

# Chemical Structure of Urea in Water

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Urea, urea dimer, and the complexes of urea and water molecules were studied using density functional theory. A hydrogen-bonded, cyclic urea dimer was found to be the most stable conformation. Its binding energy, 10.9 kcal/mol, was obtained using a gradient-corrected density functional approach. The conformations of minimum energy isomers of urea with water molecules were also determined. The stability of the urea dimer in solution was investigated by systematically increasing the number of the water molecules in the system. Our results indicate that, due to hydrogen bonding between urea and water, the urea dimer would be unstable and would separate into monomers when the number of water molecules becomes sufficiently large.

## Introduction

The behavior of urea in aqueous solutions is a very important subject in biological and environment studies, especially because of the involvement of urea in our everyday lives as a waste product. Due to the complicated hydrogen bonding and the acid–base properties associated with both the amine and carbonyl groups in the urea molecule, there are not many theoretical studies on the chemical properties of aqueous urea solutions at the molecular level.

On the basis of different types of model potentials, molecular dynamics simulations have been applied to study the structure of urea dimer in water.<sup>1–4</sup> The molecular dynamics results of Cristinziano and co-workers<sup>1,2</sup> using GROMOS potentials<sup>3</sup> found that the urea dimer was only partially stable in aqueous solution. Recently, an energy minimization using force field potentials also found that the existence of urea dimers in urea solutions is very improbable.<sup>4</sup>

Two different models were proposed to explain the thermodynamic properties of the urea solutions. According to the structure-breaking model, the hydrogen bonds between water molecules are destroyed by the urea in solution.<sup>5</sup> However, another model suggested that the solvent structure actually remains unchanged and that there is significant urea dimerization in solution.<sup>6–8</sup> The molecular dynamics simulations carried out by Tanaka and co-workers<sup>9</sup> and Kuharski and Rossky<sup>10,11</sup> supported the latter model and established the importance of urea self-association in solution. In a very recent work, the hydrogen bond formation between urea and water was observed in the hydration shell of urea using Raman spectroscopy, but no evidence of urea dimerization was detected.<sup>12</sup>

Most of the molecular dynamics potentials used in the calculation of the urea and water interaction were obtained at the Hartree–Fock level using relatively small basis sets. In the present work, density functional calculations<sup>13</sup> are applied to study the stability of the urea dimer in a cluster of water molecules. Two different basis sets, DZ94 and DZ94P, which are optimized to minimize the local energy functional, are used for the calculation.

## Computational Methods

Local and gradient-corrected density functional approaches were used in this study. The Slater exchange energy functional

with  $\rho^{1/3}$  is used along with the correlation energy functional of Vosko, Wilk and Nusair (VWN)<sup>14</sup> for local density functional computations. For the gradient-corrected density functional case, we used Becke exchange<sup>15</sup> and Lee–Yang–Parr correlation<sup>16</sup> functionals (BLYP).

All the calculations are carried out with the density functional program DGauss, which is a part of the UniChem package developed at Cray Research, Inc.<sup>17</sup> Two basis sets, DZ94 and DZ94P, are used in this study. These were recently developed by optimizing Gaussian exponents to produce the lowest atomic energy using local density functional of VWN. The corresponding Coulomb-fitting basis sets were optimized by obtaining the best possible agreement between the Coulomb-fitted and exact energy expressions. Details of the Coulomb fitting procedure used in DGauss are available.<sup>17</sup> The DZ94 basis is a valence-double- $\zeta$  basis of the form (5s/2s) for H and (9s5p/3s2p) for atoms C, N, and O. The DZ94P basis adds d-functions to DZ94 for C, N, and O, but it does not include p-functions on hydrogen atoms. The Coulomb-fitting basis sets, DZ94AUX, consist of four uncontracted s-functions for H and an uncontracted (7s3p3d) basis for the other atoms. In previous implementations, the p- and d-functions were required to have the same exponents; this restriction has been removed in the DZ94AUX fitting basis, and the exponents for each angular momentum have been optimized separately. We expect to publish the details of these new basis sets shortly.

