Congruent Multiple Michael Addition for the Synthesis of Biomimetic Heme Analogues

James P. Collman,* Xumu Zhang, Paul C. Herrmann, Erich S. Uffelman, Bernard Boitrel, Andrei Straumanis, and John I. Brauman

Department of Chemistry, Stanford University Stanford, California 94305-5080

Received December 14, 1993

Heme proteins and enzymes play many critical roles in biological systems. Although all heme biomolecules possess similar iron porphyrin active sites, they perform a diverse array of tasks: O_2 transport and storage (hemoglobin and myoglobin), catalytic oxygenation of organic molecules (peroxidase, cytochrome P-450), O_2 reduction (cytochrome *c* oxidase), and electron transport (cytochrome *c*). These different heme functions are dictated by the protein tertiary structure, which determines the type of axial ligands as well as the polarities and shapes of the protein environment surrounding the active site. A basic strategy in biomimetic heme chemistry involves the synthesis of porphyrins having superstructures which serve the same function as the protein backbones in the natural systems.

Herein we describe a powerful, general method which can be used to prepare analogues of several heme protein active sites. By preparing acrylamides from atropisomers of tetrakis(*o*-aminophenyl)porphyrin, we have introduced Michael acceptors in fixed geometries around the porphyrin plane. Macrocycles and other superstructures can then be introduced by multiple congruent Michael additions of primary and secondary amines to these fixed acrylamide sites.[1] When the amine has a geometry complementary to the Michael acceptor, high yields can be achieved in a single step. It is significant that this reaction proceeds smoothly with metalated porphyrins, e.g., **14** (Figure 1). Scheme 1 shows an array of unusual porphyrins that have been synthesized by this procedure.

The Michael acceptor **1** was prepared by condensing acryloyl chloride with $\alpha,\alpha,\alpha,\alpha$-tetrakis(*o*-aminophenyl)porphyrin (70% yield). The macrocycle-capped porphyrins **2**, **3**, **4**, and **5** were obtained in high yields through the reaction of cyclam, cyclen, 1,4,7-triazacyclononane, and 1,5,9-triazacyclododecane, respectively, with **1**. Compounds **4** and **5** are particularly useful ligands for mimicking the binuclear site (heme a3 and CuB) of cytochrome *c* oxidase.[2] A family of superstructure porphyrins **6**, **7**, and **8** were made efficiently by the Michael addition of primary amines to **1**. We have named these "pup-tent" porphyrins (**6**, C_2PTP; **7**, C_3PTP; **8**, C_4PTP) on the basis of their structural similarity to a tent. Using the Michael addition, a crown ether porphyrin **9** and a bis-strapped porphyrin **10** were synthesized.

Scheme 2 shows the synthesis of a novel crown ether porphyrin. The A-frame diacid chloride **11** was condensed under dilute conditions with $\alpha,\beta,\alpha,\beta$-tetrakis(*o*-aminophenyl)porphyrin. Due to the preorganized geometries of the acid chloride and the porphyrin, this reaction proceeds in very high yield to give mono-A strapped porphyrin and bis-A strapped porphyrin. The mono-A porphyrin was isolated from the reaction mixture by column chromatography and allowed to react with acryloyl chloride to produce mono-A bis(acrylamide) porphyrin **12**. The reaction of **12** with 1,10-diaza-18-crown-6 forms the mono-A crown ether porphyrin **13** in high yield.

Below we demonstrate the use of this technique to prepare two biomimetic heme models: an Fe(II) porphyrin which binds dioxygen reversibly and a mercaptide Fe(II) carbonyl complex which exhibits the unique spectral characteristics of cytochrome P-450.

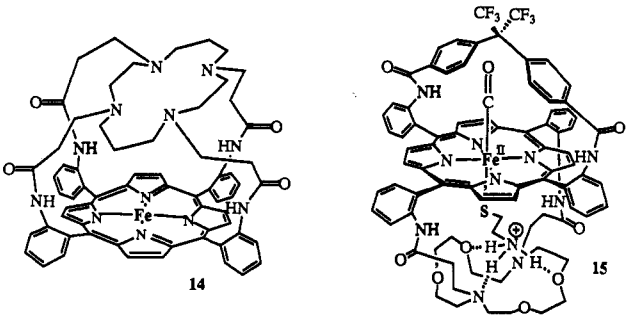


Figure 1.

