

# A critical evaluation of DFT, including time-dependent DFT, applied to bioinorganic chemistry

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## Introduction

The past decade has witnessed an explosive activity in the application of quantum chemical methods to problems of bioinorganic chemistry. It is now almost commonplace to publish an experimental paper together with quantum chemical calculations. The calculations serve either to validate the conclusions that have been reached from the analysis of the experiments or to distinguish between those possibilities that were left open. In addition, there are many purely theoretical investigations which address various structural and mechanistic aspects of metalloprotein structure and function. In this context the term ‘quantum chemical methods’ has been applied almost synonymously with density functional theory (DFT). Despite the enormous popularity of DFT in bioinorganic chemistry, one frequently voiced complaint from the experimental community is that the calculations often take too little or no notice of the available experimental results. For example, a number of theoretically proposed structures and mechanisms might have been excluded from consideration altogether if the spectroscopic data that are available for the species proposed had been included as constraints in the modelling of the structures of the reaction intermediates. Concerning the actual kinetics of the reactions investigated, it is to be noted that even an inaccurately measured rate constant is of much help to the theoretician since rate constants are very sensi-

tive functions of the barrier height (see the contribution by Siegbahn in this volume). Nevertheless, in many cases the mechanisms investigated are difficult to dissect unambiguously by kinetics means. Given this situation, the central opinion voiced in this commentary is the following: owing to (1) the enormous complexity of bioinorganic electronic structure problems and (2) the limited accuracy of every theoretical method which is applicable in this area, it is necessary to search for as close a similarity to experimental data as possible in the theoretical investigations. In trying to match the computations with the known experimental constraints, the large body of spectroscopic data that has been accumulated in bioinorganic chemistry over the decades is extremely useful for the theoretician to gauge his or her calculations. Viewed together with other experimental data, such as rate and equilibrium constants or kinetic isotope effects, one hopes to successfully discriminate between alternative formulations of the reaction mechanisms with the highest possible degree of confidence. Since spectroscopy on trapped species does not yield rate constants, it is the geometric structure of the reaction intermediates which can most fruitfully be studied by the theoretical spectroscopy approach. With this in mind, an attempt is made here to summarize the experience that our group has had with DFT in the past few years.

## Geometries

Geometries predicted by DFT methods tend to be quite reliable. Moreover, the predicted geometries converge quickly with basis set size, thus making the prediction of structures with DFT rather economical.

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Basis sets of double- $\zeta$  plus one set of polarization functions for the ligands and triple- $\zeta$  plus one set of p functions (plus perhaps one set of f-functions) for the metal are usually enough to get almost converged results for geometries (a basis set of this size is called Def-2 in the following). Smaller basis sets without polarization functions are not recommended. The most efficient presently available program packages (e.g. [1–4]) can perform complete DFT geometry optimizations on molecules with more than 100 atoms and Def-2 type basis sets in usually not more than 1–2 days on a single CPU of an ordinary personal computer. For heavy atoms (second transition row and beyond), the use of effective core potentials presents an efficient way to calculate reasonable geometries and at the same time take into account the leading effects of relativity. However, for first-row transition metals this is neither necessary nor particularly desirable. With this type of approach, intraligand distances are typically predicted to within approximately 2 pm of their experimental values and angles are predicted to within a few degrees. For metal–ligand distances our experience is that the short, strong and stiff metal ligand bonds (such as bonds to CO, NO<sup>+</sup>, NO, O<sup>2-</sup> and N<sup>3-</sup>) are predicted with excellent accuracy, while the weaker metal–ligand bonds (such as bonds to neutral amines or carboxylates) are typically predicted too long by approximately 5 pm (Fig. 1). Even weaker bonding interactions, like weak hydrogen bonds, are known to be problematic with DFT owing to the wrong asymptotic behaviour of the exchange–correlation potential [5]. Different DFT functionals generally behave similarly as long as at least gradient corrections are taken into account (e.g. one has to go beyond the local density approximation, LDA). In our experience, structures predicted with the popular BP86 functional are no worse or in many cases are even slightly better than those predicted by the hybrid B3LYP functional, which incorporates a fraction of Hartree–Fock (HF) exchange. However, there are exceptions to this statement. Since many programs allow the use of the very efficient density fitting (or resolution-of-the-identity) approximation [6–10] in the

absence of HF exchange, one can invest the savings in computer time into a better basis set or a more realistic (larger) model of the molecule to be modelled. A typical example (taken from [11]) is the complex [Fe(TMC)(O)(CH<sub>3</sub>CN)]<sup>2+</sup> (TMC is 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) reported by Rohde et al. [12] (Fig. 1); here, the Fe=O distance is predicted with excellent accuracy, while the distances to the equatorial nitrogens are overestimated by all DFT methods.