Because of its lower computational requirements, we initially used the smaller DZ94 basis set to locate the minimum energy structures. This optimized DZ94 geometry provided the starting point for the optimization using the polarized DZ94P basis. The DZ94P optimization yields better structural descriptions and more acceptable binding energies.

Initial calculations for the clusters contained only two molecules: urea dimer, water dimer, and the urea–water system. Cluster sizes were systematically increased by adding two water molecules at a time, maintaining symmetry, and reoptimizing the geometry. This step by step increase in the number of water molecules helps to insure a reasonable geometry. The largest size cluster calculated contains two urea and six water molecules.

For simplicity we use the notations U for urea and W for water. The molecules studied in this work include U, W, U<sub>2</sub>, W<sub>2</sub>, UW, UW<sub>2</sub>, UW<sub>3</sub>, U<sub>2</sub>W<sub>2</sub>, U<sub>2</sub>W<sub>4</sub>, and U<sub>2</sub>W<sub>6</sub>, and isomers for some clusters.

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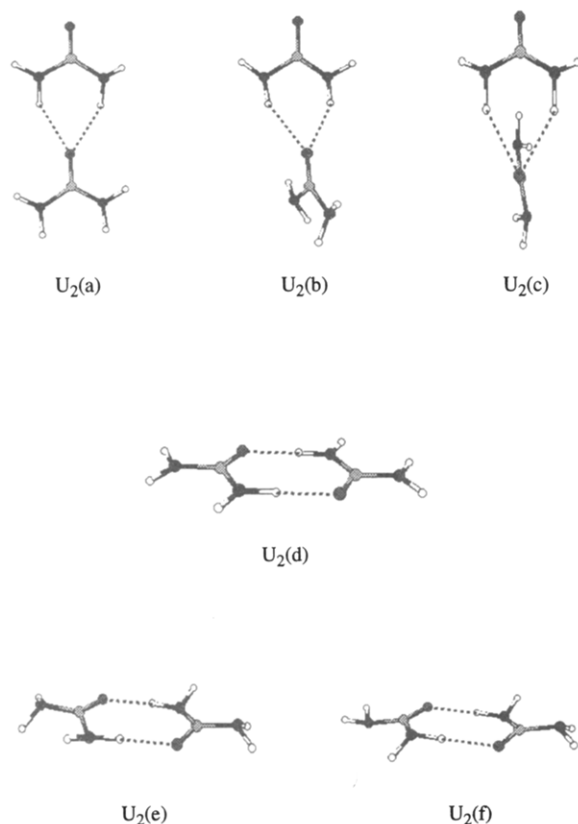


Figure 1. Molecular structures of urea dimer,  $U_2$ .

## Results and Discussion

We have performed geometry optimizations using both the DZ94 and DZ94P basis sets. We have calibrated these basis sets with calculations on the water dimer. The predicted BLYP interaction energies for water dimer are 8.68 and 5.71 kcal/mol with the DZ94 and DZ94P basis sets, respectively.<sup>18</sup> DZ94P gives very good agreement with the experimental result,  $5.4 \pm 0.7$  kcal/mol.<sup>19</sup> All further results discussed here are for the DZ94P basis set calculations.

One of our goals is to study the stability of the urea dimer in water. Therefore, by systematically increasing the number of water molecules in the cluster, we can observe the changes of the structure during the geometry optimization from different starting configurations. This allows us to monitor the hydrogen bonding in urea–urea, water–water, and urea–water as a function of cluster size, and it facilitates our prediction of the structure and binding nature of urea in aqueous solution.

In order to compare the stability of the molecules, we have calculated the binding energies for all the molecular systems in this work. The binding energies in our calculations are defined by the energy difference between the total energy of the cluster and the sum of the energies of the isolated water and the minimum energy conformer of the urea monomer.

