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Iron(IV) Porphyrin Difluoride Does Not Exist: Implications for DFT Calculations on Heme Protein Reaction Pathways

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Abstract: DFT (B3LYP as well as a number of common exchange-correlation functionals) predicts a low-spin Fe(IV) ground state for $Fe(P)F_2$ (P = porphyrinato), whereas electrochemical evidence has apparently indicated an Fe(III) porphyrin π-cation radical formulation for such a species. Ab initio CASPT2 calculations favor a high-spin porphyrin π-cation radical as the ground state by a significant energetic margin, thus dramatically overturning the DFT results. In contrast, both DFT and CASPT2 calculations correctly indicate a true Mn(IV) ground state for $Mn(P)F_2$. The remarkable failure of DFT to correctly predict the metal- versus ligand-oxidized nature of $Fe(P)F_2$ may have significant ramifications for the theoretical modeling of heme protein reaction pathways where until now the performance of DFT has raised little concern.

Introduction

It is not often that the nonexistence of something makes an interesting story, but in this case we believe that it does. In a narrow sense, our main conclusion here is that difluoroiron porphyrins do not exist as ground-state Fe(IV) species.[1] However, the wider implications of our results *potentially* impact many theoretically derived insights into the reaction pathways of iron enzymes such as cytochrome P_{450}.[2] One such insight is that a particular heme protein-mediated oxidation may involve multiple electronic states of a high-valent iron (compound I) intermediate[3] or even multiple reactive oxygen species,[4] such as a compound I *and* an Fe-(III) hydroperoxide. Clearly, it would be of interest to evaluate the energetics of the different conceivable reaction pathways by means of high-quality quantum chemical methods, and, indeed, DFT calculations have already resulted in significant progress in this area.[2b,3] Unfortunately, there has been little calibration of the quality of the DFT energetics results against more reliable methods such as CASPT2 and CCSD(T),[5] which should not be particularly surprising, given

that any even moderately realistic models of heme protein intermediates are plainly beyond the reach of current implementations of high-level ab initio correlated methods. A key problem with DFT is that most, if not all, currently available functionals provide an unreliable description of the energetics of the low-lying spin states of open-shell transition-metal complexes. In particular, for high-valent transition-metal complexes,[6] DFT does not always correctly describe the relative energetics of metal- versus ligand-centered oxidation.[7] For example, for one-electron-oxidized five-coordinate iron(III) porphyrin derivatives, DFT unduly favors low-spin Fe(IV) oxidized states relative to high-spin Fe(III) porphyrin π-cation radical states.[7a]

To calibrate the performance of DFT vis-à-vis these problems, we have investigated the energetics of the low-lying states of the highly symmetric (D_{4h}) species, $Fe(P)F_2$ (P = porphyrinato), the point being to determine whether it is an Fe(IV) species or an Fe(III) porphyrin "π-cation" radical. While DFT calculations— regardless of the functional (for a number of common functionals tested)—prefer an S = 1 Fe(IV) ground state, electrochemical evidence[1a] suggests the latter description. The authors of a DFT study suggested that solvent effects such as hydrogen bonding interactions involving the axial fluorides might destabilize the Fe(IV) states in the electrochemical studies, favoring instead an Fe-

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Table 1. B3LYP, CASPT2(AS1), and CASPT2(AS2) Energies (eV) for Selected Low-Lying States of $Fe(P)F_2$, $Mn(P)F_2$, and $[Zn(P)]^{+a}$

