Dioxygen and carbon monoxide binding in dendritic iron(ii)porphyrins

James P. Collman,*[a] Lei Fu,[a] Adrien Zingg[b] and François Diederich*[b]

[a] *Department of Chemistry, Stanford University, Stanford, CA 94305, USA*
[b] *Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland*

Equilibrium O_2 and CO binding behaviour of two dendritic iron(II) porphyrin systems is reported.

Tetrameric haemoglobin (Hb) and monomeric myoglobin (Mb) are haem proteins responsible for dioxygen storage and transport in biological systems. In the deoxy forms of both Hb and Mb the haem iron is bound to a single, 'proximal', axial imidazole resulting in a five-coordinate high-spin (S = 2) Fe^{II}; upon oxygenation at the opposite 'distal' face, a diamagnetic $Fe^{III}O_2^-$ complex forms reversibly. The protein superstructure is responsible for the kinetic stabilization of the oxygenated form; amino acid residues on the 'distal' porphyrin face appear to destabilize a competing complex derived from the endogenous toxic CO. Thus the '*M*' value (*i.e.* the ratio of the two equilibrium binding constants K_{CO}/K_{O_2}) for Hb and Mb is about 100, small enough that the body can tolerate low, endogenous levels of CO. The 'picket fence' iron(ii) model† complex also binds O_2 reversibly, exhibiting an O_2 affinity about the same as that of Mb; the polar O_2 binding cavity kinetically stabilizes the intrinsically bent O_2 adduct. In contrast, the linear CO ligand binds very strongly to the 'picket fence' porphyrin; *M* for the T (tense)-state model is 4280.[1] Several subsequent model systems such as 'pocket',[2] 'hybrid',[3] and 'capped'[4] porphyrins effect some distortion of the CO ligand and, as a consequence, *M* is lowered to *ca.* 150; with more hindered cavities, *M* can fall below 1.[5] The detailed interaction between structural distortion and equilibrium affinities of CO remains controversial.[6]

Stabilization of bound O_2 is also poorly understood. A distal histidine residue in Hb and Mb forms a weak [stability *ca.* 2 kcal mol^{-1} (1 cal = 4.184 J)] hydrogen bond to the terminal oxygen in the $Fe^{III}O_2^-$ adduct. There have been some attempts to imitate such a hydrogen bond with model iron(ii) porphyrins.[7] Some haem proteins have an unusually high O_2 affinity; for example in the blood worm *Ascaris*,[8] the O_2 affinity is 10^4-fold higher compared with Hb. One can speculate that a strong hydrogen bond is responsible for this high O_2 affinity.

With the recent surge in dendrimer technology,[9] dendritic porphyrins were prepared as synthetic models of globular haem proteins.[10,11] It was shown for aqueous solutions that, in analogy to the protein surroundings in electron transfer proteins, a densely packed dendritic shell around a deeply buried iron haem profoundly influences the redox potential of the biologically relevant Fe^{III}–Fe^{II} couple.[10*b*] Recently, Jiang and Aida[11*b*] reported a dendritic iron(ii) porphyrin with aryl ether branches which exhibits reversible dioxygen binding. However, in their study, a 1-methylimidazole was used. This ligand is known to form a six-coordinate, low-spin iron(ii) complex. This factor complicates any measure of O_2 affinity.

Herein we report a gas equilibrium binding study with two dendritic iron(ii) porphyrins of first (G1-Fe^{II}, M_r = 3956) and second (G2-Fe^{II}, M_r = 11296) dendritic generation (Fig. 1). These were prepared from the corresponding free-base dendritic porphyrins[10*b*] *via* metallation with $FeBr_2$ in THF in an inert atmosphere box and subsequently purified chromatographically (SiO_2, MeOH–CH_2Cl_2).‡ The dendritic iron(ii) porphyrins were each dissolved in toluene, 1000 mol equiv. of 1,2-dimethylimidazole (dmim) were added to form the five-coordinate, high-spin iron(ii) complex, and the solution was loaded into a tonometer for gas binding studies. The dmim ligand forms only a 1 : 1 high-spin iron(ii) adduct obviating the problem of controlling the number of axial ligands. Furthermore, the resulting iron(ii) porphyrin is a good model for the lower affinity T-state of Hb.[12]

Gas flow: O_2, then N_2, then O_2 UV–VIS experiments showed reversible O_2 binding in toluene solution at 25 °C. Using a tonometer, we measured the O_2 and CO equilibrium binding constants (K_{O_2} and K_{CO})[13] for both dendrimers G1-Fe^{II} and G2-Fe^{II}. These $P_{1/2}(O_2)$ (= $1/K_{O_2}$) and $P_{1/2}(CO)$ (= $1/K_{CO}$) values are displayed in Table 1 compared with those of T-state Hb, the corresponding T-state 'picket fence' model, and of the blood worm *Ascaris.*

It is remarkable that the O_2 affinities [K_{O_2} = $1/P_{1/2}(O_2)$] of the dendritic porphyrins are about 1500 times greater than those of T-state Hb; these values approach the high affinity of *Ascaris* (Table 1). The CO affinities of the dendritic porphyrins are lower than those of the 'picket fence' model but are close to the value of Hb in the T-state. The combination of high O_2 and low

