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Porphyrins Bearing Stable *meso*-Alkylidenyl Double Bonds. A New Family of Nonplanar Porphyrinoids

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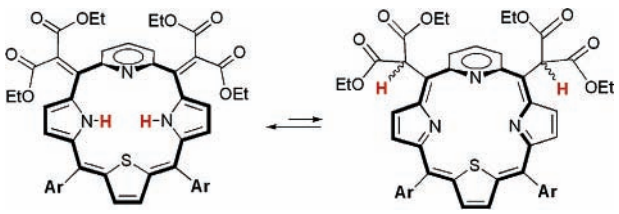
ABSTRACT



Unique core-modified porphyrinoids, such as oxabenziporphyrins, oxapyriporphyrins, and thiapyriporphyrins, bearing exocyclic C–C double bonds at *meso*-positions, have been synthesized and characterized. The synthesis was accomplished by utilizing typical "3+1"-type condensation. Two different stable tautomeric forms were isolated, and the two tautomeric forms can be interconvertible upon treatment with base. In contrast, only the structure bearing an exocyclic double bond was isolated in the case of oxapyriporphyrin and oxabenziporphyrin.

Recently, many structural surrogates of porphyrins, including porphyrin isomers, porphyrin analogues, and expanded porphyrins, have been reported. One of the incentives for this work has been a desire to understand better the electronic features of porphyrin-related macrocycles. Various core-modified porphyrinoids, including carbaporphyrinoids[1] and their metal complexes,[2] pyridine-containing porphyrinoids,[3] and thia- or oxaporphyrinoids,[4] have been synthesized and studied. As a result of these efforts, it was found that the benziporphyrins and pyriporphyrins[5,6] bearing a benzene or pyridine subunit as a part of the core structure did not exhibit porphyrin-like macroaromatic properties, presumably reflecting the fact that the full conjugation pathway is broken. In fact, it was found empirically that the presence of tautomerizable functional groups is essential and required to maintain aromaticity.[7] Although these and other kinds of porphyrinoids have been studied extensively, so far, much less attention has been paid to porphyrinoids bearing exocyclic C−C double bonds at multiple *meso*-positions. The first structurally characterized porphyrinoid bearing four carbonyl groups at the *meso*-positions, the so-called "xanthoporphinogen", was reported in 1976.[8] The Ni(II) complexes of 5,10,15,20-tetraisopropylporphyrin containing exocyclic methylenes,[9] oxidation products of *meso*-tetrakis(3,5-di-*tert*-butyl-4-hy-

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(3) Berlin, K.; Breitmaier, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 219−220.
(4) Hung, C. H.; Lin, C. Y.; Lin, P. Y.; Chen, Y. J. *Tetrahedron Lett.* **2004**, *45*, 129−132.
(5) (a) Berlin, K.; Breitmaier, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1246−1247. (b) Lash, T. D.; Chaney, S. T.; Richter, D. T. *J. Org. Chem.* **1998**, *63*, 9076−9088.
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(8) Sheldrick, W. S. *J. Chem. Soc., Perkin Trans. 2* **1976**, 453−456.
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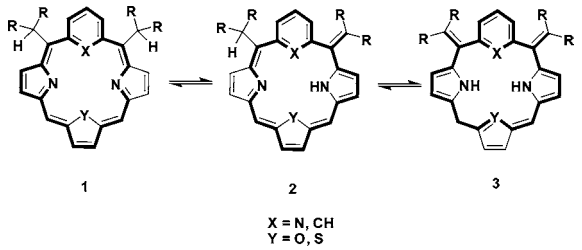
droxyphenyl)porphyrin,[10] and tetra-*meso*-methyleneporphyrinogen[11] have also been reported.