**A. Urea Dimer.** There are two types of configurations of the urea dimer, linear and cyclic, which appear to be stable. These structures have been reported using ab initio and molecular dynamics simulations. The linear dimers with collinear carbonyl groups are shown in Figure 1,  $U_2(a)$  and  $U_2(b)$ , the “forked” dimer is  $U_2(c)$ , and the cyclic dimers are  $U_2(d)$ ,  $U_2(e)$ , and  $U_2(f)$ . As shown in Figure 1, isomers  $U_2(d)$ ,  $U_2(e)$ , and  $U_2(f)$  may exist for urea dimer by changing the orientation of the hydrogen atoms in the  $NH_2$  group. However, the configuration of  $U_2(f)$  is the most stable structure of all the isomers studied in this work.

TABLE 1: Binding Energies of Urea Dimer Isomers (kcal/mol)

|          | VWN   | BLYP  |
|----------|-------|-------|
| $U_2(a)$ | 12.60 | 8.00  |
| $U_2(b)$ | 14.66 | 9.04  |
| $U_2(c)$ | 17.75 | 8.69  |
| $U_2(d)$ | 23.02 | 10.67 |
| $U_2(e)$ | 24.93 | 14.34 |
| $U_2(f)$ | 25.03 | 14.51 |

The binding energies based on VWN and BLYP calculations for each configuration are given in Table 1. Table 1 shows that linear configurations of  $U_2(a)$  and  $U_2(b)$  and the “forked” dimer  $U_2(c)$  are less stable than those of the cyclic structures. This is consistent with the results from several other studies. We found that linear and “forked” configurations are less stable than the cyclic structure by roughly 10 kcal/mol and 4 kcal/mol for VWN and BLYP, respectively. Being considerably less stable, the linear and “forked” configurations were not considered for further study in this work.

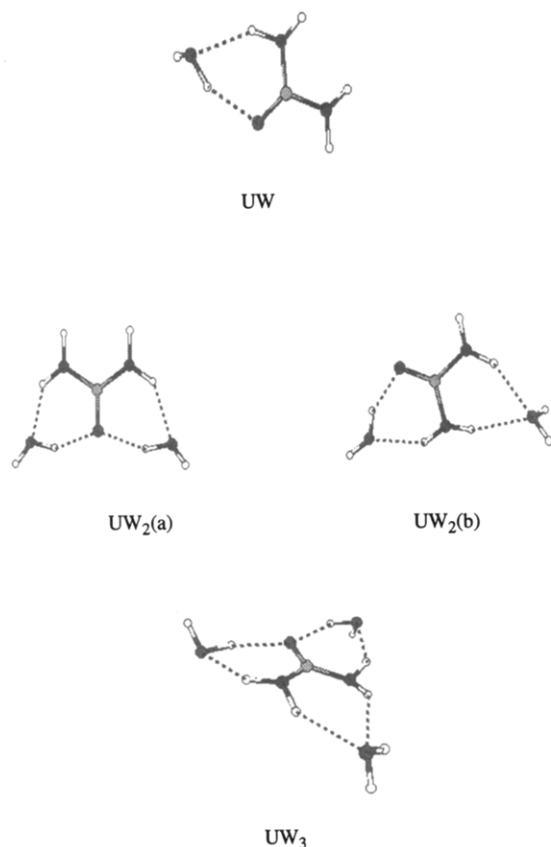
As seen in Table 1, both VWN local density functional approximation and BLYP calculations predict  $U_2(f)$  to be the most stable structure of all the urea dimer isomers shown in Figure 1. The binding energies are 25.03 and 14.51 kcal/mol for VWN and BLYP, respectively. The interaction energy is about two times larger than in the water dimer, indicating approximately twice the amount of hydrogen bonding in the urea dimer.