Many synthetic iron porphyrins have been used to mimic the oxygen binding of hemoglobin and myoglobin.[3] Notable examples are the "picket fence",[4] "pocket",[5] and "basket handle" [6] porphyrin complexes. Iron derivatives of these porphyrins, supported by an axial nitrogenous ligand, bind dioxygen reversibly at room temperature. Considerable effort has been devoted to developing synthetic iron porphyrins which have relatively low CO binding affinity.[7] We report here an iron(II) porphyrin **14** (Figure 1) which shows no affinity for CO at 1 atm and yet binds dioxygen reversibly at room temperature in the presence of 1,2-dimethylimidazole or pyridine as the axial ligand. The UV–visible spectrum of **14** in the presence of 1,2-dimethylimidazole shows a Soret absorption at 444 nm. After O_2 binding, the Soret shifts to 424 nm. Upon purging with N_2, the 444-nm peak reappears. No change in the Soret is observed in the presence of CO. This oxygen affinity ($P_{1/2}(O_2) \sim 25$ Torr) is comparable to the oxygen affinity of the iron picket fence porphyrin. The ^{1}H NMR spectrum of **14** in d_5-pyridine shows the chemical shifts of the β-pyrrolic protons at 48 and 55 ppm, which indicates that the iron is five-coordinate ($S = 2$).[8] Addition of CO causes no change in the NMR spectrum of **14**, whereas addition of O_2 results in a diamagnetic ^{1}H NMR spectrum indicative of a stable dioxygen complex ($S = 0$).[3a,9] To the best of our knowledge, this selective binding of O_2 over CO is unprecedented. Work is ongoing to elucidate the structural factors involved in this selective binding.

(1) For an example of this with single picket attachment, see: Bulach, V.; Mandon, D.; Weiss, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 572.

(2) (a) Lee, S. C.; Holm, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 5833. (b) Nanthakumar, A.; Fox, S.; Murthy, N. N.; Karlin, D.; Ravi, N.; Huynh, B. H.; Orosz, R. D.; Day, E. P.; Hagen, K. S.; Blackburn, N. J. *J. Am. Chem. Soc.* **1993**, *115*, 8513.

(3) For reviews, see: (a) Collman, J. P. *Acc. Chem. Res.* **1977**, *10*, 265. (b) Jones, R. D.; Summerville, D. A.; Basolo, F. *Chem. Rev.* **1979**, *79*, 139. (c) Collman, J. P.; Halbert, T. R.; Suslick, K. S. In *Metal Ion Activation of Dioxygen*; Spiro, T. G., Ed.; Wiley: New York, 1980; Chapter 1. (d) Traylor, T. G. *Acc. Chem. Res.* **1981**, *14*, 102. (e) Scheidt, W. R.; Reed, C. A. *Chem. Rev.* **1981**, *81*, 543. (f) Jameson, G. B.; Ibers, J. A. *Comments Inorg. Chem.* **1982**, *2*, 97. (g) Niederhoffer, E. C.; Timmons, J. H.; Martell, A. E. *Chem. Rev.* **1984**, *84*, 137. (h) Baldwin, J. E.; Perlmutter, P. In *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer: Berlin, 1984; p 181. (i) Suslick, K. S.; Reinert, T. *J. Chem. Educ.* **1985**, *62*, 974. (j) Momenteau, M. *Pure Appl. Chem.* **1986**, *58*, 1493.

(4) (a) Collman, J. P.; Gagne, R. R.; Halbert, T. R.; Marchon, J. C.; Reed, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 7868. (b) Collman, J. P.; Gagne, R. R.; Reed, C. A.; Halbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 1427.

(5) Collman, J. P.; Brauman, J. I.; Iverson, B. L.; Sessler, J. L.; Morris, R. M.; Gibson, Q. H. *J. Am. Chem. Soc.* **1983**, *105*, 3052.

