

# Density Functional Theoretical Study of Oxo(porphyrinato)iron(IV) Complexes, Models of Peroxidase Compounds I and II<sup>1</sup>

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Local density functional (LDF) calculations, including geometry optimization, have been carried out on oxo-(porphyrinato)iron(IV), PFeO, and the corresponding cation, [PFeO]<sup>+</sup>, which have been chosen as simple models of peroxidase compounds II and I, respectively. In the optimized structure of PFeO, the Fe–O distance was 1.622 Å and the iron atom was positioned 0.215 Å above the plane of the four porphyrin nitrogens. The harmonic Fe–O stretching frequencies of PFeO and [PFeO]<sup>+</sup> were 934 and 964 cm<sup>-1</sup>, respectively. A three-body (P–Fe–O) vibrational analysis revealed negligible coupling between the Fe–O stretch and the displacement of the iron atom out of the porphyrin plane. In both PFeO and [PFeO]<sup>+</sup>, two unpaired spins, corresponding to a ( $\pi^*$ )<sup>2</sup> configuration, were cleanly localized on the ferryl moiety, being divided among Fe and O in the ratio 1.2:0.8. The third unpaired spin of [PFeO]<sup>+</sup> was distributed over the porphyrin ring as an “A<sub>2u</sub>”-type cation radical. Overall, these LDF results represent good agreement between first-principles theory and experiment. Spin-restricted Hartree–Fock theory is known to provide a poor description of both the porphyrin ligand and the ferryl group. The CASSCF method provides a good description of the ferryl group but is computationally unwieldy for large molecules such as hemes. Density functional theory appears to provide an expedient solution to the problem of several configurations with significant contributions to the wave functions of ferryl intermediates and is a practical theoretical tool for studying ferryl species.

## Introduction

High-valent oxo-iron (“ferryl”) porphyrin intermediates have been detected for various peroxidases<sup>2</sup> and synthetic model compounds<sup>3</sup> and are believed to be involved in the reaction mechanisms of other heme enzymes, such as the cytochromes P450.<sup>4</sup> For over a decade, the electronic structure of enzymatic and synthetic ferryl porphyrin complexes have been studied by an array of physical techniques, including electronic absorption,<sup>5</sup> Raman,<sup>6,7e</sup> EPR,<sup>7</sup> Mössbauer,<sup>7</sup> NMR,<sup>3a,d,7e–g,8</sup> ENDOR,<sup>1,9</sup> MCD,<sup>10</sup> and EXAFS<sup>11</sup> spectroscopies and magnetic susceptibility<sup>3a,d,12</sup> and X-ray crystallography.<sup>8c,13</sup> Ferryl intermediates have also been studied by a variety of quantum chemical methods including extended Hückel (EH),<sup>14</sup> semiempirical INDO-type UHF<sup>15</sup> and RHF<sup>16</sup> SCF MO methods,  $X\alpha$  multiple scattering,<sup>17</sup> and *ab initio* UHF, RHF and CASSCF<sup>18</sup> methods.<sup>1</sup> As a result of this intense scrutiny, the basic features of the chemical bonding in the ferryl group are considered to be relatively well understood. The subject of electronic structure of ferryl intermediates is far from being a closed chapter, though. For instance, the influence of sixth, axial ligands and of porphyrin peripheral substituents on the properties of the ferryl center remain to be clearly elucidated. An accurate and computationally facile first-principles theoretical method should be of great value for studying the electronic and geometric structures of large, substituted ferryl porphyrin complexes.

Semiempirical methods have been applied with notable success to heme systems by Loew and co-workers.<sup>16</sup> Wishing to adopt a different approach, we chose to search for an appropriate first-principles method to study ferryl intermediates. Unfortunately, the choice of available first-principles methods, which are both reliable and computationally expedient for large molecules such as hemes, is extremely limited. Hartree–Fock (HF) wavefunction instability problems for tetrapyrrole ring systems<sup>19</sup> and the presence of open-shell transition-metal centers demand the use of a correlated method. The issue of macrocycle buckling<sup>20</sup> is of great current interest in porphyrin chemistry. Our method of choice should therefore be facile enough for full geometry

optimizations of large molecules of little or no symmetry. Density functional theoretical (DFT)<sup>21,22</sup> methods appear to uniquely satisfy these requirements, since they are considerably faster than wavefunction-based methods of comparable performance, and since they account for electron correlation in a computationally expedient manner. In this paper, we describe the performance of local density functional (LDF) theory in calculations on oxo-(porphyrinato)iron(IV) (PFeO) and the [PFeO]<sup>+</sup> cation, which we choose as models for compounds II and I, respectively. The computed results consist of geometrical parameters, Fe–O stretching frequencies, and charge and spin densities.

