meso-Unsubstituted Porphyrinogens and Hexaphyrinogens: The First X-ray Characterization

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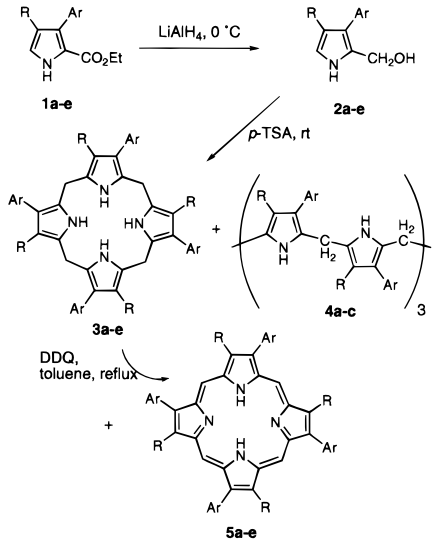
Received February 8, 2000

Recently, *meso*-octasubstituted porphyrinogens, namely calix[4]pyrroles,[1] have been extensively studied due to their interesting anion-binding ability[1,2] and ability to π-donate to metal cations.[3] The structures and reactivities of their neat and complexed forms with anions,[1,2] metals,[3] and guest molecules[4] have been fully investigated by NMR and X-ray analyses. Porphyrinogens bearing hydrogen atoms at their *meso* position are very important as key intermediates in bio- and Rothemund syntheses of porphyrin dyes.[5] Their structures and isomerization[6] are of particular interest in connection not only with biological peripheral isomerism of naturally occurring porphyrinoids,[7] but also with N−C confusion of pyrroles[8] and formation of higher homologues[9] of porphyrin such as pentaphyrins and hexaphyrins. Porphyrinogens have been, however, treated just as unstable intermediates and readily oxidized to the targeted dyes without isolation in most cases. Consequently, structural characterization of porphyrinogens has not yet been done. In this contribution, we will show the first successful X-ray structural analysis of the *meso-unsubstituted* porphyrinogen **3** and hexaphyrinogen **4** and some properties of these compounds.

Scheme 1[a]



[a] **a**: R = CO_2Et; Ar = Mesityl. **b**: R = CO_2Et; Ar = 2,6-dichlorophenyl. **c**: R = CO_2Et; Ar = Ph. **d**: R = CF_3; Ar = Ph. **e**: R = CF_3; Ar = 2,6-dichlorophenyl.

Acid-catalyzed oligomerization of ethyl 2-(hydroxymethyl)-3-mesitylpyrrole-4-carboxylate (**2a**), which was obtained by regioselective reduction of the corresponding pyrrole-2,4-dicarboxylate **1a**,[10] was carried out by treatment with *p*-toluenesulfonic acid in dichloroethane (Scheme 1). After the oligomerization, the mixture was oxidized with DDQ at room temperature to give a mixture, from which white powdery crystals were obtained in 20% yield by rinsing with chloroform. FAB mass and NMR analyses revealed the crystals were a highly symmetric hexamer, which proved to be hexaphyrinogen **4a**. Silica gel chromatography of the residue obtained from the mother liquor gave type I porphyrin **5a** only in 3% yield and a small amount of the hexaphyrinogen (Table 1).

When the acid-treated mixture from the pyrrole **2a** was directly chromatographed on silica gel, the hexaphyrinogen **4a** (16%) and a small amount of an inseparable mixture of porphyrinogen **3a** and the porphyrin **5a** (Table 1) were obtained.[11] Separation of **3a** and **5a** could not be achieved mainly due to the instability of **3a** toward oxidation. Although other cyclic oligomers such as pentaphyrinogens were suggested to exist from the NMR and GPC analyses of the reaction mixture, these oligophyrinogens could not be isolated either. In the ^{1}H NMR spectra of **4a** in $CDCl_3$, *meso*-methylene protons appeared at δ 3.18 and 4.05 as an AB-quartet, and pyrrolic protons appeared in a rather lower field (δ 9.81) compared to the parent pyrrole (δ 9.01 for **2a**). The nonequivalence of the *meso* protons persisted in toluene-d_8 solution even at 100 °C. This fact and the stretching of NH (3319 cm^{-1}) and C═O (1666 cm^{-1}) in the IR spectrum strongly suggested

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(1) (a) Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140−5141. (b) Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998**, 1−8.

