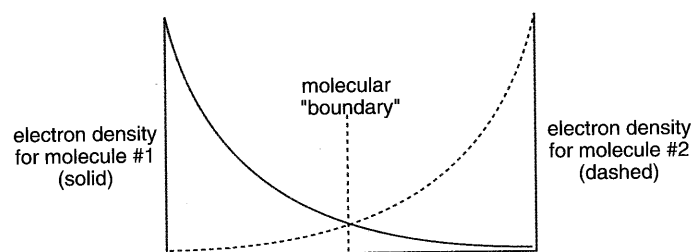
Space-filling models for ammonia, trimethylamine and quinuclidine show how “big” these molecules are. Ammonia is the smallest, and quinuclidine the biggest. The models also show that the nitrogen in ammonia is more “exposed” than the corresponding nitrogen atoms in trimethylamine and quinuclidine.

Electron Density Surfaces. An alternative technique for portraying molecular size and shape relies on the molecule’s own electron cloud. Atoms and molecules are made up of positively-charged nuclei surrounded by a negatively-charged electron cloud, and it is the size and shape of the electron cloud that defines the size and shape of an atom or molecule. Quantum mechanics provides the mathematical recipe for determining the size and shape of the electron cloud, and computer programs can carry out the necessary calculations.

The size and shape of an electron cloud is described by the “electron density” (the number of electrons per unit volume). Consider a graph of electron density in the hydrogen atom as a function of distance from the nucleus.



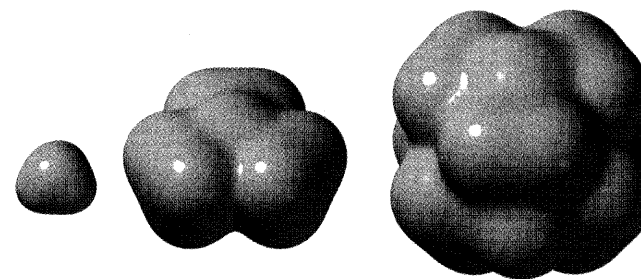
The graph brings up a problem for chemists seeking to define atomic and molecular size. The electron cloud lacks a clear boundary. While electron density decays rapidly with distance from the nucleus, nowhere does it fall to zero. Therefore, when atoms and molecules “rub up against each other”, their electron clouds overlap and merge to a small extent.



The only way to solve the “boundary” problem is to make an arbitrary decision about which part of the electron cloud to pay attention to and which part to ignore. For example, we see that when two electron clouds overlap there is a point where both clouds have the same electron density. This is a logical place to mark each molecule’s “boundary”.

We can also mark the rest of the molecule’s boundary by finding all of the other points where the molecule’s electron density has the same critical value. When all of these boundary points are joined together they form a surface that looks like the molecule’s “outer skin”, and we can use the volume inside this surface to define molecular size. This approach is used throughout this book, but to simplify things we will abbreviate “outer skin electron density surface” to just “electron density surface”.

The following picture shows electron density surfaces for ammonia, trimethylamine and quinuclidine. The surfaces are qualitatively very similar to the space-filling models.

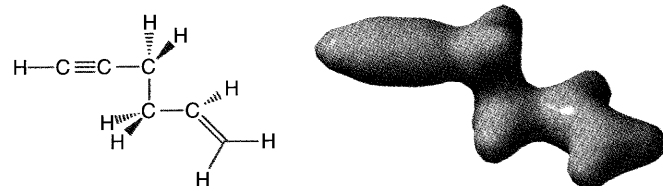


electron density surfaces of ammonia (left), trimethylamine (center) and quinuclidine (right)

Both space-filling and electron density models yield similar molecular volumes, and both show the obvious differences in overall size. Because the electron density surfaces provide no discernible boundaries between atoms (and employ no colors to highlight these boundaries), the surfaces may appear to be less informative than space-filling models in helping to decide to what extent a particular atom is “exposed”. This “weakness” raises an important point, however. Electrons are associated with a molecule as a whole and not with individual atoms. The space-filling representation of a molecule in terms of discernible atoms does not reflect reality, but rather is an artifact of the model. The electron density surface is more accurate in that it shows a single electron cloud for the entire molecule.

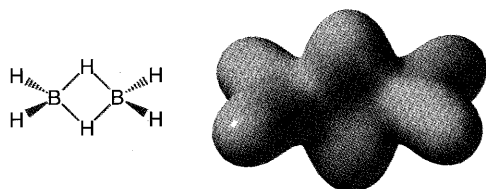
Bond Density Surfaces. The electron density surface is only one of many useful surfaces that can be obtained from an electron cloud. Another useful surface, termed the “bond density surface”, is one that marks points corresponding to a much higher (bonding) level of electron density. Since points of high electron density are located much closer to the atomic nuclei, bond density surfaces enclose relatively small volumes and do not give a true impression of molecular size. On the other hand, bond density surfaces identify regions corresponding to bonding electron density, and the volume of these surfaces may be roughly correlated with the number of electrons that participate in bonding. Therefore, bond density surfaces can be used to construct a bonding model that is analogous to a conventional skeletal model.

The following bond density surface for hex-5-en-1-yne clearly allows you to see which atoms are connected. It does not, however, distinguish single, double and triple carbon-carbon bonds as clearly as a simple skeletal model.



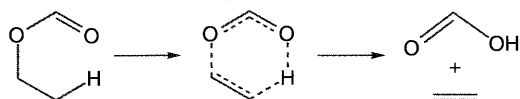
bond density surface of hex-5-en-1-yne

The usefulness of the bond density surface is more apparent in the following model of diborane. The surface shows that diborane is not flat. It also shows that there is relatively little electron density between the two borons. Apparently there is no boron-boron bond in this molecule. This is information that we can extract from the bond density surface model. We do not have to assume this information in order to construct a model. We would need it in order to construct a conventional model.

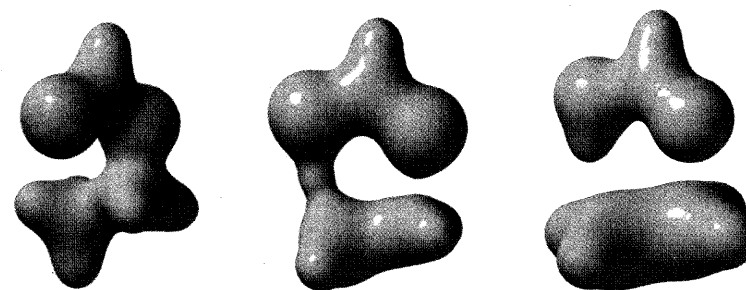


bond density surface of diborane

Bond density surfaces are also superior to conventional models when it comes to describing chemical reactions. Chemical reactions can involve many changes in chemical bonding, and conventional formulas are not sufficiently flexible to describe what happens (conventional plastic models are even worse). For example, heating ethyl formate to high temperatures causes this molecule to fragment into two new molecules, formic acid and ethene. A conventional formula can show which bonds are affected by the reaction, but it cannot tell us if these changes occur all at once, sequentially, or in some other fashion.



On the other hand, the bond density surface is able to provide quantitative information. The three surfaces shown below correspond, respectively, to the reactant, the transition state (a transition state is a molecule that is “on the way” to becoming the products and its energy defines how fast the reaction can proceed), and the two products.



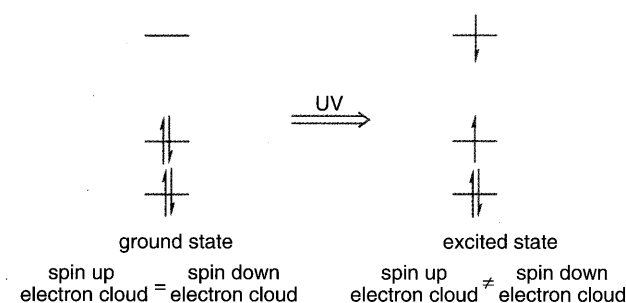
bond density surfaces of the reactant, ethyl formate (left), pyrolysis transition state (center) and of the products, formic acid and ethene (right)

Compare the bonding surface in the transition state to those of the reactant and the products. The CO single bond of the reactant is clearly broken in the transition state. Also, the migrating hydrogen seems more tightly bound to oxygen (as in the product) than to carbon (as in the reactant). It can be concluded that the transition state more closely resembles the products than the reactants, and this provides an example of what chemists call a “late” or “product-like” transition state.

Spin Density Surfaces. Electrons have a property called “spin” that allows them to exist in either of two spin states: “spin up” or “spin down”. Almost all of the molecules that you will encounter will involve each “spin-up” electron paired to a “spin down” electron. Thus, the number of “spin up” and “spin down” electrons will be the same, and the electron clouds due to each spin will be identical.

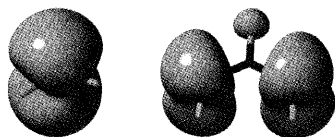
There are some notable exceptions. Free radicals are molecules that contain an odd number of electrons. Since the number of “spin up” and “spin down” electrons in a free radical cannot be equal, the “spin up” and “spin down” electron clouds cannot be identical.

Another, more subtle, exception arises when “normal” molecules absorb ultraviolet radiation. Light absorption causes one electron to jump to a formerly unoccupied orbital and produces a molecule in an “excited state”. While the molecule is in this excited state, the “spin up” and “spin down” electron clouds are not identical.



The “spin density surface” is a tool which helps us find the unpaired electrons in these unusual molecules. “Spin density” is defined as the difference between the “spin up” and “spin down” electron clouds, and a spin density surface is constructed by connecting together points in the electron cloud where the spin density has an arbitrarily chosen value.

The usefulness of spin density surfaces can be seen in the following models of methyl radical, CH_3 , and allyl radical, $\text{CH}_2=\text{CHCH}_2$. In each case, the surface is shaped somewhat like a 2p atomic orbital on carbon. There are some interesting differences between the two radicals, however. While the unpaired electron is confined to the carbon atom in methyl radical, it is delocalized over the two terminal carbons in allyl radical.



spin density surfaces of methyl radical (left) and allyl radical (right)

Electrostatic Potential Maps and Molecular Charge Distributions

The charge distribution in a molecule can provide critical insight into its physical and chemical properties. For example, organic molecules that are charged, or highly polar, tend to be water-soluble, and polar molecules may stick together in specific geometries, such as the “double helix” in DNA. Chemical reactions are also associated with charged sites, and the most highly charged molecule, or the most highly charged site in a molecule, is often the most reactive. The type of charge is also important. Positively-charged sites in a molecule invite attack by bases and nucleophiles, while negatively-charged sites are usually targeted by acids and electrophiles.

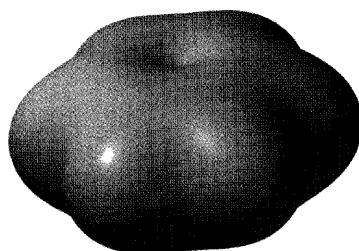
One way to describe a molecule’s charge distribution is to give a numerical “atomic charge” for each atom. A particularly simple recipe yields so-called “formal charges” directly from Lewis structures (see **Chapter 1, Problem 5**). Unfortunately, all of the available methods for assigning charge necessarily bias the calculated charges in one way or another. Calculated charges can be misleading in that they give only the total atomic charge. Because they do not break the charge down by region, they cannot be used to study atoms that contain both electron-rich and electron-poor regions.

An attractive alternative for describing molecular charge distributions makes use of a quantity termed the “electrostatic potential”. The electrostatic potential is defined as the energy of interaction of a point positive charge with the nuclei and electrons of a molecule, and its value depends on the location of the point positive charge. If the point charge is placed in a region of excess positive charge (an electron-poor region), the point charge-molecule interaction is repulsive and the electrostatic potential is positive. Conversely, if the point charge is placed in a region of excess negative charge (an electron-rich region), the interaction is attractive and the electrostatic potential is negative. Thus, by moving the point charge around the molecule, a “map” of the molecular charge distribution can be created.

Electrostatic potentials can be depicted in various ways. For example, it is possible to make an electrostatic potential “surface” by finding all of the points in space where the electrostatic potential matches some particular value. A much more useful way to show molecular charge distribution, however, is to construct a map that can show variation in electrostatic potential. This is normally done in two steps. First one constructs the molecule’s electron density surface or “outer skin” to define the locations being mapped. Then one constructs a map by using different colors to represent the different values of the electrostatic potential on this surface. Mapping requires an arbitrary choice for a color scale. We use the most intuitive color scale, the rainbow, to color all of the maps in this book. Red, the low energy end of the spectrum, is used to color the regions of most negative (least positive) electrostatic potential, and blue is used to color the regions of

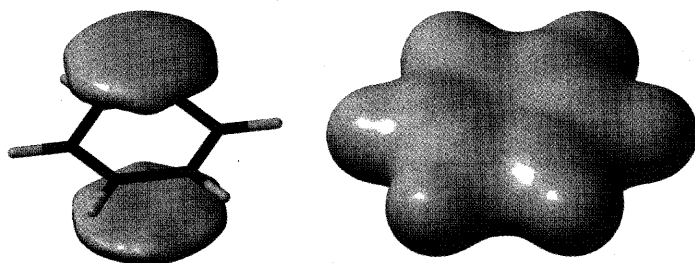
most positive (least negative) electrostatic potential. Intermediate colors represent intermediate values of the electrostatic potential, so that potential increases in the order: red < orange < yellow < green < blue.

The connection between a molecule's electron density surface, an electrostatic potential surface, and the molecule's electrostatic potential map can be illustrated for benzene. The electron density surface defines molecular shape and size. It performs the same function as a conventional space-filling model by indicating how close two benzenes can get in a liquid or crystalline state.



electron density surface for benzene

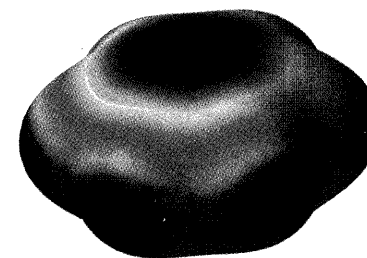
An electrostatic potential surface corresponding to points where the potential equals -0.03 au (≈ -20 kcal/mol) shows two different surfaces, one above the face of the ring and the other below. Since the molecule's π electrons lie closest to these surfaces, we conclude that these electrons can attract a point positive charge (or an electrophile) to the molecule. A "positive" electrostatic potential surface corresponding to points where the potential equals $+0.03$ au ($\approx +20$ kcal/mol) has a completely different shape. It is disk-shaped and wrapped fairly tightly around the nuclei. The shape and location of this surface indicates that a point positive charge is repelled to this region, or that a point negative charge (a nucleophile) would be attracted here.



electrostatic potential surfaces for benzene
 -0.03 au (left) and $+0.3$ au (right)

The electrostatic potential map of benzene conveys the molecule's size as well as its charge distribution in a much more compact manner. The size and shape of the map are, of course, identical to that of the electron density surface, and indicate what part of the molecule is easily accessible to other molecules (the "outside world"). The colors reveal

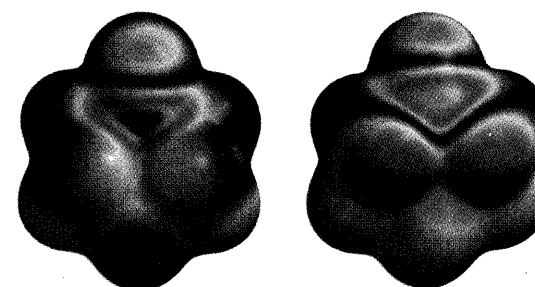
the overall charge distribution. The faces of the ring, the π system, are "red" (electron rich), while the plane of the molecule (and the hydrogens especially) is "blue" (electron poor). Although it is not strictly correct to identify color with local charge (the entire molecule is responsible for the map color), this is the simplest interpretation and the one that we will use.



electrostatic potential map for benzene

Electrostatic potential maps have a myriad of uses as the problems in this book will illustrate.

Although the most important, the electrostatic potential is not only the quantity which when mapped onto an electron density surface may provide useful chemical information. Maps of certain key molecular orbitals, in particular, the HOMO and LUMO, may also lead to informative models. Consider, for example, a map of the (absolute) value of the lowest-unoccupied molecular orbital (LUMO) in cyclohexanone, two views of which are shown below.

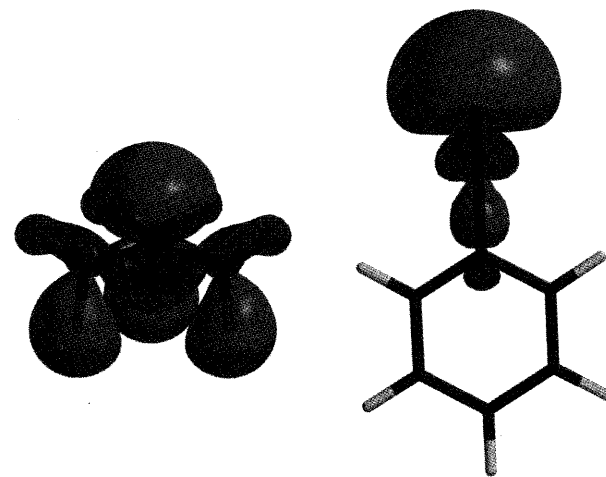


LUMO map for cyclohexanone: axial face (left) and equatorial face (right)

The LUMO delineates areas which are most electron deficient, hence subject to nucleophilic attack. On the maps above, regions where the absolute value of the LUMO is greatest are indicated in "blue", while regions where it is least are indicated in "red". As expected, the "blue" regions are directly over the carbonyl carbon. More interesting, note that the "blue" spot over the axial face is larger than that over the equatorial face. This suggests that nucleophilic attack onto the axial face is likely to be more favorable than attack onto the equatorial face, in accord with experimental observation.

Lewis Structures and Resonance Theory

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lone pairs in trimethylamine (left) and phenylisocyanide (right) dictate the chemistry of these molecules (see problem 10)

Are All Chemical Bonds the Same?

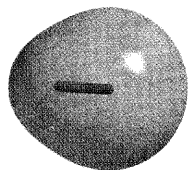
Chemists refer to the bond in a molecule like sodium chloride as “ionic”, meaning that its electron pair resides entirely on chlorine. At the other extreme is the “covalent” bond in the hydrogen molecule, where the electron pair is shared equally between the two hydrogens. Intermediate cases, such as the bond in hydrogen fluoride which is clearly “polarized” toward fluorine, are generally referred to as “polar covalent” bonds (rather than “partially ionic” bonds). Are these situations really all different or do they instead represent different degrees of the same thing?

Examine electron density surfaces for *hydrogen, lithium hydride, beryllium hydride, borane, methane, ammonia, water* and *hydrogen fluoride*. First, focus on the shape of the surface (corresponding to the shape of the underlying electron density). For which molecule is the “size” of hydrogen the smallest? For which is it the largest? Is there a correlation between size of the density around hydrogen and the difference in electronegativities between hydrogen and the element to which it is bonded? (See table at left.) Explain.

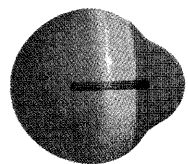
Next, examine electrostatic potential maps for the same set of compounds. Focus your attention on the value of the potential around hydrogen. For which molecule is it most positive? For which is it most negative? Is there a correlation between the value of the potential and the difference in electronegativities? Plot charge on hydrogen (vertical axis) vs. difference in electronegativities (horizontal axis). Is there a correlation?

What electronegativity difference, large or small, creates a more polar bond? A more covalent bond?

Electron density surface for hydrogen fluoride depicts overall molecular size and shape.



Electrostatic potential map for lithium hydride shows negatively-charged regions (in red) and positively-charged regions (in blue).



Electronegativities

H 2.2	Li 1.0	Be 1.6	B 2.0
C 2.6	N 3.0	O 3.4	F 4.0

Bond Lengths in Hydrocarbons

Carbon-carbon bond lengths in hydrocarbons depend both on the formal bond order (single, double, triple) and on the detailed environment.

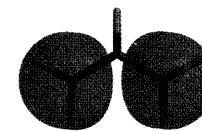
Measure and record the carbon-carbon bond lengths in *ethane, ethene* and *ethyne*. These will serve as “standards” for single, double and triple bonds, respectively.

Is the single bond incorporated into *1,3-butadiene* shorter, longer or about the same length as that in ethane? Is the double bond significantly different (more than $\pm 0.05 \text{ \AA}$) from that in ethene? Rationalize your results based on what you know about the different hybrid orbitals used in the construction of ethane, ethene and 1,3-butadiene. What changes from standard bond lengths would you expect for the single and triple bonds incorporated into *1,3-butadiyne*? Compare its structure to those of ethane and ethyne to see if you are correct.

Is the double bond incorporated into *allene* significantly shorter, significantly longer or about the same length as the bond in ethene? Draw a Lewis structure for allene to justify your conclusion.

Measure the carbon-carbon bond length in *benzene*. Would you describe it as a single bond, a double bond, or somewhere in between? Draw whatever resonance contributors are needed to justify your conclusion.

Are the carbon-carbon bond distances in *allyl cation, allyl radical* and *allyl anion* all similar, or are they significantly different? The three molecules differ mainly in the number of electrons they assign to one particular molecular orbital. (This is the lowest-unoccupied molecular orbital (LUMO) in allyl cation, and the highest-occupied molecular orbital (HOMO) in allyl radical and allyl anion.) Examine the shape of this orbital. Are the changes in electron occupancy consistent with the changes in CC bond length? Explain.



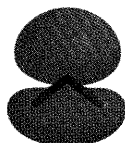
Allyl cation, allyl radical and allyl anion differ in the number of electrons contained in a nonbonding π -type orbital, the LUMO in the cation and the HOMO in the radical and anion.

$$\mu \text{ (debyes)} = 4.8 \left| q_A r_{AB} \right| \quad (1)$$

q_A is the charge on atom A

r_{AB} is the distance between atoms A and B (in Å)

Electronegativities				
H	2.2	C	2.6	F 4.0
				Cl 3.2
				Br 3.0
				I 2.7



HOMO of methylene shows location of highest-energy electrons.

Dipole Moments and Molecular Polarity

The dipole moment provides a measure of charge separation in a molecule. Measure the bond distance and the charge on hydrogen in **hydrogen fluoride**, **hydrogen chloride**, **hydrogen bromide** and **hydrogen iodide**. Using equation (1) at left, estimate the dipole moment in each molecule. Next, measure the “exact” dipole moments. How well do these agree with dipole moments estimated from equation (1)?

Large dipole moments are generally associated with large differences in electronegativity. Do the dipole moments in hydrogen halides parallel electronegativity differences between hydrogen and the halogens?

The exact expression for the dipole moment does not consider atoms as point charges, but rather as nuclei (each with a positive charge equal to the atomic number) and electrons (each with unit negative charge). Atoms with lone pairs may contribute to the dipole moment, even if the atom is neutral, as long as the lone pair electrons are not symmetrically placed around the nucleus.

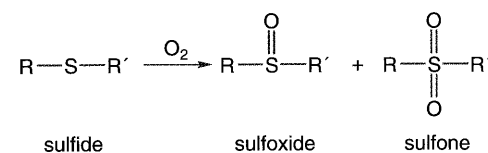
Draw a Lewis structure for singlet methylene, CH_2 (all of the electrons in singlet methylene are spin-paired). How many electrons remain after all bonds have been formed? Where are the “extra” electrons located, in the plane of the molecule or perpendicular to the plane? Examine the highest-occupied molecular orbital (HOMO) of **methylene** to tell.

Hydrocarbons normally have very small dipole moments. Why? (Hint: Consider the relationship between electronegativity differences and dipole moments established above for hydrogen halides.) Does singlet methylene possess a small dipole moment? Explain. What direction do you expect singlet methylene’s dipole to point? Explain. In what direction does it point?

Chromatography and Molecular Polarity

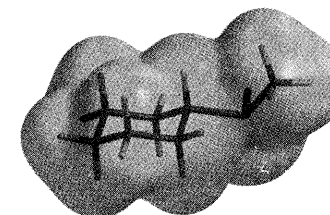
Chromatography is an important practical methodology for separating mixtures of organic compounds. While there are many chromatographic techniques, all basically involve passing the mixture of compounds to be separated over an immobile support contained in a column (the “stationary phase”). Molecules that “stick” strongly to the stationary phase pass more slowly through the column than molecules that stick less strongly.

Oxidation of sulfides results both in sulfoxides and sulfones, as well as starting material.



These can usually be easily separated by thin layer chromatography (TLC) on silica gel.

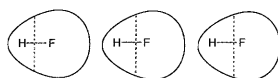
Measure dipole moments and atomic charges, and display and compare electrostatic potential maps for **methyl cyclohexyl sulfide**, **sulfoxide** and **sulfone**. Which molecule has the largest dipole moment? The smallest? Focusing only on the functional groups, which atoms in each are most positively charged? Most negatively charged? Does increased oxidation lead to sulfur becoming more positively charged, more negatively charged or leave it unchanged? Explain. Overall, which molecule is most polar (positive and negative charge most widely separated) and which is least polar? Were a mixture of these molecules to be dissolved in a non-polar solvent and passed over a highly-polar stationary phase, which isomer would you expect to elute first and which would you expect to elute last? Explain your reasoning.



Electrostatic potential map for methyl cyclohexyl sulfoxide shows negatively-charged regions (in red) and positively-charged regions (in blue), either of which is capable of “sticking to” a polar stationary phase.

Formal Charge vs. Atomic Charges

There is actually no unique way to calculate (or measure) atomic charges, simply because there is no way to uniquely partition a molecule's electrons among the atoms. For example, it is impossible to say what fraction of the electrons contained in the electron density surface for hydrogen fluoride belongs to fluorine. None of the partitions shown below is "more reasonable" than any of the others.



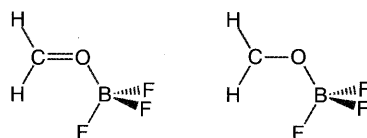
Organic chemists have devised a very simple set of rules allowing assignment of a formal charge for each atom of a particular Lewis structure.

- 1) Start with the number of valence electrons in the neutral atom, e.g., H=1, C=4, O=6.
- 2) Subtract all nonbonding electrons (2 for each lone pair).
- 3) Subtract half the number of bonding electrons, e.g., 1 for each single bond, 2 for each double bond, etc.

Formal charges are merely a bookkeeping device, and do not reflect the actual charge on an atom. Molecular modeling may provide a more realistic description.

Draw Lewis structures for methanol, protonated methanol and methoxide, and assign formal charges. Which atom bears the formal positive charge in protonated methanol? Which atom bears the formal negative charge in methoxide? Are your results consistent with the ordering of atomic electronegativities: $O > C > H$? Obtain atomic charges for *methanol*, *protonated methanol* and *methoxide anion*. Which atom bears the greatest positive charge in protonated methanol? Which atom bears the greatest negative charge in methoxide? Are these data in "better accord" with the ordering of electronegativities?

Lewis acids such as BF_3 coordinate to carbonyl groups. Two "reasonable" bonding patterns for a formaldehyde/ BF_3 complex are provided below.



Add lone pair electrons and assign formal atomic charges in each (do not change bond types). Compare to calculated charges for *formaldehyde* BF_3 complex. Which structure, if either, is more reasonable?

Resonance Structures. The Sum of the Parts

While the majority of molecules may be adequately represented by a single resonance contributor, there are numerous situations where two or more contributors are needed. The simplest case is where all the contributing resonance structures are equivalent. Here, the proper description is in terms of an unweighted average.

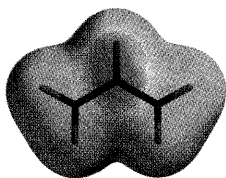
Draw appropriate resonance contributors for benzene. Are all contributors equivalent? Measure the six carbon-carbon bond lengths in *benzene*. Are they all the same? Are they intermediate in length between "normal" single bonds (in *ethane*) and "normal" double bonds (in *ethene*)? Is benzene properly described in terms of an equal weighting among its resonance contributors? Repeat your analysis with *formate anion*, and address the same issues as above. Refer to *methanol* and *formaldehyde* as examples of molecules incorporating carbon-oxygen single and double bonds, respectively.

The situation is more complicated when the set of "reasonable" contributing structures are not all equivalent. Examine the geometry and atomic charges for *phenoxide anion*. Do these data fit any one of the possible resonance structures (draw all reasonable possibilities), or is a combination of two or more resonance contributors necessary?

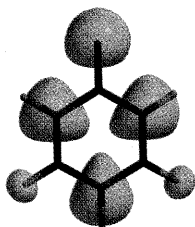
Repeat your analysis for *pyridazine*. Do any of the resonance contributors provide an adequate description of its geometry? Does pyridazine incorporate a nitrogen-nitrogen double bond? (Refer to *hydrazine* and to *diimide* as examples of molecules incorporating NN single and double bonds, respectively.)

Resonance Energy

CC bond distances in localized allylic systems have been held at 1.5 Å and 1.3 Å (typical of CC single and double bond lengths, respectively), and at 1.4 Å for delocalized systems.



Electrostatic potential map for delocalized allyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).



Spin density for phenoxy radical shows location of unpaired electron.

Resonance theory tells us that molecules which cannot be adequately represented in terms of a single Lewis structure are likely to be unusually stable. What the simple theory does not tell us is the magnitude of the effect, the so-called resonance energy. This can be assessed via molecular modeling.

Draw Lewis structures for allyl cation. Where is the positive charge? Examine atomic charges as well as the electrostatic potential map for *localized* and *delocalized* forms of *allyl cation*. Which carbon (s) carries the charge in each?

Repeat your analysis for *localized* and *delocalized allyl radical* and *allyl anion*. Focus on location of the spin density in the former and on the negative charge in the latter.

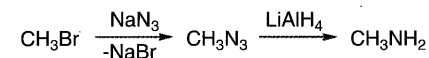
Calculate the difference in energy between localized and delocalized forms for allyl cation, radical and anion. Does it increase, decrease or remain approximately the same with increasing number of π electrons? Rationalize your result.

Compare atomic charges as well as electrostatic potential maps for *formate anion* and *formate anion at formic acid geometry*, and for *phenoxide anions* and *phenoxide anion at phenol geometry*. Is there a large shift in negative charge in going from the geometries of neutral precursors to “relaxed” geometries? Does charge delocalization require reorganization of geometry? Calculate the energy gained by allowing the two ions to “relax” from these initial geometries to their final geometries.

Repeat your analysis for *phenoxy radical*. Instead of charge, focus on the spin density. Calculate the delocalization energy using *phenoxy radical at phenol geometry*. Is it of the same order of magnitude as that for phenoxy anion? Explain.

Azide

Azide anion (N_3^-) is an excellent nucleophile which has important synthetic application in converting alkyl halides to amines, e.g.



Draw three Lewis structures for azide anion (assign formal charges and make certain that each nitrogen has a filled valence shell). Compare the NN bond length in *azide anion* with those in *hydrazine*, *diimide* and *nitrogen*, i.e., molecules incorporating formal single, double and triple NN bonds, respectively. Do the NN bonds correspond to single, double or triple likages, or do they adopt an intermediate value? On the basis of geometry, which (if any) of your Lewis structures provides the best description of azide anion?

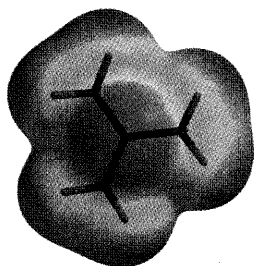
Is azide anion linear or bent? Name a common neutral organic molecule that is isoelectronic (same number of valence electrons) with azide anion. Is this molecule linear or bent?

According to the resonance picture, where is the excess negative charge in azide anion? Will the center nitrogen or a terminal nitrogen act as the nucleophilic site? Examine atomic charges and the electrostatic potential map. Do they substantiate your conclusion? Explain.



Electrostatic potential map for azide anion shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

Molecular Geometry and the Number of Electrons



Electrostatic potential map for pyramidal 2-methyl-2-propyl anion shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

Molecular geometry depends not only on the constituent atoms, but also on the total number of electrons. Molecules with identical formulas but with varying numbers of electrons may prefer different geometries.

Step through the sequence of structures depicting puckering of the central carbon in **2-methyl-2-propyl cation**. Plot energy (vertical axis) vs. CCC bond angle (horizontal axis). What is the favored geometry? What is the energetic “cost” to distort by 10° from this geometry?

Repeat your analysis for **2-methyl-2-propyl radical** and **2-methyl-2-propyl anion**, and assign preferred equilibrium geometry and the energy required to distort (by 10°) away from this geometry to each.

Summarize your results for the three systems. What changes, if any, do you observe with increasing number of valence electrons? Changes in preferred geometry? Changes in energy required for distortion? What is the origin of these changes? Hint: Draw Lewis structures for the three systems, and identify what parts of the molecule are directly affected.

Compare electrostatic potential maps for **planar** and **pyramidal** forms of **2-methyl-2-propyl anion**. For which is the negative charge more delocalized? Is this the lower-energy structure? For this case, does charge delocalization lead to stabilization? Explain.

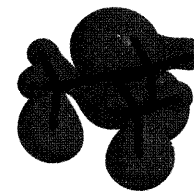
Too Many Electrons. Lone Pairs

What happens to electrons which are “left over” after all bonds have been formed? Do they associate with individual atoms or are they spread “uniformly” throughout the molecule? Draw a Lewis structure for trimethylamine. How many electrons are needed to make bonds? How many are left over? Where are they? Display the highest-occupied molecular orbital (HOMO) for **trimethylamine**. Where is it located?

Examine the “HOMO-2” for **phenylisocyanide**. Is it directly involved in any σ or π bonds? If so, which bonds? If not, describe where it is located. Draw a Lewis structure for the molecule which is consistent with your result.

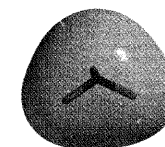
Electrons which are left over after bonds have been formed are referred to as “lone pairs”. Although they may not contribute (directly) to bonding, they do take up space. You cannot actually “see” lone pairs, but you can see the space which they occupy and infer whether or not they contribute significantly to a molecule’s overall size and shape.

Draw Lewis structures for methyl anion, ammonia and hydronium cation. How many electrons are left over in each after all bonds have been made? Display and compare electron density surfaces for **methyl anion**, **ammonia** and **hydronium cation**. Which is the smallest molecule? Which is the largest? Rationalize your observation. (Hint: Compare the number of electrons in each molecule, and the nuclear charge on the central atom in each molecule.)



HOMO for trimethylamine shows location of electrons which are left over after all bonds have been formed.

Lone pairs are not necessarily the highest-energy electrons. In the case of phenylisocyanide, the two highest-energy molecular orbitals are delocalized π orbitals.



Electron density surface for ammonia depicts overall molecular size and shape.

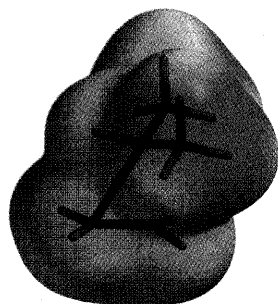
11

Too Few Electrons. Multicenter Bonding



Bond density surface for diborane locates bonds.

Energy minima have all real frequencies, while molecules with one or more imaginary frequencies are not minima.



Electrostatic potential map for bridged 3-methyl-1-butyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

What happens if there are not enough electrons to form “conventional” two-electron bonds? Diborane (B_2H_6) provides a good example. Were the molecule to look like *ethane*, how many valence electrons would be required to hold it together? How many valence electrons does diborane possess? Examine the actual structure for *diborane*.

Based on its structure and valence electron count, draw a Lewis structure or series of Lewis structures for diborane. Examine the bond density surface. Does it substantiate or refute your speculation?

Even where there are sufficient electrons to form all bonds, alternative “non-conventional” geometries may lead to more stable arrangements. Which is lower in energy, *open* or *bridged* forms of *3-methyl-1-butyl cation*? Is the higher-energy structure an energy minimum? Examine its vibrational frequencies to tell. Examine the geometry (in particular, bond distances), atomic charges and the electrostatic potential map for the lower-energy structure. Also display its bond density surface. Based on your observations, draw an appropriate Lewis structure or series of Lewis structures to describe the geometry and charge distribution of the cation.

Draw a Lewis structure (or series of Lewis structures) for *2-norbornyl cation* which adequately describes its geometry, charge distribution and bond density surface. Relate this structure to your description of 3-methyl-1-butyl cation.

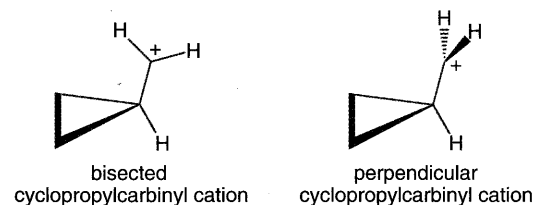
Localized vs. Delocalized Charge

Resonance theory provides a qualitative description of the location of excess (positive or negative) charge in a molecule. Each resonance contributor assigns charge to a particular center, and the extent to which charge is delocalized, and hence stabilized, may be judged simply by counting the number of contributing structures.

Draw all reasonable resonance contributors for both planar and perpendicular conformers of benzyl cation. Identify the site(s) of the positive charge in each. Which cation would you expect to be more stable? Which is the more stable? Compare energies of *planar* and *perpendicular* conformers of *benzyl cation*.

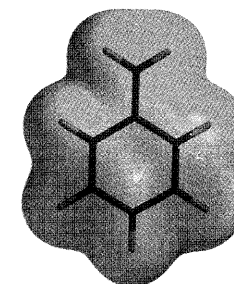
Electrostatic potential maps provide a measure of the charge distribution in carbocations. Localized ions will show areas of high positive potential (large positive charge), while the potential in delocalized ions will be more uniform. Display electrostatic potential maps for both planar and perpendicular conformers of benzyl cation. Is the charge in the lower-energy conformer more or less delocalized than that in the higher-energy conformer?

A closely related stable cation which also exhibits a strong conformational preference is cyclopropylcarbinyl cation.



Display electrostatic potential maps for both *bisected* and *perpendicular* conformers of *cyclopropylcarbinyl cation*. For which is the charge more delocalized? Is the more delocalized cation also the lower-energy cation?

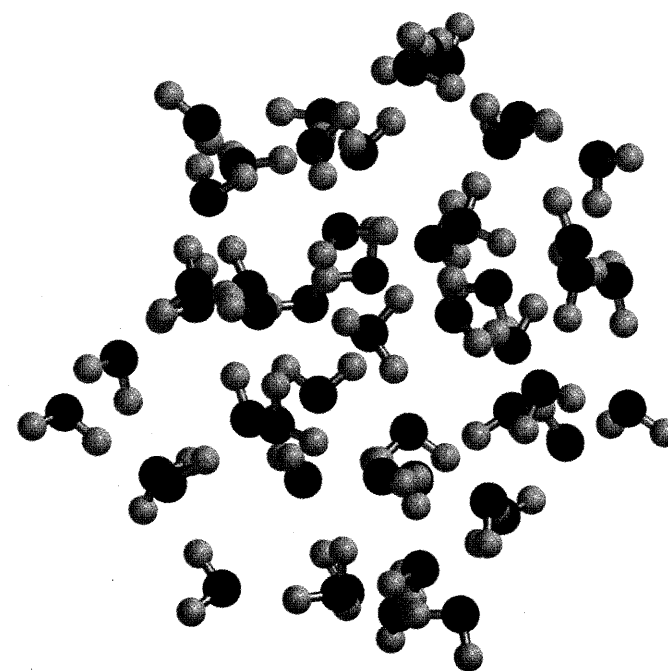
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Electrostatic potential map for planar benzyl cation shows most positively-charged regions (in blue), and less positively-charged regions (in red).

Acids and Bases

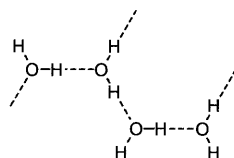
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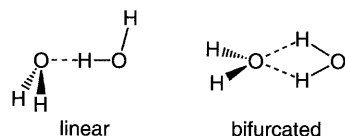
hydronium ion in water
(see problem 3)

Liquid Water

Water boils at a much higher temperature than would be expected based solely on its molecular weight. The reason is that liquid water exhibits a highly structured network of hydrogen bonds.



Liquid water is a sample of 36 water molecules in one of a nearly infinite number of possible ordered arrangements. Identify at least ten hydrogen bonds between pairs of water molecules. Would you characterize most of them as “linear” or as “bifurcated”?



What is the range of OHO bond angles for the linear hydrogen bonds in your sample (see also **Chapter 2, Problem 2**)?

Measure at least five hydrogen-bond lengths (O—H---O) in the sample. What is the range of distances in your sample? Is the average hydrogen-bond length shorter, longer or about the same as the sum of the van der Waals radii for hydrogen and oxygen (see table at left)? Display liquid water as a space-filling model. Are the atoms involved in hydrogen bonds “just touching” (distances ~ sum of van der Waals radii) or do they interpenetrate (distance < sum of van der Waals radii)?

van der Waals radii (Å)

H	1.2	O	1.4
---	-----	---	-----

Structure of Hydrogen-Bonded Complexes

Hydrogen-bonded complexes are common throughout chemistry. They generally involve a hydrogen attached to a heteroatom (usually nitrogen or oxygen) interacting with another heteroatom.

Water dimer distance variation provides a sequence of structures for water dimer at different nonbonded OH distances. Plot energy (vertical axis) vs. nonbonded OH distance (horizontal axis). What is the optimum distance? How much energy is required to increase this distance by 10%? How much is required to reduce the distance by 10%? Are the two distortion energies about the same magnitude? If not, explain why not.

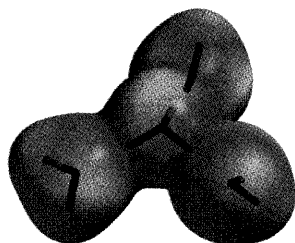
Water dimer angle variation provides a series of structures at different O—H---O bond angles. Plot energy (vertical axis) vs. O—H---O bond angle (horizontal axis). What is the optimum angle? How much energy is required to alter this angle by $\pm 10\%$? Are the two distortion energies about the same magnitude? If not, explain why not. Is angle distortion easier or harder than distance distortion? Explain.

One after the other, examine **methanol dimer** and **acetic acid dimer**. Do the hydrogen-bond lengths in these systems differ significantly from the optimum distance in water dimer? Are the hydrogen-bond angles in these compounds significantly different from those in water dimer? Rationalize your results.

Identify all hydrogen bonds in **AT pair** and **GC pair** (complexes involving the nucleotide bases adenine, thymine, guanine and cytosine, respectively). These systems involve both nitrogen and oxygen. Do the hydrogen-bond distances and angles differ significantly from those in the oxygen systems discussed previously?

What is Hydronium?

Reactions in water often involve a ubiquitous species known as hydronium (H_3O^+). Is hydronium properly described as an isolated ion, or at the other extreme, as a proton “dissolved in water”?



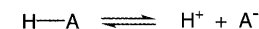
Electrostatic potential map for hydronium+3 water molecules shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Examine electrostatic potential maps for “free” *hydronium* and for hydronium complexed to three and nine water molecules (*hydronium+3 water* and *hydronium+9 water*, respectively). What happens to the positive charge as more and more water molecules are involved? Rationalize your result.

Hydronium in liquid water shows hydronium “immersed” in a sample of 50 water molecules. The particular arrangement shown is one of a nearly infinite number of possibilities. First identify the hydronium ion. Next, identify hydrogen bonds between the oxygen and hydrogens on hydronium ion and the surrounding water molecules, and also between the water molecules themselves. What is the average hydrogen-bond length involving hydronium and the surrounding water molecules? Is it shorter, longer or about the same length as the average hydrogen-bond length involving water molecules alone? Rationalize your result.

Acid-Base Properties and Partial Charge

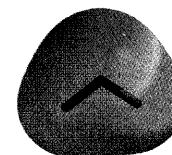
Acids are defined as proton (H^+) donors.



The HA bonds in stronger acids are polarized $\text{H}^{\delta+}-\text{A}^{\delta-}$ so that H is already “proton-like”. Consequently, an acid’s proton-donating ability (“acid strength”) is usually correlated with the partial charge on hydrogen. This can be obtained from an electrostatic potential map.

Compare atomic charges and electrostatic potential maps for *methane*, *ammonia*, *water* and *hydrogen fluoride*. Which molecule contains the most electron-poor hydrogen (largest $\delta+$)? Which molecule contains the least electron-poor hydrogen (smallest $\delta+$)? What relationship, if any, exists between the atomic charge on hydrogen and the electronegativity of the atom bonded to hydrogen (see table at right)? What relationship, if any, exists between atomic charge and experimental pK_a (see table at right)?

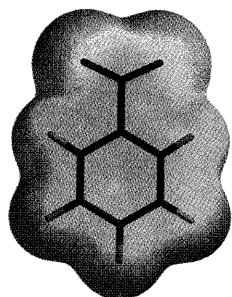
Electrostatic potential map for water shows negatively-charged regions (in red) and positively-charged regions (in blue).



Electronegativities			
C	2.6	N	3.0
O	3.4	F	4.0
pK_a			
CH_4	50 (est.)		
NH_3	36 (est.)		
H_2O	15.7		
HF	3.2		

Acid-Base Properties and Charge Delocalization. I

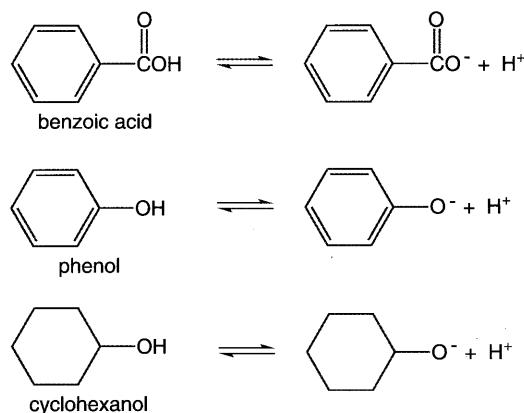
Electron delocalization in an acid, or its conjugate base, can have a large impact on both stability and reactivity. Consider the following acids and their conjugate bases.



Electrostatic potential map for benzoate anion shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

Energy (H^+) = 0 au

	pK_a
benzoic acid	4.2
phenol	9.9
cyclohexanol	18 (est.)



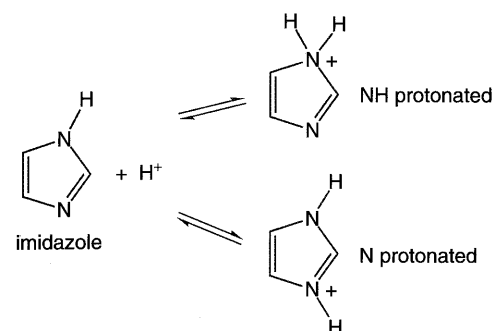
Cleavage of the OH bond gives oxygen a negative charge. However, electron delocalization may spread this charge over several atoms and stabilize the ions to varying degrees.

Compare atomic charges and electrostatic potential maps for **benzoate anion**, **phenoxide anion** and **cyclohexanoxide anion**. Which ion concentrates the most negative charge on a single atom? Which ion spreads the charge around most effectively? Which ions seem to spread charge into the ring? Is the phenyl ring or the cyclohexane ring better able to delocalize charge? Draw whatever Lewis structures are needed to describe each ion's charge distribution.

Obtain energies for each ion and for their corresponding precursors (**benzoic acid**, **phenol** and **cyclohexanol**). Use this information to calculate the energy for each of the above deprotonation reactions. (The energy of proton is given at left.) Is the trend consistent with the experimental pK_a data (see table at left)? Does deprotonation energy parallel charge delocalization in these systems? Explain how electron delocalization affects the reactivity of these acids.

Acid-Base Properties and Charge Delocalization. II

Electron delocalization can dictate the site of chemical reaction within a molecule. Consider, for example, two alternative acid-base reactions for imidazole:

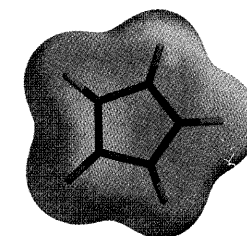


Both protonated forms place the formal positive charge on one of the nitrogens. Is charge delocalization more effective for one of the structures over the other, making it the more stable?

Compare atomic charges and electrostatic potential maps for **imidazole NH protonated** and **imidazole N protonated**. In which ion is the positive charge more delocalized? Compare carbon-nitrogen bond distances in each ion to those in **imidazole** as a standard. Are these distances consistent with the bonding patterns shown above for each ion? Draw whatever Lewis structures are needed to describe each ion's geometry and charge distribution.

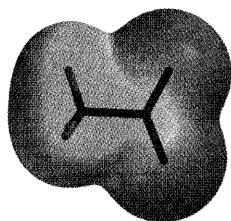
Obtain the energy of each ion. Which one is more stable? Is the delocalized ion more stable?

Which nitrogen in imidazole would you predict to be more basic?



Electrostatic potential map for N protonated imidazole shows most positively-charged regions (in blue) and less positively-charged regions (in red).

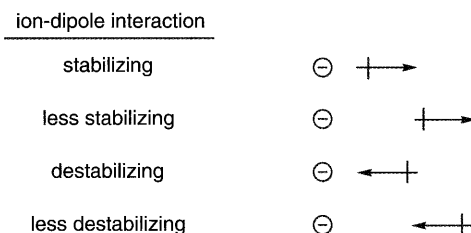
Acid-Base Properties and Ion-Dipole Interactions



Electrostatic potential map for acetate anion shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

	pK _a
acetic acid	4.8
chloroacetic acid	2.9
trichloroacetic acid	0.7
2-chlorobutyric acid	2.9
4-chlorobutyric acid	4.5

The favorability of acid-base reactions is affected, in part, by electrostatic interactions between charged atoms and dipoles within the same molecule. The equilibrium will shift in the direction of an ion that is stabilized by intramolecular ion-dipole interactions.



The larger the charge and the closer the dipole is to the charge, the greater will be the stabilization (or destabilization).

Display the dipole moment for *methyl chloride*. Is chlorine at the + or – end?

Next, display electrostatic potential maps for *acetate*, *chloroacetate*, *trichloroacetate*, *2-chlorobutyrate* and *4-chlorobutyrate anions*. Compare potentials at the position between the two oxygens. Classify the anions as having large, intermediate or small charge in this region.

Finally, examine the geometries of the anions, and classify the distance between the center of negative charge and the positive end of the dipole as small (<2Å), intermediate (<3Å) or large (>3Å).

Combine these factors (as well as the number of CCl dipoles) to anticipate the stabilizing effect of ion-dipole interactions. Is there a correlation with the conjugate acids pK_a (see table at left)?

Alkyl = H. Fact or Fiction?

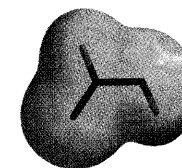
Experimental pK_a data suggests that simple alkyl groups all affect acid-base reactivity in roughly the same way. What is more, this “universal alkyl effect” is roughly equivalent to the effect of a hydrogen atom. For example, the difference in pK_a between water and ethanol is approximately the same as that between formic acid and propanoic acid (see table at right).

One way to explain this similarity is to compare the effect which alkyl groups and H have on the charge distribution in these acids and their conjugate bases.

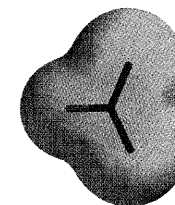
Display electrostatic potential maps for *water*, *ethanol*, *formic acid* and *propanoic acid*, and examine the value of the electrostatic potential at the most electron-poor site. What causes a larger change in electrostatic potential, switching the alkyl group for H, or changing the structure of the acidic functional group?

Display electrostatic potential maps for the conjugate bases of the acids above (*hydroxide*, *ethoxide*, *formate* and *propionate anions*), and examine the value of the electrostatic potential at the most electron-rich site. What causes a larger change in electrostatic potential, switching the alkyl group for H, or changing the structure of the functional group?

	pK _a
water	16
ethanol	17
formic acid	3.8
propanoic acid	4.9



Electrostatic potential map for formic acid shows negatively-charged regions (in red) and positively-charged regions (in blue).



Electrostatic potential map for formate anion shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

The analysis presented here is greatly oversimplified in that “H⁺_{aq}” is treated as a “free proton” immersed in water. In fact, “free protons” do not form during chemical reactions. Rather, the proton is transferred directly from Cl⁻ to H₂O.

Acid Dissociation in the Gas Phase and in Water

Hydrochloric acid (HCl) is a strong acid in water and dissociates completely into H⁺ (more accurately, H₃O⁺) and Cl⁻.



HCl shows no tendency to dissociate in the gas phase, however, and HCl is less prone to dissociate in less polar solvents, such as methanol.

Step through the sequence of structures depicting dissociation of *HCl* in the *gas* phase. Plot energy (vertical axis) vs. interatomic distance (horizontal axis). How many energy minima are there? Do these structures correspond to “molecular” or “dissociated” HCl?

Repeat the above steps for dissociation of *HCl* in *water* (label the vertical axis “aqueous phase” energy). The energies contained in this sequence have been obtained by calculating the effect a polar medium like water would have on the dissolved species. How many energy minima are there? What species do these minima correspond to?

Describe and account for any differences between the gas and aqueous phase energy profiles for dissociation of HCl.

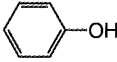
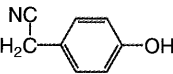
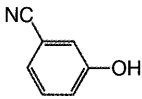
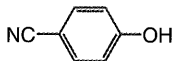
Long-Range Substituent Effects

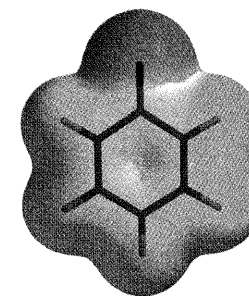
Experimental pK_a data suggest that cyano substitution can exert substantial long-range effects on phenol acidity, but the reason for these effects is not obvious. If ion-dipole interactions were to blame, the effect would fall off with increasing ion (O⁻) - dipole (CN) separation. If electron delocalization were responsible, then the effect would be accompanied by charge transfer between the ionic site (O⁻) and other atoms in the molecule.

Examine atomic charges and display electrostatic potential maps for *phenoxide*, *3-cyanophenoxide*, *4-cyanophenoxide* and *4-cyanomethylphenoxide anions*. Which ions contain the most and the least electron-rich oxygen? Is the electronic character of oxygen consistent with the trend in pK_a's (see table at right)? Explain.

Decide if ion-dipole interactions are responsible for the observed substituent effects. Obtain the charge on carbon and nitrogen in each cyano group. What evidence is there for a polar CN bond? Should the ion (O⁻)-dipole (CN) interaction be stabilizing or destabilizing? Can these interactions explain the trends in electrostatic potential? (Hint: Focus on changes in O---CN distance and in orientation of the cyano group.)

Now decide if electron delocalization is responsible for the substituent effects. What evidence is there for electron transfer from oxygen to other atoms? Is electron transfer accompanied by reasonable changes in geometry? (Hint: Focus on changes in the CO bond distance and in the C_{ring} - C_{cyano} distance.) Draw whatever Lewis structures are needed to describe each ion's charge distribution and geometry. Can electron delocalization explain the variation in electrostatic potential on oxygen? How do you explain the long-range effect of each substituent on phenol acidity?

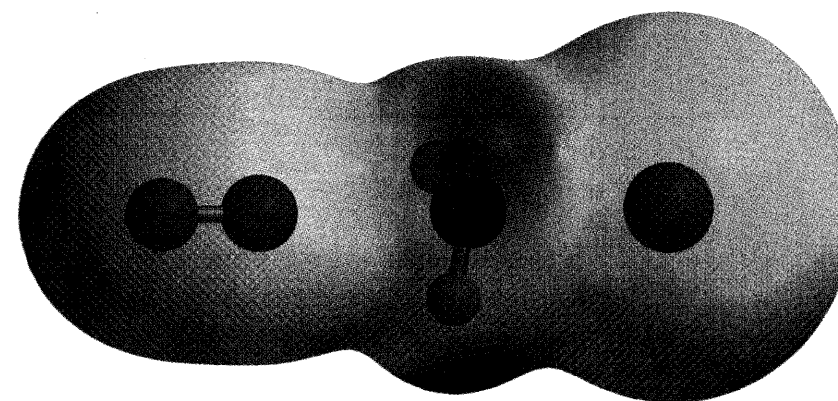
	pK _a
	9.9
	9.7
	8.6
	8.0



Electrostatic potential map for phenoxide anion shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

Reaction Pathways and Mechanisms

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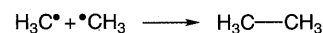


electrostatic potential map shows shifts in charge during S_N2 displacement of iodide from methyl iodide by cyanide (see problem 3)

Reaction Energy Diagrams

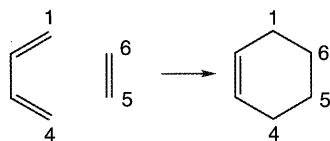
Chemical reactions involve the making and breaking of bonds. Such changes in bonding are accompanied by changes in energy, and graphs of energy vs. geometry (also known as “reaction energy diagrams”) provide a useful tool for analyzing these changes.

