

Binding of dioxygen in a picket-fence porphyrin complex of iron. A theoretical QM/MM study

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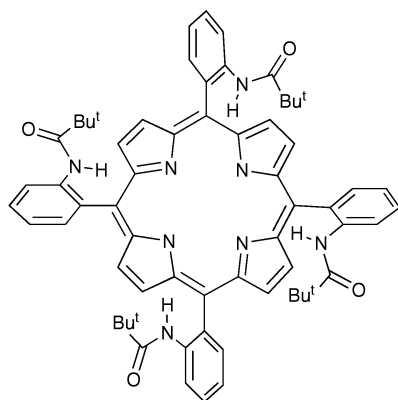
The hybrid quantum mechanics/molecular mechanics method IMOMM is applied to the calculation of the structure of the oxygenated picket-fence porphyrin complex of iron $\text{Fe}(\text{T}_{\text{piv}}\text{PP})(1\text{-MeIm})(\text{O}_2)$, with results in good agreement with available X-ray data. An investigation on the role of the picket-fence substituents in the binding of dioxygen through comparison with additional calculations on a system with the “naked” porphyrin complex $\text{Fe}(\text{P})(1\text{-MeIm})(\text{O}_2)$ shows that the presence of the amide groups of the picket-fences contribute to the binding with *ca.* 5 kcal mol^{-1} . The largest contribution to this stabilization is found to correspond to an $\text{O} \cdots \text{H}(\text{N})$ interaction.

The binding of dioxygen to heme groups is one of the most important interactions in biochemistry. It plays a central role in the activity of several relevant proteins and enzymes, like hemoglobin¹ and cytochromes.² A lot of insight on this interaction is to be gained from a precise knowledge and understanding of the geometrical features of different structures containing a dioxygen bound to a heme group. Because of this, a substantial effort has been invested in obtaining reliable crystal structures of biological molecules containing these units and of its bioinorganic models.^{3–8} In this context, complexes containing the picket-fence porphyrin, *meso*-tetrakis(α , α , α , α -*o*-pivalamidophenyl)porphyrin, to be referred to from here on as $\text{T}_{\text{piv}}\text{PP}$ (Scheme 1), occupy a prominent position. X-Ray diffraction data on $\text{Fe}(\text{T}_{\text{piv}}\text{PP})(1\text{-MeIm})(\text{O}_2)$ (**1**)⁴ and $\text{Fe}(\text{T}_{\text{piv}}\text{PP})(1\text{-MeIm})(\text{O}_2)$ ⁵ were reported almost 20 years ago by Collman and coworkers. These complexes still constitute the closest synthetic X-ray model of the active sites of hemoglobin and myoglobin, with the imidazole ligand modelling the proximal histidine group.

The difficulty in the experimental collection of structural data provides a challenge for the application of theoretical methods to the structural determination of these species. Molecular mechanics methods, very valuable in a number of transition metal chemistry problems,^{9,10} have little predictive

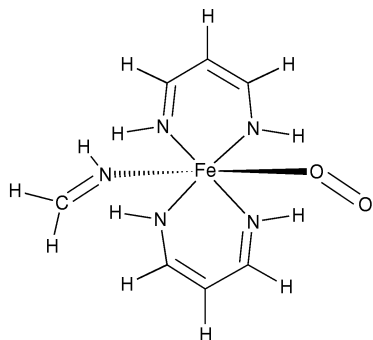
value in the absence of a previous body of structural data, although some progress is currently being made.¹¹ Pure *ab initio* methods, that are indeed making a powerful entry in biochemistry in the study of proteins containing a dicopper core in its active center,¹² face serious problems for their application to heme systems in both the size of the system and the apparent need for electron correlation, which makes the computation very expensive. A number of pure *ab initio* studies have already been presented on metalloporphyrins and related compounds.^{13–23} Reference to the earliest work can be found in a review by Bytheway and Hall.¹³ Among these earlier works, maybe the most remarkable are those by Rohmer and coworkers,¹⁴ who determined the nature of the ground state for tetracoordinated $\text{Fe}(\text{P})$ (P = “naked” porphyrin, $\text{N}_4\text{C}_{20}\text{H}_{12}$), pentacoordinated $\text{Fe}(\text{P})(\text{NH}_3)$ and the hexacoordinated $\text{Fe}(\text{P})(\text{NH}_3)(\text{O}_2)$, mostly on frozen geometries and with RHF-based CI methods, with results in agreement with experiment. Later on, Almlöf and coworkers studied the properties of isolated porphyrin ligands with RHF and MP2 methods.¹⁵ Rosa and Baerends applied DFT methods to the comparison of metal porphyrins and phthalocyanins on frozen geometries.¹⁶ Very recent studies involving geometry optimizations consist in plane wave DFT calculations on the structure of a bacteriochlorophyll crystal¹⁷ and of iron porphyrin complexes,²⁴ a local DFT study on the coordination of heptane to an iron porphyrin,¹⁸ and an ROHF study on model intermediates for peroxidases.¹⁹