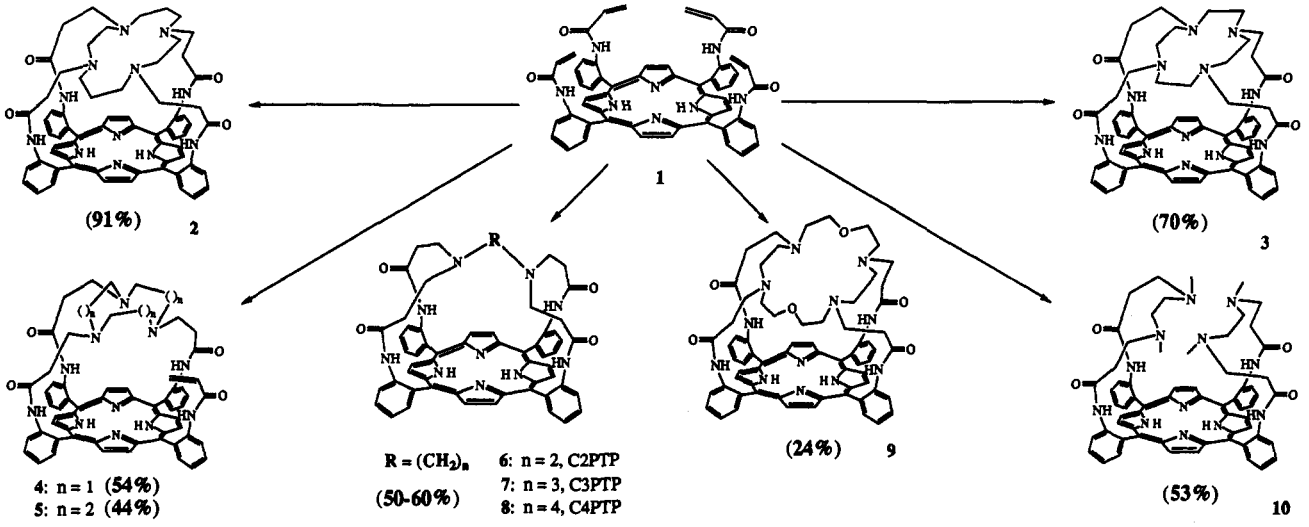
(6) (a) Momenteau, M.; Lavalette, D. *J. Chem. Soc., Chem. Commun.* **1982**, 341. (b) Mispelter, M.; Momenteau, M.; Lavalette, D.; Lhoste, J.-M. *J. Am. Chem. Soc.* **1983**, *105*, 5165.

(7) (a) Collman, J. P.; Brauman, J. I.; Halbert, T. R.; Suslick, K. S. *Proc. Natl. Sci. U.S.A.* **1976**, *73*, 3333. (b) Collman, J. P.; Brauman, J. I.; Inverson, B. L.; Sessler, J. L.; Morris, R. M.; Gibson, Q. H. *J. Am. Chem. Soc.* **1983**, *105*, 3052. (c) Johnson, M. R.; Seok, W. K.; Ibers, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 3998. (d) Tétreau, C.; Boitrel, B.; Rose, E.; Lavalette, D. *J. Chem. Soc., Chem. Commun.* **1989**, 1805–1806.

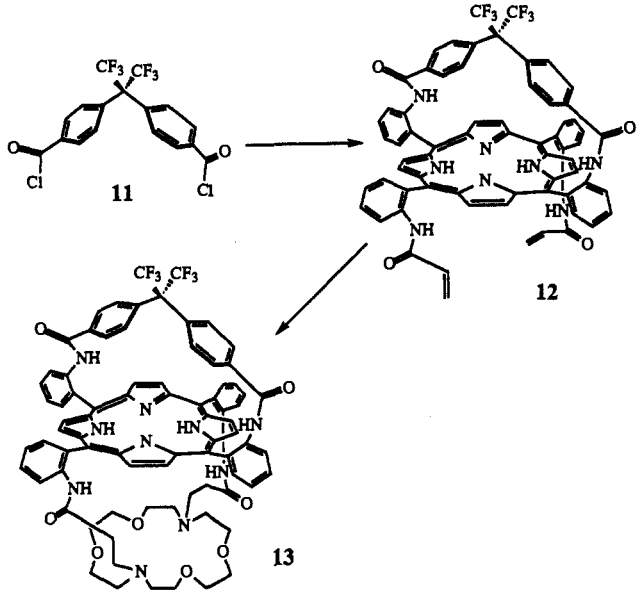
(8) (a) LaMar, G. N.; Eaton, G. R.; Holm, R. H.; Walker, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 63. (b) LaMar, G. N.; Walker, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 1782. (c) Goff, H.; LaMar, G. N.; Reed, C. A. *J. Am. Chem. Soc.* **1977**, *99*, 3641. (d) Goff, H.; LaMar, G. N. *J. Am. Chem. Soc.* **1977**, *99*, 6599. (e) Collman, J. P.; Brauman, J. I.; Collins, T. J.; Iverson, B. L.; Lang, G.; Pettman, R. B.; Sessler, J. L.; Walter, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 3038.

0002-7863/94/1516-2681$04.50/0

Scheme 1



Scheme 2



Synthetic metalloporphyrins with axial thiolate ligands have been synthesized to model cytochrome P-450 at various stages in its catalytic cycle. In the past, ferrous–CO species with a Soret absorption at 450 nm have been reproduced with thiolate ligands bound to synthetic iron porphyrins.[10] The thiolate ligands were used either as an excess in solution or covalently attached to the porphyrins. Herein we introduce an innovative axial ligand delivery system utilizing host–guest chemistry to mimic the cytochrome P-450 active site. A crown ether covalently attached to a porphyrin serves as a host, while an ammonium cation linked to a thiolate acts as the guest. The crown ether binds avidly to the ammonium functional group of the thiolate ligand and forces the thiolate into the coordination sphere of the iron. In the past several crown ether capped porphyrins have been made.[11] However, none of these were used to deliver biologically relevant ligands for modeling heme proteins.