Realistic modelling of the protein environment can be achieved by modern quantum mechanics/molecular mechanics (QM/MM) approaches which will, however, not be covered in this commentary.

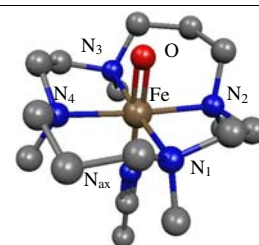
### Total energies

The accuracy and reliability of DFT for the prediction of reaction energies and transition states is covered in the contribution by Siegbahn in this volume and will only briefly be touched on. A frequently made statement is that energetic predictions with the B3LYP functional (which is systematically more accurate than generalized gradient approximation (GGA) functionals in this respect (the term GGA refers to functionals which depend not only on the electron density but also on its first derivative)) are accurate to within 2–3 kcal mol<sup>-1</sup> on the basis of benchmark calculations on the so-called G2 set of test molecules [5]. In the author's opinion, it is too optimistic to think that DFT systematically comes close to this level of accuracy in bioinorganic chemistry. The G2 set only contains small and mainly closed-shell molecules made of main-group atoms. It is by no means clear that the high accuracy obtained for these molecules persists over the whole periodic table, in particular when it comes to the complicated open-shell situations which are a trademark of bioinorganic chemistry. This should be kept in mind if one wants to discriminate between alternative mechanisms on the basis of total energies alone. One complication is that there is little highly accurate

**Fig. 1** Accuracy of a typical density functional theory (DFT) geometry optimization with a polarized triple- $\zeta$  basis set

	Exp <sup>a</sup>	BPW91 <sup>b</sup>	BP86 <sup>c</sup>	B3LYP <sup>c</sup>	LDA <sup>c</sup>
R(Fe=O)	1.646	1.650	1.645	1.625	1.632
R(Fe-N <sub>ax</sub> )	2.057	2.075	2.076	2.131	1.963
R(Fe-N <sub>i</sub> )	2.068	2.130	2.123	2.124	2.057
R(Fe-N <sub>j</sub> )	2.110	2.162	2.157	2.135	2.092
R(Fe-N <sub>k</sub> )	2.116	2.162	2.155	2.157	2.091
R(Fe-N <sub>l</sub> )	2.066	2.130	2.123	2.124	2.054

<sup>a</sup> Ref. [12] <sup>b</sup> Ref. [13] <sup>c</sup> Ref. [11]



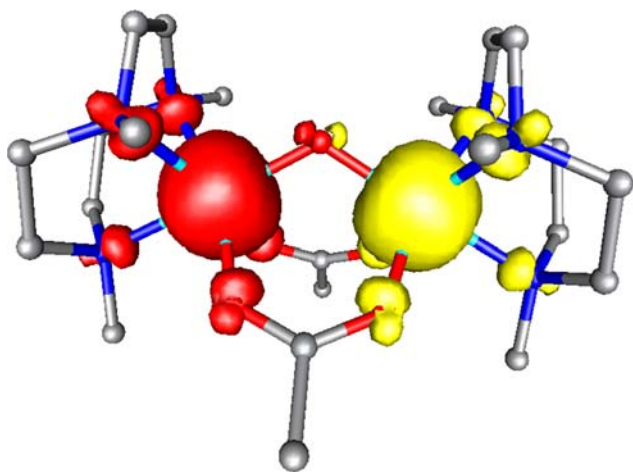
experimental information available on sufficiently large molecules that are sufficiently similar to systems usually met in bioinorganic chemistry. As pointed out by Siegbahn, results obtained for coordinatively unsaturated gas-phase species are not necessarily indicative of what one would obtain for coordinatively saturated or nearly saturated species which prevail in bioinorganic chemistry [14, 15]. Secondly, bioinorganic systems are always studied in the condensed phase and therefore the question of with what accuracy one is able to model the interaction of the active site with the protein and solvent environment comes into play (see also the contribution by Noodleman and Han in this volume). Popular approaches are continuum dielectric treatments such as the polarizable continuum model (PCM) [16, 17] or the conductor-like screening model (COSMO) [18] and/or QM/MM approaches.