Various interaction energies for the similar cyclic urea dimer have been reported from other groups. The molecular dynamics simulations gave an interaction energy of 10.3 kcal/mol for a similar cyclic minimum.<sup>1–4</sup> Hartree–Fock evaluation using an STO-3G basis set predicts a cyclic molecule with an interaction energy of 20 kcal/mol.<sup>20</sup> The NEMO potential, which was constructed on the basis of the interaction energy at the Hartree–Fock level, gave an interaction energy of 21.9 kcal/mol.<sup>21,22</sup>

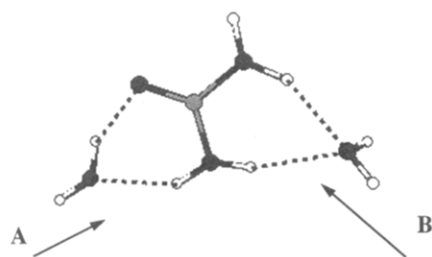
**B. Urea Monomer–Water Complexes.** The most energetically favorable urea–water configuration is a cyclic non-planar geometry, shown in Figure 2. The binding energies for urea–water complexes of urea interacting with one, two, or three water molecules are collected in Table 2. The binding energy of the urea–water complex, 20.13 and 10.89 kcal/mol for VWN and BLYP, respectively, was found to be only a few kilocalories per mole less than that of the urea dimer, 25.03 and 14.51 kcal/mol for VWN and BLYP, respectively. This suggests that there should be a similar degree of hydrogen bonding in these two dimers. The interaction energy obtained with BLYP calculation for urea–water is in very good agreement with the NEMO approach, which predicts a binding energy of 10.9 kcal/mol.<sup>23</sup>

When urea interacts with more than one water molecule, the binding energy increases, as does the number of hydrogen bonds. The interaction energies of urea with two and three water molecules are shown in Table 2. With two water molecules, it is easy to see that there are two different isomers,  $UW_2(a)$  and  $UW_2(b)$ , which are shown in Figure 2. There are two different orientations, A and B (see Figure 3), for the formation of hydrogen bonds between urea and water molecules. The calculation indicates the A-orientation is preferred. In the case of urea interacting with two water molecules, the isomer formed with two waters approaching from the A-direction,  $UW_2(a)$ , is more stable than the isomer  $UW_2(b)$  formed with one water approaching from the A- and one from the B-direction. The computed relative stability of  $UW_2(a)$  is 5.94 and 2.4 kcal/mol for the VWN and BLYP methods, respectively.

A planar geometry is located when the urea interacts with three water molecules,  $UW_3$  in Figure 2. There are other



**Figure 2.** Molecular structures of the urea monomer and water molecules UW, UW<sub>2</sub>(a), UW<sub>2</sub>(b), and UW<sub>3</sub>.



**Figure 3.** Direction for the formation of hydrogen bonds between urea and water.

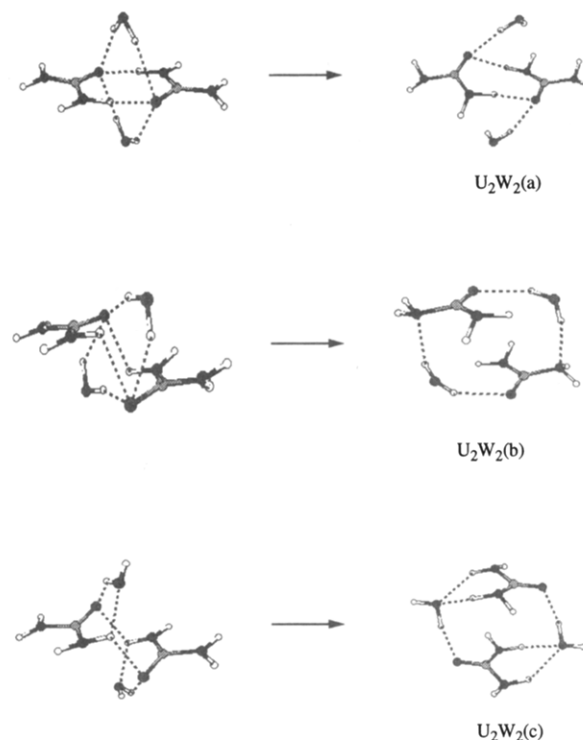
**TABLE 2: Binding Energies of Urea Monomer and Water Complexes (kcal/mol)**

