Chirality

Enantiomeric Resolution of a Ruffled Porphyrinoid**

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Porphyrins have been utilized as platforms for molecular-recognition systems, including examples for chiral substrate recognition.[1] Chiral porphyrins were also used in the enantiocontrol of metalloporphyrin-catalyzed transformations.[2] The synthesis of chiral porphyrins has mainly been through modification of the porphyrin periphery with chiral side chains or by utilizing the chirality of certain atropisomers of *ortho*-phenyl-substituted *meso*-tetraarylporphyrins, and chiral resolution was accomplished in some cases.[3] Alternative methods employ chirality transfer from chiral substrates to nonchiral porphyrins.[4,5]

We have reported the Ni^{II} complexes of porphyrinic chromophores in which one of the pyrrolic building blocks of a porphyrin was formally replaced by a morpholine unit (Scheme 1 A).[6,7] The acid-catalyzed reaction of secochlorin bisaldehyde **1** with EtOH resulted in the formation of the morpholinochlorin chromophore **2**, which further converted into double acetal **3**. The chromophores of secochlorin **1** and morpholinochlorin **3** possess near-identical nickel (II)-induced ruffled conformations of idealized C_2-symmetry (Scheme 1 B and C).[8]

In addition to the helicity of the ruffled chromophore, the sp^3 ring-carbon atoms in **3** are also stereogenic centers. Thus, six possible stereoisomers of **3** are theoretically possible.[9] However, only two isomers are observed. Cooperative action of steric and stereo-electronic effects limit the number of isomers formed: the Ni^{II}-induced twist in secochlorin **1** aligns the *meso*-aryl groups "*anti*" to each other with respect to their deviation from the chromophore plane, and aligns the two aldehyde functional groups to lie on top and parallel to each other and parallel to the chromophore plane (Scheme 1 B). This alignment then directs the attack of the nucleophile on the prochiral aldehyde center to occur from one of the two homotopic *exo* sides (Scheme 1 B). Stereoelectronic effects favor the *anti*-configuration of the alkoxy and hydroxy groups in the ring-closed hemiacetal **2** and of the two alkoxy groups in acetal **3**. This *anti*-configuration is also the sterically

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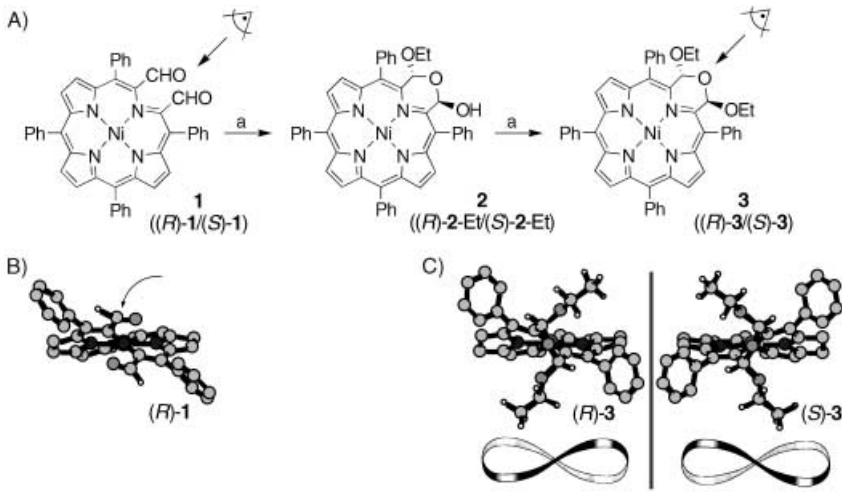


Scheme 1. A) Preparation of (*R*)-**3**/(*S*)-**3**. Reaction Conditions: a) $CHCl_3$/EtOH, [H^+].[6] B) Ball-and-stick representation of (*R*)-**1** along the idealized N–Ni–N bond axis indicated in (A); the arrow indicates the likely *exo*-attack of a nucleophile on the prochiral carbonyl center. C) Ball-and-stick representation of the enantiomeric forms of morpholinochlorin **3**, together with a stylized representation of the twisted chiral chromophore, viewed along the idealized N–Ni–N bond axis indicated in (A). Models are based on X-ray crystal data.[6] Distal phenyl groups and all the hydrogen atoms attached to the phenyl groups and the porphyrin framework are removed for clarity.

