A Molecular Mechanics Model of the Metalloporphyrins: the Role of Steric Hindrance in Discrimination in Favour of Dioxygen Relative to Carbon Monoxide in some Haem Models

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A Molecular Mechanics (M.M.) model of complexes of P^{V}, Ni^{II}, Fe^{II}, Zn^{II}, and Pb^{II} with porphyrins is discussed, which predicts with considerable accuracy the bond lengths and angles, and the extent of S_4 ruffling of the porphyrin core as the metal ions are changed; the model suggests that there is a considerable steric contribution to the depression of carbon monoxide relative to dioxygen loading onto capped Fe^{II} porphyrins.

The mechanisms whereby a variety of metalloenzymes operate involve suggested steric components, which should make them ideally suited for investigation using molecular mechanics (M.M.) techniques. Examples amongst the metalloporphyrins are the prevention of irreversible oxidation of Fe^{II} in haems leading to formation of an oxide-bridged dimer,[1,2] Perutz's co-operativity model for controlling dioxygen loading in haemoglobin,[3] and the depression of carbon monoxide binding relative to dioxygen binding in haemoglobin and myoglobin.[4] Steric effects are also thought to be important in the enzymatic reactions which require vitamin B_{12} derivatives as cofactors.[5]

A suitable starting point for an M.M. investigation of steric effects in metalloporphyrins would be the depression of carbon monoxide relative to dioxygen loading in model compounds such as the capped Fe^{II} porphyrins.[6,7] It has been proposed[7,8,9] that linearly co-ordinated CO requires more space to co-ordinate to the Fe atom than does O_2, which is co-ordinated in a bent fashion; hence with the cap in place above the co-ordination site,[6,7] binding of CO is depressed more severely. Conversely, polar solvents favour loading of the more polar O_2 molecule,[6] and it has been proposed that the fact that the pyridine-containing cap of (a) in Figure 1 produces strong depression of CO, whereas the non-polar anthracene cap of (b) does not, is due to the polar nature of the pyridine cap.

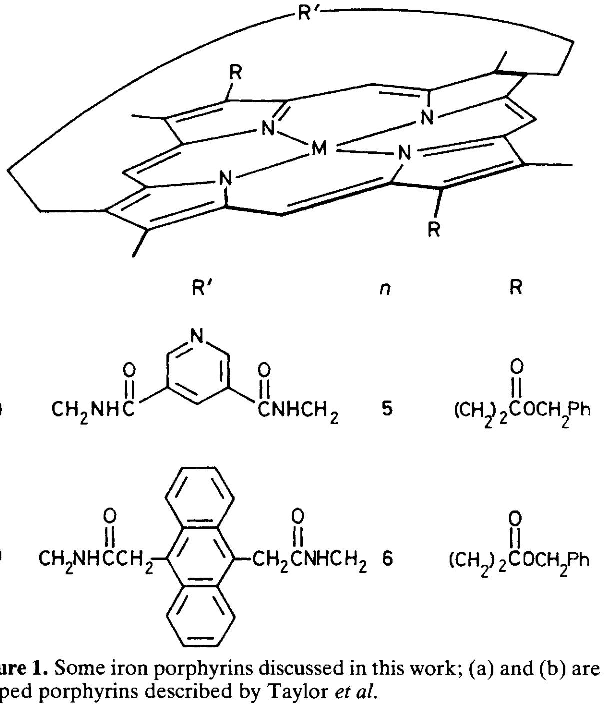

Figure 1. Some iron porphyrins discussed in this work; (a) and (b) are capped porphyrins described by Taylor *et al.*

