Synthesis of Biomimetic Heme Precursors: The "Double Picket Fence" 5,10,15,20-Tetrakis(2′,6′-dinitro-4′-*tert*-butylphenyl)porphyrin

Eric Rose,* Alain Kossanyi, Mélanie Quelquejeu, Michèle Soleilhavoup, Frédéric Duwavran, Nicolas Bernard, and Alexandra Lecas

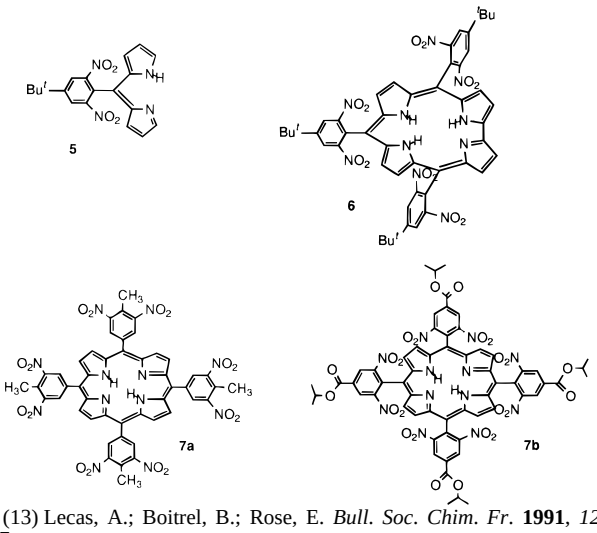
Laboratoire de Synthèse Organique et Organométallique URA CNRS 408, Tour 44, 4 Place Jussieu 75230 Paris Cedex 05, France

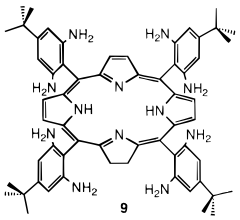
Received August 1, 1995

The various atropisomers of tetrakis(*o*-aminophenyl)porphyrin have served as synthons for the creation of many biomimetic hemes for the preparation of kinetically stable Fe dioxygen complexes[1] and for the creation of shape-selective and chiral porphyrin oxygenation catalysts.[2a] These otherwise useful synthetic approaches have two principal limitations: the separation of the desired atropisomers[2b] and the problem of creating chiral faces simultaneously on both sides of the porphyrin. An obvious solution to these problems could be attained through the symmetric octakis(*o*-aminophenyl)porphyrin. In fact, two papers describe the synthesis of this substance.[3] All attempts to reproduce this synthesis have failed; mute testimony to these failures is the fact that no functionalized derivatives of this octaamino porphyrin have ever been applied to biomimetic reactions. Herein we describe an efficient synthesis of a similar octaamino porphyrin bearing a *tert*-butyl group in the para position of each *meso*-phenyl substituent; we also report "double picket fence" type derivatives of this new porphyrin which augur well for the creation of a new family of functional heme analogues.

Condensation of pyrrole and 2,6-dinitro- or 2,6-diaminobenzaldehyde did not succeed in our hands.[3] We thought that a solubility problem could explain this failure, so we decided to use substituted alkyl, alkoxy, or alkoxycarbonyl 2,6-dinitrobenzaldehydes. For example, we prepared 4-*tert*-butyl-2,6-dinitrotoluene (**1**) (Chart 1) by nitration of 4-*tert*-butyltoluene (75% yield).[9] Bromination with NBS yielded 1-(bromomethyl)−2,6−dinitro−4−*tert*-butylbenzene (**2**) in 90% yield. Oxidation of **2** by $(Py)_4Co(HCrO_4)_2$[10] gave aldehyde **3** in 60% yield. Condensation of 2,6-dinitro-4-*tert*-butylbenzaldehyde (**3**) and pyrrole in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$[11] at room temperature led to a reproducible yield of 10.5% of 5,10,15,20-tetrakis(2′,6′-dinitro-4′-*tert*-butylphenyl)porphyrin, H_2TDNPP (**4**).[12] In order to scale up this reaction, we undertook the same condensation with 12 g of aldehyde **3**, pyrrole (3.3 mL), and $BF_3{\cdot}OEt_2$ (6 mL) in CH_2Cl_2 (480 mL), which gave, after column chromatography and precipitation, porphyrin **4** (1.28 g, 9% yield). The octanitro porphyrin H_2TDNPP (**4**) was dissolved in CH_2Cl_2 saturated with concentrated HCl and reduced with excess $SnCl_2{\cdot}2H_2O$ at −4 °C for 8 days,[6c,d,13] affording 65% of 5,10,15,20-tetrakis(2′,6′-diamino-4′-*tert*-butylphenyl)porphyrin, H_2-TDAPP (**8**). An 88% yield is obtained if the reaction is carried out for 3 weeks at −18 °C.[14] We have been able to make octa-substituted derivatives of **4**. For example, treating **8** with excess (*R*)-Mosher's acid chloride[15] resulted in the formation of the highly soluble 5,10,15,20-tetrakis(4′-*tert*-butyl-2′,6′-bis((*R*)-α-(trifluoromethyl)-α-methoxyphenylacetamido)phenyl)porphyrin (**10**) (45% yield). Similarly, H_2TAPP (**8**) and (*R*)-α-methoxyphenylacetyl chloride gave the soluble 5,10,15,20-tetrakis(4′-*tert*-butyl-2′,6′-bis((*R*)-α-methoxyphenylacetamido)phenyl)porphyrin (**11**) in 45% yield.

