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Helimeric Porphyrinoids: Stereostructure and Chiral Resolution of *meso*-Tetraarylmorpholinochlorins

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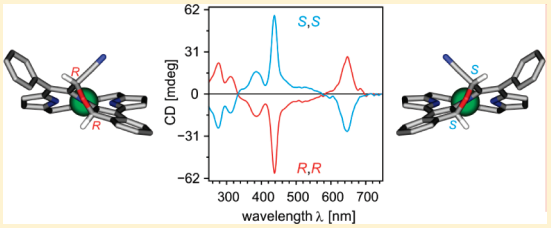
Supporting Information

ABSTRACT: The synthesis and chiral resolution of free-base and Ni(II) complexes of a number of derivatives of *meso*-tetraphenylmorpholinochlorins, with and without direct β-carbon-to-*o*-phenyl linkages to the flanking phenyl groups, is described. The morpholinochlorins, a class of stable chlorin analogues, were synthesized in two to three steps from *meso*-tetraphenylporphyrin. The conformations and the relative stereostructures of a variety of free-base and Ni(II) complexes of these morpholinochlorins were elucidated by X-ray diffractometry. Steric and stereoelectronic arguments explain the relative stereoarray of the morpholino-substituents, which differ in the free-base and Ni(II) complexes, and in the monoalkoxy, β-carbon-to-*o*-phenyl linked morpholinochlorins, and the dialkoxy derivatives. The Ni(II) complexes were all found to be severely ruffled whereas the free-base chromophores are more planar. As a result of the helimeric distortion of their porphyrinoid chromophores, the ruffled macrocycles possess a stable inherent element of chirality. Most significantly, resolution of the racemic mixtures was achieved, both by classical methods via diastereomers and by HPLC on a chiral phase. Full CD spectra were recorded and modeled using quantum-chemical computational methods, permitting, for the first time, an assignment of the absolute configurations of the chromophores. The report expands the range of known pyrrole-modified porphyrins. Beyond this, it introduces large chiral porphyrinoid π-systems that exist in the form of two enantiomeric, stereochemically stable helimers that can be resolved. This forms the basis for possible future applications, for example, in molecular-recognition systems or in materials with chiroptic properties.



INTRODUCTION

Chiral porphyrins are rewarding platforms for stereoselective molecular-recognition systems, as chiral ligands in catalysis, and as chiral optical probes.[1−3] Their large aromatic π-systems make them particularly interesting for these applications, since porphyrinoids generally possess intense optical spectra, large interaction surfaces, and the capability of inducing large diatropic shifts. In classical examples, chiral porphyrins were generated by linking achiral meso-substituents along a chiral axis to the macrocycle,[2] such as in porphyrin **1**,[4] or by the synthesis of porphyrins containing chiral *meso*-substituents, such as porphyrin **2**.[5] In the field of chiral bisporphyrins, the groups of Osuka;[6] Borovkov, Kobayashi, and Inoue;[7] Chmielewski;[8] Zheng;[9] and of some of us[10,11] have reported on the synthesis and stereostructural characterization of porphyrin dimers that gave rise to atropo-enantiomers, such as dimers **3**[10] and **4**[11] (Chart 1). The stereo*dynamic* properties of intrinsically chiral dimers, such as **3**, have also been investigated.[10]

A chiral porphyrin dyad has been utilized by Tashiro, Aida and co-workers for the enantioselective extraction of a chiral C_{76} fullerene out of a racemic mixture.[12] Monomeric and dimeric porphyrins as CD reporter groups have also been extensively investigated by Berova and co-workers in chiral environments.[13]

Unsubstituted tetraarylporphyrins in the ruffled conformation are D_{2d}-symmetric and, thus, achiral. However, modifications of the β-positions may lead to a desymmetrization of the porphyrinoid, giving rise to helically chiral conformers. We have previously observed that the chiral dialkoxymorpholinochlorin **5Ni** is particularly ruffled and that it crystallizes as a racemate.[14,15] This inspired a preliminary report on the enantiomeric resolution of the β-carbon-to-*o*-linked morpholinochlorin Ni(II) complex **6bNi** by a classical diastereomer separation.[16]

Received: March 17, 2011
Published: May 02, 2011

dx.doi.org/10.1021/ja202451t | *J. Am. Chem. Soc.* 2011, 133, 8740–8752

Chart 1. Representative Structures of Chiral Porphyrins

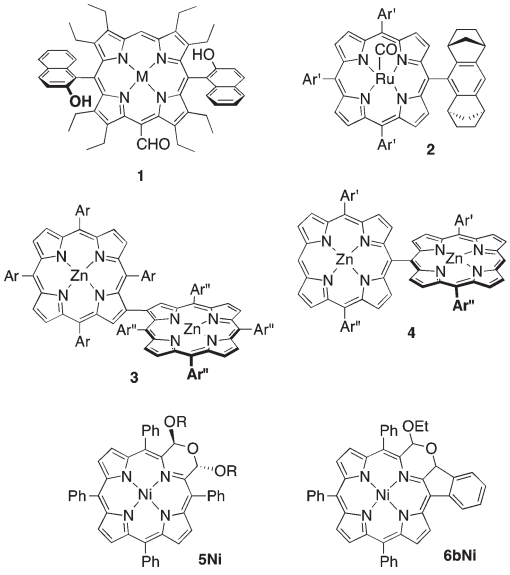
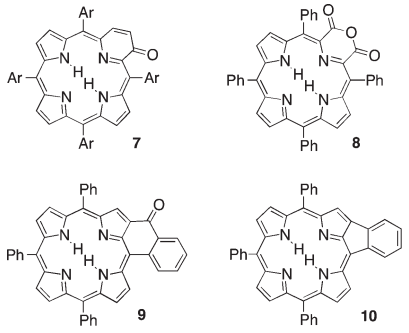


Chart 2. Representative Pyrrole-Modified Porphyrins and *meso*-Phenylporphyrins Containing β-to-*o*-Phenyl Linkages



We now report on the assignment of the relative stereostructure and the absolute configuration of the two enantiomers and demonstrate the generality of the syntheses of morpholinochlorins with or without β-carbon-to-*o*-phenyl linkages, and their enantiomeric resolution. This is the first report in which enantiomeric conformers of chiral nonplanar porphyrinoids were separated. This has previously been hampered because of the generally very low barriers of racemization. For similarly ruffled and chiral metallocorroles, the inversion barrier was computed to lie between 5 and 7 kcal/mol.[17]

Beyond their intriguing stereostructures, morpholinochlorins of type **5Ni**[14,18] and **6bNi**[16] are also interesting because they represent examples of so-called pyrrole-modified porphyrins, that is, porphyrinoids in which a pyrrolic subunit in a porphyrin is replaced by a nonpyrrolic moiety.[19] Most of what is known about heteroporphyrins and pyrrole-modified porphyrins containing benzene,[20,21] pyridine,[22,23] pyridinone,[21,23,24] or azulene[25] has been gleaned from compounds made by total synthesis. Still, a range of these, including morpholinochlorins **5Ni**[14,18] and **6bNi**[16] and also oxypyriporphyrin **7**[18,26] and anhydride **8** (Chart 2),[27] can be obtained by the stepwise derivatization of the β-carbons of preformed porphyrins.[12,15,16,18,27−34,38] Our flexible approach toward the conversion of porphyrins to pyrrole-modified systems follows one common strategy: An OsO_4-mediated dihydroxylation of a *meso*-tetraarylporphyrin β,β'-double bond generates a 2,3-dihydroxychlorin.[14,35,33] Thus activated, the β,β'-bond is oxidatively cleaved to generate a secochlorin bisaldehyde. Its carbonyl groups are subsequently reacted in such a manner that a ring closure takes place, generating a pyrrole-modified porphyrin.