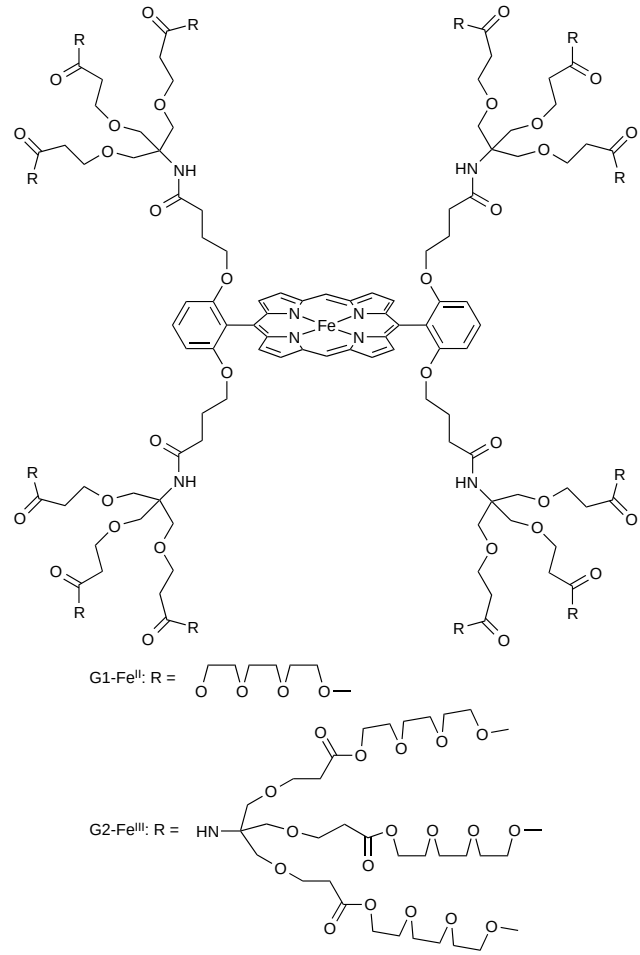

Fig. 1 Dendritic porphyrins G1-Fe^{II} and G2-Fe^{II}

Table 1 Oxygen and carbon monoxide binding data

	$P_{1/2}$/Torr		M $P_{1/2}(O_2)/P_{1/2}(CO)$
	O_2	CO	
Hb (T-state)[a]	40	0.30	135[14]
Fe (picket fence)/dmim[b]	38	0.0089	4280[2b]
Ascaris[c]	0.002	0.1	0.02[8b]
G1-Fe^{II}/dmim[b]	0.035	0.35	0.10
G2-Fe^{II}/dmim[b]	0.016	0.19	0.08

Conditions: [a] H_2O, pH 7, 25 °C. [b] Toluene, 25 °C. [c] H_2O, pH 7, 20 °C. Changing solvent polarity may slightly affect the affinities.[15]

CO affinities yields very low values for *M*. The dendritic *M* values show a trend similar to *Ascaris*.

Why are the O_2 affinities so great? These may result from a hydrogen bond to the amide N–H group. Molecular models suggest that the terminal O of bound O_2 can form such a hydrogen bond with the NH of the amide group linking together the porphyrin core and the first-generation dendritic branches, but more evidence is needed; studies are in progress. The lower CO affinities may be caused by a congested pocket over the CO binding site much like the sterically distorted model complexes mentioned above.

In conclusion, we have studied two dendrimer-based myoglobin T-state models. Each exhibits reversible O_2 and CO binding activities. The measured O_2 affinities are about 1500 times higher than those of a haemoglobin and 'picket fence' porphyrin, implying a possible hydrogen bonding between the terminal O of bound O_2 and an amide N–H group. In terms of CO affinity, the dendritic model systems are more like Hb than uncapped haem (*e.g.* 'picket fence' porphyrin) suggesting that, as with Hb, bound CO experiences a steric interaction that distorts binding from a favourable linear conformation.

Footnotes

† 'Picket fence' porphyrin: *meso*-tetra(α,α,α-*o*-pivalamidophenyl)-porphyrin. For a general reference, see also: L. Stryer, *Biochemistry*, 4th edn., W. H. Freeman and Co., New York, 1955, pp. 152.

‡ UV–VIS spectra in toluene of G1-Fe^{II}: λ_{max} (ε) = 428 nm (4.1×10^5 m^{-1} cm^{-1}); and G2-Fe^{II}: λ_{max} (ε) = 408 nm (2.2×10^{-5} m^{-1} cm^{-1}).

References

1 J. P. Collman, J. I. Brauman, T. R. Halbert and K. S. Suslick, *Proc. Natl. Acad. Sci. USA*, 1976, **73**, 3333; J. P. Collman, R. R. Gagne, T. R. Halbert, J.-C. Marchon and C. A. Reed, *J. Am. Chem. Soc.*, 1973, **95**, 7868; J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lang and W. T. Robinson, *J. Am. Chem. Soc.*, 1975, **97**, 1427.