|                     | VWN   | BLYP  |
|---------------------|-------|-------|
| UW                  | 20.13 | 10.89 |
| UW <sub>2</sub> (a) | 38.10 | 19.36 |
| UW <sub>2</sub> (b) | 32.16 | 16.87 |
| UW <sub>3</sub>     | 51.09 | 26.59 |

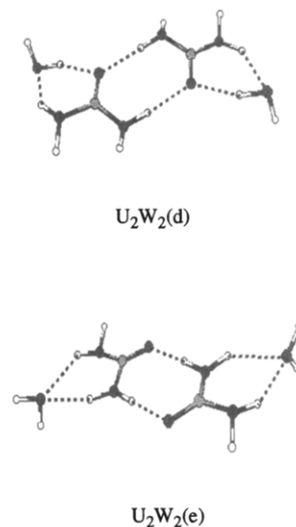
conformations for this cluster with different orientations of the hydrogen atoms in the water molecules. As we add one water molecule each time in the clusters UW, UW<sub>2</sub>(a), and UW<sub>3</sub>, the binding energies increase about 8 kcal/mol with the BLYP method.

**C. Urea Dimer and Water Complexes.** In order to investigate the stability of the urea dimer in water, we have carried out density functional calculations starting at different initial geometries by adding water molecules to the urea dimer and reoptimizing the geometry. We added two water molecules each time for larger clusters calculation in order to hydrate the urea molecules symmetrically. The binding energies for all the optimized configurations, including U<sub>2</sub>W<sub>2</sub>, U<sub>2</sub>W<sub>4</sub>, and U<sub>2</sub>W<sub>6</sub>, are given in Table 3.

(1) *U<sub>2</sub>W<sub>2</sub> Complexes.* We started with the U<sub>2</sub>W<sub>2</sub> system,



**Figure 4.** Geometrical optimization of urea dimer with two water molecules, U<sub>2</sub>W<sub>2</sub>.



**Figure 5.** Conformations of the urea dimer and two water molecules, U<sub>2</sub>W<sub>2</sub>(d) and U<sub>2</sub>W<sub>2</sub>(e).

which contains two water and two urea molecules (see Figures 4 and 5). In Figure 4, the initial geometry is presented on the left-hand side of the arrow and the fully optimized geometry is on the right-hand side of the arrow. We began the geometry optimization with the initial configuration, which is shown at the top of Figure 4, by adding two water molecules, one above and one below the planar-shaped urea dimer. We found that the urea molecules are shifted in the geometry optimization, but they are still bonded to each other through two hydrogen bonds. The optimized structure U<sub>2</sub>W<sub>2</sub>(a) shown in Figure 4 shows that the planar structure of the unhydrated dimer is destroyed by the addition of the water.

Starting with the optimized geometry U<sub>2</sub>W<sub>2</sub>(a), we rotated the orientation of the two water molecules in order to seek other stable initial configurations which contain more hydrogen bonds. The geometry optimization transitions are shown in the second and third rows of Figure 4. We located the minimum energy

**TABLE 3: Binding Energies of the Optimized Urea and Water Clusters (kcal/mol)**

|             | VWN    | BLYP  |
|-------------|--------|-------|
| $U_2W_2(a)$ | 45.80  | 25.24 |
| $U_2W_2(b)$ | 55.85  | 27.42 |
| $U_2W_2(c)$ | 67.32  | 34.91 |
| $U_2W_2(d)$ | 61.21  | 32.83 |
| $U_2W_2(e)$ | 47.39  | 24.81 |
| $U_2W_4(a)$ | 105.73 | 53.77 |
| $U_2W_4(b)$ | 108.82 | 57.45 |
| $U_2W_4(c)$ | 82.26  | 44.32 |
| $U_2W_6(a)$ | 142.94 | 75.19 |
| $U_2W_6(b)$ | 147.38 | 76.53 |
| $U_2W_6(c)$ | 107.96 | 54.00 |
| $U_2W_6(d)$ | 126.82 | 66.97 |

