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Steric Control in the Synthesis of *p*-Benziporphyrins. Formation of a Doubly N-Confused Benzihexaphyrin Macrocycle

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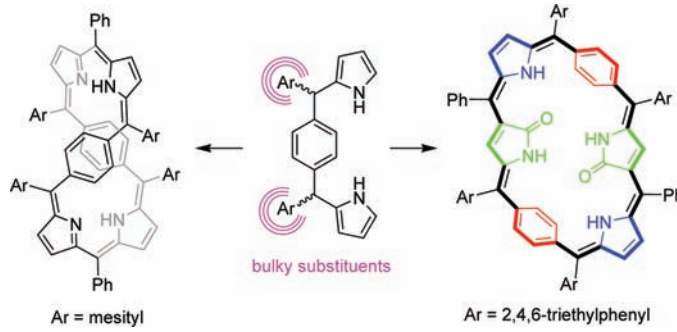
ABSTRACT



The use of 1,4-phenylene-containing tripyrrane analogs provides a general route to expanded *p*-benziporphyrins. The course of macrocyclization shows a striking dependence on the steric bulk of meso substituents.

Benziporphyrins are a class of porphyrinoids combining pyrrolic and phenylene rings into a macrocyclic structure.[1] *p*-Benziporphyrins, which contain 1,4-linked phenylene units are of particular interest, as they exhibit coordinating abilities of porphyrins while providing nontrivial examples of macrocyclic aromaticity (Figure 1). For instance, in the generic *p*-benzi[18]porphyrin(1.1.1.1) (**1**), the electronic structure of the benzene ring is so strongly affected by macrocyclic conjugation that the ^{1}H NMR shifts of the inner (21,22-H) and outer phenylene protons (2,3-H) differ by 5.36 ppm, which is indicative of a macrocyclic ring current.[2] Simultaneously, the phenylene ring retains much of its benzenoid character, as evidenced by X-ray structural data and the

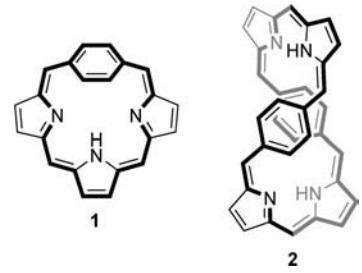


Figure 1. Macrocyclic cores of *p*-benziporphyrin (**1**) and A,D-di-*p*-benzi[28]hexaphyrin(1.1.1.1.1.1) (**2**).

(1) For general reviews see: (a) Stępień, M.; Latos-Grażyński, L. *Acc. Chem. Res.* **2005**, *38*, 88–98. (b) Stępień, M.; Latos-Grażyński, L. Aromaticity and Tautomerism in Porphyrins and Porphyrinoids. *Topics in Heterocyclic Chemistry Volume 19. Aromaticity in Heterocyclic Compounds*; Springer: Berlin/Heidelberg, 2009; pp 83−153. For related recent work, see, for example: (c) Sim, E.-K.; Jeong, S.-D.; Yoon, D.-W.; Hong, S.-J.; Kang, Y.; Lee, C.-H. *Org. Lett.* **2006**, *8*, 3355–3358. (d) Reddy, J. S.; Anand, V. G. *Chem. Commun.* **2008**, 1326–1328.

(2) Stępień, M.; Latos-Grażyński, L. *J. Am. Chem. Soc.* **2002**, *124*, 3838–3839.

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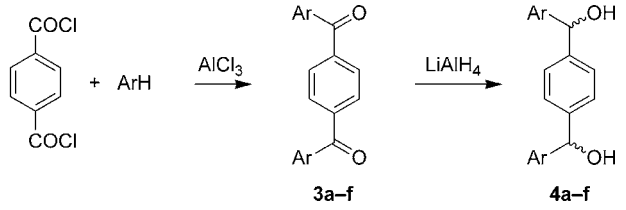
conformational flexibility of the macrocycle observable by NMR spectroscopy.

Furthermore, the recently reported A,D-di-*p*-benzi[28]-hexaphyrin(1.1.1.1.1.1) (**2**) provided an unprecedented example of conformational switching between Hückel and Möbius aromaticity.[3] Since the original proposal of Heilbronner, Möbius aromaticity has been the subject of intense theoretical and computational investigation,[4] but synthetic examples of Möbius aromatics are still rare, compound **2** being only the second documented case.[5] The switching mechanism in **2** relies on the internal rotations of phenylene rings, which act as topology selectors.