Step through the sequence of structures corresponding to combination of two methyl radicals to give ethane (*methyl radical combination*).



Plot energy (vertical axis) vs. carbon-carbon distance (horizontal axis). Is this reaction endothermic or exothermic? Is there a point on the diagram that can be identified as a transition state? If so, what is the barrier for this reaction?

Step through the sequence of structures corresponding to the combination of *cis*-1,3-butadiene and ethene to give cyclohexene (*Diels-Alder reaction*).



Plot energy (vertical axis) vs. C_1C_6 bond distance (horizontal axis), and repeat the analysis described above.

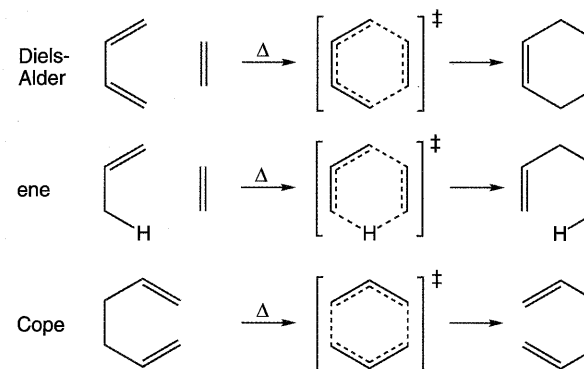
Both of the reactions, radical combination and Diels-Alder cycloaddition, cause new bonds to be made. Bond making normally releases energy. Why then are the barriers for the two reactions so different? (Hint: Consider the **net** bond making/bond breaking in the two reactions.)

What Do Transition States Look Like?

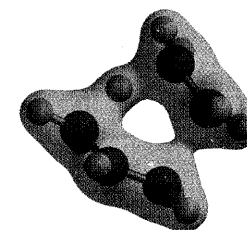
A large body of experimental evidence confirms that covalent bonds have characteristic distances depending on bond type. Carbon-carbon single and double bond lengths are around 1.54 Å and 1.32 Å, respectively, while partial double bond distances, e.g., in benzene, are about 1.40 Å.

Transition states, because they represent a molecule in which bonds are being made (or broken), necessarily contain partial bonds. There are no experimental data, however, that can tell us how long these bonds are, or whether partial bonds even have characteristic distances.

Examine transition-state structures and bond density surfaces for the *Diels-Alder*, *ene* and *Cope* reactions.



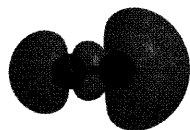
Draw the two resonance contributors that are needed to describe each transition state. Identify all partial carbon-carbon double bonds (—) and measure their distances. Are these values like that found in benzene, or do transition states have their own characteristic partial double bond distance? Identify all partial single CC bonds (—) and obtain their distances. Is there a characteristic partial single bond distance? How does it compare to a normal single bond distance? How does it compare to the sum of two carbon atomic radii? Do bond density surfaces show a significant concentration of electrons for atoms connected by partial single bonds? Repeat your analysis for the partial CH bonds in the ene transition state.



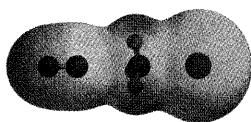
Bond density surface for transition state for ene reaction shows making and breaking of bonds.

van der Waals radii (Å)			
H	1.2	C	1.7

Electronic Structure of Transition States

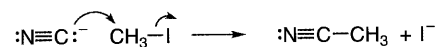


HOMO of cyanide anion shows location of highest-energy electrons and identifies the most nucleophilic regions.



Electrostatic potential map for cyanide + methyl iodide C attack shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

Chemists use curved arrows to show the electronic changes that occur during a chemical reaction. For example, the arrows describing the S_N2 reaction below show formation of a CC bond and loss of a CI bond.



However, arrows do not tell us the actual geometry or electron distribution found in the transition state. Examine the geometries of the reactants (*cyanide anion* and *methyl iodide*) and products (*acetonitrile*), as well as the transition state for the nucleophilic displacement (*cyanide+methyl iodide C attack*). Obtain distances for all of the bonds in each (include the CC and CI “bonds” of the transition state). Which bonds show significant changes in distance ($> 0.1\text{\AA}$) from reactants and which do not? Do these changes signify bond forming or bond breaking? Based on these data, draw a molecular structure for the transition state using solid lines for normal bonds and dashed lines for partially made/broken bonds.

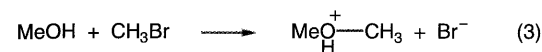
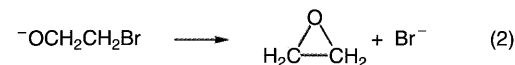
Examine the highest-occupied molecular orbital (HOMO) of cyanide anion. Is the larger lobe on carbon or nitrogen? Would you expect cyanide to act as a carbon or nitrogen nucleophile? Does this lead to the lower energy transition state (compare the energy of cyanide+methyl iodide C attack and *cyanide+methyl iodide N attack*)?

Examine atomic charges and the electrostatic potential map for the lower-energy transition state. Which atoms appear to be most electron rich in each? Is the negative charge concentrated on a single atom in the transition state or delocalized? Add this charge information (either “-” or “ δ^- ”) to the molecular structure for the transition state which you drew previously.

Does your transition state drawing look more like a single Lewis structure or a resonance hybrid? If the latter, what resonance contributors must you combine to generate all of the features of this hybrid?

Mechanistic Families

Similar chemical reactions often proceed by similar mechanisms. It's important to recognize these similarities when they exist because this makes it easier to compare such quantities as reaction rates and product selectivity.



The reactions shown above are nucleophilic substitutions that involve replacement of bromine by oxygen. The reactions may or may not proceed by similar mechanisms.

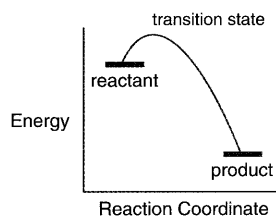
One after the other, step through the sequence of structures corresponding to the three nucleophile substitution reactions shown above (*reaction 1, reaction 2, reaction 3*). Decide whether loss of Br^- occurs with or without the assistance of RO^-/ROH . The nucleophile-assisted and unassisted mechanisms are called “ S_N2 ” and “ S_N1 ” mechanisms respectively. Label each reaction as S_N2 or S_N1 as appropriate.

For each reaction, plot energy (vertical axis) vs. the number of the structure in the overall sequence (horizontal axis). Do reactions that share the same mechanistic label also share similar reaction energy diagrams? How many barriers separate the reactants and products in an S_N2 reaction? In an S_N1 reaction? Based on your observations, draw a step-by-step mechanism for each reaction using curved arrows (\curvearrowright) to show electron movements. The drawing for each “step” should show the reactants and products for that step and curved arrows needed for that step only. Do not draw transition states, and do not combine arrows for different steps.

Selectivity in Exothermic Reactions

The Hammond Postulate implies that the transition state of a fast exothermic reaction resembles the reactants (see reaction energy diagram at left). This means that it will be hard to predict the selectivity of competing exothermic reactions; both barriers may be small and similar even if one reaction is more exothermic than the other.

Consider abstraction of a hydrogen atom from propane by fluorine atom. This can generate either of two propyl radicals, depending on which hydrogen is attacked.



$$E(\text{F}^\bullet) = -99.3650 \text{ au}$$

$$\frac{N_1}{N_2} = e^{-1060(E_1 - E_2)} \quad (1)$$

N_i is the number of i molecules

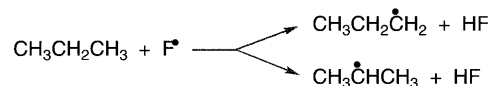
E_i is the energy of molecule i (in au)

$$\frac{N_1}{N_2} = e^{-1060(E_1^\ddagger - E_2^\ddagger)} \quad (2)$$

N_i is the number of i molecules

E_i^\ddagger is the energy of transition state i (in au)

Add the energies of **propane** and fluorine atom (at left) (the reactants), and then the energies of **1-propyl radical** (or **2-propyl radical**) and **hydrogen fluoride** (the products). Are these reactions exothermic or endothermic? If the former, then calculate the relative concentrations of 1-propyl radical and 2-propyl radical that would exist in an equilibrium mixture at 298 K. Use equation (1).

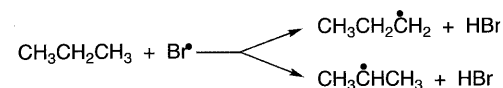


The Hammond Postulate applies only if both forward reactions are fast. Obtain energies for the transition states leading to 1-propyl and 2-propyl radicals (**propane+F end** and **propane+F center**). Draw an energy diagram for each hydrogen abstraction reaction (place the diagrams on the same axes). Do these diagrams indicate that use of the Hammond Postulate is justified? Calculate the barrier for each reaction, and calculate the relative concentrations of 1-propyl and 2-propyl radicals that would form at 298 K if each reaction were irreversible. Use equation (2). How does this (kinetic) ratio compare to the equilibrium (thermodynamic) ratio of these radicals?

Obtain the “partial” CH and HF bond distances in each transition state, and compare them to the CH and HF bond distances in propane and hydrogen fluoride, respectively. Does the Hammond Postulate correctly predict which bond distances will be most similar? Explain.

Selectivity in Endothermic Reactions

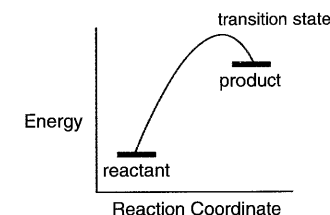
The Hammond Postulate implies that the transition state of an endothermic reaction resembles the product, providing that the reverse reaction is fast (see reaction energy diagram at right). This can be used to predict selectivity for competing reactions; the lowest-energy product should form most rapidly because it is connected to the reactants by the lowest-energy (closest) transition state. Consider abstraction of hydrogen atom from propane by bromine atom, leading either to 1-propyl or 2-propyl radical.



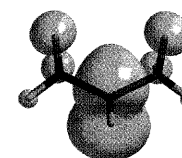
Add the energies for **propane** and bromine atom (at right) to give the total energy of reactants, and the energies for **1-propyl radical** (or **2-propyl radical**) and **hydrogen bromide** to give the total energy for products. Are these reactions exothermic or endothermic? If the latter, predict which products will form more rapidly.

Radical stability can often be explained in the same way as ion stability; molecules that delocalize unpaired electrons tend to be more stable. Display spin density surfaces for 1-propyl and 2-propyl radicals. In which is the unpaired electron more delocalized? Is this also the lower-energy radical?

Use of the Hammond Postulate requires that the reverse reactions both be fast. Obtain energies for the transition states leading to 1-propyl and 2-propyl radicals (**propane+Br end** and **propane+Br center**), and draw a reaction energy diagram for each (place the diagrams on the same axes). Is use of the Hammond Postulate justified? Compare the “partial” CH and HBr bond distances in each transition state to the corresponding distances in propane and hydrogen bromide, respectively. Does the Hammond Postulate correctly predict which bond distances will be most similar? Explain.



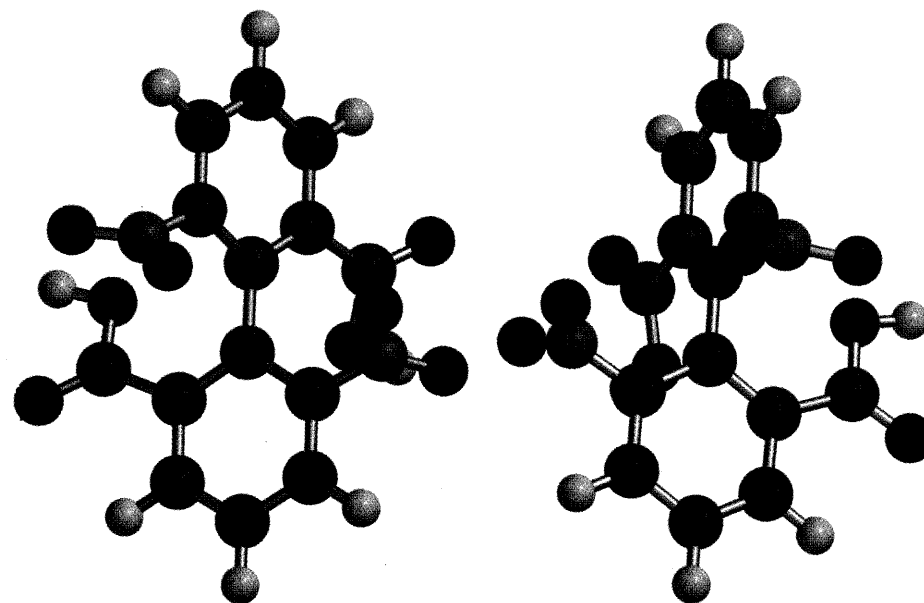
$$E(\text{Br}^\bullet) = -2560.2446 \text{ au}$$



Spin density surface for 2-propyl radical shows location of unpaired electron.

Stereochemistry

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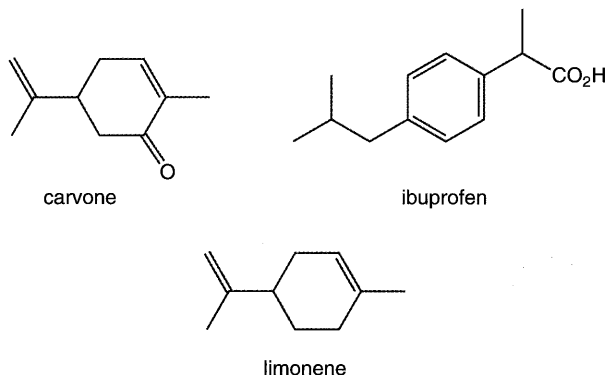


enantiomers of 2,2'-dinitro-6,6'-diphenic acid may be resolved
(see problem 3)

Enantiomers

Most of the molecules we take into our bodies, whether in food or in medicine, are chiral. As a rule, different enantiomers of these molecules have different biological consequences.

Each of the molecules below (carvone, ibuprofen and limonene) incorporates a single chiral center. Identify it and draw both R and S forms of each.



Examine actual three-dimensional structures for the two enantiomers of *carvone*. One occurs naturally in caraway while the other is found in spearmint oil, and are responsible for the characteristic odors of these materials. Determine which form, R or S, is responsible for which odor.

Ibuprofen is an analgesic sold under various names, including Advil, Motrin, and Nuprin. The material is sold as a racemic mixture, but only one enantiomer acts as an analgesic. The other enantiomer is inactive. Assign R or S forms to the two enantiomers of *ibuprofen*.

The two enantiomers of limonene have completely different tastes. One has the taste of lemon (as the name implies) and the other of orange. Assign R or S forms to the two enantiomers of *limonene*.

Are the energies and dipole moments for the two enantiomers of carvone (ibuprofen and limonene) the same or are they different? Explain your result.

Diastereomers vs. Conformers

2,3-Difluorobutane contains two chiral atoms, and can exist as any one of three stereoisomers. Predicting the properties of these molecules is complicated due to the fact that each exists as a mixture of three conformers because of rapid internal rotation about the central carbon-carbon bond.

Examine *stereoisomer A*, *stereoisomer B* and *stereoisomer C*. Each provides a set of three staggered conformers for that 2,3-difluorobutane.

What are the configurations (R or S) of the chiral carbons in each stereoisomer? Does internal rotation affect the configuration of a chiral atom? Why or why not?

Consider the stereochemical relationships between these flexible stereoisomers. A flexible molecule is chiral only if each of its conformers is chiral and if no two conformers are mirror images. Which, if any, of the stereoisomers are chiral? Flexible chiral molecules are enantiomers only if each of their conformers are mirror-images. Which, if any, of the stereoisomers are enantiomers and which are diastereomers?

Now, consider the physical properties of these stereoisomers. Enantiomers should have many of the same physical properties, such as energy and dipole moment, but diastereomers should not. Obtain the energy of each conformer and use equation (1) to calculate the composition of a large sample of each stereoisomer at 298 K. Then, obtain the dipole moment of each conformer and use equation (2) to calculate the dipole moment of a large sample of each stereoisomer at 298 K. Do enantiomers have the same dipole moment? Do diastereomers have different dipole moments?

$$\frac{N_1}{N_2} = e^{-1060(E_1 - E_2)} \quad (1)$$

N_i is the number of molecules of conformer i

E_i is the energy of conformer i (in au)

$$\mu = \frac{\mu_1 N_1 + \mu_2 N_2 + \mu_3 N_3}{N_1 + N_2 + N_3} \quad (2)$$

μ_i is the dipole moment of conformer i (in debyes)

μ is the dipole moment of sample (in debyes)

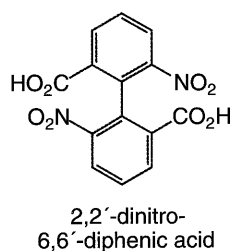
Chiral Molecules without Chiral Centers

Energy minima have all real frequencies, while molecules with one or more imaginary frequencies are not minima.

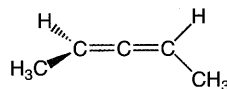
$$\tau_{1/2} = \frac{0.69}{k} \quad (1)$$

$$k = 6.2 \times 10^{12} e^{-1060 \Delta E^\ddagger}$$

ΔE^\ddagger is the energy barrier (in au)

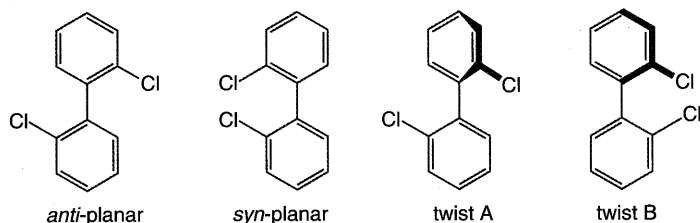


A chiral molecule need not contain a chiral center. Examine the two enantiomers of **2,3-pentadiene** (**A** and **B**).



Which is the one shown above, and which is its mirror-image? Is 2,3-pentadiene chiral or achiral? Is there a way to interconvert the two without breaking any bonds?

Among the possible CC bond conformers for 2,2'-dichlorobiphenyl (DCBP) are *syn* and *anti* planar structures and two twist structures.



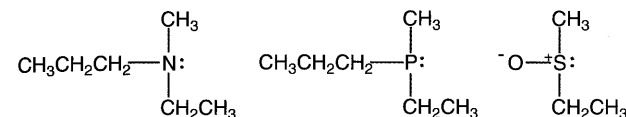
Examine the vibrational frequencies of each of the conformers of **DCBP** to determine whether it corresponds to an energy minimum or to a transition state. Using these results and the relative energies for the four structures, construct an energy diagram for twisting about the central CC bond. Which conformers will be found in a large sample of DCBP? Are these molecules enantiomers or diastereomers? Explain the conformational preferences of DCBP by referring to space-filling models.

Do you think it would be possible to resolve DCBP into different enantiomers at room temperature? Answer this question by calculating the effective energy barrier, ΔE^\ddagger , for internal rotation (choose the lowest possible barrier), and then calculating the half-life ($\tau_{1/2}$) of the favored conformers at 298 K (use equation 1).

2,2'-Dinitro-6,6'-diphenic acid can actually be resolved into two enantiomeric forms, but heating the samples causes them to racemize. Explain.

Configuration Inversion

Each of the following molecules might be resolved into two enantiomers if: 1) the molecule's preferred geometry is chiral, and 2) the molecule's enantiomeric forms do not readily interconvert (this interconversion is called "configuration inversion").



Examine both pyramidal and planar forms for each of the above molecules (**amine**, **phosphine** and **sulfoxide**). Assume that the lower and higher-energy forms correspond, respectively, to the preferred molecular structure and the transition state for configuration inversion.

Which, if any, of the above molecules prefer a pyramidal geometry? Are the pyramidal molecules chiral? For any which prefer a pyramidal geometry, is there a relationship between the pyramidal-planar energy difference (the energy barrier, ΔE^\ddagger , for configuration inversion) and the average bond angle involving the central atom?

Do you think it would be possible to resolve each chiral molecule into different enantiomers at room temperature? Answer this question by calculating the half-life ($\tau_{1/2}$) of the pyramidal molecules at 298 K (use equation 1).

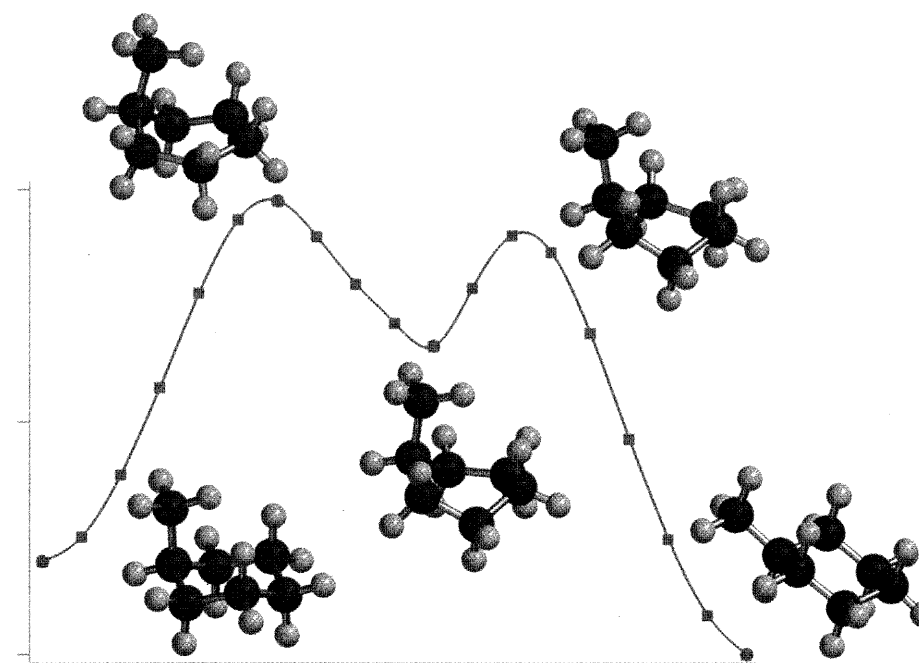
$$\tau_{1/2} = \frac{0.69}{k} \quad (1)$$

$$k = 6.2 \times 10^{12} e^{-1060 \Delta E^\ddagger}$$

ΔE^\ddagger is the energy barrier (in au)

Alkanes and Cycloalkanes

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2	Eclipsed vs. Staggered. Trigonal Carbons	75
3	Steric Control of Alkane Conformation	76
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9	Fused Rings	82
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interconversion of axial and equatorial conformers of methylcyclohexane
(see problem 8)

Eclipsed vs. Staggered. Tetrahedral Carbons

It has been observed that ethane prefers a staggered conformation. Unfortunately, experiments do not tell us why this preference exists.

Step through the sequence of structures depicting bond rotation in *ethane*. Plot energy (vertical axis) vs. HCCH torsion angle (horizontal axis). Do the minima correspond to staggered structures? Do the maxima correspond to eclipsed structures? If not, to what do they correspond?

Nonbonded hydrogens repel each other at short distances, and one explanation for ethane's behavior is that staggered structures minimize "steric repulsion" between hydrogens on different carbons. Steric repulsion might be detected by its effect on HCC bond angles. Plot HCC bond angle (vertical axis) vs. HCCH torsion angle (horizontal axis) for each geometry. Do these data support the steric repulsion hypothesis? Explain.

Estimate the "cost" of nonbonded HH repulsion as a function of distance by plotting energy (vertical axis) vs. HH separation (horizontal axis) for *methane+methane* (two methanes approaching each other with CH bonds "head on"). Next, measure the distance between the nearest hydrogens in eclipsed ethane. What is the HH repulsion energy in the methane dimer at this distance? Multiplied by three, does this approximate the rotation barrier in ethane?

Most molecules can avoid high-energy, sterically-hindered structures by distorting their geometries in some way. Compare the CC and CH bond distances, and the HCC bond angle, of fully staggered and eclipsed ethane. Which, if any, of these parameters undergoes distortion in order to relieve steric repulsion in the eclipsed molecule? Explain.

Steric repulsion occurs when two atoms with filled valence shells are forced so close together that their electron clouds must occupy, in part, the same region of space.

Eclipsed vs. Staggered. Trigonal Carbons

Molecules prefer conformations that stagger bonds on neighboring tetrahedral carbons (see **Chapter 5, Problem 1**). Does the same apply to trigonal carbons?

Step through the sequence of structures depicting bond rotation in *propene* and *acetaldehyde*. For each, plot energy (vertical axis) vs. torsion angle (horizontal axis). (Use the HCCC torsion angle for propene and the HCCO torsion angle for acetaldehyde.) Do the minima on your graphs correspond to structures in which a CH bond staggers or eclipses the CC (CO) double bond? Do the maxima correspond to the opposite arrangements?

Organic chemists usually think of a double bond as the combination of a σ bond and a π bond. An alternative is to consider a double bond as made up of two equivalent "bent bonds" (these bonds point above and below the internuclear axis).



"bent" bond model

Apply the bent-bond model to the preferred conformations of acetaldehyde and propene. Do bent-bonds maintain or remove eclipsing interactions in the equilibrium structures of the two molecules? Formulate a simple rule based on the bent-bond model for predicting conformational preferences in systems containing trigonal atoms.

Compare energies for eclipsed and staggered conformers of *toluene*. What is the preferred conformation, one in which a CH bond eclipses the phenyl ring or one where it staggers the ring? Is the difference in energy of the same order of magnitude as propene and acetaldehyde or larger or smaller? Explain your result.

Steric Control of Alkane Conformation

Alkanes prefer structures that stagger bonds on adjacent tetrahedral carbons (see **Chapter 5, Problem 1**). However, steric repulsion can affect the relative energies of staggered conformations.

Step through the sequence of structures depicting bond rotation about the central carbon-carbon bond in *n*-butane. Plot energy (vertical axis) vs. CCCC torsion angle (horizontal axis). How many minima and maxima are there on the graph? Draw Newman projections that show each of these conformations (draw your projection so that you are looking down the central CC bond). Label each staggered conformation as either *anti* (CCCC angle = 180°) or *gauche* (CCCC angle ≈ 60°). Do not label the maximum energy conformations.

Which conformation is more stable, *anti* or *gauche*? What evidence is there for steric repulsion between methyl groups in the *gauche* conformation? (Hint: Look for distortions in the CCC bond angles as a function of conformation.)

Examine the maximum energy conformations. What evidence is there for steric repulsion between methyl groups in the conformation that eclipses these groups?

Internal rotation in isooctane (2,2,4-trimethylpentane) creates a large number of staggered conformations. However, only rotation about the C₃-C₄ bond produces conformations with different structures. Plot the energy of *isooctane* (vertical axis) vs. HCCC_{tBu} torsion angle, i.e., about the C₃-C₄ bond (horizontal axis). How many minimum energy structures are there? Are they all fully staggered? Draw Newman projections that show the conformation of these structures. How does steric repulsion affect isooctane conformation?

Ring Conformation

Internal rotation in cycloalkanes is restricted by the need to maintain bonding between adjacent ring atoms. Aside from this restriction, though, cycloalkanes obey the same structural rules as alkanes: staggered conformations that minimize steric repulsion are preferred.

Identify the lowest-energy conformer from among those provided: *cyclopropane*, *planar* and *puckered cyclobutane*, *planar* and *puckered cyclopentane* and *chair*, *half-chair*, *boat* and *twist-boat cyclohexane*. (If only one conformer is provided, then assume that this is the only “reasonable” structure.) Examine vibrational frequencies for each structure to decide whether it is or is not an energy minimum. Do two or more energy minima exist for any of the molecules? If so, what is the equilibrium ratio of the various forms at room temperature? Use equation (1).

Calculate the average CCCC torsion angle for the lowest-energy structure of each molecule (use absolute values). Order these structures from “most eclipsed” to “most staggered”. Which ring adopts the most eclipsed structure? Which ring adopts the most staggered structure?

Next, calculate the average CCCC torsion angle for each of the higher-energy minima of each molecule (use absolute values). What relationship, if any, exists between the difference in average torsion angle between minimum energy forms and the difference in molecular energy? (Only compare alternative structures of the same molecule.)

Cyclobutane, cyclopentane, and cyclohexane all undergo rapid conformational changes. These changes convert the lowest-energy structure into an equivalent structure in which one or more atoms occupy new positions around the ring. Calculate the energy barrier for this conformation change. Use “planar” geometries for cyclobutane and cyclopentane and the half-chair geometry for cyclohexane to represent the “top” of the energy curve. Which molecule undergoes conformational change with the lowest energy barrier? With the highest energy barrier?

Energy minima have all real frequencies, while molecules with one or more imaginary frequencies are not minima.

$$\frac{N_1}{N_2} = e^{-1060(E_1-E_2)} \quad (1)$$

N_i is the number of molecules of conformer i

E_i is the energy of conformer i (in au)

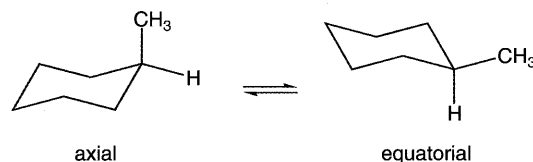
Steric Control of Ring Conformation. I

Methylcyclohexane exists as a mixture of equatorial and axial chair conformers.

$$\frac{N_1}{N_2} = e^{-1060(E_1-E_2)} \quad (1)$$

N_i is the number of molecules of conformer i

E_i is the energy of conformer i (in au)



Obtain the energies of the equatorial and axial chair conformers of **methylcyclohexane**. Which conformer is more stable? What would be the composition of a methylcyclohexane sample at 298 K? Use equation (1).

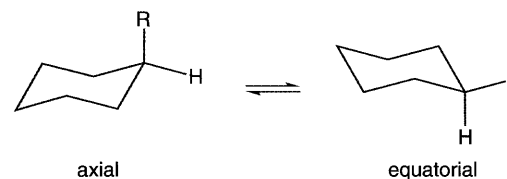
Try to explain the conformational preference in terms of steric repulsion. Which ring atom(s) in the higher-energy conformer approach the CH_3 group most closely? (Make sure that you find all significant nonbonded interactions.) Which of these interactions are absent in the lower-energy conformer? Can interactions that appear in both conformers account for the conformational preference?

CH_3 -ring interactions might also be expected to control the conformational preferences of dimethylcyclohexanes. It might even be anticipated that the energy differences between a diequatorial conformer and a diaxial conformer will be twice the equatorial-axial energy difference in methylcyclohexane.

Obtain energies for diequatorial and diaxial conformers of **cis-1,3-dimethylcyclohexane**, **trans-1,2-dimethylcyclohexane** and **trans-1,4-dimethylcyclohexane**. Identify the preferred conformer for each. Are the energy differences in line with your expectations, or are there significant deviations? If the latter, what additional nonbonded interactions can explain these “deviations”? Which factor plays the larger role in determining conformational preferences, the “additional” interactions or CH_3 -ring interactions?

Steric Control of Ring Conformation. II

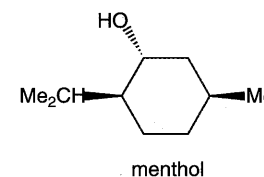
Alkylcyclohexanes exist as a mixture of equatorial and axial chair conformers.



Compare energies for equatorial and axial chair conformers for **methylcyclohexane**, $\text{R} = \text{Me}$, and **tert-butylcyclohexane**, $\text{R} = \text{CMe}_3$. Which is more stable in each molecule? Use equation (1) to calculate the ratio of major to minor conformers for each system at 298 K. Which molecule shows a larger preference? Why? (Hint: Compare nonbonded interactions and/or geometrical distortions in the higher-energy conformers that are absent in the lower-energy conformers.)

Which is more stable, the equatorial or axial chair conformer of **i-propylcyclohexane**, $\text{R} = \text{CHMe}_2$? Calculate the ratio of major to minor conformers at 298 K. Is it more like that found for **tert-butylcyclohexane** or for **methylcyclohexane**? Why?

Examine the two chair conformers of **menthol**, and label each substituent in each conformer as equatorial or axial.



What effect does a ring flip have on substituent positions? Do all of the substituents change position or only certain ones? If the latter, then which substituents are affected? Obtain the energies of the two conformers. Which conformer is preferred? Why?

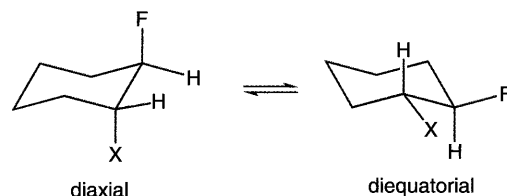
$$\frac{N_1}{N_2} = e^{-1060(E_1-E_2)} \quad (1)$$

N_i is the number of molecules of conformer i

E_i is the energy of conformer i (in au)

Electronic Control of Ring Conformation

The conformation of alkylcyclohexanes is determined largely by steric repulsion (see **Chapter 5, Problems 6 and 7**). More polar substituents may show different conformational preferences due to a combination of steric and electronic factors.



Compare energies for both diaxial and diequatorial chair conformers of **trans-2-fluoromethylcyclohexane** ($X = \text{Me}$). Which conformer is preferred? Examine a space-filling model of each conformer. Which group is largest: methyl, fluorine, or hydrogen? Which is smallest? Does the preferred conformer minimize steric repulsion? Explain.

Compare energies for both diaxial and diequatorial chair conformers of **trans-1,2-difluorocyclohexane** ($X = \text{F}$). Which conformer is preferred? Does the preferred conformer minimize steric repulsion? Explain. Examine dipole moments for the two conformers. Does the preferred conformer minimize electrostatic repulsion (or maximize electrostatic attraction)? Explain.

Compare energies for both diaxial and diequatorial chair conformers of **trans-2-fluorocyclohexanol** ($X = \text{OH}$). Which conformer is preferred? Does the preferred conformer minimize steric repulsion? Is it reasonable to attribute the conformational preference solely to steric effects? Explain. Examine dipole moments for the two conformers. Does the preferred conformer minimize electrostatic repulsion (or maximize electrostatic attraction)? Is it reasonable to attribute the conformational preference solely to electrostatic effects? Explain.

Mechanism of Ring Inversion

Ring inversion, leading to interconversion of different ring conformers, is typically as facile a process as single-bond rotation. Particularly important are six-membered rings, where interconversion leads to interchange of axial and equatorial positions.

One after the other, step through (or animate) the sequence of structures depicting ring inversion in **cyclohexane**, **methylcyclohexane** and **trans-1,2-dimethylcyclohexane**. Is the overall “motion” involved in the ring inversion similar in all three? Describe any differences.

For each molecule, plot energy (vertical axis) vs. “frame number” (horizontal axis). Identify all minimum and maximum energy structures. Identify all of the molecular structure(s) that might be observed experimentally (sketch structure and give frame number). If more than one structure might be observed, then calculate the composition of an equilibrium mixture of the various observable structures at 298 K (use equation 1). Are your three energy diagrams qualitatively similar, or are there significant differences? Elaborate.

For each molecule, calculate the overall energy barrier for ring inversion in each direction. Use this barrier to calculate the half-life ($\tau_{1/2}$) of an individual molecule at 298 K (use equation 2). Which molecule inverts most rapidly? Most slowly? Why? (Hint: What geometrical changes are required for inversion?)

$$\frac{N_1}{N_2} = e^{-1060(E_1 - E_2)} \quad (1)$$

N_i is the number of molecules of conformer i

E_i is the energy of conformer i (in au)

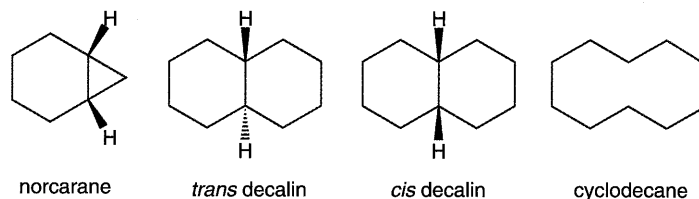
$$\tau_{1/2} = \frac{0.69}{k} \quad (2)$$

$$k = 6.2 \times 10^{12} e^{-1060 \Delta E^\ddagger}$$

ΔE^\ddagger is the energy barrier (in au)

Fused Rings

“Fused-ring” molecules contain two (or more) rings in which the rings share a bond. The atoms that are common to both rings are called “bridgehead atoms”. Fused-ring systems can differ in many ways: in the size of the fused rings, in the stereochemistry of the bridgehead atoms, and in their conformational properties.



Examine the geometry of **norcarane**. What is the conformation of the cyclohexane ring? Choose a name (chair, twist boat, half-chair, etc.; see **Chapter 5, Problem 4**) that accurately describes its shape. The bridgehead hydrogens in norcarane are *cis*. Do you think a *trans* stereoisomer is possible? Explain.

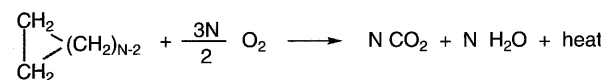
Examine the structures of **trans** and **cis-decalin**. What is the conformation of the two cyclohexane rings in each isomer? Obtain the energy of each decalin isomer. Which is more stable and why?

Make a sketch of each decalin isomer, and label the orientation of the bridgehead hydrogens with respect to each ring (equatorial or axial). Build a plastic model of each isomer and determine its conformational flexibility (a “flexible” molecule can undergo a ring flip, but a “locked” molecule cannot). Is flexibility responsible for stability?

Examine the structure of **cyclodecane**, a molecule which contains the same number of carbons as decalin, but only has one ring (a model of the most stable conformation is provided). Compare it to *cis* and *trans* decalin. Make a plastic model of cyclodecane. Is it “flexible” or “locked”? What conformational properties of cyclodecane can be anticipated from the properties of decalins? What properties cannot be anticipated? How do you account for this?

Ring Strain

Cycloalkane properties depend on ring size. “Strained” molecules, i.e., molecules with distorted geometries, tend to be more reactive in ring-breaking chemical reactions. For example, combustion of a strained cycloalkane should release more energy per CH_2 group than combustion of an unstrained molecule.



Obtain energies for **cyclopropane**, **cyclobutane**, **cyclopentane**, **cyclohexane**, **cycloheptane** and **cyclooctane**. Calculate the combustion energy of each ring (total energy and energy per CH_2 group). (Energies for oxygen, carbon dioxide and water are provided at right.) Plot combustion energy per CH_2 group (vertical axis) vs. ring size (horizontal axis). Which ring shows the least strain? Which shows the most strain? Try to explain the changes in ring strain in terms of geometrical factors. Consider CCC bond angles, eclipsing interactions, and steric repulsion; van der Waals nonbonded radii are provided at right.

Examine and compare electrostatic potential maps for the cycloalkanes. Is there any evidence of carbon-carbon bonds being especially electron rich (subject to electrophilic attack), or of CH bonds being especially electron poor (subject to deprotonation)?

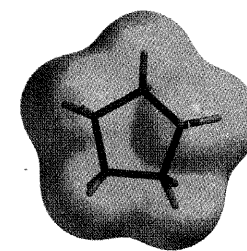
$$E(\text{O}_2) = -148.7691 \text{ au}$$

$$E(\text{CO}_2) = -186.5613 \text{ au}$$

$$E(\text{H}_2\text{O}) = -75.5860 \text{ au}$$

van der Waals radii (Å)

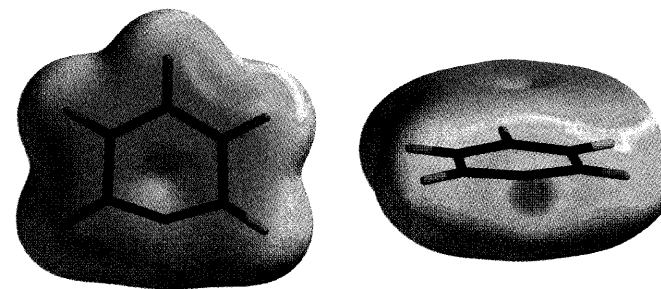
H	1.2	C	1.7
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Electrostatic potential map for cycloheptane shows negatively-charged regions (in red) and positively-charged regions (in blue).

Nucleophilic Substitution and Elimination

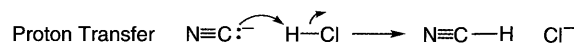
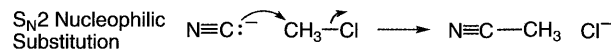
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two views of the electrostatic potential map for phenyl cation show positive charge localized in the plane of the molecule (see problem 12)

S_N2 and Proton-Transfer Reactions

S_N2 reactions can be thought of as “alkyl transfer” reactions, and “S_N2 characteristics” can be anticipated by examining analogous proton transfer reactions.



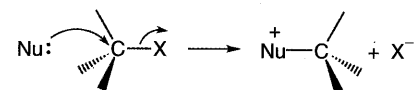
One after the other, step through (or animate) the sequence of structures depicting the *S_N2* and *proton transfer* reactions shown above. Compare the two. From what direction does cyanide approach the hydrogen in HCl? From the same side as Cl (“frontside”), or from the other side (“backside”) ? Does the S_N2 reaction follow a similar trajectory?

Describe what happens to the negative charge during the course of the proton transfer reaction. Plot charge on “CN[−]” (sum of the charges on C and N) (vertical axis) vs. number of the frame in the sequence (horizontal axis). Also on the same graph, plot the charge on hydrogen (vertical axis). Is a “proton” generated during the course of reaction, or is charge buildup limited as the hydrogen is passed between chlorine and carbon?

Repeat the analysis for the S_N2 reaction. Is there significant buildup of positive charge on “CH₃”?

S_N2 Nucleophiles

S_N2 reactions are triggered by the collision of an alkyl halide with a nucleophile.

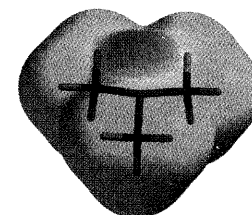


Since nucleophilic atoms have nonbonding electrons they can be identified by inspection of Lewis structures. Draw Lewis structures of trimethylamine, methyl fluoride, and phenol. Draw all nonbonding electron pairs and identify all nucleophilic atoms.

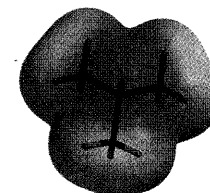
Nucleophilic atoms can also be identified by inspection of electrostatic potential maps. Reactive sites appear as negative electrostatic potentials. Examine electrostatic potential maps for *trimethylamine*, *methyl fluoride*, and *phenol*. Identify the most nucleophilic atom in each molecule. Are these the same as you identified above using Lewis structures? Are all sides of the nucleophilic atoms equally electron rich, or only particular regions?

Enhanced nucleophilicity is often correlated with more negative electrostatic potential. Which of the three molecules listed above is most nucleophilic according to this criterion? Which is least nucleophilic? (The least nucleophilic molecule does not, in fact, undergo S_N2 reactions.)

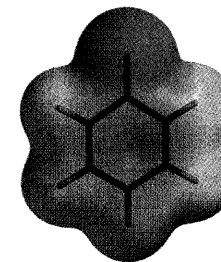
Nucleophiles can also act as acids and bases, and this behavior substantially alters their nucleophilicity. At pH 5, trimethylamine exists mainly as its conjugate acid, trimethylammonium cation. First draw a Lewis structure, and then examine the electrostatic potential for *trimethylammonium ion*. On the basis of the map, which is the better nucleophile, the cation or the corresponding neutral amine? At pH 12, phenol exists mainly as its conjugate base, phenoxide anion. First draw a Lewis structure (or series of Lewis structures), and then examine the electrostatic potential map for *phenoxide anion*. Which is the better nucleophile, phenoxide or phenol?



Electrostatic potential map for trimethylamine shows negatively-charged regions (in red) and positively-charged regions (in blue).



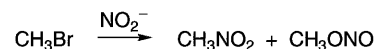
Electrostatic potential map for trimethylammonium ion shows most positively-charged regions (in blue).



Electrostatic potential map for phenoxide anion shows most negatively-charged regions (in red).

Ambident S_N2 Nucleophiles

Molecules that possess more than one nucleophilic site are referred to as “ambident” nucleophiles. S_N2 reactions involving these nucleophiles may lead to mixtures of products. For example, nucleophilic attack by nitrite on methyl bromide gives both nitromethane and methyl nitrite.

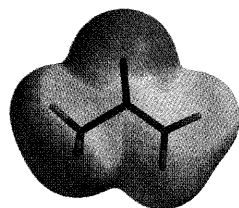


Examine atomic charges and the electrostatic potential map for **nitrite anion**. Which atom(s) is most electron rich? Which product would be obtained if this atom behaved as a nucleophile in its reaction with methyl bromide.

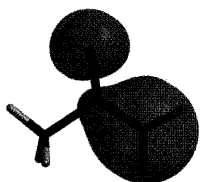
Other possible ambident nucleophiles include **cyanide anion** (CN[−]), **methyl sulfinate anion** (CH₃SO₂[−]), and **acetone enolate** (CH₃COCH₂[−]). Identify the most electron-rich atom(s) in each anion (based on charges alone), and indicate the major product that should result from an S_N2 reaction with methyl bromide at this atom(s).

Another way to assess nucleophilic reactivity is to examine the shape of the nucleophile’s electron-donor orbital (this is the highest-occupied molecular orbital or HOMO). Examine the shape of each anion’s HOMO. At which atom would an electrophile, like **methyl bromide**, find the best orbital overlap? (Note: This would involve overlap of the the HOMO of the nucleophile and the lowest-unoccupied molecular orbital or LUMO of CH₃Br.) Draw all of the products that might result from an S_N2 reaction with CH₃Br at these atoms.

Can the ambident nucleophilicity of any of these anions be explained solely on electrostatic grounds? Solely on orbital overlap grounds? Explain your reasoning.



Electrostatic potential map for acetone enolate shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).



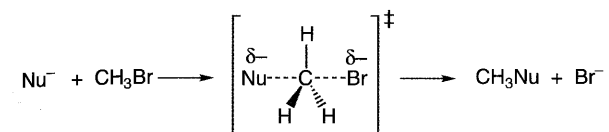
HOMO of acetone enolate reveals most likely site of electrophilic attack.



LUMO of methyl bromide reveals the likely site of nucleophilic attack.

Stereochemistry of S_N2 Reactions

S_N2 reactions proceed with inversion at the electrophilic carbon. This suggests that the nucleophile attacks from the “backside” of carbon, i.e., the side of carbon furthest away from the leaving group.

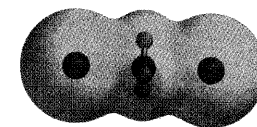


Backside attack may be favored for electrostatic reasons. Examine electrostatic potential maps for **bromide + methyl bromide backside attack** and **bromide + methyl bromide frontside attack**, transition states involving “frontside” and “backside” attack of Br[−] (the nucleophile) onto CH₃Br, respectively. Which atoms in the transition states are most electron-rich? Which trajectory better minimizes electrostatic repulsion?

Backside attack may be favored in order to facilitate transfer of nonbonding electrons from the nucleophile into the electrophile’s lowest-unoccupied molecular orbital (LUMO). Efficient electron transfer requires maximal overlap of the LUMO and the donor orbital (usually a nonbonded electron pair on the nucleophile). Examine the LUMO of **methyl bromide**. How would a nucleophile have to approach in order to obtain the best overlap? Is your answer more consistent with preferential “backside” or “frontside” attack?

Electron transfer into the LUMO might also cause bonding changes. What are the CBr bonding characteristics of the LUMO in methyl bromide? Is it “bonding” (one surface extends over the bond) or “antibonding” (two surfaces meet in middle of the bond)? How would electron transfer from a nucleophile affect the CBr bond length?

Apply the same analysis to **trimethyloxonium ion**, Me₃O⁺ a cationic electrophile. Examine the LUMO. What are the best sites for nucleophile-LUMO overlap? How would electron transfer affect CO bond lengths?



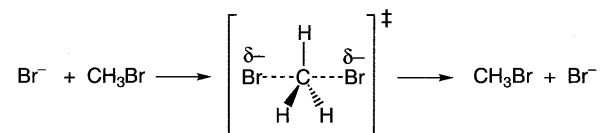
Electrostatic potential map for bromide+methyl bromide backside attack shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).



LUMO of methyl bromide reveals the likely site of nucleophilic attack.

Steric Hindrance of S_N2 Reactions

S_N2 reactions proceed through transition states in which the central carbon has five neighbors instead of the usual four, e.g., for reaction of bromide and methyl bromide.



Does this imply that steric effects will be “amplified” in the transition state, and that the rates of S_N2 reactions will decrease with increased substitution at carbon?

Calculate activation barriers for bromide addition to *methyl bromide*, *ethyl bromide*, *2-propyl bromide* and *2-methyl-2-propyl bromide* using energies for S_N2 transition states (*bromide+methyl bromide*, *bromide+ethyl bromide*, *bromide+2-propyl bromide* and *bromide+2-methyl-2-propyl bromide*) and Br[−] (at left). Which reaction is fastest? Slowest?

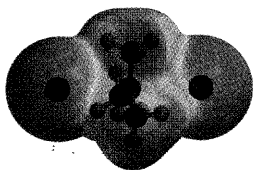
Next, examine the S_N2 transition states as space-filling models. Are you able to identify unfavorable nonbonded (steric) interactions that are not present in the reactants? If so, which S_N2 reaction is likely to be most affected by steric interactions? Least affected? Rationalize your observations. Hint: Compare CBr bond distances in the S_N2 transition states. How do these change with increased substitution at carbon? What effect, if any, does this have on crowding?

What other factors might be responsible for differences in activation energies? Compare atomic charges and electrostatic potential maps for the S_N2 transition states. Does the increase in steric crowding lead to enhanced or diminished charge delocalization? Explain. How, if at all, would this be expected to affect the energy barrier? Why?

What is the origin of the change in rate of S_N2 reactions with change in substitution at carbon?

$$E(\text{Br}^-) = -2560.2998 \text{ au}$$

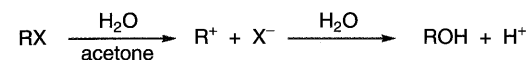
Given the simplicity of the models employed, only comparisons of relative (and not absolute) barrier heights are meaningful.



Electrostatic potential map for bromide+2-methyl-2-propyl bromide shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

S_N1 Reaction of Alkyl Halides and Water

Water-acetone mixtures offer a sufficiently polar medium that certain alkyl halides can dissociate into a halide anion and a carbocation. The latter then reacts with water to give an “S_N1” substitution product.

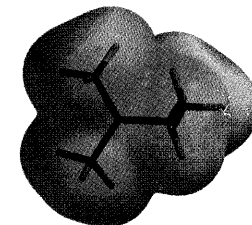


Obtain energies for *2-methyl-2-butyl bromide*, *3-methyl-2-butyl bromide* and *3-methyl-1-butyl bromide*, and their corresponding carbocations (*2-methyl-2-butyl cation*, *3-methyl-2-butyl cation* and *3-methyl-1-butyl cation*). Calculate the energy required for bond dissociation in each. (The energy of bromide is given at right.) Which of these alkyl bromides will dissociate most readily? Which is least likely to dissociate?

Draw the Lewis structure of each carbocation (show all formal charges). Do these structures provide any indication of which carbocation will form most readily? Explain. Examine the electrostatic potential map of each carbocation. Which carbocation shows the greatest localization of positive charge? Which shows the greatest delocalization of charge? Where does the positive charge go in the most delocalized ion? Do these observations provide any indication of which carbocation will form most readily?

2-Halo-2-methylbutanes (X = F, Cl, Br) all produce the same carbocation upon dissociation, yet one of these halides is unreactive. Calculate the dissociation energies for *2-methyl-2-butyl fluoride* and *2-methyl-2-butyl chloride*. (Energies of fluoride and chloride are given at right.) Compare these to the dissociation energy of the corresponding bromo derivative. Which halide is most likely to be unreactive?

$$E(\text{Br}^-) = -2560.2998 \text{ au}$$



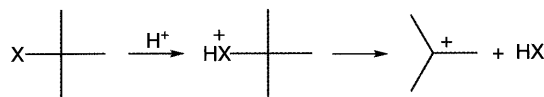
Electrostatic potential map for 2-methyl-2-butyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

$$E(\text{F}^-) = -98.7721 \text{ au}$$

$$E(\text{Cl}^-) = -457.4441 \text{ au}$$

Acid-Catalyzed S_N1 Reactions

Strong acids promote S_N1 substitution reactions by converting an electron-rich (“basic”) atom on the substrate into a good leaving group, e.g., for substitution reactions of *tert*-butyl derivatives.



Is it necessary that the substrate be a strong base, or that the protonated substrate dissociate readily, or are both of these important? Calculate reaction energies for both steps in S_N1 reactions of *tert*-butyl fluoride (leading first to *protonated tert-butyl fluoride* and then to *2-methyl-2-propyl cation* and hydrogen fluoride), *tert*-butyl chloride, *tert*-butyl alcohol and *tert*-butylamine. (Energies for proton, hydrogen fluoride, hydrogen chloride, water and ammonia are given at left.) Which neutral compound is the most basic substrate? Which protonated compound will lose HX most easily?

Experiments have shown that sulfuric acid enhances the rate of substitution of alcohols sufficiently to make this a practical reaction, but substitution of amines is not practical under these conditions, and substitution rates for fluorides and chlorides are not significantly affected by H₂SO₄. Why?

Experimental observations indicate that acid strength significantly affects the reaction rate. For example, sulfuric acid promotes nucleophilic substitution of alcohols by bromide, but acetic acid does not. How would a change in acid strength affect your calculated reaction energies?

$$E(\text{H}^+) = 0 \text{ au}$$

$$E(\text{HF}) = -99.4602 \text{ au}$$

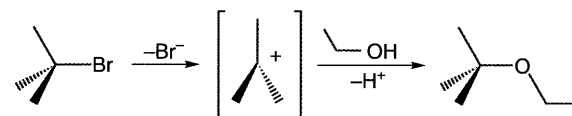
$$E(\text{HCl}) = -457.9814 \text{ au}$$

$$E(\text{H}_2\text{O}) = -75.5860 \text{ au}$$

$$E(\text{NH}_3) = -55.8722 \text{ au}$$

Stability of Carbocation Intermediates

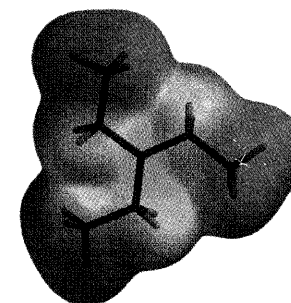
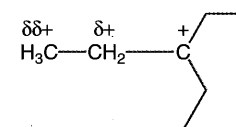
tert-Butyl bromide reacts rapidly with ethanol to give ethyl *tert*-butyl ether. This does not involve S_N2 displacement, but rather the reaction proceeds via a two-step “S_N1” mechanism and a carbocation intermediate.



S_N1 reactivity follows the order: 3° > 2° > 1°. Is this the ordering of stabilities of the carbocation intermediates?

Display and examine electrostatic potential maps for *ethyl cation*, *2-propyl cation* and *2-methyl-2-propyl cation*. Which cation shows the greatest localization of positive charge? If you find that the methyl groups delocalize the positive charge, where does the charge go? Write resonance contributors for the three cations to rationalize your conclusion. (Note: You may need to draw resonance contributors that contain a CC double bond and are missing a CH bond; see also **Chapter 7, Problem 8.**)

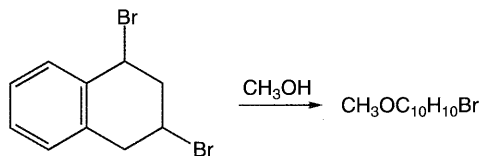
Examine and compare atomic charges and electrostatic potential maps for 2-methyl-2-propyl cation and *3-ethyl-3-pentyl cation*. Are the methyl groups in 2-methyl-2-propyl cation and the methylene and methyl groups in 3-ethyl-3-pentyl cation positively charged? Are the ethyl groups in 3-ethyl-3-pentyl cation more effective, less effective or about as effective as the methyl groups in 2-methyl-2-propyl cation in delocalizing positive charge? Are the methylene groups in 3-ethyl-3-pentyl cation more positively charged than the methyl groups? Do your results support or refute the usual inductive picture?