molecule; electronic configuration	S	metal d d_{xy} (b_{2g})	d_{xz},d_{yz} (e_g)	d_{z2} (a_{1g})	d_{x2-y2} (b_{1g})	porphyrin a_{1u}	a_{2u}	B3LYP	CASPT2 (AS1)	CASPT2 (AS2)
				$Fe(P)F_2$						
S = 1 Fe(IV); $d_{xy}^2(d_{xz}d_{yz})^2$	1	2	2	0	0	2	2	**0.00**	**0.00**	**0.00**
S = 2 Fe(IV); $d_{xy}^1(d_{xz}d_{yz})^2d_{x2-y2}^1$	2	1	2	0	1	2	2	0.95	0.57	0.47
S = 2 Fe(IV); $d_{xy}^1(d_{xz}d_{yz})^2d_{z2}^1$	2	1	2	1	0	2	2	1.07	1.01	
S = 5/2 Fe(III); a_{1u} radical; ferro	3	1	2	1	1	1	2	0.59	0.47	0.16
S = 5/2 Fe(III); a_{1u} radical; antiferro	2	1	2	1	1	1	2	0.59	0.47	
S = 5/2 Fe(III); a_{2u} radical; ferro	3	1	2	1	1	2	1	0.30	−0.31	−0.42
S = 5/2 Fe(III); a_{2u} radical; antiferro	2	1	2	1	1	2	1	0.35	−0.27	
				$Mn(P)F_2$						
S = 3/2 Mn(IV); $d_{xy}^1(d_{xz}d_{yz})^2$	3/2	1	2	0	0	2	2	**0.00**	**0.00**	**0.00**
S = 2 Mn(III); a_{1u} radical; ferro	5/2	1	2	0	1	1	2	1.02	1.31	1.19
S = 2 Mn(III); a_{1u} radical; antiferro	3/2	1	2	0	1	1	2	1.03	1.32	
S = 2 Mn(III); a_{2u} radical; ferro	5/2	1	2	0	1	2	1	0.75	0.59	0.60
S = 2 Mn(III); a_{2u} radical; antiferro	3/2	1	2	0	1	2	1	0.75	0.61	
S = 2 Mn(III); a_{1u} radical; ferro	5/2	1	2	1	0	1	2	1.55	2.05	
S = 2 Mn(III); a_{1u} radical; antiferro	3/2	1	2	1	0	1	2	1.58	2.06	
S = 2 Mn(III); a_{2u} radical; ferro	5/2	1	2	1	0	2	1	1.35	1.22	
S = 2 Mn(III); a_{2u} radical; antiferro	3/2	1	2	1	0	2	1	1.34	1.23	
				$[Zn(P)]^{0,+}$						
Zn(P)	0	2	4	2	2	2	2	**0.00**	**0.00**	**0.00**
$[Zn(P)]^+$; a_{2u} radical	1/2	2	4	2	2	2	1	6.75	6.27	6.29
$[Zn(P)]^+$; a_{1u} radical	1/2	2	4	2	2	1	2	6.77	6.78	6.59

[a] D_{4h} irreps are used throughout. Energy zero levels are indicated in bold. Abbreviations: ferro = ferromagnetic coupling; antiferro = antiferromagnetic coupling.

(III) π-cation radical.[1a] In light of our recent critical evaluations of DFT,[5,7] we entertained an alternative explanation for this apparent discrepancy between theory and experiment: we surmised that perhaps a nonradical Fe(IV) species is not observed simply because it does not exist! We present here ab initio multiconfiguration reference second-order perturbation theory (CASPT2) calculations with large basis sets and different active spaces (denoted below as AS1 and AS2) that lend support to our suspicion. As control studies, similar calculations were also carried out for the low-lying electronic states of $Mn(P)F_2$, where a true Mn(IV) ground state seems well-established[8,9] as well as for the two lowest π-cation radicals of zinc porphine, Zn(P).[10]

Methods

DFT geometry optimizations for different electronic configurations of $Fe(P)F_2$, $Mn(P)F_2$, and $[Zn(P)]^{+,0}$ were carried out with the B3LYP functional, D_{4h} symmetry constraints, and default grids and convergence criteria implemented in the TURBOMOLE program system.[11] The basis sets used in these calculations were of TZP quality, with an extra diffuse sp set on Cl and an extra d and an f function on the transition metal.

CASSCF and CASPT2 calculations were carried out on the B3LYP optimized structures with the MOLCAS 5.1 program system.[12] (Attempts were also made to perform coupled-cluster calculations, but these proved too computationally demanding.) The basis sets used in the CASPT2 calculations comprised correlation-consistent polarized valence double-ζ (cc-pVDZ) basis sets on H, C, and N,[13] the augmented aug-cc-pVDZ set on Cl,[14] and a new [6s 5p 4d 3f 2g] atomic natural orbital (ANO) basis on Mn.[15] The latter basis set is designed to properly account for 3s3p correlation. The zeroth-order Hamiltonian for the CASPT2 calculations was the g3 choice suggested by Andersson[16] and an imaginary level shift of 0.3 au (based on exhaustive investigation of smaller transition-metal-containing molecules) as proposed by Forsberg and Malmqvist[17] was used to ensure convergence of the CASPT2 iterative equations. In the CASPT2 calculations, all valence electrons were correlated, including the iron 3s and 3p electrons.

For Zn(P), the smaller active space AS1 comprised the four porphyrin frontier MOs, viz. the highest occupied a_{1u} and a_{2u} MOs and the lowest unoccupied e_g MOs. However, although this active space is adequate for describing the absorption spectrum, it is less satisfactory for ionization potentials, for which it was necessary to extend the active space (now called AS2) by adding four more MOs, namely the highest occupied e_g MOs and the lowest empty a_{1u} and a_{2u} MOs.