Unfortunately, the available syntheses of benziporphyrins, while preparatively convenient, are often low-yielding and produce mixtures of products.[2,3a] Here we show an improved route to the expanded *p*-benziporphyrin **2**, which provides enhanced yields and superior selectivity. We also report on a doubly N-confused benziporphyrinoid, whose formation is dependent on the steric demand of meso substituents.

p-Benziporphyrins are normally synthesized from dicarbinols of the general formula **4**, according to a Lindsey-type protocol.[6] To date, when used for porphyrinoid synthesis, dicarbinols **4** have been prepared by two routes: (1) from terephthalaldehyde and a Grignard reagent[2] and (2) from 1,4-dibromobenzene via lithium−halogen exchange followed by aldehyde addition.[3a] Both of these two approaches involve the use of air-sensitive reagents, which makes them less convenient for large-scale work. In many instances, these two routes can be replaced with a synthesis shown in Scheme 1, which, to our knowledge, has not been

Scheme 1



3a–f 4a–f

a Ar = phenyl (Ph)
b Ar = *p*-tolyl (*p*-Tol)
c Ar = anisyl (An)
d Ar = 2,4,6-trimethylphenyl (Mes)
e Ar = 2,3,5,6-tetramethylphenyl (Dur)
f Ar = 2,4,6-triethylphenyl (Tep)

systematically explored.[7] The present method consists of a Friedel−Crafts reaction between terephthaloyl chloride and an appropriate arene, followed by a reduction of the resulting diketone with lithium aluminum hydride. For this method to work efficiently, the arene must be sufficiently active toward acylation. Additionally, the formation of regioisomers has to be avoided by choosing arenes with appropriate symmetry (**4a**,**d**−**f**) or reactivity patterns (**4b**,**c**). To achieve complete reduction of diketones **3**, it was necessary to use $LiAlH_4$ in refluxing THF as milder reduction conditions were not effective in our hands.

Dicarbinols **4** were subsequently reacted with an excess of pyrrole to yield tripyrrane analogues **5**, which were subjected to a Lindsey macrocyclization with benzaldehyde followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, Scheme 2). In the case of the mesityl derivative **5d**, the reaction indeed provided hexaphyrin **2d** as the only isolable macrocyclic product (11%). This result is an improvement over the original condensation between **4d**, pyrrole, and benzaldehyde.[3a] The latter method provided a mixture of products, from which **2d** could be isolated in 6% yield. Additionally, by using tripyrrane analogue **5e**, the new duryl-substituted derivative **2e** was prepared for the first time. Unfortunately, this compound is unstable during chromatography, which is a reason for the low isolated yield (ca. 3%). Interestingly, we were unable to isolate any expanded benziporphyrins from reactions involving tripyrrane analogs **5a**−**c**, which afforded only small amounts of the respective *p*-benziporphyrins. This observation indicates that the presence of *ortho*-substituents on the *meso*-aryl groups is required for effective ring closure.

To our surprise, when **5f** was condensed with benzaldehyde, we observed no formation of the expected hexaphyrin **2f**. Instead, a new macrocycle, **6f**, was isolated with yields up to 14%. This reactivity is more general, as the mesityl analogue **6d** forms in small amounts during the synthesis of **2d**. The macrocyclic system of **6**, which can be named 8,23-dioxo-7,22-diaza-33,37-dicarba-A,D-di-*p*-benzi[28]hexaphyrin-(1.1.1.1.1.1) using the standard porphyrinoid nomenclature, differs from the structure of **2** by the presence of two N-confused rings (B and E, Scheme 2).[8] These two rings are oxidized at the free α-pyrrolic positions (8 and 23), providing two lactam functionalities.[9]

The isolation of an isomerically pure doubly N-confused system is of interest because such molecules are normally obtained from predesigned N-confused precursors rather than via direct *β*-condensation of nonconfused units.[10] In the case

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(4) (a) Heilbronner, E. *Tetrahedron Lett.* **1964**, *5*, 1923–1928. For a review of conceptual and synthetic advances, see: (b) Herges, R. *Chem. Rev.* **2006**, *106*, 4820–4842.