This paper presents an application to metalloporphyrin systems of the hybrid quantum mechanics/molecular mechanics method IMOMM.²⁵ This method has already proved to be very successful in the study of large systems,²⁶ and, in particular, in the quantitative introduction of pure steric effects in transition metal complexes.²⁷ In this method, the system is divided into two parts, one to be treated with quantum mechanics (QM) and another to be treated with molecular mechanics (MM). The choice made for the quantum mechanical part of the picket-fence porphyrin complex **1** is presented in Scheme 2. The choice of this relatively small quantum mechanical part, where only a part of the aromaticity is retained, allows full geometry optimizations with a DFT functional including nonlocal corrections and sufficiently large basis sets, which are critical for the reproduction of experimental features (see below in the Computational Details section). The modelling of a porphyrin ring by two amidinato ligands has been previously used in theoretical calculations,^{21–23} and



Scheme 1

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Scheme 2

finds experimental support in the activity of some non-heme Fe^{II} metal sites.²⁸ We are also currently carrying out a systematic study on tetra-, penta- and hexacoordinated heme systems to prove the general validity of this modeling.²⁹

Although hybrid methods have a long story in the field of theoretical biochemistry,³⁰ their previous applications have been mostly concentrated on the MM introduction of solvent effects on the different features of a solute described at the QM level, with the usual application of molecular dynamics. The application presented in this paper is original in the sense that the QM/MM separation is within the studied molecule, which could not be otherwise described at the high computational level required.

Computational Details

IMOMM calculations are performed with a program built from modified versions of two standard programs: GAUSSIAN 92/DFT³¹ for the quantum mechanics part and mm3(92)³² for the molecular mechanics part. QM calculations are carried out on the Fe(NHCH₂CH₂CH₂NH)₂(NHCH₂)(O₂) model system (Scheme 2) at the B3LYP level.³³ A quasi-relativistic effective core potential replaces the 10-electron core of the Fe atom³⁴ and the corresponding valence double- ζ basis set is used.^{31,34} The basis set is also valence double- ζ for all other atoms,³⁵ complemented with a d polarization shell³⁶ on atoms directly attached to the metal and on C and O atoms of the axial ligands.

Molecular mechanics calculations on the full systems Fe(T_{piv}PP)(1-MeIm)(O₂) and Fe(P)(1-MeIm)(O₂) use the mm3(92) force field.³⁷ Van der Waals parameters for the iron atom are taken from the UFF force field³⁸ and torsional contributions involving dihedral angles with the metal atom in the terminal positions are set to zero. All geometrical parameters are optimized except the bond distances between the QM and MM regions of the molecule. The frozen values are 1.019 Å (N—H),³² 1.101 Å (C—H)³² in the QM part; and 1.378 Å (N—C, porphyrin ring),³⁹ 1.332 Å (C—C),³² 1.414 Å (N—C, imidazole ring)⁴ in the MM part.

The need for a nonlocal density functional B3LYP description in the *ab initio* part is supported by the very poor result of an IMOMM(RHF : MM3) geometry optimization of Fe(T_{piv}PP)(1-MeIm)(O₂) with the same basis set. This preliminary calculation did not find the dioxygen ligand to be coordinated, with an Fe—O distance longer than 3 Å.