For $Fe(P)F_2$ and $Mn(P)F_2$, the smaller AS1 active space comprised the four porphyrin frontier MOs mentioned above, the five metal 3d orbitals, the highest metal-F bonding MO (a_{1g}) and its antibonding counterpart (a_{1g}). The larger active space AS2 included the extra four porphyrin MOs mentioned above for Zn(P). These active spaces were chosen by detailed consideration of CASPT2 natural orbital occupation numbers.

Table 2. Selected CASSCF Atomic Spin Populations for Fe(P)F$_2$, Mn(P)F$_2$, and [Zn(P)]$^+$

molecule; electronic configuration	S	M	F	C$_\alpha$	C$_\beta$	C$_{meso}$	N
			Fe(P)F$_2$				
S = 1 Fe(IV); d$_{xy}^2$(d$_{xz}$d$_{yz}$)^2	1	2.1676	−0.0087	0.0000	−0.0003	−0.0012	−0.0356
S = 2 Fe(IV); d$_{xy}^1$(d$_{xz}$d$_{yz}$)^{2}d$_{x2-y2}^1$	2	4.1051	−0.0882	0.0070	0.0024	0.0068	−0.0078
S = 2 Fe(IV); d$_{xy}^1$(d$_{xz}$d$_{yz}$)^{2}d$_{z2}^1$	2	4.2287	−0.1051	0.0006	−0.0001	0.0000	−0.0054
S = 5/2 Fe(III); a$_{1u}$ radical; ferro	3	4.9584	0.0157	0.1187	0.0272	−0.0302	−0.0090
S = 5/2 Fe(III); a$_{1u}$ radical; antiferro	2	4.6312	0.0141	−0.0621	−0.0173	−0.0037	−0.0021
S = 5/2 Fe(III); a$_{2u}$ radical; ferro	3	4.9561	0.0182	−0.0112	0.0008	0.2005	0.0694
S = 5/2 Fe(III); a$_{2u}$ radical; antiferro	2	4.6291	0.0127	−0.0046	−0.0027	−0.1024	−0.0460
			Mn(P)F$_2$				
S = 3/2 Mn(IV); d$_{xy}^1$(d$_{xz}$d$_{yz}$)^2	3/2	3.2168	−0.0207	0.0006	−0.0004	−0.0020	−0.0422
S = 2 Mn(III); a$_{1u}$ radical; ferro	5/2	4.0204	−0.0160	0.1188	0.0269	−0.0307	−0.0079
S = 2 Mn(III); a$_{1u}$ radical; antiferro	3/2	3.6138	−0.0142	−0.0559	−0.0154	−0.0028	−0.0007
S = 2 Mn(III); a$_{2u}$ radical; ferro	5/2	4.0185	−0.0136	−0.0114	0.0005	0.2006	0.0721
S = 2 Mn(III); a$_{2u}$ radical; antiferro	3/2	3.6160	−0.0174	−0.0039	−0.0021	−0.0913	−0.0410
S = 1 Mn(III); a$_{1u}$ radical; ferro	5/2	3.6056	−0.0186	−0.0039	−0.0022	−0.0888	−0.0407
S = 1 Mn(III); a$_{1u}$ radical; antiferro	3/2	1.3373	0.0043	−0.0312	−0.0090	−0.0010	−0.0050
S = 1 Mn(III); a$_{2u}$ radical; ferro	5/2	3.6051	−0.0145	−0.0544	−0.0167	−0.0024	0.0007
S = 1 Mn(III); a$_{2u}$ radical; antiferro	3/2	1.3380	0.0027	−0.0027	−0.0015	−0.0495	−0.0276
			[Zn(P)]$^{0,+}$				
Zn(P)	0	0		0	0	0	0
[Zn(P)]$^+$; a$_{1u}$ radical	1/2	0.0000		0.0949	0.0262	0.0056	0.0018
[Zn(P)]$^+$; a$_{2u}$ radical	1/2	0.0195		0.0102	0.0092	0.1508	0.0544

[a] D_{4h} irreps are used throughout. Abbreviations: ferro = ferromagnetic coupling; antiferro = antiferromagnetic coupling; M = metal.

Because the two S = 2 Fe(IV) states studied (shown in Table 1) are of different symmetries — $^5B_{1g}$ and $^5A_{1g}$ — they were optimized separately with B3LYP calculations, exploiting full D_{4h} point group symmetry. However, the CASSCF/CASPT2 calculations could only be performed with D_{2h} symmetry where both Fe(IV) quintet states fall in the same irreducible representation. We therefore performed a two-root CASSCF/CASPT2 calculation for the two quintet states; such a calculation produces a slightly different energy for the lower state relative to what is obtained in a single-root calculation. For the best estimate for the energy of the higher S = 2 Fe(IV) state, we combined the calculated (two-root) energy difference between the two states with the single-root energy for the lower state.