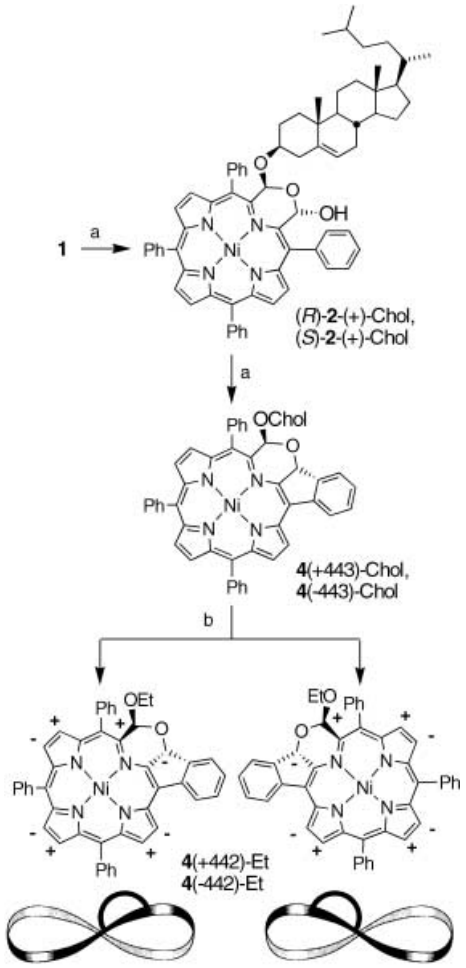
favored orientation of the alkoxy substituents. As a result, the stereochemistry of the two sp^3-hybridized carbon centers are fixed to be homochiral and unique with respect to the chirality of the screw axis of the chromophore. Thus, only two enantiomeric forms of **3** are observed and morpholinochlorin **3** crystallizes as a racemic pair ((*R*)-**3**/(*S*)-**3**) in an achiral space group.[6,8] Moreover, electrochemical experiments inferred that the conformation of the morpholinochlorins is locked.[7] This, in turn, suggests that the chiral resolution of a racemic mixture of (*R*)-**3**/(*S*)-**3** should be possible.

We report herein, for the first time, that the enantiomeric resolution of chiral conformers of morpholinochlorin chromophores is possible. In the course of this work, we discovered a novel chiral morpholinochlorin-derived chromophore incorporating an *o*-phenyl-to-β-position linkage.

HCl-catalyzed reaction of brown **1** with (+)-cholesterol ((+)-Chol) yielded two major green products which, based on their identical mass spectra, were assigned the composition $C_{71}H_{74}N_4O_3Ni$, as expected for the diastereomeric hemiacetals (*R*)-**2**-(+)-Chol and (*S*)-**2**-(+)-Chol (Scheme 2).[10] These products were, however, not stable and converted quantitatively into two green compounds, **4**(+443)-Chol and **4**(−443)-Chol.[11] The products could be isolated by preparative thin layer chromatography ($\Delta R_f = 0.05$) in 30% yields.[10] Their mass spectra were identical and corresponded to the composition $C_{71}H_{72}N_4O_2Ni$, that is, not to the expected bis(cholesteroxy)-substituted product. Instead, the mass indicated the formation of a product derived from **2**-Chol by loss of H_2O. The UV/Vis spectra of **4**(+443)-Chol and **4**(−443)-Chol are identical and significantly bathochromically shifted compared to the spectrum of [morpholinochlorinato]nickel **3** (Figure 1a).[11]

