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# Facile Preparation of Doubly Dipyrrolylquinoxaline-Bridged Expanded Porphyrins. Synthesis and Structural Characterization of an Unprecedented [20]Tetraphyrin-(2.1.2.1)

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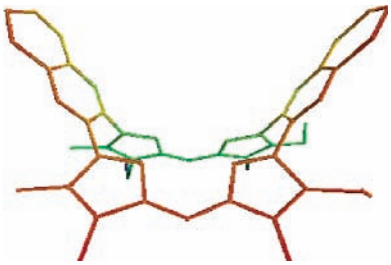
**ABSTRACT**



**An unprecedented V-shape (2.1.2.1) expanded porphyrin incorporating an extended $\pi$-conjugated system is described. Its efficient synthesis relied on the use of a new peralkyl tetrapyrrolylquinoxaline building block that constitutes the ideal intermediate for the versatile preparation of new quinoxaline-containing macrocycles.**

Over the past few decades, tremendous effort has been devoted toward the synthesis of porphyrins and porphyrin analogues. Undoubtedly, their crucial role in areas as different as molecular recognition, coordination, and biomedical chemistries legitimizes an extensive literature.[1] Several porphyrin isomers possessing different cavity shapes and exhibiting unique binding and electronic properties have been prepared.[2a] Correlatively, considering that only relatively small cations fit in the porphyrin core, additional pyrroles or coordinating atoms were incorporated in the macrocycle.[2] This synthetic tactic allowed the preparation of an impressive variety of new macrocycles capable of coordinating large cations, such as lanthanides. Although some systems are too large for the coordination of a single cation, they were proven to be interesting ligands for the close-binding of two metals[3] as well as for the coordination of anionic species.[4]

In 1999, Sessler et al. demonstrated that dipyrrolylquinoxaline (DPQ) constitutes an original system for the naked-eye detection of anions.[5] After this pioneering report, several elaborated dipyrrolylquinoxaline-based anion sensors were reported.[6] Quite surprisingly, only one report concerned the use of the DPQ building block for the preparation of expanded porphyrins.[7] Most probably, the limited number of DPQ-containing macrocycles is ascribable to the difficulty

(1) For a complete overview, see: *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2000.

(2) (a) Sessler, J. L.; Weghorn, S. J. In *Expanded, Contracted and Isomeric Porphyrins*; Elsevier Science Ltd.: Trowbridge, UK, 1997; Vol. 15. (b) Jasat, A.; Dolphin, D. *Chem. Rev.* **1997**, *97*, 2267−2340. (c) Sessler, J. L.; Seidel, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5134−5175.

(3) See for instance: Charrière, R.; Jenny, T. A.; Rexhausen, H.; Gossauer, A. *Heterocycles* **1993**, *36*, 1561−1575.

(4) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17−55.

(5) Black, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438−10439.

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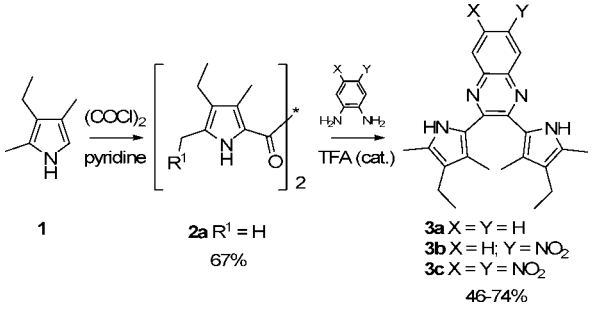
to functionalize the DPQ moiety. Indeed, in addition to a poor solubility, the possibility for the pyrrole electrons to delocalize over the heterocycle often prevents any selectivity and forbids classical pyrrole chemistry.[8]

For some time, due to the remarkable potential of the quinoxaline moiety for the preparation of macrocyclic structures with extended $\pi$-conjugated systems, we have been interested in the development of quinoxaline-containing expanded porphyrins. To this end, we developed a synthetic strategy based on the use of kryptopyrrole **1** for the preparation of highly soluble and easy-to-functionalize polypyrrolic quinoxalines.

