Porphyrinoids

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Synthesis, Structure, and Complexation Properties of Partially and Completely Reduced *meso*-Octamethylporphyrinogens (Calix[4]pyrroles)**

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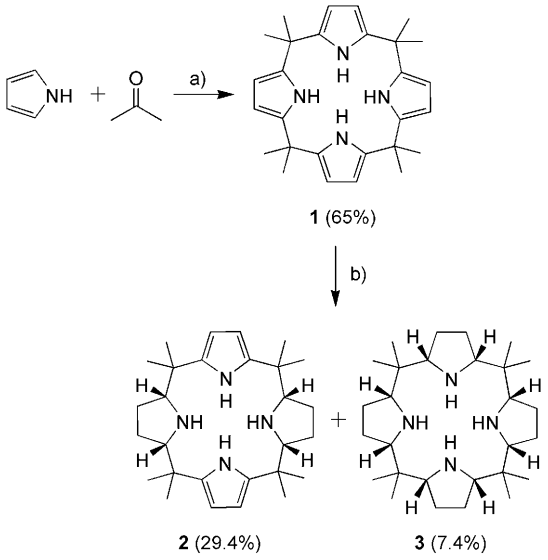
Many organic ligands used by nature in important biological processes[1–5] are formed by the condensation of simple starting materials.[6–9] Uroporphyrinogen III, the biosynthetic precursor of the "pigments of life", forms metal complexes only under specific reaction conditions.[10–12] Most uroporphyrinogens acquire this capacity by oxidation or by tautomerization of the ligand.[2,12,13]

The first *meso*-octaalkylporphyrinogen was synthesized more than 120 years ago by Baeyer.[14] The correct structure was proven by Rothemund in 1955.[15–17] Forty years later the X-ray structure analysis of this class of compounds showed alternating conformations of the pyrrole rings in the solid state.[18] The X-ray structures of these macrocycles acting as ion-pair receptors revealed a conelike conformation and resembled the structures observed for calixarenes.[18–20] For this reason the name calix[4]pyrroles was proposed as a trivial name for the *meso*-octaalkylporphyrinogens.[18] Hydrogen bonding, the dominating mode of interaction of neutral calixpyrroles, allows these compounds to be used as anion sensors.[21–23] Many interesting modifications of calixpyrroles have been reported: calixphyrins,[24,25] hybrids between calixpyrroles and porphyrins, expanded calixpyrroles like the calix[6]pyrroles,[26] and calixpyridines, hybrids containing pyrroles and pyridines.[27–29] Many of these studies were carried out with the aim to improve the anion-binding properties.[19,30,31] To obtain Werner-type metal complexes from calix[4]pyrroles the ligand must be deprotonated using butyllithium.[10,32–34]

As they have numerous applications, macrocyclic nitrogen-containing ligands and their metal complexes have been thoroughly studied.[35–41] Reducing calixpyrroles might lead to new nitrogen-containing ligands with interesting properties. Here we report the synthesis and structures of partially and total reduced *meso*-octamethylporphyrinogens and the complexes formed with Cu^{II}, Ni^{II}, and Pd^{II} salts. To the best of our knowledge the successful reduction of *meso*-octaalkylporphyrinogens has not been described previously. Reductions of pyrroles usually require relatively harsh conditions.[42] Most efficient reductions of alkyl pyrroles require an acid as the solvent or as a component of the solvent mixture. Acidic conditions are also used to synthesize *meso*-octaalkylporphyrinogens but at the same time these conditions trigger the opening of the macrocycle. It was not apparent whether experimental conditions could be found that would allow the reduction of all pyrrole rings before the macrocycle would be destroyed.[17]

We started to screen reduction conditions with the hope of finding an experimental procedure for the reduction of *meso*-octamethylporphyrinogens (Scheme 1). First we avoided the use of acids as we feared competition between acid-catalyzed destruction and acid-catalyzed reduction. Our initial attempts, where we varied the temperature (from 50 °C to



Scheme 1. Synthesis and catalytic hydrogenation of *meso*-octamethylcalix[4]pyrrole (**1**). a) H_3CSO_3H, EtOH, 35→45 °C, 15 min; b) H_2 (100 atm), Pd/C, CH_3COOH, 100 °C, Pd/substrate 13.3:100, 24 h.

