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Free Base *meso*-Tetraaryl-morpholinochlorins and Porpholactone from *meso*-Tetraaryl-2,3-dihydroxy-chlorin

Jason R. McCarthy,[†] Hilary A. Jenkins,[‡] and Christian Brückner*,[†]

Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060,
and Department of Chemistry, X-ray Crystallography Laboratory, Saint Mary's
University, Halifax, NS B3H 3C3, Canada

c.bruckner@uconn.edu

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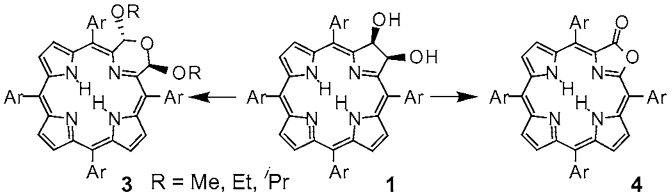
ABSTRACT



***meso*-Tetraaryl-2,3-dihydroxychlorins (1) were converted in one step to the novel free base macrocycles *meso*-tetraaryl-2,3-dialkoxy-2a-oxa-2a-homoporphyrins (morpholinochlorins, 3). Their bathochromically shifted chlorin-type UV−vis spectra indicate the presence of a nonplanar chromophore. The structure of *meso*-tetratolyldiethoxymorpholinochlorin (3b), as determined by X-ray crystallography, was found to be largely planar, suggesting significant conformational flexibility of these macrocycles. Oxidation of diol 1 with MnO_4^- generates known porpholactone 4 in high yields.**

Nature modulates the electronic properties of porphyrins and chlorins by distorting them from planarity. As a consequence, the synthesis and study of nonplanar porphyrinic structures is a topic of current interest.[1,2] As well, the synthesis of porphyrin-like chromophores with spectroscopic and coordination properties tuned to a variety of applications is being intensely investigated.[3]

Pyrrole-modified porphyrins, i.e., porphyrinic pigments in which one pyrrolic subunit is (formally) replaced with a nonpyrrolic heterocycle,[4] can be prepared either by total synthesis[5] or by modification of a porphyrin.[6] We have shown that diol chlorin [*meso*-tetraaryl-2,3-dihydroxychlorinato]Ni(II) can be subjected to diol cleavage, generating a

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[†] University of Connecticut.

[‡] St. Mary's University.

(1) (a) Ravikanth, M.; Chandrashekar, T. K. *Struct. Bond.* (*Berlin*) **1995**, *82*, 107−188. (b) Shelnutt, J. A.; Song, X.-Z.; Ma, J.-G.; Jentzen, W.; Medforth, C. J. *Chem. Soc. Rev.* **1998**, *27*, 31−41.

(2) Parusel, A. B. J.; Wondimagegn, T.; Ghosh, A. *J. Am. Chem. Soc.* **2000**, *122*, 6371−6374.

(3) (a) Sessler, J. L.; Gebauer, A.; Vogel, E. Porphyrin Isomers. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2000; Vol. 2, pp 1−54. (b) Sessler, J. L.; Gebauer, A.; Weghorn, S. J. Expanded Porphyrins. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2000; Vol. 2, pp 55−124. (c) Lash, T. D. Synthesis of Novel Porphyrinoid Chromophores. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2000; Vol. 2, pp 125−200.

(4) The term "homoporphyrins" (ref 6a) is not specific as to where in the macrocycle the homologation has taken place. We suggest the term "pyrrole-modified porphyrin" for this class of compounds and the name "morpholinochlorin" for compounds such as **3** to specify the type of modification of their spectral characteristics (vide infra).

(5) See, e.g.: (a) Berlin, K.; Breitmaier, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 219−220. (b) Lash, T. D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2533−2535. (c) Lash, T. D. *Chem.−Eur. J.* **1996**, *2*, 1197−1200.

(6) (a) Callot, H. J.; Tschamber, T. *J. Am. Chem. Soc.* **1975**, *97*, 6175−6178. (b) Crossley, M. J.; King, L. G. *J. Chem. Soc., Chem. Commun.* **1984**, 920−922. (c) Crossley, M. J.; Hambley, T. W.; King, L. G. *Bull. Soc. Chim. Fr.* **1996**, *133*, 735−742. (d) Adams, K. R.; Bonnett, R.; Burke, P. J.; Salgado, A.; Vallés, M. A. *J. Chem. Soc., Chem. Commun.* **1993**, 1860−1861. (e) Adams, K. R.; Bonnett, R.; Burke, P. J.; Salgado, A.; Asunción Vallés, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1769−1772.