According to the procedure described by Oddo,[9] we prepared the soluble peralkyl dipyrrolyldiketone **2a** in 67% yield (Scheme 1).[10] Next, **2a** was converted to the corresponding peralkyl DPQs **3a**−**c** using an excess of diamine in refluxing toluene and in the presence of a catalytic amount of trifluoroacetic acid.

**Scheme 1.** Synthesis of the Peralkyl Quinoxalines **3a**−**c**




As expected, DPQs **3a**−**c** are well soluble in most nonpolar organic solvents. Single crystals suitable for X-ray diffraction analyses were obtained by slow evaporation of a dichloromethane solution containing **3a**. Despite the presence of the bulky alkyl groups, the crystal structure revealed "inverted" pyrroles with NH pointing toward the quinoxaline nitrogen atoms (Figure 1). Such an inverted conformation was already observed in the solid state for nonalkylated DPQ.[11] The dihedral angle between the two pyrroles was estimated at 17.9°. In addition, the presence of the alkyl groups induces a slight deformation of the quinoxaline departing the rigid skeleton from planarity.

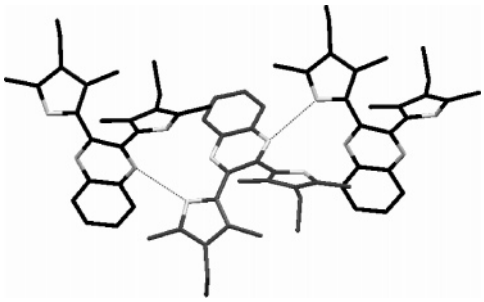
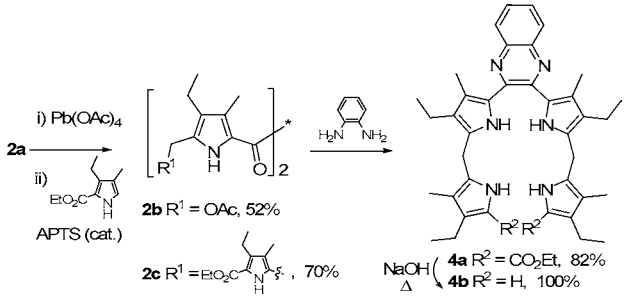


**Figure 1.** X-ray crystal structure of **3a** showing a hydrogen bonding network in the solid state. Hydrogen atoms are omitted for clarity.

As a direct functionalization of **3a**−**c** failed in our hands, we converted the precursor **2a** to the corresponding diacetoxymethyl derivative **2b** using $Pb(OAc)_4$ in acetic acid in 52% yield (Scheme 2). The latter was then reacted with ethyl 3-ethyl-4-methyl-1*H*-pyrrole-2-carboxylate, affording the diester-protected tetrapyrrolyldiketone **2c** in 70% yield. Finally, the tetrapyrrolylquinoxaline (TPQ) **4a** was obtained using the mild procedure established for the preparation of **3a**−**c** in 82% yield. A subsequent saponification/decarboxylation sequence using NaOH in refluxing ethylene glycol afforded the bis α-free tetrapyrrolylquinoxaline **4b** quantitatively. Thus, starting from the commercially available kryptopyrrole, the key intermediate **4b** was efficiently prepared in five steps and 21% overall yield.

**Scheme 2.** Synthesis of the Acyclic Tetrapyrrolylquinoxaline **4b**




Having in hands a unique quinoxaline-containing macrocycle precursor, we considered different ring closing options (Scheme 3).

We first envisaged a macrocyclization via a direct pyrrole−pyrrole $\sigma$-bond coupling. Unfortunately, the different oxidative cyclizations—metal-templated or not—we tested did not afford any quinoxaline-containing corrphycene **5**.[12,13] Considering that the quinoxaline moiety may prevent the

(6) See for instance: (a) Anzenbacher, P.; Try, A. C.; Miyaji, H.; Jursíková, K.; Lynch, V. M.; Marquez, M.; Sessler, J. L. *J. Am. Chem. Soc*. **2000**, *122*, 10268−10272. (b) Pohl, R.; Aldakov, D.; Kubat, P.; Jursíková, K.; Marquez, M.; Anzenbacher, P. *Chem. Commun.* **2004**, 1282−1283.

