Inorg. Chem. **2008**, *47*, 10357−10365

Inorganic Chemistry
Article

Bioinorganic Chemistry Modeled with the TPSSh Density Functional

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Received May 8, 2008

In this work, the TPSSh density functional has been benchmarked against a test set of experimental structures and bond energies for 80 transition-metal-containing diatomics. It is found that the TPSSh functional gives structures of the same quality as other commonly used hybrid and nonhybrid functionals such as B3LYP and BP86. TPSSh gives a slope of 0.99 upon linear fitting to experimental bond energies, whereas B3LYP and BP86, representing 20% and 0% exact exchange, respectively, give linear fits with slopes of 0.91 and 1.07. Thus, TPSSh eliminates the large systematic component of the error in other functionals, reducing rms errors from 46−57 to 34 kJ/mol. The nonhybrid version of the functional, TPSS, gives a slope of 1.08, similar to BP86, implying that using 10% exact exchange is the main reason for the success of TPSSh. Typical bioinorganic reactions were then investigated, including spin inversion and electron affinity in iron−sulfur clusters, and breaking or formation of bonds in iron proteins and cobalamins. The results show that differences in reaction energies due to exact exchange can be much larger than the usually cited ∼20 kJ/mol, sometimes exceeding 100 kJ/mol. The TPSSh functional provides energies approximately halfway between nonhybrids BP86 and TPSS, and 20% exact exchange hybrid B3LYP: Thus, a linear correlation between the amount of exact exchange and the numeric value of the reaction energy is observed in all these cases. For these reasons, TPSSh stands out as a most promising density functional for use and further development within the field of bioinorganic chemistry.

Introduction

Density functional theory (DFT) constitutes the most widely used theoretical method for describing electronic structure.[1] In principle, DFT can describe any molecular system to any accuracy, but unfortunately, no universally applicable functional exists, since there is no analytical form known that captures universally the connection between any electron density and its associated energy. However, one can distinguish functionals that depend locally on the density only (local spin density approximations) from those that depend also on the gradient of the density (generalized gradient approximation, GGA), and on the kinetic energy density as well (meta functionals).[2,3] In addition, the incorporation of some amount of exact exchange into so-called hybrid functionals has been seen to enhance performance when studying molecular systems.[4] With these four ingredients, modern DFT has a rigorous path toward improvement. In this ongoing process, it is crucial that functionals are constantly evaluated against experimental benchmark data, in order to understand and improve them to the point where they can be used with confidence for studying a particular problem.[5]

The most commonly used density functionals have been parametrized to fit data primarily for main group molecules.[6] For this task, hybrid functionals have achieved outstanding accuracy and use. The best known example is the three-parameter hybrid functional B3LYP,[4] which displays an impressive mean absolute error (MAE) of ca. 10 kJ/mol for enthalpies of formation, and 0.013 Å for bond distances for the G2 test set. The amount of exact exchange was optimized to be ca. 20% for these benchmarks, and entered as a fixed

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10.1021/ic800841t CCC: $40.75

parameter in the functional.[4] This success has made B3LYP the most widely used functional today, probably even within the field of transition metal chemistry.[7]

However, when moving from main block elements to transition metals, problems arise, as electronic configurations come very close in energy and increase electron correlation through so-called nondynamical correlation.[8] Certain properties, including structures, frequencies, and some types of reaction energies, can be modeled accurately[9,10] using either B3LYP[4] or nonhybrid functionals such as BP86,[11,12] which have been applied to transition metal systems since the advent of these methods.[13] Good performance of DFT for modeling structures is, however, not always observed when encountering structures of weak or unusual specific interactions, such as, e.g., van der Waals interactions in large molecules[14] or agostic interactions in Nb complexes,[15] where the poor performance is in fact due to shortcomings in the correlation part of the functional.

The two types of functionals perform similarly when nondynamic correlation is not changing substantially during the studied process, as exemplified by isodesmic reactions such as isomerizations or heterolytic cleavage of bonds. Errors of ~20 kJ/mol (~5 kcal/mol) in DFT studies of transition metal reactions have often been stated.[10,16] However, it is now known that errors can be significantly larger for nonisodesmic reactions involving transition metals, such as binding of ligands to metal centers,[7] homolytic cleavage,[17] one-electron transfer, and spin inversion.[18] These errors depend mainly on the treatment of exchange. Exact exchange favors the more open-shell electronic configurations. This leads to a bias toward high-spin configurations in hybrid functionals,[17−19] and to underestimated bond dissociation energies by favoring the dissociated state. In some of these cases, nonhybrid functionals such as BP86 perform much better than hybrid functionals.[17,20]

Recent studies have shown that, for a series of 80 transition metal diatomics, the 20% hybrid B3LYP and 25% hybrid PBE0 underestimate bond strengths, whereas nonhybrid functionals BP86, PBE, and BLYP overestimate bond strengths.[21] Even more troubling, the average errors in these energies are 43−52 kJ/mol with the largest errors of more than 100 kJ/mol, giving a more realistic account of the errors in modeling nonisodesmic reactions of transition metal systems. Importantly, since errors in the two types of functionals have a large systematic component,[21] there is reason to investigate how well a 10% hybrid functional would perform in this context. Along these lines, a version of B3LYP with 15% exact exchange was found earlier to perform better for iron(II) complexes,[22] and a version of BP86 with 10% exact exchange was found to provide the best results for some FeNO and FeO_2 complexes.[23] This study clearly shows that the use of 10% exact exchange hybrid functionals is warranted in the field.