Geometry Optimization of Fe(T_{piv}PP)(1-MeIm)(O₂)

The IMOMM-optimized structure of Fe(T_{piv}PP)(1-MeIm)(O₂) (Table 1, Fig. 2) shows a good agreement with the X-ray diffraction data,^{4,40} the main features being well-reproduced. The coordination around iron is octahedral, with the dioxygen and the imidazole ligands occupying *trans* positions. The dioxygen is coordinated in a bent η^1 fashion and the iron atom is near the center of the porphyrin ring. This section is devoted to the detailed comparison of the computed and experimental geometries. It has to be noted that the oxygen atom O13 (Fig. 1) is delocalized in four different sites in the crystal structure,⁴ and the position of the methyl-substituted N17 atom of the imidazole ring is also delocalized with that of C18. As a result, the experimental data have a larger imprecision than usual and they show a symmetry that is not present in the real system.

The computed value (1.766 Å) for the Fe—O12 distance is only 0.02 Å larger than the experimental value (1.75 Å), a difference that is of the same order as the experimental error (0.018 Å). This constitutes a noticeable success, since this parameter seems to be the most demanding in terms of

Table 1 IMOMM(B3LYP : MM3)-optimized values for some selected geometrical parameters (Å and degrees) in Fe(T_{piv}PP)(1-MeIm)(O₂) (1), Fe(P)(1-MeIm)(O₂) (2), Fe(T_{piv}PP)(1-MeIm) (3) and Fe(P)(1-MeIm) (4). X-Ray values available for 1 are shown in parentheses. The atomic numbering scheme is presented in Fig. 1

	1	2	3	4
Fe1—N2	1.945	1.943	2.027	2.029
Fe1—N3	1.970	1.962	2.030	2.028
Fe1—N4	1.947	1.943	2.028	2.031
Fe1—N5	1.968	1.963	2.032	2.032
Fe—N _p ^a	1.958 (1.98)	1.953	2.029	2.030
Fe1—O12	1.766 (1.75)	1.761	—	—
Fe1—N14	2.118 (2.07)	2.135	2.210	2.209
O12—O13	1.279 (1.16)	1.276	—	—
N _p —Fe1—N _p (<i>cis</i>) ^a	89.7 (90)	89.9	89.0	88.7
N _p —Fe1—N _p (<i>trans</i>) ^a	176.0 (178)	176.1	164.4	162.4
N _p —Fe1—O12 ^a	92.0 (91)	91.9	—	—
N _p —Fe1—N14 ^a	88.1 (89)	88.1	97.8	99.8
O12—Fe1—N14	178.6 (180)	179.1	—	—
Fe1—O12—O13	116.4 (131)	117.5	—	—
Fe1—N14—C15	131.5	131.6	134.9	134.2
Fe1—N14—C16	126.9	126.8	123.9	124.7
Fe1—N14—C ^a	129.2 (125)	129.2	129.4	129.5
N2—Fe1—O12—O13	−46.7 (−42)	−45.8	—	—
N2—Fe1—N14—C15	131.5 (160)	133.7	135.1	135.7
Fe plane ^{b,c}	0.041 (0.014)	0.063	−0.300	−0.395
RMS deviation from plane ^b	0.055 (0.07)	0.011	0.036	0.052

^a Average value. ^b Plane defined by the 24-atom porphyrin ring. ^c Displacements towards oxygen are considered positive.

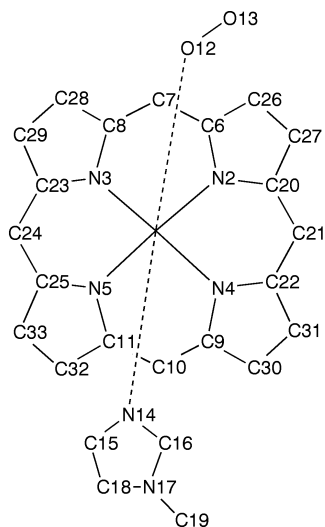


Fig. 1 Atomic numbering used in the description of geometrical parameters. The atoms in the QM part are numbered from 1 to 15

required computational level. The location of the second oxygen atom O13 is not very precise in the X-ray structure,⁴ as a result of disorder over four sites. The measured X-ray value of 1.16 Å implies a shorter O—O separation than the 1.21 Å of molecular oxygen.⁴¹ We therefore consider our computed value (1.279 Å) to be a better estimate of the real value. Moreover, it is also consistent with the postulated superoxide character of this ligand. Similar reasoning can be applied to explain the 15° discrepancy in the Fe—O12—O13 angle