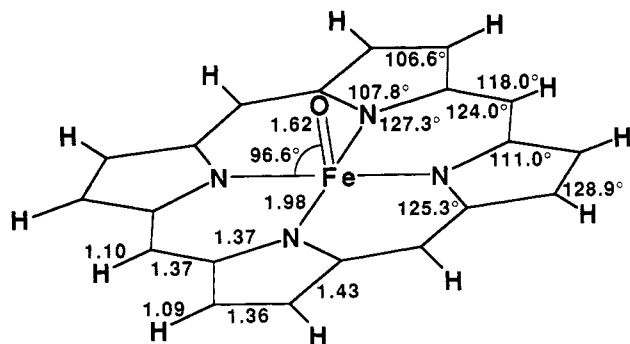
## Methods

The LDF calculations reported here were carried out using the program system DMol.<sup>23</sup> A set of numerically tabulated LDF atomic functions served as basis functions. In this work, a double numeric plus polarization (DNP) basis set was used for all atoms. A fine mesh was used to ensure high accuracy of the numerical integration procedure used in the evaluation of matrix elements. All calculations were of the spin-unrestricted type, using the local von Barth–Hedin exchange–correlation functional for spin-polarized calculations.<sup>24</sup>

Both the electronic and geometric structures of PFeO were calculated using  $C_{4v}$  symmetry. This optimized geometry was adopted for [PFeO]<sup>+</sup>, with only the position of the oxygen atom reoptimized. A formally (P<sup>2-</sup>)(Fe<sup>4+</sup>)(O<sup>2-</sup>) electronic configuration with an  $S = 1$   $d_{xy}^2 d_{xz}^1 d_{yz}^1$  3d-subshell occupancy was assumed for PFeO, so that in  $C_{4v}$  symmetry, the orbitals with the unpaired electrons belonged to the irreducible representation  $e$ . The symmetries of the orbitals with unpaired electrons in the ground state of [PFeO]<sup>+</sup> were  $a_1$  and  $e$  in  $C_{4v}$ .

A two-coordinate potential energy surface was used to calculate the Fe–O stretching frequency of PFeO. The two variables, viz., the Fe–O distance ( $q_1$ ) and the displacement of the Fe atom from the center of mass of the porphyrin ligand ( $q_2$ ), were chosen to examine the possibility of coupling between vibrations

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**Figure 1.** LDF/DNP  $C_{4v}$  optimized geometry of PFeO. Internuclear distances and angles are in angstroms and degrees, respectively.

along these two coordinates. A potential energy function,  $V(q_1, q_2)$ , expressed as a general cubic polynomial in  $q_1$  and  $q_2$ , was fitted to molecular total energies from some twenty single-point LDF calculations on PFeO, and a harmonic vibrational analysis was carried out. Since the interaction constant between  $q_1$  and  $q_2$  ( $\partial^2 V / \partial q_1 \partial q_2$ ) turned out to be extremely small, the effect of including anharmonicity on the Fe–O stretching frequency was examined using an anharmonic one-dimensional potential, refitted to include up to quartic terms.

## Results and Discussion

**A. Molecular Geometry.** Figure 1 shows the LDF/DNP optimized geometry of PFeO. The optimized Fe–O distance in PFeO is 1.623 Å. The iron atom sits 0.215 Å above the plane containing the four porphyrin nitrogens. Each Fe–N distance is 1.976 Å. The calculated bond distances and angles in the remainder of the PFeO molecule are in excellent agreement with crystallographic data on typical metalloporphyrins, but are otherwise unremarkable.