In constructing an M.M. model of metalloporphyrins, it was assumed initially that it would be appropriate to treat the porphyrin ring as an aromatic ring, and that bond length and bond angle deformation constants, non-bonded interaction parameters, as well as torsional parameters and out-of-plane parameters for aromatic rings, would apply. Use of the parameters from the M.M.2 force field[10] produced a very good agreement with the observed bond lengths and angles, as seen in Figure 2 and Table 1. The bonds between the metal ions and the porphyrin were modelled using constants for other M–N bonds,[11,12] and adjusted by fitting the calculated to the observed structures for P^{V}, Ni^{II} ($S = 0$), Fe^{II}, Zn^{II}, and Pb^{II}; selected parameters are shown in Table 2. The bond angles and lengths for the co-ordinated oxygen and carbon monoxide molecules were taken from crystal structures.[13,14] To simplify the calculations, substituents on the porphyrin ring were omitted; the calculations were carried out using the programmes ALCHEMY (Tripos Associates, St. Louis, Miss.) and MOLBLD.[15]

One of the most important features of the metalloporphyrins to reproduce accurately is the S_4 ruffling,[16] whereby the ring undergoes progressively larger buckling to a saddle-like shape as the size of the metal ion decreases. The porphyrin ring is surprisingly flexible, and the extent of such ruffling may lead to important steric effects in metalloporphyrin chemistry. The metalloporphyrins studied here show a range of M—N bond lengths from very short P^{V} to very long Pb^{II}, with different amounts of ruffling. It was found necessary to adjust the torsional constants involving the ring atoms in order to reproduce (Figure 2) the ruffling accurately, as will be detailed in a future publication.

Figure 3 shows the energy-minimised pyridine capped Fe^{II} porphyrin with (a) co-ordinated O_2 and (b) co-ordinated CO. The porphyrin ring is clearly buckled by the pyridine cap,

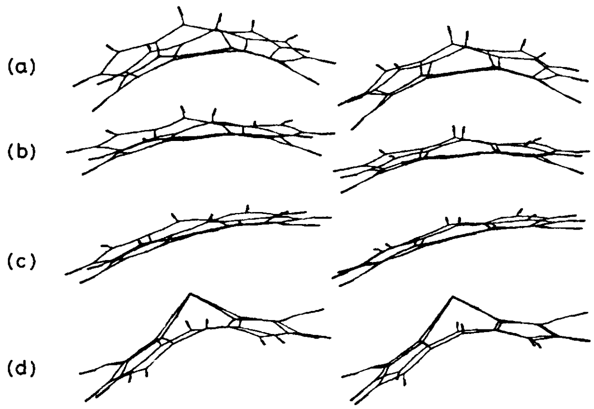

Figure 2. Stereo views of energy-minimised metalloporphyrins as calculated by the force field described in this work. (a) P^{V}; (b) Ni^{II} ($S = 0$); (c) Zn^{II}; (d) Pb^{II}.

Table 1. Selected structural parameters calculated by M.M. and observed in crystal structures of metalloporphyrins. (Bond lengths in Å; bond angles in degrees; for numbering see Figure 4.)

	P^V		Ni^{II}		Zn^{II}		Pb^{II}	
Metal ion	Calc.	Obs.[17]	Calc.	Obs.[18]	Calc.	Obs.[19]	Calc.	Obs.[20]
Bond lengths								
M–N	1.86	1.86	1.93	1.92	2.00	2.03	2.37	2.37
N–Ca$_1$	1.38	1.38	1.38	1.38	1.38	1.38	1.38	1.38
Ca–Cm	1.39	1.39	1.39	1.39	1.39	1.39	1.39	1.39
Bond angles								
N(1)MN(2)	90.0	91.2	90.0	90.2	90.4	89.9	76.8	75.3
Ca(1)N(1)Ca(2)	106.7	106.9	105.0	105.7	107.1	106.5	105.7	105.8
N(1)Ca(2)Cm	124.9	124.7	125.2	124.7	126.2	126.0	125.2	125.6
Ca(2)CmCa(1)′	118.4	118.4	120.9	120.3	123.7	124.4	121.9	123.2
Torsional angles								
MN(1)Ca(2)Cm	12.8	8.4	0.0	0.0	5.8	7.2	8.8	10.9
MN(1)Ca(2)Cb	176.9	180.0	178.4	180.0	177.2	170.3	173.5	169.7
N(2)MN(1)Ca	27.3	27.0	13.2	16.6	10.0	5.3	34.0	26.6
Ca(2)Cb(2)Cb(1)Ca(1)	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0
Cb(2)Ca(2)CmCa(1)′	153.3	150.4	161.4	158.1	165.2	172.2	140.0	139.0

Table 2. Selected force field parameters involving metal ions.

