Validation of Exchange−Correlation Functionals for Spin States of Iron Complexes

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Spin state energies of iron complexes are important for biochemical applications such as the catalytic cycle of cytochrome P450. Due to the size of these systems and the presence of iron, accurate computational results can be obtained only with density functional theory (DFT). Validation of exchange−correlation (xc) DFT functionals for predicting the correct spin ground state of iron complexes is a rather unexplored area. In this contribution we report a systematic study on the performance of several xc functionals for seven iron complexes that are experimentally found to have either a low, intermediate, or high spin ground state. Standard xc functionals like LDA, BLYP, and PBE are found to disfavor high spin states, whereas hybrid and some meta-GGA functionals do provide the correct spin ground state for all molecules. Recently improved pure DFT functionals such as Handy's optimized exchange (OPTX) also perform well. The origin for the apparent performance of the DFT functionals has been addressed and seems to be related to the inclusion of fourth-order terms (s^4) of the dimensionless (or reduced) density gradient s in the exchange functional.

The catalytic cycle of cytochrome P450[1] is a challenge for computational chemistry.[2] Both the iron atom and the porphyrin moiety of the heme in which it is positioned require explicit quantum mechanical treatments,[3] making the system quite sizable when also a substrate is included.[4] Moreover, the active site of the heme is difficult to treat by theoretical methods, as its spin state is sensitive to the heme's surroundings. For example, a spin flip from low to high spin is observed in the substrate binding step of the P450 catalytic cycle.[1] This enables the first electron reduction to take place upon which dioxygen binds as a sixth ligand to iron, giving another spin flip, now to a singlet system.[2,5] The following steps occur too fast to monitor experimentally,[6−8] but theoretical studies[9−15] on compound I, a transient intermediate,[7] suggest a subtle balance between a doublet and quartet state.[11]

The question arises whether the sheer size of the active site of cytochrome P450 and the complexity of the electronic states involved in the catalytic cycle are amenable to treat accurately with density functional theory (DFT).[16−18] Over the past twenty years the performance of many DFT functionals[17,19,20] have been validated against G2 or G3 ab initio data on small molecules containing first and second row atoms,[21,22] but hardly for systems containing transition metals. Most efforts have been directed toward accurately predicting geometries and bonding energies,[17,23,24] but not that of spin state energies. However, such a validation is a must if DFT functionals are to be used to delineate the mechanism by which metalloenzymes function with some level of confidence.[25] We therefore set out to establish the performance of different exchange−correlation functionals to calculate properly the spin state energies of several transition metal complexes.

A recent theoretical study[26,27] highlighted three Fe(III) complexes with experimentally established different ground states, i.e., a doublet for **1**,[28] a quartet for **2**,[29] and a sextet for **3**[30] (Figure 1). It showed B3LYP to predict the proper spin state
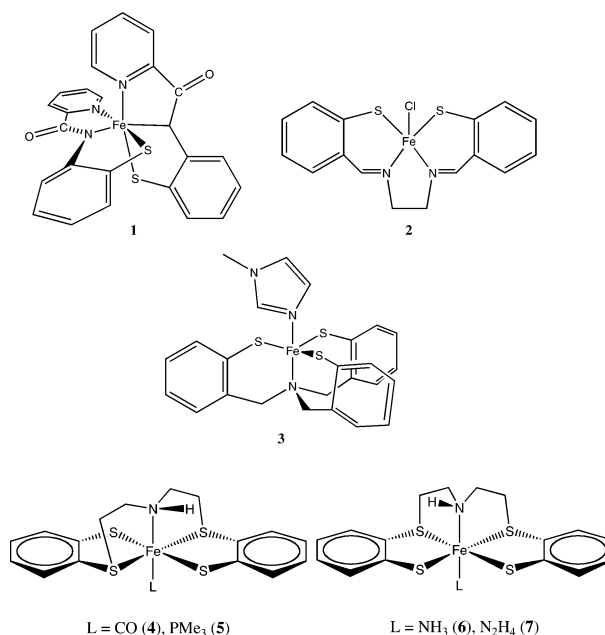