The synthesis of pyrrole-modified porphyrins, chlorins, porphyrin isomers, heteroporphyrins, and other porphyrin analogues is driven by the search for chromophores with optimized electronic properties for a number of biomedical and technical applications, such as photodynamic therapy[36] or solar-energy conversion.[37−39] One strategy to further modulate the optical spectra of *meso*-arylporphyrins is to establish β-to-*o*-phenyl-linkages.[40] Typical examples of this class of compounds are the ketone-bridged porphyrin **9**[41] and the fused porphyrin **10**.[10,42] The link forces an idealized co-planarity of the aryl groups with the porphyrinic π-system.[43] The combined effect of the conjugation of porphyrinic π-electrons with the *meso*-aryl group (and the linker) and the possibly altered conformation of the chromophore framework is the origin of a significant perturbation of the electronic structure of the overall porphyrinic π-system.[32,34,44]

The porphyrinoid **6bNi** represents to date the only example of a morpholinochlorin containing a β-carbon-to-*o*-phenyl linkage.[16] Neither the effects of this linkage on the conformation of the morpholinochlorin, nor the formation of corresponding free-base analogues has been investigated.

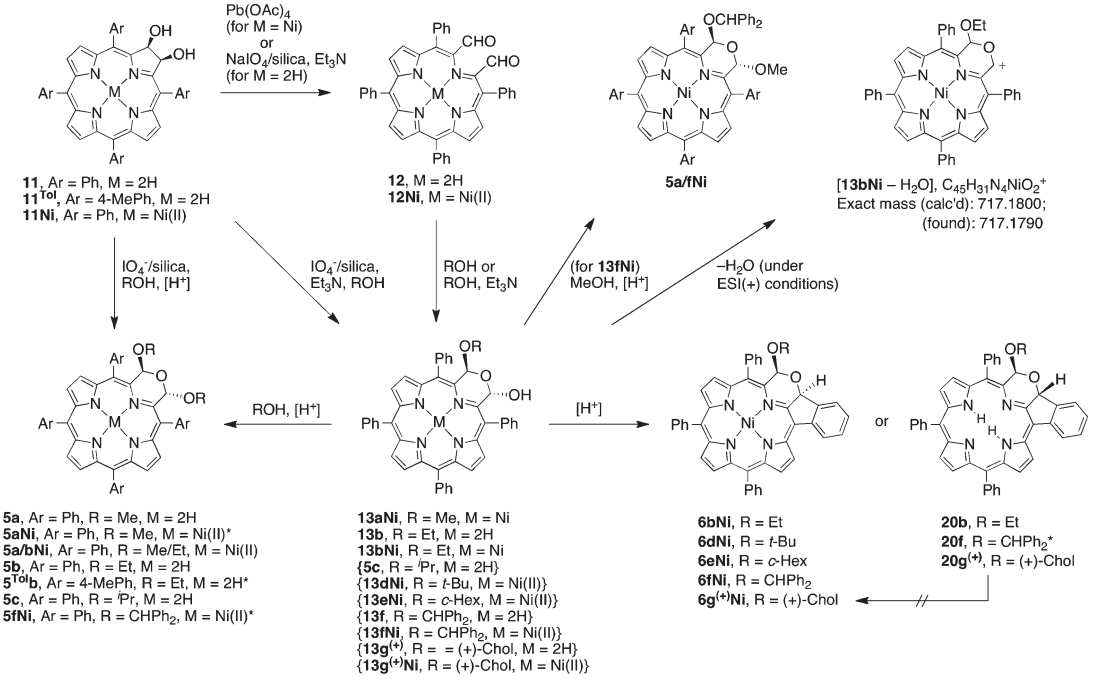
We describe here general synthetic strategies toward free-base and Ni(II) complexes of alkoxymorpholinochlorins (type **5Ni**) and directly β-to-*o*-phenyl-linked morpholinochlorins (type **6Ni**). We also report on the solid-state conformations of their free-base and Ni(II) complexes, revealing their surprising stereostructures. Focus of this investigation is the stereochemical characterization of the conformers of the morpholinochlorins, including a description of the conformational and configurational effects caused by the β-carbon-to-*o*-phenyl linkage. We describe the resolution of the enantiomers and the assignment of their absolute stereostructures by online LC−CD measurements in combination with quantum-chemical calculations of the CD spectra (TDB3LYP/6-31G*//PBE0/TZV(P) or MRCI//PBE0/TZV(P)) and comparison of the computed CD spectra with the experimental ones.[45] We thus demonstrate, for the first time, the scopes and limitations of the chiral resolution of monomeric helically chiral porphyrinic chromophores.

RESULTS AND DISCUSSION

Synthesis of Free-Base and Ni(II) Complexes of *meso*-Tetraarylmorpholinochlorins with Two, One, or No Substituent(s) on the Morpholine Moiety, Including a β-to-*meso*-Phenyl Linkage. We begin with a brief overview of the syntheses of the broad variety of the compounds discussed (Schemes 1 and 2), before we focus the discussion on the conformational and stereostructural aspects of the morpholinochlorins. All compounds were spectroscopically characterized (for details, see Supporting Information). Spectroscopic features will be described only where particularly diagnostic for their stereostructural properties.

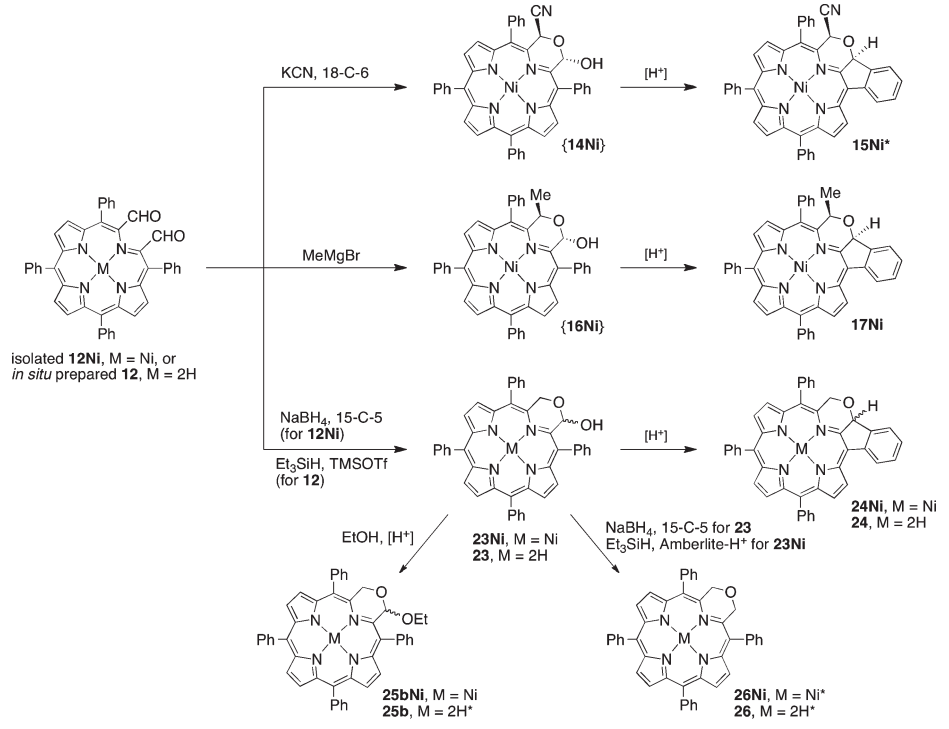
We have previously shown that the oxidative diol cleavage of dihydroxychlorins **11**/**11Ni** using a number of methods leads to

Scheme 1. Synthesis of Dialkoxymorpholinochlorins and Monoalkoxymorpholinochlorins Containing a β-to-Phenyl Linkage[a,b]



[a] Asterisk (*) indicates compounds for which the single-crystal structure is reported here. [b] Curly brackets { } indicates products that were not isolated.