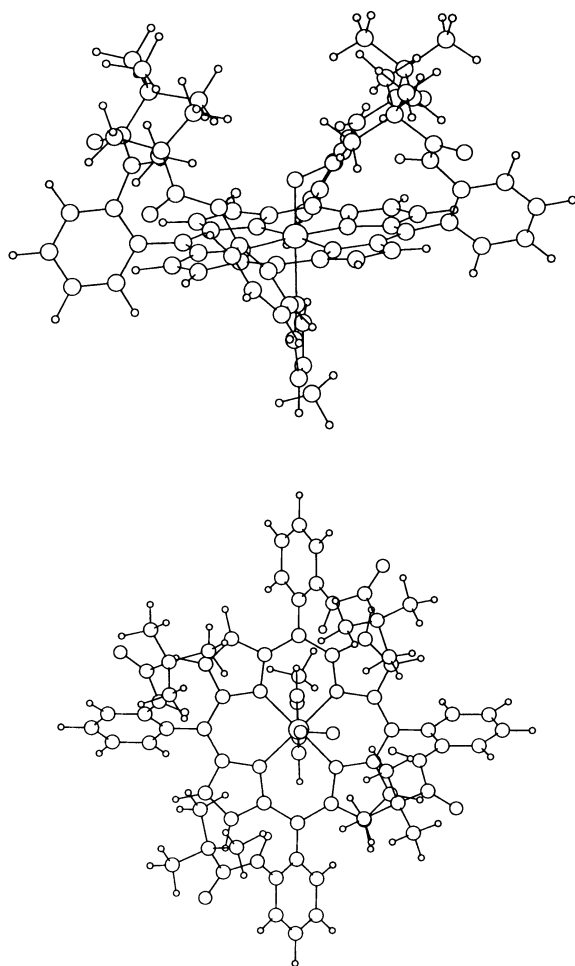


Fig. 2 Two views of the IMOMM(B3LYP : MM3)-optimized structure of the Fe(T_{piv}PP)(1-MeIm)(O₂) complex 1

(116.4° *vs.* 131°). The computed orientation of the Fe1—O12—O13 plane, on the bisector of the N2—Fe1—N5 and N3—Fe—N4 planes, is in agreement with experiment, as proved by the value of the N2—Fe—O12—O13 dihedral angle (−46.7° in calculation, 42° in experiment).

The Fe—N_{imidazole} (Fe1—N14) distance presents the largest discrepancy (0.05 Å) in the metal–ligand distances (2.118 *vs.* 2.07 Å). This discrepancy might be related to the drastic modelization of the imidazole ligand in the QM part. Additional calculations will have to be carried out to check this possibility. The computed values for the geometrical parameters in the imidazole ring are quite unremarkable, with the possible exception of the Fe—N—C angles. This angle is smaller for the carbon closer to the methyl-substituted nitrogen (Fe1—N14—C16, 126.9°) than for the other carbon (Fe1—N14—C15, 131.5°). The steric effect of this methyl substituent must therefore be quite small. The Fe1—N14—C15 plane is on the bisector of the N2—Fe1—N5 and N3—Fe—N4 planes (N2—Fe1—N14—C15 dihedral angle of 131.5°) and perpendicular to the Fe1—O12—O13 plane (N2—Fe1—O12—O13 dihedral angle of −46.7°). This result is not in agreement with experiment, where the N2—Fe1—N14—C15 dihedral angle is 160°. This discrepancy may be related to the packing effects associated to the close presence of a solvation molecule in the crystal. The possible effect of this intermolecular interaction on this particular geometrical parameter was already suggested in the report of the X-ray structure.⁴