Figure 1. Fe-(PyPepS)₂ (**1**, PyPepSH₂ = *N*-(2-mercaptophenyl)-2-pyridinecarboxamide), Fe(tsalen)Cl (**2**, tsalen = *N,N'*-ethylenebis-(thiosalicylideneiminato)), Fe(N(CH₂-*o*-C₆H₄S)₃)(1-Me-imidazole) (**3**), (Fe(NH)S₄)L, L = CO (**4**), PMe₃ (**5**), NH₃ (**6**), N₂H₄ (**7**) ((NH)S₄ = bis(2-((2-mercaptophenyl)thio)ethyl)amine).

for all three complexes and BLYP for only **1** and **2**. The study used a small basis set. In another study,[31] low and high spin state energies were investigated with BP86 and B3LYP for several Fe(II) molecules that were experimentally[32−34] found to have a singlet (**4**, **5**) or quintet (**6**, **7**) ground state (Figure 1). We felt it to be desirable to evaluate a broad set of DFT functionals for which purpose we used the Amsterdam density functional (ADF) program.[35,36] It will be shown that standard functionals such as LDA,[37] BLYP,[38,39] and PBE[40] disfavor high spin states, whereas hybrid functionals, some meta-GGAs, and

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recently improved pure DFT functionals give correct spin states for all iron complexes. The origin of this behavior will also be addressed. Before starting, we focus on the different types of DFT functionals that are used in this study.

DFT Functionals

The many DFT functionals that have been constructed over the past twenty years can be grouped into the following four classes. (1) For the simplest functionals the energy depends only on the charge density ρ. This is termed the local density approximation (LDA). (2) An improvement results when the energy depends also on the density gradient $\nabla\rho$, i.e., the generalized gradient approximation (GGA). (3) For the meta-GGA functionals the energies depend also on the Laplacian of the density $\nabla^2\rho$ and/or the orbital kinetic energy. (4) Last, there are the so-called hybrid functionals that include a portion of the exact (Hartree–Fock) exchange.

DFT functionals typically have exchange and correlation parts that are constructed independently. The most popular pure GGA exchange functional is Becke88,[38] whereas frequently used GGA correlation functionals are those from Perdew[41] or from Lee, Yang, and Parr (LYP).[39] Their combination for exchange and correlation gives the Becke–Perdew (BP) or BLYP functionals.

DFT functionals can also be divided into empirical and nonempirical ones. Nonempirical functionals such as PBE[40] are derived by theoretical considerations and contain physical constants as parameters. The revised (revPBE)[42] and modified (mPBE)[43] PBE functionals differ slightly in the exchange part and are included in this study because of their improved performance.[42–44] Empirical functionals have been optimized for sets of molecules mimicking the G2-set like HCTH,[45–47] which contains a set of 15 fitting parameters.

The newly developed GGA exchange functional OPTX[48] reportedly gives an improvement over the widely used Becke88. When combined with LYP, it competes with the widely used B3LYP hybrid functional for the electronic description of organic molecules,[49] but its performance appears less satisfactory for transition metal complexes.[23] We will use OPTX in combination with the LYP (OLYP), PBE (OPBE), and Perdew (OPerdew) correlation functionals.

The OPTX functional may also be combined with the new meta-GGA correlation functional LAP3[50] (to give OLAP3); although the LAP3 parameters were obtained in combination with Becke88 exchange, the same parameters are used for OLAP3.[51] Other new meta-GGAs are those developed by Filatov–Thiel (FT97),[52] van Voorhis–Scuseria (VS98),[53] Krieger–Chen–Iafrate–Savin (KCIS),[54] Becke (Becke00),[55] and Perdew's latest (and most accurate) TPSS and TPSSh;[19,56] the TPSSh functional includes 10% exact exchange.

Computational Details

All calculations were performed with the Amsterdam density functional (ADF) program,[35,36] using a triple-ζ valence plus polarization basis set (TZP) of uncontracted Slater type orbitals with frozen cores.[36] Energies for some functionals (including meta-GGAs and hybrids) were obtained post-SCF with PBE orbitals and densities in which case an all-electron basis set was used to obtain the kinetic orbital energy needed for some meta-GGAs. The difference between SCF and post-SCF energies is negligible (see Supporting Information).