Scheme 2. Formation and Reactivity of Tetraphenylmorpholinochlorin Hemiacetals[a,b]



[a] Asterisk (*) indicates compounds for which the single-crystal structure is reported here. [b] Curly brackets { } indicates products that were not isolated.

the formation of the corresponding secochlorin bisaldehydes **12**/**12Ni** (Scheme 1).[14,30,31,33] The particular reaction conditions used need to be selected dependent on whether the free-base or metal complexes of the diolchlorin are used. The Ni(II)-templated synthesis of [*meso*-tetraphenylmorpholinochlorinato]Ni(II) **5a/bNi** by acid-catalyzed, alcohol-induced ring closure of secochlorin bisaldehyde Ni(II) **12Ni** is known and occurs smoothly for MeOH and EtOH.[14] Likewise, *in situ* prepared free base bisaldehyde **12** can be ring-closed to form free-base morpholinochlorins.[30] We demonstrate here that these reactions

dx.doi.org/10.1021/ja202451t |*J. Am. Chem. Soc.* 2011, 133, 8740–8752

are quite general and can also be applied to sterically more demanding alcohols in excellent yields (above 75% at 10 mmol scales). The optical absorptions of the dialkoxymorpholinochlorins are chlorin/metallochlorin-like and red-shifted compared to the corresponding diolchlorin **11**/**11Ni**, with virtually no effect of the nature of the alkoxy substituents on their UV−vis spectra (see Supporting Information).

Alkoxy-hydroxymorpholinochlorins of type **13**/**13Ni** are observed as intermediates in the formation of dialkoxymorpholinochlorins **5**/**5Ni**.[14,16] Their directed, high-yield synthesis is also possible: Reaction of the nonpolar secochlorin bisaldehydes **12**/**12Ni** with bulky alcohols (such as *t*-butanol, benzhydrol, or cholesterol) under acid catalysis (traces of HCl or TFA vapors), or reaction of the secochlorins with less bulky primary alcohols in the presence of base (Et_3N), generates the polar hemiacetals **13**/**13Ni** in near-quantitative yields. ESI(+) mass spectra showed, in addition to the expected $[M + H^+]$ peak, a prominent fragment ion that resulted from the loss of water, indicating the pronounced and characteristic ease of this hemiacetal to form a carbocation at the sp^3-hybridized carbon of the morpholino moiety. This property is rationalized by the charge stabilization that the porphyrinic π-system and the neighboring oxygen can provide. Because of the high reactivity of the hydroxymorpholinochlorins, it is best to use them immediately in crude form in subsequent reactions. For instance, treatment of these hemiacetals with alcohols under more forcing acidic conditions forms the corresponding bisacetals, such as **5aNi** or **5fNi**, or the mixed alcohol double acetals, such as **5a**/**fNi**.[14]

Upon exposure of hemiacetals **13**/**13Ni** to catalytic quantities of acid (TFA or conc.-HCl fumes) in the absence of any external nucleophile, less polar compounds with red-shifted UV−vis spectra (see Supporting Information) were obtained (Scheme 1). The compositions of these compounds correspond to that of the starting hemiacetal minus a molecule of water. The NMR spectra of the products indicate the absence of a symmetry axis, with pattern of correlated signals diagnostic for the presence of an *o*-linked *meso*-phenyl group.[32] This identified the products as the phenyl-fused alkoxymorpholinochlorins **6Ni** and **20**. The β-carbon-to-*o*-phenyl linkage was established as a result of an acid-catalyzed intramolecular Friedel−Crafts-type substitution of the *o*-position of the *meso*-phenyl group by the neighboring morpholine cation.

Alcohols are not the only nucleophiles suited to induce the ring-closing reaction of a secochlorin bisaldehyde to form the morpholine moiety (Scheme 2). The *C*-nucleophiles KCN (in the presence of 18-crown-6) and methyl-Grignard also effect this reaction in **12Ni**, providing hemiacetals **14Ni** and **16Ni**, respectively. Hydrides (in the form of EtSiH/TMSOTf or $NaBH_4$,[29] or $NaBH_4$/15-crown-5) can also act as nucleophiles, forming hemiacetals **23**/**23Ni**. As in the alcohol-induced ring-closures, the products **14Ni**, **16Ni**, **23**, and **23Ni** were immediately treated with acid to provide the fused morpholinochlorins **15Ni**, **17Ni**, **24**, and **24Ni**, respectively. The ^{1}H NMR spectra of, for instance, methyl-substituted fused morpholinochlorin derivative **17Ni** were sufficiently resolved to permit a near-complete assignment (see Supporting Information). Hemiacetals **23**/**23Ni** can also be converted with ethanol under acid catalysis to the corresponding acetals **25b**/**25bNi**. Interestingly, **23** and **23Ni** can be deoxygenated to provide the parent, unsubstituted, systems **26** and **26Ni**, respectively.

Conformation of Ni(II) Complexes of *meso*-Tetraarylmorpholinochlorins with Two or No Alkoxy Substituent(s) on the Morpholine Moiety. To probe to which extent the alkoxy substituents influence the conformation of the morpholinochlorins, we prepared a number of alkoxy derivatives **5Ni** using alcohols of varying steric demand. Since the UV−vis spectrum of, for example, the benzhydrol derivative **5fNi** is nearly identical to that of the dimethoxy derivative **5aNi** (see Supporting Information), the influence of the bulk of the alkoxy substituent on the conformation of the chromophore was expected to be minimal. This hypothesis was confirmed by their X-ray structural analysis (Figure 1).[46]

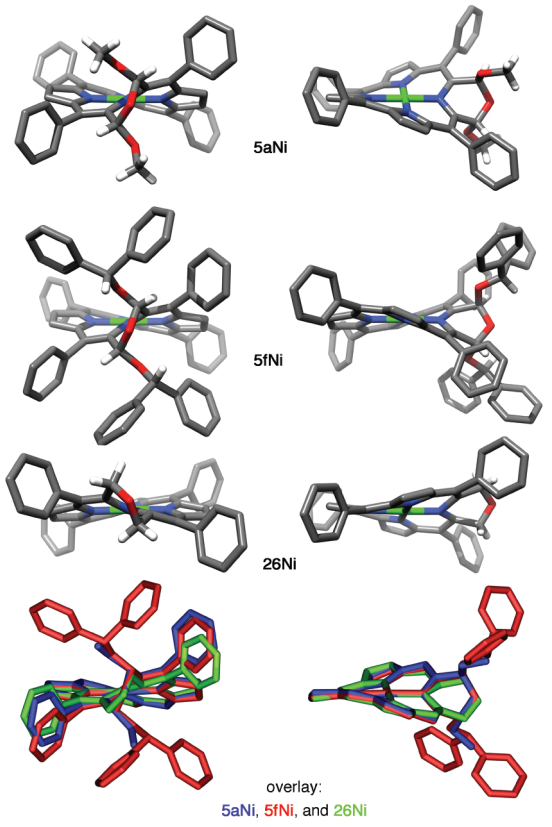


Figure 1. Stick representations of the front and side views of the X-ray structures of **5aNi**, **5fNi**, and **26Ni**; all hydrogens attached to sp^2 carbons removed for clarity. Bottom images: Overlay of the macrocycle conformation of **5aNi** (blue), **5fNi** (red), and **26Ni**; front view, all hydrogens removed for clarity.

