Linear Free Energy Relationships in CO, and H_2O binding to Various Amino Acid 'Bis-handle' Porphyrins

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Water and carbon monoxide binding to 'bis-ansa' porphyrins have been investigated and the possibility of linear free energy relationships connecting this series with amino acid 'basket-handle' porphyrins is discussed.

Various iron(II) 'bis-handle' porphyrins incorporating amino acids in their handles have been recently synthesized in order to investigate the influence upon ligand binding of steric hindrance and polarity in the vicinity of the haem.[1,2] A previous study of CO binding to basket-handle porphyrins containing an internal chelated imidazole as a proximal base and phenylalanine or valine in their distal handle has revealed incidentally the unusual co-ordination of water as a sixth ligand in the distal cavity.[3] The aquo-complex is stabilized by hydrogen bonds with the amino acid residue(s) of the distal handle. The kinetic rate constants for water binding and dissociation were determined. In the present work, we have studied the binding of CO and H_2O with a different new class of sterically constrained haem models, the bis-ansa porphyrins (**1**) and (**2**). In this series the proximal base is a constrained pyridine and the distal handle also contains four peptidic bonds. The comparison of the kinetic data shows that both classes of haem-models form a homogeneous family with respect to water and presumably CO binding and display well specific linear free energy relationships.

The bimolecular combination rate constants k^+_{CO} and $k^+_{H_2O}$ and the first-order dissociation rate $k^-_{H_2O}$ were obtained from the kinetics of equilibrium relaxation following laser photodissociation of toluene solutions of the respective carboxyhaemochromes (*i.e.* base–Fe^{II} porphyrin–CO complexes) in the presence of determined amounts of water using the apparatus and methods described elsewhere.[3,4] Oxygen and carbon monoxide affinities were obtained by photometric titration. The O_2 adduct of compound (**2**) was stable in toluene for several days; a value $P^{1/2}_{O_2}$ = 21 Torr could be determined. In contrast, (**1**) gave fast autoxidation. The k^-_{CO} and K_{H_2O} were respectively calculated as k^+_{CO}/K_{CO} and $k^+_{H_2O}/k^+_{H_2O}$. Attempts to measure oxygen binding constants failed as well as CO binding to (**2**). Ligand exchange experiments including more than two species often lead to very complicated kinetics which cannot be safely interpreted. We therefore give only the results obtained when clean exchange kinetics could be unambiguously observed, in particular at isosbestic wavelengths. The data are listed in Table 1 and the values for some other representative haem models are also given for comparison.[5—9] A previous study including up to fifteen different haem models has shown that comparisons of randomly selected compounds may be misleading. Linear free energy relationships (LFER) provide a much more objective means for comparing the reactivity of whole series of related molecules.[4] In Figure 1 we have plotted ln k^+ and ln k^- *vs.* ln K for water and for CO binding to amino acid 'bis-handle' porphyrins. In spite of the small number of data, Figure 1 suggests that these compounds might behave as one reactive family.

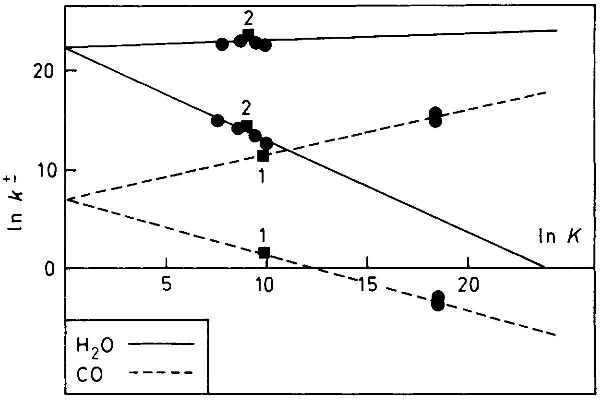
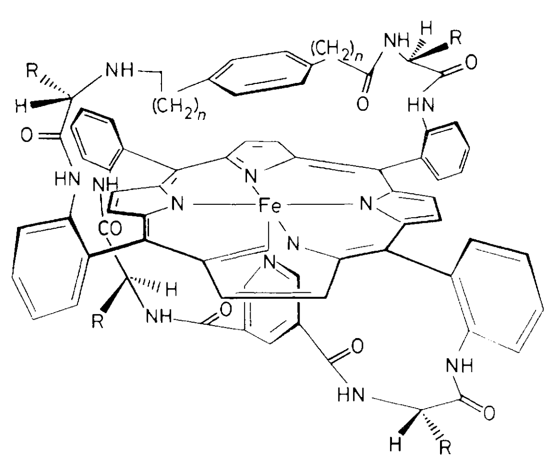


Figure 1. Linear free energy relationships between rate and equilibrium constants for binding of CO and H_2O with 'bis-handle' porphyrins in toluene (this work and ref. 3). The existence of regression lines means that the 'on' and 'off' rate constants can be respectively expressed as $\ln k^+ = \ln k_0 + \alpha \ln K$ and $\ln k^- = \ln k_0 - (1-\alpha) \ln K$, where K is the equilibrium constant, ln k_0 the common intercept and α the LFER parameter. The models entering the correlation are bis-ansa porphyrins (■) and amino acid basket-handle porphyrins of ref. 3 (●). Least-square fits; $k^+_{H_2O}$: slope = 0.04±0.07, intercept = 22.37±0.63, correlation coefficient r = 0.12; $k^-_{H_2O}$: slope = −0.96±0.06, intercept = 22.38±0.58, r = −0.94; k^+_{CO}; slope = 0.42±0.01, intercept = 7.00±0.08, r = 0.99; k^-_{CO}: slope = −0.58±0.01, intercept = 6.98±0.08, r = 0.99.