The crown ether porphyrin **15** (Figure 1) employs the above method to facilitate binding of a thiolate to the iron center. One successful example uses 2-aminoethanethiol ($H_2NCH_2CH_2SH$) as the guest molecule. The high binding affinity of 1,10-diaza-18-crown-6 for primary alkyl ammonium cations ($K \sim 10^8$ in $CHCl_3$) converts the thiol ($H_2NCH_2CH_2SH$) to the zwitterion ($H_3N^+CH_2CH_2S^-$). Bubbling CO into a solution of the iron(II) crown porphyrin generates the characteristic UV–visible Soret of the ferrous–CO thiolate complex (446 nm in toluene, Figure 2). This cytochrome P-450 analogue represents one example of such a biomimetic ligand delivery system. The approach is quite general and should be applicable to the modeling of other heme proteins: phenolate ligands could be delivered to mimic catalase, and imidazole ligands to model peroxidase, hemoglobin, and myoglobin.

In conclusion, the congruent multiple Michael addition is a powerful strategy for the synthesis of biomimetic model hemes. We are actively investigating these heme protein analogues and exploring the further utility of the congruent Michael addition.

Acknowledgment. We thank the NIH (Grant 5R37 GM-17880-ZZ) and the NSF (Grant CHE 9123187-002) for financial support. X.Z. thanks the Stanford Chemistry Department for a Franklin Veatch Fellowship, E.S.U. thanks the NIH for a postdoctoral fellowship, and B.B. thanks NATO and the CNRS for a postdoctoral fellowship. P.C.H. thanks CMR of Stanford University for financial support. We thank the Mass Spectrometry Facility, University of California, San Francisco, supported by the NIH (Grants RR 04112 and RR 01614). We also thank Professor R. Guilard for helpful discussions and C. Kellen-Yuen for proofreading the manuscript.

Supplementary Material Available: Synthetic details for the preparation of **1–15** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) A sharp diamagnetic ^1H NMR spectrum at room temperature is probably the quintessential criterion of a pure Fe(II) dioxygen complex: Collman, J. P.; Bauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Bunnenberg, E.; Linder, R. E.; LaMar, G. N.; Del Gaudio, J.; Lang, G.; Spartalian, K. *J. Am. Chem. Soc.* **1980**, *102*, 4182.

(10) (a) Stern, J. O.; Peisach, J. *J. Biol. Chem.* **1974**, *249*, 7495. (b) Collman, J. P.; Sorrell, T. N. *J. Am. Chem. Soc.* **1975**, *97*, 4133. (c) Chang, C. K.; Dolphin, D. *J. Am. Chem. Soc.* **1975**, *97*, 5948. (d) Traylor, T. G.; Mincey, T. C.; Berzinis, A. P. *J. Am. Chem. Soc.* **1981**, *103*, 7084. (e) Collman, J. P.; Groh, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 1391. (f) Battersby, A. R.; Howson, W.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1982**, 1266. (g) Tatsuno, Y.; Tomita, K.; Tani, K. *Inorg. Chim. Acta* **1988**, *152*, 5. (h) Staubi, B.; Fretz, H.; Piantini, U.; Woggon, W.-D. *Helv. Chim. Acta* **1987**, *70*, 1173.

(11) (a) Chang, C. K. *J. Am. Chem. Soc.* **1977**, *99*, 2819. (b) Richardson, N. M.; Sutherland, I. O.; Camilleri, P.; Page, J. A. *Tetrahedron Lett.* **1985**, *26*, 3739. (c) Gunter, M. J.; Johnston, M. R. *Tetrahedron Lett.* **1990**, *31*, 4801. (d) Hamilton, A.; Lehn, J. M.; Sessler, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 5158. (e) Hamilton, A.; Lehn, J. M.; Sessler, L. J. *J. Chem. Soc., Chem. Commun.* **1984**, 311. (f) Gubelmann, M.; Harriman, A.; Lehn, J. m.; Sessler, J. L. *J. Chem. Soc., Chem. Commun.* **1988**, 77. (g) Gubelmann, M.; Harriman, A.; Lehn, J. M.; Sessler, J. L. *J. Phys. Chem.* **1990**, *94*, 308. (h) Collet, A. *Tetrahedron* **1987**, *43*, 5725.