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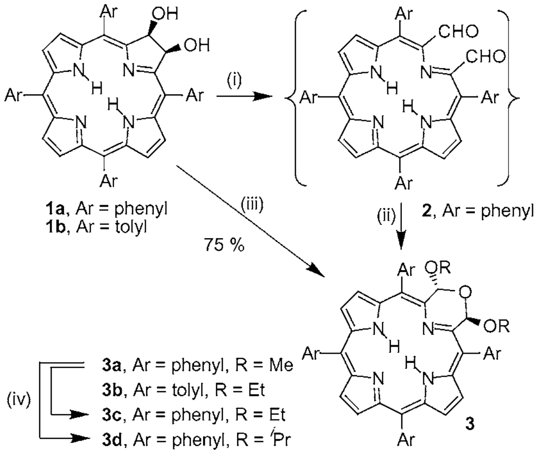
bisaldehyde derivative in which a β,β'-pyrrole bond of the porphyrin framework is broken.[7] Nucleophile-induced intramolecular ring-closure of this bisaldehyde generated a number of morpholine- and pyrazine-derived pyrrole-modified porphyrins.[7,8] These high-yielding syntheses were characterized by a pronounced metal template effect: only Ni(II) chlorins allowed the preparation of these chromophores, as their Ni(II) complexes.[7−9] Although their free base analogues are of potentially greater utility, the central metal ion could not be removed without concomitant destruction of the macrocycle. The X-ray structures of the Ni(II) bisaldehyde and the [morpholinochlorinato]Ni(II) complexes provide a rationale for these findings.[10] The small central metal induces an extremely ruffled conformation in the secochlorin shortening the N−Ni bonds to better accommodate the metal ion.[11] The ruffling also aligns the aldehyde groups, enabling a facile intramolecular ring closure reaction to take place.

Considering the metal template effect, it is not clear if free base diol chlorins undergo analogous diol cleavage and ring-closure reactions to generate free base morpholinochlorins. We demonstrate herein that this is possible.

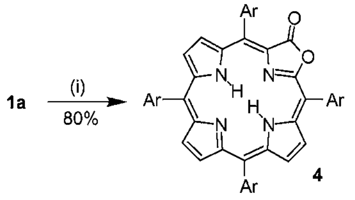
Using free base diol chlorin **1a**,[7] we began a systematic search for diol cleavage conditions commensurate with the lability of putative free base secochlorin **2** (Scheme 1). $NaIO_4$ heterogenized on silica gel[12] and suspended in a $CHCl_3$[13] solution of **1a** was found to react rapidly to produce a brown, low-polarity ($R_f = 0.50$, 1:1 silica-petroleum ether/CH_2Cl_2) compound of the expected mass for **2** ($m/z = 647$, ESI+, corresponding to $C_{44}H_{31}N_4O_2^+$, MH^+). The product was sufficiently stable to be isolated immediately by flash chromatography (silica-CH_2Cl_2); its ^1H NMR spectrum indicates the required 2-fold symmetry of secochlorin **2**. The presence of an aldehyde functionality is indicated by a singlet at 9.46 ppm and a C═O stretching band in its IR spectrum (KBr) at 1709 cm^{-1}. The rate of decomposition of **2**, however, limited the scope of its characterization.

Scheme 1. Synthesis of Morpholinochlorin[a]



[a] Reaction conditions: (i) $CHCl_3$ (EtOH-free), $NaIO_4$/silica; (ii) ROH, cat. HCl; (iii) $CHCl_3$ (EtOH-free)/ROH (10%), $NaIO_4$/silica, N_2 atmosphere; (iv) EtOH or ^{i}PrOH, reflux, cat. HCl.

Scheme 2. Synthesis of Porpholactone **4**[a]



[a] Reaction conditions: (i) $KMnO_4$/18-crown-6, THF or cetyltrimethylammonium MnO_4^-, CH_2Cl_2.

