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The Ferric−Oxo Moiety in Porphyrin Complexes − a Ferryl in Disguise?

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*Mononuclear ferric-oxo moieties are known in non-heme environments, and have been proposed as reaction intermediates in some hemoproteins. Recently, such hemoprotein adducts have been detected spectroscopically via low-temperature cryoradiolytic reduction of their Fe^{IV}-oxo counterparts. Here computational results (UBP86/6-31G**) are shown indicating that the electronic structures of such adducts are well described as S=1 Fe^{IV}-oxo coupled to a porphyrin radical, as opposed to the clean ferric state predicted at the same level of theory (and demonstrated experimentally) for the non-heme systems.*

Introduction

Mononuclear ferryl species, formally Fe^{IV}-oxo, are known to play central roles in catalysis within several classes of hemoproteins, and have consequently received much attention.[1-5] Mononuclear ferric-oxo moieties are particularly reactive, and their recent characterization in a non-heme environment has required some remarkable synthetic efforts[6] in order to protect/stabilize the oxo ligand with sterics and especially with hydrogen bonding. In such adducts, the ferric moiety is *S*=5/2 and features an Fe-O bond distinctly longer (~0.15 Å) than typical Fe^{IV}-oxo counterparts.[6-9] Heme ferric-oxo adducts have been discussed as possible reaction intermediates in proteins,[10] and have very recently been detected spectroscopically via low-temperature cryoradiolytic reduction of their Fe^{IV}-oxo counterparts, with some interesting connotations to an on-going debate about the protonation state of the latter.[11] Here, a computational description is provided for models of the ferric-oxo moieties in histidine- and cysteine-ligated hemoproteins, unexpectedly finding that ferryl descriptions, rather than ferric, are better suited for such species.

Experimental

Geometries for models shown in Figure 1 (formally ferric oxo, with an imidazole or methylthiolate ligand, respectively, and an unsubstituted porphyrin) were optimized for *S*=1/2, *S*=3/2 and *S*=5/2 spin states, respectively, with the BP86 functional, which uses the gradient-corrected exchange functional proposed by Becke (1988),[12] the correlation functional by Perdew (1986),[13] and the DN** numerical basis set (comparable in size to 6-31G**), as implemented in Spartan.[14] For the SCF calculations, a fine grid was used, and the convergence criteria were set to 10^{-6} (for the root-mean square of electron density) and 10^{-8} (energy), respectively. For geometry optimization, convergence criteria were set to 0.001 au (maximum gradient criterion) and 0.0003 (maximum displacement criterion). Charges and spin densities were derived from Mulliken population analyses after DFT geometry optimization. Energies for selected models were also computed with an SCRF procedure within the Gaussian 98[15] software package, using the UBP86/6-31G** functional and the CPCM[15] model with the default solvent number 13 (dielectric constant 4.335, mimicking the interior of a protein). A convergence criterion of 10^{-8} hartree was set for these calculations.

Results and Discussions

Table 1 lists relative energies for the ferric-oxo models of Figure 1.

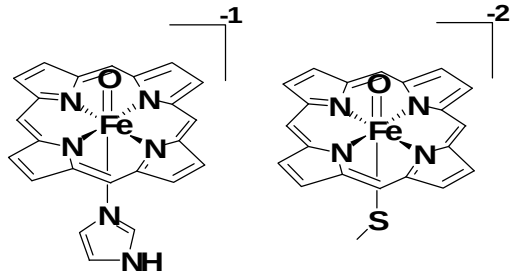

Figure 1. Ferric oxo models examined in the present study.

Table 1. Relative energies (kcal/mol).

Spin state\model	thiolate	imidazole
S=1/2	0	0
S=3/2	1.1	2.6
S=5/2	15.4	22.5

For both the thiolate- and imidazole-ligated models, the *S*=1/2 and *S*=3/2 states are essentially degenerate, with the *S*=5/2 somewhat higher in energy; considering the known propensity of non-hybrid functionals to favour lower-spin states,[16] it cannot be ruled out based on our results that in reality the *S*=3/2 and *S*=5/2 are also accessible. On the other hand, Davydov *et al*. do find that the *S*=1/2 form of the ferric oxo adduct is observable experimentally at low temperature.[11]