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200 °C), the hydrogen pressure (from 80 to 150 atm) and the catalyst (for example, Raney nickel and Rh on Al_2O_3), met with no success. We isolated either recovered starting material or reduced monopyrroles. We started to add increasing amounts of acids in the hope of accelerating the reduction process and avoiding as much as possible the competing ring-opening.

Initially this approach was not successful, and only reduced degradation products could be isolated. However, when we used glacial acetic acid as the solvent, we could isolate a product that a molecular-ion peak at *m*/*z* 437 $[M+H]^+$ in its electrospray ionization mass spectrum (ESI-MS). This indicated that four of the eight double bonds of the *meso*-octamethylporphyrinogen **1** had been reduced. Under these unoptimized conditions (Pd/C, 85 atm H_2 at 55 °C) the partially reduced product was obtained as a mixture of two diastereoisomers, as indicated in the ^{13}C NMR spectrum of the raw material. On refining the hydrogenation conditions (higher temperatures and pressures) we obtained only the major diastereoisomer **2** (Scheme 1). The ^{13}C NMR spectrum of **2** shows only seven signals indicating that the pyrrolidine rings and pyrrole rings are alternating. The X-ray structure[43] of the partially reduced *meso*-octamethylporphyrinogen **2** (Figure 1) confirmed this hypothesis.

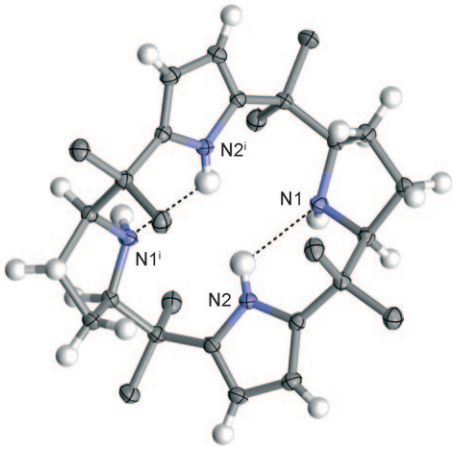


Figure 1. Molecular structure of **2** with thermal ellipsoids drawn at the 50% probability level. Atoms N1 and N1ⁱ and N2 and N2ⁱ are related by the crystallographic twofold axis. N–H···N hydrogen bonds are shown as dashed lines.

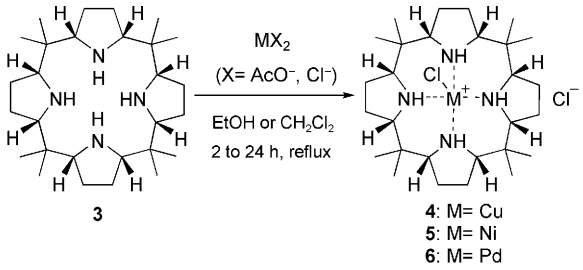
The conformation of **2** is dramatically different from that of the starting compound **1**. The two pyrrole rings in **2** are almost coplanar, and the two hydrogen atoms on the nitrogen atoms point towards the center of the macrocycle. The two pyrrolidine rings are almost orthogonal to the plane of the macrocycle. The hydrogen atoms at the ring junctions as well as those on N1ⁱ and N1 of the pyrrolidine residues point towards the outside of the macrocycle. The protons of the pyrroles are hydrogen-bonded to the basic nitrogen atoms of the pyrrolidine rings. The hydrogen-bonding network determines the conformation of this compound in the crystal (see also ref. [29]) and is responsible for the properties of this compound, which is a weak base.