Electrostatic potential map for 3-ethyl-3-pentyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Resonance-Assisted S_N1 Reactions

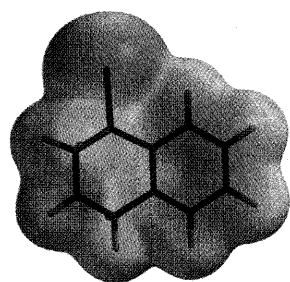
Dibromobenzocyclohexene undergoes S_N1 substitution in methanol to give a single methyl ether.



The rate of S_N1 substitution is determined by the rate of carbocation formation. Therefore, you should expect the ether to be derived from the carbocation that forms more rapidly. Using energies for the *dibromobenzocyclohexene*, the two intermediate carbocations (**carbocation A** and **carbocation B**) and bromide (given at left), and assuming no barrier to carbocation formation, draw a reaction energy diagram that shows formation of each carbocation from the reactant (energy on vertical axis, reaction progress on the horizontal axis). Draw the ether that will form most rapidly.

What is the difference between the two secondary carbocations? Compare CC bond distances in the reactant to those in the two carbocations. What changes does Br[−] loss cause in each of the carbocations? How do you explain these changes? (Hint: Changes in C hybridization, such as sp³ → sp², may be responsible for some changes in distance.)

Compare atomic charges and electrostatic potential maps of the two carbocations. In which is the positive charge more delocalized? For each carbocation, draw whatever resonance contributors are needed to account for all of your observations. Which carbocation is better stabilized by resonance?

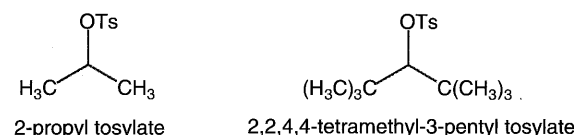


Electrostatic potential map for carbocation B shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Strain Effects on S_N1 Reaction Rates

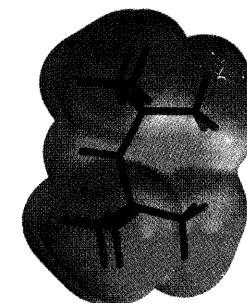
Strain can affect the rate of a chemical reaction in different ways. If strain increases, i.e., if the transition state is more strained than the reactant, then the barrier will be higher and the reaction will be slower. On the other hand, if strain is relieved during the reaction, the reaction will be faster.

One of the tosylates shown below undergoes S_N1 substitution 100,000 times faster than the other. Intermediate carbocations are involved.



Compare the structure of *2-propyl tosylate* to that of *2-propyl cation* and the structure of *2,2,4,4-tetramethyl-3-pentyl tosylate* to that of *2,2,4,4-tetramethyl-3-pentyl cation*. What changes in bond distances and angles are most apparent? Use space-filling models to expose changes in the extent of nonbonding interactions. Using energies for the two tosylates, their respective carbocations and tosylate anion (given at right), and assuming no barrier to carbocation formation, which tosylate do you conclude is the more reactive? Display electrostatic potential maps for the two cations. Does the more reactive tosylate lead to the more delocalized cation? What role, if any, does strain play? Explain.

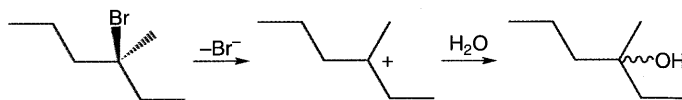
E (tosylate anion) =
−886.6849 au



Electrostatic potential map for 2,2,4,4-tetramethyl-3-pentyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Stereochemistry of S_N1 Reactions

Enantiomerically pure 3-methyl-3-hexyl bromide and water react in S_N1 fashion to give racemic 3-methyl-3-hexanol.



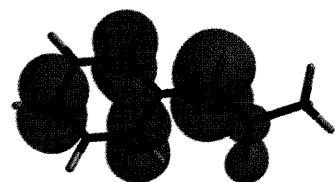
Examine the geometry of **3-methyl-3-hexyl bromide**, and assign the configuration (R or S) to the chiral atom. Examine the geometry of **3-methyl-3-hexyl cation**. Is it chiral?

Next, examine the lowest-unoccupied molecular orbital (LUMO) for the cation. The components of the LUMO (its “lobes”) identify locations where the cation might bond to a water molecule. How many lobes are associated with C⁺? For each lobe, draw the alcohol that will be produced (show stereochemistry). How many alcohol enantiomers will form? If more than one is expected, decide which will form more rapidly based on the relative sizes of the lobes.

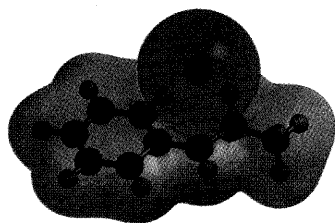
(S)-1-phenyl-1-ethyl chloride, CH₃CH(Cl)Ph, reacts with water in S_N1 fashion to give (R) and (S)-1-phenyl-1-ethanol, CH₃CH(OH)Ph. The product contains a slight excess of “inverted” (R) alcohol (R:S = 59:41). What is the enantiomeric excess, %ee, for this reaction?

Examine the structure of **1-phenyl-1-ethyl cation**. Is it chiral? Examine the LUMO. Would you expect the cation to give a racemic mixture of alcohols or the mixture that is actually obtained? Explain.

Next, examine the structure of **1-phenyl-1-ethyl cation-chloride anion**, an ion pair that is initially generated. What evidence is there for carbon-chlorine bond cleavage? Examine the electrostatic potential map for the ion pair. Which face of the cation is more available for attack? How could the other enantiomer form?



LUMO of 1-phenyl-1-ethyl cation reveals where the cation is able to bond to water.



Electrostatic potential map for 1-phenyl-1-ethyl cation-chloride anion shows negatively-charged regions (in red) and positively-charged regions (in blue).

Phenyl vs. Benzyl Cation

Benzene rings have a dramatic effect on S_N1 reaction rates. This depends on the position of the ring relative to the leaving group. Consider the following reactions.

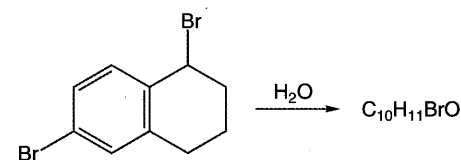


Calculate energies for reaction of **2-methyl-2-propyl chloride** (to **2-methyl-2-propyl cation**), **2-phenyl-2-propyl chloride** (to **2-phenyl-2-propyl cation**) and **phenyl chloride** (to **phenyl cation**). (The energy of chloride is given at right.) Assuming that reaction (1) is “normal”, what is the effect of a benzene ring? Does it facilitate or hinder loss of chloride?

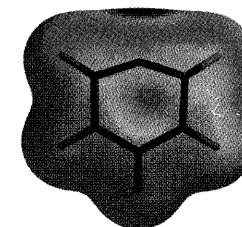
Compare CCl distances in the reactants. If shorter bonds are stronger, which reactants will show unusual reactivity, and in what direction? Compare the cation structures with each other and with the reactants. If the structural changes in reaction (1) are “normal”, then what unusual changes, if any, occur in reactions (2) and (3)?

Compare atomic charges and electrostatic potential maps for the three cations. For each, is the charge localized or delocalized? Is it associated with an empty σ-type or π-type orbital? Examine the lowest-unoccupied molecular orbital (LUMO) of each cation. Draw all of the resonance contributors needed for a complete description of each cation. Assign the hybridization of the “C⁺” atom, and describe how each orbital on this atom is utilized (σ bond, π bond, empty). How do you explain the benzene ring effects that you observe?

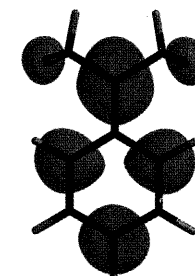
Based on your results, what would you expect is the product of the following reaction?



$$E(\text{Cl}^-) = -457.4441 \text{ au}$$



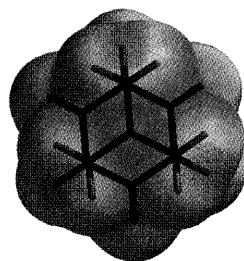
Electrostatic potential map for phenyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).



LUMO of 2-phenyl-2-propyl cation reveals location of positive charge.

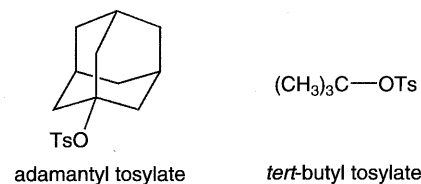
Solvent Effects on S_N1 Reaction Rates

Adamantyl tosylate undergoes S_N1 substitution 1,000 times more slowly than *tert*-butyl tosylate.

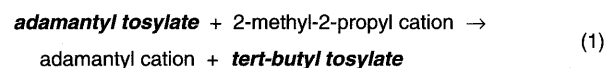


Electrostatic potential map of adamantyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

$E(\text{H}_2\text{O}) = -75.5860 \text{ au}$

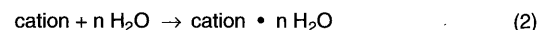


One possible explanation is that adamantyl cation, an intermediate in the reaction, is particularly unstable because it cannot accommodate a planar carbocation center (see **Chapter 1, Problem 9**). Examine the geometry of **adamantyl cation**. Does it incorporate a planar carbocation center? Compare electrostatic potential maps of adamantyl cation and **2-methyl-2-propyl cation**. Which cation better delocalizes the positive charge? Assuming that the more delocalized cation is also the more stable cation, would you expect adamantyl tosylate to react slower or faster than *tert*-butyl tosylate? Calculate the energy of the reaction.



Which cation forms more easily from its tosylate? Is your result consistent with the observed ordering of S_N1 rates?

Another possible explanation is that 2-methyl-2-propyl cation allows better access to solvent than adamantyl cation. Examine **hydrates** of **2-methyl-2-propyl** and **adamantyl cations**. How many water molecules does each accommodate? Calculate hydration energies for the two cations. (The energy of water is provided at left.)

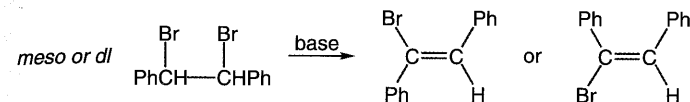


Which cation benefits more from the solvent? Recalculate the energy of reaction (1) taking account of hydration of the two cations (only).

Account for the observed S_N1 rate difference.

Stereochemistry of E2 Elimination

Base-promoted E2 eliminations involving 1,2-dibromo-1,2-diphenylethane have been used to learn about the stereochemical preferences of this reaction. The *meso* starting material gives one alkene and the *dl* starting material gives another.



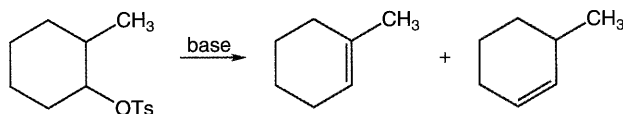
Assuming that the breaking CH and CBr bonds must lie roughly in the same plane, then the HCCBr torsion angle must either be close to 0° (*syn* elimination) or close to 180° (*anti* elimination).

Step through the sequence of structures depicting rotation about the carbon-carbon bond in the two dibromoethane isomers (**1,2-dibromo-1,2-diphenylethane A** and **B**). For each, plot energy (vertical axis) vs. BrCCBr torsion angle (horizontal axis), and identify all minimum-energy structures. Which of these are “reactive conformers”, that is, conformers which are set up for either *syn* or *anti* elimination of HBr? Which are “non-reactive conformers”, that is, which do not meet the requirements for elimination? Do the reactive conformers correspond only to *syn* elimination, only to *anti* elimination, or are both pathways represented? Which alkene would these reactive conformers lead to? Are your results consistent with the observation that each isomer of the starting material gives only one alkene? Explain.

Do any or all of the reactive conformations correspond to the lowest-energy conformations? What, if anything, does this tell you about the rate of interconversion of conformers relative to the rate of elimination?

Conformational Control of E2 Elimination

Base-promoted E2 elimination involves simultaneous loss of H^+ and X^- from neighboring carbons. Applying this rule to 2-methylcyclohexyl tosylate suggests that two different products might form, but the actual situation is more complicated. One tosylate isomer gives only one of the two possible alkenes, while the other gives both.



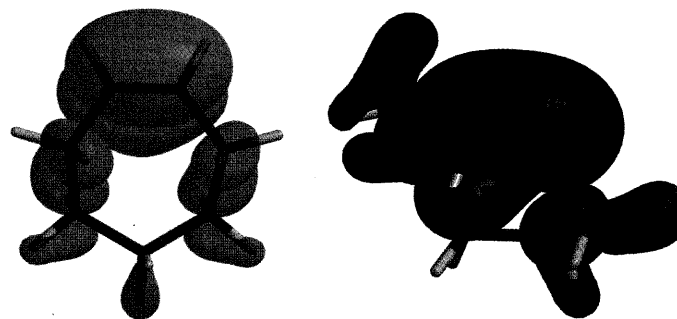
Examine all of the low-energy (within .004 au or ≈ 3 kcal/mol of the lowest-energy conformer) conformers of **cis-2-methylcyclohexyl tosylate**. Identify every conformer that can undergo *anti* elimination of OTs^- and H^+ , and predict the alkene that will be produced. What alkenes will be obtained from the *cis* tosylate?

Analyze the low-energy conformers of **trans-2-methylcyclohexyl tosylate** in the same way. What alkenes will be obtained from the *trans* tosylate?

Another interesting question concerns the rate at which each tosylate undergoes elimination. A tosylate sample contains molecules with several different conformations. The size of each conformer population depends on conformer energy, and the more reactive tosylate will probably be the one with the largest population of “reactive” conformers, i.e., molecules whose geometries allow *anti* elimination. Which tosylate, *cis* or *trans*, will have a larger population of “reactive” conformers? Explain how you reached this conclusion.

Alkenes and Alkynes

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highest-occupied molecular orbital in cycloheptene (left) and *trans*-cycloheptene (right) shows distortion of π bond (see problem 5)



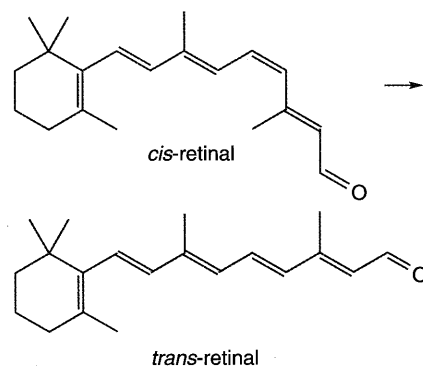
HOMO of transition state for *cis-trans* isomerization in 2-butene shows distortion of the π bond.

cis-trans Isomerization

Two different isomers of 2-butene may be isolated and individually characterized. Which isomer, *cis-2-butene* or *trans-2-butene*, is lower in energy? Compare space-filling models to see if one molecule is more crowded than the other, and dipole moments to see if one is more polar than the other. What do you suspect is the origin of the thermodynamic preference?

Calculate the activation barrier for *cis-trans* isomerization as the difference in energies between *cis-2-butene* and the **transition state** for *cis-trans* isomerization. Is it smaller, larger, or about the same as the energy required for *gauche-trans* isomerization in *n*-butane (see **Chapter 5, Problem 3**)? What is the origin of the barrier? Hint: Examine the central carbon-carbon bond in the transition state for *cis-trans* isomerization in 2-butene. Is it still a double bond (as in either *cis* or *trans-2-butene*) or has it lengthened to the value in *n-butane*? Also compare the highest-occupied molecular orbital (HOMO) of the transition state with that for either *cis* or *trans-2-butene*. What, if anything, does this tell you about the integrity of the double bond in the transition state?

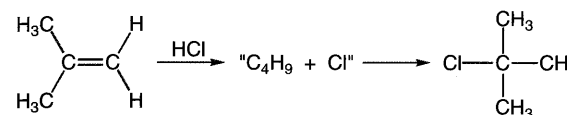
Cis-trans isomerization is an important step in the chemistry of vision, for example, the light-initiated, enzyme-catalyzed isomerization of *cis* to *trans*-retinal.



Compare energies for *cis* and *trans-retinal*. Is isomerization endothermic or exothermic? What do you suspect is the origin of the thermodynamic preference?

Electrophilic Addition to Alkenes

Addition of HCl to an alkene generally proceeds by a step-wise mechanism. The HCl bond breaks as the CH bond forms and this gives two reaction intermediates. The intermediates are not observed, but they persist until a second collision brings Cl close to the other carbon of the alkene.



How does H initially add to the alkene? Does it behave as an electrophile? A nucleophile? A neutral atom (radical)? Step through the sequence of frames depicting addition of the “H end” of HCl to 2-methylpropene (**CIH+ 2-methylpropene**). Plot both the charge on H and on Cl (vertical axis) vs. frame number (horizontal axis). Do the charges change significantly during addition or remain constant? Why?

At which point in the initial addition is there the greatest separation of charge? Draw Lewis structures for “C₄H₉” and “Cl” that show all nonbonding electrons and formal charges.

How does “Cl” add to “C₄H₉”? Does it behave as an electrophile? A nucleophile? A neutral atom (radical)? Step through the sequence of frames depicting addition of the “Cl end” of HCl to the first “intermediate” (**Cl+butyl**). Plot charge on Cl (vertical axis) vs. frame number (horizontal axis). Rationalize any changes that occur.

Considering the overall sequence, H addition followed by Cl addition, where is there the greatest separation of charge? Would you expect this addition to occur more rapidly in a nonpolar medium like hexane, or a polar medium like water? Explain.

The animations in this problem have been artificially constrained to reveal electronic changes. They do not show realistic geometries for these reaction pathways, and should not be used to estimate reaction barriers.

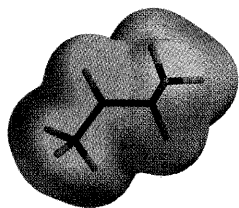
3

Alkene Reactivity toward Electrophiles

The rates of hydration of alkenes increase dramatically with increasing alkyl substitution (see table at left). This is usually attributed to the relative stabilities of carbocations formed as intermediates in the initial (and rate-limiting) step of the reaction, e.g., for hydration of propene.

alkene	relative rate of hydration
ethene	1
propene	1.6×10^7
2-methylpropene	2.5×10^{12}

The proton affinity is defined as the negative of the energy of protonation. For example, the proton affinity of propene is given by $-\Delta H$ for the reaction:

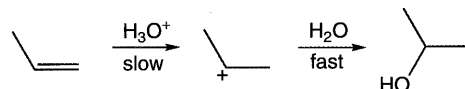


Electrostatic potential map for 2-butyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Calculate the energy of protonation of **propene** (leading to **2-propyl cation**) and of **2-methylpropene** (leading to **2-methyl-2-propyl cation**), relative to the energy of protonation of **ethene** (leading to **ethyl cation**). Does methyl substitution lead to an increase in proton affinity? Why? Does the effect appear to be additive, or does the second methyl group have a lesser or greater effect on proton affinity than the first methyl group? Rationalize what you observe.

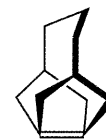
Does the alkyl group effect on proton affinity depend on the position of substitution? Is the proton affinity of **trans-2-butene** (leading to **2-butyl cation**) larger, smaller or about the same as that of its isomer, 2-methylpropene? Rationalize what you observe.

Compare electrostatic potential maps for ethyl, 2-propyl, 2-methyl-2-propyl and 2-butyl cations. Does the extent to which positive charge is localized at the carbocation center parallel proton affinity? Explain.

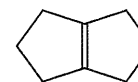


Electrophilic Addition to Strained Alkenes

Electrophilic addition of HX to an alkene involves a two-step mechanism, the overall rate being given by the rate of the initial protonation step. Differences in protonation energies are usually explained by considering differences in carbocation stability, but the relief or buildup of strain can also be a factor. One of the following alkenes protonates much more easily than the other.



alkene A



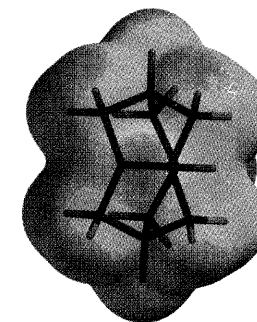
alkene B

Identify which protonation reaction (**alkene A** \rightarrow **protonated alkene A**, **alkene B** \rightarrow **protonated alkene B**) is more favorable. The energy of proton is given at right. Compare geometries of the two alkenes. Which is more strained? Why? How is this likely to affect the proton affinity? Compare electrostatic potential maps for the two alkenes. Is the π bond in one more susceptible to protonation than that in the other? Compare maps for the two protonated forms. Is the charge in one more delocalized than that in the other? Suggest an explanation to account for both the reactivity difference and the structural changes.

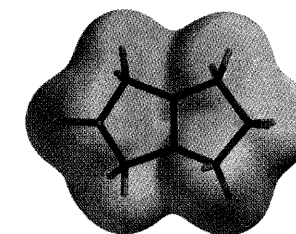
Both *cis* and *trans*-cyclohexene have been synthesized, but only one of them can be isolated. Electrophilic addition of ROH to one isomer occurs spontaneously, while addition to the other isomer occurs only in the presence of a strong acid, such as sulfuric acid. Calculate the energy of protonation for each isomer (**cyclohexene** \rightarrow **protonated cyclohexene**, **trans-cyclohexene** \rightarrow **protonated trans-cyclohexene**), and identify the more reactive isomer. Also examine electrostatic potential maps. Suggest an explanation to account for both the reactivity difference and the structural changes. (See also **Chapter 7, Problem 5**.)

4

$$E(\text{H}^+) = 0 \text{ au}$$



Electrostatic potential map for alkene A shows negatively-charged regions (in red) and positively-charged regions (in blue).



Electrostatic potential map for protonated alkene B shows most positively-charged regions (in blue) and less positively-charged regions (in red).

trans Cycloalkenes

Even some *cis* cycloalkenes have very large strain energies when compared to analogous cycloalkanes.

strain energies; au (kcal/mol)

ring size	cyclo-alkane	<i>cis</i> -cyclo-alkene
3	.043 (27)	.086 (54)
4	.041 (26)	.054 (34)
5	.010 (6)	.011 (7)
6	.000 (0)	.003 (2)
7	.016 (10)	.011 (7)
8	.021 (13)	.014 (9)



HOMO of *trans*-cycloheptene reveals distortion of the molecule's π system.

While it is relatively easy to introduce a *cis* double bond into a small ring, it is very difficult to introduce a *trans* double bond. In fact, the smallest *trans* cycloalkene which has actually been isolated to date is cyclooctene.

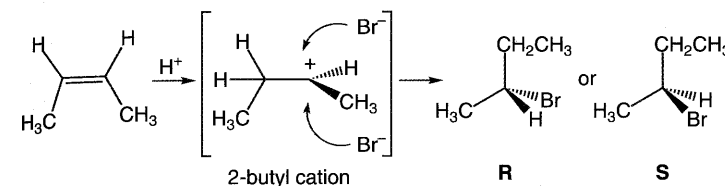
Calculate energy differences between *cis* and *trans*-cycloheptene and *cis* and *trans*-cyclooctene. Which is the more stable isomer for each compound? Is there a significant ($>.008$ au or 5 kcal/mol) increase in the energy difference between *cis* and *trans* isomers in going from the seven to eight-membered cycloalkene? Are your results consistent with the fact that *trans*-cyclooctene is an isolable, stable compound while *trans*-cycloheptene is not?

Compare geometries of the *cis* and *trans* cycloalkenes. Are the double bonds incorporated into the *trans* compounds significantly more distorted than those incorporated into the analogous *cis* cycloalkenes? Consider carbon-carbon bond lengths and the twisting and/or puckering of the double bond. Are any distortions greater in *trans*-cycloheptene than in *trans*-cyclooctene?

Another measure of distortion is the shape of the highest-occupied molecular orbital (HOMO). This corresponds to the π bond. Is the orbital relatively undistorted in the *cis* compounds (as in *cis*-2-butene)? Is it more distorted in *trans*-cycloheptene than in *trans*-cyclooctene? Explain why distortion in the HOMO is likely to be energetically unfavorable.

Stereochemistry of Electrophilic Additions

Electrophilic addition of HBr to 2-butene gives 2-butyl bromide. The product is chiral, and HBr addition may selectively form one enantiomer.



The chiral center in 2-butyl bromide is created when Br^- adds to 2-butyl cation. The key, then, is to predict the enantioselectivity of this step. **2-Butyl cation** exists as a mixture of three conformers: *planar*, *perpendicular A*, and *perpendicular B*. Compare their energies and use equation (1) to calculate the relative amounts of each conformer at 298 K. Should all three conformers participate in the reaction to a significant extent?

2-Butyl cation acts as an electrophile, and the shape of its electron-acceptor orbital (the lowest-unoccupied orbital or LUMO) should determine the direction of Br^- addition. Display the LUMO of each cation conformer. Is attack on one side of C^+ preferred over the other? Explain.

Next, examine each cation's LUMO while displaying the cation as a space-filling model. Assuming that Br^- preferentially attacks the side of C^+ that is both less hindered and permits better overlap with the LUMO, predict the major product obtained from each cation conformer (if the two sides of C^+ seem equally reactive, then predict a racemic product mixture).

Finally, use the relative amounts of the different cation conformers along with the reactivity preference of each conformer to determine the overall enantioselectivity of the addition reaction. Do you expect more R or S 2-butyl bromide to form? Explain how you arrived at this answer.



LUMO of perpendicular 2-butyl cation reveals the likely site of nucleophilic attack.

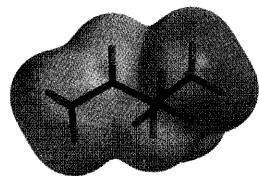
$$\frac{N_1}{N_2} = e^{-1060(E_1 - E_2)} \quad (1)$$

N_i is the number of i molecules

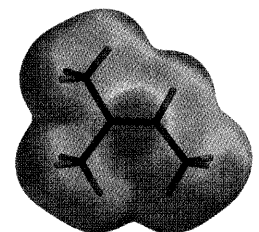
E_i is the energy of molecule i (in au)

Regiochemistry of Electrophilic Additions

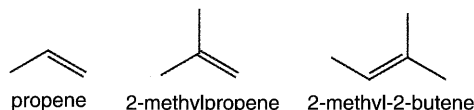
Markovnikov's rule is used to predict the regiochemistry of HX (electrophilic) addition reactions. The rule states that HX adds to an unsymmetrical alkene mainly in the direction that bonds H to the less substituted alkene carbon and X to the more substituted alkene carbon.



Electrostatic potential map for 3-methyl-2-butyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).



Electrostatic potential map for 2-methyl-2-butene shows negatively-charged regions (in red) and positively-charged regions (in blue).



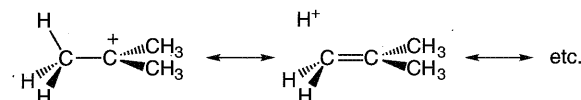
Use Markovnikov's rule to predict the products of HBr addition to the alkenes shown above.

The "modern view" of HX addition is that "H⁺" is transferred from HX to the alkene to give a carbocation. The major product is the one derived from the more stable carbocation. Compare the energies of **1-propyl** and **2-propyl cations** (protonated propene), **2-methyl-1-propyl** and **2-methyl-2-propyl cations** (protonated 2-methylpropene), and **2-methyl-2-butyl** and **3-methyl-2-butyl cations** (protonated 2-methyl-2-butene). Identify the more stable cation in each pair. Is the product derived from this cation the same product predicted by Markovnikov's rule? Is the more stable carbocation also the one for which the positive charge is more delocalized? Compare atomic charges and electrostatic potential maps for one or more pairs of carbocations.

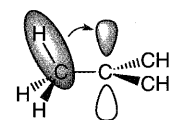
Is the stable cation that formed as a result of protonation of the more electron-rich end of the alkene? Examine electrostatic potential maps for **propene**, **2-methylpropene** and **2-methyl-2-butene**. For each, can you tell whether one end of the π bond is more electron rich than the other end? If so, does protonation on the more electron-rich end lead to the more stable carbocation?

Hyperconjugation

Resonance theory suggests that the positive charge in 2-methyl-2-propyl cation is dispersed onto the hydrogens.

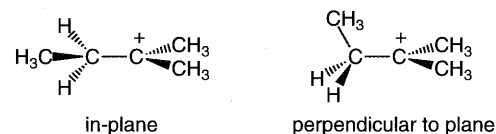


Hyperconjugation, as it is termed, implies that the electron pair associated with an out-of-plane CH bond is donated into the empty p orbital at the carbocation center.



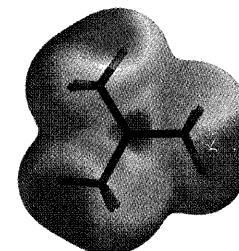
What effect, if any, should hyperconjugation have on the geometries of carbocations? Are the CC bonds in **2-methyl-2-propyl cation** shorter, longer, or about the same as those in **2-methylpropane**? Are all CH bonds in 2-methyl-2-propyl cation the same length, or does bond length depend on conformation? Explain. Examine atomic charges and the electrostatic potential map for 2-methyl-2-propyl cation. Relate any differences between in-plane and out-of-plane hydrogens both to the resonance picture and to differences in CH bond lengths.

Step through the sequence of structures depicting rotation about the C_{Et} - C⁺ bond in **2-methyl-2-butyl cation**. Plot energy (vertical axis) vs. CCCC dihedral angle (horizontal axis). What is the preferred conformation, with the ethyl group in plane or perpendicular to the plane?



Does the C₃C₄ distance change between these two conformers? Explain. Are your data consistent with CC hyperconjugation?

What does your result tell you about the relative importance of CH and CC hyperconjugation? Explain.



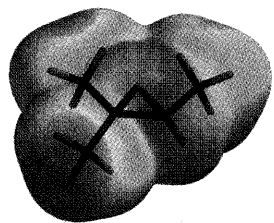
Electrostatic potential map for 2-methyl-2-propyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

$$\frac{N_1}{N_2} = e^{-1060(E_1 - E_2)} \quad (1)$$

N_i is the number of *i* molecules

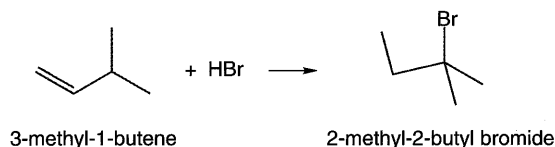
E_i is the energy of molecule *i* (in au)

Skeletal Rearrangements of Carbocation Intermediates



Electrostatic potential map for hydride shift shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Carbocations initially formed upon addition of an electrophile to an alkene may be able to undergo skeletal rearrangement depending on whether or not a more stable cation exists and, if it does exist, whether or not it can be reached via a low-energy pathway. Consider addition of HBr to 3-methyl-1-butene, the product of which is 2-methyl-2-butyl bromide.



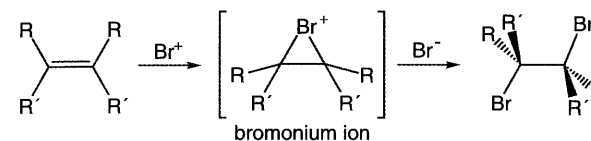
Draw Lewis structures for the possible carbocations resulting from protonation of the double bond in 3-methyl-1-butene, and decide which is favored. (Check your result using available energy data for C_5H_{11} **carbocations**.) What would be the product of bromide addition to the more stable cation? Is this the observed product?

Draw a Lewis structure for the carbocation which would result from a 1,2-hydride shift in the more stable (initially-formed) cation. Is this carbocation more stable than the initially-formed ion? What would be the product of bromide addition to this cation? Is this the observed product?

Examine the transition state for the **hydride shift**. Calculate the barrier from the more stable initial carbocation. Is the process more facile than typical thermal rearrangements of neutral molecules (.05 to .08 au or approximately 30-50 kcal/mol)? Is the barrier so small (<.02 au or approximately 12 kcal/mol) that it would be impossible to stop the rearrangement even at very low temperature? Where is the positive charge in the transition state? Examine atomic charges and the electrostatic potential map to tell. Is the name “hydride shift” appropriate? If not, propose a more appropriate name.

Electrophilic Addition of Br_2 to Alkenes

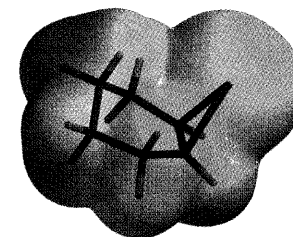
Addition of hydrogen halides to alkenes is not stereospecific. In contrast, addition of Br_2 proceeds exclusively with *anti* stereochemistry.



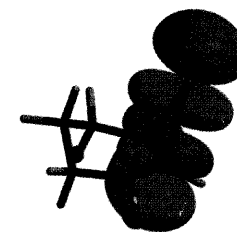
In order to explain the observed product, a cyclic “bromonium ion” intermediate has been proposed.

Examine the geometry and atomic charges of **cyclohexylbromonium ion**, the proposed intermediate in the electrophilic bromination of cyclohexene. Measure both carbon-bromine bond distances. Are they shorter, longer or about the same as in typical alkyl bromides, e.g., **methyl bromide**? Is the bromine centered between the two carbons? Measure the carbon-carbon bond distance. Is it consistent with a single bond or more typical of a double bond? (Compare with structures for **cyclohexane** and **cyclohexene**.) Does bromine bear a full positive charge, or has some charge dispersed onto the rest of the ion? Examine atomic charges and the electrostatic potential map. Draw an appropriate Lewis structure (or series of Lewis structures) to account for the geometry and charge distribution of cyclohexylbromonium ion? Is it best portrayed as a “ring” or as a weak complex between Br^+ and cyclohexene?

Display the lowest-unoccupied molecular orbital (LUMO) for cyclohexyl bromonium ion. From which side will the Br^- attack? Will this lead to formation of *cis*-1,2-dibromocyclohexane or *trans*-1,2-dibromocyclohexane? Is this also the thermodynamic product? Compare energies of ***cis*-1,2-dibromocyclohexane** and ***trans*-1,2-dibromocyclohexane**.



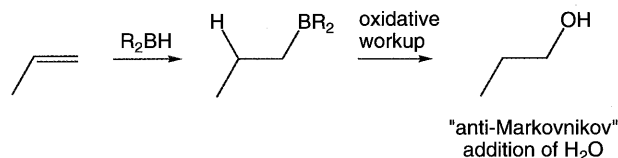
Electrostatic potential map for cyclohexylbromonium ion shows most positively-charged regions (in blue) and less positively-charged regions (in red).



LUMO of cyclohexylbromonium ion reveals the likely site of nucleophilic attack.

Hydroboration of Alkenes

Conversion of alkenes to alcohols by hydroboration is a synthetically-valuable reaction as it leads to the *anti*-Markovnikov product.

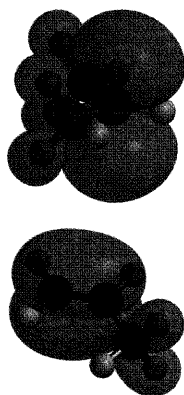


Dimethylborane+propene C1 depicts the transition state for addition of dimethylborane onto the terminal alkene carbon of propene. Examine and describe the vibration with the "imaginary" frequency. Which bonds stretch and compress the most? What simultaneous changes in bonding are implied by these motions? Simultaneously display the highest-occupied molecular orbital (HOMO) of *propene* and the lowest-unoccupied molecular orbital (LUMO) of *dimethylborane*. Is the overall geometry of the transition state consistent with constructive overlap between the two? Explain.

Obtain the energies of propene, dimethylborane, and **1-propyldimethyl borane**, and calculate ΔH_{rxn} for dimethylborane addition. Is this reaction exothermic or endothermic? Use this result and the Hammond Postulate to predict whether the transition state will be more "reactant like" or more "product like". Compare the geometry of the transition state to that of the reactants and products. Does the Hammond Postulate correctly anticipate the structure of the transition state? Explain.

Dimethylborane+propene C2 and **2-propyldimethyl borane** depict the regioisomeric transition state and addition product. Calculate the energies of these species relative to those of the alternative transition state and product. Given these energy differences, and the experimental observation that this addition is almost completely selective for the anti-Markovnikov product, does it appear that this reaction is under kinetic or thermodynamic control? Explain.

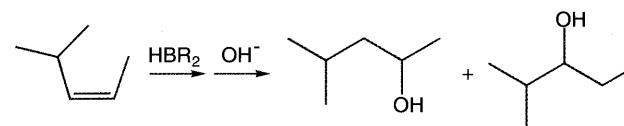
Transition states have a single imaginary frequency which corresponds to the reaction coordinate.



LUMO of dimethylborane (top) and HOMO of propene (bottom) need to overlap constructively for favorable orbital interactions.

Regioselectivity in Hydroboration of Alkenes

Hydroboration of *cis*-4-methylpent-2-ene followed by basic workup yields two isomeric alcohols, the ratio of which depends on the hydroboration reagent, HBR₂.

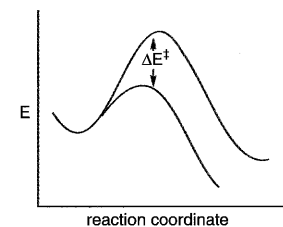


BH₃+4-methylpent-2-ene C2 and **BH₃+4-methylpent-2-ene C3** are transition states for hydroboration by BH₃ at the C₂ and C₃ positions of *cis*-4-methylpent-2-ene, respectively. Which transition state has the lower energy? Calculate the ratio of major to minor regioproducts at room temperature (use equation 1). Is this reaction likely to be highly regioselective? Explain your reasoning.

9-BBN+4-methylpent-2-ene C2 and **9-BBN+4-methylpent-2-ene C3** are transition states for hydroboration by 9-BBN at the C₂ and C₃ positions, respectively. Which transition state is the lower energy? Calculate the ratio of major to minor regioproducts at room temperature. Is this reaction likely to be more or less regioselective than the corresponding reaction involving BH₃? Explain your reasoning.

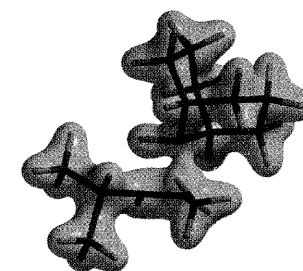
Calculate activation energies for the preferred addition mode of each reagent. (Data for *borane*, *9-BBN* and *cis*-4-methylpent-2-ene are available.) Which reaction will be faster? Is the faster reaction more or less regioselective than the slower reaction? Compare the structures of the two transition states and identify specific interactions that can account for differences in regioselectivity and reactivity. Use space-filling models.

Finally, examine bond density surfaces for the lower-energy transition state for each reaction. Are all bonds broken and formed to roughly the same extent, or are some bonds made or broken to greater extent?



$$\frac{[\text{major product}]}{[\text{minor product}]} = e^{-1060\Delta E^\ddagger} \quad (1)$$

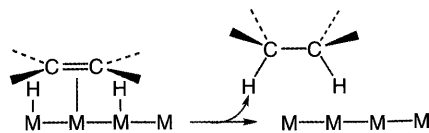
ΔE^\ddagger is the energy difference between lower-energy and higher-energy transition states (in au).



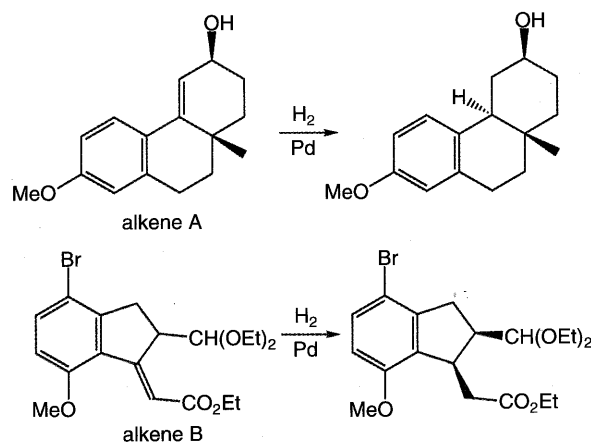
Bond density surface for 9-BBN+4-methylpent-2-ene at C2 reveals to what extent bonds are formed in hydroboration transition state.

Stereochemistry of Alkene Hydrogenation

Alkene hydrogenation occurs on the surface of metal particles which act as a catalyst for the reaction. This usually means that both hydrogens are added to the same face of the alkene (*syn* addition).



Hydrogenation of each of the following chiral alkenes gives only a single stereoisomer.

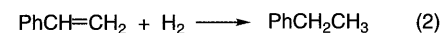
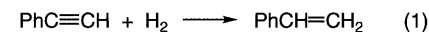


Draw the other stereoisomer that might have been obtained from *syn* addition of hydrogen to each alkene. Is the observed product for each addition also the thermodynamic product? Compare energies for **alkene A + H₂ observed** and **not observed** and **alkene B + H₂ observed** and **not observed**. What structural factors seem to be responsible for the relative stabilities of the two products of each hydrogenation reaction?

Examine space-filling models and electron density surfaces for **alkene A** and **alkene B**. For each, which face of the double bond is less hindered? Which atoms cause steric hindrance of the alkene? Is this reaction controlled by steric hindrance? If so, explain which step(s) in the catalytic mechanism would be most affected.

Alkyne vs. Alkene Reactivity

A simple-minded picture suggests that the CC π bonds in alkynes and alkenes ought to be similar. Are they? Consider the thermodynamics of reduction of **phenylacetylene** to first give **styrene** and then **phenylethane**. (The energy for H₂ is given at right.)



Which addition is more favorable thermodynamically? Assuming that the difference is entirely due to different π -bond energies, then which contains the stronger π bond, the alkyne or the alkene? What flaws might there be in the basic assumption?

Metals that catalyze reaction (2) generally catalyze reaction (1) as well, and the rate for (1) is usually somewhat higher. Given such a catalyst, what product(s) would be obtained were phenylacetylene to be combined with one equivalent of H₂? What would happen if the catalyst accelerated reaction (2) more effectively than reaction (1)?

Thermodynamics and kinetics need not go hand in hand. Consider all possible products resulting from addition of one equivalent of bromine to phenylacetylene (**phenylacetylene + Br₂**) and to styrene (**styrene + Br₂**). Calculate the heat of reaction for each addition. (The energy of Br₂ is given at right.) Is addition to the alkyne or to the alkene more favorable?

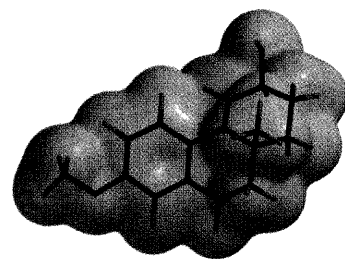
Bromination usually follows a two-step mechanism, the rate-limiting step involving formation of an adduct with Br⁺. Calculate energies for Br⁺ addition to phenylacetylene and styrene, leading to **phenylacetylene + Br⁺** and **styrene + Br⁺**, respectively. (The energy of Br⁺ is given at right.) Which reaction is more favorable? Is this the same preference as seen for Br₂ addition?

$$E(\text{H}_2) = -1.1230 \text{ au}$$

$$E(\text{Br}_2) = -5120.5302 \text{ au}$$

$$E(\text{Br}^+) = -2559.7644 \text{ au}$$

Electron density surface for alkene A shows extent of steric hindrance for the two faces of the double bond.

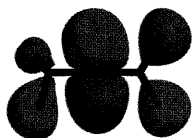


Electrophilic Additions to Alkynes. Vinyl Cations

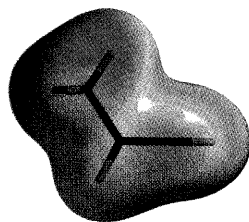
Electrophiles react with alkynes in much the same way as with alkenes. Alkynes are typically much less reactive toward electrophiles than alkenes (see **Chapter 7, Problem 14**), however, and the initial product from addition to the triple bond usually undergoes further electrophilic addition.

The first step in the addition of an electrophile such as HBr to an alkyne involves protonation and subsequent formation of an intermediate vinyl cation. Where does propyne protonate? Compare energies of **1-methylvinyl** and **2-methylvinyl cations**. Which is more stable? Why? Measure CC bond distance in the more stable cation. Does the cation incorporate a full triple bond (as in **propyne**) or a double bond (as in **propene**). Examine atomic charges and electrostatic potential maps to locate the positive charge in the two cations. Is the more stable ion the one in which the charge is better delocalized? Use the charges together with information about the ions' geometry to draw Lewis structures (or a series of Lewis structures) for 1-methylvinyl and 2-methylvinyl cations.

Is the location of positive charge in the more stable cation also where the lowest-unoccupied molecular orbital (LUMO) is most concentrated? Rationalize what you observe. Does attack by a nucleophile (bromide) lead to the Markovnikov or anti Markovnikov product?



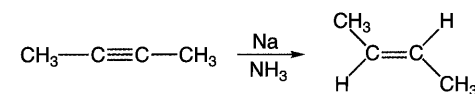
LUMO of 1-methylvinyl cation reveals the likely site for nucleophilic attack.



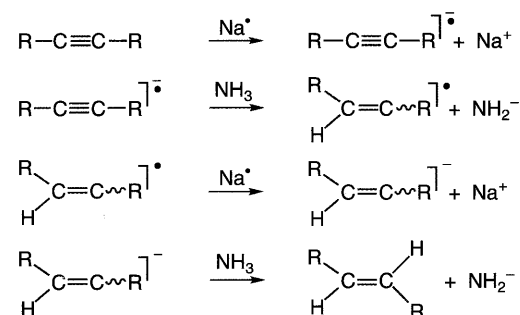
Electrostatic potential map for 2-methylvinyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Hydrogenation of Alkynes

Catalytic hydrogenation of alkynes on a metal surface provides *cis* alkenes (see **Chapter 7, Problem 13**), while treatment with sodium in liquid ammonia nearly always leads to *trans* alkenes, e.g., hydrogenation of 2-butyne.



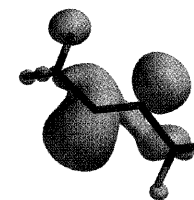
Several intermediates are involved in the latter reaction. The first is a radical anion resulting from electron transfer from sodium to the alkyne. This then deprotonates ammonia leading to a vinyl radical. The process repeats (electron transfer and deprotonation), and involves a vinyl anion intermediate.



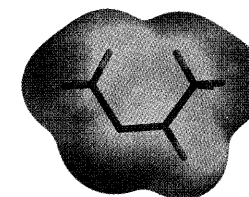
One after the other, examine **linear**, **cis** and **trans** structures for **radical anion**, **radical** and **anion** intermediates involved in the reduction of 2-butyne. For each, examine the vibrational frequencies to establish whether a structure corresponds to an energy minimum or to a transition state. For each energy minimum, assign preferred geometry, linear or bent. If bent, is a *cis* or *trans* geometry preferred? Calculate the interconversion barrier (through a linear structure). Draw an appropriate Lewis structure based on the geometry and atomic charges as well as spin density surfaces and electrostatic potential maps.

Where is the *trans* stereochemistry of the overall reduction decided? Which is the first intermediate that shows a preference for a *trans* geometry? Is this preference maintained for all successive intermediates?

Energy minima have all real frequencies, while transition states have one imaginary frequency.



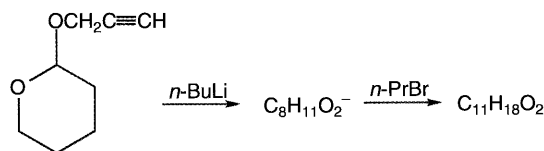
Spin density surface for *trans* radical anion shows location of unpaired electron.



Electrostatic potential map for *cis* anion shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

Anions from Alkynes

One way to generate carbanions is to combine an acidic molecule with one equivalent of a very strong base, such as *n*-butyl lithium (*n*-BuLi). For example, reaction of the alkyne shown below with *n*-BuLi leads to a carbanion of formula $C_8H_{11}O_2^-$, which then undergoes an S_N2 reaction with *n*-propyl bromide (*n*-PrBr).

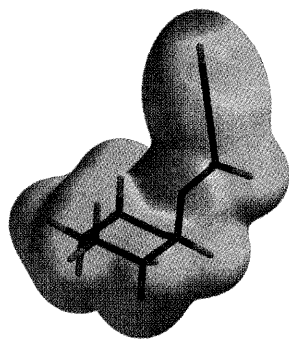


You should be able to predict the structure of the product by determining which hydrogen in the starting material is most acidic, that is, by assigning the structure of the intermediate carbanion.

First, attempt to identify the most acidic hydrogen in the starting material, based on hybridization or on the nature of neighboring atoms. Explain your rationale. Next, examine the electrostatic potential map for starting material (*alkyne*). Which hydrogen appears to be most electron poor? Is this the one that you predicted? What makes this hydrogen more electron poor than the others?

Obtain the energies of the different possible carbanions (*alkyne-H⁺*). Which one is most stable? Does it correspond to removal of the most electron-poor proton? Examine the geometry and atomic charges of the favored carbanion. Where is the negative charge? Draw the Lewis structure of this ion. Predict the structure of the S_N2 product.

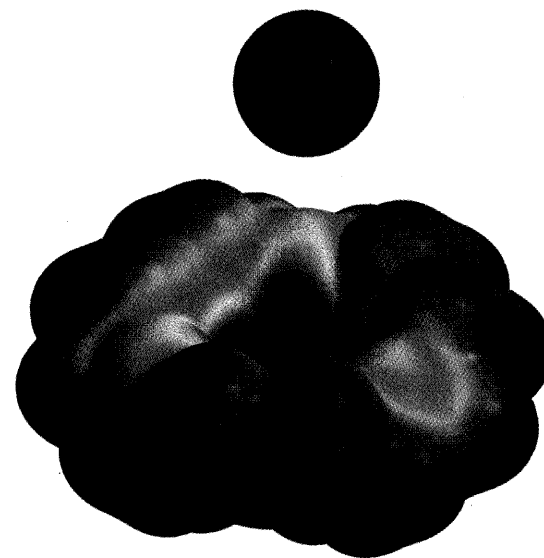
Note, that the $OCH_2C\equiv CH$ group in the alkyne starting material occupies an axial position. Why is this unexpected? Offer an explanation.



Electrostatic potential map for alkyne shows positively-charged regions (in blue) as likely acidic sites.

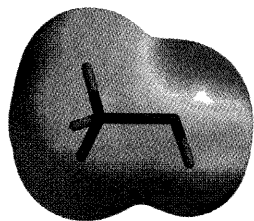
Alcohols and Ethers

1	Hydrogen Bonding in Alcohols	120
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electrostatic potential maps show size and charge complementarity between 18-crown-6 (bottom) and potassium cation (top) (see problem 12)

Hydrogen Bonding in Alcohols



Electrostatic potential map for methanol shows negatively-charged regions (in red) and positively-charged regions (in blue).

Ethers typically have much lower boiling points than isomeric alcohols, e.g., dimethyl ether boils at -25°C compared to 78°C for ethanol. The usual explanation is that alcohols are more associated due to hydrogen bonding. The latter is a term used to describe the interaction between an electron-poor hydrogen (the OH hydrogen in an alcohol), and an area of excess negative charge (the lone pairs on oxygen in an alcohol).

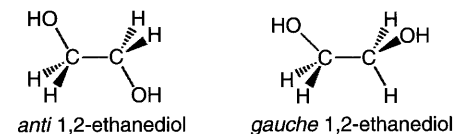
Display the electrostatic potential map for *methanol*. Identify regions of greatest positive charge and greatest negative charge. Find another copy of methanol on screen and display its electrostatic potential map. Orient the two molecules such that the region of highest positive charge in one molecule is “just touching” the region of highest negative charge in the other molecule. This should correspond approximately to the structure of a hydrogen-bonded dimer. Sketch your predicted structure, and compare with that of *methanol dimer*.

Is hydrogen bonding possible in an ether? Display the electrostatic potential map for *dimethyl ether*. Does it contain both highly positively and highly negatively-charged regions? Compare the potential to that of methanol as a reference. Find the second copy of dimethyl ether on screen and orient the two molecules as best you can to allow favorable charge-charge interactions. What is the difference between this structure and that for methanol dimer?

Why are the boiling points of ethers typically lower than those of isomeric alcohols?

Conformations of 1,2-Ethanediol

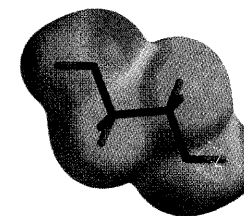
1,2-Ethanediol, like *n*-butane, exists as an equilibrium mixture of two distinct conformers: *anti* (OCCO dihedral angle = 180°) and *gauche* (OCCO dihedral angle $\sim 60^{\circ}$).



Examine space-filling models for the two conformers and identify any likely unfavorable nonbonded interactions. Based on steric effects, which conformer would you anticipate would be the more stable? Compare energies of *anti*-1,2-ethanediol and *gauche*-1,2-ethanediol to see if you are correct. Is this the same ordering of conformer energies as seen for *n*-butane (see **Chapter 5, Problem 3**)?

Display electrostatic potential maps for both *anti* and *gauche* conformers of 1,2-ethanediol. Do you see any examples of destabilizing interactions (between like charges) or stabilizing interactions (between unlike charges) in either conformer? Are you able to explain the observed conformational preference?

Examine *anti* and *gauche*-1,2-dimethoxyethane. Is the lower-energy conformer here the same as that in 1,2-ethanediol? Rationalize your observations with the aid of space-filling models and electrostatic potential maps for the two conformers.



Electrostatic potential map for *trans*-1,2-ethanediol shows negatively-charged regions (in red) and positively-charged regions (in blue).

pK_a's of Alcohols

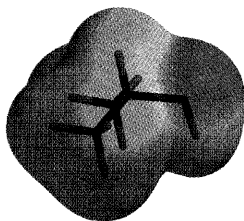
Alcohols are typically very weak acids with pK_a values in the range of 7 - 20 (compared with a pK_a value of 4.8 for acetic acid).

Display and compare electrostatic potential maps for *methanol*, *ethanol*, *2-propanol* and *trifluoroethanol*. Identify the acidic sites as those where the potential is most positive and, assuming that the more positive the potential the more acidic the site, rank the acidities of the compounds. Does increased alkyl substitution have a significant effect on acid strength? What is the effect of replacing the methyl group in ethanol by a trifluoromethyl group? Why? Do you find a correlation between the most positive value of the potential and the experimental pK_a?

Phenol has different chemical properties from those of typical alcohols. Display the electrostatic potential map for *phenol*. Does this suggest that phenol is likely to be a stronger or weaker acid than any of the compounds discussed above? Compare the electrostatic potential map for *4-nitrophenol* to that for phenol. What effect does substitution by nitro have on acid strength? Explain your result by considering charge delocalization in the conjugate base. Draw all reasonable Lewis structures for phenoxide anion and for 4-nitrophenoxide anion. Which is more delocalized? Is this consistent with experimental pK_a's?

Obtain the charge on the atom for which the electrostatic potential is most positive in each of the above molecules. Plot this charge (vertical axis) vs. experimental pK_a (horizontal axis). Is there a correlation?

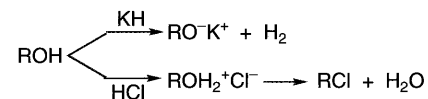
	pK _a
methanol	15.5
ethanol	15.9
2-propanol	18
2,2,2-trifluoroethanol	12.4
phenol	10.0
4-nitrophenol	7.2



Electrostatic potential map for 2-propanol shows positively-charged regions (in blue) as likely acidic sites.

Metal Hydrides vs. Hydrogen Halides

Alcohols react with metal hydrides, MH, and with hydrogen halides, HX, but in very different ways. Proton transfer is involved in both reactions, but different molecules act as the proton donor and acceptor.