Table 2. Iron-axial ligand distances and average iron-porhyrin (Å) in imidazole ("N") and methylthiolate (S) –ligated ferric oxo models.

model	Fe-O	Fe-N/S	Fe-N(porphyrin)
S=1/2,N	1.68	2.19	2.030
S=3/2,N	1.67	2.18	2.041
S=5/2,N	1.68	2.30	2.115
S=1/2,S	1.71	2.48	2.045
S=3/2,S	1.70	2.46	2.045
S=5/2,S	1.70	2.48	2.115

The data in Table 2 show that the iron-oxygen distance remains constant regardless of spin state, which suggests that the electronic structure of the [FeO] moiety remains essentially constant in all models; this value is less than 0.05 Å different from that seen in the related ferryl (formally Fe^{IV} states) examined with similar methodology,[2,4] and, even in the *S*=5/2 model, remain more than 0.1 Å shorter compared to non-heme *S*=5/2 ferric-oxo adducts.[6,8] Likewise, the iron-thiolate and iron-imidazole distances do not show the variations seen in other iron complexes when examining different spin states,[5,17] suggesting again that certain elements of the electronic structure at the iron remain similar in all spin states of the ferric-oxo heme models.

Figure 2 shows spin densities computed for *S*=1/2 and *S*=5/2 imidazole-ligated models; while delocalization of spin density onto the porphyrin would not be unexpected for *S*=3/2 or *S*=5/2 ferric compexes, the significant negative spin density on the porphyrin in the *S*=1/2 models cannot be reconciled with a ferric-oxo description, and can only be explained in terms of an Fe^{II}-oxo moiety coupled to a porphyrin cation radical, or an Fe^{IV}-oxo moiety coupled to a porphyrin anion radical. Neither Fe^{II}-oxo, nor Fe^{IV} + porphyrin anion radical states have to our knowledge been previously described in any heme complexes.

Table 3 shows d-orbital populations for all spin states of the ferric-oxo models examined here. In the *S*=1/2 imidazole model, the iron $d_{x^2-y^2}$ and d_{z^2} orbitals must both

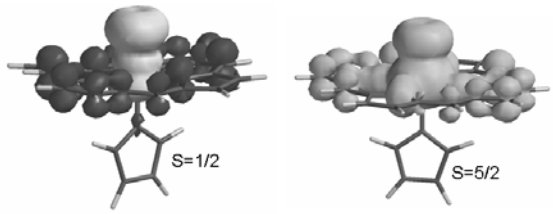

Figure 2. Spin densities on imidazole-ligated *S*=1/2 and *S*=5/2 ferric-oxo models; white-positive, black-negative).

be formally empty (indeed, as expected, LUMOs are found with distinct $d_{x^2-y^2}$ and d_{z^2} contributions for all *S*=1/2 models – data not shown); the total of 0.96 and 1.29 electrons, respectively, that are found in these two orbitals come from covalent mixing (and may also partly be a manifestation of often invoked[18] shortcomings of unsophisticated population analyses such as Mulliken). On the other hand, in the same model, d_{xy}, which features 1.37 electrons, is formally doubly-occupied. These observations, together with the 1.5 electrons found in the d_{xz} and d_{yz} orbitals, respectively, and together with a total spin density on the Fe-O moiety of 1.84 (1.03 on Fe, 0.81 on O), lead us to a description of the Fe-O bonding as a classical *S*=1 ferryl moiety, in no way different from other ferryls previously characterized. Such $[FeO]^{2+}$ groups are indeed typically characterized by 4 electrons clearly placed in iron d orbitals (d_{xy}^2, d_{xz}^1, d_{yz}^1), with an additional two electrons shared equally between iron and oxygen within the two Fe-O π^* orbitals.[2,5,19] This ferryl in our formally ferric-oxo models must then be antiferromagnetically coupled to a porphyrin anion radical. The *S*=3/2 imidazole model has an electronic structure almost identical to that of the *S*=1/2 counterpart, except that the *S*=1 ferryl and *S*=1/2 porphyrin are now ferromagnetically coupled. Similarly, the *S*=5/2 counterpart is described as *S*=2 ferryl + *S*=1/2 porphyrin radical. Table 3 also shows that the thiolate-ligated ferric-oxo models feature exactly the same electronic descriptions as their imidazole-ligated counterparts – ***i.e.*** ferryls coupled to porphyrin radicals.