As discussed earlier by Perdew and co-workers, the amount of exact exchange to be incorporated in a functional depends on the coupling between electrons in the system of study, as given by the adiabatic connection formula.[25] Perturbation theory can be used to rationalize why 20−25% exact exchange, as seen in B3LYP and PBE0, performs well for main group elements.[24] Furthermore, it was suggested that near-degenerate ground states of the uncorrelated wave functions, i.e., states with a large component of nondynamical correlation, will require a smaller amount of exact exchange, sometimes giving better performance of nonhybrid functionals.[24]

Our particular interest is modeling of bioinorganic chemistry. Owing to the systematic errors in B3LYP and BP86,[21] we anticipate that the first-row transition metals available in bioinorganic chemistry imply an electronic coupling that corresponds to an exact exchange component between 0% and 20%. One could modify the B3LYP to obtain such a functional, or, which has been done here, use a particular promising functional of the meta-type already available, the TPSSh functional.[2,26] This functional is nonempirical except for the $a = 0.1$ coefficient of exact exchange, implying that it does not rely on the additional parameters optimized empirically for other functionals such as B3LYP and BP86.[2] As was seen in a benchmark study,[27] this functional generally performs similarly to B3LYP for the G3/99 set (it is slightly better for heats of formation and slightly worse for electron affinities, ionization potentials, and proton affinities). However, for certain properties of transition metal systems, it outperforms both B3LYP and nonhybrid functionals, indicated by studies of some transition metal hydrides, oxides, fluorides, and nitrides.[28] These results suggest that TPSSh may be very accurate for modeling bioinorganic chemistry.

The purpose of this paper is to test the validity of the promising conclusions regarding TPSSh in a more extensive data set including more metals and also larger, more covalently bound ligands, i.e., transition metal chlorides, bromides, sulfides, and carbides, and in relation to typical

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bioinorganic model chemistry exemplified by several classical bioinorganic problems, viz., Co−C bond cleavage in cobalamins, O_2 binding to deoxyheme and di-iron enzymes, and spin inversion and reduction of iron−sulfur clusters. Altogether, our results confirm that TPSSh with $a = 0.1$ outperforms other functionals in describing reactions of transition metal systems, and show that the TPSSh energies fall in between those of B3LYP and BP86/TPSS, implying a linear correlation between exact exchange and such reaction energies. Thus, the TPSSh is a most promising candidate for further developments of bioinorganic DFT.

It is worth mentioning that several other research groups are working along similar lines: One study has shown that, for transition metal−metal bonds, the nonhybrid TPSS performs best,[29] most likely because these systems represent the limit of very strongly coupled, degenerate systems. Other benchmarks of transition metal systems with other functionals include studies of equilibrium geometries,[30] bond energies,[31] and excitation energies.[32] An important and similar approach has already been taken for the homonuclear first-row transition metal diatomics,[33] all showing clear differences between hybrid and nonhybrid functionals and shortcomings in both. Work by Truhlar and co-workers used a variety of data to benchmark a large number of functionals.[31] For 21 metal−ligand bond energies, relevant to the present study, good performance was seen for some functionals within all the four classes of nonhybrid, hybrid, meta, and hybrid meta, and a correlation with exact exchange was therefore not apparent.[31] However, for a larger and more systematic 80-molecule set presented before,[21] the results very clearly show that performance is directly related to the amount of exact exchange. The present work is the first to apply TPSSh to bioinorganic chemistry; it shows clearly a linear dependence of reaction energies on the amount of exact exchange, and provides a strong case for the use of TPSSh as a tool in bioinorganic chemistry.

Methods

Calculations were performed with the Turbomole 5.8 software.[34] The test set consisted of all possible neutral diatomic molecules of Sc−Zn bound to H, F, Cl, Br, N, C, O, or S, altogether 80 species. These were geometry optimized in all relevant spin states, to find the ground state in each case. Energies were converged down to 10^{-6} hartree, and the gradient was converged down to 10^{-3} a.u. Unrestricted calculations were performed in all cases, even where closed-shell states might be possible, to avoid singlet instabilities. This approach is more direct than attempting to compute closed-shell states in individual cases and then probing for instabilities afterward. Computation of configurations with lower M_S values and lower energies can systematically be computed from higher M_S values (vide infra), as the orbitals will tend to converge to such lower minima.

The basis set used was TZVP by Schafer et al.[35] We have shown earlier[21] that a larger QZVPP basis set performs marginally better, giving a 1 kJ/mol smaller rms error for BDEs. Therefore, and because the TZVP basis set is more realistic to be used in actual modeling, the latter basis set was applied. Zero-point energies and enthalpy corrections were calculated from geometry optimization and subsequent harmonic frequency analysis. For TPSSh, analytical gradients are not implemented with the current version of Turbomole, so numeric gradients were computed using the NumForce script. Differences in zero-point energies amount to less than 2 kJ/mol when computed with various functionals (see Supporting Information).

The bond dissociation energy (BDE) was computed for all 80 molecules by computing the ground-state energies of the corresponding atoms and subtracting the energy of the diatomic molecule. ZPE corrections and enthalpy corrections were added for comparison with experimental data at standard conditions. The experimental data that we compare with are from gas-phase experiments,[36] and thus, our calculations have not been corrected for medium effects.