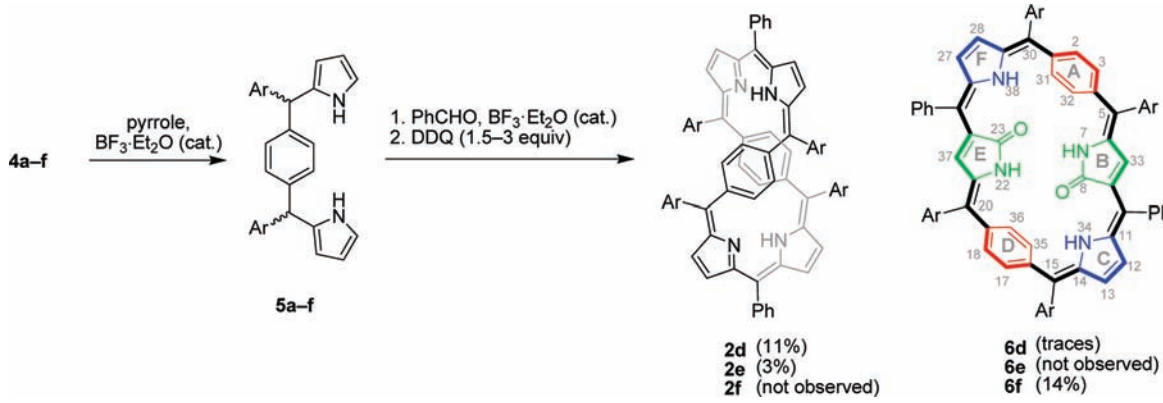
(5) (a) For the first example, see: Ajami, D.; Oeckler, O.; Simon, A.; Herges, R. *Nature* **2003**, *426*, 819–821. Subsequent work on Möbius porphyrinoids: (b) Pacholska-Dudziak, E.; Skonieczny, J.; Pawlicki, M.; Szterenberg, L.; Ciunik, Z.; Latos-Grażyński, L. *J. Am. Chem. Soc.* **2008**, *130*, 6182–6195. (c) Tanaka, Y.; Saito, S.; Mori, S.; Aratani, N.; Shinokubo, H.; Shibata, N.; Higuchi, Y.; Yoon, Z. S.; Kim, K. S.; Noh, S. B.; Park, J. K.; Kim, D.; Osuka, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 681–684. (d) Park, J. K.; Yoon, Z. S.; Yoon, M.-C.; Kim, K. S.; Mori, S.; Shin, J.-Y.; Osuka, A.; Kim, D. *J. Am. Chem. Soc.* **2008**, *130*, 1824–1825. (e) Sankar, J.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 13568–13579. (f) Saito, S.; Shin, J.-Y.; Lim, J. M.; Kim, K. S.; Kim, D.; Osuka, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9657–9660. (g) Kim, K. S.; Yoon, Z. S.; Ricks, A. B.; Shin, J.-Y.; Mori, S.; Sankar, J.; Saito, S.; Jung, Y. M.; Wasielewski, M. R.; Osuka, A.; Kim, D. *J. Phys. Chem. A* **2009**, *113*, 4498–4506. (h) Tokuji, S.; Shin, J.-Y.; Kim, K.-S.; Lim, J.-M.; Youfu, K.; Saito, S.; Kim, D.; Osuka, A. *J. Am. Chem. Soc.* **2009**, *131*, 7240–7241.

(6) Lindsey, J. S. Synthesis of meso-Substituted Porphyrins. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 1, Chapter 2, pp 45−118.

(7) The majority of compounds **3** and **4** were previously obtained by a variety of methods, usually not related to the one described here. For details and references, see the Supporting Information.

(8) *N*-Confusion in porphyrin chemistry: (a) Furuta, H.; Maeda, H.; Osuka, A. *Chem. Commun.* **2002**, 1795–1804. (b) Harvey, J. D.; Ziegler, C J. *Coord. Chem. Rev.* **2003**, *247*, 1–19.