Indeed, the conformations of **5aNi** and **5fNi** are very similar to each other and to the previously reported mixed alkoxide structure **5a**/**bNi**.[14] The chromophores of **5aNi** and **5fNi** are severely ruffled (rms of 0.535 and 0.518 Å of the $C_{20}N_4O$ macrocycles),[47] with an idealized screw axis along the $O_{morpholine}-N_{morpholine}-Ni-N$ axis. Both compounds are C_2-symmetric, chiral and crystallized as racemic mixtures in nonchiral space groups ($P\bar{1}$ and *Pbca*). The conformation of the morpholino moiety is best described as twist-boat. The Ni(II)-induced ruffling of porphyrinoid chromophores is well understood and can be traced back to the small size of the central Ni(II) ion.[15,48−50] Importantly, the bulk of the alkoxy groups in the dialkoxymorpholinochlorins has only a minimal effect on the conformation of the morpholinochlorins. This is because the alkoxy groups occupy a wide cleft within the molecule defined by the two neighboring *meso*-phenyl groups. Thus, removal of the alkoxy groups does not substantially affect the framework conformation. As a consequence, the

dx.doi.org/10.1021/ja202451t |*J. Am. Chem. Soc.* 2011, 133, 8740–8752

conformation of the parent [morpholinochlorinato]Ni(II) complex **26Ni** is nearly identical (rms of 0.412 of the $C_{20}N_4O$ macrocycle) to those of the bisalkoxy analogues **5aNi** and **5fNi** (Figure 1).[51] As will be described below, the presence of alkoxy substituents is, however, crucial for the *stereochemical stability* of these porphyrinoids.

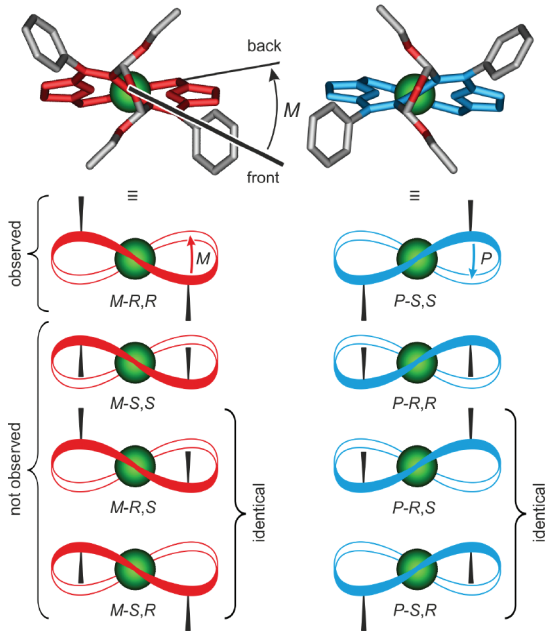


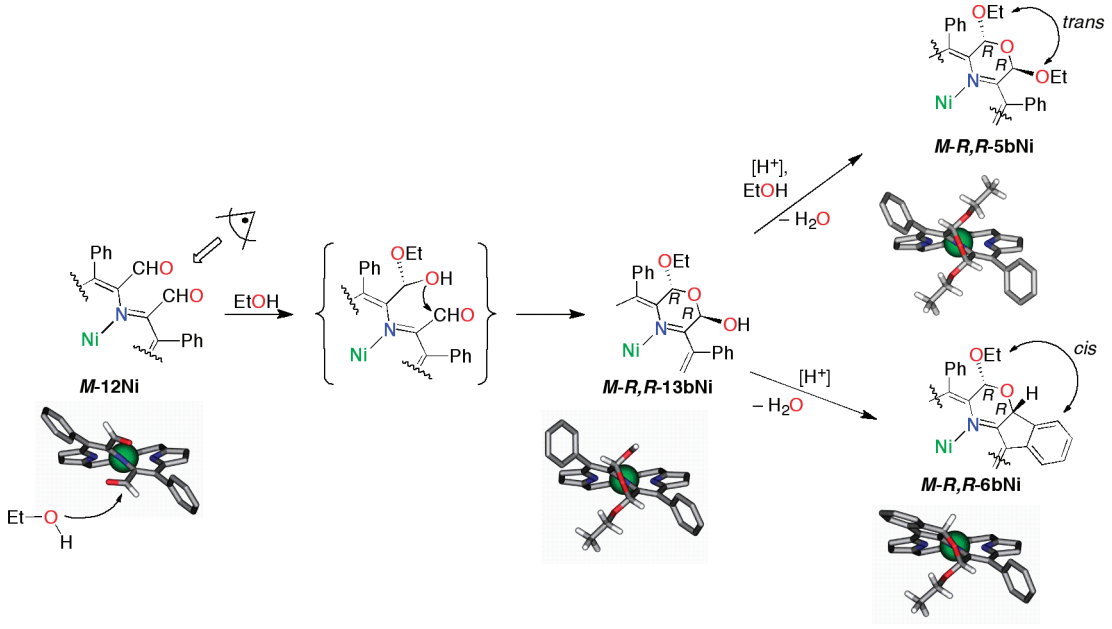
Figure 2. Schematic representation of the stereoisomers possible for dialkoxymorpholinochlorins of type **5Ni**, and their nomenclature. The black wedges indicate (identical) alkoxy substituents attached to the sp^3 carbons of the morpholine ring in the two possible configurations.

This finding permits a reliable prediction of the conformation and stereochemical alignment of the intermediates between the secochlorin **12Ni** (also of ruffled conformations)[15,52] and the dialkoxymorpholinochlorins **5Ni**. This predictive ability forms the basis for a number of mechanistic and stereochemical projections.

The Origin of the Homochirality of the Morpholinochlorin Substituents. In addition to the Ni(II)-induced helicity of the ruffled chromophore **3Ni**, designated by the helical chirality descriptors *P* and *M*, the two sp^3 ring carbons in the morpholine moiety are stereogenic centers (*R* or *S*). Thus, eight (2^3) stereoisomers are theoretically possible, though internal constitutional symmetry reduces this number to six (Figure 2).[53] However, the formation of only one racemic pair is observed in the crystals of **5a**/**bNi**,[14] **5aNi** and **5fNi**, namely, those designated as *P-S,S* and *M-R,R*. The existence of other diastereomers in solution was excluded by NMR spectroscopy.

The observed stereoselectivity can be rationalized by the cooperative action of steric and stereoelectronic effects (Scheme 3). X-ray diffractometry has shown that the two aldehyde functionalities of the ruffled starting material secochlorin **12Ni** lie on top of, and parallel to, each other and parallel to the chromophore plane.[15,52] The Ni(II)-induced twist in this secochlorin also positions the *meso*-aryl groups *anti* to each other with respect to their relative position to the chromophore plane. This alignment provides a steric shield and directs the attack by a nucleophile on the prochiral aldehyde centers to occur from an unshielded homotopic *exo* side. The hemiacetal hydroxy group (or its anion) should subsequently attack the second aldehyde intramolecularly from the *endo* side, forming the morpholine moiety. The anomeric effect favors the *trans*-configuration of the alkoxy and hydroxy groups in the ring-closed hemiacetal **13Ni** and of the two alkoxy groups in the final product **5Ni**.[54] In either

Scheme 3. The Ni-Induced Chromophore Twist as the Assumed Origin of the Relative Configuration Found in the Dialkoxy- (5Ni) and Phenyl-Linked (6Ni) Morpholinochlorins[a,b]



[a] Note that even though the relative *trans*-stereostructure of the morpholine substituents in **5bNi** inverts to *cis* in **6bNi**, the stereodescriptors remain unchanged *R,R* because the substituent priorities according to the CIP rules also change. [b] Models shown based on crystal structures (**12Ni**, **5bNi**, **6bNi**) or computations (**13bNi**).