### Spin-state energetics

Nevertheless, given the difficulty to obtain good reaction energies from high-level *ab initio* calculations it is probably fair to state that the price/performance ratio of the DFT predictions for total energies is extremely good if the predictions are viewed with sufficient care (see the contribution by Siegbahn in this volume). One notorious exception is the calculation of spin-state energies when the different spin states arise from different electronic configurations (e.g. high-spin/low-spin problems). Here the errors of DFT can be substantial and may exceed 10 kcal mol<sup>-1</sup>. A case in point is detailed studies carried out on the hexaquo and hexamino ferrous ions [19, 20]. In general, GGA functionals tend to be biased in favour of low-spin states. The HF method, on the other hand, is hugely biased in favour of high-spin states owing to the imbalance between Fermi and Coulomb correlation [21]. In an *ab initio* context this situation requires extensive dynamic correlation treatments in order to arrive at good energetic predictions (the term dynamic electron correlation is perhaps most easily understood as a correction to the mean-field electron–electron repulsion included in HF theory arising from instantaneous electron–electron interactions; its accurate calculation is the major challenge of *ab initio* quantum chemistry). It is therefore not surprising that hybrid functionals are a better choice than either the HF or the GGA methods. The high-spin/low-spin gap has been found to be a nearly linear function of the fraction of HF exchange mixed in the DFT functional [22]. The subject is further discussed by Noodleman and Han as well as by Ghosh in this volume.

### Exchange couplings

A different quality of spin-state energetics is met in the case of magnetically interacting transition metal ions where the problem of exchange coupling occupies a central role. Owing to the developments of Noodleman and co-workers, such systems are presently handled in the DFT framework by the broken-symmetry approach, which gives access to exchange coupling constants, geometries and total energies. Experience indicates that hybrid functionals such as B3LYP may be slightly more accurate than GGA functionals for the prediction of exchange coupling constants. Among the GGA functionals, PW91 seems to perform best [23, 24]. However, in comparing experiment and theory, one first of all should recall that usually one compares vertically calculated exchange couplings (the Heisenberg–Dirac–van Vleck Hamiltonian does not include any geometry dependence) with adiabatically measured energy differences. Secondly, the effects of zero-field splitting are usually neglected in both the computations and the analysis of the experimental data, but may be important as well [25, 26]. There are also different formalisms to extract the exchange coupling constants from separate high-spin and broken-symmetry calculations [27–32]. Among the available methods, we favour Yamaguchi's approach which correctly reproduces the limits of both weak and strong interaction [31, 32]. In our view (summarized in [33]), the broken-symmetry method provides excellent electron densities since it has the variational freedom to adjust the ionic and neutral components of the wavefunction. Consequently it will also be able to predict geometries which will faithfully reflect those of the true low-spin states. In cases where the exchange coupling becomes very large it may be beneficial to extrapolate the total energy of the broken-symmetry state to that of a pure spin state using the calculated exchange coupling constant. For example, in an interesting case of metal–radical interaction this was found to have a decisive effect of approximately 4 kcal mol<sup>-1</sup> [34]. However, if one wishes to calculate magnetic properties based on the broken-symmetry approach it is mandatory to apply spin projection techniques [35, 36] since the spin density in the broken-symmetry approach is unphysical (Fig. 2). For example, from fundamental theory, the spin density in a spin singlet state has to be identically zero everywhere in space [37]. This is not the case for broken-symmetry solutions, which give large regions of artefactual positive and negative spin density and only the integral over all space gives zero. Perhaps even more serious is the calculation of excited states of exchange-coupled cen-



**Fig. 2** The unphysical spin density of broken-symmetry solutions exemplified for the case of  $[\text{Fe}^{\text{III}}_2(\text{TMC})(\mu\text{-HCOO}^-)(\mu\text{-O}_2^-)]^{2+}$  calculated with a Def-2 type basis and the B3LYP functional [38] (red positive spin density, yellow negative spin density). TMC 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane

tres based on the broken-symmetry approach, which (subject to debate) cannot, in general, be expected to lead to realistic results.

### Vibrational frequencies

Closely related to the problem of predicting equilibrium geometries is the prediction of vibrational frequencies and IR spectra. Here it has been found that the predicted harmonic frequencies with the BP86 functional typically agree very well with measured vibrational fundamentals if basis sets of polarized triple- $\zeta$  quality are used. It has been shown that this excellent accuracy is a result of systematic error cancellation between the neglect of anharmonicities and systematic errors in the prediction of the true harmonic frequencies [39]. The B3LYP method provides harmonic frequencies of slightly higher quality which then agree somewhat worse with experimental fundamentals owing to the neglect of anharmonicities. Unfortunately, anharmonicities are presently impossible to calculate for molecules of bioinorganic interest.