The novel features of these modified porphyrinoids have inspired us to synthesize new porphyrin analogues bearing stable exocyclic double bonds at the multiple *meso*-positions. In this context, we noted that benziporphyrinoids or pyriporphyrinoids bearing exocyclic double bonds at multiple *meso*-positions would represent interesting targets. Such systems would be excellent model systems with which to study the relationship between macroaromaticity and the stabilizing effects of substituents at *meso*-positions. Accordingly, we report here the synthesis, isolation of each tautomeric form, and spectroscopic properties of several porphyrinoid analogues bearing multiple exocyclic double bonds. The placement of these exocyclic double bonds at multiple *meso*-positions serves to destroy full macrocyclic conjugation, and the compounds have proven to be rather unstable with many tautomeric forms apparently coexisting.

Benziporphyrin is well-known as being a nonaromatic porphyrinoid, a finding that is ascribed to the interruption in the conjugation pathway caused by a benzene moiety.[5] On the basis of this important precedence, it is predicted that the presence of a six-membered ring, combined with exocyclic double bonds off the macrocycle, will act to destabilize the whole π-system with the consequence that the system should show even greater distortion from planarity.

Scheme 1



The desired porphyrinoids **1**−**3** can be synthesized via the well-known "3+1" strategy starting from tripyrrane analogues and appropriate furan (or thiophene) diols. As shown in Scheme 2, 2,6-bisvinyl derivatives **4** and **5**, obtained by aldol condensation of diethyl malonate with 2,6-pyridinedicarboxaldehyde or isophthalaldehyde,[12] were converted to the corresponding tripyrrane analogues **6** and **7** in high yield. Many different conditions were tested in an effort to optimize this latter condensation, and it was found that the highest yield of **6** was obtained when $InCl_3$ was used as the catalyst. On the other hand, TFA gave the highest yield of **7**. While these reactions afforded a single regioisomer in good yield, it is important to appreciate that the proton NMR spectra of **6** and **7** revealed the existence of two diastereomeric forms.

(10) Milgrom, L. R.; Hill, J. P.; Yahioglu, G. *J. Heterocycl. Chem.* **1995**, *32*, 97−101.
(11) Otto, C.; Breitmaier, E. *Liebigs Ann. Chem.* **1991**, 1347−1348.
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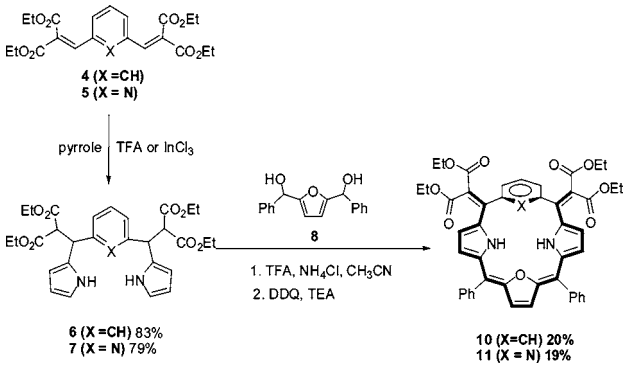
Scheme 2



The carbinol **8** (or **9**) was synthesized by treating furan (or thiophene) with *n*-butyllithium, followed by the addition of benzaldehyde or *p*-tolualdehyde.[13] With this building block in hand, an effort was made to condense **6** with **8** to obtain the corresponding macrocycle. A solution of **6** and **8** in acetonitrile was thus treated with trifluoroacetic acid and then subjected to subsequent oxidation with DDQ; this afforded the desired oxabenziporphyrin **10** in 20% yield.

The expanded macrocycle formed by the condensation of two molecules of **6** with two carbinols **8** bearing four exocyclic double bonds was also isolated in lower yield. On the other hand, a similar condensation involving **7** and **8** afforded only the oxapyriporphyrin **11** in 19% yield.