The OLYP[39,48] geometry optimizations were performed for **1**–**3** with the coordination parameters around iron constrained to those of the crystal structures.[28–30] For complexes **4**–**7**, the crystal structures were used. With these geometries the energies

of the spin states were obtained using the unrestricted DFT formalism.[16,18]

The spin states of iron complexes are known to be close in energy and sensitive to the occupation of the iron d orbitals; no symmetry restrictions were applied to remove this sensitivity. For each spin state, the iron d orbital occupation was confirmed to be the same for all DFT functionals. Although no symmetry is present and the ligands are not lying exactly along the coordinate axes, the occupation of iron d orbitals is found as predicted by ligand field theory, e.g., with the t_{2g} orbitals (d_{xy}, d_{xz}, d_{yz}) occupied for low spin states.

Results and Discussion

A range of DFT functionals was used to calculate the energies of three spin states for the iron complexes **1**–**3** (doublet, quartet, and sextet) and **4**–**7** (singlet, triplet, and quintet). The relative energies are given in Tables 1 and 2, respectively. Because the spin eigenvalues S^2 (also listed in the tables) show that spin contamination is not an issue for either system, we will not discuss these.

Spin State Energies for Complexes 1–3. All DFT functionals correctly predict for Fe–(PyPepS)$_2$ (**1**) the doublet state (d_5 "t_{2g}^5") to be lowest in energy. The quartet (d_5 "$t_{2g}^4e_g^1$") is predicted to be 22–30 kcal/mol higher in energy. The sextet state (d_5 "$t_{2g}^3e_g^2$") is in all cases predicted to be the highest one. An apparent feature is that the DFT functionals for this high spin state can be divided into two groups, one giving a rather large energy difference with the doublet of about 50 kcal/mol and the other in the range of 31–38 kcal/mol. Standard pure DFT functionals such as LDA, BLYP, and PBE, but also modified PBE functionals, belong to the group that disfavor the high spin state most. To the second group belong the hybrid functionals B3LYP and TPSSh, the GGAs containing the OPTX exchange functional (OLYP, OPerdew, OPBE), and the semiempirical HCTH as well as all of the meta-GGAs (except for FT97 and KCIS that belong to the first group). This distinction, though present, is less clear for the quartet state. Differences attributable to the basis sets effects (double-ζ vs triple-ζ) are relatively small (about 2 kcal/mol) compared to those caused by different functionals.

All DFT functionals also predict the same ground state for Fe(tsalen)Cl (**2**), namely, the ($d5$ "$t_{2g}^4e_g^1$") quartet. The doublet is less favorable and the sextet state is the least favorable one. Remarkably, the entire set of DFT functionals can be split into the same two groups as for **1**, one that gives energy differences with the doublet and sextet states of about 5 and 25–28 kcal/mol, respectively, and the other of around 12 and 18 kcal/mol, respectively.

For Fe(N(CH$_2$-o-C$_6$H$_4$S)$_3$)(1-Me-imidazole) (**3**) the set of DFT functionals do not give the same ground state. One group (LDA, FT97, PBE, revPBE, mPBE, BLYP, and Becke–Perdew) prefers a low spin (doublet) ground state, which does not concur with experimental data,[30] whereas the high spin (sextet) ground state is instead favored by another group of functionals (OLYP, OPerdew, OPBE, HCTH, OLAP3, Becke00, VS98, TPSSh and B3LYP). Interestingly, this division in DFT functionals is similar to that found for both **1** and **2**.

Can a further distinction be made among the functionals that correctly predict a sextet found state for **3**? In part, this is indeed possible by focusing on computational cost. Hybrid functionals are more "expensive" than pure DFT functionals and GGAs are faster than meta-GGAs. As computational programs using GGA generally calculate the potential, the energy can be obtained in a self-consistent manner; this is not necessarily the

Exchange−Correlation Functionals for Fe Spin States

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TABLE 1: Spin State Energies (kcal/mol) for Fe−(PyPepS)₂ (1), Fe(tsalen)Cl (2), and Fe(N(CH₂-o-C₆H₄S)₃)(1-Me-imidazole) (3)^a