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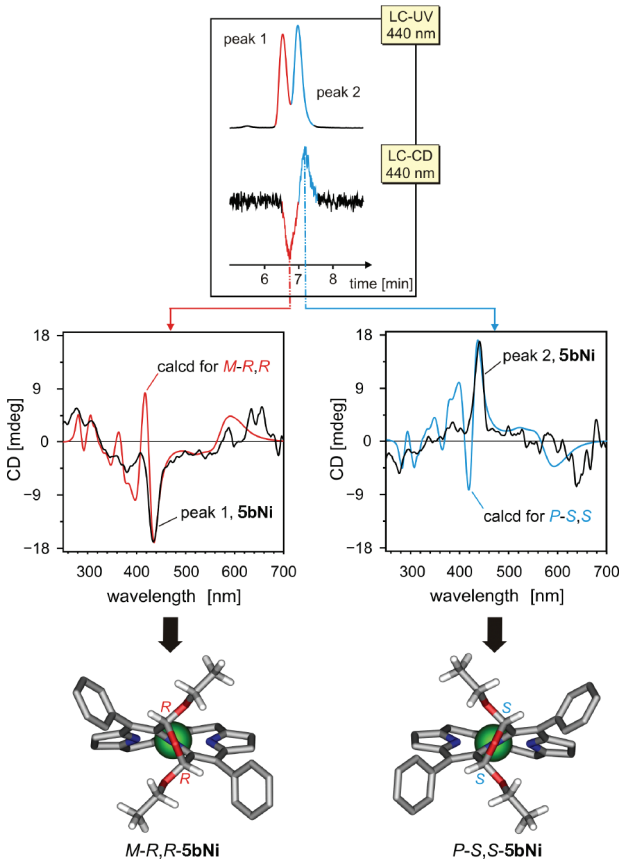


Figure 3. Results of the HPLC separation of a racemic mixture of **5bNi** on a chiral phase (Chirex-3010 column, Phenomenex; ambient temperature; *n*-hexane-CH_2Cl_2 (v/v) 70:30, isocratic flow: 0.8 mL/min) and stereochemical assignment of the two enantiomers by comparison of the experimental CD spectra with the computed curves.[45] The rear phenyl substituents and all hydrogens at the sp^2-carbon atoms were omitted for clarity.

case, both substituents adopt a pseudoaxial position. Importantly, this *trans*-configuration is clearly also the sterically favored orientation of the alkoxy substituents as both alkoxides then point away from the flanking phenyl groups so that, independent from the above kinetic considerations, the *trans*-product is the thermodynamically favored product, also in agreement with the DFT calculations. As a result, the configurations of the two sp^3 centers are fixed to be homochiral (relative *like*-configuration). The *M*-conformer of the bisaldehyde *M*-**12Ni** thus leads exclusively to the thermodynamically more stable *R,R*-configuration in the product. Consequently, the *P*-conformer, *P*-**12Ni**, yields the *S,S* isomer. Therefore, only one of the several possible diastereomers of **5Ni** (in its two enantiomeric forms) is observed. This mechanism implies identical chirality of the sp^3 centers in the alkoxy-hydroxy intermediate **13Ni** and the final dialkoxy product **5Ni**. This further means that an S_N1 reaction pathway for the transformation of **13Ni** to **5Ni** must have taken place. Given the propensity of **13Ni** to form an oxocarbenium ion (see above), this implication is reasonable.

Resolution of [Morpholinochlorinato]Ni(II) by HPLC on a Chiral Stationary Phase. An electrochemical investigation of **5bNi** had indicated that its conformation is locked,[29] raising the question whether the enantiomeric conformers of **5bNi** can be resolved. This succeeded by subjecting the racemic porphyrinoid **5bNi** to HPLC on a chiral stationary phase, resulting in a good separation of two components in a 1:1 ratio (Figure 3). The CD of the 440 nm absorption of the two species, measured online by LC−CD, provided a first indication that the two compounds were indeed enantiomers. The more rapidly eluting component (peak 1) showed a negative Cotton effect at 440 nm, while the slower component (peak 2) exhibited a positive one of equal intensity. Full online CD spectra were recorded in the stopped-flow mode, providing a CD spectrum with a negative Cotton effect for the Soret band and a positive one in the Q-band region in the case of peak 1, and a perfect mirror-image spectrum for the higher-R_f component (peak 2), demonstrating their enantiomeric relationship. No indications of epimerizations of the *M-R,R* and *P-S,S* enantiomers of **5bNi** were found at ambient conditions.

A lack of precedents precluded an empirical assignment of the absolute stereostructure of the enantiomers of **5bNi**. We therefore determined their absolute configurations by comparison of the experimental CD spectra with quantum-chemically computed ones. The conformational space of the two enantiomers *P-S,S*-**5bNi** and *M-R,R*-**5bNi** was investigated by the PBE0/TZV(P) method, resulting in four minimum geometries, which differed only in the orientation of the phenyl substituents. The global minimum structure fitting best the solid-state conformations of **5aNi**/**5fNi** was used as the basis for CD calculations at the TDB3LYP/6-31G* level.[45] The simulated CD spectra were UV-corrected[55] and compared with the experimental spectra, revealing an excellent agreement, even though solvent effects were not taken into account in the calculations (Figure 3). This permitted the unequivocal assignment of the absolute configurations of the enantiomers as shown.

In sharp contrast to the ability to separate the enantiomeric conformers of the dialkoxy derivative **5bNi**, we could not find conditions to achieve any resolution of the also ruffled nonalkoxy-substituted [morpholinochlorinato]Ni(II) complex **26Ni**. Computations suggested that the inversion barrier between the two enantiomers of **26Ni**, that is, *M*-**26Ni** and *P*-**26Ni**, is only ~50 kJ/mol, enabling rapid racemization at room temperature (for the details of the computation, see Supporting Information). Since the alkoxymorpholinochlorin Ni(II) complex **5bNi** did not racemize, we conclude that the alkoxy substituents fix a given helical conformation. The ability of these substituents to lock a given helicity is because helimer inversion (without concomitant high-energy inversion of the morpholine sp^3 carbons) would bring the alkoxy substituents into a steric clash with the adjacent phenyl substituents. Thus, these results mirror the conclusions derived from the electrochemical measurements and highlight the importance of the interplay between Ni(II)-induced ruffling and the stereochemical stabilization of the resulting helical conformers provided by the alkoxy substituents.[29]

Solid-State Conformations of Free-Base Morpholinochlorins with Two, One, or No Alkoxy Substituents. The single-crystal structure of free base diethoxymorpholinochlorin $\mathbf{5}^{\mathbf{Tol}}\mathbf{b}$ exhibits the homochiral *trans*-configuration of the ethoxy side chains that also characterizes the corresponding Ni(II) complexes **5aNi**/**5fNi** (Figure 4).[30] The moderate nonplanarity of the morpholine unit, best described as a half-twist, translates only minimally into the $C_{18}N_4$ chromophore, with an rms deviation from planarity of the $C_{20}N_4O$ macrocycle of only 0.012 Å. In analogy to its Ni(II) complex, the distortion mode of the free-base chromophore can also be classified as ruffled, albeit the distortion is only minor. As a result, the solid-state structure of $\mathbf{5}^{\mathbf{Tol}}\mathbf{b}$ is (idealized) C_2-symmetric and

dx.doi.org/10.1021/ja202451t |*J. Am. Chem. Soc.* 2011, 133, 8740–8752

chiral and the compound crystallized in a racemic form in the achiral space group $P\bar{1}$.