(a) Metal–nitrogen bond lengths

Metal	Force constant /kcal mol^{-1} Å^{-1}	Bond length /Å
P^V	600	1.840
Ni^{II} ($S = 0$)	288	1.900
Fe^{II}	288	1.960
Zn^{II}	216	2.040
Pb^{II}	72	2.400

(b) Nitrogen–metal–nitrogen bond angles

Metal	Force constant/ kcal mol^{-1} deg^{-1}	Bond angle[b]/ deg.
P^V	0.002	90
Ni^{II} ($S = 0$)	0.010	90
Fe^{II}	0.010	90
Zn^{II}	0.008	90
Pb	0.002	70
	0.002	130

[a] 1 cal = 4.184 J. [b] Unless otherwise specified, identical force constant used for *trans* N–M–N bond angle (180°).

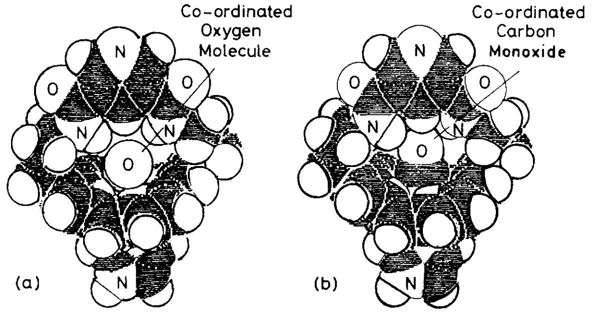

Figure 3. Space-filling drawing of the energy-minimised cyclophane–haem compounds of Traylor *et al.* with dioxygen co-ordinated to the iron (a) and with carbon monoxide co-ordinated to the iron (b). The drawings clearly show the greater space above co-ordinated O_2, corresponding to the lower strain energy induced in the metalloporphyrin as discussed.

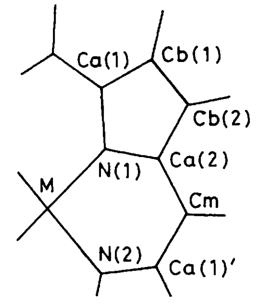

Figure 4

leaving sufficient space for O_2, but not for CO. Although the strain in the different molecules cannot be compared directly, the strain in the capped porphyrins can be compared once the CO or O_2 is removed after energy minimisation. It was found that the strain in the CO-containing porphyrin was 17 kJ mol^{-1} higher than in the O_2-containing porphyrin (after removal of CO and O_2, respectively). As is seen in Figure 3, the pyridine part of the cap is oriented away from the co-ordination site on iron, and so seems unlikely to affect the environment of the co-ordinated ligand by virtue of the polar nature of the pyridine nitrogen atom. In contrast, the M.M. calculations showed that the anthracene-type cap (Figure 1b) allows sufficient room for co-ordination of CO as well as O_2. It is thus suggested that the reason (a) in Figure 1 shows good depression of CO loading is not because of the polar nature of the pyridine cap, but because the strap in (a) is shorter than that in (b). Calculations on Momenteau's porphyrins with alkane straps of varying length showed results in accord with those observed experimentally,[7] *viz.*, with shorter straps the depression of CO relative to O_2 is large. With a six-methylene group strap, CO-co-ordination gave a complex 5.0 kJ mol^{-1} higher in energy than the corresponding O_2 complex; an increase in strap length to eight and ten methylene groups caused this energy difference to drop to 2.5 and 0.7 kJ mol^{-1}, respectively.

These calculations demonstrate the potential usefulness of M.M. calculations in understanding the operation of metalloenzymes. We are currently attempting to model the suppression of irreversible oxidation by steric effects as in the 'picket-fence' porphyrins, and ultimately hope to investigate the interaction of haem itself with the proteins, and the co-operative effects in haemoglobin.

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