### Ground-state electronic properties

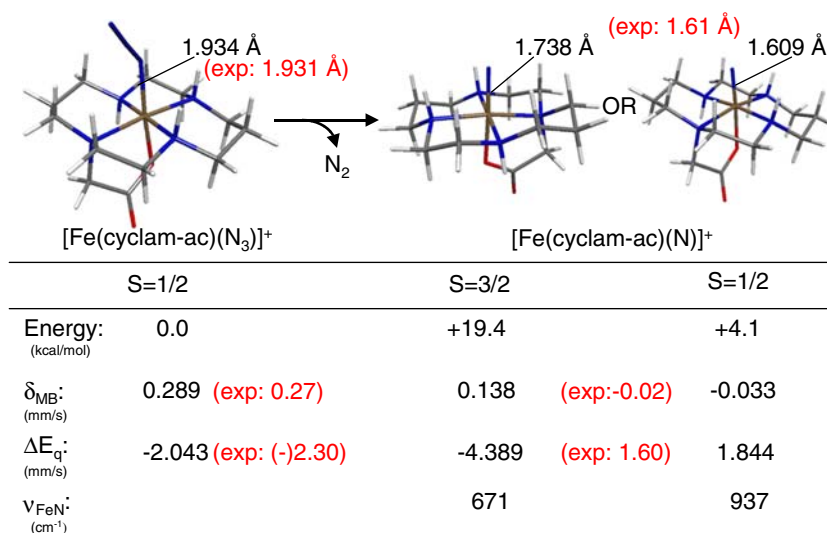
Ground-state spectroscopic properties which depend on the predicted electron density alone have typically been found to be of quite pleasing accuracy from DFT calculations. Foremost in this respect are quadrupole coupling constants measured in electron paramagnetic

resonance (EPR) ( $^2\text{H}$ ,  $^{14}\text{N}$ ,  $^{17}\text{O}$ ) and Mössbauer ( $^{57}\text{Fe}$ ) spectroscopy. Perhaps the largest body of data has been accumulated for the  $^{57}\text{Fe}$  nucleus. Several authors have consistently found predictions from DFT which are typically within  $0.3 \text{ mm s}^{-1}$  of the experimental observations provided sufficiently flexible basis set are used in the core region. The recommended value for the quadrupole moment of the  $^{57}\text{Fe}$  nucleus from these studies is approximately 0.16 barn [40, 41]. Most calculations of the quadrupole couplings of light elements have been rather encouraging, with most results being in 10–20% agreement with experimental values (e.g. see [42]). A really big success has been the prediction of Mössbauer isomer shifts with DFT as pursued almost simultaneously by several groups [40, 43–47]. Although the procedures recommended by different authors differ slightly, an accuracy of better than  $0.1 \text{ mm s}^{-1}$  has been consistently reported. This is good enough to address many exciting questions in the biochemistry of iron as has been exemplified in many application studies. As an example, the recent identification of a non-haem Fe(V) species is quoted [48]. Here, the comparison of calculated and experimental Mössbauer parameters clearly revealed that the result of the photolysis of  $[\text{Fe}(\text{cyclam-acetate})(\text{N}_3)]^+$  is  $[\text{Fe}(\text{cyclam-acetate})(\text{N})]^{+}$  ( $S = 1/2$ ) and *not*  $[\text{Fe}(\text{cyclam-acetate})(\text{N})]^{+}$  ( $S = 3/2$ ) (as expected) or any protonated species or decay product (Fig. 3).

### Magnetic spectra

The field of genuine magnetic spectroscopic parameters has been somewhat more challenging. The performance of DFT for organic radicals has generally been found to be quite good for hyperfine couplings [49] and  $g$ -tensors [50, 51]. In particular for the latter property, the available DFT procedures approach maturity. In many cases agreement between theory and experiment within approximately 100 ppm can nowadays be achieved. As an example, the results of a recent study on phenoxyl radicals fused with an imidazole ring in an attempt to model tyrosine D in photosystem II are quoted [52]. B3LYP calculations predicted that the result of the one-electron oxidation of the parent compounds depends on the substituents on the imidazole rings. For  $\text{C}_6\text{H}_5$  substituents the NH form was predicted to be more stable, while for  $\text{MeOC}_4\text{H}_9$  the OH form was predicted to be  $7.7 \text{ kJ mol}^{-1}$  more stable. However, comparison of the calculated and measured  $g$  tensors revealed that in all oxidation products only the NH forms occur. In this case, the calculated  $g$  values were in better than 100 ppm agreement with experiment, while the errors