The ^1H and ^{13}C NMR spectra of these compounds (400 MHz, [D6]benzene, 25 °C) confirmed the presence of a cholesteroxy group, indicated the presence of a non-symmetrically pyrrole-modified porphyrin (observation of six non-equivalent β-protons, $^3J = 4.8$ Hz), and the formation of the morpholine moiety (diagnostic singlet at $\delta = 6.72$ and 5.40 ppm for the hydrogen atoms attached to the sp^3-hybridized carbon centers). An H,H-COSY spectrum allowed the identification of a spin system characteristic of one unsymmetrically 1,2-disubstituted phenyl group (doublet at $\delta = 8.10$ ppm, $^3J = 7.4$ Hz, coupled into a multiplet, $\delta =$ 7.75–7.25 ppm, which is coupled to a multiplet at $\delta = 7.16$–7.13 ppm, which itself is coupled to a doublet, $\delta =$ 7.01 ppm, $^3J = 7.5$ Hz, all 1H). This motif is characteristic of an *o*-phenyl-to-β-linkage.[12]

Thus, the spectroscopic data are consistent with the formation of the novel chromophores **4**(+443)-Chol and



Scheme 2. Reaction conditions: a) cholesterol, benzene, HCl vapors; b) $CHCl_3$, EtOH, HCl vapor. The "+" and "−" in the structures indicate the ruffled conformation, that is, the relative position of the carbon atoms with respect to the mean plane of the macrocycle.

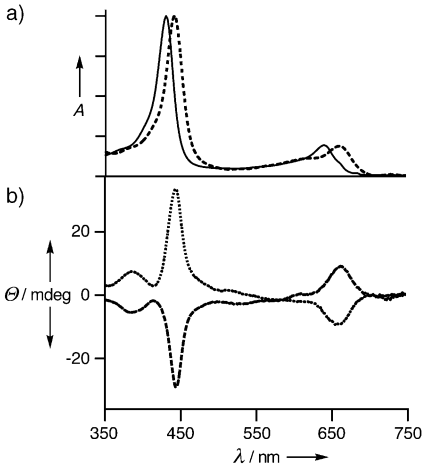


Figure 1. a) Normalized UV/Vis spectra (benzene) of **4**(+443)-Chol (– – –) and **3** (——). b) CD (8.0×10^{-6} M, benzene, $T=20$ °C) spectra of **4**(+443)-Chol (••••) and **4**(−443)-Chol (– – –).

4(-443)-Chol in which the *ortho*-position of one *meso*-phenyl group is fused to a (former) β-pyrrole carbon atom. This linking presumably causes a (near)-planar arrangement of the phenyl ring with the porphyrinic chromophore. The resulting extension of the π conjugation rationalizes the bathochromically shifted UV/Vis spectrum of **4** (Figure 1 a).[12]

A stepwise mechanism rationalizes the formation of **4**(+443)-Chol and **4**(−443)-Chol. Nucleophilic attack of the cholesterol from the *exo*-side generates the two diastereomeric hemiacetals (*R*)-**2**-Chol and (*S*)-**2**-Chol. Perceivably, the steric bulk of the cholesterol side chain prevents the approach of a second cholesterol unit and, instead, facilitates an intramolecular electrophilic aromatic substitution of the adjacent *ortho*-phenyl position by the carbocation formed by acid-induced dehydroxylation of (*R*)-**2**-Chol or (*S*)-**2**-Chol. Although the *trans*-arrangement of the linkage to the phenyl ring and the alkoxy substituent can be rationalized on steric and stereo-electronic grounds, it could not be shown directly.[13]

Most significantly, the CD spectra of the two diastereomers **4**(+443)-Chol and **4**(−443)-Chol are mirror images of each other, demonstrating the successful separation of the two enantiomeric chromophores (Figure 1 b).[14] The isolation of a combined fraction of **4**(+443)-Chol and **4**(−443)-Chol yields a diastereomeric mixture which shows no CD signal. This result suggests that cholesterol reacts indiscriminately with both pre-formed enantiomers of **1**, and does not induce any chirality.