Results and Discussion

Table 1 presents B3LYP and CASPT2 energies for the B3LYP optimized geometries of a number of Fe(P)F2, Mn-(P)F2, and [Zn(P)]$^{0,+}$.

With the B3LYP functional (as well as with most other common functionals), generally believed to be one of the best for transition-metal calculations, the low-spin Fe(IV) ground state is clearly indicated for Fe(P)F$_2$. In contrast, at the CASPT2 level with the smaller AS1 active space, the ground state is a high-spin Fe(III) porphyrin A$_{2u}$ radical; as expected on the basis of orthogonality of the metal d and porphyrin a$_{1u}$ and a$_{2u}$ MOs, ferromagnetic versus antiferromagnetic coupling between the metal and the radical does not seem to significantly affect the energy of the species. At the CASPT2(AS1) level, the low-spin Fe(IV) state is about 0.3 eV above the ground state, while the lower of two high-spin Fe(IV) states studied (see Table 1) is about 0.8 eV above the ground state. In addition, a high-spin Fe(III)

porphyrin A$_{1u}$ radical is also about 0.8 eV above the ground state at the CASPT2(AS1) level.

CASPT2 calculations with the larger active space AS2 essentially confirm the above picture: the ground state is a high-spin Fe(III) porphyrin A$_{2u}$ radical, while the low-spin Fe(IV) state and a high-spin Fe(III) A$_{1u}$ radical state are about 0.5 and 0.6 eV, respectively, higher in energy. In other words, the CASPT2 calculations are consistent with the experimental observation of an electrooxidized porphyrin radical state.

To what extent should we believe the CASPT2 results? To explore this issue, we turn to our controls, Mn(P)F$_2$ and [Zn(P)]$^{0,+}$. Consistent with experimental evidence[8] and earlier DFT(PW91/TZP) calculations,[9] CASPT2(AS1) calculations clearly indicate an S = 3/2 Mn(IV) ground state, while high-spin Mn(III) porphyrin π-cation radical states are several tenths of an eV above the ground state (see Table 2).

For a particular metal electronic configuration, the CASPT2-(AS1) energy difference between the A$_{1u}$ and A$_{2u}$ radicals may seem excessive, in view of the four-orbital model, which stipulates near-degenerate porphyrin HOMOs. However, the larger active space AS2 results in comparatively smaller differences in the A$_{1u}$ and A$_{2u}$ radical energies, e.g., as shown in Table 1, the A$_{1u}$ π-cation radical of Zn(P) is only 0.3 eV higher in energy than the A$_{2u}$ radical, which is reasonably in line with the four-orbital model.

Table 2 presents the CASSCF Mulliken spin populations for the various open-shell species studied. In general, these do not warrant much comment. The various A$_{1u}$ and A$_{2u}$ radicals exhibit their typical and well-known spin density profiles.[9,10] For the S = 1 Fe(IV) and S = 3/2 Mn(IV) states, note the significant minority spin populations on the por-

phyrin nitrogens, something that has also been observed in DFT calculations on a number of other metalloporphyrins.[9,18]

The reasonableness of the CASPT2 results for $Mn(P)F_2$ and $Zn(P)$ lends credence to our conclusions regarding Fe-$(P)F_2$, where CASPT2 results in a major upheaval of the DFT energetics of the low-lying spin states. Hence, we feel comfortable concluding that $Fe(P)F_2$ probably does not exist as a ground-state Fe(IV) species. The broader implications of our results may be illustrated with reference to the following mechanistic and electronic-structural problems: (a) describing the relative energetics of alkene epoxidation by a compound I (typically an $Fe^{IV}O$ porphyrin π-cation radical) versus an $Fe^{III}OOH$ intermediate; (b) describing the relative energetics of homolysis versus heterolysis of an $Fe^{III}OOH$ intermediate (Both pathways have been proposed for heme oxygenase.);[19] and (c) describing the issue of metal- versus ligand-oxidized nature of Fe(corrolato)Cl complexes.[20] To reliably address these problems, we need to accurately calculate the relative energetics of different Fe spin and oxidation states. As shown above, this is clearly a problem for DFT. There can be little doubt that the importance of these and other problems will spur continued development of high-quality exchange-correlation functionals as well as efforts to expand the range of application of high-level correlated ab initio methods to larger, more biologically relevant systems.

Supporting Information Available: Optimized B3LYP Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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