Scheme 2



of **6**, two pyrrole rings undergo N-confusion during macrocyclization (as previously observed in several singly N-confused porphyrinoids[11]). The isolated isomer is one of the three possible doubly N-confused structures that can be obtained in the absence of pyrrole scrambling.

Compound **6f** is only formed efficiently in the presence of excess DDQ (3 equiv per 1 mol of **5f**). The use of 1.5 equiv of DDQ, which is a sufficient amount for the formation of **2**, provides only traces of **6f**. However, we were unable to identify any intermediate oxidation products from the resulting mixture.

In the solid state,[12] compound **6f** adopts a quasiplanar conformation, with the N-confused rings inverted toward the center of the macrocycle (Figure 2). This conformation, which is significantly different from the figure-eight structure **2**, is stabilized by two intramolecular hydrogen bonds linking amine hydrogens of rings C and F with lactam oxygens of rings B and E, respectively (NH···O distance of 1.95 Å). The NH···O distances between the two inverted pyrroles equal 2.51 Å, suggesting that the transannular interaction between rings B and E is insignificant. The phenylene rings are tilted at an angle of 46° relative to the macrocyclic plane. Apart from the phenylene rings, which show only a slight quinoidal distortion from the regular benzene structure, the macrocyclic system exhibits bond length alternation, in accord with the expected antiaromatic character of **6f**.

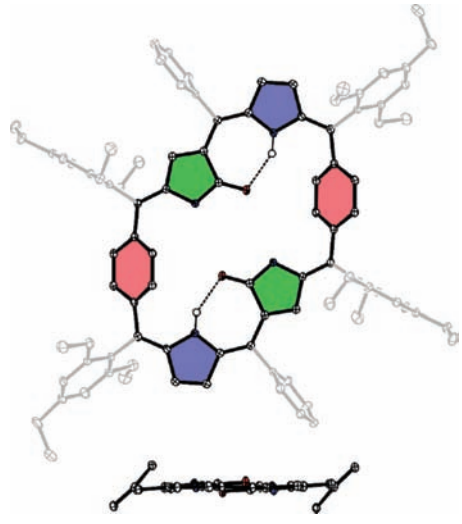


Figure 2. X-ray rystal structure of **6f** with vibrational ellipsoids at the 50% probability level. Solvent molecules, hydrogen atoms, and disorder in one of the Tep substituents are not shown for clarity. Intramolecular hydrogen bonds are shown as dotted lines. The side view at the bottom shows the orientation of the phenylene rings.

The conformation of **6f** observed in the solid state is largely preserved in solution, as confirmed by proton magnetic resonance spectroscopy (Figure 3, top). The macrocycle is moderately paratropic, in line with its [28]annulenoid formulation, leading to observable shielding of the peripheral protons in the molecule. In particular, the signals at 5.61 and 5.49 ppm were identified as corresponding to the β-pyrrolic protons of rings C/F, whereas the signal at 4.81 ppm was assigned to the lone β proton of the flipped rings B/E. Accordingly, the downfield signals at 10.83 and 14.12 ppm were assigned to the inner NH signals of rings B/E and C/F, respectively. The large downfield shift of the C/F NH signal combines the deshielding effects of paratropicity and strong intramolecular hydrogen bonding. The observed four-bond couplings between pyrrolic β and NH signals are consistent with the different connectivity patterns of the regular pyrrolic unit (C/F) and the α-oxidized N-confused unit (B/E).

At room temperature, the phenylene rings (A/D) are represented by an AA′BB′ spin system at 7.87 and 7.74 ppm. This spectral pattern corresponds to fast phenylene libration, which rapidly exchanges positions of the "outer" and "inner" protons. The libration is a very fast process, and consequently, decoalescence of the phenylene signals can only observed below 190 K (dichloromethane-d_2, 600 MHz). In a supercooled solution at 160 K, two broad overlapping signals are observed at ca. 9.4 and 9.3 ppm, corresponding to the inner phenylene protons, whereas the outer protons give rise to a signal of double intensity at 6.24 ppm. Such differentiation of chemical shifts corresponds to that observed for pyrrolic rings, and is characteristic of a paratropic system.