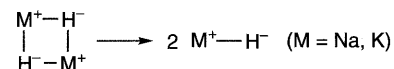


Examine electrostatic potential maps for *potassium hydride* and *hydrogen chloride*. How are they similar and how are they different? (Focus on whether the molecules are polar or nonpolar (compare dipole moments), and on the electronic character of hydrogen.) Draw the “ionic” Lewis structure that is most consistent with each electrostatic potential map. Does each atom have a filled valence shell?

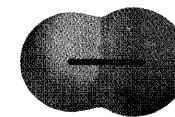
Examine the electrostatic potential map of *1-propanol*. Which atom is most negatively charged? Most positively charged? Use the maps to explain propanol's reactivity toward KH and HCl.

Both NaH and KH are used to deprotonate alcohols. KH is more reactive than NaH. Compare atomic charges and electrostatic potential maps of potassium hydride and *sodium hydride*. For which is the hydrogen more negatively charged? Which should be the better source of hydride?

Another factor to consider is the energy required to break solid MH into individual molecules. Calculate the dissociation energies for *sodium hydride dimer* and *potassium hydride dimer*, i.e.



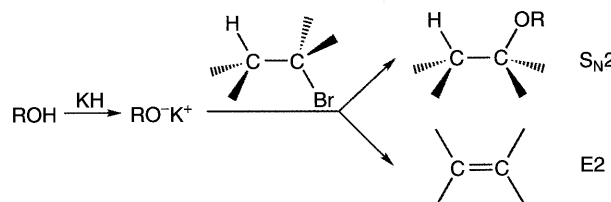
Which “solid” should dissociate into molecules more readily?



Electrostatic potential map for potassium hydride shows negatively-charged regions (in red) and positively-charged regions (in blue).

Alkoxides. Bases or Nucleophiles?

Alkoxides, RO^- , have dual reactivity, and can act as bases or nucleophiles.



Electrostatic potential map for $\text{exoO}_\text{exoCH}_2\text{Br}$ shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

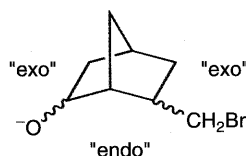


LUMO for $\text{endoO}_\text{endoCH}_2\text{Br}$ shows likely site for intramolecular nucleophilic attack.

Many factors influence the chemical behavior of an alkoxide, including leaving group, metal ion, solvent and temperature. Electrophile geometry can also promote one type of alkoxide behavior over another.

Examine space-filling models of *ethyl bromide* and *2-methyl-2-propyl bromide*. Given that $\text{S}_\text{N}2$ reactions require “backside” attack, which of these is more likely to react with EtO^- in an $\text{S}_\text{N}2$ fashion? What will the product be? What E2 products would be obtained from each alkyl bromide?

The molecule below has four stereoisomeric forms: *exoO_exoCH₂Br*, *exoO_endoCH₂Br*, and so on. Examine electrostatic potential maps of the four isomers and identify the most nucleophilic (electron-rich) atom in each. Examine the electron-acceptor orbital (the lowest-unoccupied molecular orbital or LUMO) in each and identify electrophilic sites that are in close proximity to the nucleophilic. Which isomers can undergo an intramolecular E2 reaction? Draw the expected $\text{S}_\text{N}2$ and E2 products. Which isomers should not readily undergo intramolecular reactions? Why are these inert?



Thionyl Chloride and Phosphorus Trichloride

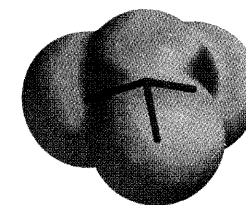
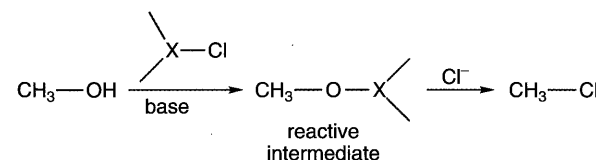
Thionyl chloride, SOCl_2 , and phosphorus trichloride, PCl_3 , are reagents that convert alcohols into the corresponding chloroalkane. The following drawings suggest that the reagents are different, but you be the judge.



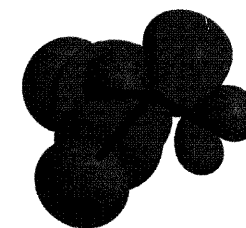
Compare geometries, atomic charges and electrostatic potential maps of *thionyl chloride* and *phosphorus trichloride*. How are they similar? How are they different? Can you redraw the Lewis structure of SOCl_2 so that it gives a better description of the electrostatic potential map?

Alcohols react with these reagents by displacing Cl^- , i.e., the alcohol acts as an oxygen nucleophile. Examine the electron acceptor orbitals of each reagent (this is the LUMO or lowest-unoccupied molecular orbital), and identify the best electron acceptor site in each. (Hint: Display the molecule as a space-filling model to see LUMO sites that are most available for intermolecular attack.) Is the LUMO bonding or antibonding with regard to the sulfur-chlorine (phosphorus-chlorine) bond? What bonding changes should accompany alcohol attack? Base your answer on the LUMO shape.

Alcohol attack generates an unstable intermediate that undergoes nucleophilic attack by Cl^- at carbon. Compare electrostatic potential maps of *methanol*, *thionyl chloride intermediate*, and *phosphorus trichloride intermediate*. What features of these maps are consistent with an electrophilic reactive intermediate?



Electrostatic potential map for phosphorus trichloride shows negatively-charged regions (in red) and positively-charged regions (in blue).



LUMO of thionyl chloride reveals the best electron-acceptor sites.

$$E(\text{tert-BuOH}) = -230.8738 \text{ au}$$

$$E(\text{OH}^-) = -74.8686 \text{ au}$$

Activating Oxygen as a Leaving Group

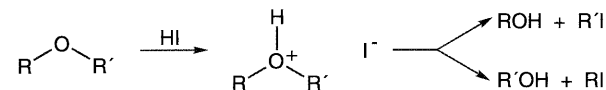
Neutral alcohols, ROH, and ethers, ROR, do not undergo either substitution or elimination reactions, presumably because OH[−] (OR[−]) is a poor leaving group. Acids can “activate” OH (OR) by converting it into a better leaving group.

The simplest way to assess “leaving group ability” is to calculate the energetics of dissociation leading to a carbocation (the first step in an S_N1 substitution), relative to that of a “standard”, e.g., dissociation of *tert*-butyl alcohol to 2-methyl-2-propyl cation and hydroxide anion. Consider as substrates *protonated tert-butyl alcohol*, *tert-butyl methyl ether*, *protonated tert-butyl methyl ether*, *tert-butyl acetate* and *tert-butyl tosylate* (leading to *water*, *methoxide anion*, *methanol*, *acetate anion* and *tosylate anion* as leaving groups). Calculate dissociation energies relative to *tert*-butyl alcohol, i.e., substrate + hydroxide → *tert*-butyl alcohol + leaving group. (Energies for hydroxide and *tert*-butyl alcohol are provided at left.) Are these results consistent with the observation that neutral alcohols and ethers are relatively unreactive? Are all of the other groups good leaving groups, or are some much better than others?

It is frequently said that “a good leaving group is the conjugate base of a strong acid.” Look up pK_a values for the conjugate acids of the leaving groups. To what extent can you use pK_a values to predict leaving group ability?

Cleavage of an Unsymmetric Ether

Unsymmetric ethers, ROR′, react with HI by a protonation-substitution mechanism that can lead to two different product combinations.

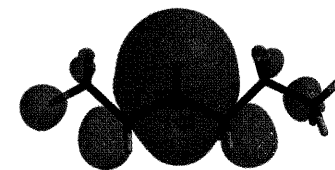


Interestingly, some unsymmetric ethers undergo selective cleavage and give only one of the two possible product combinations.

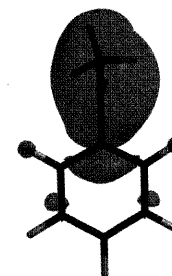
Consider the reaction of ethyl propyl ether with HI. Write the two different possible product combinations. Compare the energies of the two products (*1-propanol* and *ethyl iodide*; *ethanol* and *1-propyl iodide*). Which is the lower-energy combination? Is the energy difference significant (>.002 au or 1 kcal/mol)? Based on thermochemistry alone, is this reaction likely to be selective? Explain.

Selective ether cleavage comes about during the substitution step, which obeys an S_N2 mechanism. Therefore, selective cleavage requires selective attack by I[−] on one of the electrophilic carbons in the protonated ether. Determine if selective attack is likely by examining the shape of the lowest-unoccupied molecular orbital (LUMO) in *protonated ethyl propyl ether*. Is this orbital larger near one carbon than the other? If so, what product combination will result? What other atom(s) contribute to the LUMO? What would happen if I[−] attacked this atom(s)?

Repeat this analysis for the reaction of phenyl methyl ether with HI leading to *phenol* and *methyl iodide* or *methanol* and *phenyl iodide* and involving *protonated phenyl methyl ether* as an intermediate. (Note: In this case, the appropriate empty molecular orbital is LUMO+2; the LUMO is concentrated primarily on the CO bond.) Which reaction, with ethyl propyl ether or phenyl methyl ether, appears to be more likely to give selective ether cleavage?



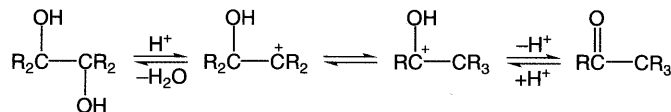
LUMO of protonated ethyl propyl ether reveals likely site of nucleophilic attack.



LUMO+2 of protonated phenyl methyl ether reveals likely site of nucleophilic attack.

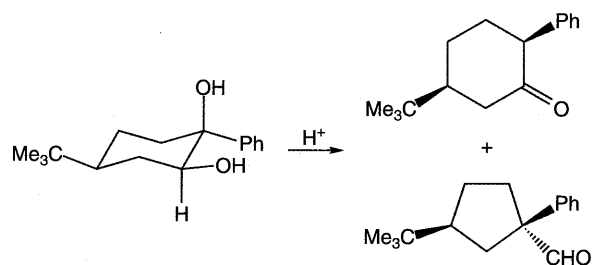
The Pinacol Rearrangement

The pinacol rearrangement is a dehydration reaction that converts a 1,2-diol into a ketone. The reaction involves two carbocation intermediates.

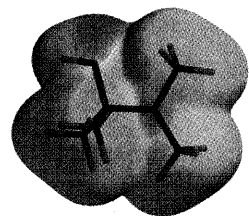


Obtain energies for the carbocation intermediates for the case of $\text{R} = \text{CH}_3$ (**2,3-dimethyl-3-hydroxy-2-butyl cation** and **3,3-dimethyl-2-hydroxy-2-butyl cation**). Is the carbocation rearrangement exothermic? Compare electrostatic potential maps for the two carbocations. Is positive charge more delocalized in the more stable cation? Why is one cation more stable than the other?

Unsymmetrical diols typically give a mixture of pinacol products. For example, the diol shown below might give eight distinct products (counting *cis* and *trans* diastereomers as distinct products). In fact, it gives only the two shown.



Draw the six other pinacol products. Pinacol selectivity is controlled, in part, by the site of carbocation formation. Use the energies of **conjugate acids** and **carbocations** to calculate the energy required to form each carbocation (the energy of H_2O is given at left). Which carbocation forms more easily? Why? Is this the carbocation that leads to the observed products? Explain. Which groups migrate (and to which face of the carbocation carbon) to generate the observed products?

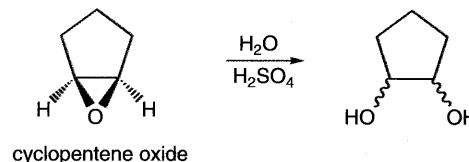


Electrostatic potential map for 2,3-dimethyl-3-hydroxy-2-butyl cation show most positively-charged regions (in blue) and less positively-charged regions (in red).

$E(\text{H}_2\text{O}) = -75.5860 \text{ au}$

Stereoselectivity of Epoxide Ring Opening

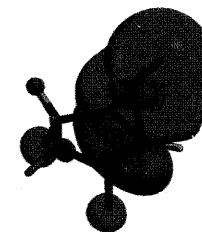
Epoxides, like other ethers, are cleaved by nucleophiles under acidic conditions. For example, cyclopentene oxide produces a mixture of 1,2-cyclopentanediol stereoisomers when treated with water and sulfuric acid.



How many stereoisomers of 1,2-cyclopentanediol are there? What are their stereochemical relationships? Are they enantiomers?

The cleavage reaction occurs in three steps: O protonation of the epoxide, $\text{S}_{\text{N}}2$ nucleophilic attack on the protonated epoxide, and deprotonation of the ring-opened product. Draw the complete mechanism. How many intermediates are there? Which step determines diol stereochemistry?

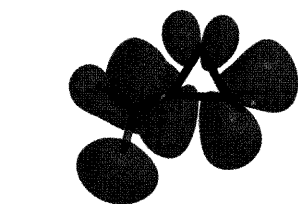
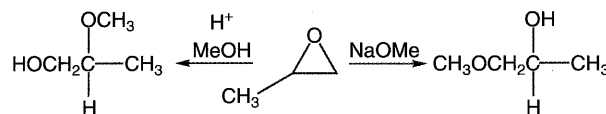
The product of nucleophilic attack can be anticipated by examining the lowest-unoccupied molecular orbital (LUMO) on **protonated cyclopentene oxide**. From which direction (top or bottom) would a nucleophile be more likely to approach each epoxide carbon in order to transfer electrons into this orbital? Explain. Does one carbon contribute more to the LUMO, or is the orbital evenly spread out over both epoxide carbons? Assuming that LUMO shape dictates product stereochemistry, predict which stereoisomers will be obtained, and their approximate relative amounts. Is the anticipated “kinetic product” also the thermodynamic product? (Compare energies of **1,2-cyclopentanediol** stereoisomers to tell.)



The LUMO of protonated cyclopentene oxide reveals the likely site of nucleophilic attack.

Regioselectivity of Epoxide Ring Opening

Epoxides, in contrast to ethers, readily undergo nucleophilic attack, resulting in ring opening and relief of strain. Ring opening proceeds by a different mechanism, and may lead to different products, depending on reaction conditions.



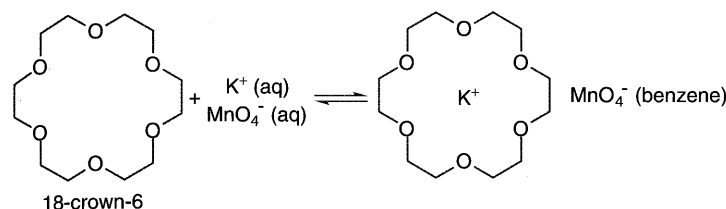
LUMO +1 of propylene oxide reveals the likely site of nucleophilic attack. The LUMO is primarily localized on the ring hydrogens.

With strong nucleophiles such as methoxide, ring opening follows an $\text{S}_{\text{N}}2$ mechanism. Examine the next to lowest-unoccupied molecular orbital (LUMO+1) for *propylene oxide*. On which carbon is it most heavily concentrated? Is this also the “least crowded” carbon? (Examine a space-filling model for propylene oxide.) What should be the product of $\text{S}_{\text{N}}2$ addition?

With weak nucleophiles such as methanol, and in the presence of acid, the reaction proceeds via nucleophilic attack on the protonated epoxide. Examine the LUMO of *protonated propylene oxide*. Does this properly identify the site for nucleophilic attack which will lead to the observed product? (Hint: The most accessible parts of the LUMO are best identified by simultaneously displaying the molecule as a space-filling model and the LUMO as a “mesh” surface.)

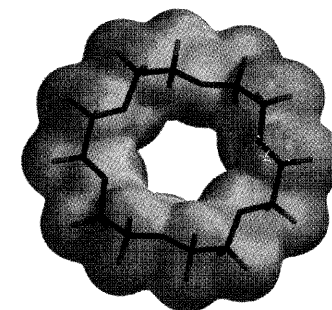
Crown Ethers

Crown ethers are cyclic polyethers. Larger crown ethers contain a cavity that can partially engulf atomic ions. 18-crown-6 actually binds K^+ so tightly that it can extract this ion into benzene from water, driving counterions, like MnO_4^- , into the benzene layer, i.e.



Different size crown ethers bind selectively to different size cations. Compare the sizes of *lithium*, *sodium*, and *potassium cations*, with the size of the cavities in *12-crown-4* and *18-crown-6* (use space-filling models to estimate molecular size). Predict the relative binding ability of each crown ether for the three ions. (Assume that ion binding falls in the order: tight fit > loose fit >> too tight a fit.) It is believed that ion-crown ether interactions are electrostatic in nature. Cations should be electrostatically attracted to the electron-rich cavity environment created by the oxygen nonbonding electrons. Examine electrostatic potential maps of 12-crown-4 and 18-crown-6. Identify the most electron-rich region(s) in each molecule. Which crown ether’s cavity is more negatively charged?

The “crown” conformation is not necessarily the most stable structure for “free” (uncomplexed) crown ethers. Examine the *lowest energy* structure of *18-crown-6*, and compare it to the “crown” structure. Explain why the “crown” structure is less stable. Use equation (1) to calculate the equilibrium ratio of lowest-energy and “crown” conformers of 18-crown-6 at room temperature. What causes a shift in conformation in the presence of metal cations?



Electrostatic potential map for 18-crown-6 shows negatively-charged regions (in red) and positively-charged regions (in blue).

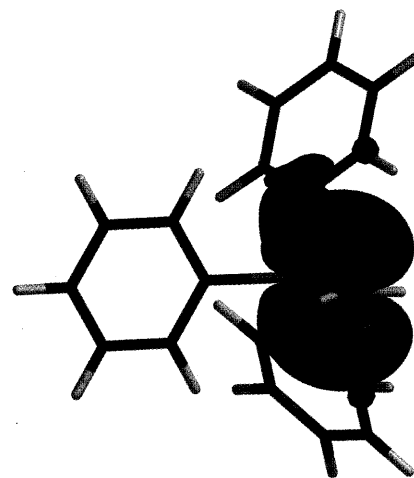
$$\frac{N_{\text{lowest}}}{N_{\text{crown}}} = e^{-1060(E_{\text{lowest}} - E_{\text{crown}})} \quad (1)$$

N_i is the number of molecules of conformer i

E_i is the energy of conformer i (in au)

Ketones and Aldehydes. Nucleophilic Addition

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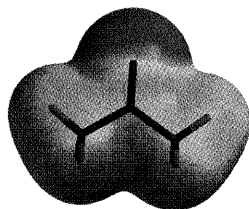


highest-occupied molecular orbital ("π-bond") of triphenylphosphinemethyldene
(see problem 11)

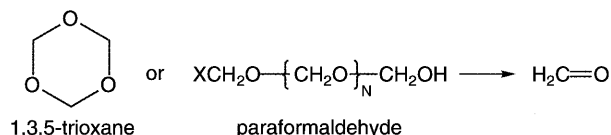
Formaldehyde

Formaldehyde, $\text{H}_2\text{C}=\text{O}$, cannot be purchased in molecular form as a pure substance. When formaldehyde is needed, it is common to purchase either 1,3,5-trioxane or paraformaldehyde, and then “crack” these substances into formaldehyde *in situ*.

$$\Delta G = \Delta H - T\Delta S \quad (1)$$



Electrostatic potential map for acetone shows negatively-charged regions (in red) and positively-charged regions (in blue).

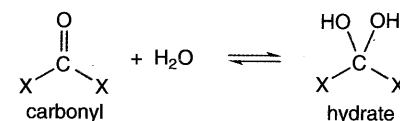


Obtain the energies of **formaldehyde** and **1,3,5-trioxane**. What is ΔH_{rxn} for trioxane “cracking”? Is the process endothermic or exothermic? Is ΔS_{rxn} for the “cracking” reaction likely to be positive or negative? Explain. Given the direction of the change in entropy, should one “crack” trioxane at higher or lower temperatures? Explain (use equation 1).

One can imagine methylated derivatives of 1,3,5-trioxane that would yield either acetaldehyde, CH_3CHO , or acetone, CH_3COCH_3 , upon “cracking”. Calculate energies of the cracking reactions, **2,4,6-trimethyl-1,3,5-trioxane** \rightarrow 3 **acetaldehyde** and **hexamethyl-1,3,5-trioxane** \rightarrow 3 **acetone**. What effect does adding one or two methyl groups have on ΔH_{rxn} ? Rationalize your observations. Are there large differences in the polarities of the products which would encourage or discourage cracking? Compare charges, dipole moments and electrostatic potential maps for formaldehyde, acetaldehyde and acetone. Are the substituted trioxanes significantly “more crowded” than the parent compound? Examine space-filling models.

Carbonyl Hydration

Ketones and aldehydes, because they are unsaturated, readily add water to give a 1,1-diol or “hydrate”



The position of this equilibrium depends greatly on the substituents, X. Formaldehyde (X = H) exists mainly as the hydrate in aqueous solutions, while acetone (X = CH_3) exists mainly in the carbonyl form (see table at right).

Use the aqueous-phase energies of water (given at right) and the appropriate **carbonyl compounds** and **carbonyl hydrates** to calculate ΔH of hydration reactions for X = H and CH_3 . Do your reaction energies reliably predict the position of equilibrium? If the energies are not reliable, then what other factors must be considered and how would they affect your predictions? For example, ΔS for reactions such as above is typically on the order of -40 to -60 eu (1 eu or “entropy unit” = $1\text{ cal/mol}\cdot\text{K}$). Use an “average” value of ΔS together with your ΔH values above to estimate ΔG for the hydration reactions at 298 K (use equation 1). Are these in better agreement with observation? Must exothermic reactions lead to favorable equilibria?

Do the relative reaction energies for formaldehyde and acetone reproduce the change in the position of the hydration equilibrium? Explain your reasoning. Calculate hydration energies for hexafluoroacetone (X = CF_3), cyclopropanone (X₂ = CH_2CH_2), and methyl acetate (X = OCH_3 , X = CH_3). Compare these energies to the hydration energies of formaldehyde and acetone, and predict the dominant form (carbonyl or hydrate) of each molecule in water. Can you explain these results using either electronic or structural reasons?

X	[hydrate]/[carbonyl]
H	2300
CH_3	0.0014

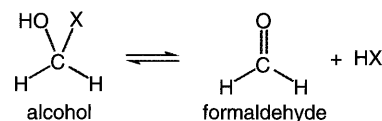
$$\Delta G = \Delta H - T\Delta S \quad (1)$$

$E(\text{H}_2\text{O in water}) = -75.5961\text{ au}$

“Aqueous-phase” energies give the energy of a single molecule dissolved in water at infinite dilution and 298K.

Non-Existent Alcohols

The fact that we can draw a reasonable formula for a molecule is no guarantee that it will be stable. Consider an alcohol that contains a “good” leaving group attached to the hydroxyl carbon. The alcohol’s formula looks reasonable, but the molecule may still spontaneously fragment into HX and the corresponding aldehyde.



Obtain energies for *fluoromethanol*, *chloromethanol*, *bromomethanol*, *hydroxymethanol*, *thiomethanol* and *cyanomethanol*, and calculate ΔH_{rxn} for decomposition into formaldehyde and HX (energies for formaldehyde and for hydrogen fluoride, hydrogen chloride, hydrogen bromide, water, hydrogen sulfide and hydrogen cyanide, are given at left). Which alcohols are likely to be stable? Which ones are likely to be non-existent?

ΔS_{rxn} values for fragmentation reactions like the one shown above are typically of the order of 40 to 60 eu (1 eu or “entropy unit” = 1 cal/mol·K). Use an “average” value for ΔS_{rxn} and your calculated ΔH_{rxn} to estimate ΔG_{rxn} at 298 K (use equation 1). Do these new data affect any of your conclusions about which alcohols are likely to be stable and which are likely to be nonexistent?

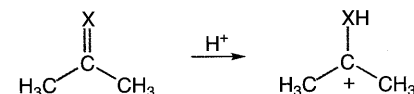
If you have access to Chemical Abstracts, look up each alcohol in the Formula Index and see if it has been prepared, or if it is only a theoretical curiosity.

$$\Delta G = \Delta H - T\Delta S \quad (1)$$

Carbonyl Basicity

Experiments show that both alkenes and ketones undergo acid-catalyzed reactions. Alkene reactions usually require use of a very strong acid, H_2SO_4 or HX , while ketone reactions occur under milder conditions. This suggests that ketones are stronger bases, and that their conjugate acids enjoy special stabilization.

Consider protonation of 2-methylpropene ($\text{X} = \text{CH}_2$) versus protonation of acetone ($\text{X} = \text{O}$).



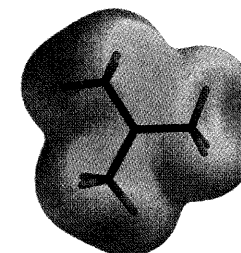
Use the energies of *2-methylpropene*, *2-methyl-2-propyl cation*, and H^+ (given at right) to calculate the alkene’s protonation energy. Next, use the energies of *acetone* and its conjugate acid, *dimethylhydroxy cation*, to calculate the ketone’s protonation energy. Which molecule is the stronger base? Is the difference significant? Draw the resonance contributors that best describe the geometries and electrostatic potential maps of the two carbocations. Do these data provide a useful guide to experimental reactivity patterns?

Experimental reactivity patterns are based on solution behavior which are influenced by interactions between solvent and reacting molecules (especially ions). Compare electrostatic potential maps of 2-methyl-2-propyl cation and dimethylhydroxy cation. Identify sites that might form strong hydrogen bonds with water. Which ion will be better stabilized by its interaction with water?

Use the *aqueous* energies of the reacting molecules to calculate alkene and ketone protonation energies in water (the aqueous energy of H^+ is given at right). Which molecule is the stronger base in water? Is the difference significant? Do these data provide a useful guide to experimental reactivity patterns?

$$E(\text{H}^+) = 0 \text{ au}$$

$$E(\text{H}^+ \text{ in water}) = -.4032 \text{ au}$$



Electrostatic potential map for 2-methyl-2-propyl cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

$$E(\text{H}_2\text{CO}) = -113.2218 \text{ au}$$

$$E(\text{HF}) = -99.4602 \text{ au}$$

$$E(\text{HCl}) = -457.9814 \text{ au}$$

$$E(\text{HBr}) = -2560.8428 \text{ au}$$

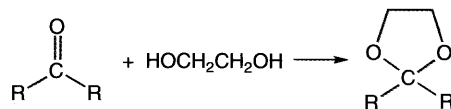
$$E(\text{H}_2\text{O}) = -75.5860 \text{ au}$$

$$E(\text{H}_2\text{S}) = -396.8196 \text{ au}$$

$$E(\text{HCN}) = -92.3541 \text{ au}$$

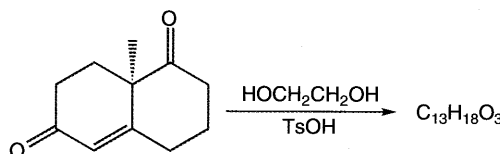
Selective Formation of Ketals

Ketones react with 1,2-ethanediol under acidic conditions to give cyclic ketals.



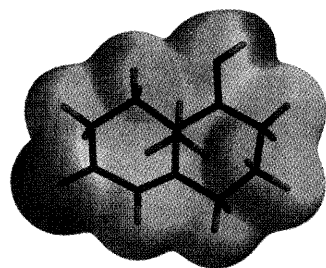
The reaction proceeds by a multistep mechanism and normally is reversible. Therefore, we expect the reaction to be thermodynamically controlled.

The following reaction provides an example of selective ketal formation. The product of the reaction is a single ketone-ketal with the formula $\text{C}_{13}\text{H}_{18}\text{O}_3$.



In order to predict the structure of the product, you must identify the factors that will tend to favor selective ketal formation. Consider selective carbonyl protonation first. Obtain energies and atomic charges, and display electrostatic potential maps of the alternative protonated ketones (*protonated ketone A*, *protonated ketone B*). Identify the more stable isomer. Compare geometries and draw whatever Lewis structures are needed to account for your data. Why is one isomer more stable than the other? Is the more stable isomer also that in which the positive charge is better delocalized? Will the more stable isomer undergo nucleophilic attack more or less easily than the other? Explain.

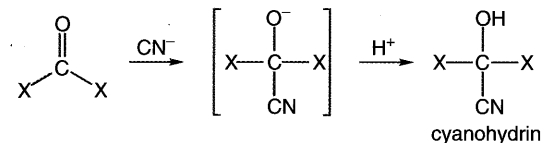
Since all of the steps in ketal formation are reversible, we expect the more stable ketal to form selectively. Obtain the energies of the alternative ketone-ketals (*ketone-ketal A* and *ketone-ketal B*). Which one is more stable? What factors do you think contribute to the stability of this ketal?



Electrostatic potential map for protonated ketone B shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Cyanohydrin Formation

Cyanide is a sufficiently strong nucleophile that it can add directly to aldehydes and ketones, ultimately giving a cyanohydrin.

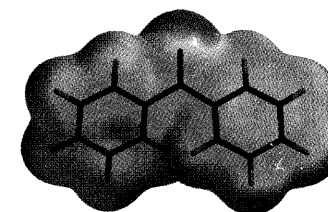


The reactivity of aldehydes and ketones toward cyanide may be influenced by the steric and/or electronic properties of the carbonyl substituents, X. Examine space-filling models of *formaldehyde* (X=H), *acetone* (X=Me), and *benzophenone* (X=Ph). Which compound offers the least steric hindrance to nucleophilic attack? The most?

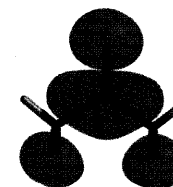
Compare electrostatic potential maps for formaldehyde, acetone, and benzophenone. Which compound contains the most electron-poor carbonyl carbon? Rationalize what you observe.

Another useful way to think about carbon electrophilicity is to compare the properties of the carbonyls' lowest-unoccupied molecular orbital (LUMO). This is the orbital into which the nucleophile's pair of electrons will go. Examine each compound's LUMO. Which is most localized on the carbonyl group? Most delocalized? Next, examine the LUMOs while displaying the compounds as space-filling models. This allows you to judge the extent to which the LUMO is actually accessible to an approaching nucleophile. Which LUMO is most available? Least available?

Finally, examine transition states for cyanide addition (*cyanide+formaldehyde*, *cyanide+acetone*, *cyanide+benzophenone*) What relationship, if any, is there between the length of the forming CC bond and the various carbonyl properties determined above? Try to rationalize what you find, and see if there are other structural variations that can be correlated with carbonyl reactivity.



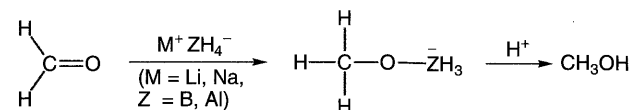
Electrostatic potential map for benzophenone shows negatively-charged regions (in red) and positively-charged regions (in blue).



LUMO of acetone reveals likely site of nucleophilic attack.

Hydride Reducing Agents

So-called “hydride” reducing agents can transform carbonyl groups into alcohols, but their reducing ability depends on the nature of the hydride reagent.



Compare atomic charges for *sodium borohydride* and *lithium aluminum hydride*. Which ion contains the most electron-rich “hydride”? The least electron-rich “hydride”? Based on these results alone, which hydride reagent should be the better reducing agent? Explain. Obtain atomic charges for “free” *borohydride* and *aluminum hydride anions*. What changes, if any, does the counterion produce?

Next consider the energetics of reduction. Calculate ΔH_{rxn} for the first step in the reduction process using free reagents (BH_4^- and AlH_4^-). Energies for formaldehyde, and for the two intermediate adducts are provided at left. Which reduction is thermodynamically more favorable? Are these results consistent with the predictions made using atomic charges?

Chemists generally rank reducing agent power as $\text{LiAlH}_4 > \text{NaBH}_4$. Is this ranking consistent with the reaction energetics and atomic charges?

Interestingly, “true” hydrides, such as NaH and KH , do not reduce carbonyl groups. Using energies of hydride and methoxide (at left), calculate ΔH_{rxn} for the reduction of formaldehyde by H^- . Is this reaction more or less favorable than those based on ZH_4^- ? Can the low reactivity of NaH and KH be attributed to thermodynamic factors, or must kinetic factors be responsible?

$$E(\text{H}_2\text{CO}) = -113.2218 \text{ au}$$

$$E(\text{CH}_3\text{OBH}_3^-) = -140.1136 \text{ au}$$

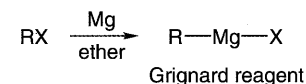
$$E(\text{CH}_3\text{OAlH}_3^-) = -356.2664 \text{ au}$$

$$E(\text{H}^-) = -0.4004 \text{ au}$$

$$E(\text{MeO}^-) = -113.7248 \text{ au}$$

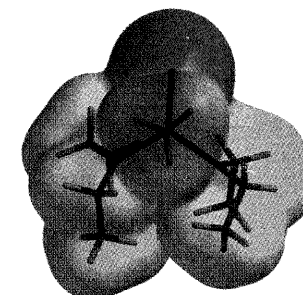
Grignard Reagents

A convenient method for generating carbon nucleophiles is to combine an organic halide, RX , with magnesium metal. This yields RMgX , a “Grignard reagent”.



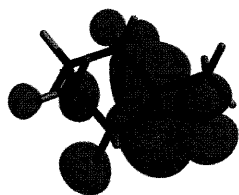
Examine the geometry and charges of *methylmagnesium chloride-diethyl ether complex*, a model for a Grignard reagent in solution. Pay particular attention to the “methyl group”. Does its structure resemble that of *methyl anion*? Does it carry a full negative charge?

What effect does the solvent have on the structure, charges and reactivity of Grignards? Compare geometries, atomic charges and electrostatic potential maps of the diethyl ether complex to that of *methylmagnesium chloride* itself. How does solvent-magnesium bond formation affect the reactivity of the methyl group? Explain.

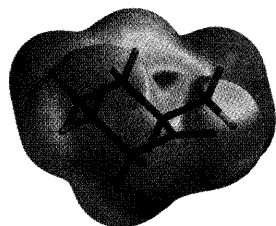


Electrostatic potential map for methylmagnesium chloride-diethyl ether complex shows negatively-charged regions (in red) and positively-charged regions (in blue).

Stereochemistry of Nucleophilic Additions. Methylcyclohexanone



LUMO for equatorial methylcyclohexanone reveals likely site of nucleophilic attack.



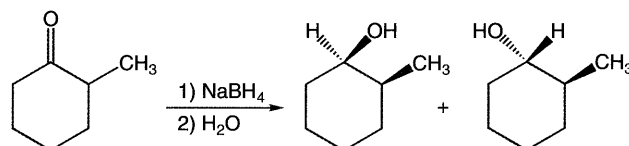
LUMO map for equatorial methylcyclohexanone shows (in blue) where the LUMO is most-heavily concentrated.

$$\frac{N_{eq}}{N_{ax}} = e^{-1060(E_{eq}-E_{ax})} \quad (1)$$

N_i is the number of molecules in conformer i

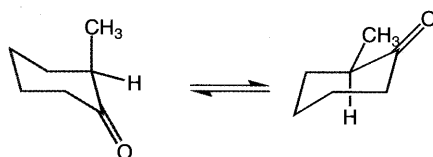
E_i is the energy of conformer i (in au)

Hydride addition to methylcyclohexanone leads either to *cis* or *trans* alcohols, depending on which face is attacked preferentially.



Display the lowest-unoccupied molecular orbital (LUMO) for *equatorial methylcyclohexanone*. This is the orbital into which the nucleophile's pair of electrons will go. Is it larger on the axial or equatorial face? A clearer picture follows from the LUMO map, which gives the value of the LUMO on the electron density surface, that is, the "accessible" surface of the molecule. Display the LUMO map for equatorial methylcyclohexanone. Which face of the carbonyl group is more likely to be attacked by a nucleophile? Which alcohol will result?

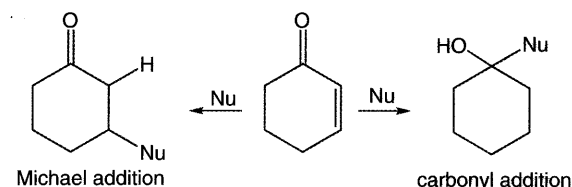
It was assumed above that the methyl group adopts an equatorial conformation. Actually, methylcyclohexanone exists as a mixture of axial and equatorial conformations.



Obtain the energy for *axial methylcyclohexanone*, and use equation (1) to calculate the room temperature equilibrium distribution of equatorial and axial conformers. Is the amount of the axial conformer significant (>5%)? Perform a similar analysis as above and decide which face of the carbonyl in the axial conformer is more likely to undergo nucleophilic attack. Does addition lead to the same alcohol as before?

Michael Addition

α,β -Unsaturated carbonyl compounds may undergo nucleophilic addition either at the carbonyl carbon (carbonyl addition) or at the β carbon (Michael addition), thus leading to different products, e.g., in cyclohexenone.

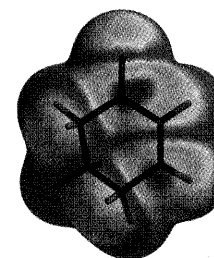


Draw a Lewis structure for cyclohexenone that involves charge separation for the most polar bond. Then, draw a Lewis structure that will delocalize one or both charges. Next, examine the actual geometry of *cyclohexenone*. Are the bond distances consistent with the Lewis structure shown above, or have they altered in accord with your alternative (charge separated) Lewis structure? (Structures for *cyclohexene* and *cyclohexanone* are available for reference.)

Display and describe the lowest-unoccupied molecular orbital (LUMO) for cyclohexenone. This is the orbital into which the nucleophile's pair of electrons will go. Does it anticipate both carbonyl and Michael products of nucleophilic addition? Explain. A clearer picture is provided by a LUMO map for cyclohexenone. This gives the value of the LUMO on the "accessible" surface of the molecule, i.e., on the molecule's electron density surface. Does it anticipate both of the observed products? If so, which should be the dominant? Explain your choice.



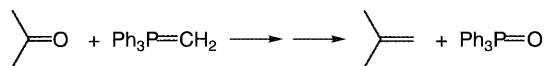
LUMO for cyclohexenone reveals the likely sites of nucleophilic attack.



LUMO map for cyclohexenone shows (in blue) where the LUMO is most heavily concentrated.

Phosphorous Ylides

The Wittig reaction, for which George Wittig received the 1979 Nobel Prize in Chemistry, is an important synthetic procedure for converting aldehydes and ketones into alkenes. The active reagent is a phosphorous ylide which undergoes nucleophilic addition to the carbonyl carbon, e.g., for addition of triphenylphosphinemethylidene to acetone.

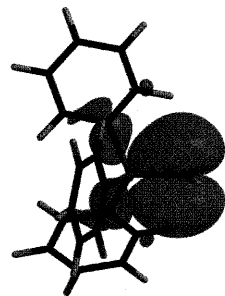


Phosphorous ylides such as triphenylphosphine-methylidene may either be represented as hypervalent species incorporating a phosphorous-carbon double bond, or in terms of a zwitterion, that is, a molecule with separated positive and negative charges.

Draw a series of Lewis structures depicting these alternative interpretations of triphenylphosphine-methylidene. Compare these to the geometry of **triphenylphosphinemethylidene**. Focus, in particular, on the local geometry around the CH_2 group. Is it planar as would be expected of a system incorporating a double bond, or is it puckered as would be a carbanion? Is the phosphorous-methylene bond length similar to the distances involving the phenyl groups, or is it significantly shorter? Which appears to be the better representation for the geometry of the ylide, hypervalent or zwitterionic?

Examine the charge on the methylidene group, as well as the magnitude and direction of the molecule's dipole moment. Are they consistent with representation of the ylide as a hypervalent molecule or as a zwitterion?

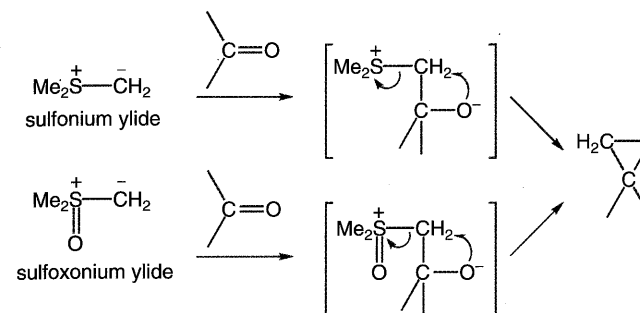
Finally, display the highest-occupied molecular orbital (HOMO) of triphenylphosphinemethylidene. Is it primarily concentrated on the methylene carbon as would be expected of a fully-developed anion, or is it delocalized over both phosphorous and carbon? Does this suggest that the molecule incorporates a π bond?



HOMO of triphenylphosphine-methylidene provides evidence for or against a fully-developed π bond.

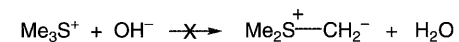
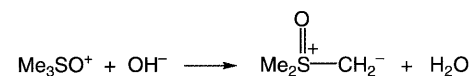
Sulfur Ylides

Sulfonium ylides and sulfoxonium ylides are useful reagents for converting ketones and aldehydes into epoxides.



Examine electrostatic potential maps for **dimethylsulfonium** and **dimethylsulfoxonium ylides**. Which contains the more negatively-charged carbon? Do either or both of the ylides incorporate a fully formed π bond? Compare bond distances involving methylene and methyl carbons. Also examine the highest-occupied molecular orbital (HOMO) for evidence of π bonding.

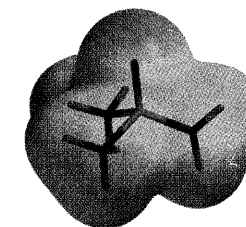
Me_3SO^+ and OH^- react to form an ylide, but Me_3S^+ and OH^- do not react.



Calculate the energy of proton transfer from **trimethylsulfoxonium cation** to its ylide, relative to that for **trimethylsulfonium cation** to its ylide, i.e.



Which ylide is more easily formed in this way? Is your result in accord with the experimental ordering of reactivity? Is this the ylide with the more negative carbon?



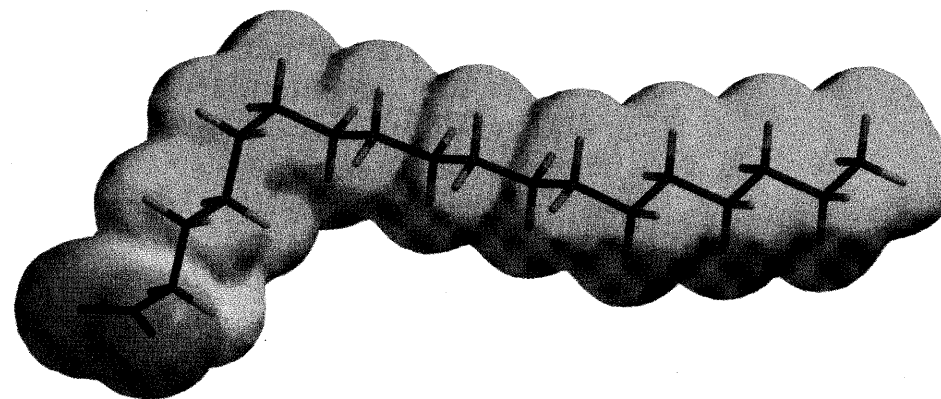
Electrostatic potential map for dimethylsulfoxonium ylide shows negatively-charged regions (in red) and positively-charged regions (in blue).



HOMO of dimethylsulfonium ylide describes the extent to which a π bond is present.

Carboxylic Acid Derivatives. Nucleophilic Substitution

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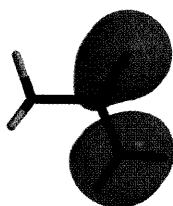
electrostatic potential map for a long chain carboxylate anion reveals both polar and non-polar regions (see problem 10)

Conformational Properties of Carboxylic Acids and Amides

$$\frac{N_1}{N_2} = e^{-1060(E_1-E_2)} \quad (1)$$

N_i is the number of molecules of conformer i

E_i is the energy of conformer i (in au)



HOMO of acetamide reveals the extent to which the molecule incorporates a π bond.

The ^1H NMR spectra of acetic acid and acetamide are quite different. The OH proton generates a single sharp peak at room temperature, while the NH_2 protons generate a broad, double-humped peak that turns into two sharp peaks at lower temperatures. This suggests that the NH_2 protons occupy different chemical environments, while the OH proton occupies a single environment.

Step through the sequence of structures depicting rotation about the CO single bond in **acetic acid**. Plot energy (vertical axis) vs. HOCO torsion angle (horizontal axis). Identify and describe any minimum energy structures. Assuming that each minimum generates a unique OH peak, and that the relative magnitudes of different peaks is proportional to their relative abundances, describe the NMR spectrum of acetic acid. Use equation (1) to estimate the relative populations of the minimum energy structures. Note that this analysis assumes equilibration between minimum-energy structures, and requires a low barrier ($<.03$ au or 20 kcal/mol) to interconversion. What is the rotation barrier? Is interconversion likely to be rapid or slow?

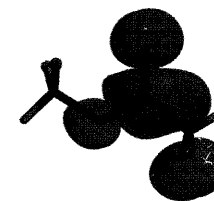
Next, examine the equilibrium structure of **acetamide** (see also **Chapter 16, Problem 8**). Are the two NH protons in different chemical environments? If so, would you expect interconversion to be easy or difficult? Calculate the barrier to interconversion (via **acetamide rotation transition state**). Rationalize your result. Hint: Examine the highest-occupied molecular orbital (HOMO) for both acetamide and its rotation transition state. Does the molecule incorporate a π bond. If so, is it disrupted upon rotation?

Electrophilic Properties of Carboxylic Acid Derivatives

Carboxylic acid derivatives, $\text{CH}_3\text{C}(=\text{O})\text{Z}$, are similar to aldehydes and ketones in that they contain a polar carbonyl group. Therefore, nucleophiles should add to the carbonyl carbon, although the rate of addition may depend on the Z group.

One way to investigate the electrophilic properties of these molecules is to examine the orbital that each uses to accept electrons from a nucleophile. This orbital is the lowest-unoccupied molecular orbital (LUMO). Examine the LUMO for **methyl acetate** ($\text{Z}=\text{OCH}_3$), **acetaldehyde** ($\text{Z}=\text{H}$), **N,N-dimethylacetamide** ($\text{Z}=\text{N}(\text{CH}_3)_2$) and **acetyl chloride** ($\text{Z}=\text{Cl}$) (acetaldehyde is not a carboxylic acid derivative, but is included here for comparison). What is the shape of the LUMO in the region of the carbonyl group? Is it a σ or π orbital? Is it bonding or antibonding? What other atoms contribute to the LUMO? Which bonds, if any, would be weakened when a nucleophile transfers its electrons into the LUMO?

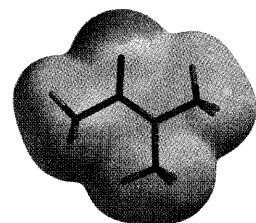
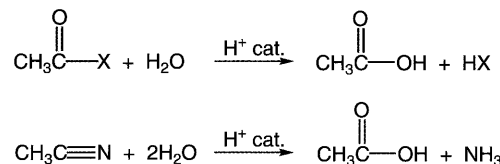
A molecule with a low energy LUMO can accept electrons more readily than a molecule with a higher energy LUMO. The LUMO energies (in au) for the above molecules are: 0.192 (methyl acetate), 0.161 (acetaldehyde), 0.212 (N,N-dimethylacetamide), and 0.132 (acetyl chloride). Order these molecules from most electrophilic to least electrophilic.



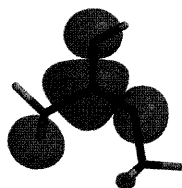
LUMO of methyl acetate reveals the likely site of nucleophilic attack.

Acid Cleavage of Esters, Amides and Nitriles

Esters, amides, and nitriles are not readily hydrolyzed under neutral conditions, but they are hydrolyzed by aqueous acid.



Electrostatic potential map for dimethylacetamide shows negatively-charged regions (in red) and positively-charged regions (in blue).



LUMO for protonated methyl acetate reveals likely site of attack by water.

Two mechanisms for acid-catalyzed hydrolysis can be imagined depending on the initial site of protonation. One mechanism begins with protonation at X; this makes X a better leaving group. The alternative is protonation of the carbonyl oxygen.

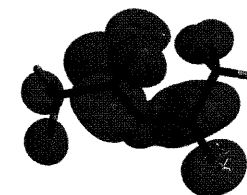
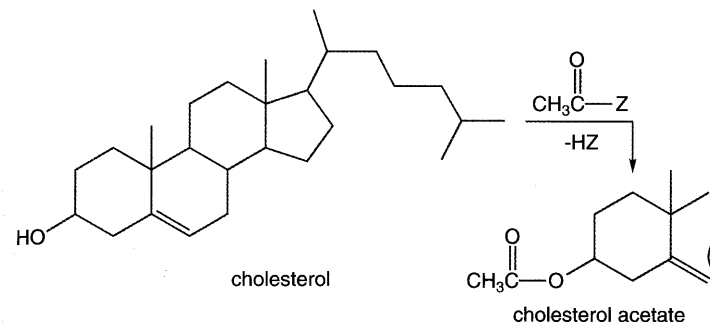
Examine electrostatic potential maps for *methyl acetate* (X=OMe), *dimethylacetamide* (X=NMe₂), and *acetonitrile*. What is the most electron-rich site in each molecule? Does this site correspond to a bonding pair of electrons or a nonbonding pair of electrons? Assuming that protonation occurs onto the most electron-rich site, where would you expect each molecule to protonate?

Compare energies for the two alternative conjugate acids of methyl acetate (*protonated methyl acetate* and *methoxy protonated methyl acetate*) and dimethylacetamide (*N-protonated dimethylacetamide* and *O-protonated dimethylacetamide*). Which acid in each pair is more stable? Draw resonance contributors for the more stable conjugate acid for each system.

Examine the lowest-unoccupied molecular orbital (LUMO) for the most stable conjugate acid of each compound (include *protonated acetonitrile*). Which atom makes the largest contribution to this orbital? Is this the site of H₂O attack? Will adding electrons to the LUMO strengthen or weaken the C=O (C≡N) π bond? Explain.

Esters vs. Anhydrides

Anhydrides and esters are routinely used as acylating agents. Anhydrides, however, are the reagents of choice for acylating alcohols. For example, acetylation of cholesterol is carried out using acetic anhydride (Z = OC(=O)CH₃), and not ethyl acetate (Z = OCH₂CH₃).



LUMO of acetic anhydride reveals the likely site of nucleophilic attack.

Anhydrides and esters may differ in two ways. One may undergo nucleophilic addition more rapidly (kinetics), but the other may create a more favorable equilibrium constant for ester formation (thermodynamics).

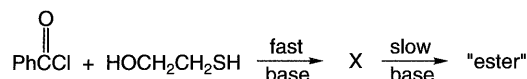
Kinetic reactivity can be assessed by examining the lowest-unoccupied molecular orbital (LUMO). This is the orbital into which the nucleophile's pair of electrons will go. Compare the LUMO for *acetic anhydride* and *ethyl acetate*. For each, determine on which atom(s) the orbital has the largest lobes? Do both reagents appear to be susceptible to nucleophilic attack at the carbonyl carbon?

A molecule with a lower energy LUMO will generally react more rapidly. The LUMO energies of acetic anhydride and ethyl acetate are 0.143 and 0.193 au, respectively. Which reagent is a better acylating agent in the kinetic sense?

Calculate the thermodynamics of acetylation of *cholesterol* (to *cholesterol acetate*) using both acetic anhydride and ethyl acetate. Data for *acetic acid* and *ethanol* are available. Which reaction is more favorable?

Esters vs. Thioesters

Benzoyl chloride reacts with 2-mercaptoethanol in base to give an ester. When the reaction is monitored carefully, the rapid buildup of an intermediate, "X", of molecular formula $C_9H_{10}O_2S$, is observed. This is slowly transformed into the ester of the same molecular formula. Although ester formation is known to be a multi-step process, X does not correspond to any of the usual intermediates in ester formation. What is going on here?

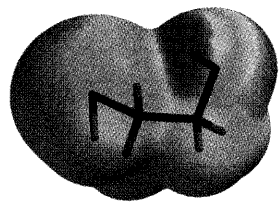


The base may control some of this chemistry by selectively converting 2-mercaptoethanol into a stronger nucleophile. Display an electrostatic potential map for **2-mercaptoethanol**. Which proton, that attached to oxygen or sulfur, is more acidic, that is, more likely to be removed by strong base? Rationalize your result.

Next, step through the sequence of structures depicting interconversion of the two **conjugate bases** resulting from deprotonation of 2-mercaptoethanol. Plot energy (vertical axis) vs. frame number (horizontal axis). Which conjugate base is more stable, that resulting from deprotonation at oxygen or at sulfur? Calculate the barrier from the less stable to the more stable base. Is interconversion of the two likely to be easy or difficult? Use this information to propose a structure for X.

The ultimate reaction product, the "ester", is an isomer of X. Logically, the ester must be more stable than X. Examine the various **esters**, and identify the most stable molecule. Is it more stable than X? Is it an ester?

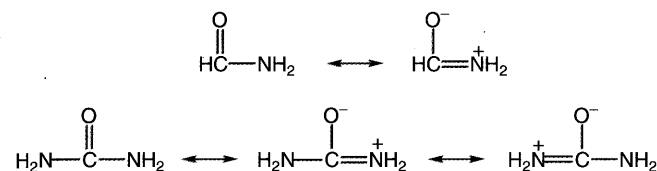
It is not at all obvious why esters should have lower energies than thioesters. It is generally observed that SH bonds are about .03 au (20 kcal/mol) weaker than OH bonds. Given this, which bond must be stronger, S–CO or O–CO? Estimate the difference in bond energies between the two?



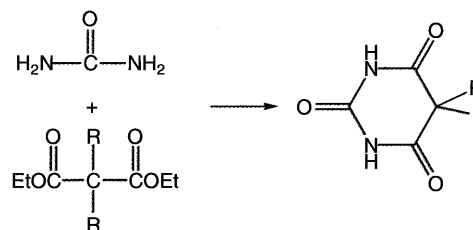
Electrostatic potential map for 2-mercaptoethanol reveals most acidic sites as positively-charged regions (in blue).

Amides vs. Ureas

Amides and ureas are believed to be stabilized by the following type of resonance.

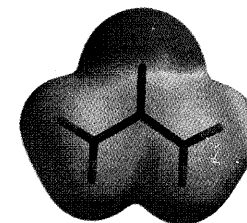


This makes the nitrogens electron poor, and they should not act as either bases or nucleophiles. Nevertheless, urea reacts with malonic esters to make barbiturates. A key step in this reaction involves nucleophilic attack by the urea nitrogen on the malonic ester.



Establish the role of resonance by comparing geometries, dipole moments, atomic charges and electrostatic potential maps for **urea** and **formamide**. Which molecule contains shorter CN bonds? Which contains a more electron-rich oxygen? A more electron-poor nitrogen? (Compare electrostatic potentials on nitrogen at the point above the molecular plane.) Is the dipole moment of urea twice that of formamide? What do these data imply about electron donation from nitrogen to oxygen? Explain.

Nitrogen basicity in these compounds may be taken as an indicator of their nucleophilicity. Calculate the energy of protonation (at nitrogen) of urea (leading to **N-protonated urea**) and of formamide (leading to **N-protonated formamide**). (The energy of the proton is given at right.) Which molecule is the stronger (nitrogen) base? What structural changes occur in each molecule when it is protonated? Can you account for these changes using a resonance model?



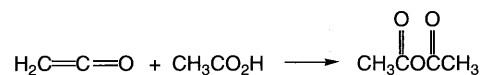
Electrostatic potential map for urea shows negatively-charged regions (in red) and positively-charged regions (in blue).

Note, that both urea and formamide actually protonate on oxygen rather than on nitrogen.

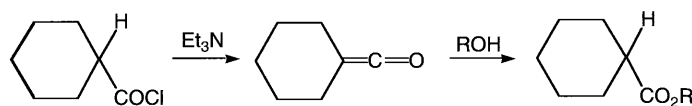
$E(\text{H}^+) = 0 \text{ au}$

Ketene

Ketene, $\text{CH}_2=\text{C}=\text{O}$, is an extremely reactive, toxic gas that sees little use in the laboratory, but is very important in the commercial synthesis of acetic anhydride.