In isolating the 1,3-bis-reduced compound **2**, we were surprised not to find the 1,2-bis-reduced isomer. One explanation is that the 1,3-regioisomer is protected against the acid-catalyzed degradation, whereas the 1,2-bis-reduced compound can still undergo acid-catalyzed ring-opening.

Compound **2** is water soluble in its diprotonated form, whereas the monoprotonated ligand precipitates out of water. The hydrogen-bonding network (vide supra) influences the acid–base behavior and probably the solubility of this new compound. Finally, it seems reasonable that once one of the pyrrole rings had been reduced on the surface of the catalyst, the second reduction should occur on the same face of the molecule. So with hindsight the structure of compound **2** can be rationalized. Attempts to reduce **2** further were not successful even under optimized conditions.

In the ESI mass spectrum of the crude product we detected a compound exhibiting a peak at *m*/*z* 445, which corresponds to the monoprotonated form of the completely reduced calixpyrrole **3** (Scheme 1). Isolating this compound in pure form proved to be difficult. By careful chromatography using neutral aluminum oxide we finally obtained small quantities of the completely reduced compound **3** as a white solid. The ^{13}C NMR spectrum of **3** shows five signals, which consistent with a structure in which all the hydrogen atoms at the ring junctions point in the same direction. Despite considerable efforts we have not been able to improve significantly the yield of the completely reduced compound **3**. Currently the conditions given in Scheme 1 are the best compromise we have found between the degradation of the macrocycle and the formation of the completely reduced product **3**.

In order to test the ability of ligand **3** to chelate different metals, we prepared complexes of Cu^{II}, Ni^{II}, and Pd^{II} following a similar procedure by mixing one equivalent of **3** with one equivalent of the metal salt in an appropriate solvent (Scheme 2). The complexation with Cu^{II} occurs smoothly when copper(II) chloride is heated with the reduced compound **3** in ethanol for 2 h. The complex formation can be conveniently followed by UV absorption at 284 nm. The UV spectra of the reaction mixture showed an isosbestic point at 248 nm. The nickel complex was prepared by the same procedure. The Pd^{II} complex was prepared from palladium(II) acetate in dichloromethane. In this case, according to



Scheme 2. Synthesis of complexes **4**–**6**. **4**: $CuCl_2 \cdot H_2O$, EtOH, reflux, 2 h. **5**: $NiCl_2 \cdot 6H_2O$, EtOH, reflux, 24 h. **6**: $Pd(AcO)_2$, CH_2Cl_2, reflux, 24 h.

mass and NMR analyses, the acetate ligands were partially exchanged by chloride during the reaction. Chlorinated solvents contain and continuously form small quantities of hydrogen chloride. Remaining acetate ligands were smoothly replaced by chloride when the complex was washed with a brine solution.

Suitable crystals of complexes **4**–**6** were obtained (Figure 2).[43] Interestingly, the X-ray structures of these complexes are very similar. In all the complexes, the four nitrogen atoms of the macrocycle are arranged nearly in a plane, and four of the eight methyl groups bound to the *meso* carbons are arranged in a quasi-axial arrangement, whereas the four others point away from the macrocycle in a quasi-equatorial position. The nickel and copper complexes show a quasi-octahedral coordination sphere of the metal ion, and two chloride ions are within bonding distance of the metal ion (Figure 2a, b). In the copper complex **4**, one chloride ion is linked directly to the metal center, whereas the other is held in place by the hydrogen network provided by the four NH groups of the pyrrolidine residues. In the nickel complex **5** both chloride ions are within bonding distance to the metal. The chloride labeled Cl2 is fixed through a hydrogen-bonding network similar to that in the copper complex. In the solid-state structure of the palladium complex **6** the Pd–Cl distances, ranging from 3.05 to 3.11 Å, are too long to be interpreted as formal bonds. As with the Ni^{II} and Cu^{II} complexes, hydrogen-bonding between one chloride ion and the NH groups of the pyrrolidine residues was observed. In this case, the central chloride ion is bound through four NH hydrogen bonds arranged by two symmetry-related macrocycle units (Figure 2c). Two different X-ray structures of the palladium complex have been obtained depending on the solvent used for the recrystallization. By slow evaporation of a solution of **6** in dichloromethane we obtained an orthorhombic polymorph (structure in Figure 2c), while a monoclinic polymorph, with two independent molecules per asymmetric unit, was obtained when a solution of **6** in dichloromethane and chloroform was concentrated by slow evaporation. The monoclinic and orthorhombic structures are similar, except for the position of the chloride counterions and solvent molecules of crystallization (structures and data are shown in the Supporting Information).[43]