Reaction of **2** with MeOH under acid catalysis provided a stable, green-brown and nonpolar ($R_f = 0.86$, silica-CH_2Cl_2) product. Mass spectrometry (ESI+) showed a m/z ratio of 693, corresponding to $C_{48}H_{41}N_4O_3^+$. This is the expected composition for product **3a** + H^+, resulting from addition of 2 equiv of MeOH to **2**, accompanied by the loss of H_2O. In reactions in which EtOH and ^{i}PrOH were used as nucleophiles, pigments with masses of 28 amu (**3c**) and 56 amu (**3d**) greater than that found for **3a** were observed. No evidence for the presence of an aldehyde functionality was found. The use of sterically more demanding alcohols such as ^{t}Bu alcohol or phenol led to the formation of unstable products.

Pigments **3** were made most efficiently by reaction of ROH with **2** generated in situ and under anaerobic conditions. The exclusion of air reduces the formation of decomposition products of **2**. Notably, this greatly suppresses the formation of porpholactone **4** (Scheme 2), the major isolated side product (vide infra). Thus, reaction of **1** with $NaIO_4$/silica under N_2 in the presence of the alcohol of choice produced, after isolation by column chromatography and crystallization, morpholinochlorins **3** in a crystalline and analytically pure form in yields up to 75% (1 mmol scale).

The morpholinochlorins are stable in the presence of air in both solution and the solid state as long as light is excluded. Slow decomposition of **3** in solution is observed in the presence of light, as is expected for a photosensitizing chromophore. No reaction is observed upon treatment of **3** with bases such as pyridine or Et_2NH. Exposure of **3** to a severalfold molar excess of strong acids such as HCl or TFA leads to decomposition and the formation of a number of as yet unidentified compounds. Treatment of methoxy derivative **3a** with excess EtOH or ^{i}PrOH under acid catalysis at 65 °C leads to alkoxy exchange and formation of **3**c and **3d**, respectively.

Further evidence for the identification of the pigments as the desired morpholinochlorins **3** was provided by ^1H and

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(7) Brückner, C.; Rettig, S. J.; Dolphin, D. *J. Org. Chem.* **1998**, *63*, 2095−2098.

(8) Campbell, C. J.; Rusling, J. F.; Brückner, C. *J. Am. Chem. Soc.* **2000**, *122*, 6679−6685.

(9) This observation was also made by Bonnett and co-workers in the diol cleavage of [β-octaethyldiolchlorinato]Ni(II); see refs 6d,e.

(10) Brückner, C.; Sternberg, E. D.; MacAlpine, J. K.; Rettig, S. J.; Dolphin, D. *J. Am. Chem. Soc.* **1999**, *121*, 2609−2610.

(11) Secochlorins are chlorins containing a cleaved β,β'-bond.

(12) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622−2624.

(13) EtOH-free (i.e., amylene-stabilized) $CHCl_3$ must be used.

^{13}C NMR spectra that are qualitatively similar to those of their Ni(II) complexes.[7,14] The β-hydrogen signals exhibit the splitting pattern expected for the 2-fold symmetry and composition of **3**: a pair of doublets (with a small coupling to the NH protons) and one singlet, each 2H, two sets of nonequivalent aryl groups, and a set of signals attributable to the sp^3 carbons of the morpholine-type ring and the alkoxy substituents. Though the anti configuration of the alkoxy substituents in **3** can be anticipated on stereoelectronic grounds[15] (and was observed in its Ni(II) complex),[7] it cannot be confirmed from NMR spectra.

The UV−vis spectrum of homoporphyrin **3b** is a typical chlorin spectrum but broadened and significantly bathochromically shifted ($\lambda_{\text{Soret}} = 420$ nm, $\lambda_{\max} = 676$ nm) as compared to the spectrum of the essentially planar[16] diol chlorin **1a** ($\lambda_{\text{Soret}} = 408$ nm, $\lambda_{\max} = 644$ nm) (Figure 1). This shift is generally viewed as characteristic of a nonplanar chromophore, although the origin of this shift is a matter of current debate.[17]

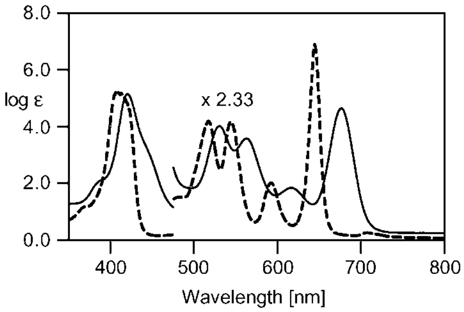

Figure 1. UV−vis (CH_2Cl_2) spectra of **1a** (dashed line) and **3b** (solid line).

meso-Tetratolyldiethoxymorpholinochlorin (**3b**) formed crystals suitable for study by single-crystal diffractometry. The ORTEP representation of the structure of **3b** shown in Figure 2 confirms its connectivity and the anti configuration of the ethoxy side chains. The presence of the nonplanar partially saturated six-membered morpholine-type subunit is also clearly evident. Much to our surprise, however, the nonplanarity of the morpholine unit translates only minimally into the chromophore (Figure 3).