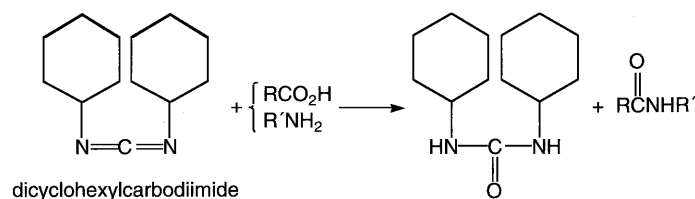


Ketene derivatives are observed as by-products of elimination reactions involving hindered carboxylic acid derivatives, and it is important to understand their chemistry.



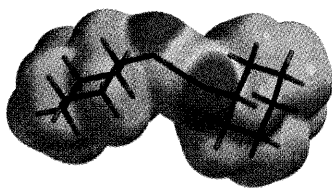
Examine the electrostatic potential map for *ketene*. Which (non-hydrogen) atom is most electron poor, and which regions around this atom are most electron poor? After oxygen, which atom is most electron rich, and which regions are most electron rich? Account for these data with a diagram that shows the orbitals on each atom, their orientation and electron occupancy, and whether or not they participate in covalent bonds (assume that oxygen is sp hybridized).

Dicyclohexylcarbodiimide is a solid material, the Lewis structure for which resembles that of ketene. The molecule is a widely used catalyst for amide synthesis and other dehydration reactions.



Analyze and describe the electronic structure of *dicyclohexylcarbodiimide* in the same way as you did for ketene.

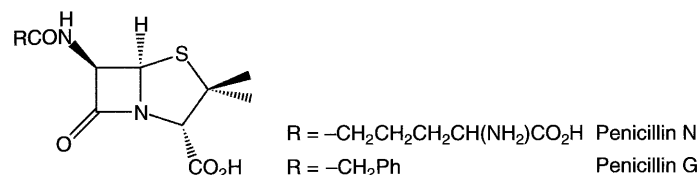
Which molecule, ketene or dicyclohexylcarbodiimide, appears to be more electrophilic? Explain your rationale.



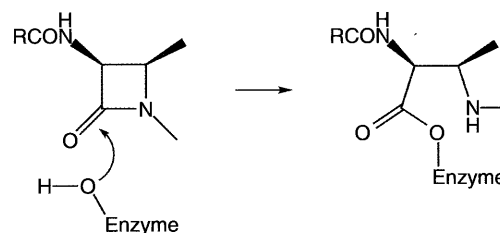
Electrostatic potential map for dicyclohexylcarbodiimide shows negatively-charged regions (in red) and positively-charged regions (in blue).

Penicillin

The antibacterial properties of a mold *penicillium notatum* were first observed by Fleming in 1928. The active compound, "penicillin N", was isolated ten years later, and soon thereafter, large-scale production of a closely-related compound "penicillin G" was initiated.

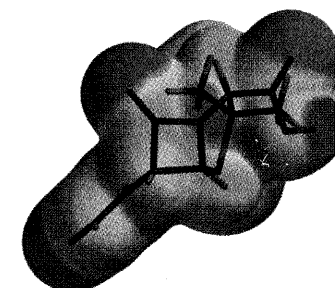


Amides are generally poor candidates for nucleophilic attack, but penicillin is apparently an exception, and reacts with bacterial enzymes as shown below.



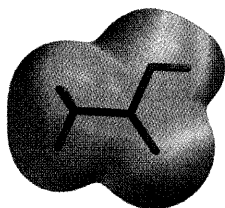
Examine the structure of *penicillin model* ($\text{R}=\text{H}$), a model for the active compounds. What, if anything, distinguishes it from a typical amide (*N,N*-dimethylacetamide, for example)? What is responsible for the differences? Compare electrostatic potential maps for penicillin model and dimethylacetamide. Which compound is more likely to undergo nucleophilic attack? Explain.

Is addition of *methanol* (a model for the enzyme) to the penicillin model (leading to *penicillin+enzyme model*) exothermic or endothermic? Rationalize your result.



Electrostatic potential map for penicillin model shows positively-charged regions (in blue) as likely sites for nucleophilic attack.

Intra and Intermolecular Hydrogen Bonding



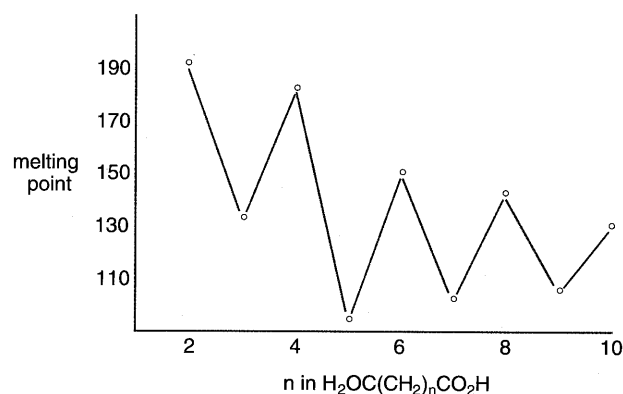
Electrostatic potential map for acetic acid shows negatively-charged regions (in red) and positively-charged regions (in blue).

Molecules of the complexity open-chain dicarboxylic acids typically exist as a collection of many different conformers, and the conformer displayed for each system corresponds to the lowest-energy structure.

The melting and boiling points of carboxylic acids are much higher than would be expected on the basis of their molecular weights. The usual explanation is that they form weak intramolecular bonds.

Display an electrostatic potential map for *acetic acid*. Where are the most electron-rich sites? Where are the most electron-poor sites? Propose a structure for the dimer of acetic acid based on favorable electrostatic interactions between electron-rich and electron-poor sites. Compare your structure to that for *acetic acid dimer*. What is another name for the types of interactions that hold the two acetic acid molecules together? (See also **Chapter 2, Problem 2**).

The melting points of open-chain dicarboxylic acids, $\text{H}_2\text{OC}(\text{CH}_2)_n\text{CO}_2\text{H}$, alternate with length of the intervening methylene chain.

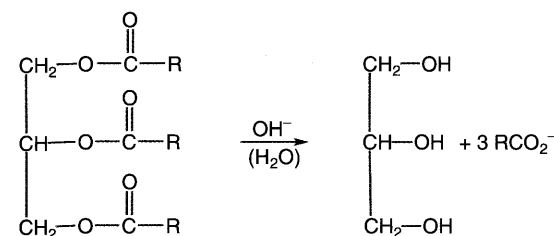


One after the other, examine structures for *octane-1,8-dioic acid*, *nonane-1,9-dioic acid* and *decane-1,10-dioic acid*. Is there any difference (in structure or conformation) between the diacids with lower and higher melting points? Which, if any, of the acids adopt structures similar to that of acetic acid dimer? Account for the variation in melting points of these three compounds.

Fatty Acids and Fats. What Makes Good Soap?

Natural fats are glycerol esters of fatty acids known as triglycerides. Unsaturated fats are generally liquids (oils) at room temperature, while triglycerides rich in saturated fatty acids are generally solids. View *tristearin* and *triolein*. Which one of these is saturated and which is unsaturated? Are the double bonds in the unsaturated fat *cis* or *trans*?

Hydrolysis of animal fats in the presence of strong base leads to glycerol and salts of long-chain carboxylic acids. The latter are known as “soaps”.



Detergents are closely related to soaps. They also incorporate long alkyl chains, but the carboxylate groups have been replaced by sulfonate groups (among other things).

Compare and contrast the electrostatic potential map of a typical *detergent* with that of a typical soap (*stearate*). Which part of each molecule will be most water soluble (hydrophilic)? Draw a Lewis structure that describes each molecule's water-soluble group (make sure you indicate all necessary formal charges and lone pairs). Which part(s) of each molecule will be most grease soluble (lipophilic)? What kinds of atoms and bonds are found in these groups?

Molecules of this complexity typically exist as a collection of many different conformers, and those shown should only be taken as representative (low-energy) conformers.

Saturated fats in the diet pose a much greater health risk than unsaturated fats because they are much more likely to lead to solid deposits on blood vessels.

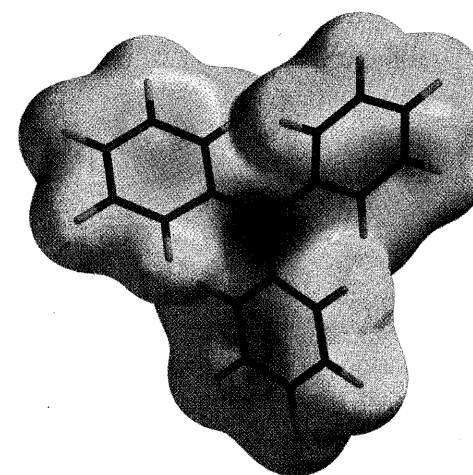
Historically, soap was made by boiling animal fat with wood ashes (which contain K_2CO_3).



Electrostatic potential map for stearate shows negatively-charged regions (in red) as well as “neutral” regions (in green).

Enolates as Nucleophiles

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electrostatic potential map for triphenylmethyl lithium showing buildup of negative charge on the central carbon (see problem 5)

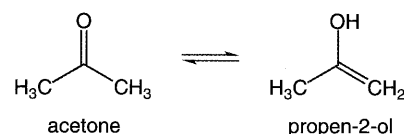
Keto/Enol Tautomerism

Aldehydes and ketones (“keto” forms) normally exist in equilibrium with their “enol” tautomers.

$$\frac{N_{\text{keto}}}{N_{\text{enol}}} = e^{-1060(E_{\text{keto}} - E_{\text{enol}})} \quad (1)$$

N_i is the number of molecules of tautomer i

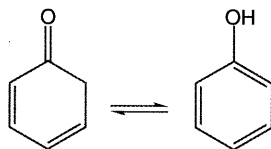
E_i is the energy of tautomer i (in au)



Tautomerism is a difficult process in the gas phase, but is generally quite facile in solution in the presence of either acid or base.

Which tautomer is lower in energy, *acetone* or *propen-2-ol*? Use equation (1) to calculate the equilibrium distribution of the two at room temperature. If an experiment is capable of detecting concentrations as low as 1% of the total, would you expect to observe both keto and enol forms of acetone at room temperature?

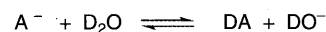
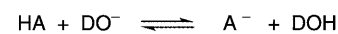
Calculate the equilibrium abundances of *2,4-cyclohexadienone* and *phenol*.



Which tautomer is more stable? Would you expect to be able to observe both tautomers at room temperature? Rationalize any differences between this keto-enol equilibrium and that above involving acetone and propen-2-ol.

H/D Exchange Reactions

Weak acids ($15 \leq \text{p}K_a \leq 30$) undergo H/D exchange when placed in NaOD/D₂O. A reasonable mechanism is:

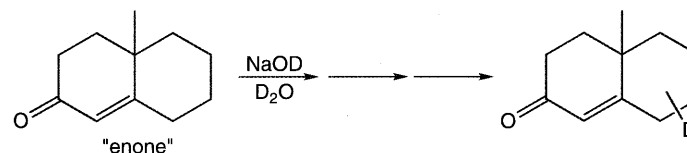


2-Methylcyclohexanone, $\text{p}K_a \sim 20$, is typical of a weak acid that undergo H/D exchange. Identify the “acidic protons” of 2-methylcyclohexanone, i.e., those most susceptible to attack by base, as positions for which the value of the lowest-unoccupied molecular orbital (LUMO) is large. Use a LUMO map (the value of the LUMO mapped onto the electron density surface). Does this analysis correctly anticipate which of the *anions* obtained by deprotonation of 2-methylcyclohexanone is actually most stable? Are any of the other ions of comparable stability, or are they all much less stable?

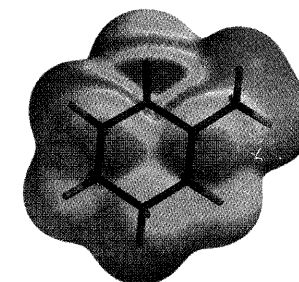
Examine the structures and charge distributions of the lowest-energy anions, and draw all of the resonance contributors necessary to describe these ions. What features account for the fact that these anions are more stable than their alternatives?

Experiments suggest that H/D exchange is not limited to a single site. Write down all the single exchange products that might be formed for 2-methylcyclohexanone. In total, how many deuteriums might be substituted for hydrogens?

Treatment of the “enone” shown below with NaOD/D₂O ultimately exchanges five H’s for D’s.



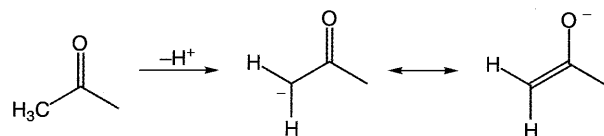
Examine the energies of the various *enone anions* resulting from deprotonation. Identify the most stable anion, and rationalize what you observe using resonance arguments. Suggest a structure for the deuterated enone.



LUMO map for 2-methylcyclohexanone reveals (in blue) acidic protons, susceptible to H/D exchange.

What Makes a Good Enolate?

Deprotonation at carbon adjacent to a carbonyl group leads to an enolate anion, e.g., deprotonation of acetone.

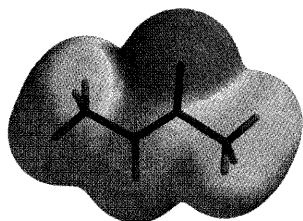


“Enolate chemistry” follows from this anion acting as a carbon nucleophile.

Examine the geometry and electrostatic potential map for **acetone enolate**. Are the CC and CO bonds in the enolate more similar to those in **acetone** or **propen-2-ol** precursors? Is the negative charge primarily located on oxygen or on carbon? Assuming this enolate is a hybrid of the two resonance contributors as shown above, which, if either, appears to be the major contributor?

Compare electrostatic potential maps of **enolates** derived from **2-butanone**, **4,4-dimethyl-2-pentanone**, **4,4,4-trifluoro-2-butanone** and **1-phenyl-2-propanone** with those of acetone. Which substituents cause significant changes in the electronic structure of these enolates and what are the nature of these changes? Justify your answers by making drawings of any important resonance contributors.

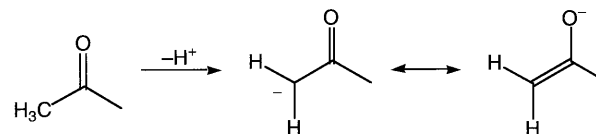
Is the most delocalized enolate also the most easily formed enolate? Calculate relative deprotonation energies from the enolate **precursors** using the deprotonation energy of acetone as a standard.



Electrostatic potential map for 2-butanone enolate shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

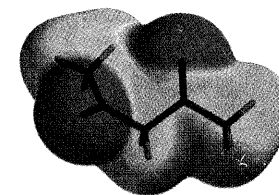
Enolate Acidity, Stability and Geometry

In general, alkyl hydrogens are not very acidic. However, alkyl hydrogens adjacent to carbonyl groups can be deprotonated by strong bases to give enolate anions, e.g., for acetone.



Compare electrostatic potential maps for **propane**, **acetone** and **2,4-pentanedione**, and identify the most positively-charged “acidic” hydrogen(s) in each. Is there a correlation between electrostatic potential and pK_a (see table at right)?

How many different enolates may arise from deprotonation of 2,4-pentanedione? Draw Lewis structures for each, and predict which is likely to be the most stable. Check your conclusions by examining the energies of the different possible enolates (**enolate A**, **B**...). Is the most stable enolate that derived from deprotonation of the most electron-poor hydrogen? Compare the electrostatic potential maps of the anions with each other and with your Lewis structures. Revise your drawings to be consistent with the maps. Why is one of the enolates preferred over the others?

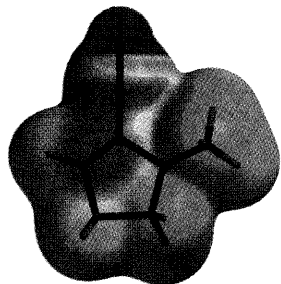


Electrostatic potential map for 2,4-pentanedione shows positively-charged regions (in blue) as likely acidic sites.

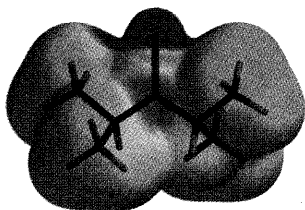
	pK_a
propane	50
acetone	20
2,4-pentanedione	9

Kinetic Enolates

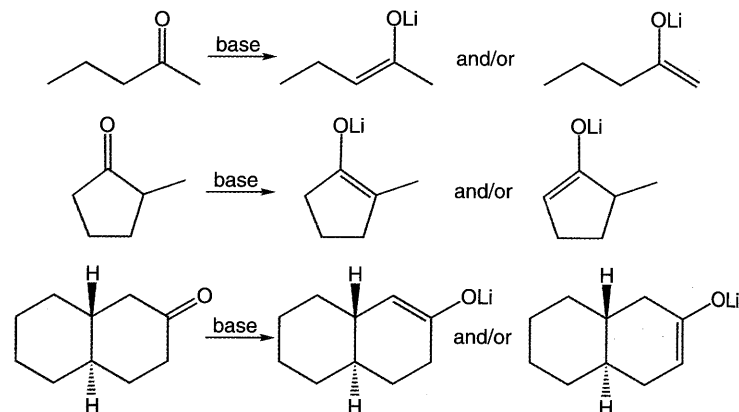
Reaction of unsymmetrical ketones with strong bases may lead to two different enolates. Whether the eventual product derives from the more stable (“thermodynamic”) enolate, or from the more rapidly formed (“kinetic”) enolate, depends on reaction conditions.



Electrostatic potential map for methylcyclopentanone lithium enolate A, shows negatively-charged regions (in red) and positively-charged regions (in blue).



Electrostatic potential map for LDA shows negatively-charged regions (in red) and positively-charged regions (in blue).

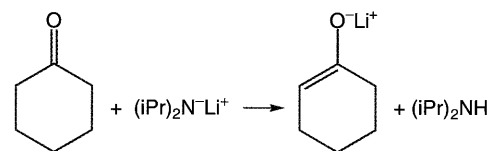


Identify the thermodynamic enolate for each system shown above (*2-pentanone enolate A and B*; *2-methylcyclopentanone enolate A and B*; *decalinone enolate A and B*). Also, compare electrostatic potential maps for each pair of enolates. What structural and/or electronic features, if any, appear to dictate which enolate is favored?

Generation of the “kinetic” enolate is encouraged by a large excess of very strong base. The identity of the kinetic enolate depends on the ketone-base interaction, and may vary with different bases. Both LDA (iPr_2NLi) and triphenylmethyl lithium react with the ketones above to give an excess of the right-hand enolates. Examine electrostatic potential maps of *LDA* and *triphenylmethyl lithium*, and identify the most negatively-charged atom. Is the negative charge localized or delocalized? Is this atom exposed or hindered? What ketone-base interactions appear to drive formation of kinetic enolates? Explain.

Real Enolates

Common reagents such as lithium diisopropylamide (LDA; see **Chapter 11, Problem 5**) react with carbonyl compounds to yield lithium enolate salts and diisopropylamine, e.g., for reaction with cyclohexanone.



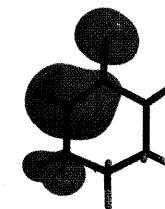
Enolate chemistry is often the chemistry of the enolate salts.

Compare the geometries of the *cyclohexanone enolate* and the *cyclohexanone lithium enolate*. Do both molecules show delocalized structures, or is the bonding in one of them more localized? For comparison, examine the geometries of *1-hydroxycyclohexene* and *cyclohexanone*.

Compare atomic charges for the enolate anion and the lithium salt. Are there major differences, in particular, for the oxygen and the α carbon? Also compare the highest-occupied molecular orbital (HOMO) in the two molecules. This identifies the most nucleophilic sites, that is, the most likely sites for attack by electrophiles. Are the two orbitals similar or do they differ substantially? Elaborate.

Do changes in geometries, charges and size and shape of the HOMO between the enolate anion and its lithium salt suggest differences in reactivities? If so, what differences are to be expected?

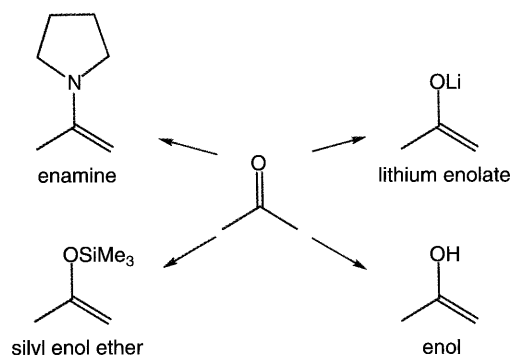
Compare energies of the two *enolates* which may result from deprotonation of *methylcyclohexanone*. Which is preferred and by how much? Next, compare energies of the corresponding *methylcyclohexanone lithium enolates*. Does the preference or the magnitude change?



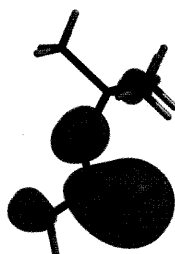
HOMO of cyclohexanone enolate reveals most nucleophilic sites.

Enolates, Enols and Enamines

Ketones and aldehydes can be converted into a number of nucleophilic molecules with similar reactivity patterns.



Electrostatic potential map for enamine shows negatively-charged regions (in red) and positively-charged regions (in blue).



HOMO of silyl enol ether reveals most nucleophilic sites.

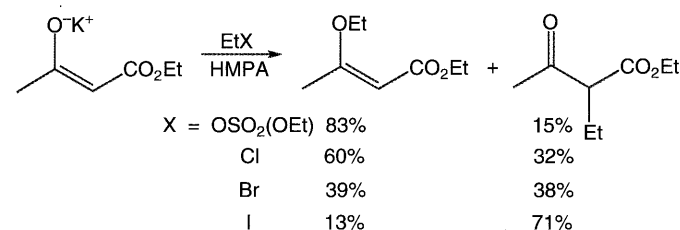
Examine the electrostatic potential map of each nucleophile (*enamine*, *silyl enol ether*, *lithium enolate* and *enol*) with emphasis on the face of the nucleophilic “alkene” carbon. Rank the nucleophiles from most electron rich to least electron rich. What factors are responsible for this order? (Hint: For each molecule, consider an alternative Lewis structure to that given above that places a negative charge on the nucleophilic carbon.)

Some electrophile-nucleophile reactions are guided more by orbital interactions than by electrostatics. The key interaction involves the donor orbital on the nucleophile, i.e., the highest-occupied molecular orbital (HOMO). Examine the HOMO of enamine, silyl enol ether, lithium enolate and enol. Which atom is most nucleophilic, i.e., which site would produce the best orbital overlap with an electrophile?

Nucleophilicity is determined by HOMO energy; the higher the energy the more reactive the nucleophile. HOMO energies (in au) for these nucleophiles are -0.275 (enamine), -0.266 (lithium enolate), -0.337 (silyl enol ether), and -0.339 (enol). Rank the nucleophiles from most reactive to least reactive. How does this ranking compare to that based on electrostatic potential?

Enolates are Ambident Nucleophiles

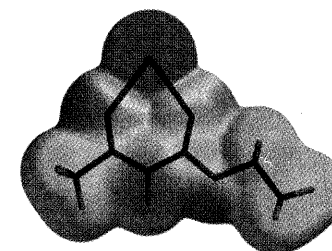
Enolates can act either as carbon or as oxygen nucleophiles. The product depends on the electrophile, e.g.



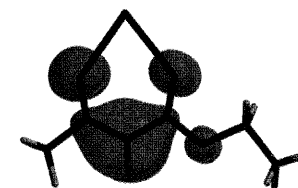
Is the *C product* or *O product* more stable? Can the experimental results be explained by thermodynamics?

Electrostatic interactions can guide alkylation under certain conditions. Examine the electrostatic potential map of the *potassium enolate* of *ethyl acetoacetate*. Is carbon or oxygen more electron rich? Are electrostatic interactions likely to favor addition of oxygen or carbon? Examine atomic charges and electrostatic potential maps for *diethylsulfate*, *ethyl chloride*, *ethyl bromide* and *ethyl iodide*; pay attention to the backside of the electrophilic carbon. Order the systems from most to least electron poor. Which reaction is most likely to be guided by electrostatics? Least likely? Can the experimental results be fully explained on this basis?

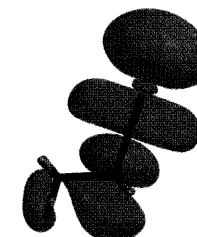
Where electrostatic interactions are relatively weak, orbital interactions can guide alkylation instead. Examine the highest-occupied molecular orbital (HOMO) of the potassium enolate of ethyl acetoacetate. Which site would act as a nucleophile in an orbital-controlled reaction? Examine the lowest-unoccupied molecular orbital (LUMO) in diethylsulfate, ethyl chloride, ethyl bromide and ethyl iodide. Is good nucleophile-electrophile “backside” overlap possible in each? The corresponding LUMO energies are 0.250, 0.198, 0.178, 0.118 au, respectively. Assuming that the lower the LUMO energy the more effective the interaction, are orbital interactions able to explain the observed products?



Electrostatic potential map of the potassium enolate of ethyl acetoacetate shows negatively-charged regions (in red) and positively-charged regions (in blue).



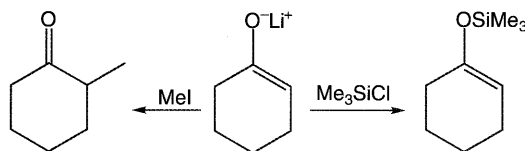
HOMO of the potassium enolate of ethyl acetoacetate is the electron-acceptor orbital and reveals most nucleophilic sites.



LUMO of ethyl iodide is the electron-acceptor orbital and reveals likely site of nucleophilic attack.

Silylation of Enolates

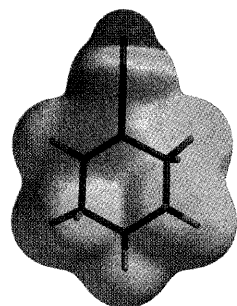
Enolate reactivity depends on the electrophile. Enolates generally form CC bonds with carbon electrophiles, and OSi bonds with silicon electrophiles.



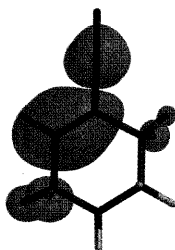
Obtain the energies of the products resulting from methylation of cyclohexanone enolate; the “**CC product**” (shown above) and the “**OC product**”. Does methylation give the more stable product? Repeat this analysis for the **CSi** and **OSi** silylation **products**.

Electrostatic and orbital interactions may steer reaction toward either carbon or oxygen. First, examine the electrostatic potential map for **cyclohexanone lithium enolate**. Which atom is more negatively charged, carbon or oxygen? Is the difference significant? If it is, what would be the favored mode of addition? Does either methylation or silylation appear to be guided by electrostatics? Explain.

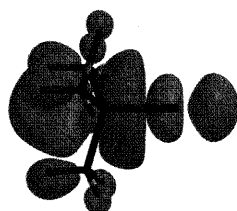
Now, examine the orbital on cyclohexanone lithium enolate most able to donate electrons. This is the highest-occupied molecular orbital (HOMO). Identify where the best HOMO-electrophile overlap can occur. Is this also the most electron-rich site? An electrophile will choose the “best HOMO overlap” site if it is not strongly affected by electrostatic effects, and if it contains a good “electron-acceptor” orbital (this is the lowest-unoccupied molecular orbital or LUMO). Examine the LUMO of **methyl iodide** and **trimethylsilyl chloride**. Is “backside overlap” likely to be successful for each? The LUMO energies of methyl iodide and trimethylsilyl chloride are 0.11 and 0.21 au, respectively. Assuming that the lower the LUMO energy the more effective the interaction, which reaction, methylation or silylation, appears to be guided by favorable orbital interactions? Explain.



Electrostatic potential map for cyclohexanone lithium enolate shows negatively-charged regions (in red) and positively-charged regions (in blue).



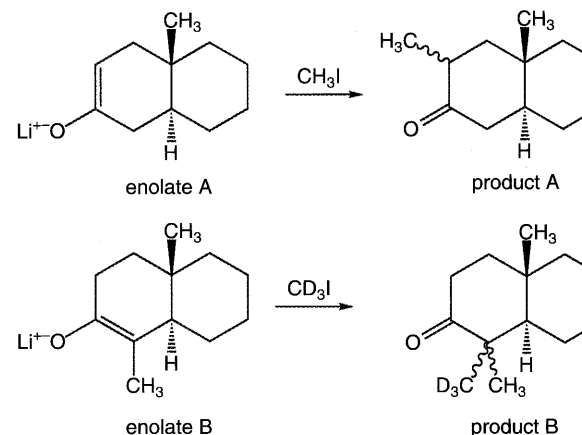
HOMO of cyclohexanone lithium enolate reveals the most nucleophilic sites.



LUMO of trimethylsilylchloride reveals likely site of nucleophilic attack.

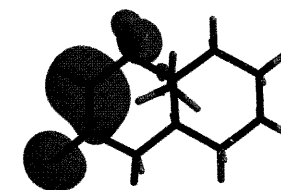
Stereochemistry of Enolate Alkylation

Enolates react with alkyl halides to form a new CC bond. A mixture of stereoisomers may result. For example, each of the reactions shown below gives two products, with the major product constituting > 90% of the mixture.

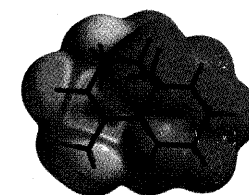


Is **product A1** or **product A2** (resulting from the top reaction) lower in energy? Why? Can product stability explain why the lower reaction is selective? Explain.

CH_3I should approach the enolate from the direction that simultaneously allows its optimum overlap with the “electron-donor” orbital on the enolate (this is the highest-occupied molecular orbital or HOMO), and minimizes its steric repulsion with the enolate. Examine the HOMO of **enolate A**. Is it more heavily concentrated on the same side of the six-membered ring as the bridgehead methyl group, on the opposite side, or is it equally concentrated on the two sides? A map of the HOMO on the electron density surface (a “HOMO map”) provides a clearer indication, as this also provides a measure of steric requirements. Identify the direction of attack that maximizes orbital overlap and minimizes steric repulsion, and predict the major product of each reaction. Do your predictions agree with the “thermodynamic” preferences? Repeat your analysis for **enolate B**, leading to **product B1** and **product B2**.



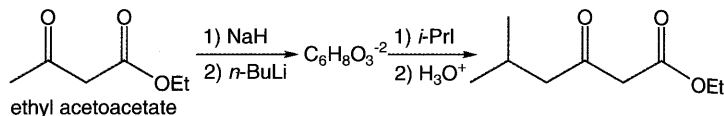
HOMO of enolate A reveals the most nucleophilic sites.



HOMO map for enolate B reveals preferred stereochemistry of electrophilic attack.

Enolate Dianions

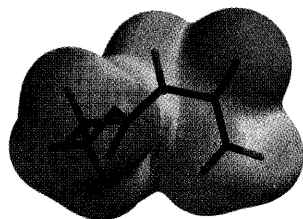
Treatment of 1,3-dicarbonyl compounds with two equivalents of strong base can give a dianion that will react selectively with alkyl halides. For example, ethyl acetoacetate reacts first with NaH to form an enolate, and then with *n*-BuLi to form a dianion. This then adds *i*-PrI.



Which of the two enolates (*enolate A* or *enolate B*) is lower in energy? Rationalize your observation by comparing their structures, charge distributions and electrostatic potential maps. Draw all of the resonance contributors needed to describe each enolate. Which enolate is generated by reaction with NaH?

Next, examine the dianion resulting from double deprotonation of ethyl acetoacetate. Draw all the resonance contributors needed to describe this ion. Next, examine the geometry, atomic charges and electrostatic potential map for *dianion*. Are you able to decide which resonance contributors are important and which are not?

The nucleophilic behavior of polyanions can be anticipated by examining the shape of “electron donor” orbitals (typically the highest-occupied molecular orbital or HOMO). Examine the HOMO of the dianion. Which part of this orbital is best able to overlap with an electrophile?



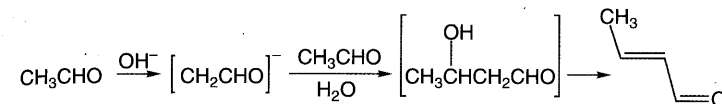
Electrostatic potential map for enolate A shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).



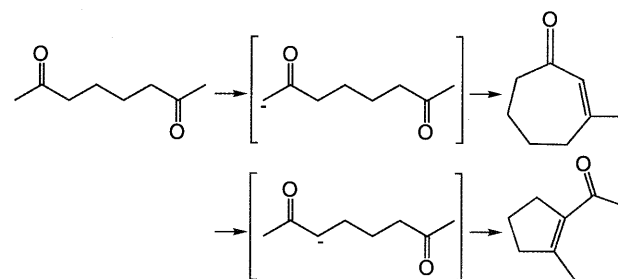
HOMO of dianion reveals the most nucleophilic sites.

Aldol Condensation

Aldehydes and ketones are deprotonated by strong bases to give enolates. These can then react with a second aldehyde or ketone, which can then eliminate water, e.g.



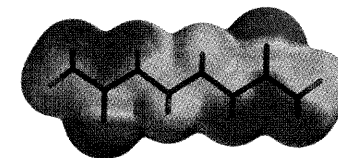
For unsymmetrical ketones, two condensation products are possible. For example, intramolecular condensation of 2,7-octadione may lead to products which follow from the two possible enolates.



Examine atomic charges and display the electrostatic potential map for **2,7-octadione**. Are you able to say which hydrogens (at C₁ or at C₃) are more likely to be abstracted by base, and conclude which is the kinetically-favored enolate? Which enolate (**2,7-octadione**, **C1 enolate** or **C3 enolate**) is the lower in energy? What do you conclude is the thermodynamically-favored enolate? Is this also the enolate in which the negative charge is better delocalized? Compare electrostatic potential maps to tell.

Finally, examine the transition states for *closure* of the C₁ enolate to the **7-membered ring** product, and of the C₃ enolate to the **5-membered ring** product. Calculate activation energy barriers from their respective enolates. Which ring closure (to the five or the seven-membered ring) occurs more readily?

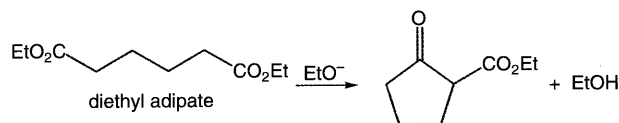
Overall, what do you conclude is the dominant condensation product of 2,7-octadione?



Electrostatic potential map for 2,7-octadione shows positively charged regions (in blue) as likely acidic sites.

Dieckmann Condensation

The Dieckmann condensation of diethyl adipate yields a keto-ester product.

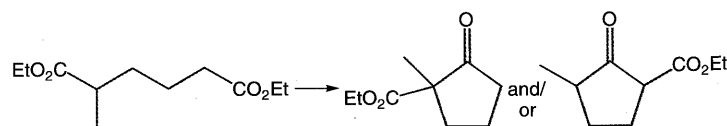


Write a detailed mechanism for this condensation using only the molecules whose models are provided. Treat all proton transfers, nucleophilic additions, and elimination reactions as separate steps, and use curved arrows to show electron movement. Which of these steps do you think will be favorable? Unfavorable? Why?

Next, calculate the energy for each step in your mechanism. Were your predictions correct? Is the Dieckmann condensation a thermodynamically favorable process overall?

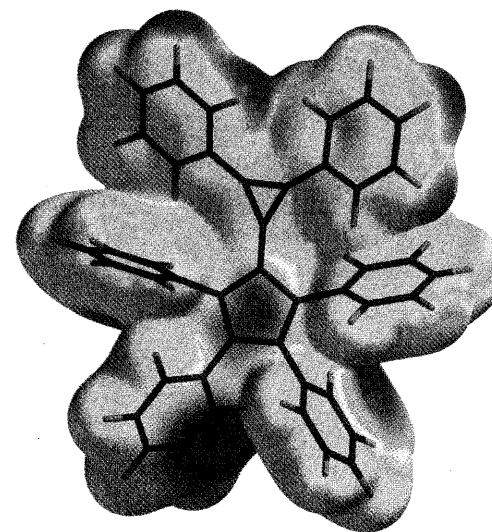
Chemists have established that a Dieckmann condensation will not succeed unless the final keto-ester product is deprotonated by a base. In our example, this would be a reaction between EtO^- and the keto-ester (it is necessary, therefore, to use excess EtO^-). What reaction products are generated by this proton transfer? Obtain the energies of the reactants and products, and calculate the energy for this final proton transfer. Is this reaction thermodynamically favorable or unfavorable? Does this step make the overall condensation reaction favorable or unfavorable?

Since the final proton transfer is essential for a successful condensation, it is important to understand what factors drive the proton transfer. Examine the electrostatic potential map of the carbanion, and draw all of the resonance contributors that are needed to describe this ion. How does this ion differ from the others? Which product, if either, would be expected from the following condensation? Explain.



Conjugated Polyenes and Aromaticity

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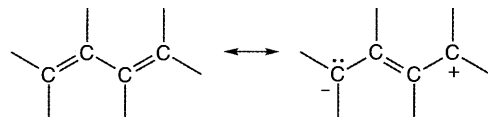


electrostatic potential map for hexaphenylthiafulvene shows extent of charge separation (see problem 8)

Electrostatic potential map for the enolate initially formed in the Dieckmann condensation of diethyl adipate shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

Conjugated Polyenes

Molecules with alternating single and double bonds (“conjugated polyenes”) often exhibit unusual physical and chemical properties. Chemists have postulated the involvement of “zwitterionic” resonance structures to account for these properties.

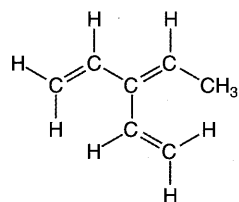


Consider 1,3-pentadiene and 1,4-pentadiene. Which, if either, would benefit from the type of resonance described above? Draw appropriate resonance contributors for this isomer. Indicate the likely importance of different zwitterionic structures which you might draw. Compare the energies of **1,3-pentadiene** and **1,4-pentadiene**. Which one is more stable?

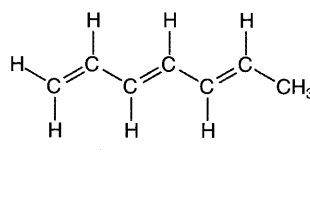
Compare carbon-carbon bond distances in each diene. Which bond distances are unusually long or short? Use **propene** as a model of a molecule with “normal” CC single and double bonds. Can resonance account for all of the unusual bond distances? Is this the only explanation?

Compare electrostatic potential maps for the two dienes. Does the more stable isomer show greater delocalization of negative charge?

Obtain the energies, carbon-carbon bond distances and electrostatic potential maps for **3-ethylidene-1,3-pentadiene** and **1,3,5-heptatriene**. Which data are consistent with the usual resonance argument and which are not?



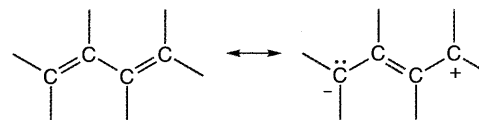
3-ethylidene-1,3-pentadiene



1,3,5-heptatriene

Resonance Control of Conformation

The following type of resonance requires π -type orbital overlap between the central carbons. This overlap can only be achieved if all four carbons and their substituents lie in the same plane.



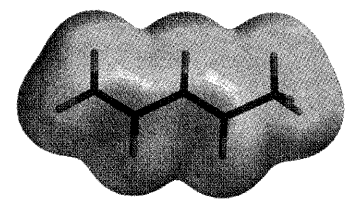
Plot the energy of **E-1,3-pentadiene** (vertical axis) vs. $\text{C}_1\text{C}_2\text{C}_3\text{C}_4$ torsion angle (horizontal axis). How many minima are there? Do they correspond to structures that offer maximum π -type orbital overlap? How can you account for differences in their energies?

What is the maximum energy structure? Does it correspond to a structure that prevents π -type orbital overlap? What is the barrier to rotation about the C_2-C_3 single bond?

Repeat this analysis for **Z-1,3-pentadiene**.

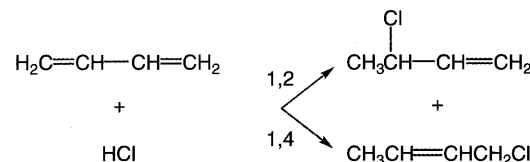
Which isomer, E or Z, has stronger conformational preferences? Are these preferences due to resonance effects or might other factors be at work? Explain.

Electrostatic potential map for 1,3-pentadiene shows negatively-charged regions (in red) and positively-charged regions (in blue).



1,2 vs. 1,4 Addition

HCl adds to conjugated dienes in the same way that it adds to simple alkenes. However, dienes often yield a mixture of 1,2 and 1,4-addition products, e.g.



HCl addition to unsymmetrical dienes can be even more complicated. For example, HCl addition to isoprene (2-methyl-1,3-butadiene) might give four different 1,2-addition products and three different 1,4-addition products.

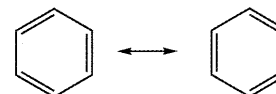
Obtain the energies of the possible products that might result from HCl addition to isoprene (*isoprene*+HCl), and rank them from most to least stable. Which product(s) would form if the reaction were controlled by thermodynamics, i.e., product energy?

HCl addition usually proceeds through a carbocation intermediate, with the dominant product resulting from the most stable cation. Compare energies for the possible cations that can be obtained from isoprene (*isoprene*+H⁺). Rank them from most to least stable. Examine the geometries of the cations, and sketch one or more Lewis structures for each which are consistent with its geometry. Be sure to point out any unusual features. What factors might be responsible for the ordering of cation stability?

Assuming selective formation of the most stable carbocation, which product(s) would be obtained from HCl addition to isoprene? Would this outcome be different from the one predicted on the basis of thermodynamic control?

Benzene or 1,3,5-Cyclohexatriene? Interpretation of Resonance Structures

Chemists traditionally represent benzene in terms of a pair of equivalent resonance structures, each with alternating single and double bonds.



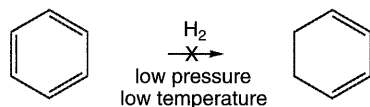
Does this mean that benzene is in fact an equilibrium mixture of two 1,3,5-cyclohexatriene molecules? Or, does this mean that benzene is a single molecule with some intermediate type of bonding?

Cyclohexatriene to benzene displays a sequence of structures from 1,3,5-cyclohexatriene (with CC single and double bonds initially set to 1.5 and 1.3 Å, respectively) to benzene (with all CC bonds set to 1.4 Å) and back to cyclohexatriene. Plot energy (vertical axis) vs. CC bond length (horizontal axis). How many energy minima are there? Do the minima look more like 1,3,5-cyclohexatriene or benzene? What is the correct interpretation of the resonance picture?

Repeat the analysis with *1,2-dichlorocyclohexatriene to 1,2-dichlorobenzene*. Are there one or two energy minima? If two, which is more stable, the structure with the “short” C₁C₂ bond or the “long” C₁C₂ bond? Explain.

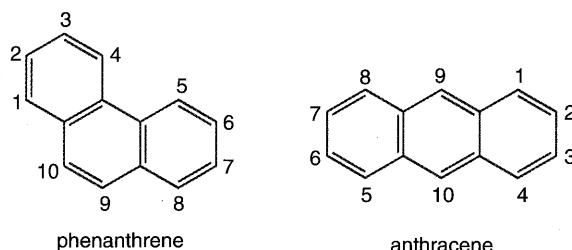
Addition Reactions involving Aromatic Rings

Benzene rings do not readily undergo electrophilic addition reactions, presumably because the loss of resonance makes these reactions unfavorable.



Polycyclic aromatic hydrocarbons, however, might undergo selective addition reactions if the change in resonance energy is small.

Consider addition of H_2 to benzene, phenanthrene, and anthracene.



Obtain energies for *benzene*, *phenanthrene*, *anthracene*, as well as for a number of their dihydro derivatives (*dihydrobenzene*, *dihydrophenanthrene*, *dihydroanthracene*). Consider a hypothetical hydrogenation reaction that would yield each dihydro derivative (always start with one of the three aromatic hydrocarbons), and calculate the energy for this reaction. (The energy for H_2 is provided at left.) Which ring system can undergo an addition reaction most easily? Which ring system would be least likely to undergo an addition reaction? Which hydrogenation reaction of phenanthrene and anthracene is most exothermic (least endothermic)? What, if anything, does this tell you about the aromatic stabilization associated with fused systems relative to that associated with a collection of isolated phenyl rings?

Does Resonance Always Stabilize a Molecule?

Delocalized π systems must be planar, or nearly so, for resonance stabilization to be most effective. Imposing planarity, however, may cause ring strain.

Examine the geometry of *planar corannulene*. Are all of its six-membered rings the same? If so, draw a Lewis structure which best represents the molecule. If not, draw one or more Lewis structures as appropriate.

According to your Lewis structure(s) and to the actual geometry of the molecule, is the bonding in planar corannulene fully delocalized (as in *benzene*), or are some CC bonds “long” and some “short”? Do your results support the notion that planar corannulene is resonance stabilized? Explain.

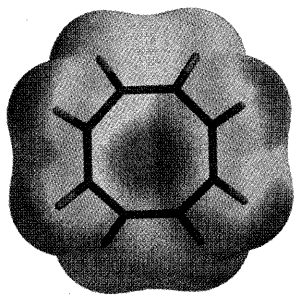
Now consider ring strain. Measure CCC angles involving the six-membered rings in planar corannulene. What is the average (unsigned) deviation from 120° (the bond angle in benzene)? Next, measure the corresponding bond angles in *basket corannulene*. What is the average (unsigned) deviation? Is ring strain relieved? A nonplanar structure should reduce π orbital overlap. Examine CC bond distances. Is the basket structure more or less delocalized than the planar structure? Which is more stable? What best accounts for the energy difference, a change in strain energy, a change in resonance stabilization, or both?

Buckminsterfullerene (C_{60} or “Buckyball”) is structurally related to corannulene. In which molecule would you expect π -orbital overlap be more effective? Explain. How many chemically unique carbons are there in C_{60} ? Measure CC bond distances. How many unique distances are there? Is each “benzene” fully delocalized or is one resonance contributor more important than the other?

Hückel's Rule. Cyclooctatetraene

Hückel's rule states that planar cyclic π systems involving $4n+2$ electrons will be unusually stable ("aromatic"), while cyclic π systems with $4n$ electrons will be unstable ("antiaromatic").

Energy minima have all real frequencies, while molecules with one or more imaginary frequencies are not minima.



Electrostatic potential map for tub cyclooctatetraene shows negatively-charged regions (in red) and positively-charged regions (in blue).

$$E(\text{H}_2) = -1.1230 \text{ au}$$

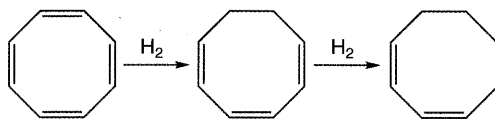
Hydrogenation of benzene to 1,3-cyclohexadiene is endothermic by .001 au (6 kcal/mol), while hydrogenation of 1,3-cyclohexadiene to cyclohexene is exothermic by .041 au (26 kcal/mol). The difference .051 au (32 kcal/mol) is one measure of the aromaticity of benzene.

Hückel's rule tells us that cyclooctatetraene (C_8H_8) should be quite unlike benzene (C_6H_6).

Compare energies of *planar* and *tub cyclooctatetraene*. Which is lower? Is the higher-energy form an energy minimum? (Examine its vibrational frequencies). Are all carbon-carbon bonds in the lower-energy form of cyclooctatetraene the same length? If so, are they the same length as those in *benzene*? If not, do they alternate between "normal" carbon-carbon single bonds and double bonds?

Display the electrostatic potential map for the lower-energy form of cyclooctatetraene. Where is the highest concentration of negative charge?

Is cyclooctatetraene aromatic? To tell, compare the first and second hydrogenation energies, leading to *1,3,5-cyclooctatriene* and then to *1,3-cyclooctadiene*. (The energy for hydrogen is provided at left.)



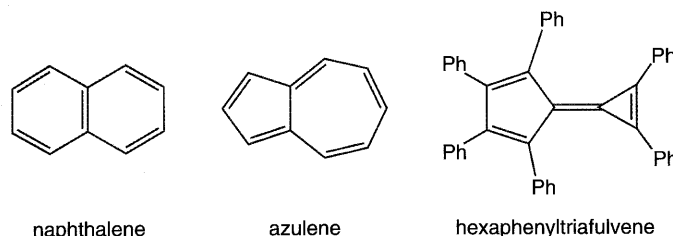
Whereas the initial hydrogenation both breaks a π bond and destroys any "aromatic stabilization", the second hydrogenation only breaks a π bond. The difference between the two then corresponds to any aromatic stabilization. Is this difference large as in benzene (see discussion at left) or is it negligible? Is cyclooctatetraene aromatic?

Examine the geometry of *cyclooctatetraene dianion*. Is it planar? If not, describe its shape. Are all the carbon-carbon bond lengths the same? If so, are they the same length as those in benzene? If not, do they alternate between single and double bonds? Do your observations suggest that cyclooctatetraene dianion is aromatic? Is this in accord with Hückel's rule?

Polar Hydrocarbons

Neutral hydrocarbons are generally nonpolar molecules. This is to be expected since carbon-carbon and carbon-hydrogen bonds are relatively nonpolar. Resonance effects can alter this picture, however, by redistributing electrons in novel ways.

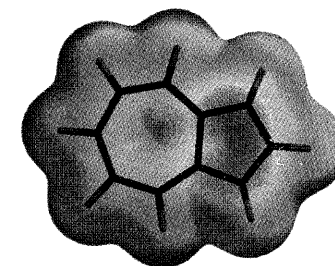
Examine electrostatic potential maps for *naphthalene*, *azulene* and *hexaphenyltriafulvene*.



Identify the most negatively-charged and most positively-charged regions in each molecule. (Ignore the phenyl rings attached to triafulvene.) The dipole moments of these molecules have been measured as 6.3, 0 and 0.8 debyes. Which molecule is responsible for which dipole moment? Explain the trend in dipole moments.

Each molecule above contains two conjugated rings (again ignore the phenyl rings in the triafulvene derivative). According to Hückel's rule, how many π electrons must each ring have in order for it to be aromatic? Which molecules must transfer π electrons from one ring to the other in order to become aromatic? Draw resonance contributors that show this electron transfer.

Some derivatives of triafulvene undergo rotation about the carbon-carbon double bond even at room temperature. Given that *cis-trans* isomerization about double bonds is normally very difficult (see **Chapter 7, Problem 1**), how would you rationalize this? Examine the electrostatic potential map for *perpendicular hexaphenyltriafulvene* (the rotational transition state). Would polar solvents tend to lower or raise the rotation barrier? Explain.

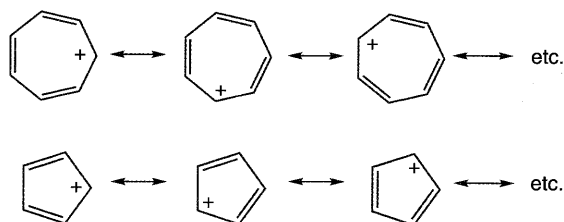


Electrostatic potential map for azulene shows negatively-charged regions (in red) and positively-charged regions (in blue).

Does Resonance Always Stabilize a Cation?

Delocalized cations, represented by two or more resonance contributors, are usually more stable than localized cations. However, the fact that several resonance contributors can be drawn for a molecule does not guarantee that the molecule will actually be resonance stabilized (see also **Chapter 12, Problem 10**).

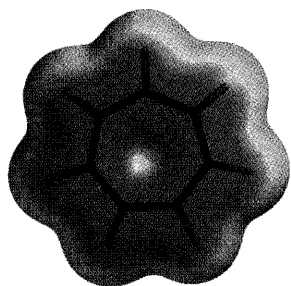
Consider tropylium ($C_7H_7^+$) and cyclopentadienyl ($C_5H_5^+$) cations, both of which are usually drawn to suggest that they are resonance stabilized and that the positive charge is delocalized.



Examine the geometries of *tropylium* and *cyclopentadienyl cations*. Are all of the carbon-carbon bond distances equal in each ion, or do long and short bonds alternate? If the latter, are the CC distances like those of a typical single bond ($\sim 1.54 \text{ \AA}$), a double bond ($\sim 1.32 \text{ \AA}$), or a partial double bond ($\sim 1.4 \text{ \AA}$) like that found in benzene? Examine electrostatic potential maps of the two ions. Do the maps show a symmetric distribution of the positive charge, or do they display alternating regions of high and low charge?

Based on these results, which ion, if either, appears to be resonance stabilized? How does Hückel's rule describe these ions?

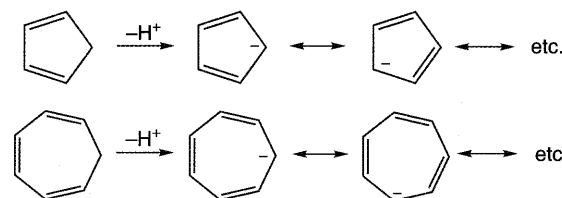
One compound, either 7-bromo-1,3,5-cycloheptatriene or 5-bromo-1,3-cyclopentadiene, dissociates into ions when dissolved in water. Which molecule do you think displays this behavior? How do you think the other molecule behaves when mixed with water?



Electrostatic potential map for tropylium cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Does Resonance Always Stabilize an Anion?

The pK_a of 1,3-cyclopentadiene is 15, making it more acidic than water, as well as more acidic than almost any other hydrocarbon. This unusual acidity is presumably due to resonance stabilization of the conjugate base, which can be drawn as a hybrid of five resonance contributors.



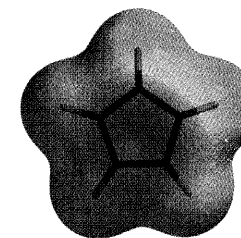
1,3,5-Cycloheptatriene might be expected to be even more acidic, since seven resonance contributors can be drawn for its conjugate base. However, the fact that several resonance contributors can be drawn for a molecule does not necessarily guarantee that it will actually be resonance stabilized (see also **Chapter 12, Problem 9**).

Examine the geometries of *cyclopentadienyl* and *cycloheptatrienyl anions*. Are the CC bond distances in each ion all equal, or do long and short bonds alternate? If the latter, are the CC distances like those of a typical single bond ($\sim 1.54 \text{ \AA}$), a double bond ($\sim 1.32 \text{ \AA}$), or a partial double bond ($\sim 1.4 \text{ \AA}$) like that in benzene? Examine atomic charges and electrostatic potential maps of the two ions. Do they show a symmetric distribution of negative charge, or do they display alternating regions of high and low charge? Based on these results, which ion, if either, appears to be resonance stabilized? How does Hückel's rule help explain the effect (or lack of effect) of resonance?

Calculate the energy for the following reaction:

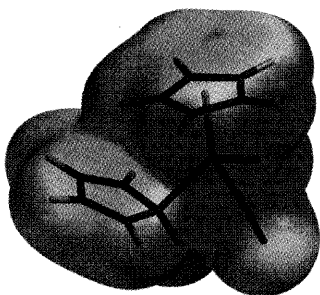


(Energies for *cyclopentadiene* and *cycloheptatriene* are available.) Is the reaction energy consistent with the other data? Explain.



Electrostatic potential map for cyclopentadienyl anion shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

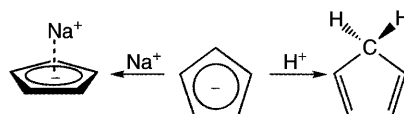
Metal-Bonded Cyclopentadienyl Anions



Electrostatic potential map for $\text{Cp}_2\text{Fe}(\text{CO})_2$ shows negatively-charged regions (in red) and positively-charged regions (in blue).