The computed arrangement of the Fe—O—O and Fe—imidazole planes, mutually perpendicular and on the bisectors of the N_{porphyrin}Fe—N_{porphyrin} axis is actually more consistent with a simple MO analysis than the experimental one. Both dioxygen and imidazole act as π -acceptors, and they place themselves in perpendicular planes to avoid competing for the same metal d orbitals. These metal d orbitals are placed on the bisectors of N_{porphyrin}Fe—N_{porphyrin} because of the π -donor properties of porphyrin. The weaker π -accepting properties of imidazole are also reflected in its facility to be deviated from its optimal electronic arrangement by packing effects.

The average of the computed values for the Fe—N_{porphyrin} distances (1.958 Å) is only 0.02 Å off the experimental value (1.98 Å). Even if this parameter is not very flexible because of the steric constraints within the ring, it takes different values for tetracoordinated, pentacoordinated and hexacoordinated iron systems, and the value computed here is in agreement with the low-spin hexacoordinated nature of 1.³ The precise location of the axial ligands in the theoretical calculation allows a discussion of their effect on porphyrin coordination that was impossible in the symmetry-averaged X-ray structure. The two nitrogen atoms closest to O13 show a considerably shorter bond distance (Fe1—N2, 1.945 Å; Fe1—N4, 1.947 Å) than the two other nitrogen atoms (Fe1—N3, 1.970 Å; Fe1—N5, 1.968 Å). The tilting of the dioxygen ligand has therefore an effect on the geometry of the porphyrin ring, an effect that concerns also its distortion from planarity, with N2, N4 being displaced from the 24-atom porphyrin plane towards the side of the imidazole ligand by 0.086, 0.077 Å and N3, N5 being displaced towards the side of the dioxygen ligand by 0.032, 0.031 Å. Agreement between computed and experimental intra-ring N—C and C—C bond distances is not very good. In particular, the values for C—C bonds within the MM part are close to 1.332 Å (the MM3 equilibrium value for C_{sp2}—C_{sp2} bonds), quite different from the experimental values of around 1.39 Å for this complex. This result would surely be improved by tuning the force field parameters. This may be done in future work, but in this paper we wanted a first principles result, without introduction of expressly fitted data.

The porphyrin ring is essentially planar, with deviations from the 24-atom average plane of 0.10 Å at most, in agreement with experiment. The Fe atom is slightly displaced from

this plane towards the dioxygen ligand by 0.041 Å (*vs.* an experimental value of 0.014 Å). The slight distortion of the porphyrin ring from planarity is towards a S_4 -like symmetry. The larger out-of-plane displacements of carbon atoms correspond to the pyrrole rings, with C26, C27, C32 and C33 being displaced towards the imidazole (maximum of 0.091 Å for C33) and C28, C29, C30 and C31 being displaced towards the dioxygen (maximum of 0.087 Å for C30). The distortion from planarity is, however, different from that observed in the experimental structure, where the larger out-of-plane displacements correspond to the methylene carbons C7, C10, C21, C24. The origin of this discrepancy is not clear.

As far as the orientation of the pivalamide substituents is concerned, the computed dihedral angles $C_{\text{porph}}-C_{\text{porph}}-C_{\text{piv}}-C_{\text{piv}}$ are between 53.5° and 64.1°, to be compared with experimental values between 77.9° and 83.2°. The picket-fence groups are therefore *ca.* 25° further from the perpendicular direction to the heme plane in the calculation, although this does not seem to have a significant effect on the binding of the ligands to the metal center.

Role of the Picket-Fence Groups in the Binding of Dioxygen

For reasons that are still unclear, picket-fence porphyrins are unique in providing the only known examples of X-ray structures of oxygenated heme complexes with imidazole ligands. There is evidence that sterically unhindered iron(II) hemes are oxidized rapidly and irreversibly in the presence of dioxygen, through a mechanism involving a μ -peroxo- Fe^{III} dimer intermediate.⁴² Whether this kinetic effect has a thermodynamic counterpart is not so clear. In this section, this question is analyzed in terms of the comparison between $\text{Fe}(\text{T}_{\text{piv}}\text{PP})(1\text{-MeIm})(\text{O}_2)$ and $\text{Fe}(\text{P})(1\text{-MeIm})(\text{O}_2)$ (**2**), a hypothetical system containing a naked “picket-fenceless” porphyrin ligand, where the pivalamidophenyl groups are replaced by hydrogen atoms.