The very short computed Fe–O distance in PFeO is in excellent accord with experiment. An Fe–O distance of 1.604 (19) Å has been reported for a crystal structure of  $\text{Fe}^{\text{IV}}(\text{O})(\text{TPpivP})(\text{THF})$ .<sup>1,8c</sup> Using EXAFS, Penner-Hahn *et al.* studied horseradish peroxidase compounds I and II and model ferryl complexes and found the Fe–O distance to be  $1.64 \pm 0.03$  Å in each case.<sup>11a</sup>

A short, qualitatively correct Fe–O distance of 1.66–1.67 Å has been calculated for PFeO(py)<sup>1</sup> at the CASSCF level.<sup>18d</sup> The *ab initio* RHF value of 1.69 Å<sup>18d</sup> for PFeO(py) is also rather good, but, as noted by Yamamoto *et al.*,<sup>18d</sup> the RHF approximation yields incorrect values for other properties of the ferryl group, such as spin densities and the Fe–O stretching frequency. The difference of about 0.04–0.05 Å between the LDF and CASSCF values of the Fe–O distance is, presumably, partially attributable to the absence of a sixth, axial ligand in our model complex, PFeO, whereas Yamamoto *et al.* used pyridine as the sixth ligand in their model complex.<sup>18d</sup>

As mentioned before, the geometry of  $[\text{PFeO}]^+$  was not fully optimized. The optimized Fe–O distance in  $[\text{PFeO}]^+$  turned out to be 1.620 Å, i.e., essentially the same as that in PFeO.

**B. The Fe–O Stretching Frequency.** The harmonic force constants of PFeO computed at the LDF/DNP level were (in  $\text{mdyn}/\text{Å}$ ):

$$\frac{\partial^2 V}{\partial q_1^2} = 6.38, \quad \frac{\partial^2 V}{\partial q_2^2} = 1.94, \quad \frac{\partial^2 V}{\partial q_1 \partial q_2} = 0.15$$

the derivatives being calculated at the potential energy minimum. The small coupling term indicates that the Fe–O stretching mode is essentially decoupled from the displacement of the iron atom from the porphyrin plane. A full three-body (P–Fe–O) vibrational analysis and a diatomic harmonic oscillator calculation yield the same value of 934  $\text{cm}^{-1}$  for the Fe–O harmonic stretching frequency. The calculated  $^{18}\text{O}$ -induced isotope shift in the Fe–O

harmonic frequency is  $-40$   $\text{cm}^{-1}$ . The anharmonic cubic and quartic corrections to the harmonic frequency are  $-18$  and  $+7$   $\text{cm}^{-1}$ , respectively.

The Fe–O harmonic force constant and stretching frequency of  $[\text{PFeO}]^+$ , which were calculated within the diatomic approximation, are 6.80  $\text{mdyn}/\text{Å}$  and 964  $\text{cm}^{-1}$ , respectively. These results are discussed below in light of available experimental data.

In this initial density functional study of ferryl species, we have chosen a simple five-coordinate compound II model, PFeO. The influence of axial ligands and peripheral porphyrin substituents on the ferryl center will be addressed in later investigations. Fortunately, resonance Raman experimental data are available on five-coordinate ferryl species, mainly from matrix isolation studies by Nakamoto *et al.*<sup>6a–c</sup> These authors have reported Fe–O stretching frequencies ( $\text{cm}^{-1}$ ) of 852 for (TPP)-FeO,<sup>1</sup> 852 for (OEP)FeO,<sup>1</sup> and 851 for (salen)FeO.<sup>1,6a,b</sup> In addition, Kitagawa *et al.* have reported a value of 843  $\text{cm}^{-1}$  for (TMP)FeO.<sup>1,6c</sup> The discrepancy between our LDF calculation on PFeO (923  $\text{cm}^{-1}$ , including anharmonicity) and experiment ( $\sim 852$   $\text{cm}^{-1}$ ) is about 70  $\text{cm}^{-1}$ . Moreover, the peripheral substituents in the experimentally studied compounds, (TPP)-FeO and (OEP)FeO, have a distinct electron-donating influence on the central region of the porphyrin ring.<sup>25</sup> Therefore, inclusion of octaalkyl or tetraphenyl substituents in our calculation would probably reduce the harmonic frequency by a modest margin, but no data are available on the magnitude of this effect. The real discrepancy between LDF and experimental values of the Fe–O stretching frequency is therefore believed to be somewhat less than 70  $\text{cm}^{-1}$ . This level of agreement between first-principles theory and experiment is quite encouraging.