For transition metal systems having many configurations close in energy, there is no simple way to guarantee convergence to the global minimum. Standard quantum chemistry packages provide guess molecular orbitals for initial computation of the wave function and density, in the case of Kohn−Sham DFT. In transition metal systems, the resulting energies often correspond to local minima which are not characteristic of the true states. This problem is symptomatic of the aforementioned presence of nondynamical correlation, implying strong electronic coupling and less justification of exact exchange. Instead, it is almost always possible to find configurations with lower energies when using orbitals from earlier converged, higher M_S values as starting points. As an example, for diatomics having a doublet ground state, simple start orbitals may not succeed in finding the proper minimum, but using the converged $M_S = 3/2$ configuration as a starting point, and spin-down coupling the electrons to $M_S = 1/2$, will usually give a good broken-symmetry approximation to the true state.

Results and Discussion

Prediction of Ground-State Spin. In the computations, specific M_S values are used as constraints in separate optimization procedures. The electronic configuration with the lowest energy is considered the DFT-approximation to the true ground state, and its associated M_S value is compared to the experimentally determined spin.

Table 1 displays the experimentally determined state at the top of each entry, and the computed value of $2M_S + 1$ for the configuration of lowest energy below. From the total test set of 80 molecules, 63 experimentally determined ground states have been described.[37] It is important to keep in mind that the standard DFT procedure produces symmetry-broken approximations to the exact wave function, so the symmetry labels shown for the experimental states in Table 1 do not apply to the computed states.

As seen from Table 1, 58 of 63 spins are correctly modeled, which parallels the average performance for other

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Table 1. Experimental Ground States Compared to TPSSh-Computed $2M_S + 1$ (Italicized)

	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
H	$^1\Sigma^+$	4Φ	$^5\Delta$	$^6\Sigma^+$	$7\Sigma^+$	$^4\Delta$	$^3\Phi$	$^2\Delta$	$^1\Sigma^+$	$2\Sigma^+$
	3	*4*	*5*	*6*	*7*	*4*	*3*	*2*	*1*	*2*
F	$^1\Sigma^+$	4Σ	?	$^6\Sigma^+$	$7\Sigma^+$	6Δ	$^3\Phi$	$^2\Pi$	$^1\Sigma^+$	$2\Sigma^+$
	3	*4*	*5*	*6*	*7*	*6*	*3*	*2*	*1*	*2*
Cl	$^1\Sigma^+$	4Σ	?	$^6\Sigma^+$	$^7\Sigma^+$	6Δ	?	?	$^1\Sigma^+$	$^2\Sigma^+$
	3	*4*	*5*	*6*	*7*	*4*	*3*	*2*	*1*	*2*
Br	$^1\Sigma^+$	$^4\Sigma$	?	?	$^7\Sigma^+$	?	?	?	$^1\Sigma^+$	$^2\Sigma^+$
	3	*4*	*5*	*6*	*7*	*6*	*3*	*2*	*1*	*2*
C	$^4\Pi$	$^3\Sigma$	?	?	?	$^3\Delta$	$^2\Sigma^+$	$^1\Sigma^+$	?	$^3\Sigma^-$
	4	*3*	*2*	*3*	*4*	*3*	*2*	*1*	*4*	*3*
N	$^1\Sigma^+$	$^2\Sigma^+$	$^3\Delta_r$	$^4\Sigma$	?	?	?	?	$^3\Sigma^-$	$^4\Sigma^-$
	1	*2*	*3*	*4*	*5*	*6*	*5*	*4*	*3*	*4*
O	$^2\Sigma^+$	$^3\Delta$	$^4\Sigma$	5Π	$^6\Sigma^+$	$^5\Delta$	$^4\Delta$	$^3\Sigma$	2Π	$^1\Sigma^+$
	2	*3*	*4*	*5*	*6*	*5*	*4*	*3*	*2*	*1*
S	$^2\Sigma^+$	$^3\Delta$	$^4\Sigma^-$	$^5\Pi$	$^6\Sigma^+$	$^5\Delta$	$^4\Delta$	$^3\Sigma$	$^2\Pi$	$^1\Sigma^+$
	2	*3*	*4*	*5*	*6*	*5*	*4*	*3*	*2*	*1*

previously tested functionals.[21] Four of the five cases where TPSSh fails to predict the correct spin are for scandium hydride and halides, which are not relevant to bioinorganic chemistry, and the difference in energy to the correct spin state is always less than 8 kJ/mol: ScH (1 kJ/mol), ScF (2 kJ/mol), ScCl (7 kJ/mol), ScBr (8 kJ/mol), and FeCl (3 kJ/mol). Thus, the functional successfully obtains electronic configurations consistent with experimentally observed spins. As transition metal systems become more coordinately saturated, the energies of configurations will move even closer, due to the increased density of configurations. This means that, in larger bioinorganic models to be discussed later, problems with assigning the correct spin state may prevail in some cases.

Equilibrium Geometries. The TPSSh-optimized equilibrium bond lengths for the 80 molecules are presented in Table 2. For each molecule, the experimental bond length,[36,38] when available, is listed above, and the computed bond length below. The mean absolute errors (MAEs) are provided for each type of atom, and for the complete data set, to identify any particular trends in the performance of the functional with respect to element.

The numbers in Table 2 confirm results from earlier tests of some of the metal hydrides, oxides, fluorides, and nitrides,[28] showing that the TPSSh functional does a very good job in modeling the metal−ligand bond lengths. In most cases, our computed equilibrium distances are similar to those computed earlier within 0.01 Å, and in all cases but one within 0.02 Å, with our calculations usually giving marginally longer bonds. This is most likely an effect of the different basis sets used. However, in one case, TiN, our computed bond length of 1.59 Å is 0.05 Å larger than that computed earlier. Our number is within the expected deviation from experiment (0.01 Å), suggesting a better description. Altogether, good agreement with earlier procedures using the same functional is found.