From a geometrical point of view, the optimized structures of **1** and **2** (Table 1) are essentially identical. The iron atom appears to be slightly more displaced towards dioxygen ($\text{Fe1}-\text{O12}$ is 0.005 Å shorter) and away from imidazole ($\text{Fe1}-\text{N14}$ is 0.017 Å longer) in the case of **2**, but the differences in bond distances are always smaller than 0.02 Å. Other geometrical parameters are also very similar, therefore suggesting a purely kinetical origin for the stability of **1**. This preliminary conclusion is, however, proved to be false by the calculation of binding energies.

In order to compute binding energies, additional calculations are carried out on the corresponding pentacoordinated complexes $\text{Fe}(\text{T}_{\text{piv}}\text{PP})(1\text{-MeIm})$ (**3**) and $\text{Fe}(\text{P})(1\text{-MeIm})$ (**4**) and on free oxygen. **3** and **4** are computed as quintuplets and dioxygen as a triplet within the unrestricted DFT (UDFT) formalism for the *ab initio* part. Optimized geometrical parameters are also included in Table 2. There are no X-ray data available for **3** and **4**, so the experimental comparison can be made only with the general trends observed in other pentacoordinated heme complexes. The most remarkable geometrical difference between the hexacoordinated **1**, **2** and the pentacoordinated **3**, **4** complexes is the out-of-plane displacement of the iron atom towards the imidazole ligand in the latter (0.300 Å for **3**, 0.395 Å for **4**), in agreement with experimental trends. The $\text{Fe}-\text{N}_{\text{porphyrin}}$ distances are longer in the pentacoordinated species by 0.05–0.08 Å, as expected for the change from the low-spin hexacoordinated complex to the high-spin pentacoordinated species. A lengthening of the $\text{Fe}-\text{N}_{\text{imidazole}}$ distance is also usual in these species, although the increase of 0.09–0.14 Å seems excessive. The validity of the QM modellization chosen for imidazole as $\text{NH}=\text{CH}_2$ seems arguable.

Differences in the binding energies of dioxygen to **1** and **2**,

Table 2 Decomposition of the formation energy (kcal mol^{-1}) of **1** and **2** from **3** + O_2 and **4** + O_2

	1	2
Total	+6.1	+10.9
QM	+11.2	+11.5
MM	−5.1	−0.6
vdW (O_2)	−4.2	−0.6

as well as their decomposition in different terms (Table 2), are very informative. While a higher and currently unaffordable computational level would probably correct the unexpected positive value for the binding energy (that is, favoring dissociation), the difference between the behavior of **1** and **2** would likely be conserved. This difference is clearly in favor of **1**, with a binding energy 4.8 kcal mol^{-1} stronger (6.1 *vs.* 10.9). The binding of dioxygen is therefore actually enhanced by the presence of the picket-fence substituents in the porphyrin. The decomposition of the interaction energy into QM (11.2 *vs.* 11.5 kcal mol^{-1}) and MM (−5.1 *vs.* −0.6 kcal mol^{-1}) contributions confirms that most of the difference is in the MM part; this is precisely where the picket-fence groups are introduced; a further decomposition shows the prominence of van der Waals (vdW) interactions (−4.2 out of 5.1 kcal mol^{-1} for **1**) involving the two oxygen atoms of the dioxygen ligand.