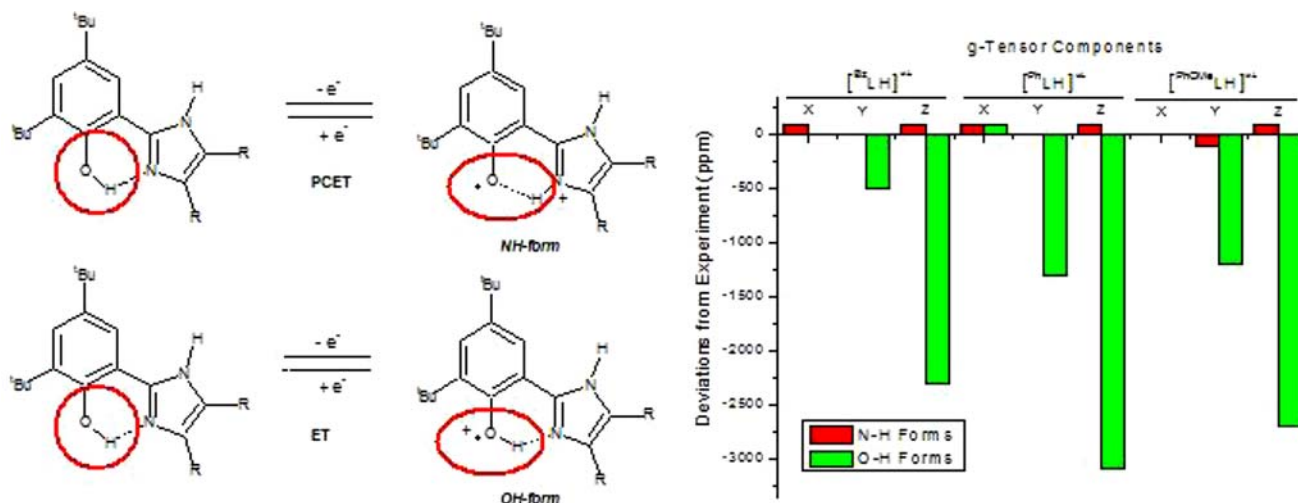
**Fig. 3** Comparison of experimental (red) and theoretical (black; B3LYP, triply polarized triple- $\zeta$  basis set) geometric and structural parameters of  $[\text{Fe}(\text{cyclam-acetate})(\text{N})]^+$  and its precursor  $[\text{Fe}(\text{cyclam-acetate})(\text{N}_3)]^+$



predicted for the OH forms amounted to several thousand parts per million (Fig. 4). Thus, the OH forms could be safely ruled out as oxidation products. Although this is an isolated example, it illustrates that spectroscopic parameters can be much more sensitive reporters of the actual situation than total energies, which are, in a sense, bulk properties that are insensitive to certain structural features and depend on all aspects of the modelling. The important point is to seek the feedback from the available experimental data in order to come to correct interpretations.

For hyperfine couplings one has to differentiate between isotropic and anisotropic contributions as well as between direct and indirect contributions (the term

‘direct contribution’ refers to a situation where the nucleus studied bears positive spin population, which would also arise in an open-shell spin-restricted treatment. Other sources of spin population arise from spin polarization and are termed ‘indirect’). In general, isotropic couplings are more difficult to predict owing to the intricacies of the singular Fermi term which probes a single point in space. It is therefore necessary to use basis sets with extra flexibility in the core region, such as the EPR-II and EPR-III bases [53]. Experience indicates that indirect hyperfine couplings, which are entirely dependent on the details of spin polarization, are more difficult to calculate than direct ones. The performance of hybrid DFT functionals, in particular



**Fig. 4** Identification of an oxidation product by a combination of high-field electron paramagnetic resonance (EPR) spectroscopy and DFT property calculations. *Left*: One-electron oxidation of the parent compounds leads either to proton migration (NH

forms) or to the corresponding OH forms. *Right*: The deviation between calculated and experimental  $g$  values is shown under the assumption of the NH forms (red) or the OH forms (green)



B3LYP and PBE0, is nevertheless quite satisfactory and is only surpassed by very expensive high-level ab initio approaches [49]. Dipolar hyperfine couplings are generally easier to calculate, converge quite quickly with the basis set and are not nearly as dependent on the functional used as isotropic hyperfine couplings [54]. EPR parameter predictions are much more difficult for open-shell transition-metal-containing molecules.  $g$ -shifts (deviations from the free-electron value of 2.002319) have usually been found to be underestimated by up to a factor of 2 even by the hybrid functionals, which overall give better agreement with experiment than pure GGA or LDA functionals [55, 56]. The results depend also quite strongly on the metal, with Cu(II) apparently being among the most difficult cases [55, 57, 58]. A case in point is the puzzlingly complicated case of copper–histidine complexes in aqueous solution where energetic predictions alone could have hardly come to a correct conclusion about the dominating forms observed experimentally [59].

