High affinity of 'arbor' iron porphyrins for dioxygen†

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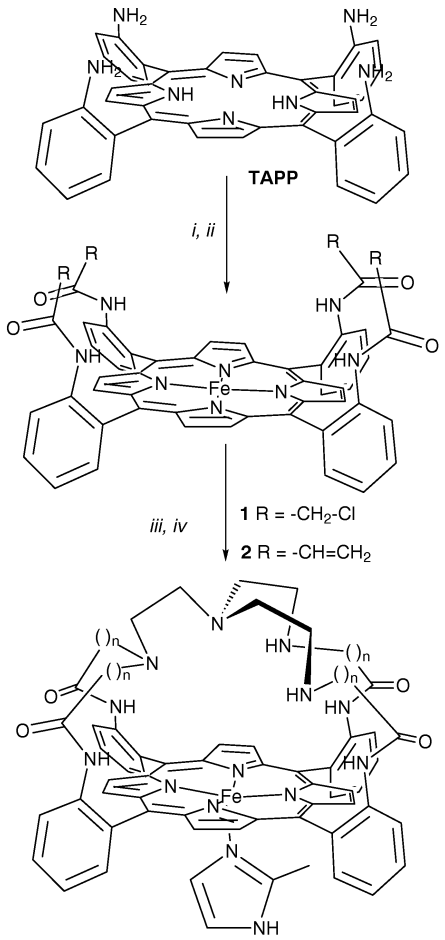
The equilibrium rates of dioxygen and carbon monoxide binding have been measured for a series of capped iron porphyrins called 'arbor'. The affinity for dioxygen of these models is 100-fold higher than the highest previously reported values.

In order to define the different structural features that could be involved in the binding and discrimination of gaseous molecules such as CO or O_2, different types of dioxygen-binding heme models have been described over the past two decades.[1] This biomimetic approach first allowed the design and synthesis of molecules possessing some properties of the protein surrounding the natural heme and mainly the reversibility of the molecular oxygen coordination.[2] Stability of the oxygenated complex and discrimination of the carbon monoxide coordination are also two significant factors. It is now well-established that the same distal histidine residue is responsible for both stabilization of O_2 *via* a hydrogen bond and destabilization of CO. Momenteau and coworkers were the first to report the existence of such a hydrogen bond[3] involving the NH amide group located on a lateral position of the model. More recently, Reed and coworkers described picket-fence-derived models possessing a potential H-bonding group in a more apical[4] position than the usual amide group linked to the *meso* aromatic group of the porphyrin.

Herein, we report a preliminary study of O_2 and CO coordination with TREN [tris(2-aminoethylamine)]-capped porphyrins, named 'arbor'. These two different porphyrins have exactly the same distal superstructure tethered at two different distances by four linkers.[5] For such models, two secondary amines are eventually able to engage a H bond with the dioxygen bound in the distal cage created by the TREN moiety. The synthesis of the iron(II) five-coordinate complexes is depicted in Scheme 1. The atropisomer αααα of the *meso*-(tetra-*o*-aminophenyl)porphyrin is functionalized by either chloroacetyl chloride or acryloyl chloride leading, respectively, to the picket porphyrins **1** or **2**. Then, iron insertion is carried out by heating the porphyrin in THF with iron bromide and 2,6-lutidine.‡ The TREN molecule is grafted at 55 °C in MeOH for 14 h, after which an excess of nitrogenous base is added to stabilize the iron(II) as a five-coordinate complex. For this purpose, we chose 2-methylimidazole.[6] The NMR spectrum of **4** in pyridine-d_5 clearly shows that the solvent cannot coordinate inside the distal pocket, hence the observation of a five-coordinate complex with typically downfield-shifted signals.§ Gas binding studies were performed by adding increasing quantities of diluted dioxygen in nitrogen to a solution of the five-coordinate species (λ_{max} = 444 nm) in a known-volume tonometer,[7] the reversibility of the binding being monitored before and after the measure. Indeed, nitrogen bubbling in the tonometer leads to the starting five-coordinate material.



Scheme 1 Reagents and conditions: (*i*) chloroacetyl chloride or acryloyl chloride in dry THF–NEt_3; (*ii*) $FeBr_2$–THF–2,6-lutidine under nitrogen; (*iii*) TREN in THF or MeOH at 55 °C; (*iv*) 1000 equiv. 2-methylimidazole.

† Non-SI units employed: 1 Torr ≈ 133 Pa.