In particular, the largest single contribution (−2.67 kcal mol^{-1}) is presented in Fig. 3, corresponding to the interaction between the terminal oxygen O13 and an amidic hydrogen atom of one of the picket-fence groups. The $\text{O}\cdots\text{H}$ distance is 2.261 Å and the corresponding $\text{O}\cdots\text{N}(\text{H})$ distance is 3.295 Å. This result agrees with the experimental observation of a decrease in O_2 affinity associated with the replacement of the amide groups by esters,⁴³ and disagrees with the suggestion of an important role for the interaction between dioxygen and the methyl groups of the pivalamido pickets.⁴⁴ Interestingly, the main argument against an $\text{O}\cdots\text{H}$ interaction comes from the large distance in the X-ray structure between the O and N atoms. These calculations call into serious question the validity of this reasoning, because in the computed structure there is a sizable tilt of the corresponding pivalamide group towards the dioxygen binding site. This tilt can be measured through the $\text{O12}-\text{N}_{\text{amide}}$ distance, which has a value of 4.494 Å for the interacting pivalamide and values of 4.900, 5.004 and

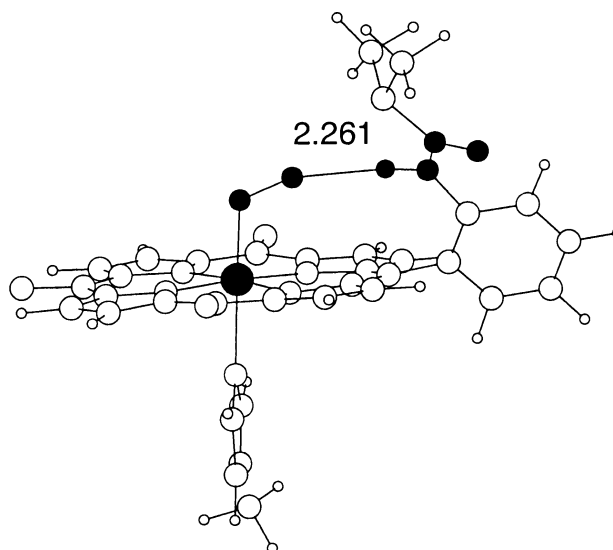


Fig. 3 Dominant van der Waals interaction between oxygen and one of the pivalamide groups. Only some of the atoms in the molecule are shown and the $\text{Fe}-\text{O}-\text{O}\cdots\text{H}-\text{N}-\text{C}=\text{O}$ group is highlighted in bold for clarity

5.230 Å for the three other groups. The corresponding values for the X-ray structure are much more symmetrical, between 4.998 and 5.061 Å, as a result of the averaging introduced by the delocalization of O23 in the crystal. The similarity of this interaction with the observed N(H)···O interactions in hemoglobin is certainly striking,⁴⁵ and hints at a closer relationship between the bioinorganic model **1** and the biological system than previously suspected.

In summary, recognizing the possible inaccuracy of the MM3 quantification of this interaction, the energy decomposition just presented strongly suggests that there is an intramolecular energy stabilization associated with the long-range interaction between the dioxygen and the picket-fence groups accounting for a stabilization energy as large as 4.8 kcal mol⁻¹. On the other hand, the similarity between the optimized geometries for **1** and **2** proves that this interaction is not responsible for the bending of dioxygen or for the orientation of the Fe—O—O plane in **1**.

Conclusions

The geometry optimization with the IMOMM(B3LYP:MM3) method of the Fe(T_{piv}PP)(1-MeIm)(O₂) complex provides results in good agreement with the experimental X-ray geometry. Dioxygen is well-described as an η¹ bent ligand and the computed value (1.279 Å) for the O—O distance is more reasonable than the experimental estimation (1.16 Å). Comparison of the Fe(T_{piv}PP)(1-MeIm)(O₂) system with the hypothetical Fe(P)(1-MeIm)(O₂) system deprived of the picket-fence groups allows a better understanding of the coordination of dioxygen in these species. Changes in geometry are found to be very small, showing that the orientation of the Fe—O—O and Fe—imidazole planes is not determined by the presence of the picket-fence groups. On the other hand, the analysis of the energetics indicates that the picket-fence groups do stabilize, by 4.8 kcal mol⁻¹, the coordination of dioxygen through an O···H(N) interaction. This interaction is not apparent in the crystal structure because of the statistical disorder in the location of the dioxygen ligand. The success of the IMOMM method in the study of this particular complex opens a promising future for its application to other systems containing heme groups.

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