We now turn the discussion to the newly computed molecules, including both some of the fluorides, nitrides, hydrides, and oxides not computed before with this functional, but in particular to the carbides and to the slightly larger and more covalent sulfides, chlorides, and bromides. As seen from Table 1, we did not encounter any particular problems in predicting the correct spin of these molecules. It can be seen that the MAEs of computed bond lengths are significantly larger for chlorides, bromides, and carbides (0.038, 0.035, and 0.034 Å) whereas errors in sulfides are average (0.022 Å). This overestimation of metal−ligand bond lengths for larger ligands was, however, observed with other functionals as well[21] and is not a particular shortcoming of the TPSSh functional.

Special attention is given to the Fe−O, Fe−S, and Co−C bonds, which are found in heme and none-heme iron proteins, iron−sulfur clusters, and cobalamins, respectively, to be discussed below. As is seen, the Fe−O and Fe−S are very well modeled with TPSSh (errors of 0.01 and 0.02 Å, respectively), and in fact, all nonhybrid GGA and hybrid functionals reported earlier performed well for modeling these ligands to iron.[21] However, the Co−C bond is not well modeled with any of the hybrid functionals TPSSh, B3LYP, and PBE0 (errors of 0.10, 0.11, and 0.13 Å, respectively).[21] As discussed previously, the hybrid functionals apparently converge to the $^2\Delta$ state of CoC, which is only 7 kJ/mol (600 cm^{-1}) above the $^2\Sigma^+$ ground state, which has an experimental bond length of 1.64 Å,[39] close to that found with the hybrid functionals.

This example illustrates that hybrid functionals not only prefer higher spin but also higher angular quantum numbers. The explanation in our opinion lies in the suggestion by Perdew and co-workers[24] that the correlation index n (where $1/n$ is the fraction of exact exchange included) scales with the degree of nondynamical correlation in the system; exact exchange is less adequate when nondynamical correlation (i.e., strong coupling of electrons) is substantial. This is also consistent with the observation that hybrid functionals perform better for late transition metals (Ni, Cu, Zn) whereas nonhybrids perform similarly across the d-block, because more configurations are involved in the middle of the d-block, in particular for Mn and Fe.[21] In a more phenomenological sense, exact exchange seems proper when one configuration is a good approximation to the true ground state, because the exchange expression simply assumes the HF exchange from antisymmetrization of the orbitals corresponding to that one electronic configuration. However, for multiconfigurational systems, shortcomings of using only one Kohn−Sham configuration in DFT are partly canceled by the self-interaction error of non-HF DFT exchange.

Bond Dissociation Energies. The bond dissociation energies are defined as the energy of the two radical fragments (in this case atoms) minus the energy of the complex, calculated for the ground states. These energies are probably the most important data to benchmark against, since bond formation and bond breaking are at the heart of most relevant chemical processes. Zero-point energies (ZPEs) should be included for good estimates, although these are not very functional-dependent.[21] Importantly, at any given

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Table 2. Experimental Bond Lengths Compared to TPSSh-Computed Bond Lengths (Italicized) (Å)[a]

	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	MAE
H	1.78	1.78	1.73	1.66	1.73	1.63	1.53	1.46	1.46	1.59	0.025
	1.79	*1.76*	*1.69*	*1.66*	*1.74*	*1.57*	*1.51*	*1.51*	*1.47*	*1.62*	
F	1.79	?	?	1.78	1.84	1.79	1.74	1.73	1.74	1.80	0.013
	1.82	*1.83*	*1.79*	*1.79*	*1.84*	*1.79*	*1.75*	*1.76*	*1.76*	*1.80*	
Cl	2.23	?	?	2.20	?	2.15	?	?	2.05	2.10	0.038
	2.27	*2.26*	*2.23*	*2.21*	*2.25*	*2.13*	*2.10*	*2.12*	*2.09*	*2.18*	
Br	2.40	?	?	?	?	?	?	?	2.17	?	0.035
	2.43	*2.42*	*2.40*	*2.36*	*2.40*	*2.35*	*2.23*	*2.20*	*2.21*	*2.32*	
C	1.90	1.70	1.60	?	?	?	1.56[b]	?	?	2.00	0.034
	1.88	*1.67*	*1.59*	*1.64*	*1.68*	*1.59*	*1.66*	*1.61*	*1.80*	*1.99*	
N	1.69	1.58	1.57	1.60	?	?	?	?	1.80	?	0.018
	1.67	*1.59*	*1.55*	*1.57*	*1.63*	*1.62*	*1.61*	*1.62*	*1.79*	*2.04*	
O	1.67	1.62	1.59	1.62	1.65	1.62	1.63	1.63	1.73	1.80	0.013
	1.67	*1.63*	*1.59*	*1.62*	*1.63*	*1.61*	*1.62*	*1.62*	*1.74*	*1.74*	
S	2.14	2.09	2.10	2.10	2.07	2.00	2.00	2.00	2.05	2.10	0.022
	2.14	*2.09*	*2.06*	*2.11*	*2.06*	*2.02*	*2.04*	*1.97*	*2.08*	*2.06*	
MAE	0.019	0.014	0.022	0.010	0.010	0.022	0.036	0.030	0.023	0.037	0.022

[a] References36 and 37 unless otherwise indicated. [b] Reference38.