In conclusion, we have developed a procedure for the partial or total reduction of *meso*-octaalkylporphyrinogens. The product of partial reduction is surprisingly stable, and only the regioisomer of the 1,3-reduction was isolated. The completely reduced compound is a strong base and smoothly forms metal complexes, as shown by the formation of the Cu^{II}, Ni^{II}, and Pd^{II} complexes. The reduction of the *meso*-octaalkylporphyrinogen **1** has changed the properties of this skeleton. The *meso*-octaalkylporphyrinogens are known to be anion binders, but in their reduced form they behave like normal nitrogen-containing macrocycles. Moreover, the metal complexes of reduced calix[4]pyrrole may maintain their anion-binding ability through the hydrogen-bond network. As a result of the four five-membered rings the conformational mobility of this ligand is rather limited. In the metal chelate, the quasi-axial arrangement of the substituents

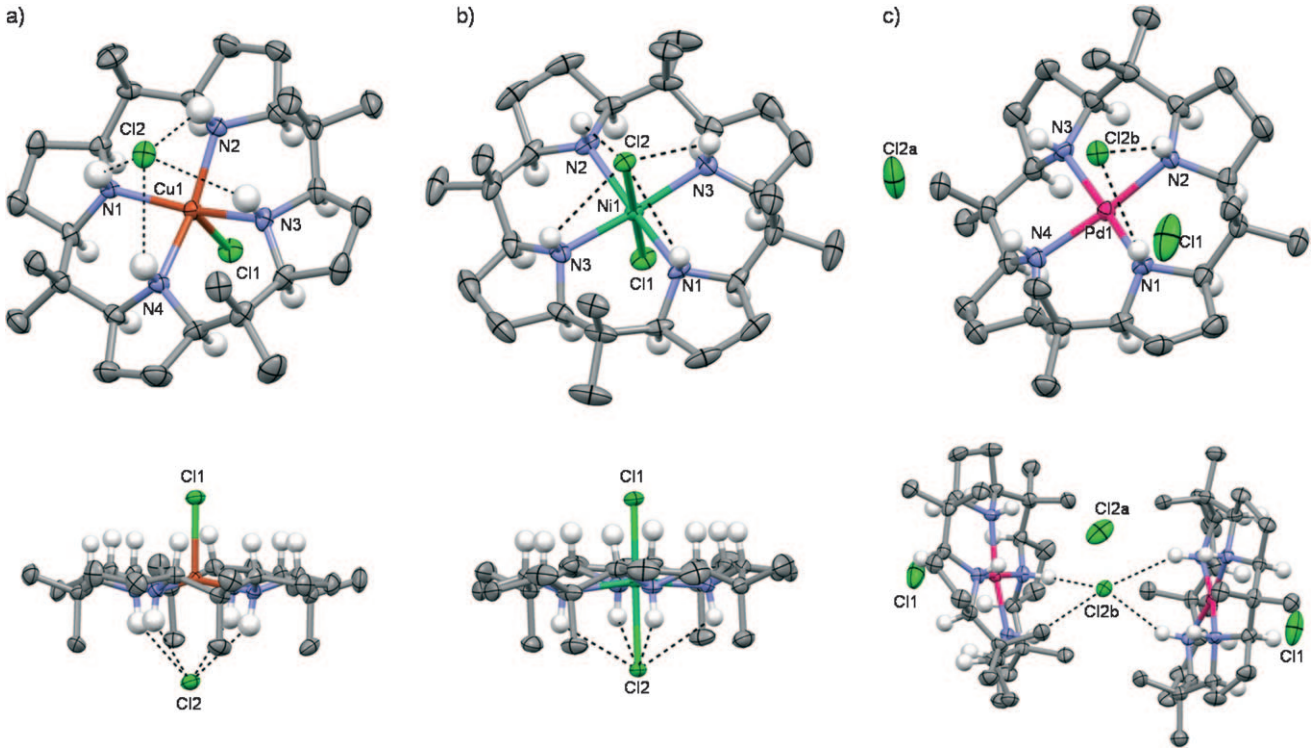


Figure 2. Molecular structure of complexes **4**, **5**, and **6** with thermal ellipsoids drawn at the 50% probability level. Dotted lines indicate NH···Cl interactions (solvent molecules and most hydrogen atoms have been removed for clarity). Selected distances (in Å): a) Cu complex **4**: Cu1–N 2.109–2.136, NH···Cl2 2.60–2.84, Cu1–Cl1 2.432(1) Å; b) Ni complex **5**: Ni1–N 2.139–2.153, NH···Cl2 2.65–2.76 Å, Ni1–Cl1 2.359(1), Ni1–Cl2 2.550(1); c) Pd complex **6**: Pd1–N 2.082–2.093; NH···Cl2b 2.68–2.93 Å, Pd1–Cl1 3.115(2) Å.

at the *meso* positions may form a cavity. These structural and chemical properties should allow the synthesis of interesting new metal complexes.