		Fe−(PyPepS)₂ (1)						Fe(tsalen)Cl (2)						Fe(N(CH₂-o-C₆H₄S)₃)(1-Me-imidazole) (3)					
		doublet		quartet		sextet		doublet		quartet		sextet		doublet		quartet		sextet	
BLYP^b	grad.	0	(0.77)	30.2	(3.81)	53.8	(8.77)	5.3	(1.20)	0	(3.79)	25.8	(8.76)	−1.8	(0.96)	−1.5	(3.82)	0	(8.76)
B3LYP^b	hybr.	0	(0.78)	23.0	(3.81)	33.1	(8.77)	12.6	(1.48)	0	(3.82)	17.3	(8.76)	16.8	(1.18)	8.7	(3.89)	0	(8.76)
LDA^d	local	0	e	28.3	e	53.2	e	5.3	e	0	e	27.5	e	−7.1	e	−4.1	e	0	e
BLYP^c	grad.	0	(0.76)	28.0	(3.78)	52.5	(8.78)	5.3	e	0	e	27.5	e	−9.3	(0.80)	−4.8	(3.82)	0	(8.76)
BP^c	grad.	0	(0.77)	27.0	(3.78)	49.2	(8.78)	5.1	(1.17)	0	(3.79)	25.8	(8.77)	−4.8	(0.86)	−2.6	(3.83)	0	(8.76)
PBE^c	grad.	0	(0.77)	26.8	(3.78)	48.8	(8.78)	5.2	(1.15)	0	(3.79)	25.5	(8.77)	−4.0	(0.87)	−2.2	(3.83)	0	(8.76)
mPBE^d	grad.	0	e	26.7	e	48.1	e	5.5	e	0	e	25.0	e	−3.2	e	−1.8	e	0	e
revPBE^d	grad.	0	e	26.4	e	47.4	e	5.7	e	0	e	24.7	e	−2.0	e	−1.2	e	0	e
OLYP^c	grad.	0	(0.77)	23.8	(3.80)	37.3	(8.79)	10.3	(1.04)	0	(3.81)	19.0	(8.77)	7.4	(0.82)	4.3	(3.87)	0	(8.76)
OPerdew^c	grad.	0	(0.79)	22.5	(3.81)	34.0	(8.79)	11.8	(1.13)	0	(3.82)	17.5	(8.77)	12.0	(0.92)	6.4	(3.89)	0	(8.76)
OPBE^c	grad.	0	(0.78)	22.5	(3.80)	33.9	(8.79)	11.9	(1.09)	0	(3.81)	17.4	(8.77)	12.4	(0.89)	6.7	(3.89)	0	(8.76)
HCTH^d	grad.	0	e	22.6	e	30.9	e	13.5	e	0	e	15.4	e	14.2	e	8.1	e	0	e
FT97^d	meta	0	e	28.0	e	50.4	e	4.6	e	0	e	26.1	e	−10.1	e	−5.1	e	0	e
KCIS^d	meta	0	e	27.1	e	47.3	e	6.1	e	0	e	24.1	e	−1.8	e	−0.7	e	0	e
OLAP3^d	meta	0	e	26.4	e	36.8	e	12.8	e	0	e	17.3	e	11.6	e	7.5	e	0	e
Becke00^d	meta	0	e	25.6	e	37.0	e	10.8	e	0	e	17.2	e	5.3	e	5.0	e	0	e
VS98^d	meta	0	e	23.5	e	27.6	e	13.8	e	0	e	12.9	e	16.1	e	10.0	e	0	e
TPSS(h)^d	hybr.	0	e	26.9	e	38.9	e	9.3	e	0	e	20.8	e	7.1	e	4.4	e	0	e
B3LYP^d	hybr.	0	e	25.9	e	31.2	e	14.4	e	0	e	18.0	e	13.9	e	7.8	e	0	e
exp		doublet						quartet						sextet					

^{a} Values in parentheses refer to computed s^2 values (for pure spin states the values are 0.75, 3.75, and 8.75 for a doublet, quartet, and sextet respectively). ^{b} Results in 6-31G* basis taken from ref 26. ^{c} SCF energy. ^{d} Post-SCF energy from PBE orbitals/density. ^{e} See PBE results.