Table 3. Experimental Bond Dissociation Energies (kJ/mol)[a]

	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
H	180	205	209	190	234	180	226	252	278	82
F	589	569	590	445	423	?	435	430	413	261
Cl	331	405	477	378	339	330	338	377	378	193
Br	444	439	439	328	314	247	331	360	331	?
C	444	423	427	?	?	?	?	?	?	68
N	469	476	477	378	?	?	?	?	?	?
O	682	672	627	461	403	390	385	382	269	?
S	477	418	450	331	301	322	331	344	276	?

[a] Reference37.

Table 4. Errors in Computed Bond Dissociation Energies, Including Zero-Point Energies and Enthalpy Corrections (kJ/mol), from TPSSh Functional

	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	rms
H	67	67	89	30	−47	50	22	−27	−20	21	49
F	2	−9	−21	10	33		−12	−39	−29	25	23
Cl		36	−24	−16	24	28	−27	−38	−26	24	26
Br	−32	−26	−23	−1	13	71	1	−23	−2		30
C		−43	−19							55	36
N	−74	−9	6	−58						37	46
O	−24	−3	15	−59	5	40	5	−5	−5		26
S	9	71	23	−30	32	31	−17	5	−1		31
rms	44	41	36	36	29	47	17	27	18	35	34

Table 5. Errors in Computed Bond Dissociation Energies, Including Zero-Point Energies and Enthalpy Corrections (kJ/mol), from TPSS Functional

	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	rms
H	72	74	96	37	−42	59	31	−20	−9	21	53
F	19	11	−1	28	52		6	−25	−11	34	26
Cl		50	−13	−9	33	38	−27	−37	−20	24	29
Br	−26	−17	−15	5	21	69	9	−20	3		28
C		0	31							66	37
N	−30	45	67	6						47	44
O	11	41	64	−10	63	88	57	49	25		52
S	30	101	56	−4	67	60	7	42	15		52
rms	37	53	53	19	49	65	29	34	16	42	42

nuclear geometry, the functionals remain to give very different relative energies, showing that the differences in energy are not particularly due to differences in the geometry.[17,21]

Table 3 shows the experimentally determined BDEs for the test set of diatomics. Values go all the way from 68 kJ/mol (ZnC) to 682 kJ/mol (ScO), with a clear trend of decreasing bond strength going down the row from Sc to Zn. Such trends have been discussed earlier and are well accounted for by any GGA nonhybrid or hybrid DFT method.[21] Our main concern here is the absolute reaction energies, as they are often used in modeling to rule out reactions if they are too unfavorable, or to compare directly with alternative reactions to see which one is more favorable.

Table 4 shows the BDEs computed with TPSSh minus the experimental BDEs, and the corresponding root-mean-square deviations (rms) from experimental numbers. A positive number implies that TPSSh overestimates the BDE. A first point to notice is that errors for hydrides are larger than average (rms of 49 kJ/mol), equally true for nitrides, and for Sc, Ti, and Fe complexes more broadly. Some of these tendencies have been observed with other functionals as well, in particular the general problem of modeling the Sc complexes, as discussed earlier.[21] In general, the TPSSh functional gives a more balanced treatment of the entire test set, with largest errors much smaller than the 112−160 kJ/mol found for other functionals.

Most importantly, the overall rms is only 34 kJ/mol, much smaller than the 46−57 kJ/mol found for BP86, PBE, PBE0, B3LYP, and BLYP.[21] On average, the BDE of any molecule is overestimated by only 3 kJ/mol, giving essentially no systematic component of the error when using TPSSh. In comparison, B3LYP on average underestimates the BDE by 30 kJ/mol and BP86 on average overestimates the BDE by 31 kJ/mol.

To test if this effect is indeed due to exact exchange, and not to other differences between the functionals (e.g., the inclusion of the kinetic energy density in the TPSSh functional), the BDEs were computed also with the TPSS functional, which is the nonhybrid version of TPSSh.[2] Table 5 shows the corresponding errors obtained with this functional: Although the average error is slightly smaller than for BP86 and B3LYP (rms of 42 kJ/mol), the systematic error is still 25 kJ/mol. In the cases where comparison is possible, these results are similar to the benchmarks performed by Furche and Perdew.[28] Thus, it can be concluded that, in the TPSSh functional, the systematic components of the errors in both BP86 and B3LYP have been removed, implying that 10% exact exchange, as opposed to 0%

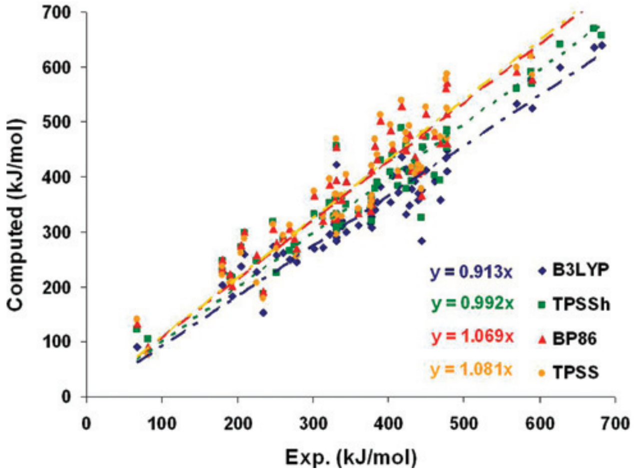

Figure 1. Computed vs experimental bond dissociation energies of transition-metal-containing diatomics.