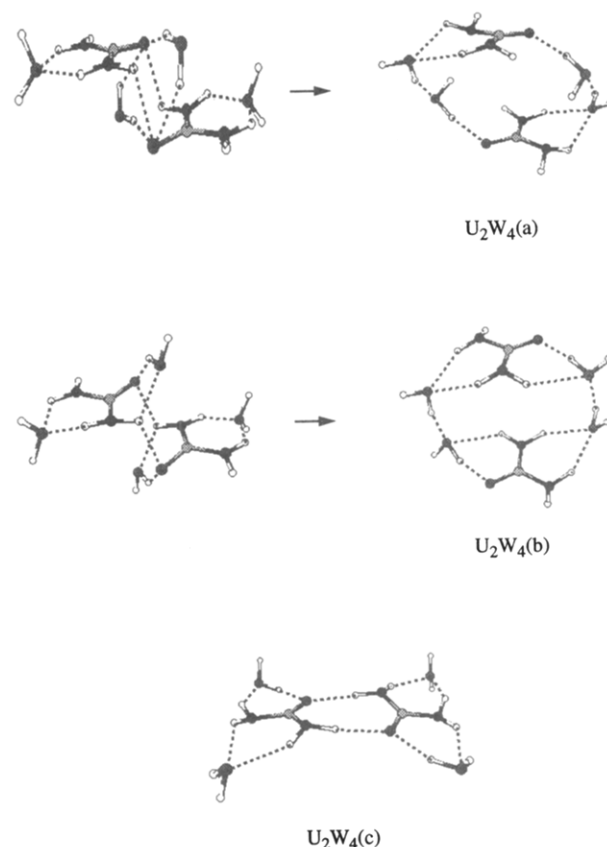
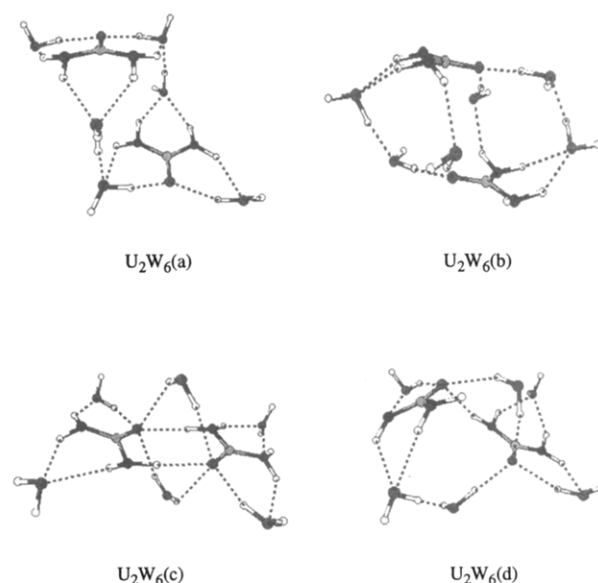
structures,  $U_2W_2(b)$  and  $U_2W_2(c)$ , which are shown in Figure 4. The binding energies of  $U_2W_2(b)$  and  $U_2W_2(c)$  are given in Table 3. The hydrogen bonds between urea molecules in the dimer have been completely destroyed, and the two urea molecules are only connected via two water molecules, as shown. The minimum energy configuration of  $U_2W_2(c)$  is more stable than  $U_2W_2(b)$  by 7.49 kcal/mol. This is because the hydrogen bond of the  $N\cdots H-O$  in  $U_2W_2(b)$  is weaker than that of the  $O\cdots H-O$  in  $U_2W_2(c)$ .