Previous theoretical studies have not addressed the question of coupling between the Fe–O stretching mode and the displacement of the iron atom from the porphyrin plane. Our three-body calculations show that the force constant  $\partial^2 V / \partial q_1 \partial q_2$  is so small that a diatomic oscillator approximation is sufficiently accurate for calculating the Fe–O stretching frequency. There is no obvious reason to suppose that this approximation should not work for ferryl complexes of other substituted porphyrin ligands. Differences in Fe–O stretching frequencies of five-coordinate compound II analogues should therefore be interpretable in terms of purely electronic effects, without complications due to differential mass effects.

Within the diatomic approximation, an isotope shift in the stretching frequency of a bond is proportional to the square root of the force constant. The experimental  $^{18}\text{O}$ -induced isotope shifts in the Fe–O stretching frequencies of (TPP)FeO or (OEP)FeO are  $-34$   $\text{cm}^{-1}$  each.<sup>6a,b</sup> For a frequency of 852  $\text{cm}^{-1}$ , the diatomic approximation leads to an  $^{18}\text{O}$ -induced shift of 38  $\text{cm}^{-1}$ , which is in satisfactory agreement with experiment.

The CASSCF calculation of Yamamoto *et al.* also overestimates the Fe–O stretching frequency in PFeO(py) by about 60  $\text{cm}^{-1}$ .<sup>18d</sup> In contrast, the Fe–O stretching frequency of PFeO(py) is underestimated by over 230  $\text{cm}^{-1}$  at the RHF level (RHF value 617  $\text{cm}^{-1}$ ),<sup>18d</sup> showing the importance of including correlation effects in describing the ferryl group.

Our calculated value of 964  $\text{cm}^{-1}$  for the Fe–O stretching frequency of  $[\text{PFeO}]^+$  is difficult to compare with experiment, since no five-coordinate compound I analogues are known.

The considerable success of LDF theory in reproducing the Fe–O stretching frequency of PFeO suggests interesting applications of DFT to predict and simulate the Raman spectra of ferryl species. For instance, a systematic, theoretical study of the influence of axial ligands<sup>6k,l,v,7e</sup> and of porphyrin peripheral substituents on the Fe–O stretching frequency of the ferryl group is well worth pursuing using DFT.

**C. Charge and Spin Distribution.** For PFeO, our calculated atomic charges (in units of  $e$ ) on the Fe, N, and O atoms are

+0.50, -0.32, and -0.40, respectively, and for  $[\text{PFeO}]^+$ , they are 0.52, -0.31, and -0.36, respectively. The significant negative charge on the oxygen is in conformity with the possibility of the ferryl oxygen engaging in hydrogen bonding interactions. In spite of the overall +1 charge of  $[\text{PFeO}]^+$ , the charge on the Fe atoms are nearly identical in PFeO and  $[\text{PFeO}]^+$ . This agrees with the experimental observation of nearly identical Mössbauer isomer shifts of about 0.1 mm/s for HRP-I and HRP-II.<sup>7b,c</sup>

Essentially all the spin density in the triplet PFeO molecule was found to be cleanly localized on the ferryl group. The calculated spin populations on the Fe and O atoms are 1.196 and 0.821, respectively. Each nitrogen atom carries a very small negative spin density of -0.011. The absolute value of the spin population on any carbon atom was negligible, <0.01, which is consistent with the observation of very small paramagnetic shifts in the <sup>1</sup>H NMR spectra of compound II analogues.<sup>7c</sup> The gross AO spin populations are 0.598 for each of the two Fe 3d<sub>x</sub> AO's and 0.410 for each of the two O 2p<sub>x</sub> AO's. The O 2p<sub>x</sub> AO (along the C<sub>4</sub> axis) carries negligible spin population. The computed data are consistent with a  $(\pi^*)^2$  configuration for the unpaired electrons.

