

Molecular Structure and Conformation of Dinitrosylheme

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Produced by the heme protein nitric oxide synthase (NOS), NO binds to the heme cofactor of guanylate cyclase which catalyzes the conversion of GTP to cGMP. The production of cGMP regulates a variety of physiological functions including vasodilation, inhibition of platelet aggregation, cell adhesion, and neurotransmission.^{1–3} The profound biological importance of heme-NO interactions has inspired the synthesis and structural characterization of a wide variety of metalloporphyrin-nitrosyl complexes.^{4–7}

The most important nitrosylmetalloporphyrins are {MNO}ⁿ systems with *n* = 6, 7, and 8, where M is a transition metal, and *n* is the total number of electrons in the metal(*d*) and NO(π^*) orbitals combined.⁸ These three cases are characterized by widely different MNO angles of approximately 180°, 140°, and 120°, respectively.⁸ Representative examples of *n* = 6, 7, and 8 are given by ferriheme-NO^{9,10} complexes, ferroheme-NO^{9,11} complexes, and cobalt(II)-NO¹² porphyrin complexes, respectively. Early theoretical studies have provided a qualitative explanation of the wide variations in MNO angles, the key orbital interaction favoring MNO bending involving a σ interaction of the metal (*d*_{z²}) orbital and an NO(π^*) orbital.¹³ A particularly interesting development in transition metal nitrosyl chemistry is the discovery of NO linkage isomers, including isonitrosyl (ON) and side-on bound NO complexes.¹⁴ A theoretical study of this phenomenon has been published.¹⁵

An important recent contribution to the chemistry of nitrosyl-metalloporphyrins is a report by Lorkovic and Ford of the generation of a unique dinitrosylheme intermediate.^{16,17} Polynitrosyl complexes are relatively uncommon, and dinitrosyl complexes with the two NO ligands trans to each other are virtually unknown,¹⁸ presumably because of the strong trans-labilizing effect of the NO ligand. Besides, given the ubiquitous role of NO in biology, dinitrosylheme intermediates may also occur in nature. These considerations prompted us to undertake a density functional theoretical (DFT) investigation of dinitrosylheme, Fe(P)(NO)₂ (P = porphyrinato), and the results proved somewhat surprising and contrary to what the experimentalists proposed in their original study.¹⁶

Addition of NO (8 mM) to a cold (213 K) 2.3 mM solution of Fe(TPP)(NO) (TPP = tetraphenylporphyrinato) in CHCl₃, which exhibits an IR ν_{NO} of 1681 cm⁻¹ ($\epsilon = 800 \text{ M}^{-1} \text{ cm}^{-1}$), resulted in the appearance of a new band at 1695 cm⁻¹ ($\epsilon = 1600 \text{ M}^{-1} \text{ cm}^{-1}$) with approximately twice the intensity of the 1681 cm⁻¹ band and another much weaker band at 1777 cm⁻¹.¹⁶ The 1695 cm⁻¹ band was identified as an NO stretching band via isotopic substitution experiments.¹⁶ Lorkovic and Ford stated that the positions and relative intensities of these bands are consistent with a trans arrangement of equivalent nitrosyl ligands.¹⁶ Now the meaning of the word trans may be slightly confusing: if the two NOs are simply meant to be on different sides of the porphyrin, that is certainly reasonable, and we have assumed this to be the case in this theoretical study. However, the authors state further that “the IR data point to a centrosymmetric *trans*-dinitrosyl configuration”,¹⁶ and we find that our DFT calculations do not agree with this conclusion.

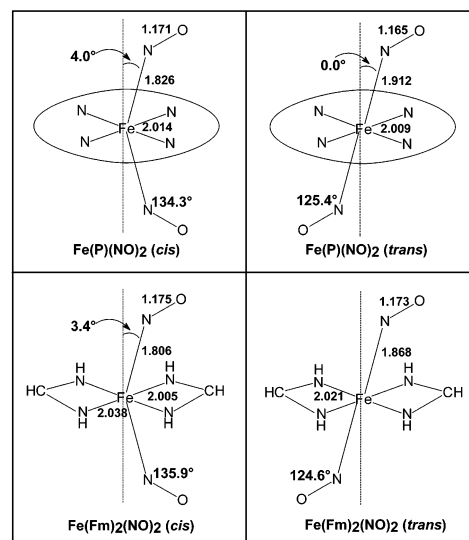


Figure 1. Selected optimized geometry parameters (Å, deg) of Fe(P)₂(NO)₂ and Fe(Fm)(NO)₂.