(7) Sessler, J. L.; Maeda, H.; Mizuno, T.; Lynch, V. M.; Furuta, H. *Chem. Commun.* **2002**, 862−863.

(8) The only noticeable exception concerns the preparation of the diformyl DPQ (see ref 6).

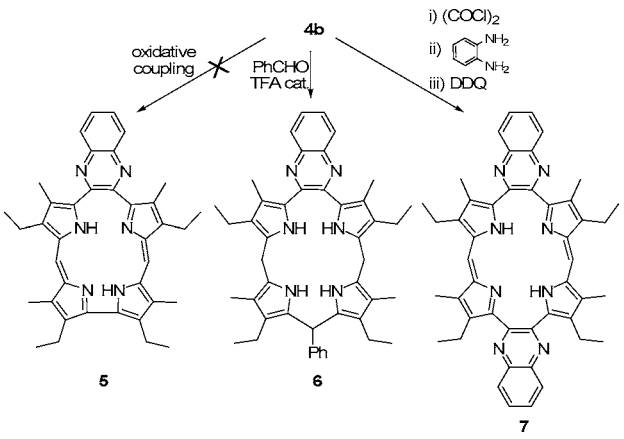
(9) Oddo, B. *Gazz. Chim. Ital.* **1911**, *41*, 248−255.

(10) Szydlo, F.; Andrioletti, B.; Rose, E.; Duhayon, C. *Tetrahedron Lett.* **2004**, *45*, 7363−7365.

(11) Sessler, J. L.; Andrioletti, B.; Anzenbacher, P., Jr.; Black, C.; Eller, L.; Furuta, H.; Jursíková, K.; Maeda, H.; Marquez, M.; Mizuno, T.; Try, A. In *Fundamentals and Applications of Anion Separations*; ACS Book ed.; Singh, R. P., Moyer, B. A., Eds.; Kluwer Academic/Plenum Publishers: New York, 2002.

(12) (a) Sessler, J. L.; Brucker, E. A.; Weghorn, S. J.; Kisters, M.; Schafer, M.; Lex, J.; Vogel, E. *Angew. Chem., Int. Ed.* **1994**, *33*, 2308−2312. (b) Aukauloo, M. A.; Guilard, R. *New J. Chem.* **1994**, *18*, 1205−1207.

**Scheme 3.** Structures of the Macrocyclic Targets




system from adopting a suitable conformation for a direct ring closing, we decided to perform a ring closure with additional *meso* carbon atoms. To this end, we reacted in parallel the bis α-free **4b** with stoichiometric amounts of benzaldehyde or oxalyl chloride. Both approaches were successful. Although the condensation of **4b** with benzaldehyde afforded the (2.1.1.1)-quinoxaline-containing porphyrinogen **6** in 33% yield, we were unable to oxidize it using DDQ, *p*-chloranil, or $FeCl_3$, yet. On the other hand, the preparation of a bisquinoxaline macrocycle appeared remarkably efficient. Indeed, not only did the equimolar condensation of oxalyl chloride with **4b** afford the expected diketone, but the subsequent condensation of the crude diketone with excess 1,2-phenylenediamine provided the bisquinoxaline porphyrinogen in 40% overall yield. Ultimately, it was efficiently oxidized using excess DDQ in $CH_2Cl_2$ at room temperature, affording the unprecedented (2.1.2.1) tetrapyrrolic macrocycle **7**.[14] The crude diketone was also condensed with 4-nitro- or 4,5-dinitro-1,2-phenylenediamine to afford the nitro-functionalized analogues in 16 and 14% overall yield, respectively.