Unexpectedly, the lack of one ethoxy group in **25b** results in a fundamentally different conformation of the morpholinochlorin framework, which is now best described as slightly saddled (rms of the $C_{20}N_4O$ macrocycle of 0.417 and 0.390 Å for the two crystallographically independent molecules), with the morpholine moiety adopting a half-boat conformation. Irrespective of its nonchiral saddled conformational distortion of the chromophore, **25b** is still a chiral compound, while removal of all alkoxy groups restores the ruffled conformation. In fact, the ruffling of the parent unsubstituted morpholinochlorin **26** (rms of the $C_{20}N_4O$ macrocycle 0.310 and 0.299 Å for the two disordered orientations of the molecules in the unit cell) is even more strongly expressed than in the diethoxy derivative $\mathbf{5^{Tol}b}$. The varying conformations of the free-base and Ni(II) morpholinochlorins illustrate the substantial flexibility of this chromophore. These morpholinochlorins therefore provide another dramatic example of the remarkable degree to which porphyrinic macrocycles, which are frequently regarded as planar and rigid, can undergo extensive 'molecular gymnastics'.[39]

Derivative **26** showed signs of dynamic processes in its room temperature NMR spectra. In fact, the morpholine methylene hydrogens in the ^{1}H NMR spectra of **26** do not display the diastereotopic differentiation of the morpholine methylene protons that is expected from the crystal structure of **26**, even when cooled to −50 °C (see Supporting Information), implying a rapid racemization of the conformers! This finding underlines once again the importance of the alkoxy substituents for the stabilization of one particular chiral conformer of the morpholinochlorins.

The parallels to the Ni(II) morpholinochlorins seen in the stereostructure of free-base morpholinochlorins $\mathbf{5^{Tol}b}$ are, perhaps, surprising since the conformation of the Ni(II) complexes was rationalized by the Ni-induced ruffling. Evidently, however, the native nonplanarity of the morpholino moiety is expressed strongly enough and induces a sufficiently pronounced ruffling to differentiate the sterically more (pointing toward the flanking phenyl group) and less (pointing away) encumbered morpholine sp^3 positions. Furthermore, the stereoelectronic arguments brought forth for the Ni(II) complexes also hold for the free-base cases.

In fact, direct evidence can be found for the steric protection by the phenyl group during the nucleophile-induced ring-closures in free-base secochlorins: 5,15-diphenylsecochlorin bisaldehyde is prepared *in situ* by oxidation of the corresponding 2,3-dihydroxychlorin **18**[56] (Scheme 4). This 5,15-diphenyl derivative features one aldehyde that is shielded by a flanking phenyl group and one unshielded aldehyde. Reaction of this secochlorin with EtOH produces only one of the two possible isomers, alkoxy-hydroxymorpholinochlorin (**22**), which results from the initial nucleophilic attack onto the unshielded aldehyde. Isomer *iso*-**22** is not observed. Conversion of **22** generates the phenyl-fused system **21b**.

Resolution of Free-Base Morpholinochlorin 5b by HPLC on a Chiral Stationary Phase. HPLC of free-base diethoxymorpholinochlorin **5b** on a chiral stationary phase resulted in a clear resolution of the racemate, giving two peaks in a 1:1 ratio with opposite CD signals at 440 nm (Figure 5), even though the helicity of free base **5b** is much less pronounced than for its Ni(II)-analogue **5bNi**. Again, full online CD spectra were recorded and compared to the computed CD traces. The calculated spectrum for the *R,R*-configured enantiomer fits the experimental CD spectrum of the faster eluting molecule, and inversely, the spectrum computed for the *S,S*-configuration matches the more slowly eluting enantiomer.[57] Once again, no signs of racemization were observed at room temperature.

Conformational and Stereostructural Consequences of the *β*-Carbon-to-*o*-Phenyl Linkage in Free-Base and Ni(II) *meso*-Arylmorpholinochlorins. NOESY spectra of the *β*-carbon-to-*o*-phenyl-linked morpholinochlorins **6bNi**, **14Ni**, and **16Ni** provided evidence for the *cis*-arrangement of the hydrogens on the morpholine sp^3 carbons, thus, implying a *cis*-relationship

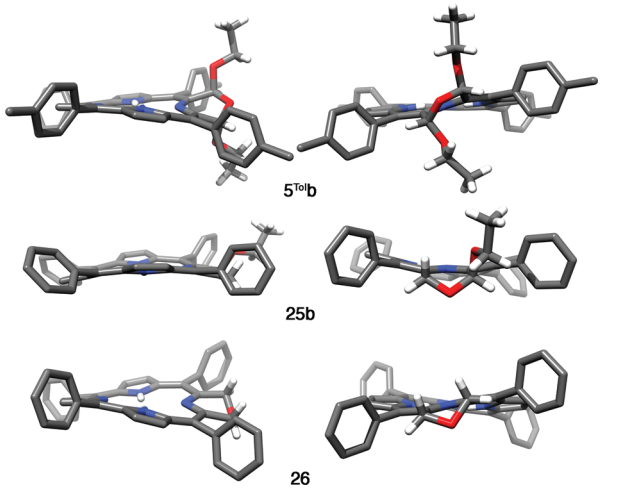
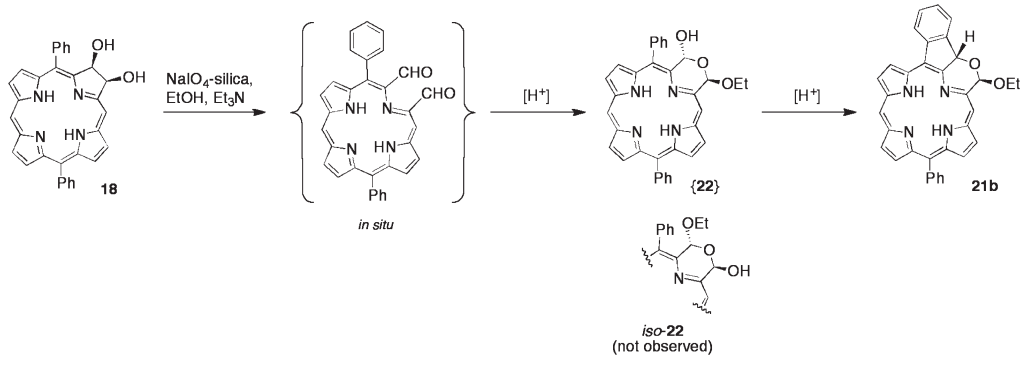


Figure 4. Side (left column) and front views (right column) of the X-ray structures of $\mathbf{5^{Tol}b}$,[30] **25b**, and **26**. All hydrogens attached to sp^2-carbons and the tolyl-CH_3 hydrogens (in $\mathbf{5^{Tol}b}$) were removed for clarity.

Scheme 4. Formation of Phenyl-Fused 5,15-*meso*-Diphenylmorpholinochlorin 21b



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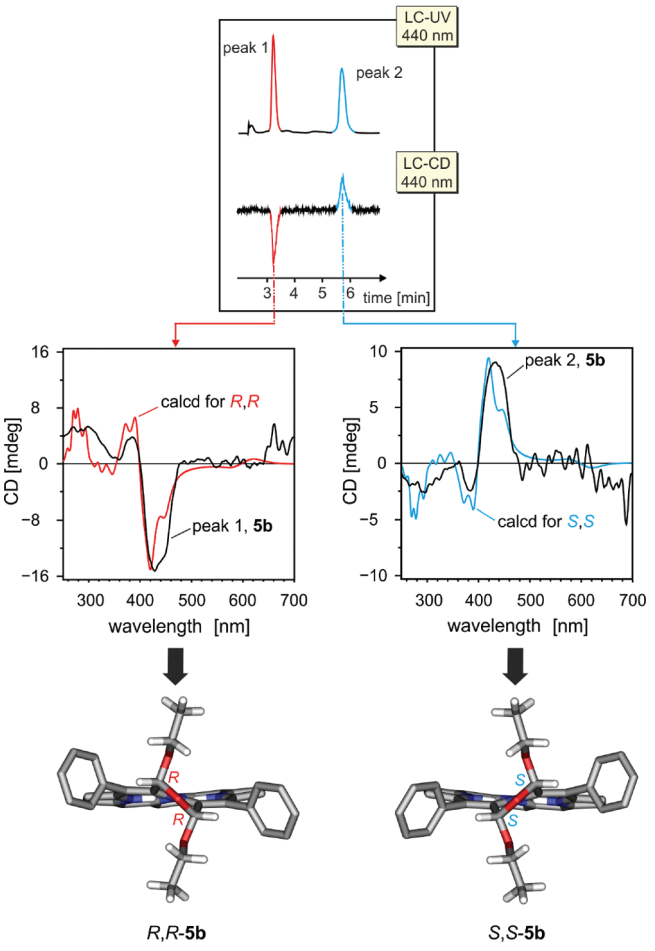