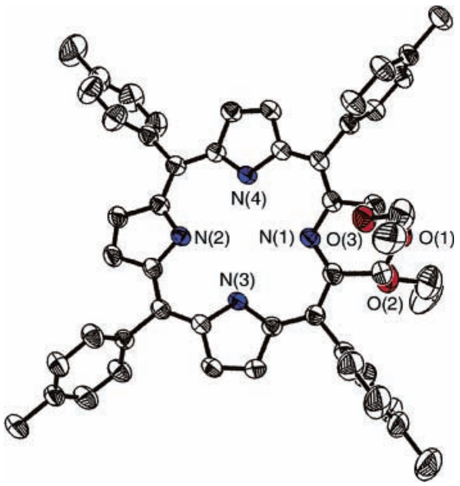

Figure 2. ORTEP representation of the crystal structure of **3b**.

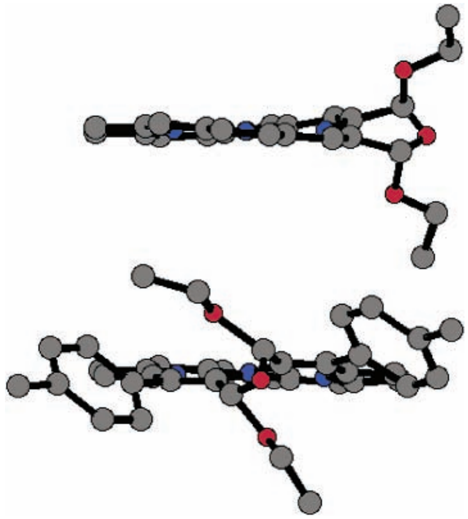

Figure 3. Top: Side view of the X-ray structure of **3b** along the N(3)−N(4) axis (all *meso*-tolyl groups and hydrogens have been removed for clarity). Bottom: Side view along the N(1)−N(2) axis (backside *meso*-tolyl groups have been omitted for clarity).

The root-mean-square (rms) deviation of the $C_{18}N_4$ chromophore core from planarity is 0.012 Å as compared to a rms of 0.468 Å measured for its drastically nonplanar Ni(II) complex.[7] Analogous to its Ni(II) complex, the distortion mode of the free base chromophore can be classified as ruffled.[1b] Thus, the findings prove the enormous influence of Ni(II) on the extent of the ruffled conformation of the macrocycle, validating our earlier deductions.[7] The findings further highlight the enormous flexibility of this chromophore.

The structure of **3b** is (idealized) C_2-symmetric, i.e., chiral. Next to the helicity of the ruffled chromophore, both sp^3 ring carbons are stereogenic centers. Six possible stereoisomers of **3b** are theoretically possible, but the crystal (of the achiral space group *P*-1) is composed of only one racemic pair.[18] No other stereoisomers are observed. Presumably, this

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(14) COSY, DEPT, and HETCOR spectra completed the NMR spectroscopic characterization of **3**; see Supporting Information.

(15) Kirby, A. J. *Stereoelectronic Effects*; Oxford University Press: Oxford, 1996.

(16) Brückner, C.; Daniell, H. W.; Krause-Bauer, J. A. Unpublished results.

(17) (a) Parusel, A. B. J.; Wondimagegn, T.; Ghosh, A. *J. Am. Chem. Soc.* **2000**, *122*, 6371−6374. (b) Wertsching, A. K.; Koch, A. S.; DiMagno, S. G. *J. Am. Chem. Soc.* **2001**, *123*, 3932−3939. (c) Ryeng, H.; Ghosh, A. *J. Am. Chem. Soc.* **2002**, *124*, 8099−8103. (d) Shellnut, J. A.; Medforth, C. J.; Qui, Y.; Haddad, R. Abstracts of Papers, 224th National Meeting of the American Chemical Society, Boston, MA, Aug 18−22, 2002; American Chemical Society: Washington, DC, 2002; INOR 116.