(2) (a) Anzenbacher, P., Jr.; Jursíková, K.; Lynch, V. M.; Gale, P. A.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 11020−11021. (b) Gale, P. A.; Twyman, L. J.; Handlin, C. I.; Sessler, J. L. *Chem. Commun.* **1999**, 1851−1852. (c) Miyaji, H.; Pavel, A., Jr.; Sessler, J. L.; Bleasdale, E. R.; Gale, P. A. *Chem. Commun.* **1999**, 1723−1724. (d) Gale, P. A.; Sessler, J. L.; Allen, W. E.; Tvermoes, N. A.; Lynch, V. *Chem. Commun.* **1997**, 665−666.

(3) (a) Bonomo, L.; Solari, E.; Martin, G.; Scopelliti, R.; Floriani, C. *Chem Commun.* **1999**, 2319−2320. (b) Crescenzi, R.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *J. Am. Chem. Soc.* **1999**, *121*, 1695−1706. (c) Benech, J.-M.; Bonomo, L.; Solari, E.; Scopelliti, R.; Floriani, C. *Angew. Chem. Int. Ed.* **1999**, *38*, 1957−1959. (d) Dubé, T.; Gambarotta, S.; Yap, G. P. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1432−1435. (e) Bonomo, L.; Dandin, O.; Solari, E.; Floriani, C.; Scopelliti, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 914−915. (f) Campazzi, E.; Solari, E.; Scopelliti, R.; Floriani, C. *Chem. Commun.* **1999**, 1617−1618. (g) Bonomo, L.; Solari, E.; Latronico, M.; Scopelliti, R.; Floriani, C. *Chem. Eur. J.* **1999**, *5*, 2040−2047. (h) Bonomo, L.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *J. Am. Chem. Soc.* **1998**, *120*, 12972−12973. (i) Crescenzi, R.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chem.* **1998**, *37*, 6044−6051. (j) Floriani, C.; Solari, E.; Solari, G.; Chiesi-Villa, A.; Rizzoli, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2245−2248. (k) Floriani, C. *Chem. Commun.* **1996**, 1257−1263 and references therein.

(4) (a) Bonomo, L.; Solari, E.; Toraman, G.; Scopelliti, R.; Latoronico, M.; Floriani, C. *Chem. Commun.* **1999**, 2413−2414. (b) Gale, P. A.; Sessler, J. L.; Lynch, V.; Sanson, P. I. *Tetrahedron Lett.* **1996**, *37*, 7881−7884. (c) Sessler, J. L.; Andrievsky, A.; Gale, P. A.; Lynch, V. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2782−2785. (d) Allen, W. E.; Gale, P. A.; Brawn, C. T.; Lynch, V.; Sessler, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 12471−12472.

(5) For reviews, see: (a) Mauzerall, D. *The porphyrins*; Dolphin, D., Ed.; Academic: New York, 1978; Vol. 2, Chapter 3. (b) Smith, K. M. *Porphyrins and Metalloporphyrins*; Elsevier: Amsterdam, 1975.

(6) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Keaney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827−836.

(7) (a) Takakura, H.; Nomura, K.; Tamino, H.; Okada, K. *Tetrahedron Lett.* **1999**, *40*, 2989−2992. (b) Petersen, P. M.; Hawker, C. J.; Stanford, N. P. J.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1531−1539. (c) Hawker, C. J.; Petersen, P. M.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1519−1530. (d) Hawker, C. J.; Spivey, A. C.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1509−1517. (e) Hawker, C. J.; Marshall, S. W.; Spivey, A. C.; Rathby, P. R.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1493−1508.

(8) (a) Geier, G. R., III; Haynes, D. M.; Lindsey, J. S. *Org. Lett.* **1999**, *1*, 1455−1458. (b) Geier, G. R.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1596−1603. (c) Chmielewski, P. J.; Latos-Grazynski, L.; Rachlewicz, K. *Chem. Eur. J.* **1995**, *1*, 68−73. (d) Chmielewski, P. J.; Latos-Grazynski, L.; Rachlewicz, K.; Glowiak, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 779−781. (e) Furuta, H.; Asano, T.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 767−768. (f) Sessler, J. L. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1348−1350.

(9) (a) Naranayan, S. J.; Sridevi, B.; Chandrashekar, T. K.; Vij, A.; Roy, R. *J. Am. Chem. Soc.* **1999**, *121*, 9053−9068. (b). Neves, M. G. P. M.; Martins, R. M.; Tomé, A. C.; Silvestre, A. J. D.; Silva, A. M. S.; Félix, V.; Drew, M. G. B.; Cavaleiro, J. A. S. *Chem. Commun.* **1999**, 385−386. (c) Brückner, C.; Sternberg, E. D.; Boyle, R. W.; Dolphin, D. *Chem. Commun.* **1997**, 1689−1690.