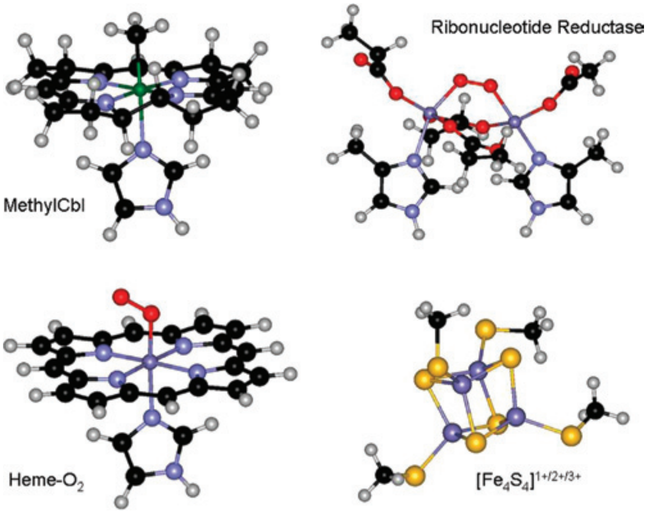

Figure 2. Four bioinorganic models studied in this work.

Table 6. Computed Reaction Energies of Bioinorganic Models of Figure 2 (Including Zero-Point Energy, in kJ/mol)

reaction	B3LYP	BP86	TPSS	TPSSh	reaction type
Heme + O_2 → HemeO_2	13	−98	−106	−49	O_2-binding
RR + O_2 → RRO_2	12	−116	−106	−40	O_2-binding
MeCbl → Cbl + Me•	66	125	122	101	Co−C homolytic bond cleavage
$^9[Fe_4S_4]^{2+}$ → $^1[Fe_4S_4]^{2+}$	−22	−68	−63	−40	spin inversion
$^1[Fe_4S_4]^{2+}$ → $^2[Fe_4S_4]^{+}$	395	448	449	418	reduction

or 20%, is an optimal value for these first-row transition metal systems.

Figure 1 shows 63 BDEs for which experimental data are available, computed with B3LYP, TPSSh, TPSS, and BP86, plotted against experimental numbers. For the whole spread in BDEs of more than 600 kJ/mol, the functionals generally do quite well in modeling trends, but when one calculates the linear correlation with experiment, the slope of the regression curve is 0.99 for TPSSh, 0.91 for B3LYP, 1.08 for TPSS, and 1.07 for BP86, showing graphically the tendency of B3LYP to underestimate bond energies and BP86/TPSS to overestimate them. In contrast, the TPSSh functional provides an almost optimal correlation with experimental data, although random deviations remain large due to inherent uncertainties in both the experimental and theoretical methodology. Thus, Figure 1 sums up the observation that exact exchange is responsible for main differences in these energies, and in addition, that 10% exact exchange is optimal for these systems.

Bioinorganic Test Models. We now turn to the description of larger models typically used in computational investigations of metalloproteins. These include (i) a methylimidazolylcorrin model of methylcobalamin (MethylCbl), the complex cobalt-containing organometallic cofactor found in methionine synthase and methylmalonyl coenzyme A mutase;[40] (ii) a model of class II ribonucleotide reductase (RR), a nonheme di-iron enzyme;[41] (iii) an imidazolyl-dioxyiron(II)porphine model resembling the heme−O_2 adduct found in globins;[42] and (iv) a cluster consisting of four irons, four sulfides, and four methylthiolate ligands as a model of the [Fe_4S_4] clusters found in many electron-transfer proteins.[43] The models are depicted in Figure 2. These models have been used in similar forms in many computational studies throughout the literature, usually using B3LYP or BP86 as the functional,[10,18] and as such our calculations serve as a test of the expected accuracy of many of these studies.

The reaction energies of five processes have been computed with B3LYP, BP86, TPSS, and TPSSh. The processes are the following: for heme, the energy of O_2 binding to deoxyheme to produce the oxy adduct; for RR, dioxygen binding to the deoxy form of the protein to generate the peroxo intermediate *P*; for methylcobalamin, the energy of homolytic cleavage of the Co−C bond; for the [Fe_4S_4] cluster, the energy of inverting the total spin state from $M_S = 4$ (8 excess unpaired spin up electrons) to $M_S = 0$ (full antiferromagnetic coupling); as well as the electron affinity of the oxidized cluster. The computed energies are presented in Table 6. There is a lack of experimental information about microscopic reaction energies such as these, and comparison is difficult in bioinorganic systems due to the complexity of the systems. However, we can still compare the spread in energies resulting from the use of different functionals and deduce their accuracy in a limited number of these relevant cases.

O_2−Binding to Deoxyheme. The binding of small ligands such as O_2 to heme constitutes a complex electronic structure problem studied in detail by computational methods.[44−48]

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The main problem is associated with the change of spin state accompanying binding of triplet O_2 to high-spin deoxyheme, forming an EPR-silent singlet dioxy adduct.[49] Because of these changes, a very accurate account of electron correlation is necessary to understand how O_2 can fast and reversibly bind to deoxyheme even though this process is formally spin-forbidden, and the following discussion shows that these energies are very dependent on the applied functional.