Compound **6f** has a deep red color in solution. The

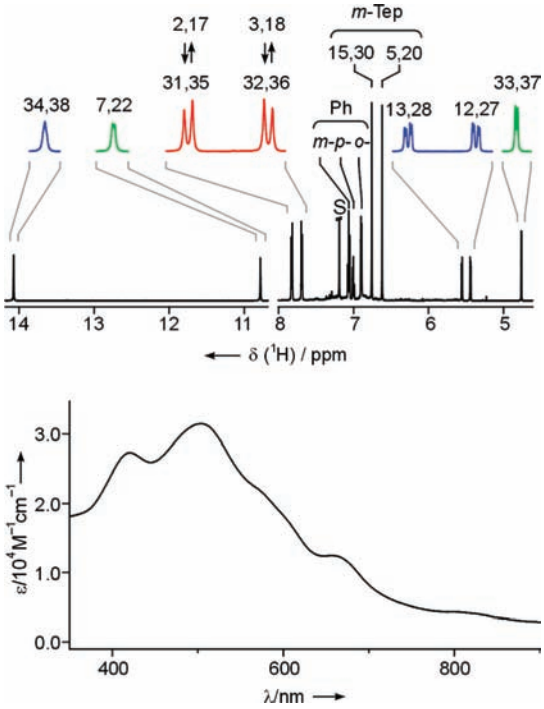


Figure 3. Top: ^{1}H NMR spectrum of **6f** ($CDCl_3$, 600 MHz, 300 K). The assignment was made on the basis of 2D NMR data. Atom numbering corresponds to that given in Scheme 2. Arrows indicate fast phenylene rotation. The alkyl region, containing signals of the ethyl groups, is not shown. Bottom: The electronic spectrum of **6f** (CH_2Cl_2, 298 K).

electronic spectrum of **6f** (Figure 3, bottom) consists of several broad overlapping bands and is characterized by the absence of a dominant Soret-like absorption. The spectrum changes insignificantly upon addition of several equivalents of trifluoroacetic acid. This behavior is expected, since **6f** contains no imine nitrogen sites that could be protonated.

In this paper, we have shown that the reactivity patterns leading to expanded benziporphyrins are highly dependent on *meso*-substitution. It was found that the presence of *o*-methyl groups on the meso substituents flanking the phenylene is a prerequisite to the formation of expanded macrocycles. Unexpectedly, further increase of the steric bulk results in the formation of a doubly N-confused system **6**, which shares the basic structural outline with **2** but no longer adopts a figure-eight conformation. While the yield of the macrocyclization leading to **2** has seen only a moderate improvement relative to the three-component condensation,[3a] the present procedure provides a more convenient access to the Hückel−Möbius macrocycle **2**, given the better scalability of the dicarbinol synthesis and the absence of macrocyclic byproducts in the cyclization step. We believe that the methodology reported herein may find use in the synthesis of other phenylene-containing porphyrinoids.

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Supporting Information Available: Synthetic procedures, X-ray crystallographic information, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Multiply N-confused porphyrinoids: (a) Furuta, H.; Maeda, H.; Osuka, A. *J. Am. Chem. Soc.* **2000**, *122*, 803–807. (b) Furuta, H.; Maeda, H.; Osuka, A. *J. Org. Chem.* **2000**, *65*, 4222–4226. (c) Araki, K.; Winnischofer, H.; Toma, H. E.; Maeda, H.; Osuka, A.; Furuta, H. *Inorg. Chem.* **2001**, *40*, 2020–2025. (d) Maeda, H.; Osuka, A.; Furuta, H. *J. Am. Chem. Soc.* **2003**, *125*, 15690–15691. (e) Sessler, J. L.; Cho, D.-G.; Stępień, M.; Lynch, V.; Waluk, J.; Yoon, Z. S.; Kim, D. *J. Am. Chem. Soc.* **2006**, *128*, 12640–12641.

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(12) Crystal data for **6f**: $C_{94}H_{96}N_4O_2{\cdot}4CH_2Cl_2$, M_w = 1653.45, monoclinic, space group $P2_1/c$ (no. 14), a = 14.7357(4) Å, b = 17.0703(3) Å, c = 17.6198(4) Å, β = 105.354(3)°, V = 4273.94(17) Å^3, Z = 2, D_{calcd} = 1.285 g/cm^3, T = 100 K, R = 0.0552, R_w = 0.1291, GOF = 0.913 .