(10) Uno, H.; Tanaka, M.; Inoue, T.; Ono, N. *Synthesis* **1999**, 471−474.

(11) For the experimental procedure, see Supporting Information.

10.1021/ja000482e CCC: $19.00 © 2000 American Chemical Society
Published on Web 06/27/2000

Table 1. Acid-Catalyzed Oligomerization of **2**

	conditions		yield/%		
substrate	acid	workup[a]	**3**	**4**	**5**
2a	BF_3·OEt_2	A	*b*	16	trace
2a	BF_3·OEt_2	B		20	3
2a	pTSA	A	*b*	22	8
2b	pTSA	A	64	6	trace
2b	TSA	A	47	13	trace
2b	BF_3·OEt_2	A	40	10	trace
2c	pTSA	C			20[c]
2d	pTSA	C			24[d]
2e	pTSA	C	17		trace

[a] Condition A: the oligomerization mixture was directly chromatographed on silica gel. Condition B: oxidation with DDQ was carried out at room temperature after termination of the oligomerization with Et_3N. Condition C: oxidation with *p*-chloranil was carried out at room temperature after termination of the oligomerization with Et_3N. [b] Existence of the porphyrinogen was detected by ^{1}H NMR, although the compound was too labile to isolate by chromatography. [c] The porphyrin was obtained as an isomeric mixture due to the peripheral substitution pattern (3:trace:2:1). [d] The porphyrin was obtained as an isomeric mixture due to the peripheral substitution pattern (4:3:8:4).

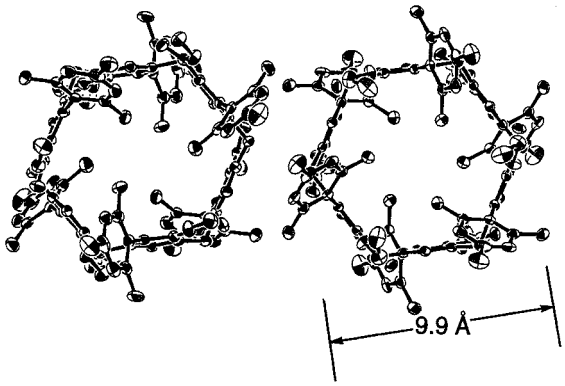

Figure 1. Ortep drawing of **4a** along the *c*-axis. Hydrogen atoms are omitted for clarity. The right and left molecules occupy the −3 and −1 symmetric positions, respectively.

the presence of intramolecular hydrogen bonding which was proved by the following X-ray analysis.

Rhombohedral crystals of **4a**·$CHCl_3$ were obtained by slow diffusion of hexane into a chloroform solution of **4a**. The space group of the crystal was determined as R-3, and an Ortep drawing of **4a** along the *c*-axis is shown in Figure 1.[12] Crystallographically, two independent hexagonal tube molecules of **4a** exist in the unit cell, occupy special positions with −3 and −1 symmetries, and adopt an almost complete *1,3,5-alternate* conformation. The diameters are both ∼9.9 Å. Solvent chloroform molecules also occupy other −3 and −1 symmetric positions with disordered structures. The pyrrole rings of **4a** are almost perpendicular to the mean plane of the six *meso* methylenes (88.8° for the −3 structure and 89.1°, 82.8°, and 88.2° for the −1 structure). The intramolecular hydrogen bond (NH···O, 2.842(5) Å for the −3 structure; 2.772(5), 2.894(5), and 2.822(5) Å for the −1 structure) keeps this conformation tightly and is probably the main reason for the structural difference with that of calix[6]pyrrole,[13] three *1,3,5-altenate* pyrroles of which point toward the center of the cavity.