To test whether the conclusions drawn from Table 3 and related data are dependent on the computational model chosen, the electronic structure of the *S*=1/2 imidazole model was also examined using a different approach, which included solvation as well as a non-hybrid functional (cf. Experimental). In this case as well, the sum of spin densities on the Fe-O moiety was essentially 2, even though a slight polarization was noticed compared to the gas-phase (Fe-1.34, O-0.64, compared to values listed above for gas-phase).

Ferric-oxo complexes in non-heme environments have been extensively characterized experimentally and computationally (including, with the same computational methodology as applied in the present work), and all available data indeed supports a ferric-oxo description.[6-9]

By contrast, the porphyrin counterparts examined in the present work all seem to prefer a ferryl description, with a porphyrin anion radical. Non-heme ferric-oxo complexes have been shown experimentally to be relatively weak oxygen atom transfer agents, with no observed propensity towards reductive activity – as opposed to ferryl species and especially to ferryl species bearing a porphyrin cation

Table 3. Iron *d* orbital populations (spin-up and spin-down values listed as α/β) on imidazole ("N") and methylthiolate (S) –ligated ferric oxo models.

	S=1/2,N	*S*=3/2,N	*S*=5/2,N	*S*=1/2,S	*S*=3/2,S	*S*=5/2,S
d_{z^2}	0.46/0.41	0.47/0.40	0.65/0.38	0.52/0.43	0.52/0.43	0.61/0.42
d_{xz}	0.96/0.50	0.98/0.46	0.99/0.32	0.95/0.49	0.96/0.47	0.99/0.43
d_{yz}	0.95/0.51	0.98/0.46	0.99/0.42	0.96/0.48	0.99/0.47	0.99/0.43
$d_{x^2-y^2}$	0.66/0.63	0.65/0.61	0.99/0.14	0.87/0.86	0.98/0.97	0.99/0.05
d_{xy}	0.70/0.67	0.73/0.70	0.99/0.18	0.48/0.43	0.38/0.32	0.99/0.29

radical on the porphyrin (the so-called Compound I), which are at the same time strong oxidizing agents and good oxygen transfer agents.[7]

We propose that the strong ligand field of the porphyrin, together with the four short iron-nitrogen(porphyrin) bonds energetically disfavour the high-spin ferric-oxo state in favour of the ferryl state, to the extent where the latter becomes preferred. To partially support our assertion, a simpler version of the imidazole-ligated S=1/2 model, where al nitrogenous ligands are replaced by ammonia and the geometry of the system is subsequently fully optimized, shows a clean ferric-oxo description, as opposed to the ferryl one seen in the porphyrin model. Thus, in this non-heme model the Fe-O elongates to 1.77 Å, and the spin densities are 0.67 on the iron and 0.39 on the oxygen, i.e. essentially equivalent to the sole unpaired electron expected of a S=1/2 Fe^{III} center.

The gas-phase proton affinities of the ferric-oxo moieties are computed to be very high. For the imidazole model this value is 362 kcal/mol, *i.e.* very similar to the 340-410 kcal/mol computed for models of similar charge, size, and chemical composition, such as thiolate-ligated ferryl or imidazole-ligated ferric-peroxo, with the same computational approach.[3] For both of these latter better-characterized species, the non-protonated form appears to be undetectable at room temperature. For heme ferric-peroxo species (overall charge identical to ferric-oxo, and with very similar stoichiometry), the non-protonated form is only detectable at low temperature, and in some hemoproteins it appears to undergo protonation even at liquid nitrogen temperature.[3,11,20,21] The very similar proton affinities found here for ferric-oxo compared to ferric-peroxo are well paralleled by the similar behaviour of the two classes of species in cryoradiolytic EPR (electron paramagnetic resonance experiments);[11] thus, our computations are consistent with, and provide support for, the recent[11] experimental observation of heme ferric-oxo species in proteins.

Conclusions

A ferryl+porphyrin radical electronic structure description is found using density functional theory methods for fomally ferric-oxo heme models. These results support to some extent and are likely to help further explore the significance of the recently described ferric-oxo moieties in hemoproteins.[11]

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