Kinetic Evidence for Dioxygen Stabilization in Oxygenated Iron(II)-Porphyrins by Distal Polar Interactions

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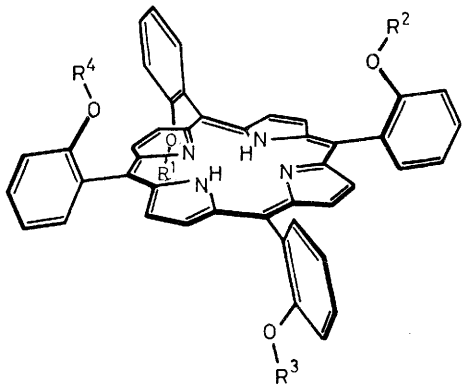
The newly synthesized iron(II) 'hanging base' porphyrins (**8**) and (**9**) provide evidence that polar groups on the distal side of the heme strongly increase the stability of the oxygenated complexes by reducing the rate constant for dissociation of dioxygen.

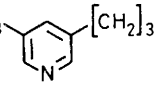
Synthetic heme models for oxygen binding should meet at least three requirements: (i) co-ordination of the iron(II) ion by a base on the proximal side; (ii) steric protection of the heme, in order to protect it from irreversible oxidation into μ-oxo-dimers; (iii) control of the O_2 environment on the distal side. Several groups have investigated these three problems separately.[1-4] Independently of Battersby and his co-workers,[5] we have developed a series of heme models protected on both faces, the so-called 'basket handle' porphyrins,[6] which can simultaneously satisfy these three criteria. Pentaco-ordination can be achieved by inserting the proximal base into one of the 'handles,' while the size and polarity of the cage on the distal side can be modified to some extent by suitable changes of the chemical nature of

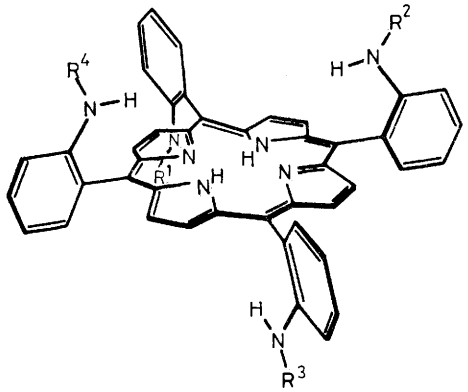


(1) $R^1=R^2=R^3=R^4=H$

(2) R^1, $R^3=[CH_2]_{12}$, $R^2=R^4=H$

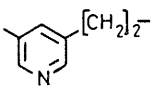
(3) R^1, $R^2=[CH_2]_{12}$, $R^3=R^4=H$

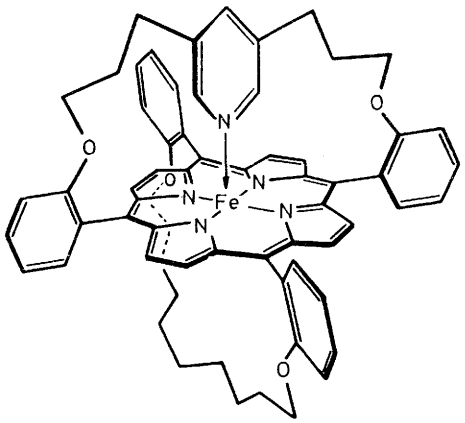
(4) R^1, $R^3=[CH_2]_{12}$, R^2, $R^4=[CH_2]_3$  $[CH_2]_3$



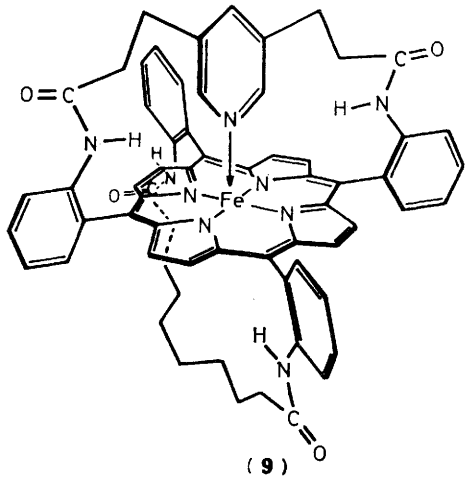
(5) $R^1=R^2=R^3=R^4=H$

(6) R^1, $R^3=CO-[CH_2]_{10}-CO$, $R^2=R^4=H$

(7) R^1, $R^3=CO-[CH_2]_{10}-CO$, R^2, $R^4=CO-[CH_2]_2$  $[CH_2]_2-CO$



(8)



(9)

the second 'handle.' We report a comparative preliminary study of the kinetics of oxygen binding on to the two newly synthesized 'hanging base' porphyrins (**8**) and (**9**), which indicates that the stability of dioxygen can be greatly affected by distal side interactions.