The reaction of pyrroles **2b**−**e**[10] was conducted under various conditions, and some of them are listed in Table 1. In the cases of pyrroles bearing a bulky electron-deficient aromatic group such as 2,6-dichlorophenyl and pentafluorophenyl, porphyrinogens

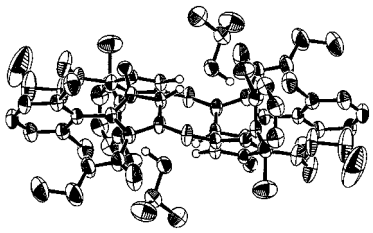

Figure 2. Ortep drawing of **3b**. Hydrogen atoms except for NH and OH are omitted for clarity.

were very stable toward oxidation even with *p*-chloranil at room temperature and were easily isolated by chromatography. On the other hand, porphyrinogens with phenyl groups were readily oxidized to the corresponding porphyrins **5c** and **5d** during the workup manipulation. Two distinctive features emerged from Table 1. First, the hexaphyrinogens were only isolated in the reactions of pyrroles with an ester group. Second, the readily formed porphyrins **5c** and **5d** were mixtures of the peripheral-substitution type isomers, whereas the other porphyrins listed in Table 1 were isomerically pure.

In the ^{1}H NMR spectra of **3b**, very broad signals due to *meso*-methylene protons were observed in δ 3.0−4.8 at room temperature and became a sharp AB-quartet at −50 °C and a broad singlet at 50 °C. The coalescence temperature was ∼35 °C. An approximate $\Delta E^{\ddagger}$ value for the conformational change was calculated as ∼58 kJ·mol^{-1}. Prismatic rods for X-ray analysis were obtained by slow evaporation of the solvent from a solution of **3b** in 2-propanol. An Ortep drawing of **3b**·2(2-PrOH) is shown in Figure 2.[14] The porphyrinogen shows an ideal *1,2-alternate* structure which is constructed by hydrogen bonds between 2-propanol oxygen and two adjacent pyrrolic NH (NH···O, 2.951(5) and 3.022(5) Å). The angles between the pyrrole rings and the mean plane of the *meso*-carbons are 56.1° and 55.0°. This *1,2-alternate* structure is very similar to that of *meso*-octamethylcalix[4]pyrrole·2DMF.[4d]

The porphyrinogens **3b** and **3e** were oxidized by refluxing with DDQ in toluene to give the isomerically pure porphyrins **5b** (66%) and **5e** (50%). Contrary to the porphyrinogens, the isolated hexaphyrinogen **4a** was resistant to oxidation. Isolated hexaphyrinogen **4a** could not be oxidized with DDQ either under reflux in toluene or in the presence of an acid such as pTSA and BF_3·OEt_2.[15]

In conclusion, we have succeeded in isolating the *meso*-unsubstituted porphyrinogens and hexaphyrinogens bearing electron-withdrawing and bulky aryl groups, and their behavior toward oxidation was examined. The X-ray structural analyses revealed the potential of these compounds as new anion binders and host molecules. It is also emphasized that the X-ray analyses of these compounds are the first examples of *meso*-unsubstituted porphyrinogens and hexaphyrinogens.

Acknowledgment. We thank Professor Atsuhiro Osuka and Dr. Hiroyuki Furuta for their helpful discussions. We also thank Dr. Takuji Ogawa and Dr. Takashi Murashima for their measurement of FAB mass.

Supporting Information Available: Experimental procedures, tables of crystal data, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for the porphyrinogen **3b** and the hexaphyrinogen **4a** in CIF format, and ^{1}H NMR spectra of variable temperature experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA000482E

(12) Crystallographic summary for **4a**·$CHCl_3$. Pale yellow crystals, rhombohedral, *R-3*, $Z = 12$ in a cell of dimensions $a = 43.981(2)$ Å, $c = 17.017(1)$ Å, $V = 28507(2)$ Å^3, $\rho_{calc} = 1.213$ g·cm^{-3}, $F(000) = 11064$. 14403 unique reflections, 6480 with $I_o > 3\sigma(I_o)$. The final $R = 0.076$, $R_w = 0.094$, goodness-of-fit = 1.74 for 765 parameters.

(13) Turner, B.; Botoshansky, M.; Eichen, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2475−2478.

(14) Crystallographic summary for **3b**·2(2-PrOH). Orange crystals, triclinic, *P-1*, $Z = 1$ in a cell of dimensions $a = 12.571(6)$ Å, $b = 14.418(7)$ Å, $c = 9.414(4)$ Å, $\alpha = 100.63(4)°$, $\beta = 95.88(4)°$, $\gamma = 112.38(4)°$, $V = 1522(2)$ Å^3, $\rho_{calc} = 1.423$ g·cm^{-3}, $F(000) = 676$. 4728 unique reflections, 3168 with $I_o > 3\sigma(I_o)$. The final $R = 0.053$, $R_w = 0.069$, goodness-of-fit = 1.98 for 387 parameters.

(15) Littler, B. J.; Ciringh, Y.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 2864−2872.