We were pleasantly surprised to find that a single pocket could be introduced in high yield and selectively by reaction





(1) Momenteau, M.; Reed, C. A. *Chem. Rev.* **1994**, *94*, 659.

(2) (a) Collman, J. P.; Zhang, X.; Lee, V. G.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404. (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.

(3) In the literature, two groups described at approximatively the same time the condensation of 2,6-dinitrobenzaldehyde and pyrrole (0.75% yield with CF_3CO_2H as catalyst[4] and 2-13% yield with $BF_3{\cdot}OEt_2$ as catalyst).[5] We and others[6] were unfortunately not able to reproduce the preparation of these interesting 5,10,15,20-tetrakis(2′,6′-dinitro- and -diaminophenyl)-porphyrins.[6]

(4) Drain, C. M.; Corden, B. B. *Inorg. Chem.* **1989**, *28*, 4374.

(5) Quintana, C. A.; Assink, R. A.; Shelnutt, J. A. *Inorg. Chem.* **1989**, *28*, 3421.

(6) (a) Collman, J. P.; Gagne, R. R.; Reed, C. A.; Halbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 1427. (b) Momenteau, M.; Mispelter, J.; Loock, B.; Lhoste, J. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 221. (c) Rose, E.; Quelquejeu, M.; Pochet, C.; Kossanyi, A.; Julien, N.; Hamon, L. *J. Org. Chem.* **1993**, *58*, 5030. (d) Rose, E.; Cardon-Pilotaz, A.; Quelquejeu, M.; Bernard, N.; Kossanyi, A.; Desmazières, B. *J. Org. Chem.* **1995**, *60*, 3919. (e) Rose, E.; Boitrel, B.; Quelquejeu, M.; Kossanyi, A. *Tetrahedron Lett.* **1993**, *34*, 7267.

(7) Condensation of 2,6-diacetamidobenzaldehyde[8a] and pyrrole did not give tetrakis(aryl)porphyrins. We reported previously that condensation of 2,6-diacetamidobenzaldehyde and dipyrrylmethane did not afford the 5,15-bis(aryl)porphyrin.[8b]

(8) (a) Lecas, A.; Levisalles, J.; Mariacher, C.; Renko, Z.; Rose, E. *Can. J. Chem.* **1984**, *62*, 2054. (b) Lecas, A.; Boitrel, B.; Rose, E. *Tetrahedron Lett.* **1992**, *33*, 481.

(9) (a) Verley, A. *Bull. Soc. Chim. Fr.* **1898**, *19*, 67. (b) Battegay, M.; Heffely, P. *Bull. Soc. Chim. Fr.* **1924**, *35*, 981.

(10) Hu, Y.; Hu, H. *Synth. Commun.* **1992**, *22*, 1491.

(11) Lindsey, J. S.; Wagner, R. W. *J. Org. Chem.* **1989**, *54*, 828.

(12) Byproducts have been isolated and fully characterized which correspond to (4-*tert*-butyl-2,6-dinitrophenyl)dipyrrylmethane (**5**) (5−10% yield) and the corrole derivative (**6**) (UV/vis: 416, 580, 617 nm). Similarly, condensation of 3,5-dinitro-4-methylbenzaldehyde and pyrrole in AcOH led to a 2.5% yield of 5,10,15,20-tetrakis(3′,5′-dinitro-4′-methylphenyl)-porphyrin, H_2TNMPP (**7a**). Condensation of 2,6-dinitro-4-((isopropyloxy)-carbonyl)benzaldehyde and pyrrole in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ gives a 5% yield of 5,10,15,20-tetrakis(2′,6′-dinitro-4′-((isopropyloxy)-carbonyl)phenyl)porphyrin, H_2TDNIOCPP (**7b**).

(13) Lecas, A.; Boitrel, B.; Rose, E. *Bull. Soc. Chim. Fr.* **1991**, *128*, 407.