Compound (**4**), which includes a distal handle with no polar groups, was synthesized in two steps following the procedure developed for the 'basket handle' porphyrins.[6] Coupling of 5,10,15,20-tetra(*o*-hydroxyphenyl)porphyrin (**1**) (mixture of four atropisomers) with 1,12-dibromododecane and chromatography of the crude compounds gave a mixture of the two singly-bridged porphyrins (**2**) and (**3**) which were not separated (64%). These compounds reacted with 3,5-[bis-(3-bromopropyl)]pyridine to give the desired cross-*trans*-linked isomer (**4**) after t.l.c. on silica gel [5% overall from (**1**)].

Compound (**6**), which includes a distal handle with two amide linkages, was prepared from 5,10,15,20-tetra(*o*-aminophenyl)porphyrin (**5**) ($\alpha,\beta,\alpha,\beta$-atropisomer). Treatment of (**5**) with decane-1,10-dicarbonyl chloride in tetrahydrofuran at room temperature in the presence of triethylamine (2 equiv.) resulted in the formation of (**6**) (33%). The cross-*trans*-linked porphyrin (**7**) was then prepared from (**6**) with 3,5-[bis-(2-chloroformyl)ethyl]pyridine following the same procedure in 42% yield. All porphyrins were characterized by absorption and n.m.r. spectroscopy as well as by elemental analysis.

Insertion of iron into the 'hanging base' porphyrins (**4**) and (**7**) was accomplished by using the iron(II) chloride method under reflux in dimethylformamide and 2-methyltetrahydrofuran respectively. Hemins were reduced by aqueous sodium dithionite under argon. The visible and ^1H n.m.r. spectra of (**8**) and (**9**) in toluene at room temperature were characteristic of pentaco-ordinated high-spin complexes.[7] The kinetics of the reactions with CO and O_2 were measured in toluene by laser flash photolysis using our modified exchange-rate law[8] (Table 1).

The distal cage has the same size in both compounds, though the shape of the cage could be slightly different owing to the presence of the more rigid amide links in (**9**). This corresponds to rate constants for binding of O_2 [$k_{on}(O_2)$] and CO [$k_{on}(CO)$] which are of the same order of magnitude for (**8**) and (**9**). However, the compounds bind CO and O_2 with higher rates than the unprotected pentaco-ordinated hemes deuteroporphyrin(pyridine)iron(II) and tetraphenylporphyrin(pyridine)iron(II).[8] As no evidence could be found for a base elimination pathway,[9,10] one may assign the higher rates to the difference in the attachment of the proximal base.

The most interesting observation is that the large difference in the oxygen affinity of the models (**8**) and (**9**) results

Table 1. CO and O_2 binding rate parameters for heme models in toluene (20 °C).

	$10^{-6}\,k_{on}(CO)$/l mol^{-1} s^{-1}	$10^{-7}\,k_{on}(O_2)$/l mol^{-1} s^{-1}	$10^{-4}\,k_{off}(O_2)$/s^{-1}	$10^{-3}\,K_{eq}(O_2)$/l mol^{-1}	$P_{1/2}(O_2)$/torr
(8)	68	30	4	7.5	18.6
(9)	35	36	0.5	70	2
Fe^{II}–TPP–Py[a]	6.5	10	10	1.1	127
Fe^{II}–Deut–Py[a]	12	20	7.5	2.5	54

[a] From ref. 8; Py = pyridine; TPP = tetraphenylporphyrin; Deut = deuteroporphyrin.

exclusively from a difference, by a factor of *ca.* 10, in the O_2 dissociation rates [$k_{off}(O_2)$]. Thus the presence of the NH (or amide) groups in (**9**) strongly increases the intrinsic stability of the oxygenated derivatives.

We had already been struck by the fact that different model compounds recently prepared by Collman *et al.*,[11] Traylor *et al.*,[12] and Chang *et al.*[13] had a larger affinity for oxygen in non-polar solvents than compound (**8**). All these models happen to contain NH groups in the distal protecting chains, but the importance of these groups was not clearly and directly estimated. A crystal-structure determination of a picket fence porphyrin does not favour a direct interaction of the amide proton with bound oxygen.[14] ^{1}H N.m.r. studies of the free base derivatives of compounds (**8**) and (**9**) clearly indicate that the proton still points toward the centre of the porphyrin, probably at a shorter distance than in a picket fence porphyrin. Whether this stabilizing effect is static or dynamic requires further investigation. Whatever its nature, it should be considered in parallel with the thermodynamics and kinetics of oxygen binding by heme proteins.[15]

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