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[1] D. Voet, J. G. Voet, *Biochemistry*, Wiley, New York, **1990**.
[2] H. Scheer, *Chlorophylls*, CRC Press, Boca Raton, **1991**.
[3] B. Kräutler, *Biochem. Soc. Trans.* **2005**, *33*, 806.
[4] B. Kräutler, S. Ostermann in *The Porphyrin Handbook*, *Vol. 11* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), Academic Press, San Diego, **2003**, p. 229.
[5] B. Kräutler, *Chimia* **1987**, *41*, 277.
[6] H.-J. Kwon, W. C. Smith, A. J. Sharon, S. H. Hwang, M. J. Kurth, B. Shen, *Science* **2002**, *297*, 1327.
[7] S. S. Lamb, G. D. Wright, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 519.
[8] A. R. Battersby, F. J. Leeper, *Top. Curr. Chem.* **1998**, *195*, 143.
[9] A. I. Scott, *J. Org. Chem.* **2003**, *68*, 2529.
[10] C. Floriani, *Chem. Commun.* **1996**, 1257.
[11] C. Floriani, R. Floriani-Moro in *The Porphyrin Handbook*, *Vol. 3* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), Academic Press, San Diego, **2000**, p. 385.
[12] A. Eschenmoser, *Angew. Chem.* **1988**, *100*, 5; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 5.
[13] L. R. Milgrom, *The Color of life*, Oxford University Press, Oxford, **1997**.
[14] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2184.
[15] V. V. Chelintzev, B. V. Tronov, S. G. Karmanov, *J. Russ. Phys.-Chem. Soc.* **1916**, *48*, 1210.
[16] V. V. Chelintzev, B. V. Tronov, *Chem. Abstr.* **1917**, *11*, 452.
[17] P. Rothemund, C. L. Gage, *J. Am. Chem. Soc.* **1955**, *77*, 3340.
[18] P. A. Gale, J. L. Sessler, V. Kral, V. Lynch, *J. Am. Chem. Soc.* **1996**, *118*, 5140.
[19] R. Custelcean, L. H. Delmau, B. A. Moyer, J. L. Sessler, W.-S. Cho, D. Gross, G. W. Bates, S. J. Brooks, M. E. Light, P. A. Gale, *Angew. Chem.* **2005**, *117*, 2593; *Angew. Chem. Int. Ed.* **2005**, *44*, 2537.
[20] V. Böhmer, *Angew. Chem.* **1995**, *107*, 785; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713.
[21] P. A. Gale, P. Anzenbacher, J. L. Sessler, *Coord. Chem. Rev.* **2001**, *222*, 57.
[22] J. L. Sessler, P. A. Gale in *The Porphyrin Handbook*, *Vol. 6* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), Academic Press, San Diego, **2000**, p. 257.
[23] P. A. Gale, *Coord. Chem. Rev.* **2000**, *199*, 181.