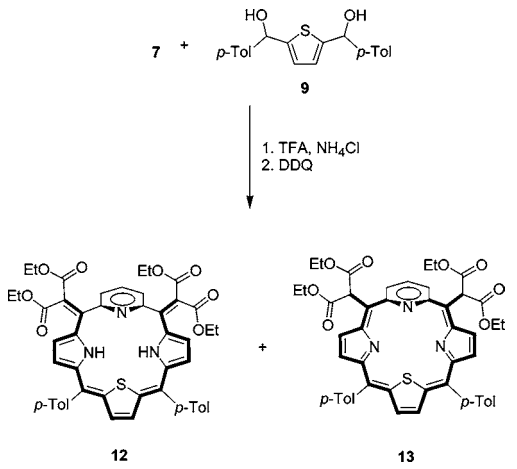
Compounds **10** and **11** were not expected to exhibit aromatic properties. Similarly, the diethyl malonate groups at the *meso*-positions were expected to reside above or below the mean plane of the macrocycle. Moreover, the benzene and pyridine moieties in **10** and **11** were expected to be distorted significantly in order to reduce steric interactions with the nearby diethyl malonate groups. The proton NMR spectrum of **11** revealed the presence of a pyrrole NH signal at 8.09 ppm, a chemical shift that is typical for an unsubstituted pyrrole. The ^{13}C NMR spectrum also revealed features, a total of 21 carbon signals were observed that were consistent with the symmetric character of the macrocycle.

Similar condensations between **7** and **9** were carried out using conditions identical to those used to generate **10**; this afforded a mixture of products, namely, **12** and **13** in 10 and 2%, respectively, as shown in Scheme 3.

The expanded macrocycle formed by the condensation of two molecules of **7** with two carbinols **9** was also isolated in trace amount. The two tautomeric forms, **12** and **13**, produced in this way proved to be very stable under conditions of column chromatography. They could thus be separated, isolated, and fully characterized using normal spectroscopic means. The two tautomers showed unique signals in proton NMR spectra. For example, the resonance of the pyrrole *NH*s was clearly observed at 8.63 ppm in **12**, while no NH signal was observed in the case of **13**. Rather, the α-protons from the diethyl malonate groups were

(13) Arumugam, N.; Ka, J. W.; Lee, C. H. *Tetrahedron* **2001**, *57*, 7323−7330 and references therein.

Scheme 3



observed at 5.18 ppm as a singlet (Figure 1). When macrocycle **12** was treated with base (EtOH/EtO$^-$), conversion to **13** was observed along with significant decomposition.

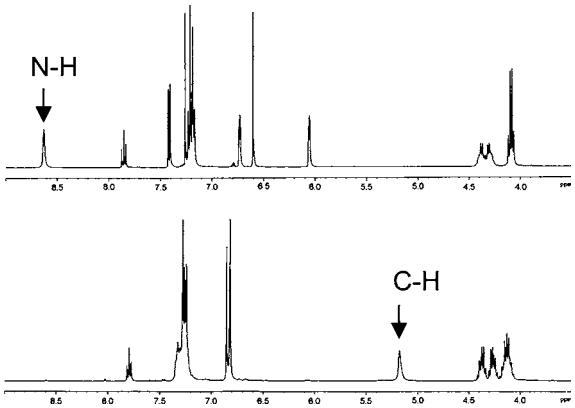


Figure 1. Selected region of the ^{1}H NMR spectra of each tautomer: **12** (top trace taken at 25 °C) and **13** (bottom trace taken at 0 °C) in $CDCl_3$.

Extensive efforts to obtain single crystals of synthesized macrocycles were successful, and the suitable crystals for X-ray analysis were obtained in the case of both the oxabenziporphyrin **10** and the oxapyriporphyrin **11**. The resulting structures, shown in Figure 2, reveal a severely puckered conformation in both instances that are best described in terms of an asymmetric saddle shape.[14] Nonetheless, the benzene (or pyridine) moiety was found to lie almost perpendicular to the mean plane of the macrocycle.