Our computed energies of O_2-binding are +13 kJ/mol (B3LYP), −98 kJ/mol (BP86), −106 kJ/mol (TPSS), and −49 kJ/mol (TPSSh). Thus, for this process, the differences due to functional are more than 100 kJ/mol, much more than the 20 kJ/mol or less cited as a typical error in bioinorganic DFT.[7] The large difference in BDEs of hybrid and nonhybrid functionals has been observed before for these cases. It is clear that the B3LYP functional does not predict any binding at all, since these energies are ZPE-corrected energies only (ZPE correction ~ 11 kJ/mol), whereas the total free energy correction from vibration analysis is ~59 kJ/mol, in favor of dissociation. Thus, the final free energy estimates are 61 kJ/mol (B3LYP), −50 kJ/mol (BP86), −58 kJ/mol (TPSS), and −1 kJ/mol (TPSSh). Electrostatic screening may contribute somewhat as well: The computed solvation correction using Cosmo[51] with $\varepsilon = 80$ is 22 kJ/mol, in favor of the adduct, and basis set effects can be ~10 kJ/mol,[52] providing an upper bound to such effects. Thus, the BP86 and TPSS values may be too exothermic considering that the reaction has to be reversible. On the other hand, the TPSSh functional has a value which is close to zero, which is in line with the reversible binding observed in the real system.

As seen from Table 6, the O_2-binding energy of TPSSh is almost halfway between that of B3LYP and BP86/TPSS, suggesting that exact exchange is *the* main effect giving rise to the different reaction energies in these reactions. Thus, the behavior of these larger models is fully consistent with the results of Figure 1.

O_2-Binding to Ribonucleotide Reductase. The RR model represents a multinuclear iron center with antiferromagnetic coupling, binding O_2 to form a μ-1,2 peroxo intermediate, P.[53] This binding is thus very different from that of heme, where O_2 binds end-on to only one iron atom, and the two reactions provide an interesting comparison. Even then, as seen in Table 6, the reaction energies of binding O_2 are very similar to those obtained for heme: 12 kJ/mol (B3LYP), −116 kJ/mol (BP86), −106 kJ/mol (TPSS), and −40 kJ/mol (TPSSh). The relative effects of the functionals are similar, implying that B3LYP does not form a stable bond, whereas the nonhybrid GGA functionals BP86 and TPSS form a very stable bond, and TPSSh is almost equally in between. It can thus be concluded that, despite the different binding mode and the presence of two irons, the general conclusion that exact exchange is a main determinant of these energies is confirmed also in this case. Importantly, when modeling such systems with only one functional, any estimate of accuracy in this type of reaction energies has to be much more conservative than the often cited 20 kJ/mol, and a use of several functionals with varying component of exact exchange is strongly encouraged from the above results.

Homolytic Co−C Bond Cleavage in Methylcobalamin. Cobalamins are found in two human proteins, one of which, methionine synthase, uses methylcobalamin and the other, methylmalonyl coenzyme A mutase, uses 5′-deoxyadenosylcobalamin.[40] In methionine synthase, the bond is broken by heterolytic cleavage upon nucleophilic attack.[40] Since this reaction is closed-shell methyl cation transfer, the effect of exact exchange is minimal and the reaction has been modeled by B3LYP.[54] In the mutase, the purpose of the Co−C bond is to provide a radical by homolytic cleavage of the Co−C bond, to initiate radical rearrangement in the substrate leading to the product. For this classical problem of Co−C bond labilization, the choice of functional to a very large extent determines the BDE, as shown previously.[17] The Co−C BDE of methylcobalamin is known experimentally in solution to be ca. 155 ± 13 kJ/mol.[55]

We have calculated ZPE-corrected BDEs of 66 kJ/mol (B3LYP), 125 kJ/mol (BP86), 122 kJ/mol (TPSS), and 101 kJ/mol (TPSSh) for this bond in the model shown in Figure 2. Although other effects contribute to those energies, it is very certain that the value of 66 kJ/mol calculated using B3LYP is a large underestimation. The ZPE makes up 21 kJ/mol of this BDE, favoring dissociation. It has been shown that all corrections for solvent, enthalpy, thermal effects, vibrations, basis set, superposition effects, and relativity almost cancel to make the computed BDE without zero-point effects very close to the best estimate in this case.[17] This means that the best estimate from each functional, including all corrections, is ~87 kJ/mol (B3LYP), 146 kJ/mol (BP86), 143 kJ/mol (TPSS), and 122 kJ/mol (TPSSh); earlier reported values were 102 kJ/mol (B3LYP) and 156 kJ/mol (BP86) with different basis sets.[17] The experimental value of 155 ± 13 kJ/mol agrees well with BP86 and TPSS, but is not in agreement with B3LYP.

It can therefore be concluded that the description of the Co−C bond in cobalamins requires a very small amount of exact exchange, close to zero and significantly smaller than the 20% found in B3LYP. TPSSh is thus a clear improvement over B3LYP in this case, and the results obtained in the literature using little or no exact exchange represent the most accurate for studying Co−C cleavage in the protein.[56]

Spin Conversion in Iron−Sulfur Clusters. Iron−sulfur clusters have antiferromagnetically coupled ground states, which represent particularly complex electronic structures and pose substantial challenges to any quantum chemical

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method.[57] The common way to obtain an electronic structure is to calculate it by fully unrestricted DFT, and obtain a broken-symmetry solution which has large spin components on all iron atoms. A good way to do this in practice is to first converge the high-spin states, and then use these orbitals to spin-down couple electrons, and ultimately converge the desired antiferromagnetic state with the lowest possible M_S quantum number. The energy gap between configurations of various M_S values indicates the degree of antiferromagnetic coupling in the system, and the computed J coupling constants are almost always qualitatively correct,[57] i.e., predict the lowest M_S number to be more favorable than higher numbers.