‡ To control that no atropisomerization has occurred, the proton NMR spectrum of the iron picket porphyrin **2** was recorded in the coordinating solvent pyridine-d_5, in which the porphyrin yields a diamagnetic six-coordinate complex. As expected for a complex possessing a C_{2v} geometry, the NMR spectrum exhibits two triplets and two doublets corresponding to the *meso* aromatic protons. ^{1}H NMR 500 MHz (pyridine-d_5, 323 K) of **2**(Pyd5)$_2$: δ 8.82 (d, J = 7.0 Hz, 4H$_{ar}$); 8.74 (s, 8H, β-pyr.); 8.23 (large s, 4H, —NHCO); 7.98 (d, J = 7.0 Hz, 4H); 7.77 (t, J = 7.5 Hz, 4H$_{ar}$); 7.47 (t, J = 7.5 Hz, 4H$_{ar}$); 5.90 (d, J = 17.0 Hz, 4H, —CH═); 5.17 (m, 4H, ═CH$_2$); 5.06 (m, 4H, ═CH$_2$).

§ The NMR spectrum of **4**(Pyd5) clearly shows four resonances corresponding to the β-pyrrolic protons at 51.07, 48.85, 46.96 and 46.22. HR-MS (LSIMS) *m/z* calcd: 1091.4132 $[M - H]^+$ for $C_{62}H_{59}FeN_{12}O_4$; found: 1091.4160 for **4** without any axial ligand.

Table 1 Selected equilibrium parameters for O_2 and CO binding ($P_{1/2}$ in Torr), in toluene at 25 °C, except for Mb and Hb (H_2O, pH 7, 25 °C)

	$P_{1/2}(O_2)$	$P_{1/2}(CO)$	M	Ref.
Mb	5×10^{-1}	2×10^{-2}	25	8
Hb (human R)	3×10^{-1}	1.4×10^{-3}	170	9
Hb (human T)	40	3×10^{-1}	133	9
Fe(picket-fence)(1,2-DiMeIm)	38	8.9×10^{-3}	4270	10
FeG2(1,2-DiMeIm)	1.6×10^{-2}	1.9×10^{-1}	8×10^{-2}	11
FeTACN(1,2-DiMeIm)	2.3	2.9	8×10^{-1}	12
FeArC2Py	21	2×10^{-1}	105	13
FeSFH-C7(1-MeIm)[a]	3×10^{-2}	3×10^{-4}	100	14
Fe4C2(2-MeIm), **4**	9.8×10^{-5}	3.1×10^{-4}	0.3	This work
Fe4Cl(2-MeIm), **3**[b]	$<10^{-5}$	$<10^{-5}$	—	This work

[a] The complex remains mostly five-coordinate at the concentration of nitrogeneous base used by the authors. [b] To obtain a precise value, higher dilutions than 10^5 would have been necessary; this is the reason why only limiting values are reported.

Our results are gathered in Table 1 together with the data observed for natural proteins and the landmark picket-fence model. In this Table are reported both the partial pressure at half-saturation for O_2 and CO binding and the partition coefficient M that characterizes the preference for CO *versus* O_2 binding. It is defined as the ratio of $P_{1/2}(O_2)$ over $P_{1/2}(CO)$, or the ratio of $K_{eq}(CO)$ over $K_{eq}(O_2)$: the lowest M gives the best discrimination against CO. For example, FeTACN(1,2-DiMeIm) recently reported by Collman *et al.*[12] (Table 1) has the same affinity for O_2 and CO, therefore an M value equal to *ca.* 1. In our case, it is striking that the porphyrin Fe4C2 (2-MeIm), **4**, has an affinity for O_2 100 times greater than the highest affinity already reported for synthetic models such as FeSFH-C7(1-MeIm) or FeG2(1,2-DiMeIm). It is very tempting to explain the very high affinity of our models by a favored distal H-bonding stabilization due to the presence of two secondary apical amines. The slightly better affinity of porphyrin **3** could be explained by a stronger H bond resulting from a shorter distance between the amino group and dioxygen, illustrating that in our models, the effective discrimination comes from stabilization of O_2 (presumably through hydrogen bonding) rather than CO destabilization by steric effects.[15] On the other hand, the observed CO affinity is also very high and quite comparable to the FeSFH-C7 (1-MeIm) of Momenteau *et al.*[14] (see Table 1). It is also worth noting that these two observations are consistent with the pocket shaped by the TREN that is apparently not congested enough to affect significantly the CO affinity in terms of steric effects.

In conclusion, 'arbor' porphyrins are the first models of myoglobin with specific features such as a polar-capped structure, including secondary amines in an almost apical position, as potential H-bonding groups. Our preliminary studies show that these models are both very stable in oxygenated solution and show reversible binding. The two different linkers, employed to graft the TREN, lead to a significant discrimination against CO, the M values being close to 0.1. Further studies are in progress, first to confirm the role of the capping structure and the potential H-bonding secondary amines, and secondly to determine the kinetic rates.

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