TABLE 2: Spin State Energies^a (kcal/mol) for (Fe(N$_H$)S₄)L ((N$_H$)S₄ = Bis(2-((2-mercaptophenyl)thio)ethyl)amine)

		L = CO (4)			L = PMe₃ (5)			L = NH₃ (6)			L = N₂H₄ (7)		
		singlet	triplet	quintet	singlet	triplet	quintet	singlet	triplet	quintet	singlet	triplet	quintet
LDA	local	0	36.0	73.3	0	31.1	63.1	5.1	8.1	0	6.5	8.7	0
BLYP	grad.	0	36.0	71.2	0	31.0	60.9	2.9	6.4	0	4.6	7.1	0
BP	grad.	0	34.6	68.8	0	29.2	58.0	8.2	9.3	0	9.7	9.9	0
PBE	grad.	0	34.6	68.8	0	29.1	57.8	8.8	9.6	0	10.2	10.2	0
mPBE	grad.	0	34.5	68.4	0	29.0	57.3	9.3	9.9	0	10.7	10.5	0
revPBE	grad.	0	34.5	67.8	0	28.8	56.5	10.1	10.4	0	11.5	11.0	0
OLYP	grad.	0	33.3	61.6	0	27.4	49.7	18.3	15.7	0	19.5	16.1	0
OPerdew	grad.	0	31.9	59.2	0	25.6	46.8	23.6	18.6	0	24.6	18.9	0
OPBE	grad.	0	32.0	59.5	0	25.6	46.9	23.6	18.6	0	24.7	18.9	0
HCTH	grad.	0	31.9	56.3	0	25.8	44.2	24.6	19.3	0	25.7	19.7	0
FT97	meta	0	36.1	72.4	0	31.4	63.2	−0.01	5.6	0	1.6	6.3	0
KCIS	meta	0	35.2	67.1	0	29.5	56.9	9.2	10.5	0	10.6	11.0	0
OLAP3	meta	0	37.0	63.6	0	30.4	50.7	17.8	17.5	0	19.2	17.9	0
Becke00	meta	0	36.5	63.6	0	30.5	52.5	12.4	14.5	0	14.3	15.2	0
VS98	meta	0	31.9	52.2	0	25.4	39.4	24.8	20.7	0	26.1	21.2	0
TPSS(h)	hybr.	0	34.4	61.1	0	27.8	47.5	17.3	15.6	0	19.5	16.3	0
B3LYP	hybr.	0	34.1	55.8	0	27.1	41.1	22.4	18.6	0	25.0	19.4	0
s^2 ^{b}		0.00	2.03	6.05	0.00	2.03	6.03	0.00	2.06	6.03	0.00	2.07	6.03
exp		singlet			singlet			quintet			quintet		

^{a} Post-SCF energy from PBE orbitals/density. ^{b} Computed s^2 values (for pure spin states the values are 0.0, 2.0, and 6.0 for a singlet, triplet, and quintet, respectively).

case for meta-GGA functionals. Of the four better performing GGAs that we considered, OLYP gives a smaller sextet−doublet energy difference (7.4 kcal/mol) than the 12.0−14.2 kcal/mol that is obtained with OPBE, OPerdew, and HCTH. As the HCTH functionals are only available to us post-SCF, we are left with OPerdew and OPBE. Taking into account the reported mean absolute deviation from the G2 set of 17.0 kcal/mol for OPerdew and 7.4 kcal/mol OPBE,[57] we favor the OPBE functional.

Spin State Energies for Complexes 4−7. For the Fe(II) complexes **4−7**, the spin state energies were calculated post-SCF with the entire set of DFT functionals using PBE orbitals/densities, as self-consistency effects on the energies are small as determined for **1−3** and reported in the literature.[58,59]

For (Fe(N$_H$)S₄)CO (**4**), the singlet ground state is favored over the triplet and quintet states by 32−37 and 52−73 kcal/mol, respectively. Likewise, the singlet state of the Fe(II) complex (Fe(N$_H$)S₄)PMe₃ (**5**) is preferred over the triplet and quintet with

similar energy differences of 25−31 and 40−63 kcal/mol, respectively. As for the Fe(III) complexes **1−3**, the better performing group of DFT functionals gives the smaller low−high spin energy differences.

All DFT functionals correctly predict a high spin ground state for the Fe(II) complexes (Fe(N$_H$)S₄)NH₃ (**6**) and (Fe(N$_H$)S₄)-N₂H₄ (**7**). The energy difference with the triplet and singlet states amounts to 6−21 and 3−25 kcal/mol, respectively, for **6**, and to 6−21 and 5−26 kcal/mol, respectively, for **7**. Again, the better performing DFT functionals give the smaller energy differences.