The changes in K_{H_2O} are entirely due to the 'off' rates. The LFER parameter is very nearly $\alpha \approx 0$, meaning that the transition state is purely reactant-like. This conclusion is in agreement with the high value of the 'on' rate for water in toluene, which is close to a diffusion-controlled rate. Differences among compounds are then only seen in the dissociation



(**1**) R = Me, n = 0: pyridine co-ordinates only in the presence of CO
(**2**) R = Me, n = 1: pyridine co-ordinates in the absence of CO

Table 1. Rate and equilibrium constants for CO and H_2O binding to bis-ansa porphyrins (**1**), (**2**), and other haem models, at 20 °C.

Compound	$10^{-7}\,k^{+}_{CO}$ /mol^{-1} l s^{-1}	$10^{3}\,k^{-}_{CO}$ /s^{-1}	$P^{CO}_{1/2}$ /Torr	$10^{-9}\,k^{+}_{H_2O}$ /mol^{-1} l s^{-1}	$10^{-6}\,k^{-}_{H_2O}$ /s^{-1}	$10^{-3}\,K_{H_2O}$ mol^{-1} l	Ref.
(**1**)[a]	0.007	3500	5.5	—	—	—	This work
(**2**)[a]	—	—	0.2	12.0	1.3	9.0	This work
a(BHP) (Val-C_8)(C_9-Im)[a,c]	0.3	2.7	9.6×10^{-4}	9.0	1.2	7.5	3
a(BHP) (C_{12})(C_9-Im)[a]	4.0	6.7	1.7×10^{-5}	—	—	—	4
7,7-Anthracene-cyclophane haem-DCIm[b,c]	0.6	50	9×10^{-4}	—	—	—	5
6,6-Anthracene-cyclophane haem-DCIm[b]	0.003	50	1.7×10^{-1}	—	—	—	5
5,5-Pyridine-cyclophane haem-DCIm[b]	0.00006	240	37	—	—	—	5
Poc Piv-1 MeIm[a,c]	0.058	8.6	1.5×10^{-3}	—	—	—	6
Med Poc Piv-1 MeIm[a,c]	0.15	9.4	6.5×10^{-4}	—	—	—	6
Piv_2-C_8-1 MeIm[b,c]	0.008	8.0	1×10^{-2}	—	—	—	7
FeSP-13-1 MeIm[b,c]	0.00006	70	12	—	—	—	8
Fe(C_2cap) (1 MeIm)[a,c]	—	—	5.4×10^{-3}	—	—	—	9

[a] Toluene. [b] Benzene. [c] a(BHP) = amide 'basket-handle' porphyrins (see refs. 3 and 4); DCIm = 1,5-dicyclohexylimidazole; Poc Piv = 'small pocket' porphyrin (see ref. 6); Med Poc = 'medium pocket' porphyrin (see ref. 6); Piv_2C_8 = 'hybrid' model with two pivalamido 'pickets' and a handle (see ref. 7); SP = 'strapped' porphyrin (see ref. 8); C_2cap = 'capped' porphyrin (see ref. 9).

rate, depending on the local strength of the stabilizing H-bonds.

Although three haem models were involved in the CO binding curve of Figure 1, only two distinct K_{CO} values are represented, which is obviously insufficient to establish a linear correlation unambiguously. However, the line drawn through the points gives a value $\alpha = 0.42$, which happens to be very close to the value $\alpha = 0.48$ previously reported for ether- and amide-basket-handle porphyrins.[4]

In fact, the main change in the amino acid series is a simple decrease of the ln k_0 value compared to the basket-handle models. The most striking result is the very low affinity of (**1**) for carbon monoxide. One of the purposes of designing new models is to lower their affinity for carbon monoxide in order to reproduce the low values reported for haemoproteins. The ansa-porphyrin (**1**) exhibits the highest CO-dissociation rate ever observed with an Fe^{II} porphyrin. As discussed elsewhere,[4] the LFER values obtained with a large number of models show that a distinction between distal and proximal constraints is not justified from a thermodynamical point of view. Both may contribute to the destabilization of the iron d_{z^2} orbital, therefore directly affecting the kinetic rates and the affinity constant. The case of the ansa-porphyrin (**1**) is quite extreme in this respect since this compound accumulates almost all documented causes of destabilization. In addition to the quite encumbered distal side, compound (**1**) contains a pyridine which is not as good a proximal base as imidazole because of its smaller pK_a. Moreover the base seems severely constrained, as shown by the fact that it co-ordinates to iron only in the presence of CO. Indeed, the optical absorption spectrum of (**1**) is typical for a four-co-ordinated iron(II) porphyrin and shows no sign of spontaneous penta-co-ordination, contrary to all other haem models incorporating an internally chelated base. In the laser-photolysis experiments, the ligand rebinds to the penta-co-ordinated species which is generated immediately after photodissociation of the carboxyhaemochrome. Since this species does not exist in the relaxed compound (**1**), rebinding must occur with a highly constrained and energetically destabilized penta-co-ordinated porphyrin. Taken together, all these factors combine to make (**1**) a molecule with a particularly low affinity for CO. Moreover, since water is intrinsically a considerably weaker ligand than CO, the same destabilizing factors may explain why water co-ordination is not observed with (**1**).

Work is in progress in order to confirm the suggested L.F.E.R. values with other related haem models.

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