In order to attempt to maintain the initial structure of the urea dimer within the hydrated cluster, two water molecules are added from two opposite sides of the urea dimer. This yielded two minimum energy configurations,  $U_2W_2(d)$  and  $U_2W_2(e)$ , shown in Figure 5. Recalling that the hydrogen bond formation from the A-direction is more stable than that formed in the B-direction, we were not surprised to see that the binding energies of  $U_2W_2(d)$  are more stable than those of  $U_2W_2(e)$ , as seen in Table 3. Although these structures indeed maintain the original planar-shaped dimer, they are not energetically favorable. The structure  $U_2W_2(c)$  is more stable than  $U_2W_2(d)$  or  $U_2W_2(e)$  by 6.11 or 19.93 kcal/mol, respectively, at the VWN level of theory, and by 2.08 or 10.10 kcal/mol, respectively, at the BLYP level of theory.

(2)  $U_2W_4$  Complexes. It is interesting to see the effect of increasing the number of water molecules on the urea dimer and water interaction. In the geometry optimization process resulting in the  $U_2W_2(c)$  structure, the water molecules in the initial geometry both had hydrogen bonds in the A-direction. In the optimized structure the hydrogen bonds between water and urea were all in the B-direction.

We have also carried out the geometry optimization with similar initial geometries shown in the second and third rows of Figure 4, but we have added two more water molecules to the system. The initial geometries are shown on the left side of the arrow in the first and second rows of Figure 6. Two minimum energy configurations,  $U_2W_4(a)$  and  $U_2W_4(b)$ , are obtained in the geometrical optimization. The two urea molecules are connected by water, but in contrast to the  $U_2W_2(c)$  structure, the urea molecules are connected to each other through two water molecules rather than one, and the distance between the two urea molecules is greater. We have also located a structure containing the planar-shaped urea dimer  $U_2W_4(c)$ , which is shown on the bottom of Figure 6. The binding energies for the  $U_2W_4$  conformers are collected in Table 3. The binding energies indicate that the planar-shaped configuration is 26.56 and 13.13 kcal/mol less stable than  $U_2W_4(b)$ , at LDA and BLYP, respectively, and it is the least stable cluster of the three clusters studied in this work.

(3)  $U_2W_6$  Complexes. The conformations become very complicated when the number of the water molecules in the cluster is increased. Four optimized configurations of  $U_2W_6$

**Figure 6.** Geometrical optimization of the urea dimer with four water molecules  $U_2W_4$ .**Figure 7.** Molecular structures of urea dimer with six water molecules,  $U_2W_6$ .

complexes are shown in Figure 7. The configuration of  $U_2W_6(a)$  can be easily constructed from the  $U_2W_4(b)$  structure by adding one water molecule to each urea molecule. The  $U_2W_6(a)$  structure contains two planar-shaped  $UW_3$  fragments which are connected through hydrogen bonds (see Figure 7). A similar configuration,  $U_2W_6(b)$ , is even more stable by 4.44 and 1.34 kcal/mol for the VWN and BLYP methods, respectively. The structure containing the planar-shaped urea dimer,  $U_2W_6(c)$ , is again found to be less stable than the other conformers, in this case by 22.53 kcal/mol at the BLYP level of theory.

The complexity increases when the system becomes large, and we believe that there are other low-energy configurations

**TABLE 4: Difference of the Binding Energies between the Most Stable Configuration and the Planar-Shaped Urea Dimer with Water (kcal/mol)**

|      | U <sub>2</sub> W <sub>2</sub> | U <sub>2</sub> W <sub>4</sub> | U <sub>2</sub> W <sub>6</sub> |
|------|-------------------------------|-------------------------------|-------------------------------|
| VWN  | 6.11                          | 26.56                         | 39.42                         |
| BLYP | 2.08                          | 13.13                         | 22.53                         |

for the U<sub>2</sub>W<sub>6</sub> cluster. For example, we have also located the minimum energy structure U<sub>2</sub>W<sub>6</sub>(d), which is shown in Figure 7, with 126.82 and 66.97 kcal/mol in binding energies using VWN and BLYP calculations. This is still considerably more stable than the structure involving the hydrogen-bonded urea dimer.