(18) $2^3 = 8$. However, due to the internal constitutional symmetry of the morpholinochlorin, two pairs of isomers are identical.

is due to the cooperative action of steric and stereoelectronic effects: the ring sp^3 carbons carry one large (the alkoxy group) and one small (hydrogen) substituent. For steric reasons, the larger of these must be oriented away from the adjacent *meso*-aryl group (see Figure 3, bottom). The chromophore twist aligns the *meso*-aryl groups “anti” to each other with respect to their deviation from the chromophore plane. This, in turn, greatly favors the anti configuration of the second alkoxy group. Thus, steric effects are operating in concert with the stereoelectronic preferences. This fixes the stereochemistry of the two sp^3 centers to be homochiral and unique with respect to the chirality of the screw axis of the chromophore. Interconversion of the enantiomers by inversion of the chromophore twist is highly unlikely due to the fact that it would orient the alkoxy substituents into a sterically demanding arrangement with their adjacent *meso*-aryl groups. This steric interaction can only be alleviated by inversion of the sp^3 carbons, a process not favored under mild conditions. Thus, the chirality of the free base macrocycle is locked in a way similar to that inferred from electrochemical experiments for its Ni(II) complexes.[8] This suggests that the chiral resolution of the racemic mixture should be possible. We are currently testing this proposition.[19]

Considering the observed planarity of the chromophore in the solid state, how can the bathochromically shifted UV−vis spectrum be explained? We believe that the chromophore is very flexible with respect to the degree of ruffling it can undergo. This flexibility in solution gives rise to the observed UV−vis spectrum. Support for this was derived by three-dimensional fluorescence spectroscopy, allowing the observation of a number of conformers.[20]

The syntheses of **2** and **3** was accompanied by the formation of variable amounts of porpholactone **4**. We found this pigment to be primarily an oxidation product of **2**. In fact, we find **4** to be the apparent thermodynamic sink for a variety of decomposition and oxidation reactions of porphyrins containing an activated or cleaved β,β'-bond. The origin of this “overoxidation” product suggested an efficient synthesis of the known pyrrole-modified porphyrin:[21,22] MnO_4^--induced cleavage of diol **1** under phase transfer catalysis presumably generates the corresponding secochlorin biscarboxylate, which spontaneously decarboxylates to form porpholactone **4** in overall excellent yields (up to 80%) (Scheme 2). This mechanism of formation was also implied when **4** was first discovered by Crossley.[21] The high yield synthesis described here is apparently applicable to a number of diol chlorins carrying substituted *meso*-phenyls and, thus, more general than previously reported syntheses.[21,22]

In conclusion, we have demonstrated, for the first time, the formal replacement of a pyrrolic subunit in free base *meso*-tetraphenylporphyrin by a morpholine-type heterocycle in two steps (hydroxylation followed by diol cleavage/ring closure). Remarkably, this reaction proceeded smoothly *in the absence of a templating metal*. The UV−vis spectra of the morpholinochlorins **3** indicate the presence of a significantly nonplanar chromophore, but analysis of **3b** by X-ray crystallography demonstrates a surprising planarity, suggesting considerable conformational flexibility of this chromophore. The long-wavelength-absorbing morpholinochlorins **3** may be useful in photomedicine and light-harvesting devices. We have also developed a mild, high-yield, and apparently general method for the synthesis of porpholactone **4**.

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Supporting Information Available: Experimental procedures and spectroscopic data for **3a−d** and **4** and experimental crystallographic details for **3b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] Photophysical evaluation of mopholinochlorins will be reported elsewhere: Brückner, C.; Frank, H. A.; Birge, R. R. and co-workers, manuscript in preparation.

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[22] (a) Gouterman, M.; Hall, R. J.; Khalil, G.-E.; Martin, P. C.; Shankland, E. G.; Cerny, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 3702−3707. (b) Jayaraj, K.; Gold, A.; Austin, R. N.; Ball, L. M.; Terner, J.; Mandon, D.; Weiss, R.; Fischer, J.; DeCian, A.; Bill, E.; Müther, M.; Schünemann, V.; Trautwein, A. X. *Inorg. Chem.* **1997**, *36*, 4555−4566. (c) Khali, G.; Gouterman, M.; Ching, S.; Costin, C.; Coyle, L.; Gouin, S.; Green, E.; Sadilek, M. Wan, R.; Yearyean, J.; Zelelow, B. *J. Porphyrins Phthalocyanines* **2002**, *6*, 135−145.