Our computed spin distribution for the quartet  $[\text{PFeO}]^+$  ion exhibited notable points of similarity between PFeO and  $[\text{PFeO}]^+$ . Two out of three electron spins of  $[\text{PFeO}]^+$  are cleanly localized on the ferryl group, as in PFeO. The Fe and O atoms carry 1.184 and 0.849 spins, respectively, in  $[\text{PFeO}]^+$ . The third electron spin is distributed over the porphyrin ring as an "A<sub>2u</sub>-type" radical. The unpaired spin populations on each nitrogen and each  $\beta$ ,  $\alpha$ , and *meso* carbon are 0.050, 0.016, -0.006, and 0.179, respectively. From ENDOR measurements on HRP-I, Roberts *et al.* estimated a spin population of 0.25 for each of the two O 2p<sub>x</sub> AO's.<sup>9b</sup> Qualitatively, the ENDOR estimate confirms our theoretical prediction that a substantial amount of spin density resides on the ferryl oxygen. Quantitatively, our computed spin population on the oxygen atom in  $[\text{PFeO}]^+$  is somewhat larger than the experimental estimate for HRP-I. Our calculated spin population at each  $\beta$ -carbon is also in good agreement with the experimental value of 0.016 estimated from an NMR study of  $[(\text{TMP})\text{FeO}]^+$ .<sup>8f,g</sup>

*Ab initio* studies by Kashiwagi *et al.* revealed that the RHF and CASSCF methods provide drastically different spin density distributions for the compound II analog, PFeO(py).<sup>18d</sup> At the RHF level, nearly all the spin population (1.91 out of 2 unpaired spins) of PFeO(py) is localized on the iron, with a very small amount (0.06) on the ferryl oxygen.<sup>18d</sup> At the CASSCF level, the iron and oxygen atoms of PFeO(py) carry unpaired spin populations of 1.17 and 0.82, respectively.<sup>18d</sup> Our LDF results, thus, are in excellent agreement with CASSCF results.

This is a particularly encouraging result. The CASSCF results revealed that the main  $(\pi^*)^2$  configuration has a weight of only around 0.8.<sup>18d</sup> The substantial spin density on the ferryl oxygen must therefore be due to the minority configurations. It is interesting that the LDF method, formally a single-reference approach, reproduces this multireference effect on the spin density distribution.

## Conclusion

We have examined the performance of local density functional theory in describing the electronic structure of five-coordinate PFeO and  $[\text{PFeO}]^+$ , which are models of peroxidase compounds II and I, respectively. The first-principles LDF approach yields an excellent Fe-O distance and realistic values of the Fe-O stretching frequency and atomic spin populations.

Among the first-principles methods, *ab initio* RHF theory is known to provide a poor description of the ferryl group. Traditional post-HF methods should lead to improved results but are prohibitively demanding on computational resources. Therefore, the excellent performance of the computationally expedient

LDF method for PFeO should be welcome to bioinorganic chemists working on ferryl intermediates. This study gives us considerable confidence in the ability of DFT to provide reliable answers to a number of important questions on ferryl species.

Prior to this study, the CASSCF calculations of Kashiwagi *et al.* were the only first-principles calculations to satisfactorily simulate the observed molecular properties of compound I and II species. Overall, there is excellent agreement between our LDF results and the previous CASSCF results. The advantage of DFT is that it is vastly more computationally facile than *ab initio* MCSCF<sup>1</sup> methods, such as CASSCF. For instance, full geometry optimizations of large molecules such as hemes are currently impossible with MCSCF methods. DFT thus appears to provide a very expedient solution to the complex problem of several configurations with significant contributions to the wavefunctions of ferryl intermediates.

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## References and Notes

- (1) Abbreviations: AO = atomic orbital; CASSCF = complete active space SCF; DFT = density functional theory; DNP = double numeric plus polarization; ENDOR = electron-nuclear double resonance; HF = Hartree-Fock; HRP I and II = horseradish peroxidase compounds I and II; LDF = local density functional; MCSCF = multiconfiguration SCF; OEP<sup>2-</sup> = octaethylporphyrinato; P<sup>2-</sup> = porphyrinato; py = pyridine; salen<sup>2-</sup> = *N,N'*-ethylenebis(salicylideneiminato); TDCPP<sup>2-</sup> = tetrakis(2,6-dichlorophenyl)porphyrinato; THF = tetrahydrofuran; TMP = tetramesitylporphyrinato; TPP<sup>2-</sup> = tetraphenylporphyrinato; TPpivP<sup>2-</sup> = tetrakis[2-(*N*-pivalamido)phenyl]porphyrinato or dianion of picket fence porphyrin; RHF = spin-restricted Hartree-Fock; SCF = self-consistent field; UHF = spin unrestricted Hartree-Fock.
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