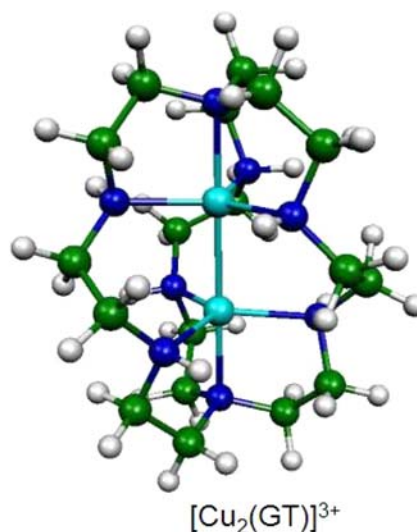
The central-metal hyperfine coupling is a particularly difficult property to calculate with good accuracy since the three contributions from the Fermi-contact, the spin-dipolar and the spin–orbit coupling are often of the same magnitude but varying sign. Since the mechanisms of the three contributions are quite different, quantitative accuracy is not commonplace. In many cases it is again the Fermi term which is predicted least accurately. All typically available functionals underestimate the core-level spin polarization, which leads to values which are too small in magnitude [56, 60, 61]. While it is possible to adjust the fraction of HF exchange to obtain better hyperfine couplings, it has also been found that the optimum admixture depends on the metal, the oxidation state

and the basis set. Thus, it can hardly be claimed that the overall physical description of the electronic structure has indeed been improved. Ligand hyperfine couplings are much easier to compute, but again the results are certainly less accurate than for organic radicals and errors on the order of approximately 30% must be tolerated [57]. Hybrid functionals are also more successful here, presumably since they provide a slightly better picture of metal–ligand covalent bonding [57, 62]. Although, the calculations typically do not give full quantitative accuracy, they can be of tremendous help in the interpretation of complicated spectra. A case in point is a recent study on the mixed-valence delocalized class III complex  $[\text{Cu}_2(\text{GT})]^{3+}$  in Fig. 5, [63]. This compound has as many as 40 magnetic nuclei which all contribute to high-resolution electron–nuclear double resonance (ENDOR) and hyperfine sublevel correlation (HYSCORE) spectra. It would probably not have been possible to come to a complete simulation of these very convoluted spectra without the help of the B3LYP calculations which provided the corrected trends in the hyperfine couplings and, in particular, reasonable orientations for the various magnetic interaction tensors.

The leading kinematic relativistic effects also start to have a noticeable influence beyond the first transition row. Results obtained with the zeroth order regular approximation (ZORA) have been quite encouraging in this area [64, 65]. The prediction of zero-field splitting parameters with DFT is still in its infancy and is particularly difficult owing to the complicated spin dependence of this property [66]. We have recently gained some initial experience with this property in transition metal complexes [11, 26] from which it seems that one should be content to predict

**Fig. 5** Comparison of experimental (black) and calculated (red; B3LYP, mixed triple- $\zeta$ , EPR-II basis) magnetic properties for the delocalized mixed-valence class III complex  $[\text{Cu}_2(\text{GT})]^{3+}$

	Exp/B3LYP			
$g$ :	$\perp$		$\parallel$	
	2.148		2.004	
	2.138		2.003	
$A^{\text{Cu}}$				
/MHz	-308		30(?)	
	-304		0	
$A^{\text{N}_\text{H}}$				
/MHz	14.7		26.5	
	14.3		31.5	
$A^{\text{N}_\text{C}}$				
/MHz	5.5		7.7	
	5.1		9.8	
$\text{N-H}$		xx	yy	zz
/MHz		-0.7	-1.6	2.3
		-1.6	-2.7	4.3
				iso
				-1.9
$\text{H}^\text{a}$				
/MHz		-1.0	-1.0	1.4
		-1.0	-1.0	2.2
				7.3
				11.7
$\text{H}^\text{c}$				
/MHz		-0.5	-0.5	1.0
		-0.5	-1.0	1.5
				3.2
				4.2



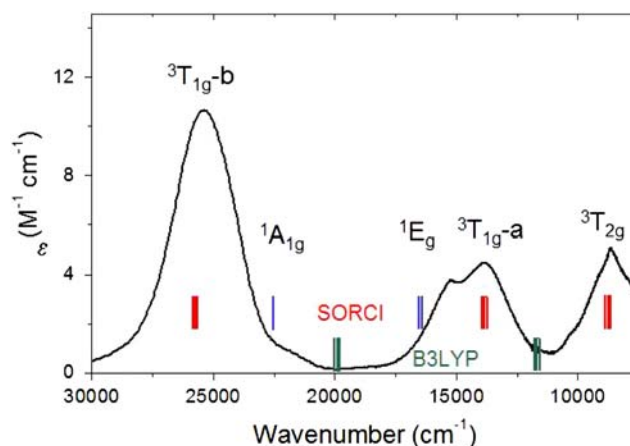
the  $D$  value within a factor of 2 and with the correct sign. However, much more careful test calculations are necessary to settle this issue.