### Conclusions

We have searched for minimum energy configurations of small clusters of urea and water. In order to extend our prediction to the solvation of the urea dimer in water, we have looked at clusters containing up to six water molecules with a urea dimer.

We have found that the hydrogen bonds between urea dimer are destroyed when the dimer interacts with only two water molecules. This remains the case when the number of water molecules increases in the urea dimer and water systems. There are several different minimum energy configurations found for each of the clusters studied in this work. The minimum energy structure containing a hydrated planar-shaped urea dimer is never found to be the most stable configuration. The difference of the binding energies between the most stable configuration and that containing the planar-shaped urea dimer is shown in Table 4 for each of the urea-water systems. This difference represents the additional stability obtained from distorting the planar-shaped urea dimer. The results in Table 4 show that this difference increases as the number of water molecules in the cluster increases. The implication of this trend is that the urea dimer would be separated into monomers in aqueous solution.

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### References and Notes

- (1) Cristinziano, P.; Lelj, F.; Amodeo, P.; Barone, V. *Chem. Phys. Lett.* **1987**, *140*, 401.
- (2) Cristinziano, P.; Lelj, F.; Amodeo, P.; Brone, G.; Barone, V. *J. Chem. Soc., Faraday Trans.* **1989**, *85*, 621.
- (3) Gunsteren, W. F.; Berendsen, H. J. C. *Groningen Molecular Simulation Library*, 1987.
- (4) Boek, E. S.; Briels, W. J. *J. Chem. Phys.* **1993**, *98*, 1422.
- (5) Frank, F. S.; Franks, F. *J. Chem. Phys.* **1968**, *48*, 4746.
- (6) Schellman, J. A.; C. R. *Trav. Lab. Carlsberg, Ser. Chim.* **1955**, *29*, 223.
- (7) Kreschek, G. C.; Scheraga, H. A. *J. Phys. Chem.* **1965**, *69*, 1704.
- (8) Stokes, R. H. *Aust. J. Chem.* **1967**, *20*, 2087.
- (9) Tanaka, H.; Nakanichi, K.; Touhara, H. *J. Chem. Phys.* **1985**, *82*, 5184.
- (10) Kuharski, R. A.; Rossky, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5786.
- (11) Kuharski, R. A.; Rossky, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5794.
- (12) Hoccart, X.; Turrell, G. *J. Chem. Phys.* **1993**, *99*, 8498.
- (13) For recent reviews on DFT, see: Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. Kryashko, E. S.; Ludena, E. W. *Energy Density Functional Theory of Many-Electron Systems*; Kluwer: Dordrecht, 1990.
- (14) Vosko, S. J.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.
- (15) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098; *J. Chem. Phys.* **1992**, *96*, 2155.
- (16) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
- (17) DGAUSS is a software product available from Cray Research, Inc. as part of the UniChem software package. For details of DGAUSS methodology, see: Andzelm, J.; Wimmer, E. *J. Chem. Phys.* **1992**, *96*, 1280.
- (18) For some other results for the binding energy of the water cluster using a density functional calculation, see: Lee, C.; Han, C.; Fitzgerald, G. *J. Chem. Phys.* **1995**, *102*, 1266.
- (19) Curtiss, L. A.; Frurip, D. J.; Blander, M. *J. Chem. Phys.* **1979**, *71*, 2703.
- (20) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657.
- (21) Astrand, P.-O.; Wallqvist, A.; Karlstrom, G.; Linse, P. *J. Chem. Phys.* **1991**, *95*, 8419.
- (22) Astrand, P.-O.; Wallqvist, A.; Karlstrom, G. *J. Chem. Phys.* **1994**, *100*, 1262.

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