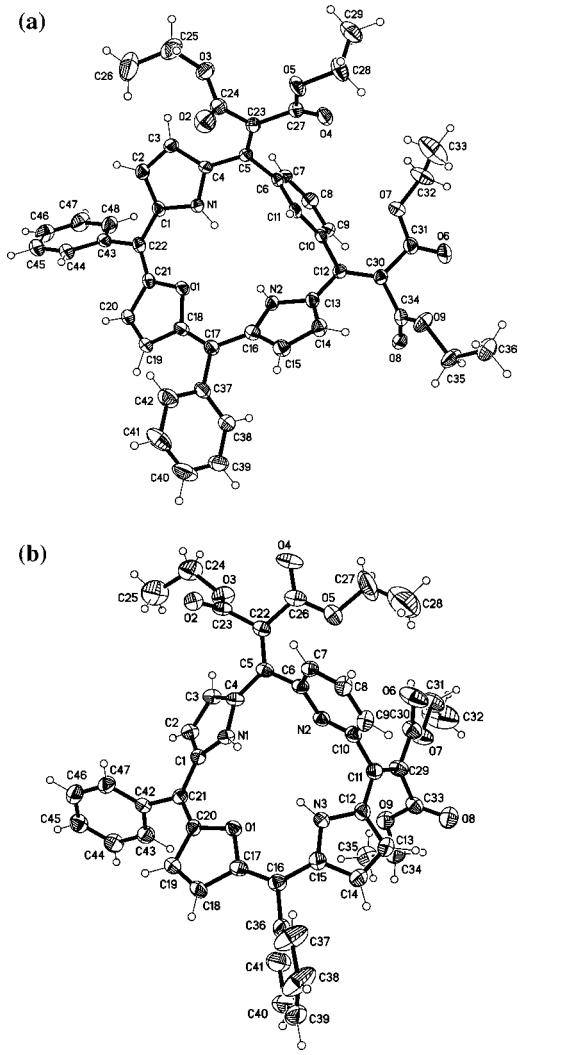


Figure 2. Solid-state structures of (a) oxabenziporphyrin **10** and (b) oxapyriporphyrin **11**, as deduced from X-ray diffraction analyses. The compounds adopt severely twisted, saddle-shaped conformations, with the benzene (or pyridine) ring lying almost perpendicular to the mean plane of the macrocycle.

On the basis of the experimental findings, we propose that appreciable conjugation must exist between the two pyrroles

(14) Crystal data for **10**: $C_{48}H_{42}N_2O_9$, triclinic, space group *Pi*, a = 12.5773(13) Å, b = 13.0527(14) Å, c = 14.9394(16) Å, α = 103.581(2)°, β = 103.794(2)°, γ = 113.814(2)°, V = 2022.1(4) Å^3, T = 173(2) K, Z = 2, GOF on F^2 = 0.941, R_1 ($I > 2\sigma(I)$) = 0.0574, $wR2$ = 0.1183. Crystal data for **11**: $C_{47}H_{41}N_3O_9$, triclinic, space group *Pi*, a = 12.1293(7) Å, b = 13.3588(8) Å, c = 13.7337(8) Å, α = 68.8260(10)°, β = 83.0250(10)°, γ = 75.2970(10)°, V = 2006.0(2) Å^3, T = 173(2) K, Z = 2, GOF on F^2 = 0.911, R_1 ($I > 2\sigma(I)$) = 0.0610, $wR2$ = 0.1359. The crystals of both 1332 and 1342 were attached to glass fibers and mounted on a Bruker SMART diffractometer equipped with a graphite monochromated Mo Kα (λ = 0.71073 Å) radiation, operating at 50 kV and 30 mA and a CCD detector; 45 frames of two-dimensional diffraction images were collected and processed to obtain the cell parameters and orientation matrix. All data collections were performed at 173(2) K. The data collection 2θ ranges for **10** and **11** are 3.68−56.52 and 3.18−56.5°, respectively. No significant decay was observed during the data collection. The raw data were processed to give structure factors using the SAINT program. The structure was solved by direct methods and refined by full matrix least squares against F^2 for all data using SHELXTL software (version 5.14).[15] All non-hydrogen atoms in both compounds were anisotropically refined. All other hydrogen atoms were included in the calculated positions and were refined by using a riding model. Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC-294116 for **10**; Deposition No. CCDC-294115 for **11**). The data can be obtained free of charge via http://www.ccdc.cam.ac.uk./perl/catreq/catreq.cgi (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

and the furan moiety. The puckered geometry appears to originate from the steric congestion between the diethyl malonyl groups and the benzene (or pyridine) ring. This has the consequence of conformational locking of the system that precludes through conjugation of entire double bonds.