## Optical spectra

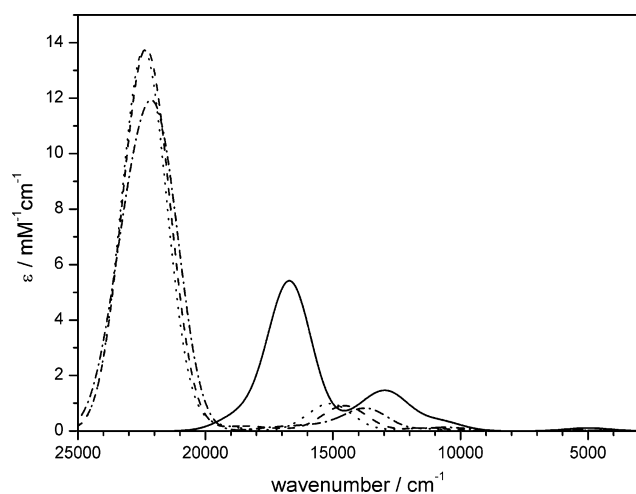
Since the foundations of DFT (the Hohenberg–Kohn theorems) [5] restrict it to ground states, the calculation of excited states and their properties has to be approached indirectly. DFT has in this respect greatly profited from the analogous developments in the ab initio area where time-dependent linear response theory has been worked out in great detail. Here, one studies the frequency dependence of a time-dependent electric field perturbation, the poles of which provide excitation energies; thus, one calculates transition energies (and also probabilities) without ever calculating the excited states themselves. While time-dependent DFT (TD-DFT) rests firmly on the Runge–Gross theorems [67], its practical applications within the so-called adiabatic approximation (commonly referred to as TD-DFT) have revealed many problems with this approach and are associated with various well-known shortcomings of the present-day DFT functionals [68–70]. In general, the predictions for neutral valence-to-valence singly excited states of closed-shell systems with TD-DFT have been found to be reasonable, with errors of only a few thousand wavenumbers. However, states that have ionic or charge transfer character are predicted rather poorly, with errors which may exceed 1–2 eV. This may result in a potentially large number of ‘ghost’ states which show up at unreasonably low transition energies and which have no counterparts in the experimental spectra. The main reason for this is the self-interaction error of DFT. Highly excited Rydberg states are also predicted poorly owing to the wrong asymptotic behaviour of the DFT potential, which falls off more rapidly than required from fundamental considerations. States which are dominated by double excitations, which are commonplace in transition metal complexes, are even entirely missing from the TD-DFT spectra. For open-shell systems one does also not obtain the correct multiplet structures of the ground or excited states. Lastly, TD-DFT does not take any account of electronic relaxation (change of orbitals upon excitation) in a similar way as configuration interaction with all single excitations (CIS) fails to do so. A typical example are the spin-allowed and spin-forbidden transitions of the complex  $[\text{Ni}(\text{H}_2\text{O})_6]^{2+}$ . Here TD-DFT predicts only one of the two excited  ${}^3\text{T}_{1g}$  states at roughly half the transition energy

between  ${}^3\text{T}_{1g}\text{-a}$  and  ${}^3\text{T}_{1g}\text{-b}$  and none of the spin-forbidden triplet–singlet excitations. The underlying reason is that the two  ${}^3\text{T}_{1g}$  states are a mixture between a single and a double  $t_{2g} \rightarrow e_g$  excitation, the latter of which is not present in TD-DFT. Also shown in Fig. 6 are the results of a simplified multiconfigurational ab initio calculation (spectroscopy-oriented configuration interaction method, SORCI method) [71], which shows that none of these problems is present in genuine multiconfigurational ab initio approaches which treat all multiplet states on an equal footing. Much more technical detail on these subjects is provided in [72].

A more biologically relevant example is the famous absorption spectrum of the Cu(II) ion in the ‘blue’ proteins. A recent study applied quasi-relativistic DFT in conjunction with QM/MM procedures in order to assess the protein effects on the magnetic and optical spectra [73]. Without going into the details of the study, the results of the calculated absorption spectra are shown in Fig. 7. It is evident that the calculated spectra at various levels of inclusion of the protein environment (dashed, dot-dashed and dotted lines) do not compare favourably with the experimental spectrum (solid line). In particular, the ‘signature’ blue band around  $16,000\text{ cm}^{-1}$  (a cysteine sulphur to copper charge transfer transition [74, 75]) is predicted approximately 1 eV too high in energy by DFT procedures. The  $d\text{-}d$  excitations within the  $d^9$  configuration, which does not lead to elaborate multiplet effects, between  $10,000$  and  $15,000\text{ cm}^{-1}$  are predicted somewhat better but are still calculated too high in energy. The overestimation of the transition energies of the  $d\text{-}d$  transitions leads to too much ‘stiffness’ of the system towards external perturba-



**Fig. 6** Time-dependent DFT (TD-DFT) calculation on the complex  $[\text{Ni}(\text{H}_2\text{O})_6]^{2+}$ . Green bars prediction of spin-allowed excitations by TD-DFT. Red and blue bars multiplets predicted by the spectroscopy-oriented configuration interaction (SORCI) method