The energy gap between $M_S = 4$ and $M_S = 0$, which was chosen as a test case, corresponds to one ferrous site having all its spins inverted. The energy of this conversion was computed to be −22 kJ/mol (B3LYP), −68 kJ/mol (BP86), −63 kJ/mol (TPSS), and −40 kJ/mol (TPSSh), with $M_S = 0$ lowest in energy. Thus, all four functionals predict the qualitatively correct order of configurations and thus predict that the iron−sulfur cluster is antiferromagnetically coupled, in agreement with experiments.[43] These energies differ less than the reaction energies of bond breaking and formation more commonly occurring in biochemical reactions, but they are still spanning 46 kJ/mol, which is again more than the typically cited uncertainty of bioinorganic DFT.[10]

Again, BP86 and TPSS perform almost identically. Thus, even though this reaction is very different from the bond breaking reactions, exchange correlation is the main reason for differences in the electronic structure description of these configurations and, thus, the energies of converting between them.[18,59] Indeed, in the same way that exact exchange favors the open-shell dissociation products and thus lowers the BDE of transition metal systems, it also favors the configurations with more aligned spins relative to the lowest M_S quantum number. The difference between TPSS and TPSSh, and the similarity of TPSS and BP86, show that the reaction is almost exclusively governed by exact exchange and not by differences in other parts of the functionals, and the effect is seen to be linear, with TPSSh ending up almost halfway between B3LYP and BP86.

Electron Affinities of Iron−Sulfur Clusters. Our final test case is another energy of the iron−sulfur cluster, namely the energy of adding an extrinsic electron to the ground state of the oxidized cluster, which is in the $Fe^{2.5}$ oxidation state. This energy is obtained from the difference in electronic energy of the fully geometry optimized reduced and oxidized structure. It is formally the relaxed electron affinity of the oxidized cluster, but also constitutes the standard approach to computing the reduction potential of a redox reaction in biochemical modeling, after correction for solvent effects, entropy, thermal effects, and a standard reference potential.

The computed electron affinities shown in Table 6 are 395 kJ/mol (B3LYP), 448 kJ/mol (BP86), 449 kJ/mol (TPSS), and 418 kJ/mol (TPSSh). Again, the different functionals give rise to different energies of up to 53 kJ/mol, with BP86 and TPSS almost identical. It is worth mentioning that these absolute energies are of course less informative as compared to relative energies, e.g., shifts in reduction potentials between similar protein mutants, which can be computed quite accurately due to cancellations of errors in the correlation treatment of both sides of the reaction.[60] Still, the differences imply that exact exchange again plays a crucial role, more crucial than any other aspect of the functionals, in determining also the electron affinity of the cluster. Thus, even in redox reactions, exact exchange is a main determinant of the outcome of the computed reaction energy, i.e., electron affinity, ionization potential, and redox potential, and the differences are significant and larger than the 20 kJ/mol cited earlier.[7]

It can also be seen that exact exchange favors the oxidized state in this case because the reducing electron spin couples with an existing electron. The presence of fewer unpaired electrons in the reduced state means that this state is less favored by B3LYP, relative to treatments by other functionals.

Conclusion

The purpose of this paper has been to show that modeling of bioinorganic chemistry, as exemplified by five typical reactions, is most sensitive to and essentially linearly dependent on the amount of exact exchange in the density functional. Other ingredients of the functionals appear to be less important, as they vary substantially among the studied functionals, and since TPSS performs very similarly to BP86 (both nonhybrid functionals) but very differently from TPSSh (which is a 10%-exact-exchange hybrid of TPSS). The energies computed with and without exact exchange span sometimes more than 100 kJ/mol.

We have shown that 10% exact exchange as represented by the TPSSh functional appears optimal: For a large test set of transition metal diatomics collected in Figure 1, TPSSh gives a slope of 0.99 for the regression line with experimental bond energies, whereas B3LYP and BP86, representing 20% and 0% exact exchange, respectively, give slopes of 0.91 and 1.07. TPSS gives a slope of 1.08, similar to BP86. Thus, TPSSh eliminates the large systematic component of the error in other functionals, reducing root-mean-square errors from 42−57 to 34 kJ/mol.

It was then shown that, for larger, more realistic bioinorganic models, the general linear correlation between reaction energies and exact exchange is retained in five representative and qualitatively distinct reactions. These reactions include spin inversion and electron affinities in

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iron−sulfur clusters, and breaking or formation of bonds in iron proteins and in cobalamins. Altogether, the results show that errors can be much larger than the usually cited ∼20 kJ/mol, and the correlation between exact exchange and the resulting reaction energy is demonstrated also for the bioinorganic models. Altogether, the TPSSh functional provides energies that are in best agreement with experiment, although in some cases, even less exact exchange is optimal. Thus, TPSSh constitutes a most reasonable choice of functional for further use and improvement in the field of bioinorganic modeling.

Acknowledgment. The Danish Center for Scientific Computing and the Villum-Kann Rasmussen Foundation are gratefully acknowledged for supporting this work.

Supporting Information Available: Table S1, showing ZPEs computed with TPSSh; Table S2, showing ZPEs computed with BP86; and Table S3, showing differences in computed zero-point energies. This material is available free of charge via the Internet at http://pubs.acs.org.

IC800841T