NMR and spectrophotometric studies confirmed the antiaromatic character of **7**. In addition, it was further characterized in the solid state. Single crystals suitable for X-ray diffraction analysis were obtained by slow diffusion of petroleum ether in a THF solution containing **7** (Figure 2).[15]

If the general arrangement of the atoms fits with expectations, it is remarkably nonplanar. Thus, in the solid state, the molecule adopts a boat-like conformation with quinoxaline moieties almost facing each other, providing a rigid-wall deep cavity. The angle α between the two quinoxalines was estimated at 59°. Another noticeable feature concerns the cone conformation of the pyrrole units. Consequently, the *meso* protons lie in the convex part of the molecule. The geometry of the cavity defined by the nitrogen atoms is almost rectangular with small and large dimensions of 2.9 and 3.1 Å, respectively. As a consequence, the core defined by the four coplanar nitrogen atoms is about 8% larger than that of a porphyrin. Preliminary binding studies were carried out. Unexpectedly, in contrast with other V-shape tetrapyrrolic macrocycles, such as calix[4]phyrins,[16] UV−vis and NMR titrations revealed very low affinities—$K_a$ values typically less than 100 $M^{-1}$—of the ligands for anions. Presumably, the negative effect of the alkyl groups that increase the electron density on the pyrroles but also impose unfavorable geometrical constraints is responsible for this observation. On the other hand, **7** appeared a good ligand for most d metals tested. In particular, it was shown to form stable complexes with first row metals, such as Zn and Cu, or larger ones, such as Pd, Cd, Sn, or Pb (see experimental section in the Supporting Information).

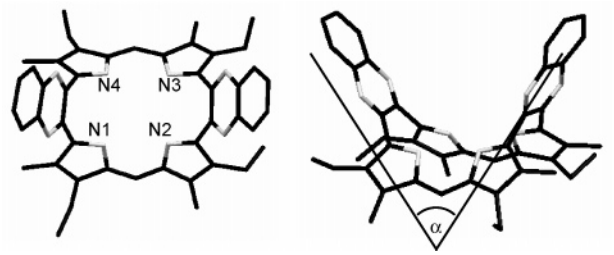



**Figure 2.** Molecular structure of **7** showing the boat-like conformation of the macrocycle. Solvent molecules and hydrogens are omitted for clarity.

In summary, we have developed a new, highly efficient route to expanded porphyrins incorporating dipyrrolylquinoxaline subunits. The versatility of the peralkyl dipyrrolyldiketone **2a** allowed the straightforward preparation of the key TPQ building block in five steps and 21% overall yield. The latter could be efficiently ring closed using stoichiometric amounts of oxalyl chloride or benzaldehyde. The X-ray crystal structure of the new bisquinoxaline macrocycle revealed a boat-like conformation and a nitrogen core 8% larger than that of a porphyrin. Preliminary complexations showed good coordinating aptitudes for most d metals. Work is currently in progress for preparing new, quinoxaline-containing isomeric or expanded macrocycles potentially useful for biomedical applications and clarifying the appropriate conditions for the coordination of lanthanoids.

(13) (a) Falk, H. *Monatsh. Chem.* **1996**, *129*, 69−75. (b) Neya, S.; Nishinaga, K.; Ohyama, K.; Funasaki, N. *Tetrahedron Lett.* **1998**, *39*, 5217−5220.

(14) Unknown for oligopyrroles, the (2.1.2.1) arrangement was already reported in the thiophene and furan series.

(15) The crystals were of very poor quality (see the low observed/unique reflection ratio (18.7%) and the low observed reflection/refined parameters ratio (4.7%). Several attempts were undertaken on different single crystals, and the results presented here were obtained on the better one we found. The residual electronic density showed several peaks (1.29 < rho < 1.11e−/Å$^3$) corresponding to another but disordered THF solvent molecule. It was not possible to modelize this disorder. This conclusion is confirmed by the analysis of solvent accessible voids in the structure. These voids where the residual peaks are located have a volume of approximately 164 Å$^3$ (a value in accordance with the volume of a small molecule, such as THF) and are located at the average positions 0.0 0.0 0.5 and 0.5 0.5 0.0 of the cell.

(16) Král, V.; Sessler, J. L.; Zimmerman, R.; Seidel, D.; Lynch, V.; Andrioletti, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1055−1058.

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**Supporting Information Available:** Experimental procedures and spectral data for new compounds. CCDC 293651 and 293652 for **3a** and **7**, respectively, 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. This material is available free of charge via the Internet at http://pubs.acs.org.

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