The CC bond distances in cyclopentadienyl anion, C_5H_5^- , are all equal, because the anion is aromatic (see **Chapter 12, Problem 10**). Electrophiles that interact electrostatically with the anion, such as Na^+ , interact equally with all five carbons, and do not disturb the anion's aromatic character. On the other hand, electrophiles that make covalent bonds, such as H^+ , might interact more strongly with one particular carbon and destroy the aromaticity of the ring.

Describe the similarities and differences in geometries, charge distributions and electrostatic potential maps for *cyclopentadienyl sodium*, *cyclopentadiene* and *cyclopentadienyl anion*.

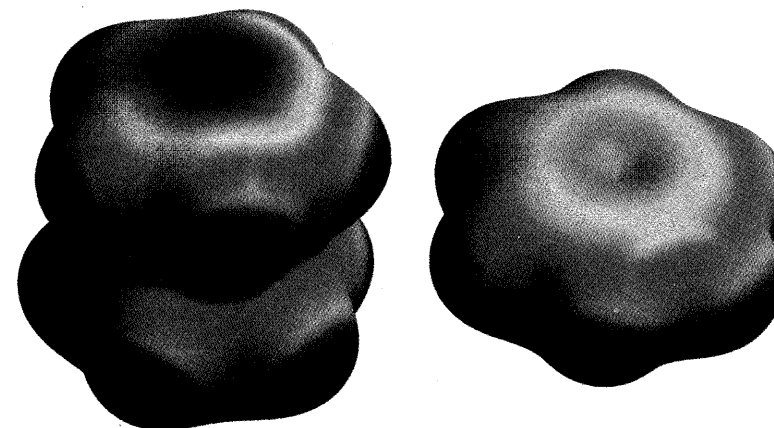


Next, consider how Fe^{2+} interacts with C_5H_5^- . Examine the geometry of *ferrocene*, $\text{Fe}(\text{C}_5\text{H}_5)_2$. Are the FeC distances all the same, or does iron bond more strongly to some carbons than to others? Are the CC bond distances all the same? Which of the above models, the electrostatic or covalent, gives the better description?

Finally, examine the geometry of *Cp_2FeCO_2* . Repeat the above analysis, and also compare FeC distances to those in ferrocene. Draw the molecule and indicate on the drawing what kind of interaction (electrostatic, covalent, or no bond) describes each FeC interaction. One normally associates shorter distances with covalent bonds because these require orbital overlap. Compare any "covalent" FeC distances with any "electrostatic" FeC distances. Are there significant differences between the two? Examine atomic charges and the electrostatic potential map of this molecule. Is the "anionic" ring more negatively charged? Based on these results, is it reasonable to view any of the FeC bonds as mainly electrostatic?

Electrophilic and Nucleophilic Aromatic Substitution

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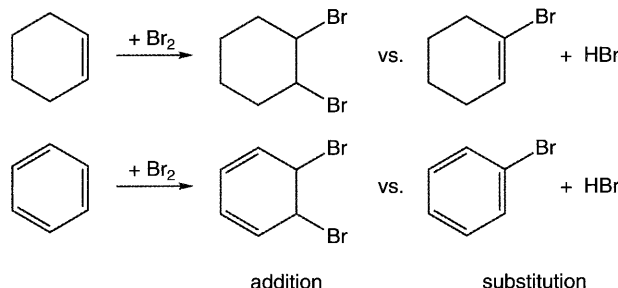
electrostatic potential maps show that ferrocene (left) is even more susceptible to electrophilic attack than benzene (right) (see problem 9)

Addition vs. Substitution

Unsaturated hydrocarbons undergo a variety of reactions. Experimentally, alkenes and alkynes undergo addition reactions, whereas aromatic molecules, such as benzene, undergo substitution reactions instead. Why?

$$E(\text{Br}_2) = -5120.5302 \text{ au}$$

$$E(\text{HBr}) = -2560.8428 \text{ au}$$



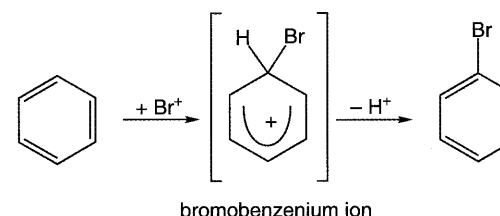
Calculate the energy of addition of bromine (energy given at left) to *cyclohexene* leading to *trans-1,2-dibromocyclohexane*. Is this reaction exothermic? Next, calculate the energy of the corresponding substitution reaction, leading to *1-bromocyclohexene* and hydrogen bromide (energy given at left). Is this reaction exothermic? Do the thermodynamics of these alternative reactions account for which pathway is followed? Explain.

Repeat this analysis for the bromine addition and substitution reactions of *benzene* leading to *trans-5,6-dibromo-1,3-cyclohexadiene* and *phenyl bromide*, respectively. Do your thermochemical results account for the experimental observations?

What aspects, if any, of cyclohexene and benzene reaction thermodynamics are similar? Why do you suppose this is? What aspects are different? Why?

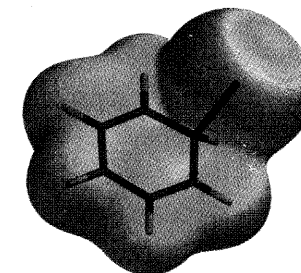
Electrophilic Bromination of Benzene

The first step in electrophilic bromination of benzene involves addition of Br⁺, leading to an intermediate bromobenzenium ion. This is then rapidly followed by loss of a proton to give bromobenzene.



Step through the sequence of structures which portray *bromination of benzene*. Plot energy (vertical axis) vs. frame number (horizontal axis). The latter may be thought of as corresponding to the “forming” CBr distance for the first stage of reaction and the “breaking” CH distance (horizontal axis) for the second stage. Is there an activation barrier to addition of Br⁺? Is there a barrier for loss of H⁺?

Does formation of bromobenzenium ion lead to disruption of the aromaticity of benzene? Is the ion highly delocalized? Examine the geometry of *bromobenzenium ion*, and measure CC bond distances. Are they all the same (as in *benzene*) or do you see alternation between “short” and “long” distances? How do they compare to bond distances in benzene, and to typical single and double bond distances (1.54 Å and 1.32 Å, respectively). Draw a Lewis structure (or series of Lewis structures) to convey what you observe. Examine atomic charges as well as the electrostatic potential map for bromobenzenium ion. Where is the positive charge? Is it localized on a single center or delocalized over several centers?



Electrostatic potential map for bromobenzenium ion shows most positively-charged regions (in blue) and less positively-charged regions (in red).



Electrostatic potential map for nitronium cation shows most positively-charged regions (in blue) as likely electrophilic sites.

CC and CO bond distances (Å)

C–C	1.54
C=C	1.32
C≡C	1.20

C–O	1.35
C=O	1.22
C≡O	1.12

Useful Electrophiles

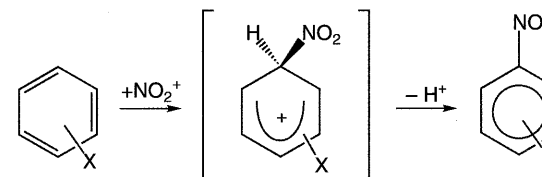
Among the most common and synthetically-useful electrophiles are nitronium and acyl cations, NO_2^+ and CH_3CO^+ , respectively. The former is the active agent in electrophilic nitration while the latter is the active reagent in Friedel-Crafts acylation.

Examine the geometry of **nitronium cation**. Is it linear or bent? Draw the ion's Lewis structure. What common neutral organic molecule is isoelectronic with NO_2^+ ? Is this molecule linear or bent? Examine the charges on the nitrogen and oxygen atoms in NO_2^+ . Is nitrogen or oxygen more positive? Does this agree with your Lewis structure? Display an electrostatic potential map for NO_2^+ . Are any additional resonance contributors needed to account for the map results? What atom (nitrogen or oxygen) would you expect to add to an arene in electrophilic nitration?

Examine charges and the electrostatic potential map for **acyl cation**. Which atom is the most positively charged? Draw the Lewis structure for acyl cation that is most consistent with its charge distribution. Is the calculated geometry of acyl cation consistent with its Lewis structure? Hint: Compare CC and CO bond distances to “typical” single, double and triple values given at left. What common neutral organic molecule is isoelectronic with acyl cation? Is the structure of this molecule similar to CH_3CO^+ ? Which atom (carbon or oxygen) would you expect to add to an arene in electrophilic acylation?

Directing Effects on Electrophilic Nitration

Electrophilic nitration of a substituted benzene may lead to *ortho*, *meta* or *para* products, depending on the substituent. According to the Hammond Postulate, the kinetic product will be that which follows from the most stable intermediate benzenium ion, i.e.

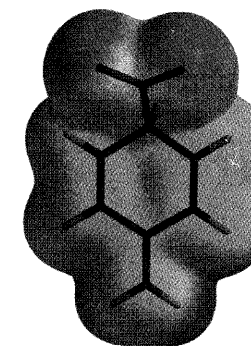


Draw a Lewis structure (or a series of Lewis structures) for nitrobenzenium ion. Where is the positive charge? Examine the electrostatic potential map for **nitrobenzenium ion**. Where would you expect electron-donor substituents to have the greatest stabilizing effect (consider *meta* and *para* positions only)? Which is the more stable, ***meta*** or ***para*-nitrotoluenium ion** (intermediates in nitration of toluene)? Compare electrostatic potential maps to that for nitrobenzenium ion. Does your result suggest that methyl acts as an electron donor?

Compare energies for ***meta*** and ***para*-nitroanilinium ions** (intermediates in nitration of aniline). Are these differentiated to a lesser or greater extent than the intermediates in toluene nitration? Examine electrostatic potential maps. What do these suggest about the relative electron-donor strengths of methyl and amino groups?

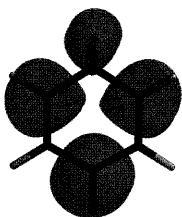
Compare energies for ***meta*** and ***para*-dinitrobenzenium ions** (intermediates in nitration of nitrobenzene). Is the ordering the same as those observed for intermediates in toluene and aniline nitration? Examine electrostatic potential maps. What does your result suggest about the electron donor/acceptor properties of the nitro substituent?

Predict the products of electrophilic nitration of toluene, aniline and nitrobenzene.



Electrostatic potential map for ***para*-nitroanilinium ion** shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Activating/Deactivating Effects on Electrophilic Aromatic Substitution

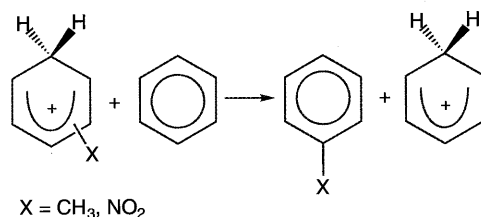


The LUMO in benzenium ion reveals where electron donor groups are likely to be most effective.

Electron-donor substituents are known to accelerate the rate of electrophilic substitution on benzene, while electron-withdrawing groups are known to retard the reaction. One explanation is that electron donors stabilize the positive charge in the benzenium ion intermediate while electron-withdrawing substituents destabilize the positive charge.

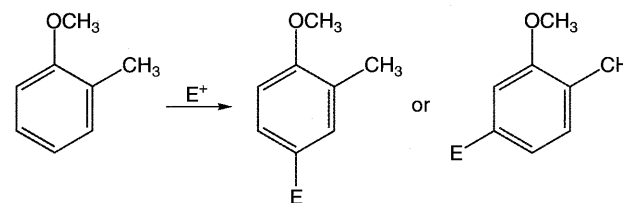
Examine the lowest-unoccupied molecular orbital (LUMO) in **benzenium ion**. On which carbon(s) is it most concentrated? Draw a Lewis structure (or series of Lewis structures) for benzenium ion, and locate the positive charge. Is it located on the same carbons where the LUMO is concentrated? Explain.

Where should electron-donor groups be placed in order to facilitate electrophilic aromatic substitution? Where should electron-withdrawing groups be placed to have the least retarding effect? (Consider only *meta* and *para* positions.) Check your predictions by calculating energetics of protonation of **toluene** and **nitrobenzene** (leading to *meta* and *para*-**methylbenzenium ions** and *meta* and *para*-**nitrobenzenium ions**, respectively), relative to the energetics of protonation of **benzene**.



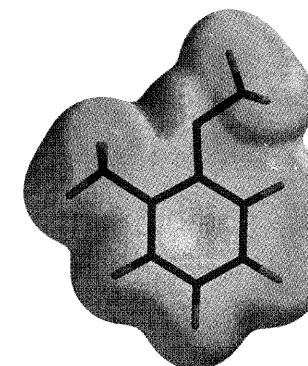
Electrophilic Aromatic Substitution in Polysubstituted Benzenes

Anticipating the products of electrophilic aromatic substitution can be more difficult when two or more substituents compete for control. For example, both methyl and methoxy groups are *ortho/para* directors, and compete for control in electrophilic substitution of 2-methylanisole. The reaction product depends on which substituent has the stronger directing influence.



Display the electrostatic potential map for **2-methyl anisole**. For which ring site, *para* to methyl or *para* to methoxy, is the electrostatic potential more negative? Where do you expect electrophilic attack to occur? Is your result consistent with the relative stabilities of intermediate benzenium ions formed upon addition of the electrophile? Compare energies for **3-methyl-4-methoxybenzenium ion** and **4-methyl-3-methoxybenzenium ion**.

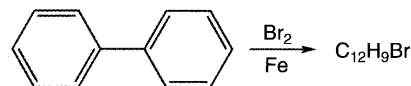
2,4,6-Trinitrotoluene (TNT) is made by nitration of toluene. Display electrostatic potential maps for **toluene**, **4-nitrotoluene** (the first nitration product) and **2,4-dinitrotoluene** (the second nitration product). Are the second and third nitration steps likely to be easier or more difficult than the initial nitration of toluene? Explain.



Electrostatic potential map for 2-methylanisole shows negatively-charged regions (in red) as the likely sites of electrophilic attack.

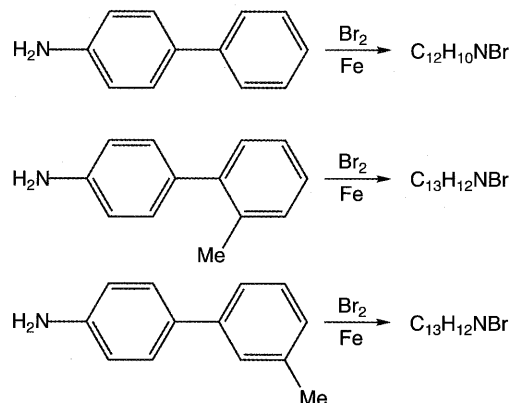
Electrophilic Aromatic Substitution in Biphenyls

Biphenyl undergoes bromination in the same manner as benzene. Unlike benzene, however, a variety of products can be imagined.



Obtain the energy of each cation that might be generated by electrophilic addition of “Br⁺” to biphenyl (**biphenyl+Br⁺**). Which one is most stable? Are there others of comparable stability? Examine the structure of the most stable cation(s), and draw all of the resonance contributors needed to describe this ion(s). Predict the product(s) of biphenyl bromination. Will the reaction be highly selective, moderately selective or unselective?

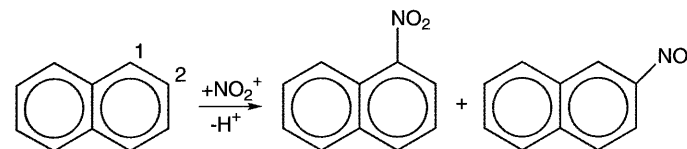
Bromination of substituted biphenyls is more complicated since bromination of each ring may lead to different products. Repeat the analysis described above for each of the following reactions.



Data on the intermediate cations are available (**4-aminobiphenyl+Br⁺**, **4-amino-2'-methylbiphenyl+Br⁺**, **4-amino-3'-methylbiphenyl+Br⁺**). Which reaction is most selective? Least selective? Why? Hint: Consider the torsion angle about the bond connecting the two phenyl rings.

Electrophilic Aromatic Substitution in Naphthalene

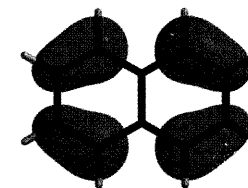
Naphthalene can undergo electrophilic substitution reactions analogous to those of benzene. Two different products can be obtained, e.g., for nitration.



Experimentally, nitration at C₁ is favored.

One way to anticipate the favored product is to consider the shape of naphthalene's best electron-donor orbital, the highest-occupied molecular orbital (HOMO). Display the HOMO in **naphthalene** and identify the sites most suitable for electrophilic attack. Which substitution product is predicted by an orbital-control mechanism? Is this the experimental result?

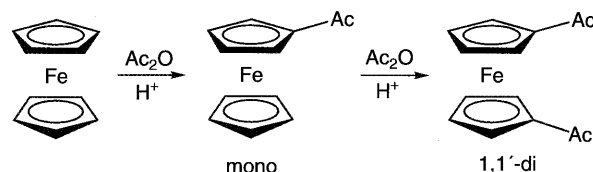
Draw Lewis structures (or a series of Lewis structures) for the intermediate ions formed by addition of NO₂⁺ to naphthalene at the 1 and 2 positions (nitronaphthalenium ions). On this basis, are you able to anticipate which intermediate is likely to be the more stable? Examine the energies of **1-nitronaphthalenium** and **2-nitronaphthalenium ions** to see which ion is actually more stable. Which substitution product should be favored? Is this the same product anticipated by inspection of naphthalene's HOMO? Is it the observed product?



The HOMO of naphthalene reveals the likely site of electrophilic attack.

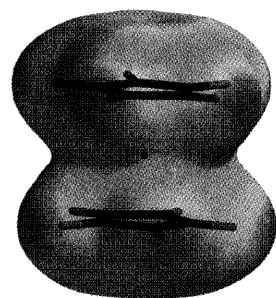
Electrophilic Aromatic Substitution in Ferrocene

The cyclopentadienyl rings in ferrocene display some of the same chemical behavior as benzene. For example, ferrocene undergoes Friedel-Crafts mono and diacylation reactions, but at different rates.



Friedel-Crafts acylation involves electrophilic attack by acyl cation (CH_3CO^+) on the ring, and the ring's electronic character should indicate its susceptibility to attack. Compare electrostatic potential maps of *ferrocene* and *acetylferrocene*. Which molecule contains the most electron-rich ring? Which acylation reaction should be faster? Does an acetyl substituent enhance or diminish ring reactivity? What should be the major product when ferrocene is combined with one equivalent of acetic anhydride?

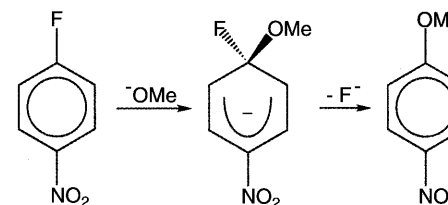
Electrophilic attack by acyl cation on ferrocene gives an electron-deficient **cation**. Compare the geometry of this cation to that of ferrocene. Which ring(s) in the adduct is best regarded as a delocalized “cyclopentadienyl anion”? Which ring(s) has a localized bond pattern? Draw a Lewis structure for this ring? Does electrophilic attack change the length (strength) of any FeC bonds? Explain.



Electrostatic potential map for ferrocene shows negatively-charged regions (in red) and positively-charged regions (in blue).

Nucleophilic Aromatic Substitution. Addition-Elimination

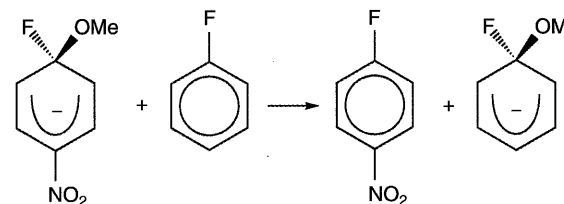
Aryl halides undergo substitution, although not through an $\text{S}_{\text{N}}2$ mechanism, but rather via a two-step “addition-elimination” mechanism. (An “elimination-addition” mechanism is also possible; see **Chapter 13, Problem 12.**)



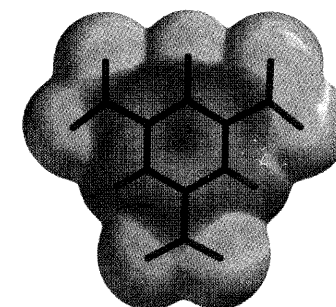
Display electrostatic potential maps for *phenyl fluoride*, *para-nitrofluorobenzene* and *2,4,6-trinitrofluorobenzene*. Which should be the most susceptible toward nucleophilic attack? Which should be the least susceptible? Explain.

Draw Lewis structures for the anion resulting from addition of methoxide to fluorobenzene. Is the negative charge highly localized or is it delocalized over several positions? Examine calculated charges for the anion. Are they in accord with those anticipated from the Lewis structures?

Is *para*-nitrofluorobenzene more or less susceptible to attack by methoxide than fluorobenzene? Calculate the energetics of the reaction. (Energies for *phenyl fluoride* and *para-nitrofluorobenzene methoxide anion adducts* are available.)



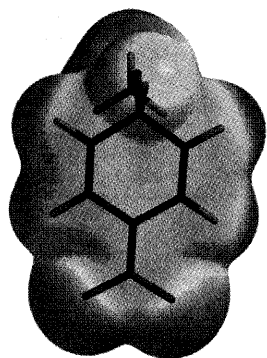
Does your result suggest that nitro is acting as an electron-donating or electron-withdrawing group? Explain.



Electrostatic potential map for *para*-nitrofluorobenzene shows positively-charged regions (in blue) as likely sites for nucleophilic attack.

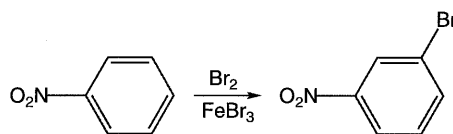
Substituent Effects on Nucleophilic Aromatic Substitution

$E(\text{CH}_3\text{O}^-) = -113.7248 \text{ au}$

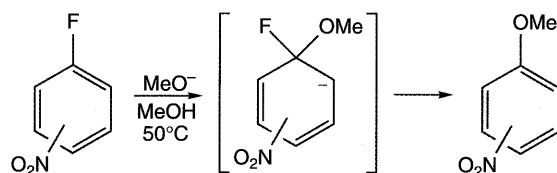


Electrostatic potential map for *para*-nitrofluorobenzene methoxide anion adduct shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

Electrophilic aromatic substitution of nitrobenzene occurs selectively at the *meta* position.



Does a nitro group have the same directing effect on nucleophilic aromatic substitution?

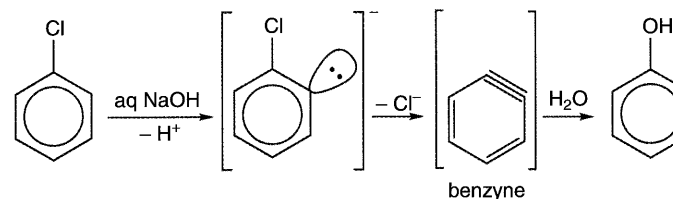


Two of three nitrofluorobenzene isomers react with methoxide, but the third is unreactive. Obtain energies of methoxide anion (at left), *ortho*, *meta* and *para*-nitrofluorobenzene, and the corresponding *ortho*, *meta* and *para*-methoxide anion adducts (so-called Meisenheimer complexes). Calculate the energy of methoxide addition to each of the three substrates. Which substrate is probably unreactive? What is the apparent directing effect of a nitro group? Does a nitro group have the same effect on nucleophilic aromatic substitution that it has on electrophilic aromatic substitution (see **Chapter 13, Problem 4**)? Examine the structures and electrostatic potential maps of the Meisenheimer complexes. Use resonance arguments to rationalize what you observe.

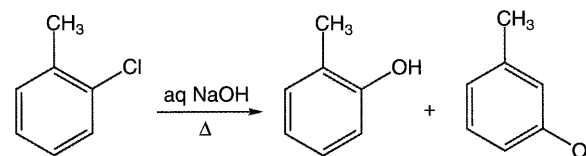
Treatment of 1,2-difluoro-3,5-dinitrobenzene with methoxide leads to a single isomer of fluorodinitroanisole. Obtain the energies of the possible *Meisenheimer complexes* and predict the structure of the product. Is this outcome consistent with the previously-established directing effect of the nitro group?

Nucleophilic Aromatic Substitution. Benzyne

In a commercially important synthesis, aqueous sodium hydroxide reacts with chlorobenzene to give phenol.

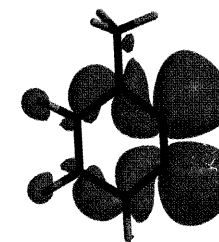


The “addition-elimination” mechanism involves two intermediates, a chlorophenyl anion and benzyne. A simple displacement mechanism can be ruled out because reaction of *ortho*-chlorotoluene gives not only *ortho*-methylphenol but also *meta*-methylphenol.



Examine the geometry of *methylbenzyne*. Measure carbon-carbon distances. Which π bonds are delocalized and which are localized? Is there really a triple bond? (Compare bond distance to triple bond in *hexa-1,5-dien-3-yne* and to partial double bonds in *benzene*). Are you able to draw a single Lewis structure which adequately represents the geometry of the molecule?

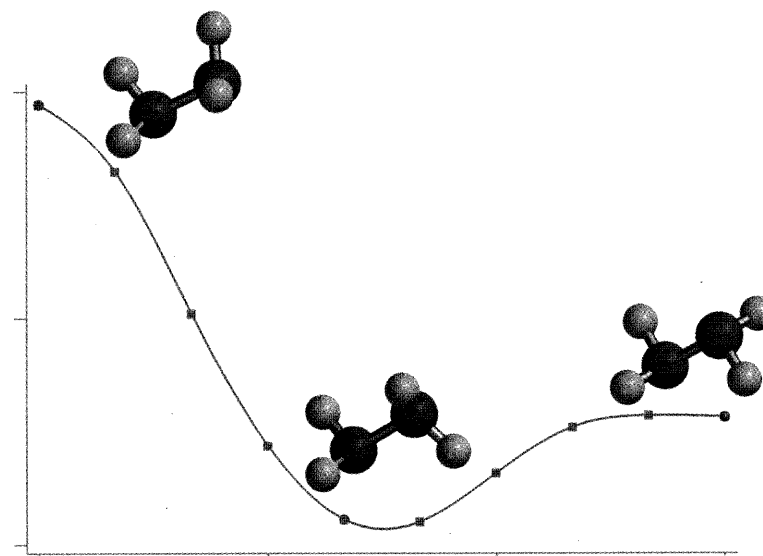
Hydration of *methylbenzyne* is believed to require nucleophilic attack by hydroxide. Examine the lowest-unoccupied molecular orbital (LUMO) of *methylbenzyne*. How many sites are there for nucleophilic attack? Does hydroxide attack in the plane of the ring, or perpendicular to the ring plane? Explain.



LUMO of methylbenzyne reveals likely site of nucleophilic attack.

Nitrogen-Containing Compounds

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conformation of hydrazine is dictated by lone pair repulsion
(see problem 2)

Pyramidal Inversion in Ammonia



HOMO of aniline provides evidence for or against π bonding between the phenyl ring and the amino group.

Different factors compete to determine the molecular geometries of amines. While the lone pair on nitrogen is better accommodated in an sp^3 hybrid than a higher-energy p orbital, conjugation with a carbonyl group in the case of amides, or with the phenyl ring in the case of arylamines, should be the most effective when the nitrogen is planar.

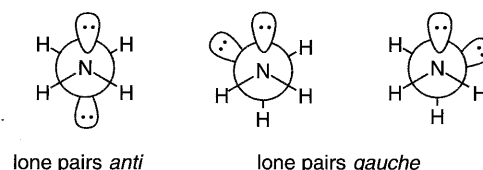
Step through the sequence of structures corresponding to **inversion of ammonia**. Plot energy (vertical axis) vs. frame number (horizontal axis). Identify the equilibrium structure. What is the preferred HNH bond angle? Identify the inversion transition state and calculate the barrier to inversion. Is it in the same range as single-bond rotation barriers (see **Chapter 5, Problems 1 and 2**), or is it significantly larger?

Repeat your analysis for the sequence of structures corresponding to **inversion of trimethylamine**. Is the inversion barrier smaller, larger or about the same as that in ammonia? If significantly different, speculate on the origin of the difference.

Examine the structure of **aniline** for evidence of conjugation. Is the CN bond length a typical single bond distance (as in **methylamine**), a typical double bond distance (as in **methyleneimine**) or somewhere in between? Is the nitrogen center planar or puckered? Does aniline incorporate a CN π bond? Examine the highest-occupied molecular orbital (HOMO). Does it suggest π bonding involving the amino group?

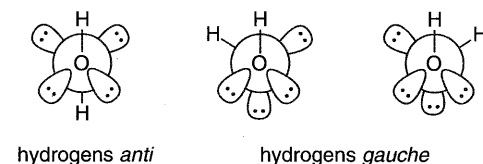
Conformations of Hydrazine and Hydrogen Peroxide

Rotation around the NN bond in hydrazine yields three “staggered” conformers, one in which the lone pairs are *anti* and the other two (equivalent structures) in which they are *gauche*.



Step through the sequence of structures corresponding to **rotation** about the NN bond **in hydrazine**. Plot energy (vertical axis) vs. HNNH dihedral angle (horizontal axis). How many energy minima are there? Do they correspond to structures in which the hydrogens stagger? What is the geometry of the lowest-energy structure? What is the energy barrier separating the minima?

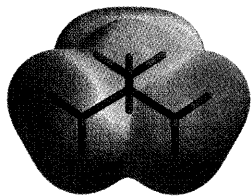
A related molecule is hydrogen peroxide. Again, it might be expected that rotation (around the oxygen-oxygen bond) would lead to three “all-staggered” conformers.



Step through the sequence of structures corresponding to **rotation** about the OO bond **in hydrogen peroxide**. Plot energy (vertical axis) vs. HOOH dihedral angle (horizontal axis). How many energy minima are there? Do they correspond to “staggered” structures? What is the geometry in the lowest-energy structure? What is the energy barrier separating the minima?

Summarize your observations on the conformations of molecules with lone pairs.

Ammonia or Trimethylamine. Which is the Stronger Base?

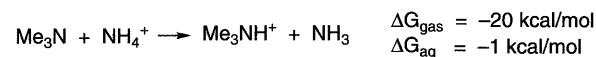


Electrostatic potential map for trimethylammonium ion shows most positively-charged regions (in blue) as likely acidic sites.

The model dealt with here is greatly oversimplified, and is only of qualitative value. It treats solvation on the ammonium ions in terms of a single layer (or shell) of solvent, and ignores solvation of neutral ammonia and trimethylamine.

$$E(\text{H}_2\text{O}) = -75.5860 \text{ au}$$

Trimethylamine is much more basic than ammonia in the gas phase, whereas in water, the two are of equal strength.



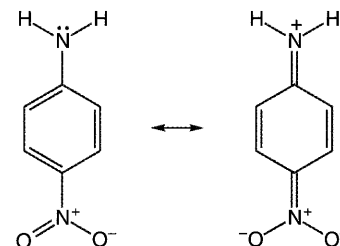
Examine atomic charges and display electrostatic potential maps for **ammonium** and **trimethylammonium ions** (protonated ammonia and trimethylamine, respectively). How many acidic hydrogens are there in each? Assuming that solvent coordinates to acidic hydrogens, how many solvation sites are there in each?

Are the acidic hydrogens in ammonium ion more or less positively charged than the corresponding hydrogen(s) in trimethylammonium ion? Would you expect solvation (on a per site basis) to be greater for ammonium or trimethylammonium ion? Calculate binding energies for **ammonium ion+water** and **trimethylammonium ion+water**, ions where a single water molecule has been attached to an acidic hydrogen. (The energy for water is given at left.) Estimate the total solvation energy in ammonium and trimethylammonium ions by multiplying this binding energy by the total number of acidic hydrogens in the two ions. Is the estimated difference in solvation energies sufficient to account for the observed reordering of base strengths from the gas to the aqueous phase?

The previous calculation assumed that the solvation energy of ammonium was equal the solvation energy of a single water molecule times the number of water binding sites. Is this a valid assumption? Compare the electrostatic potential maps of ammonium ion and ammonium ion+water. For which are the exposed hydrogens more acidic? Did the calculation underestimate or overestimate the difference in solvation energies?

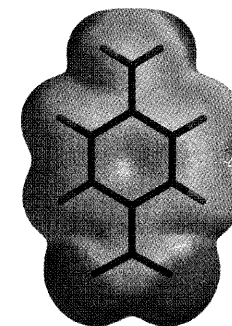
Push-Pull Resonance. The Basicity of *para*-Nitroaniline

para-Nitroaniline is a much weaker base than aniline, an observation which is usually explained by invoking so-called “push-pull” resonance contributors.



Compare the geometry of ***para*-nitroaniline** to those of both ***aniline*** and ***nitrobenzene***. Is there any evidence for push-pull resonance contributors? Is there shortening of bonds to the amino and nitro groups? Are the bonds in the ring localized? Is the dipole moment for *para*-nitroaniline smaller, larger or about the same as the sum of the dipole moments for aniline and nitrobenzene? What does your result say about the importance of push-pull resonance contributors?

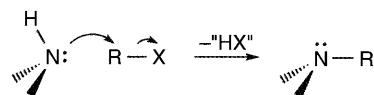
Compare electrostatic potential maps for *para*-nitroaniline and aniline. Has the NO₂ group decreased, increased or left unchanged the electrostatic potential at the amino group? What effect, if any, should this have on basicity? Also examine electrostatic potential maps for ***para*-methylaniline** and ***para*-trifluoromethylaniline**. Would you predict these to be stronger or weaker bases than aniline? Rationalize your results using changes in geometries and/or changes in dipole moments. Data for ***toluene*** and ***trifluorotoluene*** are available.



Electrostatic potential map for *para*-nitroaniline shows negatively-charged regions (in red) and positively-charged regions (in blue).

Amine Nucleophiles

Amines can be prepared by means of S_N2 reactions involving alkyl halides and nitrogen nucleophiles.

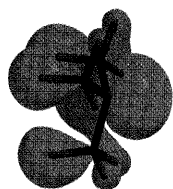


One potential problem with this procedure is that the product can sometimes act as a nitrogen nucleophile, and multiple substitutions may then occur. It is useful, therefore, to be able to distinguish the relative nucleophilicity of different amines.

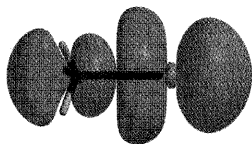
Calculate activation energies for S_N2 reactions of *ammonia* and *trimethylamine* with *methyl iodide* via transition states *ammonia+methyl iodide* and *trimethylamine+methyl iodide*, respectively. Is attack by ammonia or trimethylamine more facile? Rationalize your observation by comparing electrostatic potential maps for the two transition states. Which transition state requires more charge separation? Is this also the higher-energy transition state?

Nitrogen nucleophilicity might also be controlled by frontier-orbital interactions. Examine the highest-occupied molecular orbital (HOMO) of ammonia and trimethylamine and the lowest-unoccupied molecular orbital of methyl iodide. Do the shapes of the occupied orbitals indicate that the two amines are nitrogen nucleophiles? Explain. The HOMO energies (in au) are -0.389 (ammonia) and -0.334 (trimethylamine). Assuming that the higher (more positive) the HOMO energy the more available the electron pair for donation, which molecule should be the better nucleophile? Elaborate. Does the shape of the lowest-unoccupied molecular orbital (LUMO) in methyl iodide correctly anticipate the stereochemistry of S_N2 attack? Does it anticipate loss of iodine? Elaborate.

Electrostatic potential map for transition state for S_N2 reaction of trimethylamine and methyl iodide shows negatively-charged regions (in red) and positively-charged regions (in blue).



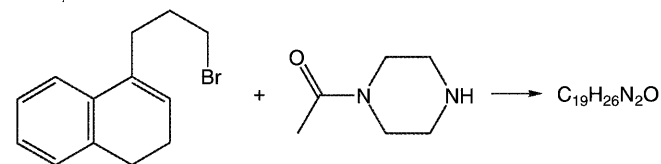
HOMO of trimethylamine reveals the nucleophilic character of the molecule.



LUMO of methyl iodide reveals the most likely site of nucleophilic attack.

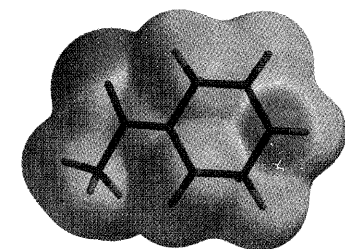
Amines or Amides. Which are Better Nucleophiles?

The following S_N2 reaction yields a single product with formula $C_{19}H_{26}N_2O$.



You should be able to identify the product by ascertaining which of the two nitrogens (amide or amine) is the more nucleophilic.

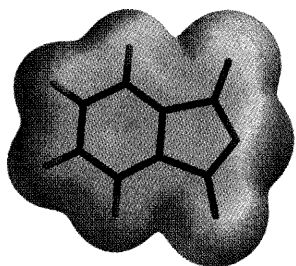
Examine the geometry, charges at the two nitrogens and electrostatic potential map of *amine-amide*. What is the geometry around each nitrogen, pyramidal or planar? If pyramidal, is the attached group (H or $C(=O)CH_3$) axial or equatorial? What does your result say about the relative “sizes” of the “substituent” (H or $C(=O)CH_3$) and the lone pair? Which nitrogen is more negatively charged? Draw a Lewis structure (or series of Lewis structures) that adequately describes the geometry and electronic character of this molecule (include all nonbonding electrons and formal charges). Assuming that the more electron-rich nitrogen acts as the nucleophile, what is the product of the reaction? Do you conclude that amides or amines are better nucleophiles?



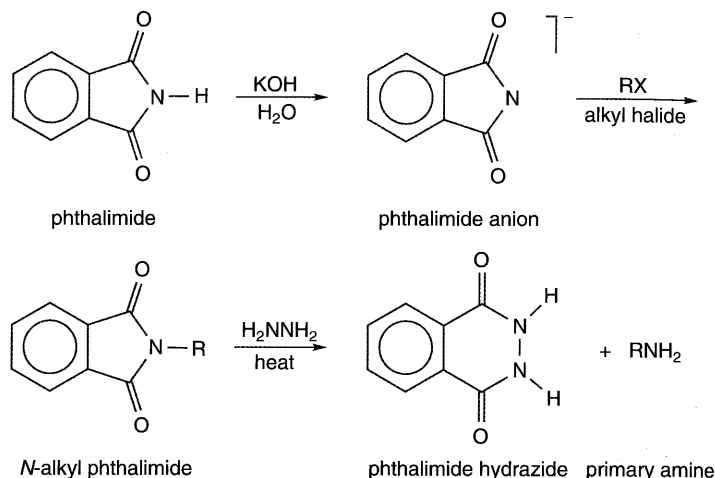
Electrostatic potential map for amine-amide shows negatively-charged regions (in red) as likely nucleophilic sites.

Gabriel Amine Synthesis

Primary amines may be prepared from alkyl halides using phthalimide. This is called the Gabriel amine synthesis.



Electrostatic potential map for phthalimide anion shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).



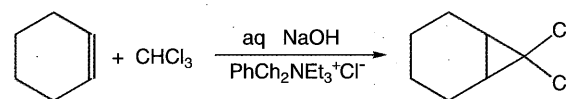
Examine the geometry, atomic charges and electrostatic potential map for **phthalimide anion**. Where is the excess negative charge? On nitrogen or oxygen? In the π system or in the σ system? Draw one or more Lewis structures which properly represents the geometry and charge distribution in phthalimide anion.

Is the second step of the overall reaction for $\text{R}=\text{Me}$ (**N-methylphthalimide** + **hydrazine** \rightarrow **phthalimide hydrazide** + **methylamine**) exothermic or endothermic? Will higher temperatures accelerate or inhibit the reaction? Is the structure drawn above for phthalimide hydrazide its lowest-energy form or are either the imine or diimine tautomers preferred? Compare energies for the hydrazide and **imine** and **diimine** tautomers. Examine the geometry of phthalimide hydrazide and any low energy tautomer, and draw the Lewis structure(s) that best describes it. Can your Lewis structures account for the energy differences? Examine electrostatic potential maps for all three molecules. Which molecule(s) are stabilized by favorable electrostatic interactions? Which are destabilized? Can this help explain the energy differences? Elaborate.

Phase-Transfer Catalysis

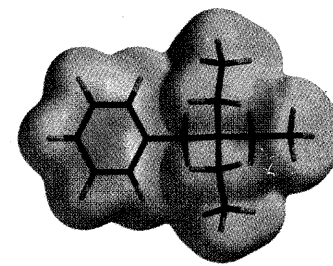
Phase-transfer catalysis describes the action of special catalysts that assist the transfer of reactive molecules from a polar (“aqueous”) solvent to a nonpolar (“organic”) solvent. In the absence of the phase-transfer catalyst, one of the reagents is confined to one solvent, and the other reagent is confined to the other solvent, so no reaction occurs. Addition of a small amount of catalyst, however, enables one of the reagents to pass into the other solvent thereby initiating a reaction.

For example, cyclohexene, chloroform and aqueous NaOH react only when combined with a phase-transfer catalyst, such as benzyltriethylammonium chloride. The organic reagents stay in the organic layer (usually chloroform), but OH^- is able to migrate between the aqueous and organic layers if accompanied by the catalyst (NaOH is insoluble in chloroform). The resulting reaction involves deprotonation of chloroform by OH^- giving dichlorocarbene, CCl_2 , which then combines with the alkene.



What properties of **benzyltriethylammonium ion** make it soluble in diverse solvents? Examine its electrostatic potential map and atomic charges. Which groups facilitate water solubility? Explain. Which groups facilitate chloroform solubility? Explain.

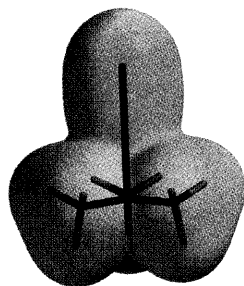
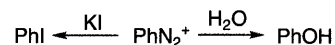
Compare electrostatic potential maps for **tetrabenzylammonium ion** and **tetraethylammonium ion** with that of benzyltrimethylammonium ion. Are they likely to be as effective or more effective as phase-transfer catalysts as benzyltrimethylammonium ion? Explain. (Hint: Predict solubility properties for the three ions.)



Electrostatic potential map for benzyltrimethylammonium ion shows most positively-charged regions (in blue) and more nearly neutral regions (in red).

Diazonium Ions

Aniline, PhNH_2 , reacts with sodium nitrite, NaNO_2 , and aqueous acid to give phenyl diazonium ion, PhN_2^+ . This ion can be isolated, but it also reacts readily with certain nucleophiles to give substitution products, e.g.



Electrostatic potential map for *tert*-butyl diazonium ion shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Alkyl amines also react with NaNO_2 and aqueous acid, but no diazonium ions can be isolated. Rather, alcohols and alkenes are obtained, products that might result from decomposition of RN_2^+ . If RN_2^+ does indeed form in these reactions (and there is evidence that it may not), why is it so unstable compared to PhN_2^+ ?

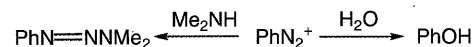
Examine the geometries (in particular, CN bond distances) of *methyldiazonium*, *tert-butyl diazonium* and *phenyl diazonium ions*. Which, if any, of these ions is best described as a weak complex between a cation and N_2 ? Which is furthest away from this description? Is your result consistent with the observed reactivity patterns? Explain.

Examine atomic charges and electrostatic potential maps of these ions. Which ion has the most electron-poor “electrophilic carbon”? Which has the least electrophilic carbon? Is the variation in charge consistent with the observed reactivity patterns? Explain.

Draw all of the resonance contributors needed to describe each ion. Why is phenyl diazonium ion so much more stable than either of the alkyl diazonium ions?

Aryl Diazonium Ions

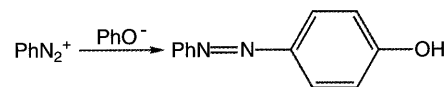
Phenyl diazonium ion, PhN_2^+ , reacts with nucleophiles in several ways. Water displaces N_2 to give phenol, while dimethylamine adds to the terminal N.



Examine the structure, atomic charges and electrostatic potential map of *phenyl diazonium ion*. Which atom(s) appears to carry most of the positive charge? Is the electron distribution around this atom(s) uniform, or are some regions more electron rich and others more electron poor? Draw appropriate resonance contributors.

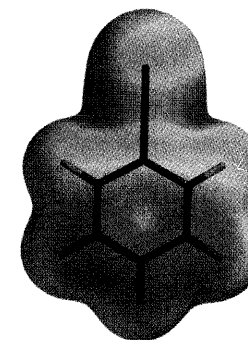
Next, consider the reactivity of phenyl diazonium ion. Are either of the reactions shown above consistent with nucleophilic attack at the ion’s most electron-poor site? Examine the lowest-unoccupied molecular orbital (LUMO) of phenyl diazonium ion. What electrophilic sites are identified by the LUMO? Are either of the reactions shown above consistent with an orbital-controlled addition?

Experimental observations indicate that electron-rich aromatic nucleophiles, such as phenoxide, add to phenyl diazonium ion in the same way as dimethylamine.

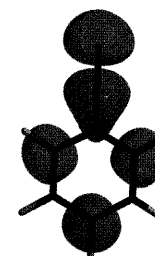


What controls selectivity? Draw the products that would result from “O addition” and from “*ortho* C addition” (as well as “*para* C addition” shown above) of *phenoxide anion* and phenyl diazonium ion. Compare the energies of these products (*para C product*, *ortho C product* and *O product*). Which is most stable? Is this the observed product? Can thermodynamics explain the outcome?

Finally, examine the highest-occupied molecular orbital (HOMO) of phenoxide anion. Is the HOMO the best electron-donor orbital? Is the orbital localized primarily on oxygen or on carbon? Is the observed product consistent with orbital control? Explain your answers.



Electrostatic potential map of phenyl diazonium ion shows most positively-charged regions (in blue) and less positively-charged regions (in red).



LUMO of phenyl diazonium ion reveals the most electrophilic sites.



HOMO of phenoxide anion reveals the most nucleophilic sites.

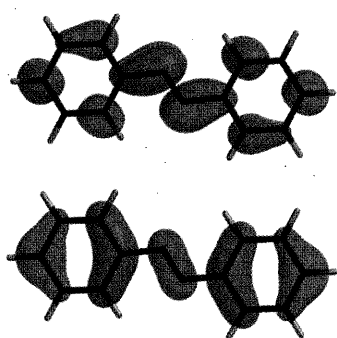
Azo Dyes

Aryl diazonium ions, ArN_2^+ , react with electron-rich aromatic rings, $\text{Ar}'\text{H}$, to give “azo dyes”, $\text{ArN}=\text{NAr}'$. A dye's color depends on its electronic structure and may change with substituents and solvent polarity.

Light absorption causes an electron in the dye molecule to “jump” from the highest-occupied to the lowest-unoccupied molecular orbital (HOMO to LUMO). Therefore, the HOMO-LUMO energy gap can be used to estimate of the color of light required for excitation. The HOMO energies for the three dyes (in au) are -0.311 (azobenzene), -0.299 (4-hydroxyazobenzene), and -0.291 (4-amino-4'-nitroazobenzene), respectively. The corresponding LUMO energies are 0.062, 0.066, and 0.026 au, respectively. Which molecule has the smallest HOMO-LUMO gap? The largest? Azobenzene is orange. Will the colors of the other dye molecules be shifted toward the red or blue end of the spectrum?

Solvent can alter a dye's color. One interpretation is that light absorption “moves” an electron from one part of the molecule to another with a resulting change in overall polarity. Examine the HOMO and LUMO of *azobenzene*, *4-hydroxyazobenzene* and *4-amino-4'-nitroazobenzene*. Which, if any, of the molecules would be expected to change color in different solvents? How does excitation change the polarity of these molecules? Explain how you reached your conclusions.

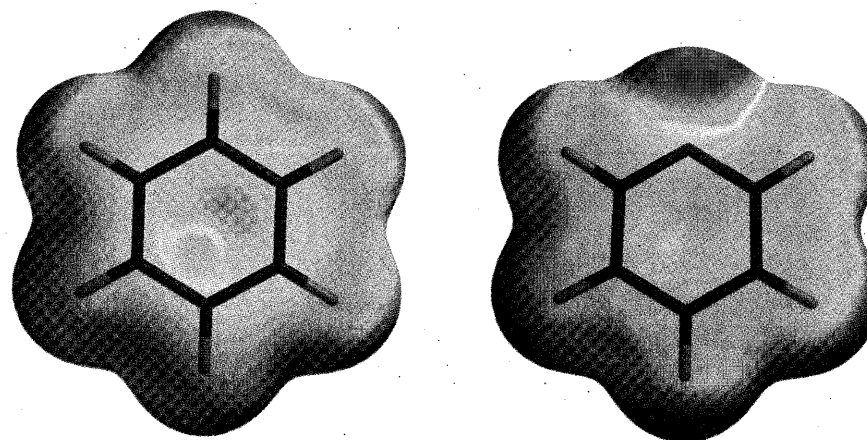
Electron-donor and electron-acceptor substituents selectively interact with different ring orbitals. Compare the HOMO and LUMO of azobenzene with the corresponding orbitals of the two substituted molecules. Which orbitals show significant substituent contributions? What are the nature of these contributions, bonding or antibonding? Try to relate this to the effect which the substituents have on orbital energies and on the HOMO-LUMO gap in azobenzene.



HOMO (bottom) and LUMO (top) of azobenzene show where an electron is removed and where it is added upon absorption of light.

Heterocycles

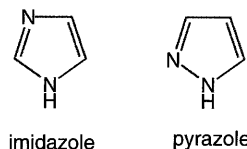
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electrostatic potential maps for benzene (left) and pyridine (right) suggest different reactivities toward electrophiles (see problem 3)

Imidazole and Pyrazole. Where is the Basic Site?

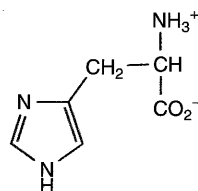
Both imidazole and pyrazole are moderately strong bases.



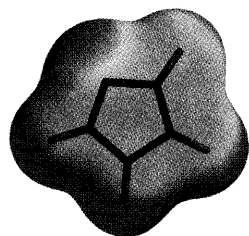
Draw a Lewis structure for each molecule that shows the location of all nonbonding electrons. Examine electrostatic potential maps for both *imidazole* and *pyrazole*. Predict which is the more basic nitrogen in each molecule. What kind of orbital contains this nitrogen's nonbonding electrons? What kind of orbital contains the other nitrogen's nonbonding electrons?

Which nitrogen in each molecule is more basic? Compare energies of the alternative conjugate acids (*N protonated imidazole*, *NH protonated imidazole*, *N protonated pyrazole* and *NH protonated pyrazole*). Which compound, imidazole or pyrazole, is more basic? Compare the energies of protonation (leading to the favored conjugate acid in each case). Rationalize your result.

Histidine, one of the 20 natural amino acids, contains an imidazole ring.



Compare the electrostatic potential map for heptapeptide *gly•gly•gly•his•gly•gly•gly* to that of imidazole. Would you expect the imidazole ring in this molecule to be more or less basic than free imidazole? Explain.



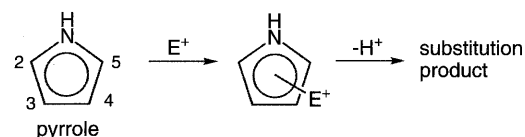
Electrostatic potential map for imidazole shows negatively-charged regions (in red) as likely protonation sites.

Pyrrole

Pyrrole (C_4H_5N) is an essential building block in a number of biologically important molecules, among them hemoglobin and vitamin B_{12} .

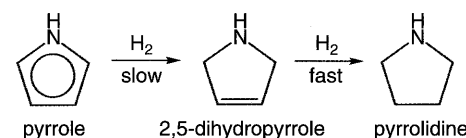
Draw appropriate Lewis structures for pyrrole. How many π electrons does pyrrole have? Is pyrrole aromatic? Would you expect the three carbon-carbon bonds to be approximately the same length? Explain. Examine the actual geometry of *pyrrole*. Are the bonds the same length?

Pyrrole undergoes electrophilic substitution much in the same way as benzene.

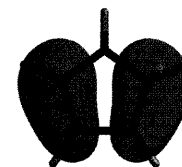


Examine pyrrole's highest-occupied molecular orbital (HOMO) to see if you can predict the most favorable protonation site. Which of the pyrrole's conjugate acids (*N protonated*, *C2 protonated*, *C3 protonated pyrrole*) is lowest in energy? Examine electrostatic potential maps to see if the lowest-energy form is also that in which the positive charged is best delocalized. Rationalize your result using resonance arguments. What should be the favored substitution product?

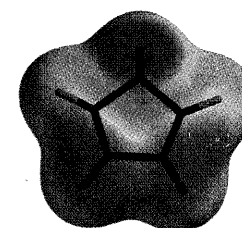
Pyrrole is known to slowly undergo hydrogenation to 2,5-dihydropyrrole, which is then easily hydrogenated to pyrrolidine.



Work out the energy of both hydrogenations (data for *2,5-dihydropyrrole* and *pyrrolidine* are available; the energy of H_2 is given at right). Are both reactions equally exothermic? If not, why not? Why is the first hydrogenation step slower than the second step?



HOMO of pyrrole reveals most likely site for electrophilic attack.

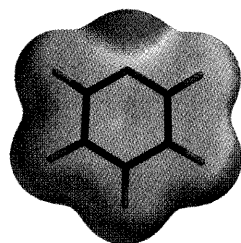


Electrostatic potential map for N-protonated pyrrole shows most positively-charged regions (in blue) and less positively-charged regions (in red).

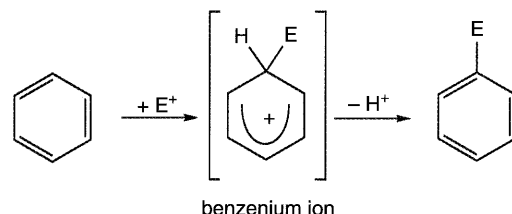
$E(H_2) = -1.1230$ au

Nucleophilicity of Benzene and Pyridine

Benzene and substituted benzenes react with electrophiles, leading to new functionality. The two-step mechanism involves initial attack by an electrophile to form an intermediate (benzenium ion), followed by elimination of a "proton" to generate the substituted benzene.



Electrostatic potential map for pyridine shows negatively-charged regions (in red) and positively-charged regions (in blue).

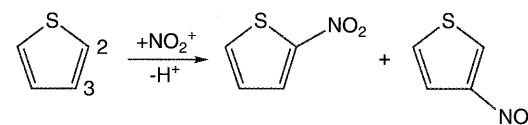


Display the electrostatic potential map for *benzene*. Which areas are most electron rich? Which are most electron poor? Would you expect an electrophile to attack from above and below the plane of the molecule or in the plane of the molecule?

Draw and compare Lewis structures for benzene and pyridine. How many π electrons does each molecule have? Where are the most accessible electrons in each? Display the electrostatic potential map for *pyridine* and compare it to the corresponding map for benzene. Would you expect electrophilic attack on pyridine to occur analogously to that in benzene? If so, should pyridine be more or less susceptible to aromatic substitution than benzene? If not, where would you expect electrophilic attack to occur? Explain.

Electrophilic Substitution of Thiophenes

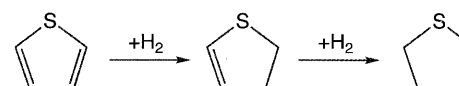
Thiophene undergoes electrophilic substitution resulting in two possible isomers, e.g., for nitration.



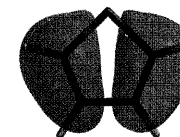
According to Frontier Molecular Orbital (FMO) theory, thiophene's most reactive site can be identified by examining the shape of its highest-occupied molecular orbital (HOMO). Which atoms contribute to *thiophene*'s HOMO? Which atom(s) contributes the most? Which nitration product should form preferentially?

Another way to assess thiophene's reactivity is to compare the intermediate ions formed by addition of NO_2^+ . Examine the structures, charge distributions and electrostatic potential maps of *thiophene+nitronium at C2* and *thiophene+nitronium at C3*. Draw all of the resonance contributors needed to describe these structures. Which, if either, better delocalizes the positive charge? Compare the energies of the two intermediates. Which product should form preferentially if the reaction is under kinetic control? Are these results consistent with FMO theory?