Figure 5. Results of the resolution of a racemic mixture of **5b** on a chiral HPLC phase (Chirex-3010 column, Phenomenex; ambient temperature; *n*-hexane-CH_2Cl_2 (v/v) 50:50, isocratic flow: 1.5 mL/min) and stereochemical assignment of the two enantiomers by comparison of the experimental and computed CD spectra.[45] The rear phenyl substituents and hydrogens at all sp^2-carbon atoms were omitted for clarity.

of the morpholine-to-*o*-phenyl linkage and the respective morpholino-substituent (ethoxy group in **6bNi**, cyano group in **15Ni**, and methyl group in **17Ni**). This relative stereoarray is opposite to the orientation of the two alkoxy substituents in the dialkoxymorpholinochlorins **5Ni**, which is rationalized by the particularly ruffled conformation of precursor **13Ni**. For steric reasons, only a *cis*-arrangement of the phenyl linkage and the second substituent of the morpholine moiety is possible (Scheme 3).

By contrast, *cis*- and *trans*-relationships of the alkoxy groups appear to be sterically equally possible in the much less ruffled free-base chromophores **20**. However, due to the absence of a signal in their NOESY spectra that correlates the two hydrogens on the morpholinochlorin sp^3 carbons, a *trans*-relationship is most likely (and could be confirmed, see below). We were also able to gather chemical findings for a differing configuration in the Ni(II) complexes **6bNi** and **6g**$^{(+)}$**Ni** and their free-base analogues **20b** and **20g**$^{(+)}$. Attempts to insert Ni(II) into the free bases under standard conditions (Ni(II) acetate in refluxing pyridine) only led to the formation of chemically unstable Ni(II) complexes in low yield (<10%) that had the expected mass, but were different by TLC when compared to the

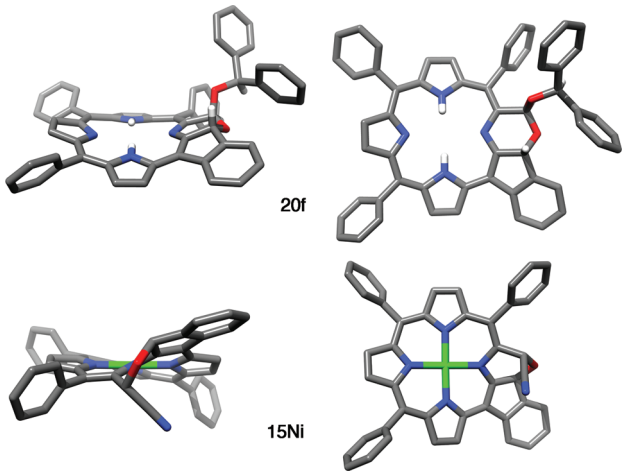


Figure 6. Stick representations of the X-ray structures of **20f** and **15Ni**. Only one of the two independent molecules in the lattice of **15Ni** is shown (see Supporting Information for representation of both molecules). All hydrogens attached to sp^2 carbons removed for clarity.

supposedly corresponding (and stable) Ni(II) complexes. Because of their instability, no further spectroscopic characterization of the compounds was possible. The instability of the Ni(II)-insertion products may be rationalized by the presence of a *cis*-configuration of the alkoxy moiety and the phenyl linkage in the near-planar free-base chromophore, which, upon Ni(II) insertion, adopts a ruffled conformation. This positions the alkoxy group in direct steric clash with the neighboring phenyl group, resulting in the observed chemical instability of the corresponding *cis*-Ni(II) complex.

The chemically and spectroscopically derived assignments of the relative configurations for the free base **20f** and the Ni(II) complex **15Ni** were confirmed by X-ray diffractometry. Accordingly, the solid-state structure of **15Ni** displays a *cis*-arrangement between the β-carbon-to-*o*-phenyl linkage and the morpholine substituent (here, the CN-group; Figure 6). The structure also shows that the ruffled conformation of the precursors,[15,52] as anticipated, is largely preserved. However, as a result of the fusion that forces one *meso*-phenyl group into idealized planarity with the chromophore, the ruffling is diminished by about 10% (rms 0.455 and 0.508 Å of the $C_{20}N_4O$ macrocycle for the two crystallographically independent molecules within the crystal lattice) when compared to the deformation of the dialkoxymorpholinochlorin derivatives (Figure 2).

The solid-state structure of the free-base analogue **20f** confirms the connectivity and *trans*-relationship between the β-carbon-to-*o*-phenyl linkage and the morpholine alkoxy substituent. Moreover, the conformation of the macrocycle is fundamentally different from the one observed in the absence of the β-carbon-to-*o*-phenyl linkage (cf. Figure 4). Instead of the slightly ruffled conformation found in **5**$^{\mathbf{Tol}}$**b**, the distortion mode for **20f** is mainly of a saddling type.[58] This once again highlights the conformational flexibility of the morpholinochlorin chromophore.

Chiral Resolution of [*meso*-Phenylmorpholinochlorinato]-Ni(II) Containing β-to-*o*-Aryl Linkages by HPLC on a Chiral Stationary Phase and Assignment of Their Absolute Stereostructures. Using the conditions for the HPLC-based enantiomer

dx.doi.org/10.1021/ja202451t |*J. Am. Chem. Soc.* 2011, 133, 8740–8752

separations described above, the phenyl-fused compound **15Ni** was also resolved (Figure 7).

The β-to-*o*-aryl linked morpholinochlorin showed the same elution order as their nonlinked analogues. The absolute stereostructure was also assigned by computational simulation of the CD spectra, except that only the conformation of the measured X-ray structure was optimized with PBE0/TZV(P). Subsequent calculation using the TDB3LYP/6-31G* method yielded the theoretical CD spectra for the *M*-*R*,*R* and the *P*-*S*,*S* configurations.[45] By comparison of the measured and calculated spectra of **15Ni**, the faster eluting enantiomer was assigned to be *M*-*R*,*R*-configured and the chromatographically slower enantiomer to be *P*-*S*,*S*.