All the porphyrins bearing exocyclic double bonds seem to be stable. For example, the solution of porphyrin **11** in CH_2Cl_2 was titrated with trifluoroacetic acid, and the absorption of the Soret-like band that appeared at 392 nm is gradually increased with a gradual red shift. The Q-bands shown at 539 nm completely disappeared, and a new absorption peak was seen to grow in at 778 nm with clear isosbestic points (Figure 3). The color of the solution changes

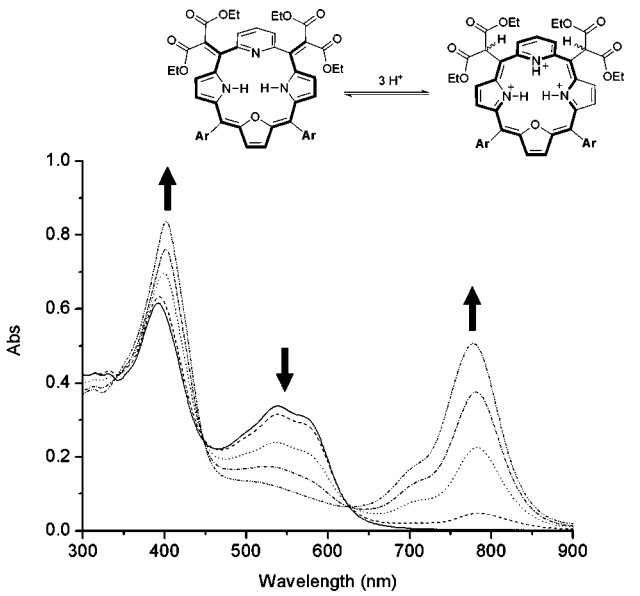


Figure 3. UV−vis absorption spectral changes of **11** observed upon titration with TFA (2.02×10^{-5} M in CH_2Cl_2). The solid line is free base, and the rest of individual spectra were recorded at increments of 0, 50, 100, and 200 equiv of TFA, respectively.

from red to green. ^{1}H NMR spectral analysis of an acidic solution of **11** (TFA/$CDCl_3$) indicated that the first protonation site is nitrogen on the pyridine moiety and the second and third protonation sites are the α-carbon on one of the diethyl malonyl groups. The appearance of a resonance line at 5.51 ppm is clearly supportive for this conclusion.

When the resulting strongly acidic solution was treated with an excess of base (triethylamine), the original free-base spectrum was fully restored, indicating that the protonation is reversible.

These results are best interpreted in terms of a situation where the combination of bulky *meso*-substituents and an endocyclic pyridine moiety serves to suppress the tautomerization. Instead, the protonation at the α-positions of the diethyl malonyl groups would release the steric congestion, and consequently, the system becomes a macroaromatic 22π system (Figure 3).

In summary, we have demonstrated that *meso*-alkylidenyl porphyrins can be prepared and isolated by the simple expedient of introducing bulky, electron-withdrawing groups at the bridging *meso*-positions in combination with the proper core modifications. The structures of the resulting porphyrins are consistent with a nonaromatic and partially conjugated electronic structure and with a severely distorted benzene (or pyridine) moiety. The exocyclic tautomer **11** can be reversibly converted to a protonated endocyclic aromatic macrocycle upon treatment with acid. Original exocyclic form is fully recovered upon treatment with base (triethylamine).

The synthetic approach presented here may allow systematic studies of the interplay between aromaticity and distortion in heterocyclic aromatic systems. A further potential benefit of the synthetic approach described here is that it should be amenable to future modification through, for example, the introduction of linking units, expansion of ring size, or formation of metal complexes. Works along these lines are currently in progress.

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Supporting Information Available: Synthetic details of all the compounds, spectroscopic data, and single-crystal X-ray data are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) *SHELXTL NT Crystal Structure Analysis Package*, version 5.14; Bruker AXS, Analytical X-ray System: Madison, WI, 1999.