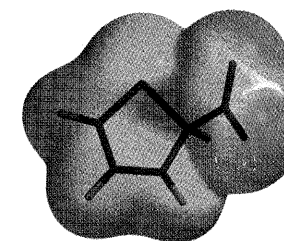
Does the fact that thiophene reacts similarly to benzene mean that it is aromatic? One way to tell is to calculate first and second hydrogenation energies of thiophene, leading to *dihydrothiophene* and *tetrahydrothiophene*, respectively. (The energy of hydrogen is provided at right.)



Whereas the initial hydrogenation both breaks a π bond, as well as destroys any aromatic stabilization, the second hydrogenation only breaks the π bond. Is this difference large as in benzene (see discussion at right), or is it much smaller or negligible? Is thiophene aromatic?



HOMO of thiophene reveals the most likely site for electrophilic attack.



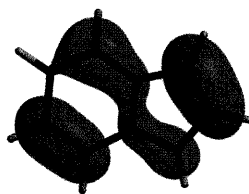
Electrostatic potential map for thiophene+nitronium at C2 shows most positively-charged regions (in blue) and less positively-charged regions (in red).

$$E(\text{H}_2) = -1.1230 \text{ au}$$

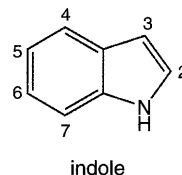
Hydrogenation of benzene to 1,3-cyclohexadiene is endothermic by .011 au (6 kcal/mol), while hydrogenation of 1,3-cyclohexadiene to cyclohexene is exothermic by .041 au (26 kcal/mol). The difference, .051 au (32 kcal/mol), is one measure of the aromaticity of benzene.

Electrophilic Substitution of Indoles

The indole ring system appears in many naturally-occurring substances including the amino acid tryptophan and the drug reserpine.



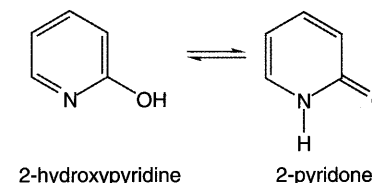
HOMO of indole reveals the most likely sites of electrophilic attack.



In addition to electrophilic attack on the pyrrole ring in indole, there is the possibility for additions to the fused benzene ring. First examine the highest-occupied molecular orbital (HOMO) of *indole*. Which atoms contribute the most? What should be the favored position for electrophilic attack? Next, compare the energies of the various *protonated* forms of *indole* (C protonated only). These serve as models for adducts formed upon electrophilic addition. Which carbon on the pyrrole ring (C₂ or C₃) is favored for protonation? Is this the same as the preference in pyrrole itself (see **Chapter 15, Problem 2**)? If not, try to explain why not. Which of the carbons on the benzene ring is most susceptible to protonation? Rationalize your result based on what you know about the reactivity of substituted benzenes toward electrophiles. Are any of the benzene carbons as reactive as the most reactive pyrrole carbon? Explain.

Tautomers of Hydroxypyridine and Hydroxypyrimidine

Many heterocyclic compounds exist as mixtures of tautomers. For example, 2-hydroxypyridine exists in equilibrium with 2-pyridone.



The equilibrium abundances of the tautomers is influenced by substituents and solvent among other factors.

Examine the geometry and atomic charges of *2-pyridone* to see if it is localized as indicated in the drawing above, or delocalized (as in *2-hydroxypyridine*). If you need to, write alternative Lewis structures to that provided above. How many π electrons does 2-pyridone possess? Is 2-pyridone aromatic?

Compare energies of 2-hydroxypyridine and 2-pyridone to see which tautomer is preferred. Use equation (1) to calculate the equilibrium concentrations of the two at room temperature.

Repeat your analysis for tautomeric equilibria between *4-hydroxypyridine* and *4-pyridone*, *2-hydroxypyrimidine* and *2-pyrimidone* and *4-hydroxypyrimidine* and *4-pyrimidone*. For each, identify the favored (lower-energy) tautomer, and then use equation (1) to calculate the ratio of tautomers present at equilibrium. Point out any major differences among the four systems and rationalize what you observe. (Hint: Compare dipole moments and electrostatic potential maps of the two pyridones and the two pyrimidones. How are these related to molecular stability?)

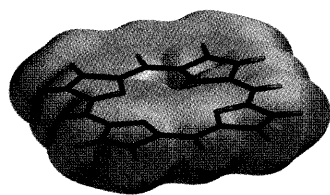
$$\frac{N_1}{N_2} = e^{-1060(E_1 - E_2)} \quad (1)$$

N_i is the number of molecules of tautomer i

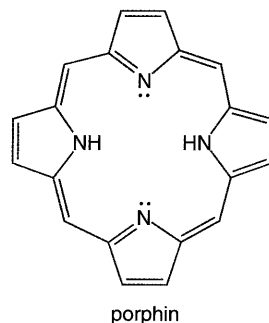
E_i is the energy of tautomer i (in au)

Porphyrins

Porphyrins, derivatives of porphin, are best known for their role as oxygen carriers in hemoglobin.



Electrostatic potential map for porphin dianion reveals negatively-charged cavity (in red).



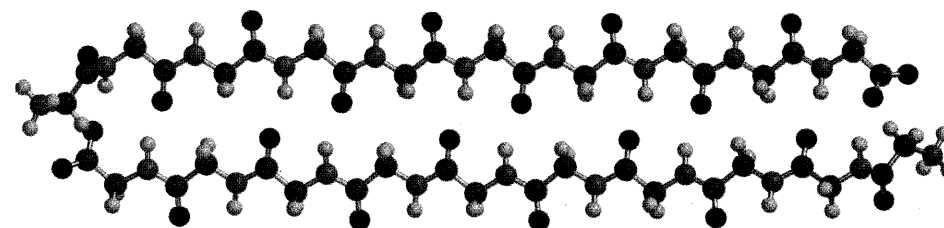
Examine the geometry of *porphin*. Is the molecule planar? Does the molecule incorporate explicit single and double bonds (as in the structure above) or bonds of intermediate length? How many π electrons are involved in porphin's central ring? Is porphin aromatic? Elaborate.

Next consider *porphin dianion*. Is it planar? How many π electrons does it possess (central ring only)? Is it aromatic? Examine a space-filling model for porphin dianion. Is there a cavity? If there is, next examine the electrostatic potential map. Is the cavity set up to receive a cation or an anion? Explain.

Finally, examine the geometry of *porphin oxygen complex*, a model for oxygen complexed to hemoglobin. You can view this as Fe^{2+} fitting into porphin dianion, and imidazole and oxygen later coordinating to form an octahedral complex. Has the cavity in porphin dianion significantly expanded or contracted to accomodate the iron?

Biological Chemistry

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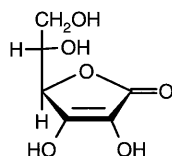


the β sheet is among the most common motifs in protein structure
(see problem 9)

1

Vitamin C. Ascorbic Acid

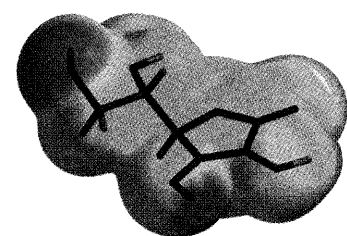
Organic acids usually contain a carboxylic acid group, $-\text{CO}_2\text{H}$. L-Ascorbic acid, commonly known as Vitamin C, is an obvious exception.



Examine atomic charges as well as the electrostatic potential map of *ascorbic acid*. Which hydrogen(s) is likely to be most acidic?

Obtain the energies of the various *conjugate bases* of ascorbic acid. Which one is the most stable? Is it the base which results from deprotonation of the hydrogen you previously assigned as the most acidic?

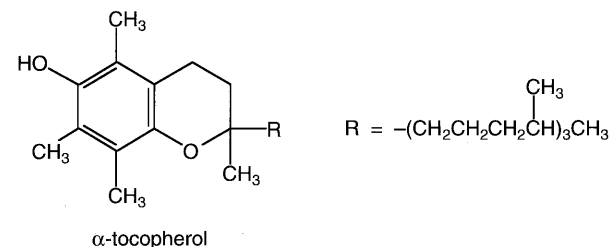
Examine the structures and atomic charges for the various conjugate bases. How do they differ? What distinctive features, if any, characterize the most stable conjugate base? Draw all of the resonance contributors needed to account for the electron distribution and geometry of the most stable conjugate base.



Electrostatic potential map for ascorbic acid shows positively-charged regions (in blue) as likely acidic sites.

Vitamin E

Although oxygen is required for life, it can also cause biochemical damage through its reaction with the unsaturated fatty acids found in cellular membranes. Vitamin E may play an active role in defending cells from attack by reacting quickly with oxidizing agents to give stable products that can then be safely excreted.

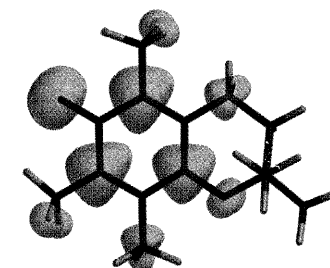


Vitamin E actually consists of a family of compounds, the most active of which is α -tocopherol. The mechanism of the vitamin's action is not completely certain, but it seems likely that it might undergo hydrogen atom transfer reactions with free radicals to give a "stable" radical (see also **Chapter 17, Problem 7**).

If hydrogen transfer is under thermodynamic control, then the vitamin will experience cleavage of the weakest CH (or OH) bond. Compare energies of *radicals* derived from hydrogen abstraction at different positions from a "model" α -tocopherol ($\text{R} = \text{CH}_3$). Which radical is most stable? Are there alternative radicals of similar stability?

Examine the geometry of the *most stable radical*. Is the bonding in the aromatic ring fully delocalized (compare to *model alpha-tocopherol*), or is it localized? Also, examine the spin density surface of the most stable radical. Is the unpaired electron localized on the carbon (oxygen) where bond cleavage occurred, or is it delocalized? Draw all of the resonance contributors necessary for a full description of the radical's geometry and electronic structure.

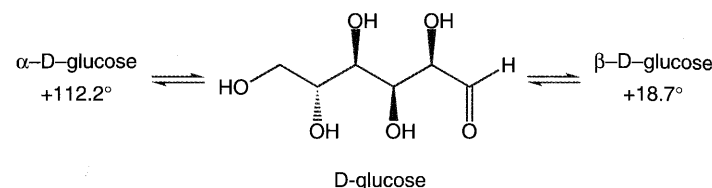
2



Spin density surface for the most stable radical formed by hydrogen atom abstraction from a model of α -tocopherol shows delocalization of the unpaired electron.

Glucose. I

D-Glucose can be crystallized in two different forms, “ α -glucose” and “ β -glucose”. The forms have different melting points, and different specific rotations when dissolved in water. These rotations change upon standing to give a solution whose specific rotation is $+52.7^\circ$.

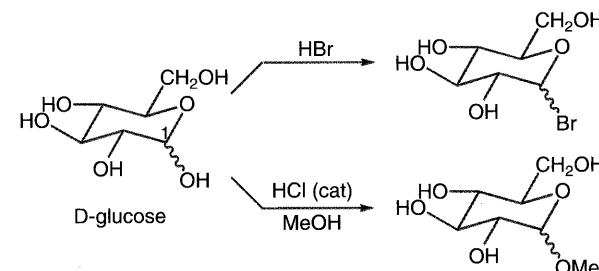


The process that equilibrates α and β -glucose is called “mutarotation”. Use the specific rotations to calculate the α : β ratio at equilibrium (ignore the acyclic form). Next, compare the different conformers of *alpha-D-glucose* and *beta-D-glucose*. Identify the most stable conformer of each and then use these to compare the α and β forms. How are α -glucose and β -glucose related? Are they constitutional isomers? Conformers? Enantiomers? Diastereomers? Is mutarotation a chemical reaction or an internal rotation? Are the relative energies of α and β -glucose consistent with the specific rotation data?

α and β -glucose are cyclic hemiacetals. Referring to the drawing above, which hydroxyl group of acyclic glucose (D-glucose) is incorporated into the hemiacetal ring? Which hemiacetal, α or β , is obtained when the hydroxyl group adds to the front face of the carbonyl group? To the back face? (Hint: Make a plastic model of glucose that looks like the formula drawn below. Do the addition reaction with your plastic model and compare the resulting structure to the computer models of α and β -D-glucose.)

Glucose. II

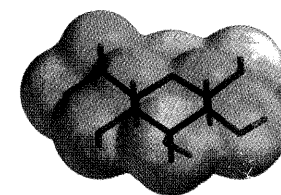
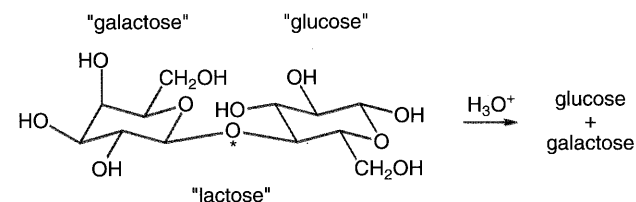
Glucose undergoes a large number of selective, acid-catalyzed substitution reactions at C_1 . Since the role of acid is to protonate the C_1 hydroxyl and make it a better leaving group, it is not apparent why only this hydroxyl group gets replaced.



Examine the electrostatic potential map of *beta-D-glucose* and identify all of the electron-rich sites. Does one site appear to be significantly more electron rich than the others, or do several sites appear to have comparable reactivity?

Protonation and subsequent loss of water should generate a carbocation. Examine all of the *carbocations* derived from protonation of β -D-glucose. Identify the most stable carbocation (this is the one that will form most readily), and draw whatever resonance contributors are needed to describe the geometry, energy, and atomic charges in this cation. Can you explain why substitution occurs selectively at C_1 ?

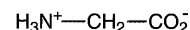
Lactose undergoes acid hydrolysis to give glucose and galactose. If the bridging O (*O) were labeled with ^{18}O , would you expect this label to be found in glucose or in galactose?



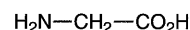
Electrostatic potential map of β -D-glucose identifies electron-rich regions (in red) as likely sites for protonation.

Structure of Glycine in the Gas Phase and in Water

Glycine and other amino acids are usually thought of as zwitterions, bearing a formal positive charge at nitrogen and a formal negative charge at oxygen.



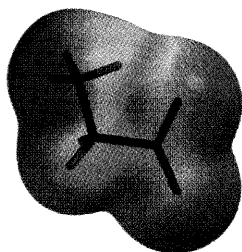
An alternative involves uncharged amino and carboxylic acid groups.



“Zwitterion” and “non-zwitterion” isomers are related by the shift of a proton, and are known as tautomers.

To what extent do zwitterions bear “full” + and - charges? Compare atomic charges in the *zwitterionic* and *non-zwitterionic* forms of *glycine*. What is the total charge on $-\text{NH}_3$ in the zwitterionic form? What is the total charge on $-\text{CO}_2$? Are these charges much greater than those on $-\text{NH}_2$ and $-\text{CO}_2\text{H}$, respectively, in the non-zwitterionic form of glycine? Is the dipole moment for zwitterionic glycine much greater than that for the non-zwitterionic tautomer? Display electrostatic potential maps for both zwitterionic and non-zwitterionic glycine. Which shows the greater charge separation?

Which form of glycine, zwitterionic or non-zwitterionic, is the lower-energy species in the gas phase? Rationalize your observation. Does the ordering or the difference in tautomer stabilities change in going to an aqueous environment? Structures, atomic charges and electrostatic potential maps for both *zwitterionic* and *non-zwitterionic* forms of *glycine* surrounded by 20 *water* molecules are available. Which is the lower energy form? Has solvation had a greater effect on atomic charges and electrostatic potentials for the zwitterionic or non-zwitterionic form? Account for your observation.



Electrostatic potential map for zwitterionic form of glycine shows negatively-charged regions (in red) and positively-charged regions (in blue).

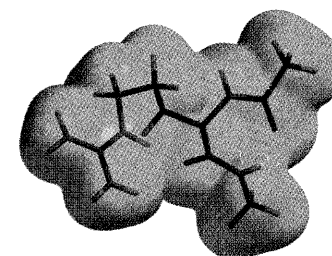
Amino Acid Sidechains

The 20 natural amino acids differ from each other by the nature of their sidechains. Differences involve overall size, hydrophobic or hydrophilic character and, perhaps most importantly, ionization state. While the sidechains are normally written in terms of “neutral” structures, some may also exist in either protonated or deprotonated forms depending on pH.

A selection of amino acids (*acid A*, *acid B*, ...) terminated at both ends by amide functionality, i.e., $\text{MeNHCO}-\text{CHR}-\text{NHCOMe}$, are provided. These are given in the ionization states found at neutral pH. For each, first identify the amino acid, and then the ionization state (neutral, protonated or deprotonated). Next compare electrostatic potential maps among the different amino acids. Which amino acids would prefer hydrophobic environments? Hydrophilic environments? Explain your reasoning.

The X-ray crystal structures of proteins show that highly polar and/or charged amino acids usually congregate on the exterior regions while less polar, uncharged amino acids congregate in interior regions. Explain. For each of the amino acids above, indicate a preference for interior or exterior regions.

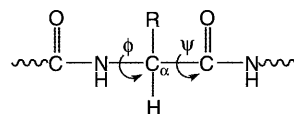
Each amino acid is characterized by an “isoelectric point”, the pH at which it exists in neutral form. Differences in isoelectric points may be exploited to separate amino acids in what is termed an electrophoresis experiment.



Electrostatic potential map for acid B shows positively and negatively-charged regions (in red and blue, respectively) and neutral regions (in green). The former would prefer hydrophilic environments while the latter would prefer hydrophobic environments.

7 Amino Acid Conformation

The structures of amino acids incorporated into polypeptides and proteins may be characterized by a pair of dihedral angles involving the so-called α carbon for each amino acid.



A set of low-energy conformers has been provided for *alanine* ($R=CH_3$) **tetramer** (terminated at both ends by amide functionality). For each conformer, identify each of the α carbons and measure the ϕ and ψ dihedral angles (see table below).

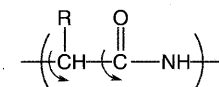
α carbon	ϕ	ψ
C_1	$C_{13}N_1C_1C_2$	$N_1C_1C_2N_2$
C_4	$C_2N_2C_4C_5$	$N_2C_4C_5N_3$
C_7	$C_5N_3C_7C_8$	$N_3C_7C_8N_4$
C_{10}	$C_8N_4C_{10}C_{11}$	$N_4C_{10}C_{11}N_5$

Make a plot of ψ (vertical axis) vs. ϕ (horizontal axis) with $\psi=0$, $\phi=0$ in the middle and ranging from -180° to 180° for both variables. Put a point on your plot for each dihedral angle (in each conformer). You have constructed what is now known as a Ramachandran plot.

Are the points randomly scattered, or are they clustered in certain regions of the plot? If the latter, see if you can see any common structural motifs (see also **Chapter 16, Problem 9**).

8 Amide Bonds

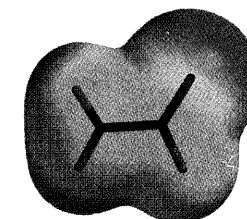
The backbone of polypeptides and, more generally, proteins is made up of a linear sequence of amino acids.



Two of the three single bonds involved in each unit are flexible, and their detailed conformation dictates overall polypeptide structures and (ultimately) function. The amide bond is generally assumed to be rigid. Why? (See also **Chapter 10, Problem 1**.)

Examine the geometry of *formamide*. Is the CN bond shorter than expected for a normal single bond (in *methylamine*), and closer to that expected for a full double bond (in *methyleneimine*)? Is the CO bond longer than that expected in a carbonyl compound (in *formaldehyde*), perhaps closer to that appropriate for a single bond (in *methanol*)? Also, compare the electrostatic potential map for formamide with those of formaldehyde and methylamine. Is the CO bond in formamide more or less polar than that in formaldehyde? Is the CN bond in formamide more or less polar than that in methylamine? Draw whatever Lewis structures are needed to properly describe the geometry and charge distribution of formamide.

Step through the sequence of structures describing bond **rotation in N-methylformamide**. Plot energy (vertical axis) vs. HNCN dihedral angle (horizontal axis). Identify and characterize all minimum energy conformers, and calculate their ratio at room temperature (use equation 1). Identify the transition state. Is the CN bond distance close to those in the equilibrium forms, or has it shortened or lengthened? Rationalize your result. Calculate the energy barrier for rotation from the lower-energy form (energy of equilibrium structure - energy of transition state). Is it closer to what you expect for rotation about a single bond ($\sim .005$ au or 3 kcal/mol in ethane) or about a double bond ($\sim .100$ au or 65 kcal/mol in ethene)?



Electrostatic potential map for formamide shows negatively-charged regions (in red) and positively-charged regions (in blue).

$$\frac{N_1}{N_2} = e^{-1060(E_1-E_2)} \quad (1)$$

N_i is the number of molecules of conformer i

E_i is the energy of conformer i (in au)

DNA Base Pairs

The two strands which make up DNA are held together by hydrogen bonds between complementary pairs of bases: adenine paired with thymine and guanine paired with cytosine. The integrity of the genetic code (and of life as we know it) depends on error-free transmission of base-pairing information.

Examine electrostatic potential maps for *adenine*, *thymine*, *guanine* and *cytosine* (A, T, G and C, respectively). Identify potential hydrogen-bond donor and acceptor sites for each. Sketch possible hydrogen-bonded geometries for the adenine-thymine pair and for the guanine-cytosine pair. How many hydrogen bonds hold together adenine and thymine? How many hold together guanine and cytosine?

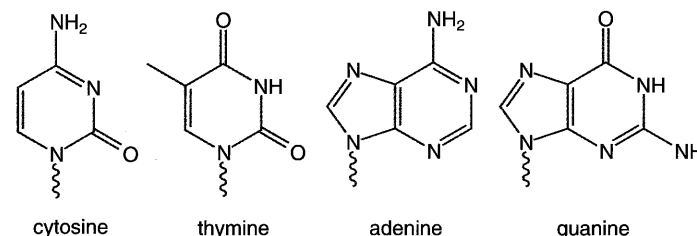
Examine *AT pair* and *GC pair*, adenine-thymine and guanine-cytosine base pairs, respectively. Identify the hydrogen bonds in each. Are they the same as those you sketched? Are the base pairs “flat” as normally drawn in textbooks, or are they significantly “puckered” or “twisted”?

Calculate binding energies for both the adenine-thymine and guanine-cytosine base pairs (energy of the base pair less the energies of the component bases). Also calculate binding energies for “incorrect” base pairs (*AG pair* and *TC pair*). Estimate the “energetic incentive” for base pairing to occur “correctly”.

Electrostatic potential map for adenine shows negatively-charged regions (in red) which may act as hydrogen-bond acceptors and positively-charged regions (in blue) which may act as hydrogen-bond donors.

Tautomers of Nucleotide Bases

Protons bound to heteroatoms in heterocyclic compounds are likely to be very mobile in solution and, where two or more heteroatoms are present in a structure, different isomers (tautomers) may be in equilibrium. As a case in point, consider the nucleotide bases (indicates the point of attachment to the sugar-phosphate backbone).



Compare energies of various tautomers of *cytosine*, *thymine*, *adenine* and *guanine*. Is the lowest-energy structure for each one the one shown above? If not, what is the lowest-energy form? Identify the tautomer which is closest in energy to the lowest-energy structure, and use equation (1) to compute the ratio of lowest-energy to next lowest-energy tautomers. If any of the alternatives are present in greater than 1% abundance, sketch possible structures for hydrogen-bonded base pairs (adenine with thymine and guanine with cytosine) where one member of the pair adopts the alternative tautomer. Is hydrogen bonding likely to be favorable?

Based on your analysis, is it likely that tautomeric equilibria involving the nucleotide bases will interfere noticeably with base pairing in DNA? Explain.

$$\frac{N_1}{N_2} = e^{-1060(E_1 - E_2)} \quad (1)$$

N_i is the number of molecules of tautomer i

E_i is the energy of tautomer i (in au)

Structure of the Double Helix

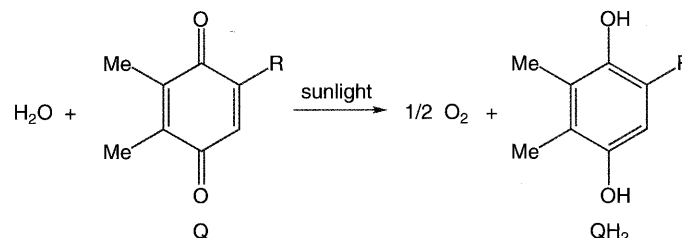
DNA is made up of two intertwined strands. A sugar-phosphate chain makes up the backbone of each, and the two strands are joined by way of hydrogen bonds between pairs of nucleotide bases, adenine, thymine, guanine and cytosine. Adenine may only pair with thymine and guanine with cytosine. The molecule adopts a helical structure (actually, a double helical structure or “double helix”).

Examine *DNA*. How many base pairs does it contain? Starting from one end, write down the sequence of bases in one strand. Write down the sequence in the complementary strand. Is this a “proper” DNA fragment, or does it contain base-pair mismatches?

How many base pairs are required for a full (360°) turn of the helix? Locate the minor and major grooves in the DNA fragment. Will a polycyclic aromatic hydrocarbon such as *anthracene* be able to fit into the major groove? Examine space-filling models to tell.

Photosynthesis

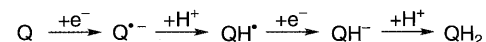
Photosynthesis is the process that plants use to convert sunlight into chemically useful energy. One part of this process involves using sunlight to convert water and a plastoquinone, Q, into oxygen and a hydroquinone, QH₂ (R = (CH₂CH=C(Me)CH₂)_nH where n = 6-10).



First, calculate the energy for the reaction of water and trimethylquinone (Q, R = Me) to give oxygen and trimethylhydroquinone (QH₂, R = Me). (Energies for water and oxygen are given at right).

Does this reaction absorb or release energy? Which side would be favored in the absence of sunlight? Suppose the reaction is promoted by 500 nm light (a typical visible light wavelength). How much of the light energy would be converted into chemical energy by this reaction? (Use equation 1 to convert wavelength into energy.)

The mechanism of the light-promoted reaction involves a series of electron and proton transfers from water to Q.



Examine the electrostatic potential map and spin density surface of *Q radical anion* (Q^{•−}). Draw all of the resonance contributors needed to account for these data. Examine the CO bond distances and spin density surface of *QH radical* (QH[•]). Draw all of the resonance contributors needed to account for these data.

Which proton transfer is easier energetically, Q^{•−} → QH[•] or QH[•] → QH₂? (The energy of H⁺ is given at right.) Use electrostatic potential maps of Q^{•−} and *QH anion* (QH[−]) to explain this difference.

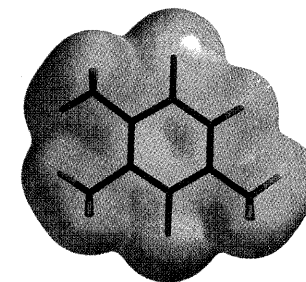
$$E(\text{H}_2\text{O}) = -75.5860 \text{ au}$$

$$E(\text{O}_2) = -148.7691 \text{ au}$$

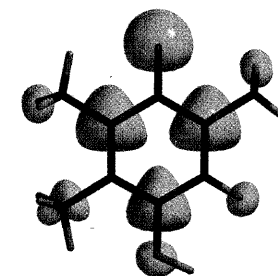
$$E = 45.6/\lambda_{\text{max}} \quad (1)$$

E is the excitation energy (in au)

λ_{max} is the excitation wavelength (in nm)



Electrostatic potential map for Q radical anion shows most negatively-charged regions (in red) and less negatively-charged regions (in blue).

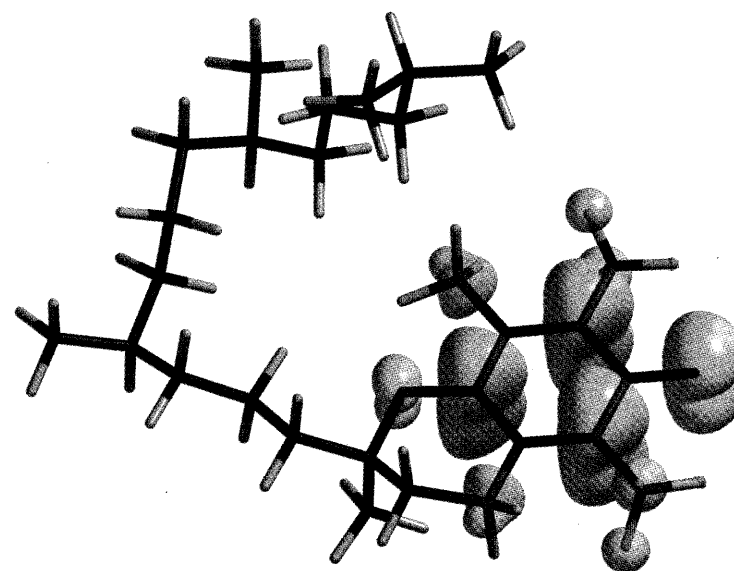


Spin density surface for QH radical reveals location of unpaired electron

$$E(\text{H}^+) = 0 \text{ au}$$

Free Radicals and Carbenes

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vitamin E, which is soluble in cell lipids, acts as an effective free radical scavenger
(see problem 7)

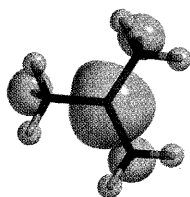
Structure of Free Radicals

What is the preferred geometry about the radical center in free radicals? Carbocation centers are characterized by a vacant orbital and are known to be planar, while carbanion centers incorporate a nonbonded electron pair and are typically pyramidal (see **Chapter 1, Problem 9**).

First examine the geometry of *methyl radical*. Is it planar or puckered? Examine the geometries of *2-methyl-2-propyl radical*, *trifluoromethyl radical*, *trichloromethyl radical* and *tricyanomethyl radical*. Classify each of the substituents (methyl, fluoro, chloro and cyano) as a π -electron donor or as a π -electron acceptor (relative to hydrogen). Does replacement of the hydrogens by π -donor groups make the radical center more or less puckered? Does replacement by π -acceptor groups make the radical center more or less puckered? Justify your observations.

Display spin density surfaces for all radicals. For which radical is the unpaired electron least delocalized from the radical center? For which is it the most delocalized? Is there any relationship between degree of puckering of the radical center and extent of spin delocalization?

Onto which atoms (carbon, nitrogen or both) is the unpaired electron in tricyanomethyl radical delocalized? Rationalize your result by drawing resonance contributors.



Spin density surface for 2-methyl-2-propyl radical shows the location of the unpaired electron.

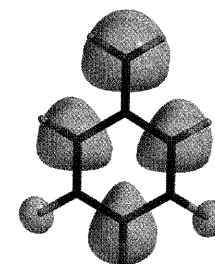
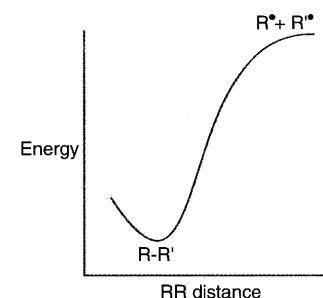
CH Bond Energies in Hydrocarbons

Homolytic bond dissociation, the breaking of a covalent bond with two radicals resulting, generally occurs without any extra activation barrier (see also **Chapter 3, Problem 1**). Thus, the rate of bond dissociation (kinetics) is directly related to the stabilities of the resulting radicals (thermodynamics).

Examine the geometry of *3-ethylpentane*. Are the CH bonds involving the methyl, methylene and methine groups of different length? (Determine averages where appropriate, and recognize that even small differences may be important.) If yes, and assuming that “shorter bonds” will be “stronger bonds”, which hydrogen will dissociate the most easily? Which will dissociate least easily?

Examine the energies of *radicals* resulting from hydrogen atom abstraction in 3-ethylpentane. Which radical is the lowest energy? Is there a relationship between the CH bond lengths in 3-ethylpentane and the stabilities of the radicals resulting from bond dissociation? Elaborate.

Calculate CH bond dissociation energies in *propene* and in *toluene*, leading to *allyl* and *benzyl radicals*, respectively. (The energy of hydrogen atom is given at right.) Is bond dissociation easier or more difficult in these systems relative to bond dissociation in 3-ethylpentane (methyl CH)? Examine spin density surfaces for allyl and benzyl radicals. Draw Lewis structures that account for the electron distribution in each radical. Does spin delocalization appear to stabilize radicals in the same way charge delocalization stabilizes ions?

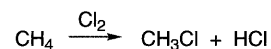


Spin density surface for benzyl radical shows location of the unpaired electron.

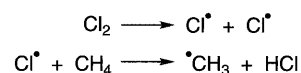
$$E(H^\bullet) = -0.4962 \text{ au}$$

Free Radical Chlorination of Alkanes

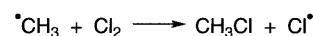
Chlorine gas reacts directly and highly exothermically with alkanes, giving rise to alkyl chlorides and hydrogen chloride, e.g., for addition to methane.



The process is believed to initiate with formation of chlorine atom (either thermally or photochemically), which then abstracts a hydrogen from methane.



The resulting methyl radical abstracts a chlorine atom from Cl_2 , leading to product and generation of another chlorine atom.



Construct a reaction energy diagram starting from chlorine atom and methane and ending with methyl chloride and chlorine atom. (Models for *methane*, *methyl radical*, *hydrogen chloride*, *chlorine* and *methyl chloride* are available; the energy of chlorine atom is given at left.) Is each step exothermic? Is there an overall thermodynamic driving force for the reaction?

Examine the structures of the two transition states (*chlorine atom+methane* and *chlorine+methyl radical*). For each, characterize the transition state as “early” (close to the geometry of the reactants) or as “late” (close to the geometry of the products)? In light of the thermodynamics of the individual steps, are your results anticipated by the Hammond Postulate? Explain.

Examine spin densities for the two transition states. Draw a “Lewis structure” (or sequence of Lewis structures) for each which properly conveys the location(s) of the unpaired electron.

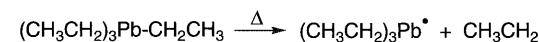


$E(\text{Cl}^\bullet) = -457.3711 \text{ au}$

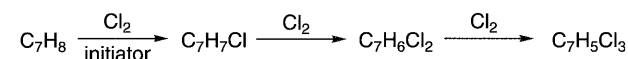
Spin density surface for chlorine atom+methane transition state shows location of unpaired electron.

Chlorination of Toluene

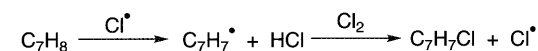
Free radical initiators play an important role in many chemical reactions (see also **Chapter 17, Problem 5**). For example, combustion of gasoline is assisted by compounds such as tetraethyl lead, heating of which results in bond breaking and generation of ethyl radical.



In the presence of chlorine gas and a free-radical initiator, three of toluene's hydrogens are sequentially replaced by chlorine atoms.



The first step in the overall process is believed to involve abstraction of hydrogen by chlorine atom, followed by reaction of the ensuing radical with Cl_2 .

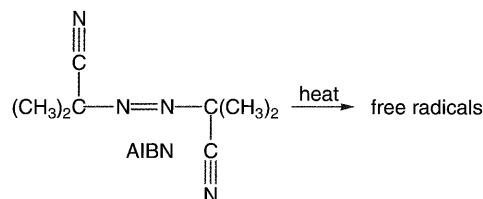


Draw resonance structures for the possible radicals resulting from hydrogen atom abstraction from toluene. Which would you anticipate to be the most stable? Why? Compare energies for the different radicals (*radical A*, *radical B*, ...). Is the lowest-energy radical that which you anticipated? Are any of the alternatives significantly better than any of the others? Explain your reasoning.

What are the three products resulting from free-radical chlorination of toluene? Why are only three hydrogens replaced?

Radical Initiators

Free radical chain reactions depend on an easily generated free radical to initiate the chain. One way to generate this radical is to irradiate halogens, such as Cl_2 and Br_2 . Another way is to add a small amount of an “initiator” molecule to the reaction mixture, such as AIBN. This molecule, when heated, decomposes into free radicals that react with other molecules to initiate a chain reaction.



Heating AIBN causes homolytic cleavage of the weakest bond(s) in the molecule. Consider cleavage of the two types of CC bonds, the CH bond, and the CN single bond. Write the reactions that would result from homolytic cleavage of each of these bonds, then use the energies of the various **radicals** and **AIBN** to calculate reaction energies (the energies of H, CH_3 , and CN are shown on the left). Which bond cleavage should occur most readily? Considering only this bond cleavage, what resonance contributors must be drawn to describe the two radicals adequately?

Homolytic cleavage of AIBN generates two radicals, either of which might initiate a radical chain reaction. If we assume that the next step is for one of these radicals to abstract a hydrogen atom from another molecule, we would expect the “reactive” radical to be the one that makes a stronger bond to hydrogen. Use the energies of H (shown on left), the relevant radicals, and the **radicals+H** products to calculate bond energies. Which radical is more likely to abstract hydrogen and initiate a chain reaction?

$$E(\text{H}^\bullet) = -4962 \text{ au}$$

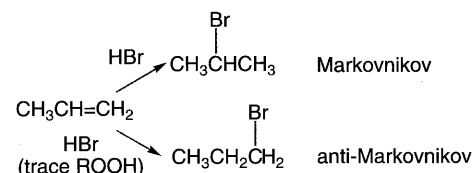
$$E(\text{CH}_3^\bullet) = -39.3426 \text{ au}$$

$$E(\text{CN}^\bullet) = -91.6848 \text{ au}$$

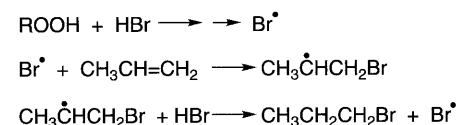
$$E(\text{N}_2) = -108.3010 \text{ au}$$

Free Radicals Add to Double Bonds

Electrophilic addition of hydrogen bromide to alkenes follows Markovnikov’s rule, leading to the product with halogen on the more-substituted position. However, trace amounts of hydroperoxides (among other “impurities”) may initiate a reaction that gives rise to the “anti-Markovnikov” product, with bromine in the less-substituted position.

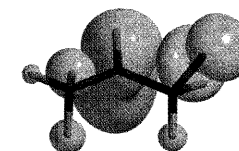


One possible interpretation is a change to a free radical chain mechanism. Bromine radical is first produced which then adds to the alkene. The resulting free radical reacts with hydrogen bromide to yield the final alkyl bromide and regenerate bromine radical.



Examine spin density surfaces for **1-bromo-2-propyl radical** and **2-bromo-1-propyl radical** (resulting from bromine atom addition to propene). For which is the unpaired electron more delocalized? Compare energies for the two radicals. Is the more delocalized radical also the lower-energy radical? Could this result have been anticipated using resonance arguments?

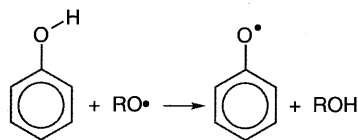
Does the lower energy radical intermediate lead to the lower energy product? Compare energies for **1-propyl bromide** and **2-propyl bromide** to tell.



Spin density surface for 1-bromo-2-propyl radical shows location of the unpaired electron.

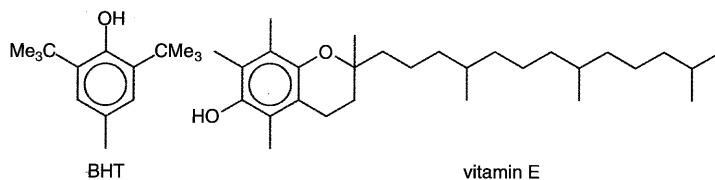
Spin Traps and Radical Scavengers

The hydroxyl hydrogen in phenol is particularly susceptible to abstraction by a free radical.



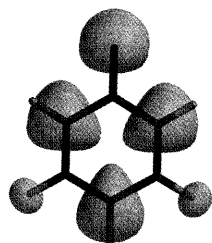
The process is exothermic, suggesting that the phenoxy radical is particularly stable. Display the spin density surface for **phenoxy radical**. Is the unpaired electron localized or delocalized over several centers? Is the unpaired electron in the σ or π system? Draw appropriate Lewis structures that account for your data.

Phenol is a “radical scavenger”. Other radical scavengers include 3,5-di-*tert*-butyl-4-hydroxytoluene (butylated hydroxytoluene or BHT) and vitamin E.

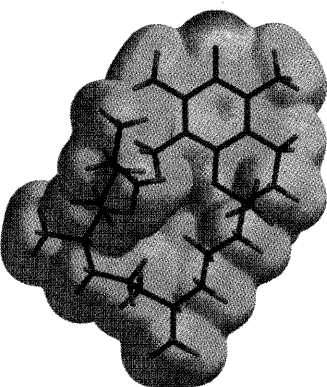


Examine the spin density surface for **BHT radical**. Is the unpaired electron localized or delocalized? Examine BHT radical as a space-filling model. What effect do the bulky *tert*-butyl groups have on the “chemistry” of the species? (Hint: BHT radical does not readily add to alkenes or abstract hydrogens from other molecules.)

Compare the spin density surface for **vitamin E radical** to those of phenoxy and BHT radicals (see also **Chapter 16, Problem 2**). Are there significant differences among the three? If so, elaborate. What is the function of the long alkyl chain in vitamin E? Examine an electrostatic potential map for vitamin E radical. Do you expect it to be soluble in aqueous (polar) or non-aqueous (non-polar) environments, or both?



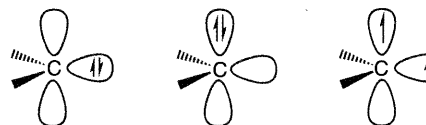
Spin density surface for phenoxy radical shows location of the unpaired electron.



Electrostatic potential map for vitamin E radical distinguishes charged regions (in red and blue) which are likely to interact strongly with polar environments from uncharged regions (in green) which are unlikely to interact.

Singlet and Triplet Methylene

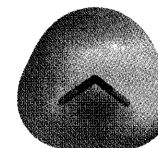
Methylene (CH_2) has six valence electrons. Four are needed for the two CH bonds. Possibilities for the other two include:



The first two arrangements are singlet states (all electrons are paired), while the last is a triplet state (with two unpaired electrons). Experimentally, the ground state of methylene is a triplet, although much of methylene's chemistry (and that of substituted methylenes) is due to the singlet state.

Examine the highest-occupied molecular orbital (HOMO) of singlet methylene. Where is the pair of electrons, in-plane or perpendicular to the plane? Next, examine the electrostatic potential map. Where is the molecule most electron rich, in the σ or the π system? Where is the most electron poor? Next, display the corresponding map for **triplet methylene**. Which molecule would you expect to be the better nucleophile? The better electrophile? Explain. Experimentally, one state of methylene shows both “electrophilic” and “nucleophilic” chemistry, while the other state exhibits chemistry typical of radicals. Which state does which? Elaborate.

Which is lower in energy, singlet or triplet methylene? What effect do substituents have on altering the singlet-triplet energy difference in methylene? One after the other, compare energies for **singlet** and **triplet difluoromethylene** and **singlet** and **triplet dicyanomethylene**, and identify the ground state for each. Does fluorine substitution favor the singlet or triplet state? Does cyano substitution favor the singlet or triplet state? Rationalize your observations. (Hint: Compare geometries among the three methylenes for both singlet and triplet states.)



Electrostatic potential map for singlet methylene shows negatively-charged regions (in red) and positively-charged regions (in blue).



HOMO of singlet methylene shows location of the molecule's highest energy pair of electrons.

Sources of Methylene

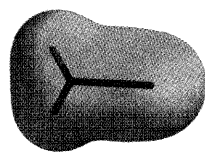
Practical thermal and photochemical routes to methylene generally involve elimination of stable neutral molecules, among them N_2 and CO .

Examine acyclic (*diazomethane*) and cyclic (*diazirine*) structures of molecular formula CH_2N_2 . Which is the more stable? Is the less stable structure an energy minimum? Examine vibrational frequencies to tell.

Describe the geometry of the more stable form of CH_2N_2 . Is it a weak complex between *singlet methylene* and nitrogen? Is the CN bond typical of single bond (1.47 Å in methylamine), a double bond (1.26 Å in methyleneimine) or a triple bond (1.14 Å in hydrogen cyanide)? Is the NN bond typical of a single bond (1.45 Å in hydrazine), a double bond (1.24 Å in *trans*-diimide) or a triple bond (1.08 Å in nitrogen)? Draw a Lewis structure (or series of Lewis structures) which adequately represent the geometry of the molecule. Does your structure (structures) adequately account for the atomic charges?

Compare electrostatic potential maps for the more stable form of CH_2N_2 and singlet methylene. Describe similarities and differences between the two.

Step through the sequence of structures representing dissociation of *ketene to methylene and carbon monoxide*. Plot energy (vertical axis) vs. carbon-carbon bond distance (horizontal axis). Would you describe ketene as a weak complex between singlet methylene and carbon monoxide? Explain. (A table of CC and CO bond lengths is found at left.) Is there an energy barrier to the dissociation?



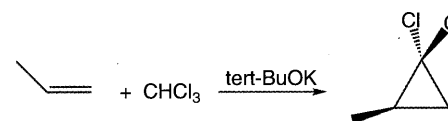
Electrostatic potential map for diazomethane shows negatively-charged regions (in red) and positively-charged regions (in blue).

bond distances (Å)

H_3C-CH_3	1.54
$H_2C=CH_2$	1.32
$HC\equiv CH$	1.19
H_3C-OH	1.44
$H_2C=O$	1.21
$C\equiv O$	1.13

Carbenes Add to Alkenes

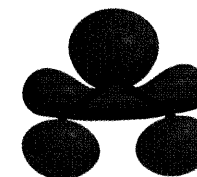
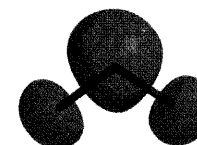
In strong base, propene reacts with chloroform to yield 2,2-dichloro-1-methylcyclopropane.



Here, the “active reagent” is believed to be singlet dichlorocarbene (CCl_2).

Step through the sequence of structures representing addition of dichlorocarbene to propene (*dichlorocarbene + propene*). Plot energy (vertical axis) vs. the length of one of the carbon-carbon bonds being formed (horizontal axis). Identify the transition state. Are the two new carbon-carbon bonds the same length? If not, which is more fully formed, that to the electron-rich end of the alkene, or that to the electron-poor end? Does this suggest that CCl_2 is acting as an electrophile or as a nucleophile? Is the reaction endothermic or exothermic? Does it have a high activation energy or little or no activation energy?

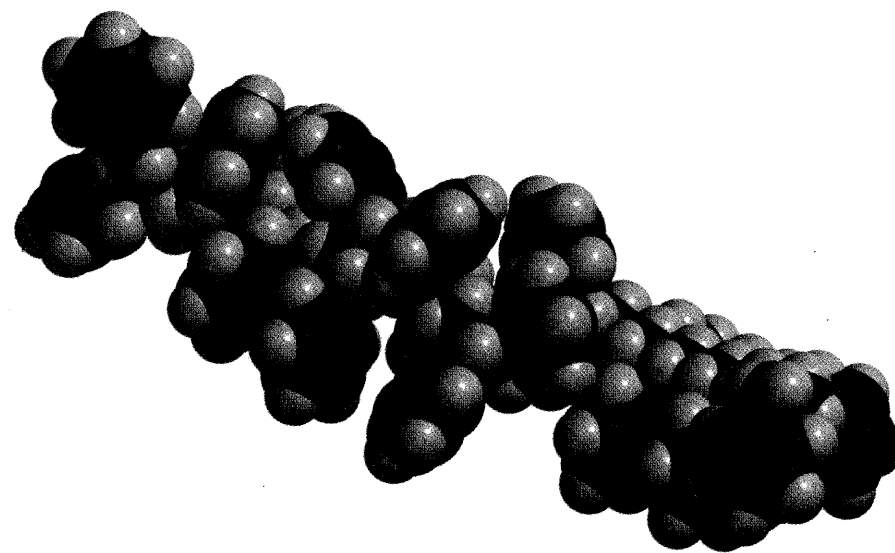
Next, examine the highest-occupied and lowest-unoccupied molecular orbitals (HOMO and LUMO) of *dichlorocarbene*. Were the reaction a “nucleophilic addition”, how would you expect CCl_2 to approach propene? Were the reaction an “electrophilic addition”, how would you expect CCl_2 to approach propene? Which interpretation is more consistent with the geometry of the transition state?



HOMO and LUMO of dichlorocarbene characterize the molecule's electrophilic and nucleophilic behavior, respectively.

Polymers

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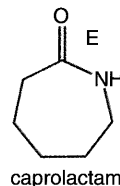


short strand of polystyrene
(see problem 2)

Nylon

One of the oldest and (still) commercially most important polymers is nylon. Actually, nylon does not refer to a single polymer, but rather to an entire class of amide polymers or “polyamides”. Two of the most common are Nylon 6 and Nylon 6,6.

Commercially, Nylon 6 is made from caprolactam.



Examine the structure of the short strand of *Nylon 6* in which all amide bonds are Z. What is the monomer unit? How many monomers are in the strand? Note: Each end of the polymer strand has been “capped” by one or more atoms. Do not count these “caps” as monomers. Compare the strand to that of a simple polypeptide, for example, *polyglycine* (see also **Chapter 16, Problem 9**), and point out any obvious similarities. Pay particular attention to hydrogen bonds.

Examine the structure of a strand of Nylon 6 in which all amide bonds are E. Describe how this differs from the strand in which the amide linkages are Z. In particular, are the same hydrogen-bond patterns found?

Examine the structure of *Nylon 6,6* (amide bonds have been assumed to adopt E geometries). What is the repeating unit? How many monomers are in the strand? Nylon 6,6 is made by combining two different molecules, a diacid and a diamine. Draw these molecules.

Synthetic Polymers

A wealth of important materials fall under the general category of synthetic polymers. All share a common theme of being made up of sequences of one or more monomer units.

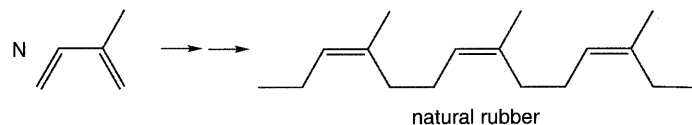
One after the other, examine the structures of a number of common *monomers*. What features, if any, do they have in common? What relevance is this to the polymerization process?

One after the other, examine the structures of a number of common *polymers*. For each, draw the repeating unit, and indicate the chain length (number of repeating units in the strand). Note: Each end of a polymer strand has been capped by adding extra atoms. Do not count these atoms as repeating units. Also, use the smallest possible repeating unit.

It is unrealistic to expect that any single conformer of a polymer will adequately represent the overall size and shape of the polymer. The low-energy conformer for each polymer strand shown here is merely meant to allow identification of the polymer in terms of its components.

Rubber

Condensation of isoprene (2-methyl-1,3-butadiene) either leads to a polymer in which all double bonds are *trans* (“natural rubber”) or in which they are *cis* (gutta-percha).



Examine structures of the different forms of **rubber** provided. Which is natural rubber and which is gutta-percha? How many monomers are in each strand?

Natural rubber is known to be more “elastic” (deformable) than gutta-percha. Is there any obvious difference in the structures in the two strands which might lead to a difference in the properties of the real polymers?

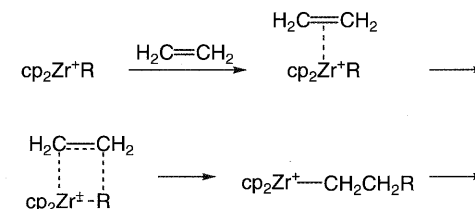
Rubber used in practical applications is crosslinked through disulfide (-S-S-) bonds, and is known as “vulcanized” rubber. Can you name another important class of “polymers” which are crosslinked through disulfide bonds? Examine **vulcanized rubber**. How many individual strands does it comprise? Are these strands of natural rubber or of gutta-percha? What is the percentage (by weight) of sulfur incorporated into the polymer? (The molecular weight of the sample is 1701 amu.) Does this classify as a low-sulfur polymer (<3%), a high-sulfur polymer (>10%) or in between?

Can you provide a qualitative explanation of why natural rubber becomes more and more hard (less deformable) as the percentage of incorporated sulfur is increased?

The name vulcanized (from Vulcan, the Greek god of fire) comes from the manner in which the polymer was first prepared by heating rubber in the presence of sulfur.

Alkene Polymerization

Stable transition-metal complexes may act as homogenous catalysts in alkene polymerization. The mechanism of so-called Ziegler-Natta catalysis involves a cationic metallocene (typically zirconocene) alkyl complex. An alkene coordinates to the complex and then inserts into the metal alkyl bond. This leads to a new metallocene in which the “polymer” is extended by two carbons, i.e.



Examine the sequence of structures corresponding to Ziegler-Natta **polymerization of ethene**, or more specifically, one addition step starting from a zirconocene-ethene complex where $R=CH_3$. Plot energy (vertical axis) vs. frame number (horizontal axis). Sketch Lewis structures for the initial complex, the “final” adduct and the transition state. Indicate “weak or partial” bonding by using dotted lines.

Is the reaction as written exothermic, i.e., is there a thermodynamic driving force? Rationalize your result. Is there an activation barrier to the reaction? If so, is it typical of that of a thermal reaction (.04 to .10 au or approximately 40-60 kcal/mol), much smaller or much larger?

Stereoregularity of Polypropylene

The properties of polymers depend not only on overall chain length, but also on the degree to which the monomers are ordered along the chain. Different methods of preparation lead to vastly different degrees of ordering. A good example is found in the polymerization of propylene. This polymerizes predominantly “head-to-tail”, and leads to a stereocenter (*) at every other atom in the polymer chain.

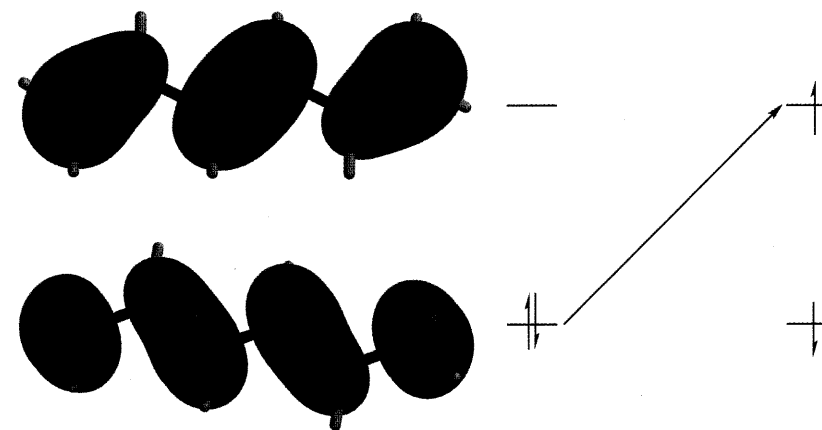


Polypropylene made by free-radical polymerization is generally “atactic”, that is to say, there is no pattern to the stereochemistry. On the other hand, both “isotactic” polypropylene (in which all the stereocenters are the same) and “syndiotactic” polypropylene (in which the stereocenters alternate) may be made via the Ziegler-Natta process (see **Chapter 18, Problem 4**). Experimentally, both isotactic and syndiotactic polypropylene generally have higher melting points than atactic polypropylene.

Examine three different strands of *polypropylene*. For each strand, assign R/S stereochemistry to each stereocenter. (All three strands have as their “terminal monomer” perfluoropropane in order to facilitate assignment of stereochemistry.) Which of the three strands corresponds to atactic polypropylene, isotactic polypropylene and syndiotactic polypropylene?

Spectroscopy

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excitation from HOMO to LUMO gives rise to the electronic absorption spectrum of 1,3,5-hexatriene (see problem 6)

Vibrational Spectrum of Water

The magnitudes of vibrational motions shown are greatly exaggerated. At room temperature atoms move only about 10% away from their equilibrium positions.