2 K. Kim, J. Fettinger, J. L. Sessler, M. Cyr, J. Hugdahl, J. P. Collman and J. A. Ibers, *J. Am. Chem. Soc.*, 1989, **111**, 403; J. P. Collman, J. I. Brauman, B. L. Iverson, J. L. Sessler, R. M. Morris and Q. H. Gibson, *J. Am. Chem. Soc.*, 1983, **105**, 3052.

3 C. Tetreau, D. Lavalette, M. Momenteau, J. Fischer and R. Weiss, *J. Am. Chem. Soc.*, 1994, **116**, 11840.

4 C. Slebodnick, M. L. Duval and J. A. Ibers, *Inorg. Chem.*, 1996, **35**, 3607.

5 J. P. Collman, P. C. Herrmann, B. Boitrel, X. Zhang, T. A. Eberspacher and L. Fu, *J. Am. Chem. Soc.*, 1994, **116**, 9783; J. P. Collman, P. C. Herrmann, L. Fu, T. A. Eberspacher, M. Eubanks, B. Boitrel, P. Hayoz, X. Zhang, J. I. Brauman and V. Day, *J. Am. Chem. Soc.*, submitted for publication.

6 T. G. Spiro, *Science*, 1995, **270**, 221; G. B. Ray, X.-Y. Li, J. A. Ibers, J. L. Sessler and T. G. Spiro, *J. Am. Chem. Soc.*, 1994, **116**, 162; M. Lim, T. A. Jackson and P. A. Anfinrud, *Science*, 1995, **269**, 962; T. G. Traylor, N. Koga and L. A. Deardurff, *J. Am. Chem. Soc.*, 1985, **107**, 6504; T. G. Traylor, *Acc. Chem. Res.*, 1981, **14**, 102; B. A. Springer, S. G. Sligar, J. S. Olson and G. N. Phillips Jr., *Chem. Rev.*, 1994, **94**, 699.

7 G. E. Wuenschell, C. Tetreau, D. Lavalette and C. A. Reed, *J. Am. Chem. Soc.*, 1992, **114**, 3346.

8 Q. H. Gibson and M. H. Smith, *Proc. R. Soc. London, Ser. B*, 1965, **163**, 206; T. Okazaki and J. B. Wittenberg, *Biochim. Biophys. Acta*, 1965, **111**, 503; A. P. Kloek, J. Yang, F. S. Mathews and D. E. Goldberg, *J. Biol. Chem.*, 1993, **268**, 17669.

9 G. R. Newkome, C. N. Moorefield and F. Vögtle, *Dendritic Molecules, Concept–Synthesis–Perspectives*, VCH, Weinheim, 1996.

10 (*a*) P. J. Dandliker, F. Diederich, M. Gross, C. B. Knobler, A. Louati and E. M. Sanford, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1739; (*b*) P. J. Dandliker, F. Diederich, J.-P. Gisselbrecht, A. Louati and M. Gross, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2725.

11 (*a*) R.-H. Jin, T. Aida and S. Inoue, *J. Chem. Soc., Chem. Commun.*, 1993, 1260; (*b*) D. L. Jiang and T. Aida, *Chem. Commun.*, 1996, 1523; (*c*) R. Sadamoto, N. Tomioka and T. Aida, *J. Am. Chem. Soc.*, 1996, **118**, 3978; (*d*) Y. Tomoyose, D.-L. Jiang, R.-H. Jin, T. Aida, T. Yamashita, K. Horie, E. Yashima and Y. Okamoto, *Macromolecules*, 1996, **29**, 5236; (*e*) P. Bhyrappa, J. K. Young, J. S. Moore and K. S. Suslick, *J. Am. Chem. Soc.*, 1996, **118**, 5708; (*f*) K. W. Pollak, J. W. Leon and J. M. J. Fréchet, *Polym. Mater. Sci. Eng.*, 1995, **73**, 333.

12 J. P. Collman and C. A. Reed, *J. Am. Chem. Soc.*, 1973, **95**, 2048; M. Momenteau and C. A. Reed, *Chem. Rev.*, 1994, **94**, 659.

13 N. J. Rose and R. S. Drago, *J. Am. Chem. Soc.*, 1959, **81**, 6138; T. J. Beugelsdijk and R. S. Drago, *J. Am. Chem. Soc.*, 1975, **97**, 6466; J. P. Collman, J. I. Brauman and K. S. Suslick, *J. Am. Chem. Soc.*, 1975, **97**, 7185.

14 V. S. Sharma, M. R. Schmidt and H. M. Ranney, *J. Biol. Chem.*, 1976, **251**, 4267; R. C. Steinmeier and L. J. Parkhurst, *Biochemistry*, 1975, **14**, 1564.

15 K. S. Suslick and M. M. Fox, *J. Am. Chem. Soc.*, 1983, **105**, 3507; T. Hashimoto, R. L. Dyer, M. L. Crossley, J. E. Baldwin and F. Basolo, *J. Am. Chem. Soc.*, 1982, **104**, 2101.

Received, 31st October 1996; Com. 6/07413H