Acid-catalyzed exchange of the cholesteroxy groups for ethoxy groups proceeds smoothly. Thus, the diastereomers **4**(+443)-Chol and **4**(−443)-Chol are each converted by stirring in acidified $CHCl_3$/EtOH into the corresponding enantiomeric pair **4**(+442)-Et and **4**(−442)-Et (Scheme 2). The NMR signature of the products and the expected mass spectra, which correspond to the composition $C_{46}H_{32}N_4O_2Ni$, indicate that no other framework change had taken place.[10] As expected, the enantiomers of **4**(+442)-Et and **4**(−442)-Et show the same CD spectra but with opposite signs (Figure 2). We have not been able to assign the absolute conformations

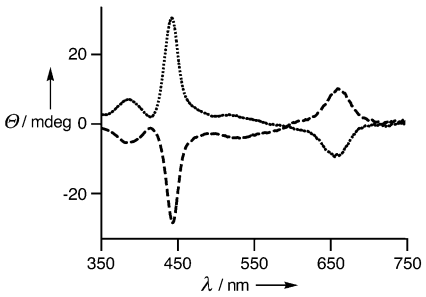


Figure 2. CD spectra (8.0×10^{-6} M, benzene, $T=20$ °C) of **4**(+442)-Et (----) and **4**(−442)-Et (– – –).

of the chromophores.[15] However, the diastereomer of **4**(+443)-Chol with a positive Cotton effect at 443 nm also generates the enantiomer of **4**(+442)-Et with a positive Cotton effect of identical magnitude at 442 nm. This result shows that no inversion or partial racemization of the chromophore takes place in the alkoxy exchange reaction. The CD spectra did not degrade over an extended time (months), which indicates the conformational rigidity of the macrocycles. The alkoxy exchange performed on a diastereomeric mixture of **4**(+443)-Chol and **4**(−443)-Chol generates a racemic mixture of **4**(+442)-Et and **4**(−442)-Et which shows a flat-line CD signal but has otherwise identical spectral properties to the enantiomerically pure fractions.[10]

In conclusion, we have shown that the chiral resolution of enantiomeric conformers is possible in case of the Ni^{II} complexes of morpholinochlorins in which the conformers are rigidly locked. The resolved conformers of **4**-Et may become a valuable element in chiral recognition studies utilizing the large chiral π-system. This Ni^{II} d^8 system is, however, ill suited for studies involving coordination to the central metal because Ni^{II} porphyrins have only weak binding capabilities for axial ligands.[16] Parallel to our earlier findings, the replacement of Ni^{II} proved unsuccessful without destruction of the macrocycle.[6] We are currently testing the application of the synthetic methods disclosed herein to free-base and other metalloporphyrin systems.[17]

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[1] H. Ogoshi, T. Mizutani, T. Hayashi, Y. Kuroda in *Porphyrin Handbook*, *Vol. 6* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), Academic Press, New York, **2000**, pp. 279 – 340.
[2] a) J.-C. Marchon, R. Ramasseul in *Porphyrin Handbook*, *Vol. 11* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), Academic Press, New York, **2003**, pp. 75 – 132; b) G. Simonneaux, P. Le Maux, *Coord. Chem. Rev.* **2002**, *228*, 43 – 60.
[3] See, for example: a) H. Nakagawa, T. Nagano, T. Higuchi, *Org. Lett.* **2001**, *3*, 1805 – 1807; b) B. Boitrel, Baveux-Chambenoît, P. Richard, *Eur. J. Org. Chem.* **2001**, 4213 – 4221.
[4] a) Y. Furusho, T. Kimura, Y. Mizuno, T. Aida, *J. Am. Chem. Soc.* **1997**, *119*, 5267 – 5268; b) E. Bellacchio, R. Lauceri, S. Gurrieri, L. M. Scolaro, A. Romeo, R. Purrello, *J. Am. Chem. Soc.* **1998**,

120, 12353 – 12354; c) Y. Kubo, T. Ohno, J. Yamanaka, S. Tokita, T. Iida, Y. Ishimaru, *J. Am. Chem. Soc.* **2001**, *123*, 12700 – 12701, Y. Mizuno, T. Aida, K. Yamaguchi, *J. Am. Chem. Soc.* **2000**, *122*, 5278 – 5285.