Molecules vibrate at characteristic frequencies, which depend both on the “difficulty” of the motion (the so-called force constant) and on the masses of the atoms involved. The more difficult the motion and the lighter the atomic masses, the higher the vibrational frequency. For a diatomic molecule the vibrational frequency is proportional to:

$$\sqrt{\frac{k}{\mu}}$$

k is the force constant which is related to the “stiffness” of the bond, and which is independent of the masses of the atoms involved, and μ is the so-called reduced mass.

Display *water* as a ball-and-spoke model. How many different vibrations are there? Explain. One after the other, animate these vibrations. For each, record the vibrational frequency and provide a description of the atomic motions. What appears to be easier (lower frequency), motions primarily associated with bond stretching or with angle bending?

Repeat the analysis with *deuterium oxide* (D_2O). Are the vibrational frequencies the same, larger or smaller than those in water? Rationalize your observations. Are the changes in vibrational frequencies greatest for bond stretching or angle bending motions?

Infrared Spectra of Carbonyl Compounds

The CO stretch in the infrared spectra of carbonyl compounds gives rise to a strong absorption around 1700 cm^{-1} , and is often used as a diagnostic.

Examine each of the vibrational motions for *acetone*, and identify the motion corresponding to the CO stretch. What is its frequency? Are there any other vibrations which have very similar frequencies? Does your result have implications for the use of the CO stretching frequency as a diagnostic for carbonyl compounds? Elaborate. Does the “CO stretching frequency” involve significant motion of any atoms other than the two which make up the carbonyl group? Rationalize your observation.

Examine each of the vibrational motions for *acetophenone*, and identify the motion corresponding to the CO stretch. Is the frequency about the same or larger or smaller than the corresponding frequency in acetone? Rationalize your observation. Hint: Draw contributing resonance structures for acetophenone. Would you expect the CO bond to be about the same or longer or shorter than that in acetone? (Compare bond lengths in acetone and acetophenone to check your reasoning.) Is there a relationship between CO bond length and CO stretching frequency? If so, try to rationalize.

Compare the geometry of *2,6-dimethylacetophenone* to that of acetophenone. In particular, consider the orientation of the phenyl ring and the carbonyl group. Is one of the molecules better suited than the other for conjugation? Next, identify the CO stretching frequency in 2,6-dimethylacetophenone. Is it significantly smaller or significantly larger than that in acetophenone, or is it about the same? What, if anything, does this tell you about the importance of conjugation in these systems?

Calculated vibrational frequencies will not exactly match measured frequencies (they are typically too large by about 12%). For example, a measured frequency of 1700 cm^{-1} would correspond to a calculated frequency of around 1900 cm^{-1} .

Concentration Effects on Infrared Spectra

The infrared spectra of alcohols change markedly with increasing concentration. For example, at very low concentration, the infrared spectrum of *tert*-butyl alcohol in carbon tetrachloride contains a single sharp band at approximately 3600 cm^{-1} corresponding to the OH stretching motion. As the alcohol's concentration increases (by adding more alcohol to the sample), a second broad OH stretch band grows in at approximately 3400 cm^{-1} and eventually replaces the other band.

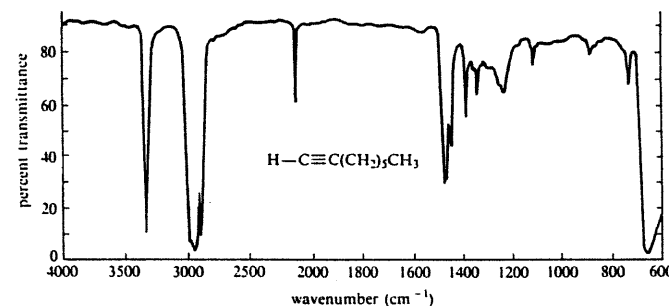
tert-Butyl alcohol serves as a model of the dominant species in a dilute alcohol solution, and *tert*-butyl alcohol dimer serves as a model of the dominant species in a more concentrated solution. Examine the vibrations of *tert*-butyl alcohol and identify vibrations that involve OH stretching. Next, identify the analogous OH vibrations in the dimer. How are these frequencies shifted from those in *tert*-butyl alcohol? Which vibrational frequency is shifted more, the one involving the "bridging" O or the one involving the "terminal" O? Does the behavior of the model provide insight into the experimental observations? Explain.

Would you expect the OH stretching frequencies in *2,3-dimethyl-2,3-butanediol* to be shifted from the value in *tert*-butyl alcohol, even in dilute solution. Identify the OH stretching frequencies in the diol and compare them to *tert*-butyl alcohol. Rationalize your observations by comparing the geometry of the diol with those of *tert*-butyl alcohol and *tert*-butyl alcohol dimer.

Vibrational Spectrum of 1-Octyne

The vibrational spectrum of a nonlinear molecule with N atoms may contain as many as $3N-6$ different absorptions. These often overlap so that only a few "bands" are observed. Also, some vibrations produce weak absorptions and are not observed. The highest-frequency bands correspond to stretching vibrations involving hydrogen, e.g., CH stretches. Bond stretches not involving hydrogen as well as angle bends involving hydrogen are of lower frequency, followed by angle bends not involving hydrogen. The lowest-frequency vibrations typically correspond to torsional motions. These are not usually recorded with spectrometers in routine use.

Display *1-octyne* as a ball-and-spoke model. Examine the individual vibrations ($> 1400\text{ cm}^{-1}$ only), and classify the bands in the experimental infrared spectrum as due to specific motions, e.g., CH, CC and $\text{C}\equiv\text{C}$ stretching, and HCH and CCC bending motions.



Each atom may vibrate along three different coordinates (giving rise to $3N$ vibrations).

However, the origin of the coordinate system and the orientation of the molecule in the coordinate system are arbitrary. This eliminates six vibrations, leaving $3N-6$. Linear molecules require only two variables to specify their orientation. Here, only five vibrations are eliminated, leaving $3N-5$.

Calculated vibrational frequencies will not exactly match measured frequencies (they are typically too large by about 12%). For example, a measured frequency of 1700 cm^{-1} would correspond to a calculated frequency of around 1900 cm^{-1} .

Spectral Identification of Short-Lived Molecules

Short-lived molecules may often be identified by their infrared spectra measured at extremely low temperatures. In most cases, the experimental spectrum will be incomplete, although a few “characteristic” lines or bands are often sufficient to decide among alternative structures.

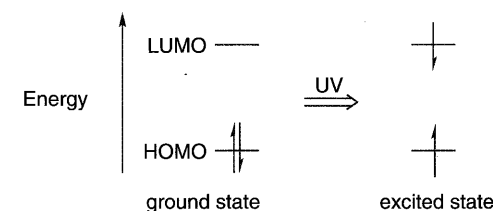
The infrared spectrum of a C_4H_4 isomer shows strong absorptions at 215, 854, 1608, 2994 and 3080 cm^{-1} . “Reasonable” C_4H_4 structures include *but-1-yne-3-ene*, *butatriene*, *singlet* and *triplet cyclobutadiene*, *methylene-cyclopropene* and *tetrahedrane*. Examine the vibrational frequencies of each. Are all of these structures actually energy minima, or can you eliminate one or more? Which structure best fits the experimental infrared spectrum? (Recall that calculated frequencies are typically 12% larger than measured frequencies.) Is it the lowest-energy C_4H_4 isomer?

Assign the vibrational frequencies in the experimental spectrum using the data from the structure you selected.

Energy minima have all real frequencies, while molecules with one or more imaginary frequencies are not minima.

Electronic Spectra of Conjugated Alkenes

Alkenes absorb ultraviolet (UV) light and use the absorbed energy to excite an electron from the HOMO (highest-occupied molecular orbital) to the LUMO (lowest-unoccupied molecular orbital).



Absorption maxima (λ_{max}) data (see table at right) show the effects of conjugation. Assuming that excitation energies, related to λ_{max} by equation (1), parallel HOMO-LUMO energy gaps, which molecule would you expect to have the smallest HOMO-LUMO gap? The largest gap? What effect does conjugation have on the HOMO-LUMO energy gap?

Another way to look at the effect of conjugation is to examine the shape of the HOMO and LUMO. First, examine the HOMO of *ethene*. Is it bonding or antibonding? Next, examine the HOMO of *1,3-butadiene*, *1,3,5-hexatriene* and *beta-carotene*. For each, count the number of bonding interactions and the number of antibonding interactions. Which HOMO (if any) are “pure” bonding orbitals? Which HOMO (if any) are nonbonding (equal number of bonding and antibonding interactions)? Order the HOMO by energy (assume that HOMO energy falls as net bonding character increases). What effect does conjugation have on HOMO shape and energy?

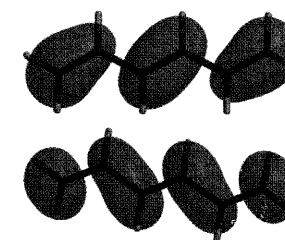
Repeat your analysis for the LUMO of ethene, 1,3-butadiene, 1,3,5-hexatriene and β -carotene, except now focus on each orbital’s net antibonding character. (Assume that LUMO energy rises as net antibonding character increases.) What effect does conjugation have on LUMO shape and energy? Are your predictions for the HOMO-LUMO energy gap consistent with the experimental data?

Alkene	λ_{max} (nm)
ethene	165
1,3-butadiene	217
1,3,5-hexatriene	253
β -carotene	452

$$E = 45.6/\lambda_{\text{max}}$$

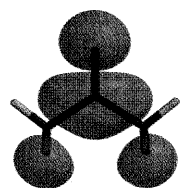
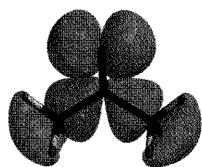
E is the excitation energy (in au)

λ_{max} is the excitation wavelength (in nm)

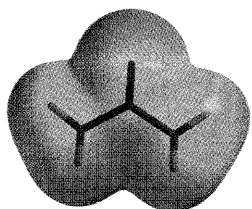


HOMO and LUMO of 1,3,5-hexatriene show origin and destination of excited electron.

Solvent Effects on Electronic Spectra



HOMO (top) and LUMO (bottom) of acetone change occupancy upon absorption of light.



Electrostatic potential map for the ground state of acetone shows negatively-charged regions (in red) and positively-charged regions (in blue).

$$E = 45.6/\lambda_{\max} \quad (1)$$

E is the excitation energy (in au)

λ_{\max} is the excitation wavelength (in nm)

The lowest-energy electronic excitation in acetone is $n \rightarrow \pi^*$, and is usually described as promotion of a nonbonding electron on oxygen to a π antibonding orbital involving the carbonyl bond. This excitation is triggered by UV radiation, and causes a significant change in molecular polarity.

Examine and describe both the highest-occupied and lowest-occupied molecular orbitals (HOMO and LUMO, respectively) of **ground state acetone**. On which atom(s) is the HOMO primarily concentrated? Is it in the σ system or in the π system? Repeat your analysis for the LUMO.

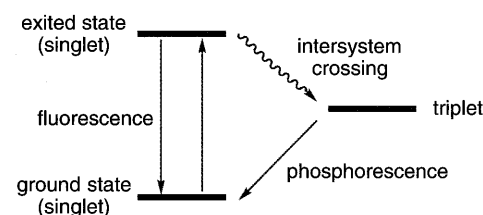
Compare the dipole moment and the electrostatic potential map for the ground state of acetone to those of the ***n to π^* state of acetone***. Which molecule is more polar? Rationalize the differences by appealing to the shape of the orbitals (in ground-state acetone) whose electron populations are changed by excitation.

The $n \rightarrow \pi^*$ transition appears at 279 nm in hexane. Calculate the energy necessary for this transition (use equation 1). Is this enough energy to cause a chemical change in the molecule, i.e., is this enough energy to break a chemical bond? π bonds typically have strengths of approximately 0.1 au (60 kcal/mol), and σ bonds typically have strengths in the range of 0.1 to 0.15 au (60 to 95 kcal/mol).

Acetone is a moderately polar molecule that can hydrogen-bond with water. Which electronic state of acetone would be stabilized more by moving the molecule from hexane to water? Will this shift the $n \rightarrow \pi^*$ transition to longer or shorter UV wavelengths? Explain.

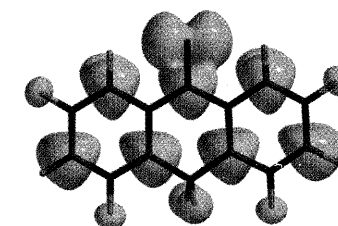
Singlet and Triplet Anthrone

Anthrone absorbs visible light leading to an excited singlet state. This state is short-lived and can either return to the ground singlet state by light emission (“fluorescence”). It can also relax to a triplet state in a process known as intersystem crossing. The triplet state is much longer lived than the excited singlet and has ample time to undergo a chemical reaction. It can also return to the ground singlet state by emission of light (“phosphorescence”).



First, try to draw resonance contributors for both ground state and triplet anthrone. Then display a spin density surface for the **triplet** state of **anthrone**. (Note that the spin density surface shows the location of **both** unpaired electrons, one of which may be in a π orbital and one of which may be in a σ orbital.) Where are the two unpaired electrons? Are they localized or delocalized? Given that spin delocalization generally leads to stabilization, would you expect the triplet state of anthrone to be stable?

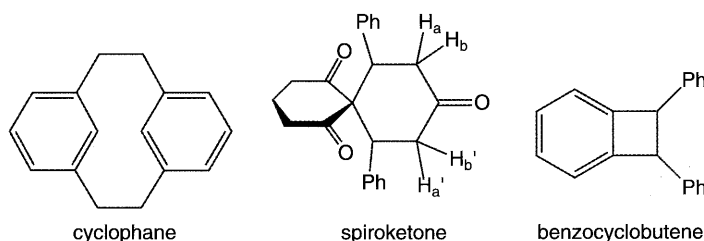
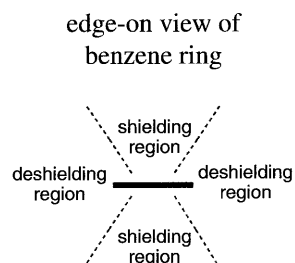
Compare the geometries of triplet and ground state **singlet anthrone**. Where do they differ the most? Focus on the carbonyl group. Has the CO bond distance altered? Does the molecule incorporate a fully-developed CO π bond (as in ground state singlet anthrone), or a single bond (as in **phenol**)? Is the carbonyl carbon planar or puckered? Rationalize your observations.



Spin density surface for triplet anthrone locates the two unpaired electrons.

Magnetic Anisotropy and Chemical Shifts

Molecules that contain a benzene ring generate local magnetic fields when placed in a strong external field (in an NMR spectrometer). The local field is anisotropic. Protons that lie in the ring plane are deshielded (signal moves to higher chemical shift), while those located above and below the ring plane are shielded (signal moves to lower chemical shift). These shifts can be used to help assign NMR spectra and establish molecular configuration.



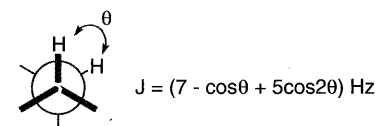
The ^1H NMR spectrum of the cyclophane shows three signals at δ 4.27, 6.97, and 7.24 (1:2:1 ratio) due to the benzene ring hydrogens. Examine *cyclophane* and identify which hydrogens are responsible for each signal.

The labeled hydrogens in the spiroketone fall into two symmetry-related pairs. H_a and $\text{H}_{a'}$ produce signals at δ 2.4, and H_b and $\text{H}_{b'}$ produce signals at δ 3.48. Examine *spiroketone* and determine which pair of hydrogens is responsible for which signals. Incorporate a sketch of the molecule showing the geometry of the rings and the orientation of the labeled hydrogens as part of your answer.

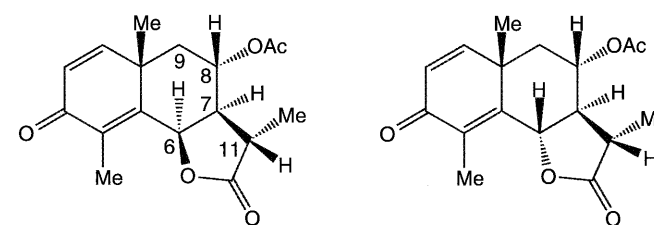
The NMR spectra of *cis* and *trans*-diphenylbenzocyclobutene are nearly the same except for the chemical shifts of the hydrogens on the four-membered ring. The hydrogens in one compound produce a singlet at δ 4.44, while those in the other compound produce a singlet at δ 5.2. Examine the geometries of *cis* and *trans* **diphenylbenzo-cyclobutane**. Which compound is responsible for which NMR spectrum? Explain your reasoning.

Vicinal H-H Coupling and the Karplus Equation

The coupling constant, J , between vicinal protons varies with dihedral angle, θ . The relationship between J and θ is given by the "Karplus equation".



The Karplus equation predicts that J is largest when the two CH bonds are staggered *anti* ($\theta=180^\circ$) or eclipsed ($\theta=0^\circ$), and J is smallest when the two bonds are perpendicular ($\theta=90^\circ$). Because of J 's dependence on dihedral angle, it can be used to distinguish between isomers such as artemisin acetate and 6-epiartemisin acetate.



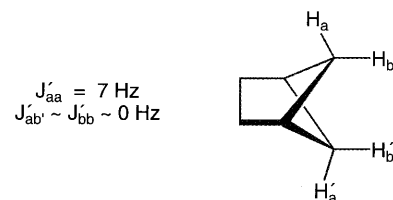
$J(\text{vicinal})$

H_a, H_b	artemisin acetate	6-epiartemisin acetate
6,7	11.6	5.7
7,8	10.9	10.5
7,11	11.5	0
8,9 _{axial}	10.9	10.5

For each molecule (*isomer A* and *isomer B*), obtain dihedral angles for the following pairs of vicinal hydrogens: $\text{H}_6\text{--H}_7$, $\text{H}_7\text{--H}_8$, $\text{H}_7\text{--H}_{11}$, and $\text{H}_8\text{--H}_{9\text{axial}}$. Use the Karplus equation to estimate coupling constants for each pair, and then compare your predictions to the experimental coupling constants (see above). Which molecule is artemisin acetate and which is 6-epiartemisin acetate?

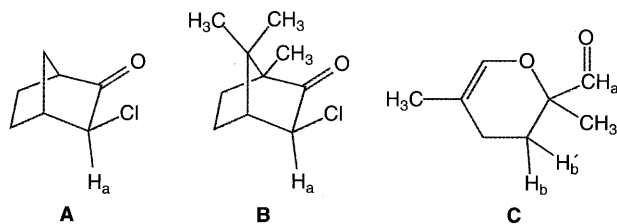
Long-Range "W" Coupling

Observable proton-proton coupling is generally limited to protons separated by two bonds (geminal coupling) or three bonds (vicinal coupling). Longer-range coupling is much weaker, but significant exceptions occur when the intervening CH and CC bonds form a planar "zig-zag" or "W" pattern, as H_aCCCH_a' in bicyclo[2.1.1]hexane.



Examine the structure of *bicyclohexane* and note the spatial relationships of the various CH and CC bonds. Do all the bonds separating H_a and H_a' lie in the same plane?

Examine the structures of the *norcamphor* and *camphor* derivatives (A and B).

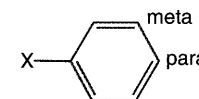


Note the relationship between H_a and the other hydrogens. Long-range coupling to H_a ($J \sim 4 \text{ Hz}$) is observed in only one of these molecules. Which molecule do you think this is? Identify the proton that is coupled to H_a .

The NMR signal due to H_a in the *dihydropyran* derivative (C) appears as a doublet ($J = 1.3 \text{ Hz}$), indicating coupling to either H_b or $H_{b'}$, but not both. Make a sketch of this molecule showing the orientation of H_a , H_b , and $H_{b'}$. Which proton, H_b or $H_{b'}$, is responsible for the long-range coupling? Why can't long-range coupling to CH_3 account for the H_a doublet?

Substituent Effects on ^{13}C Chemical Shifts

^{13}C chemical shifts depend, in part, on the amount of electron density around the ^{13}C nucleus. Since benzene ring substituents perturb the electron density at selected carbons around the ring, one might expect these substituents to exert a noticeable effect on the chemical shifts of these nuclei.



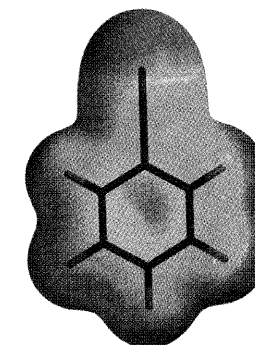
First compare electrostatic potential maps for *phenol*, *toluene*, *benzene*, *trifluorotoluene*, *benzonitrile*, *benzaldehyde* and *nitrobenzene*. Relative to hydrogen (in benzene), which substituent leads to the greatest reduction in negative charge in the π system? Which leads to the greatest increase in negative charge? Next, obtain atomic charges for the *meta* and *para* carbons for each system. (Define the *meta* charge as the average of the atomic charges on the two *meta* carbons.) Which set of charges is more sensitive to substituent structure? Is it the same set for which the chemical shifts show the greater sensitivity (see table at right)?

Plot *para* chemical shift (vertical axis) vs. *para* atomic charge (horizontal axis). Are the two properties correlated? If they are, what is their relationship? Does chemical shift increase (^{13}C becomes deshielded) or decrease (^{13}C becomes shielded) with increasing negative charge at carbon?

Draw the most important resonance contributors for nitrobenzene (include all of the contributors needed to explain for the variation in electrostatic potential, charge and chemical shift relative to benzene). Do these resonance contributors account for the different behavior of δ_{meta} and δ_{para} ? Explain.

chemical shifts in PhX

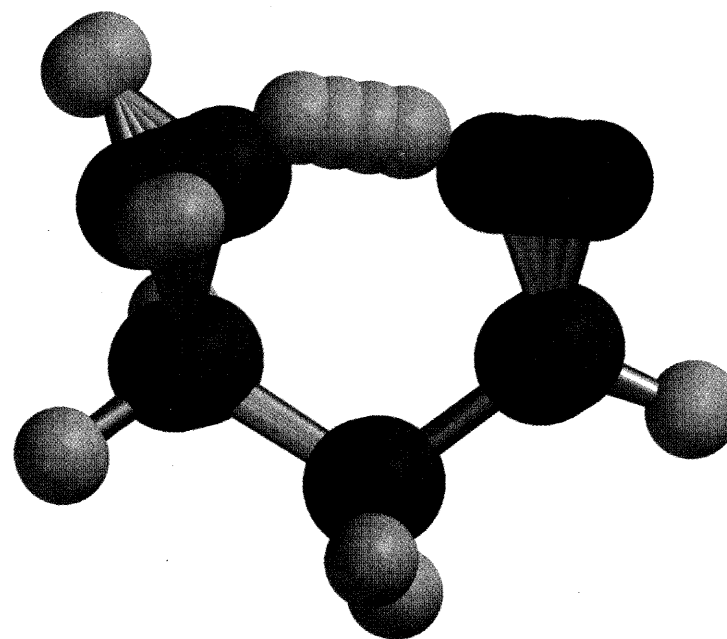
X	δ_{meta}	δ_{para}
OH	130.1	121.2
CH ₃	128.4	125.6
H	128.5	128.5
CF ₃	128.9	131.9
CN	129.1	132.8
CHO	129.1	134.3
NO ₂	129.4	134.5



Electrostatic potential map for benzonitrile shows negatively-charged regions in red and positively-charged regions (in blue).

Mass Spectrometry

- 1 Mass Spectra of Alcohols 268
- 2 Mass Spectra of Alkenes and Arenes. Resonance Stabilized Cations 269
- 3 McLafferty Rearrangement 270



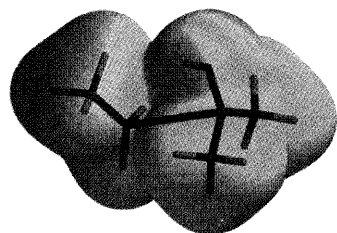
transition state for McLafferty rearrangement of butanal radical cation
(see problem3)

Mass Spectra of Alcohols

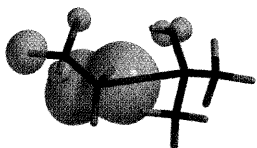
The mass spectra of alcohols often completely lack a peak corresponding to the parent ion. This is due to extremely rapid loss of neutral fragments following initial ionization. For example, the mass spectrum of 2-methyl-2-butanol lacks a parent peak and contains strong peaks at M-15 (loss of CH_3^\bullet) and M-18 (loss of H_2O).

First, consider loss of ethyl radical. Examine the geometry and electrostatic potential map of **2-methyl-2-butanol radical cation**. Are any of the carbon-carbon bonds significantly longer than normal? (Compare the geometry to that of 2-methyl-2-butanol.) Which portion of the molecule is most positively charged? Which portion carries the least positive charge? Assuming the elongated bond breaks, which fragment is likely to carry a positive charge? Examine the spin density surface of 2-methyl-2-butanol radical cation. Which atom(s) carries the unpaired electron? Assuming the elongated bond breaks, which fragment is likely to carry this electron? Write the chemical reaction that describes loss of ethyl radical and draw complete Lewis structures for all of the reactants and products.

Next, consider loss of water. This involves loss of OH and a CH hydrogen, and must yield a new radical cation (this is required because water is a neutral, even-electron molecule). Examine the geometries, electrostatic potential maps and spin density surfaces of the three radical cations that might result (**radical cation A, B, C**). Draw a single Lewis structure (or pair of equivalent Lewis structures) for each radical cation which best describes both the location of the unpaired electron and the positive charge. Which CH hydrogen must be lost in order to generate each radical cation? Which radical cation is most stable? Why? Is the most stable radical cation that in which the unpaired electron and positive charge is most delocalized?



Electrostatic potential map for 2-methyl-2-butanol radical cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).



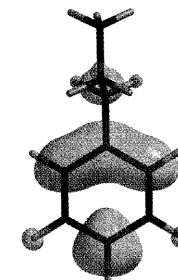
Spin density for 2-methyl-2-butanol radical cation shows location of unpaired electron.

Mass Spectra of Alkenes and Arenes. Resonance Stabilized Cations

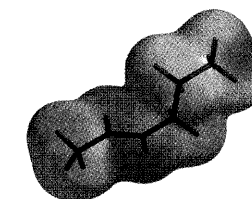
In general, fragmentation in a mass spectrometer gives rise to the most stable ions. For unsaturated compounds resonance stabilized ions may be possible.

The mass spectrum of *trans*-2-hexene shows a very strong peak at M-29. Compare the geometry of ***trans*-2-hexene radical cation** to that of ***trans*-2-hexene**. Is there any indication for pending loss of a neutral fragment of mass 29? (Pay particular attention to elongated bonds.) Explain. If there is, identify the ionic and neutral fragments. Examine both the spin density surface and electrostatic potential map for *trans*-2-hexene radical cation. Does this show evidence for any particular fragmentation? Explain.

Repeat your analysis for *n*-propylbenzene. (Compare geometries of **1-propylbenzene radical cation** and **1-propylbenzene**.) Where would you expect a strong peak in the mass spectrum? Identify the ion responsible.



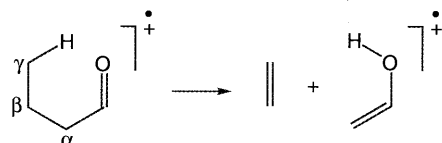
Spin density surface for 1-propylbenzene radical cation shows location of unpaired electron.



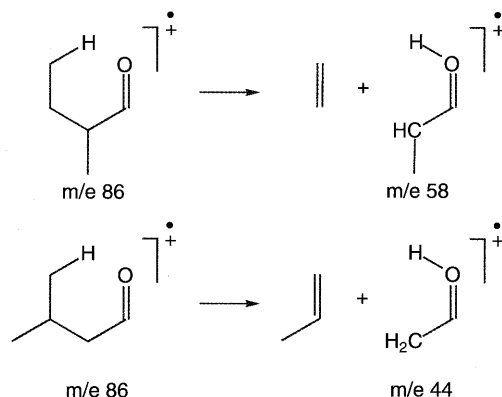
Electrostatic potential map for *trans*-2-hexene radical cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

McLafferty Rearrangement

Radical cations generated in a mass spectrometer from aldehydes and ketones with γ hydrogens undergo a rearrangement in which a γ hydrogen is first transferred and a carbon-carbon bond is then cleaved, e.g.



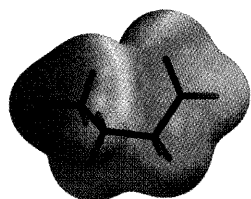
The McLafferty rearrangement, as it is known, is useful for structure identification. For example, the mass spectrum of 2-methylbutanal shows a peak at m/e 58, while that of 3-methylbutanal shows a peak at m/e 44.



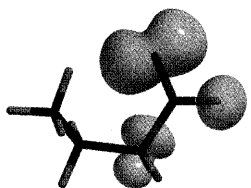
Examine energies for *butanal radical cation*, the *transition state* for hydrogen migration and the rearranged *enol radical cation*. Is the first step, hydrogen transfer endothermic or exothermic? Is the activation barrier low enough that the process will be fast in a mass spectrometer? Is the rearranged cation an energy minimum?

Use geometries, electrostatic potential maps and spin densities to help you draw Lewis structures for butanal radical cation, the transition state and product. Where is the positive charge and the unpaired electron in each? Is the positive charge (the unpaired electron) more or less delocalized in the transition state than in the reactant? In the product?

Energy minima have all real frequencies, while molecules with one or more imaginary frequencies are not minima.



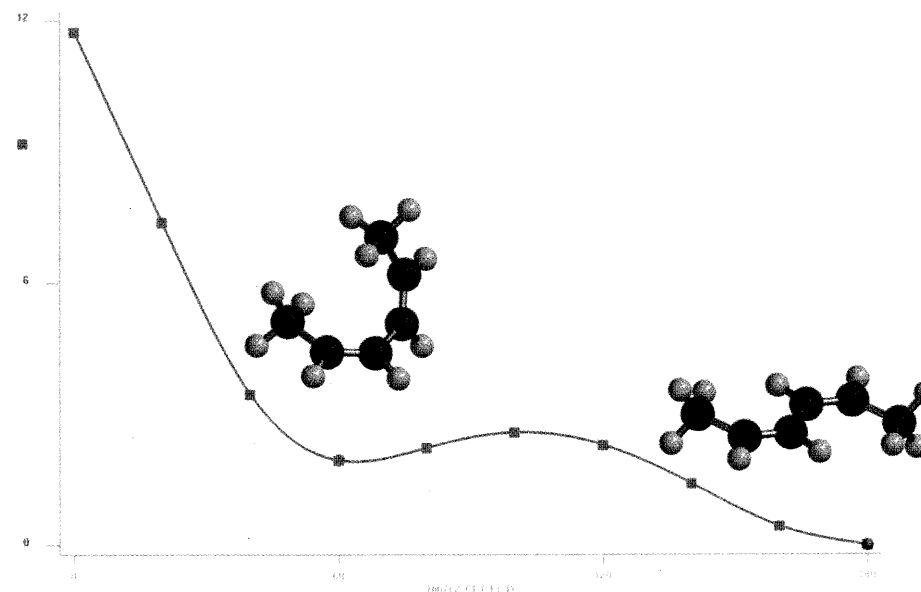
Spin density surface for butanal radical cation shows location of unpaired electron.



Electrostatic potential map for butanal radical cation shows most positively-charged regions (in blue) and less positively-charged regions (in red).

Pericyclic Reactions

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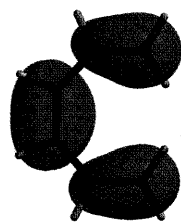
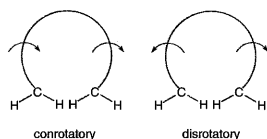
energy profile for rotation about the central carbon-carbon bond in 2,2-hexa-2,4-diene (see problem 6)

Electrocyclic Reactions

Cis-1,3,5-hexatriene readily undergoes ring closure to give 1,3-cyclohexadiene.



This is an example of an electrocyclic reaction, and involves rotation of the terminal methylene groups either in the same way ("conrotatory") or in opposite ways ("disrotatory").

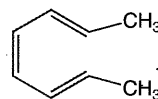


HOMO of *cis*-1,3,5-hexatriene anticipates the preferred direction of ring closure.

Woodward and Hoffmann speculated that the preferred motion was that which involved constructive (bonding) overlap between the terminal lobes of the highest-occupied molecular orbital (HOMO).

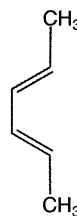
Display the HOMO for *cis*-1,3,5-hexatriene. Which motion (conrotatory or disrotatory) insures bonding overlap? Examine the geometry of the transition state for ring closure (*hexatriene to cyclohexadiene*). Is it consistent with the anticipated (conrotatory or disrotatory) motion of the terminal methylenes?

What should be the kinetic product of ring closure of the dimethylhexatriene shown below?



Is this also the thermodynamic product? (Compare energies of *cis* and *trans*-5,6-dimethylcyclohexa-1,3-diene.)

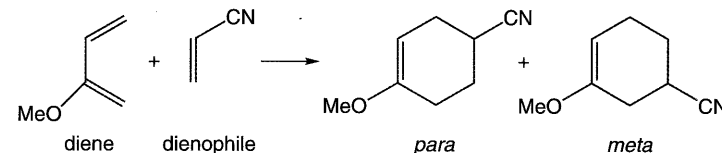
Repeat your analysis for ring closure of *butadiene to cyclobutene*. (Start by examining the HOMO of *cis*-1,3-butadiene.) What should be the preferred product of ring closure of the dimethylbutadiene shown below?



Is your predicted product also the thermodynamic product? Energies for *cis* and *trans*-3,4-dimethylcyclobutene are available.

The Diels-Alder Reaction. A Symmetry Allowed Process

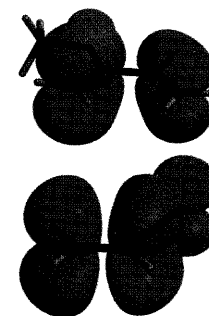
The most common and synthetically most useful Diels-Alder reactions involve the addition of an electron-rich diene and an electron-poor dienophile, e.g.



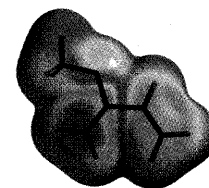
Woodward and Hoffmann pointed out that the Diels-Alder reaction involved bonding overlap of the highest-occupied molecular orbital (HOMO) on the diene and the lowest-unoccupied molecular orbital (LUMO) on the dienophile. Display the HOMO for 2-methoxybutadiene. Where is it localized? Display the LUMO for acrylonitrile. Where is it localized? Orient the two fragments such that the HOMO and LUMO best overlap (A clearer picture is provided by examining the HOMO map for 2-methoxybutadiene and the LUMO map for acrylonitrile.) Which product should result?

Examine transition states leading to *para* and *meta* adducts (2-methoxybutadiene+acrylonitrile *para* and *meta*) as well as the adducts themselves (1-methoxy-4-cyanocyclohexene and 1-methoxy-5-cyanocyclohexene). What should the kinetic product be? Is this in line with your expectations based on orbital interactions? Is this also the thermodynamic product?

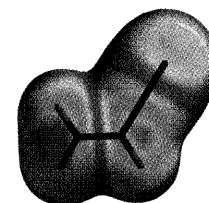
Finally, examine the geometry of the lower-energy transition state. Measure all CC bond lengths. Draw a Lewis structure representing partial bonds in terms of dashed lines (---- and - - -). How many (carbon-carbon) bonds are broken (partially broken) in the transition state? How many bonds are formed (partially formed)?



The Diels-Alder reaction involves overlap of the HOMO of the diene and the LUMO of the dienophile.

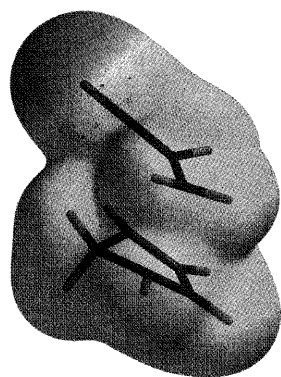


HOMO map for 2-methoxybutadiene reveals (in blue) where the HOMO is concentrated on the exposed electron density surface.



LUMO map for acrylonitrile reveals (in blue) where the LUMO is concentrated on the exposed electron density surface.

Electron Flow in Diels-Alder Reactions



Electrostatic potential map for transition state for Diels-Alder reaction of cyclopentadiene and acrylonitrile shows negatively-charged regions (in red) and positively-charged regions (in blue).

Experimental relative rates of Diels-Alder reactions involving cyclopentadiene

dienophile	relative rate
ethene	6×10^{-6}
acrylonitrile	1
tetracyanoethylene	4×10^7

Electrostatic interactions play a significant role in determining the rates of Diels-Alder reactions.

Compare electrostatic potential maps for the following Diels-Alder transition states: *cyclopentadiene+ethene*, *cyclopentadiene+acrylonitrile* and *cyclopentadiene+tetracyanoethylene*, with those of reactants: *cyclopentadiene*, *ethene*, *acrylonitrile* and *tetracyanoethylene*. Are electrons transferred from diene to dienophile in the transition states (relative to reactants) or vice versa? For which reaction is the transfer the greatest? The least? Quantify your conclusion by measuring the total charge on the diene and dienophile components in the three transition states.

Calculate activation energies for the three Diels-Alder reactions (energy of transition state - sum of energies of reactants). Which reaction has the smallest energy barrier? Which has the largest energy barrier? Do your results parallel the measured relative rates of the same reactions (see table at left)?

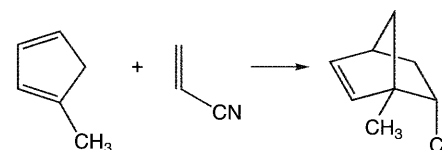
Is there a correlation between activation energy and the magnitude of charge transfer between diene and dienophile components in the transition state? Explain.

Catalysis of Diels-Alder Reactions

According to Frontier Molecular Orbital (FMO) theory, Diels-Alder reaction between an electron-rich diene and an electron-poor dienophile involves interaction between the highest-occupied molecular orbital (HOMO) on the diene and the lowest-unoccupied molecular orbital (LUMO) on the dienophile. The better the HOMO/LUMO overlap and the smaller their energy difference, the more favorable the interaction and the faster the reaction.

Lewis acids catalyze Diels-Alder reactions. Do they enhance overlap between diene and dienophile orbitals and/or do they reduce the HOMO/LUMO energy difference?

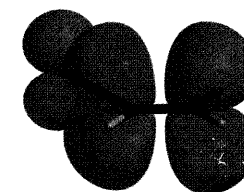
Simultaneously examine the HOMO of *1-methylcyclopentadiene* (the diene) and the LUMO of *acrylonitrile* (the dienophile). Orient the two on screen such that they are disposed for Diels-Alder addition, i.e.



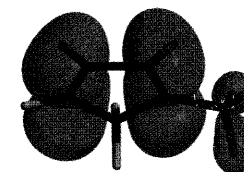
Similarly, examine the overlap between the HOMO of 1-methylcyclopentadiene and the LUMO of an *acrylonitrile BF₃* complex. Does the Lewis acid affect overlap? Would you expect BF₃ to enhance, retard, or leave unchanged the rate of Diels-Alder addition?

LUMO energies for “free” and complexed acrylonitrile are .103 and .089 au (65 and 56 kcal/mol), respectively. On the basis of orbital energies, would you expect BF₃ to enhance, retard, or leave unchanged the rate of Diels-Alder cycloaddition?

Check your predictions by calculating activation energies for Diels-Alder additions. Data for transition states: *1-methylcyclopentadiene+acrylonitrile* and *1-methylcyclopentadiene+acrylonitrile BF₃* are available.

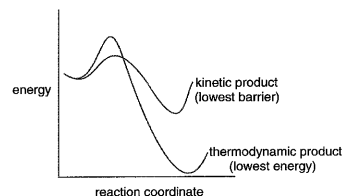


LUMO for acrylonitrile receives electrons in a Diels-Alder addition.



HOMO for 1-methylcyclopentadiene donates electrons in a Diels-Alder addition.

Stereochemistry of Diels-Alder Reactions. Thermodynamic vs. Kinetic Control



The thermodynamic product is the lowest energy product, while the kinetic product is the most easily formed product.

$$\frac{N_{\text{major}}}{N_{\text{minor}}} = e^{-1060(E_{\text{major}} - E_{\text{minor}})} \quad (1)$$

N_i is the number of molecules i

E_i is the energy of molecule i (in au)

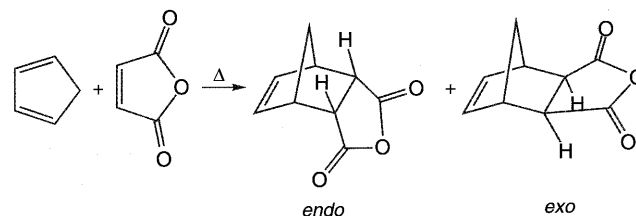
$$\frac{N_{\text{major}}}{N_{\text{minor}}} = e^{-1060(E_{\text{major}}^\ddagger - E_{\text{minor}}^\ddagger)} \quad (2)$$

N_i is the number of molecules i

E_i^\ddagger is the energy of the transition state leading to molecule i (in au)

Chemical reactions often yield entirely different product distributions depending on the conditions under which they are carried out. In particular, high temperatures and long reaction times favor the most stable (“thermodynamic”) products, while low temperatures and short reaction times favor the most easily formed (“kinetic”) products.

Consider Diels-Alder reaction of cyclopentadiene and maleic anhydride, leading to *endo* or *exo* adducts.



Display space-filling models of *endo adduct* and *exo adduct*. Which appears to be the less crowded? Identify specific interactions which disfavor the higher-energy adduct. Next, compare energies of the two adducts. Which is the more stable? Were the reaction under thermodynamic control, which would be the major product and what would be the ratio of major to minor products? Use equation (1).

Compare energies of *endo transition state* and *exo transition state*. Which of the two has the lower energy? Were the reaction under kinetic control, which would be the major product and what would be the ratio of major to minor products? Use equation (2).

Are the kinetic and thermodynamic products the same? If not, describe conditions which will favor the *endo* adduct. The *exo* adduct.

Effect of Conformation on Rates of Diels-Alder Reactions

Experimentally, the rates of Diels-Alder reactions between electron-rich dienes and electron-poor dienophiles generally increase with increased alkyl substitution on the diene. This is because alkyl groups act as electron donors and lead to buildup of electron density on the diene. An exception to this is the reaction of *Z,Z*-hexa-2,4-diene with tetracyanoethylene (TCNE), which is actually slower than the corresponding addition involving *E*-penta-1,3-diene.

Step through the sequence of structures depicting rotation around the central carbon-carbon bond in *E*-penta-1,3-diene. Plot energy (vertical axis) vs. $C_1C_2C_3C_4$ dihedral angle (horizontal axis). Identify the lowest-energy conformer, and calculate how much energy is needed to “twist” this conformer into a conformer that approximates the geometry in the transition state (*E*-penta-1,3-diene+TCNE).

Repeat your analysis for *Z,Z*-hexa-2,4-diene, and again calculate the energy to twist the diene into the same conformation as seen in the Diels-Alder transition state (*Z,Z*-hexa-2,4-diene+TCNE). Compare the two “twisting energies”, and rationalize the observed relative rates for the two cycloaddition reactions.

Examine conformational energy profiles for *Z*-penta-1,3-diene and *E,E*-hexa-2,4-diene together with transition-state geometries for cycloadditions with TCNE (*Z*-penta-1,3-diene+TCNE and *E,E*-hexa-2,4-diene+TCNE, respectively). Predict the rates of Diels-Alder reactions involving these two dienes, relative to that for cycloaddition of *E*-penta-1,3-diene with TCNE.

7

Cope and Claisen Rearrangements

The Cope and Claisen rearrangements are markedly similar reactions, although they differ in thermodynamic driving force. Whereas the Cope rearrangement of 1,5-hexadiene is thermoneutral (reactant and product are the same), the analogous Claisen rearrangement of allyl vinyl ether is exothermic. Do thermodynamic differences lead to differences in transition state geometries?

Step through the sequence of structures depicting **Cope rearrangement** of 1,5-hexadiene. Plot energy (vertical axis) vs. the length of either the carbon-carbon bond being formed or that being broken (horizontal axis). Locate the transition state. Measure all CC bond distances at the transition state, and draw a structural formula for it representing partial bonds in terms of dashed lines (----- and =====). How many carbon-carbon bonds are broken (partially broken) at the transition state? How many carbon-carbon bonds are formed (partially formed)? Are all bonds broken or formed to roughly the same extent?

Repeat the procedure for the sequence of structures depicting the **Claisen rearrangement** of allyl vinyl ether to 4-pentenal. Plot energy (vertical axis) vs. the length of either the carbon-oxygen bond being broken or the carbon-carbon bond being formed (horizontal axis). Locate the transition state. Measure all relevant bond distances and draw a structural formula for it representing partial bonds in terms of dashed lines (----- and =====). How many carbon-carbon and carbon-oxygen bonds are broken (partially broken) at the transition state? How many bonds are formed (partially formed)? Are all bonds broken or formed to roughly the same extent?

Would you describe the transition state for the Claisen rearrangement as “early” (like reactants), “late” (like products) or in between? Given the overall thermodynamics of reaction, do you conclude that the Hammond Postulate applies? Explain.

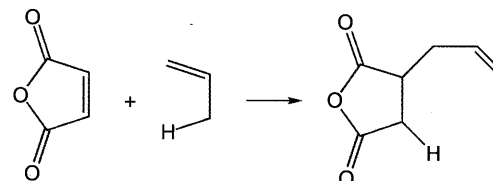
Cope rearrangement of 1,5-hexadiene.

Claisen rearrangement of allyl vinyl ether.

8

Ene Reaction. Kinetic Isotope Effects

The ene reaction involves addition of an electrophilic double bond to an alkene with an allylic hydrogen. The allylic hydrogen is transferred and a new carbon-carbon bond is formed, e.g., the addition of maleic anhydride and propene.



Compare the geometry of **maleic anhydride+propene**, the ene transition state, to those of the reactants (**maleic anhydride** and **propene**). Is bond making and breaking occurring at once? In particular, is the “migrating hydrogen” partially bonded to two carbons (rather than being fully bonded to one carbon)? Draw a Lewis structure to represent the transition state. Use dashed lines (----- and =====) to represent partial bonds.

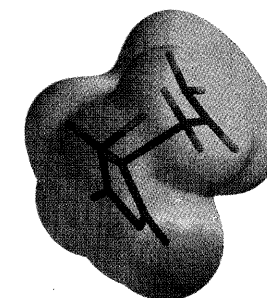
Any change in bonding from reactants to transition state leads to the possibility of rate changes in response to mass changes of the atoms immediately involve, i.e., “kinetic isotope effects”. In particular, replacement of the “migrating hydrogen” by deuterium should lead to a sizable deuterium isotope effect. Use equation (1) to calculate the isotope effect k_H/k_D . (Zero-point energies are provided at the right.) Which reacts faster, propene or deuteriopropene?

Compare atomic charges and electrostatic potential maps between reactants and transition state. Is there charge transfer from one of the reactants to the other (count the migrating hydrogen as part of propene)? If so, what is the direction of the transfer? Why? (See also **Chapter 21, Problem 3**.)

Zero-Point Energies (ZPE) (au)	
maleic anhydride	0.0606
propene (H)	0.0858
propene (D)	0.0825
transition state (H)	0.1460
transition state (D)	0.1437

$$\frac{k_H}{k_D} = e^{-1060(\Delta ZPE_H - \Delta ZPE_D)} \quad (1)$$

$$\Delta ZPE = ZPE^\ddagger - \sum_i^{\text{reactants}} ZPE_i$$



Electrostatic potential map for maleic anhydride+propene, the transition state for the ene reaction, shows negatively-charged regions (in red) and positively-charged regions (in blue).

Appendix A

Common Terms and Acronyms

Following are brief definitions of a number of terms that are commonly encountered:

Antibonding Molecular Orbital. A **Molecular Orbital** that is antibonding between particular atomic centers. The opposite is a **Bonding Molecular Orbital**.

Atomic Orbital. A function centered on an atom. Atomic orbitals typically closely resemble the solutions to the hydrogen atom (s, p, d....type orbitals).

Boltzmann Equation. The equation which relates the composition of equilibrium mixtures to relative thermochemical stabilities and temperature.

Bonding Molecular Orbital. A **Molecular Orbital** that is bonding between particular atomic centers. The opposite is an **Antibonding Molecular Orbital**.

Density; see **Electron Density**

Diradial. A molecule which is characterized by two singly-occupied molecular orbitals. It may either be a **Singlet** or a **Triplet**.

Doublet. A molecule with one unpaired electron. **Free Radicals (Radicals)** are doublets.

Electron Density. A function that gives the number of electrons per unit volume at a point in space. Summed over all space, this gives the total number of electrons.

Electron Density Surface. A surface of constant **Electron Density**.

Electrostatic Potential. A function describing the energy of interaction of a point positive charge with the nuclei and fixed electron distribution of a molecule.

Electrostatic Potential Map. A graph that shows the value of the **Electrostatic Potential** on an **Electron Density Surface** corresponding to a **van der Waals Surface**.

Equilibrium Geometry. The geometry corresponding to a **Local Minimum** on a **Potential Energy Surface**. It cannot actually be directly measured experimentally for, even at 0K, molecules do not reside at the bottom of the potential energy well, but rather at higher energy (the **Zero Point Energy**).

Free Radicals; see **Radicals**

Global Minimum. The lowest energy **Local Minimum** on a **Potential Energy Surface**.

Heterolytic Bond Dissociation. A process in which a bond is broken and a cation and anion result.

HOMO. Highest Occupied Molecular Orbital.

Homolytic Bond Dissociation. A process in which a bond is broken and two radicals result.

Imaginary Frequency. A frequency that characterizes the **Reaction Coordinate** in a **Transition State**.

Isodensity Surface; see **Electron Density Surface**

Kinetically-Controlled Reaction. A reaction the product ratio for which is determined solely by the rate at which different products form (product formation must be irreversible).

Kinetic Isotope Effect. The change in reaction rate caused by isotopic substitution.

LCAO Approximation. Linear Combination of Atomic Orbitals approximation. Expresses the **Molecular Orbitals** by linear combinations of atom-centered functions (**Atomic Orbitals**).

Local Minimum. A **Stationary Point** on a **Potential Energy Surface**. Chemically, a local minimum corresponds to an isomer.

Lone Pair. A pair of electrons contained in a **Nonbonded Molecular Orbital**.

LUMO. Lowest Unoccupied Molecular Orbital.

LUMO Map. A graph that shows the absolute value of the **LUMO** on an **Electron Density Surface** corresponding to a **van der Waals Surface**.

Molecular Orbital. A function made of contributions of **Atomic Orbitals** and delocalized throughout the entire molecular skeleton.

Nonbonded Molecular Orbital. A molecular orbital that does not show any significant bonding or antibonding characteristics. Nonbonded molecular orbitals often correspond to **Lone Pairs**.

Normal Coordinates. Coordinates which describe a molecular vibration.

Potential Energy Surface. A many-dimensional function of the energy of a molecule in terms of the geometrical coordinates of the atoms.

Radical. A molecule with one unpaired electron; see **Doublet**.

Reaction Coordinate. The **Normal Coordinate** that connects the **Local Minima** corresponding to the reactant and product. At the **Transition State**, the reaction coordinate corresponds to the normal coordinate with an **Imaginary Frequency**.

SOMO. Singly Occupied Molecular Orbital.

Singlet. A molecule in which all electrons are paired.

Spin Density. A function that gives the difference in the number of electrons per unit volume of “up” spin and “down” spin at a point in space. Summed over all space, this gives the difference in the total number of electrons of “up” spin and “down” spin.

Spin Density Surface. A surface of constant **Spin Density**.

Stationary Point. Any point on the **Potential Energy Surface** for which all energy first derivatives with respect to coordinate changes are zero.

Thermodynamically-Controlled Reaction. A reaction the product ratio for which is determined solely by the relative thermochemical stabilities of the different products (product formation must be reversible, or separate low-energy pathways interconnecting the products must exist).

Thermodynamic Isotope Effect. The change in equilibrium composition caused by isotopic substitution.

Transition State; see **Transition State Geometry**.

Transition State Geometry. The geometry corresponding to a **Stationary Point** on the **Potential Energy Surface** which is an energy minimum in all directions except one (the **Reaction Coordinate**), for which it is an energy maximum.

Transition Structure; see **Transition State Geometry**

Triplet. A molecule with two unpaired electrons.

van der Waals Surface. A surface which describes how much space a molecule occupies, i.e., in a crystal or as a liquid.

Zero Point Energy. The energy of molecular vibration at 0K.

Zwitterion. A neutral valence structure which incorporates both a formal positive charge and a formal negative charge.

Appendix B

Models on the CD-ROM

The models contained on the CD-ROM have all been generated from standard procedures using SPARTAN¹. Most models could also have been generated from MacSPARTAN *Plus*¹ or PC SPARTAN *Plus*¹.

With the exception of very large systems, e.g., polymer strands (**Chapter 18**) and polypeptides and polynucleotides (**Chapter 16**), all calculations have been carried out using *ab initio* Hartree-Fock theory with the 3-21G basis set². The performance of this technique with regard to the calculation of geometries, relative energies, dipole moments and vibrational frequencies has been extensively documented.²

Geometries: Calculated bond distances are typically within 0.02Å of experimental values and bond angles within 2°. Geometries for transition states are not available from experiment. Here it must be assumed that the calculations provide descriptions of similar quality to those for equilibrium geometries.

Relative energies: Hartree-Fock methods poorly describe bond dissociation energies (typically too small by 20 to 40%) and absolute activation energies (typically too large by 20 to 40%). Energies of chemical reactions which do not involve net bond making or breaking, and relative activation energies, are much better described with Hartree-Fock methods. With the 3-21G basis set, errors are typically on the order of $\pm .006$ au (4 kcal/mol). Calculations at the 3-21G level generally identify the correct ground-state conformer and closely reproduce experimental conformational energy differences to within 10-20%.

Dipole moments: The 3-21G method generally yields dipole moments which are too large by 0.5 to 1.0 debyes. Trends in dipole moments are usually well reproduced.

Vibrational frequencies: Calculated vibrational frequencies are larger than measured values, typically by about 12%. Systematic scaling of calculated frequencies (by 0.88) leads to values which are generally suitable for assignment and interpretation of experimental infrared/Raman spectra.

Calculations on larger molecules have been carried out using molecular mechanics techniques and the Merck force field.² This method has proven to be suitable for the calculation of equilibrium geometries and conformational energy differences.

1. Available from Wavefunction, Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612.
2. **A Guide to Molecular Mechanics and Molecular Orbital Calculations in SPARTAN**, W.J. Hehre, J. Yu and P.E. Klunzinger, Wavefunction, Inc., Irvine, CA.

Appendix C

Making New Models

Additional models may be constructed using SPARTAN, MacSPARTAN *Plus* or PC SPARTAN *Plus* for later examination with SPARTANView. The overall procedure comprises three steps.

Model calculation: Calculation of structure, energy and other properties, together with associated graphical surfaces and maps, for each model needs to be carried out using SPARTAN. Standard procedures apply and all calculation methods are available. Full details are provided in the appropriate **User Guides**.¹⁻³

Screen formatting: Models need to be positioned on screen in the way they are to appear in SPARTANView. Any graphical surfaces and maps that are to be available to SPARTANView need to be displayed. (These will not be displayed upon opening of the SPARTANView screen.)

Model export: The “full screen” of models needs to be exported. For SPARTAN and MacSPARTAN *Plus*, this is done using **Export** under the **File** menu, with the selection of “**SPARTAN Collection**”; for PC SPARTAN *Plus*, this is done using **Save As** under the **File** menu.

-
1. SPARTAN **User's Guide**, version 5.0, Wavefunction, Inc., 1997.
 2. MacSPARTAN *Plus* **Tutorial and User's Guide**, version 1.0, Wavefunction, Inc., 1997.
 3. PC SPARTAN *Plus* **Tutorial and User's Guide**, version 1.0, Wavefunction, Inc., 1997.

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