[24] C. Bucher, D. Seidel, V. Lynch, V. Kral, J. L. Sessler, *Org. Lett.* **2000**, *2*, 3103.
[25] V. Král, J. L. Sessler, R. S. Zimmerman, D. Seidel, V. Lynch, B. Andrioletti, *Angew. Chem.* **2000**, *112*, 1097; *Angew. Chem. Int. Ed.* **2000**, *39*, 1055.
[26] B. Turner, M. Botoshansky, I. Eichen, *Angew. Chem.* **1998**, *110*, 2633; *Angew. Chem. Int. Ed.* **1998**, *37*, 2475.
[27] P. A. Gale, J. L. Sessler, V. Kral, *Chem. Commun.* **1998**, 1.
[28] J. L. Sessler, W.-S. Cho, V. Lynch, V. Kràl, *Chem. Eur. J.* **2002**, *8*, 1134.
[29] V. Král, P. A. Gale, P. Anzenbacher, Jr., K. Jursíková, V. Lynch, J. L. Sessler, *Chem. Commun.* **1998**, 9.
[30] D.-W. Yoon, H. Hwang, C.-H. Lee, *Angew. Chem.* **2002**, *114*, 1835; *Angew. Chem. Int. Ed.* **2002**, *41*, 1757.
[31] K. A. Nielsen, W.-S. Cho, J. Lyskawa, E. Levillain, V. M. Lynch, J. L. Sessler, J. O. Jeppesen, *J. Am. Chem. Soc.* **2006**, *128*, 2444.
[32] D. Jacoby, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Chem. Soc. Chem. Commun.* **1991**, 220.
[33] J. Jubb, D. Jacoby, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *Inorg. Chem.* **1992**, *31*, 1306.
[34] L. Bonomo, E. Solari, R. Scopelliti, C. Floriani, *Chem. Eur. J.* **2001**, *7*, 1322.
[35] M. Studer, A. Reisen, T. A. Kaden, *Helv. Chim. Acta* **1989**, *72*, 1253.
[36] E. Kimura, Y. Kodama, M. Shionoya, T. Koike, *Inorg. Chim. Acta* **1996**, *246*, 151.
[37] P. Bryan, J. C. Dabrowiak, *Inorg. Chem.* **1975**, *14*, 296.
[38] Z. Guo, P. J. Sadler, *Angew. Chem.* **1999**, *111*, 1610; *Angew. Chem. Int. Ed.* **1999**, *38*, 1512.
[39] J. E. Hage, J. E. Iburg, J. Kerschner, J. H. Koek, E. L. M. Lempers, R. J. Martens, U. S. Racherla, S. W. Russell, T. Swarthoff, M. R. P. Van Vliet, J. B. Warnaar, L. Van der Wolf, B. Krijnen, *Nature* **1994**, *369*, 637.
[40] D. De Vos, T. Bein, *Chem. Commun.* **1996**, 917.
[41] D. E. De Vos, T. Bein, *J. Organomet. Chem.* **1996**, *520*, 195.
[42] R. A. Jones in *Comprehensive Heterocyclic Chemistry*, *Vol. 4* (Eds.: C. W. Bird, G. W. H. Cheeseman), Pergamon Press, Oxford, **1984**, p. 255.
[43] CCDC 688525 (**2**), 688526 (**4**), 704348 (**5**), 702636 (**6**-orthorhombic), and 702635 (**6**-monoclinic) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