[5] For chiral porphyrin-based entities involving two or more covalently or noncovalently linked porphyrins, see: a) T. S. Balaban, A. D. Bhise, M. Fischer, M. Linke-Schaetzel, C. Roussel, N. Vanthuyne, *Angew. Chem.* **2003**, *115*, 2190 – 2194; *Angew. Chem. Int. Ed.* **2003**, *42*, 2140 – 2144; b) V. V. Borovkov, J. M. Lintuluoto, G. A. Hembury, M. Sugiura, R. Arakawa, Y. Inoue, *J. Org. Chem.* **2003**, *68*, 7176 – 7192; c) B. Boitrel, V. Baveux-Chambenoit, R. Philippe, *Eur. J. Inorg. Chem.* **2003**, *7*, 1666 – 1672; d) Y. Mizuno, T. Aida, *Chem. Commun.* **2003**, 20 – 21; e) T. Hayashi, T. Aya, M. Nonoguchi, T. Mizutani, Y. Hisaeda, S. Kitagawa, H. Ogoshi, *Tetrahedron* **2002**, *58*, 2803 – 2811.

[6] a) J. R. McCarthy, H. A. Jenkins, C. Brückner, *Org. Lett.* **2003**, *5*, 19 – 22; b) C. Brückner, S. J. Rettig, D. Dolphin, *J. Org. Chem.* **1998**, *63*, 2094 – 2098.

[7] C. J. Campbell, J. F. Rusling, C. Brückner, *J. Am. Chem. Soc.* **2000**, *122*, 6679 – 6685.

[8] C. Brückner, E. D. Sternberg, J. K. MacAlpine, S. J. Rettig, D. Dolphin, *J. Am. Chem. Soc.* **1999**, *121*, 2609 – 2610.

[9] $2^3 = 8$. However, owing to internal constitutional symmetry (i.e. equivalency of the two homochiral morpholine sp^3-hybridized centers with respect to the twofold rotational axis of the chromophore), two pairs of the eight posible isomers are identical.

[10] For a detailed description of the experimental details, see the Supporting Information.

[11] We have not been able to assign the absolute stereochemistry of the two enantiomeric chromophores (*R*)-**4** and (*S*)-**4**. In all the experiments, we have used (+)-cholesterol. Herein the chromophores will be identified by their characteristic features in their CD-spectra, that is, **4**(+443)-Chol is the isomer with a positive Cotton effect at 443 nm and **4**(−443)-Chol the corresponding diastereomer with a negative Cotton affect at this wavelength.

[12] a) L. Barloy, D. Dolphin, D. Dupré, T. P. J. Wijesekera, *J. Org. Chem.* **1994**, *59*, 7976 – 7985; b) J. R. McCarthy, M. A. Hyland, C. Brückner, *Chem. Commun.* **2003**, 1738 – 1739.

[13] Molecular modeling (Quantum CAChe 4.9, Fujitsu, 2002; MM3 force field) also predicts the *anti*-configuration.

[14] Cholesterol has no absorption in the wavelength range 350–750 nm.

[15] Techniques currently investigated to determine the absolute stereochemistry of the conformers: X-ray structure determination; vibrational optical activity: L. A. Nafie, T. B. Freedman in *Circular Dichroism*, 2nd ed. (Eds.: N. Berova, K. Nakanishi, R. W. Woody), Wiley-VCH, New York, **2000**, pp. 97 – 131.

[16] J. K. M. Sanders, N. Bampos, Z. Clyde-Watson, S. L. Darling, J. C. Hawley, H.-J. Kim, C. C. Mak, S. Webb, *The Porphyrin Handbook*, *Vol. 3* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), Academic Press, San Diego, **2000**, pp. 1 – 48.

[17] J. R. McCarthy, P. J. Melfi, S. H. Capetta, C. Brückner, *Tetrahedron* **2003**, *59*, 9137 – 9146.