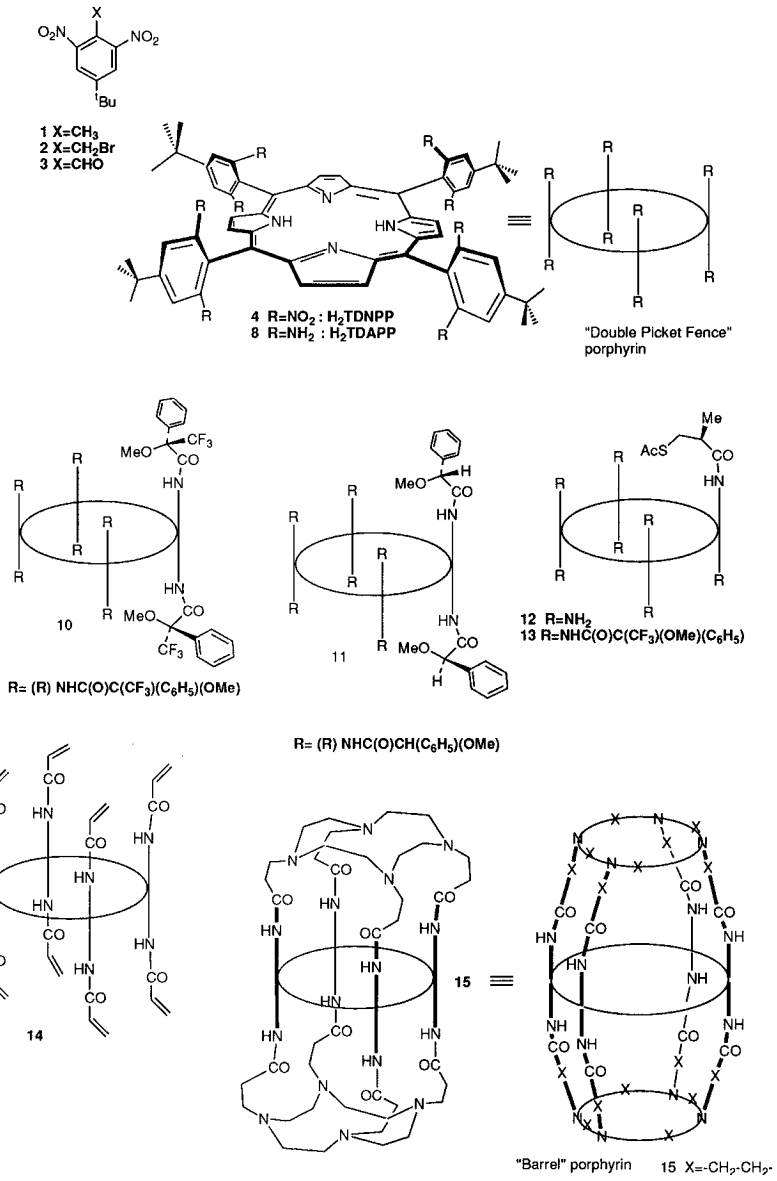
(14) (a) If reduction was undertaken at room temperature, overreduction readily occurred, giving dihydroporphyrin **9** as a minor product with an intense band at 656 nm characteristic of a chlorin band[14b] and adjacent tetrahydroporphyrin: 5,10,15,20-tetrakis(2′,6′-diamino-4′-*tert*-butylphenyl)-2,3,7,8-tetrahydroporphyrin with a double Soret band at 389 and 408 nm and a characteristic Q band at 599 nm.

(b) *The Porphyrins, Structure and Synthesis*; Dolphin, D., Ed.; Academic Press, Inc.: New York, 1978; Part B, Vol. II, p 63.

(15) Le Maux, P.; Bahri, H.; Simonneaux, G. *J. Chem. Soc., Chem. Commun.* **1991**, 1350.

0002-7863/96/1518-1567$12.00/0

Chart 1



of only one of the eight amino groups. For example, condensation of (*S*)-2-methyl-3-(acetylthio)propanoyl chloride (0.5 equiv) with porphyrin **8** (1 equiv) yielded 5,10,15-tris(4′-*tert*-butyl-2′,6′-diaminophenyl)-20-(4″-*tert*-butyl-2″-amino-6″-((*S*)-(−)-2-methyl-3-(acetylthio)propanamido)phenyl)porphyrin (**12**) (49% yield). Treatment of **12** with Mosher's acid chloride resulted in the formation of porphyrin **13** having seven "Mosher pickets" and one "acetylthio picket" (50% yield).

The octa Michael acceptor (**14**) was prepared by condensing acryloyl chloride with octaamino porphyrin H_2TAPP (**8**) (25% yield) using Collman's congruent multiple Michael addition.[16] The doubly capped macrocyclic porphyrin **15** was obtained through the reaction of cyclen with **14** (55% yield). We have named **15** "barrel" porphyrin on the basis of its structural similarity to a barrel.

In conclusion, the condensation of substituted 2,6-dinitrobenzaldehyde and pyrrole led to a reproducible yield of octanitro porphyrin **4**, which represents a basic versatile precursor for the synthesis of biomimetic model hemes. Once the eight nitro groups are reduced under mild conditions, chiral acid chlorides can be condensed on the eight amino groups in order to give a large variety of chiral "double picket fence" porphyrins.

All of these compounds have been characterized by elemental analyses, mass spectra, ^{1}H NMR, and UV/vis spectroscopy; details are in the supporting information.

Acknowledgment. E.R. thanks the CNRS for financial support, A.K. thanks the CNRS for a fellowship, and M.Q. thanks the MRES for a fellowship. We are pleased to acknowledge helpful discussions with Professor J. Levisalles; in the course of one of them, he suggested the nickname "barrel porphyrin".

Supporting Information Available: Synthetic details and spectral data for **1**−**15** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA952580J

(16) Collman, J. P.; Zhang, X.; Herrmann, P. C.; Uffelman, E. S.; Boitrel, B.; Straumanis, A.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 2681.