Origin of the Different Behavior of the DFT Functionals. Except for LDA, pure GGA, meta-GGA, and hybrid functionals are able to predict the correct ground state for **3** and hence no simple distinction in the performance of the DFT functionals is apparent. LDA is an exception as it is derived from a uniform electron gas and is expected to have more difficulties in properly describing different spin states.

Why then do some functionals perform better than others? Could it be the choice of the exchange functional? After all, BLYP and Becke−Perdew with different correlation functionals differ on average by only 3.6 kcal/mol for the sextet−doublet energy separation of **1**−**3**, whereas this amounts to 21.5 kcal/mol on comparing BLYP and B3LYP, which have different exchange components. Similarly improved results are obtained by replacing Becke88's exchange with Handy's optimized exchange (BLYP vs OLYP). Hence, the ordering of the spin state energies may depend foremost on the choice of the exchange functional even though that of the correlation functional cannot be ignored as illustrated by OLYP, OLAP3, and OPBE (see Table 1). Baerends and co-workers[51,60] showed recently that when the exchange part is the determining factor, improved transition state energies are obtained with exchange functionals that have as leading contribution the fourth power (s^4) of the dimensionless (or reduced) density gradient s ($s = |\nabla\rho|/\rho^{4/3}$). They showed that LDA, which is independent of s, underestimates bonding, whereas generally too strong bonding is found for GGAs, which contain s^2 terms, but that new functionals such as OPTX that contain the s^4 term seem to correct this effect in the bonding region of the molecule, where $s < 1.0−1.5$.[51]

The same pattern is observed in the present study. Only hybrid functionals and those functionals with a leading s^4 term in the exchange part perform well for **3**. Of the less performing functionals none have a dominant s^4 term in the exchange part. As exact exchange can be viewed as a four-particle term, inclusion of the s^4 term appears relevant for a reliable prediction of the spin state energies of iron complexes. The suggested relationship between the parametrization of the exchange functional and the ordering of spin state energies might have implications for other transition metal complexes as well.

Conclusions

We have examined the performance of a diversity of DFT functionals for predicting the relative spin state (low, intermediate, or high) energies of seven iron complexes for which experimentally determined ground states are known.

All DFT functionals correctly predict a ground state doublet for Fe−(PyPepS)$_2$ (**1**), quartet for Fe(tsalen)Cl (**2**), singlet for (Fe(N$_H$)S$_4$)CO (**4**) and (Fe(N$_H$)S$_4$)PMe$_3$ (**5**), and quintet for (Fe(N$_H$)S$_4$)NH$_3$ (**6**) and (Fe(N$_H$)S$_4$)N$_2$H$_4$ (**7**), but for each system the magnitude of the energy difference with the other spin states depends strongly on the choice of the functional. The investigated set can be divided into two groups, one that particularly disfavors high spin states, i.e., standard functionals such as LDA, BLYP, and PBE (group 1), and the other where this is much less the case as for hybrid and improved GGAs and most of the meta-GGAs (group 2). The energy difference between these two groups can amount to as much as 20 kcal/mol. Their performance differs strongly for Fe(N(CH$_2$-o-C$_6$H$_4$S)$_3$)(1-Meimidazole) (**3**), which has an experimentally determined sextet ground state. Only functionals of group 2 predict the correct ground state with an energy difference of 7−17 kcal/mol with the doublet and quartet, whereas those of group 1 erroneously favor a doublet ground state. These differences emphasize that great care has to be exercised in choosing the DFT functional to calculate properly the spin state of biochemically relevant Fe(II) and Fe(III) complexes. On the basis of cost efficiency, the OPBE functional performs best.

The origin for the different performance of the DFT functionals is related to the inclusion of fourth-order terms (s^4) of the dimensionless (or reduced) density gradient s in the exchange functional. Only hybrid functionals and those with a leading s^4 term in the exchange part are present in group 2. Conversely, none of group 1 have a dominant s^4 exchange term. The seemingly direct connection between the parametrization of the exchange functional and the ordering of the spin state energies of the seven iron complexes suggests similar behavior for other transition metal containing systems.

Supporting Information Available: Tables with spin state energies using a frozen-core and all-electron TZP basis set, and using SCF and post-SCF formalisms. This material is available free of charge via the Internet at http://pubs.acs.org.

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