Given that the system of interest may be described as an {Fe-(NO)₂}⁸ complex, the NO ligands are expected to be bent, and we wished to find out whether they are bent in the same direction, a conformation henceforth described to as *cis* or *C_{2v}*, or in opposite directions, which would correspond to a *trans* or *C_{2h}* conformation. In our calculations on these two conformations, the Fe(NO)₂ plane also contained a pair of opposite *meso*-carbons. DFT(PW91/TZP) geometry optimizations of the two conformations clearly favored the *cis* conformation over the *trans* one by a substantial margin of 0.85 eV or 19.5 kcal/mol. This result may be considered unexpected for two reasons. First, both the *cis* and the *trans* conformations feature essentially the same interatomic contacts, and such a massive energetic preference for one conformer is therefore surprising. Second, contrary to Lorkovic and Ford's proposal,¹⁶ our calculations favor the noncentrosymmetric *cis* conformation.

Some salient structural features of the two conformations are shown in Figure 1, the following points being worth noting. (a) The Fe–N(NO) bond distances in the *cis* and *trans* conformations are 1.826 and 1.912 Å, respectively, qualitatively consistent with the greater calculated stability of the *cis* conformation. The M–N(NO) distance in the *cis* conformation is actually similar to that observed for Co(OEP)(NO)¹² (1.844 Å) and calculated for Co-(P)(NO)¹⁹ (1.817 Å). By comparison, the Fe–N(NO) distance in the *trans* conformation is unusually long as compared with other known first-row transition metal nitrosyl complexes. (b) The N–O bond lengths in the *cis* and *trans* conformations are 1.171 and 1.165 Å. (c) As expected, the FeNO units in both the *cis* and the *trans* conformations are strongly bent, the FeNO angles being 134.3° and 125.4°, respectively, which are reasonably similar to M–N–O angles in mononuclear {MNO}⁸ complexes. (d) The Fe–N(NO) vectors in the *cis* conformation are tilted from the heme normal by about 4°, a somewhat unusual feature of certain nitrosyl complexes

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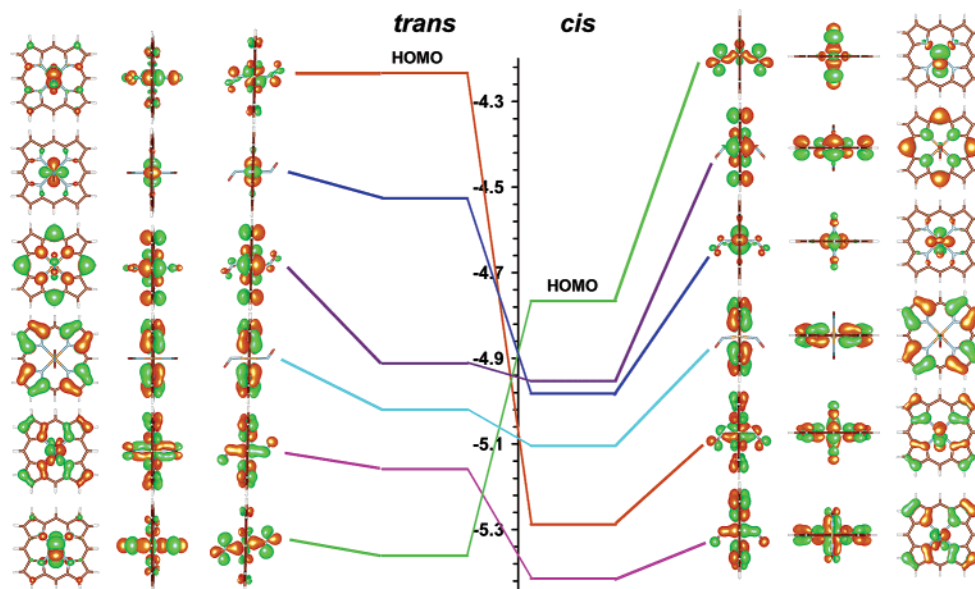