**Fig. 7** Comparison of calculated (B3LYP/TD-DFT) absorption spectra for the Cu(II) site in plastocyanin with the reconstructed experimental spectrum (*solid line*). Theoretical results are from gas phase (*dotted line*), continuum (conductor-like screening model, *dashed line*) and quantum mechanics/molecular mechanics (*dot-dashed line*) protein calculations. Theoretical spectra were convoluted with Gaussian peaks of full width at half-height of  $2,000\text{ cm}^{-1}$  in order to facilitate the comparison with the experimental data

tions like electric and magnetic fields and is the ultimate reason for most of the observed significant errors in linear response calculations of the magnetic properties of plastocyanin [73]. Much better results for the absorption spectra of blue copper proteins have been obtained with the CASPT2 method by Pierloot et al. [76] in high-quality studies.

There are several pragmatic combinations of DFT with ligand field theory which are successful in transition metal calculations [77–80] but the general multiplet problem has still not been solved satisfactorily. Some of the known failures of TD-DFT have been corrected, mostly in rather ad hoc procedures, but a fully satisfactory and practical DFT treatment of excited states is not yet in sight. In general, the admixture of HF exchange in the hybrid functionals reduces many of the problems but does not eliminate them. An alternative to TD-DFT is, of course, the use of separate self-consistent-field (SCF) calculations for each state of interest (Delta-SCF approach). Traditionally, Delta-SCF or Slater's transition-state theory was the method of choice in DFT calculations before the invention of TD-DFT. The attractive feature of both approaches is that electronic relaxation is included in the treatment. Nevertheless, there are also important arguments against the use of Delta-SCF or transition-state approaches: (1) both are not general methods in the sense that it will not always be possible to converge on all states that one might be interested in, (2) the

approaches are computationally laborious since they require potentially many SCF calculations, (3) orthogonality of ground and excited states is not guaranteed, (4) intensities can usually not be accessed by Delta-SCF calculations (this is not true for the transition-state approach), (5) degenerate excited states are difficult to treat with this methodology. All of these drawbacks exist relative to TD-DFT; others are shared by both methods. Nevertheless, for selected problems Delta-SCF is certainly a viable alternative to TD-DFT, in particular if electronic relaxation is important.

In conclusion, one is certainly well advised to view TD-DFT results with care and caution. It is not enough to simply identify broad maxima of experimental absorption spectra on a one-to-one basis with calculated transitions. That is not to say that TD-DFT cannot yield useful results. On the contrary, when viewed in conjunction with detailed experiments, such calculations can give quite useful insights as exemplified by many publications of Brunold and co-workers (e.g. [81–84] and reference therein). Still, the field of optical spectra, especially when it comes to their finer details, is certainly one of the most difficult for DFT and it is here where, perhaps, correlated ab initio methods can compete well with DFT methods. A case in point is the blue copper site, where TD-DFT results are of low quality but high-level CASPT2 results provide satisfactory results [76]. Initial results obtained with the simplified SORCI method have also been mostly encouraging [11, 19, 20, 26, 85–87].

## Summary

In summary it may be stated that DFT indeed is a very useful tool in bioinorganic chemistry. However, as alluded to before it is not without problems and there is no reason to believe everything that a given DFT program predicts. Thus, a careful comparison of calculated and measured observables may greatly increase the trust one can have in the results of computations and add to their credibility.

It appears that the accuracy of DFT is uniformly good for geometries and vibrational frequencies and probably good for total energies. A number of spectroscopic properties of interest to the bioinorganic community can be predicted with reasonable to good accuracy with DFT and can be enormously helpful in the analysis of experimental data even if the numbers fall short of true quantitative accuracy. A critical comparison is, however, always warranted, in particular when it comes to optical spectroscopy.



The biggest advantage of DFT-based procedures is that they converge quickly to the basis set limit and can be used in a very straightforward black-box fashion also by nonexperts. The variation of the results with the functional itself is, in our opinion, not very pronounced and the two functionals BP86 and B3LYP are entirely representative of the classes of GGA and hybrid functionals. The strengths of the former are in the prediction of geometries and vibrational frequencies, while the latter has advantages in the prediction of energies and spectroscopic properties.

Extrapolating to the future, it seems likely that DFT will continue to play a very prominent role for some time to come. However, since the progress in the DFT functionals (as opposed to their implementations) has been slow since the introduction of hybrid functionals in 1993 [88], it appears to be likely that simplified correlated ab initio methods will regain importance, at least for the calculation of properties. The recent development of linear scaling correlation methods is certainly an exciting prospect in this direction.

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