Figure 2. Correlation diagram for the top six occupied MOs of Fe(P)(NO)_2 with the orbital energy scale in eV. Three views are shown for each MO.

first noted by Scheidt and co-workers¹¹ and also studied theoretically by one of us.¹⁹ In contrast, the Fe–N(NO) vectors in the trans conformation lie almost exactly along the heme normal, although they are not constrained to do so by symmetry. (e) Optimizing Fe(P)(NO)_2 using a starting geometry where the two NO units are in mutually perpendicular planes and a C_s symmetry constraint invariably led to a cis conformation. Interestingly, however, as long as the two NOs are cis, they do not exhibit a significant orientational preference in relation to the porphyrin ring. Thus, a cis conformation in which the two NOs lie in a symmetry plane containing two opposite porphyrin nitrogens is only 0.04 eV or 0.89 kcal/mol higher in energy than a cis conformation in which the two NOs lie in a plane containing two opposite *meso*-carbons, suggesting that the conformational preference of this species. (f) Consistent with this observation, we found that a small dinitrosylheme model, $\text{Fe(Fm)}_2(\text{NO})_2$ (Fm = formamidinato), also prefers a cis conformation over a trans one by about 0.74 eV or 17.06 kcal/mol, roughly the same margin as that observed for Fe(P)(NO)_2 .

We have sought an MO explanation for the strong cis conformational preference of dinitrosylheme by constructing MO energy level diagrams for the top few occupied MOs of Fe(P)(NO)_2 (Figure 2) and also of $\text{Fe(Fm)}_2(\text{NO})_2$ (Figure S1 in Supporting Information).¹³ Qualitatively consistent with the greater stability of the cis conformations, they exhibit a much larger HOMO–LUMO gap (not shown in Figures 2 and S1) than do the trans conformations. For both the cis and the trans conformations, there are two important metal(d)–NO(π^*) orbital interactions that are symmetric with respect to reflection across the Fe(NO)_2 plane (Figures 2 and S1). For both Fe(P)(NO)_2 and $\text{Fe(Fm)}_2(\text{NO})_2$, the HOMO of the trans conformations, which may be described as an NO(π^*)–Fe(d_{xz})–NO(π^*)-based MO, is stabilized in the cis conformation by more than an eV, where it appears as the HOMO–4. In contrast, the HOMO–5 of the trans conformation of Fe(P)(NO)_2 , which is largely an NO(π^*)–Fe(d_{z^2})–NO(π^*)-based MO, appears to rise in energy in the cis conformation by about 0.6 eV, where it appears as the HOMO. Similarly, the NO(π^*)–Fe(d_{z^2})–NO(π^*)-based HOMO–3 of the trans conformation of $\text{Fe(Fm)}_2(\text{NO})_2$ appears to rise in energy also by about 0.6 eV in the cis conformation, where it appears as the HOMO–1. Thus, the strong preference of dinitrosylheme for the cis conformation cannot be ascribed to a single metal(d)–NO(π^*) orbital interaction, but it reflects a balance of at

least two and possibly more orbital interactions. This MO picture is somewhat more complex than that found for mononitrosyl complexes where the metal(d_{z^2})–NO(π^*) is the critical orbital interaction that appears to control the MNO unit.¹³

In conclusion, DFT calculations indicate a strong cis conformational preference for the NO ligands of dinitrosylheme, which is puzzlingly contrary to what the original experimental researchers concluded about the structure of dinitrosylheme.¹⁶ Given that both the cis and the trans conformations are closed-shell species and given the successful track record of DFT in describing transition metal nitrosyl complexes, we consider it highly unlikely that the calculations are literally “wrong”. Obviously, more work will need to be done to reconcile these divergent conclusions.

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Supporting Information Available: Optimized Cartesian coordinates of the molecules studied (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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