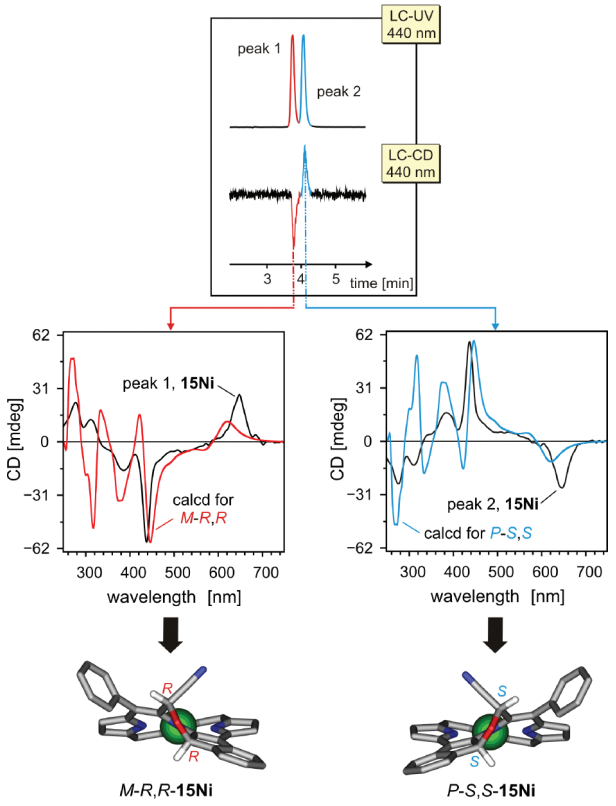


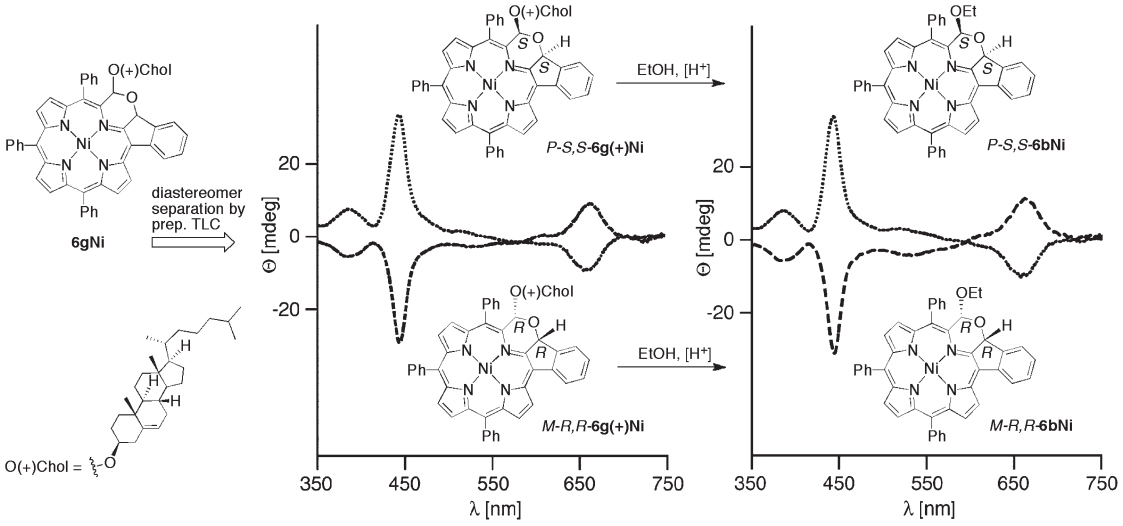
Figure 7. Results of the HPLC resolution of a racemic mixture of **15Ni** (Chirex-3010 column, Phenomenex; ambient temperature; *n*-hexane-CH_2Cl_2 (v/v) 50:50, isocratic flow: 1.5 mL/min) and stereochemical assignment of the two enantiomers by comparison of the experimental CD spectra with the computed ones.[45] The rear phenyl substituents and all hydrogens located at sp^2-carbon atoms were omitted for clarity.

In a similar way, the phenyl-fused ethoxy derivative **6bNi** was resolved by HPLC and its absolute stereostructure assigned using the same methodology as described for the assignment of the cyano derivative **15Ni**, and with comparable results (for details, see Supporting Information). Unfortunately, however, even intense efforts to optimize the separation conditions for chiral free base **20b** resulted only in a poor resolution, insufficient for online-CD measurements. We attribute this to the less pronounced chiral conformation of the near-planar chromophore and the enhanced conformational flexibility of the metal-free macrocycle.

Racemate Resolution through Diastereomer Separation by Preparative TLC of [*meso*-Phenylmorpholinochlorinato]Ni(II) 6bNi Containing a β-Carbon-to-*o*-Phenyl Linkage. Using a chiral alcohol, (+)-cholesterol, the *M*- and *P*-conformers of secochlorin bisaldehyde **12Ni** furnished two green products with the expected composition of the diastereomeric hemiacetals *P*-*S*,*S*-**13g**$^{(+)}$**Ni** and *M*-*R*,*R*-**13g**$^{(+)}$**Ni** (Scheme 1).[16] They were immediately converted to the green β-carbon-to-*o*-phenyl-linked compounds *P*-*S*,*S*-**6g**$^{(+)}$**Ni** and *M*-*R*,*R*-**6g**$^{(+)}$**Ni** of identical compositions ($C_{71}H_{72}N_4O_2Ni$). These products were isolated in 30% yield each by preparative thin layer chromatography ($\Delta R_f = 0.05$).

The successful separation of the two diastereomeric compounds *P*-*S*,*S*-**6g**$^{(+)}$**Ni** and *M*-*R*,*R*-**6g**$^{(+)}$**Ni** was demonstrated by their mirror-imaged CD spectra (Scheme 5). Since cholesterol has no absorption in the wavelength range from 350 to 750 nm, the CD spectra of the diastereomers solely reflect the stereoorientation of their ruffled chromophores. An unresolved diastereomeric mixture of *P*-*S*,*S*-**6g**$^{(+)}$**Ni**/*M*-*R*,*R*-**6g**$^{(+)}$**Ni** showed no CD signal. This shows that cholesterol reacts indiscriminately with both preformed *M*- and *P*-enantiomers of **12Ni**; that is, this nucleophile does not display any

Scheme 5. Racemate Resolution of 6bNi by Preparative TLC Diastereomer Separation[a]



[a] Conditions for the CD spectra: [**6g**$^{(+)}$**Ni**] and [**6bNi**] = 8.0×10^{-6} M, benzene, T = 20 °C.

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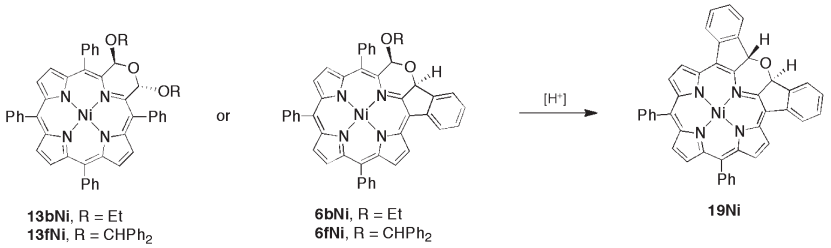
Scheme 6. Formation of Bis-Phenyl-Fused Morpholinochlorin 19Ni



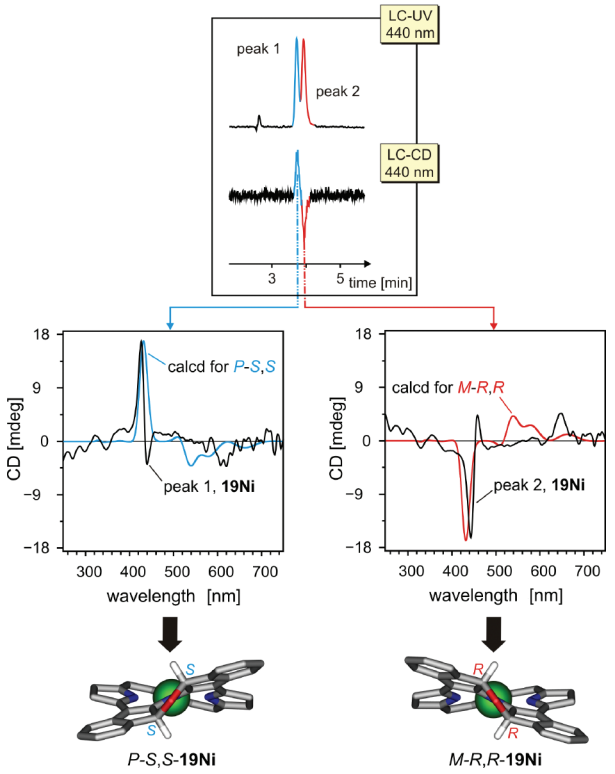


Figure 8. Stereochemical assignment of the two enantiomers of **19Ni** by online HPLC-CD coupling (Chirex-3010 column, Phenomenex; ambient temperature; *n*-hexane-CH_2Cl_2 (v/v) 45:55, isocratic flow: 1.5 mL/min) in combination with quantum-chemical CD calculations.[45] The rear phenyl substituents and hydrogens at sp^2-carbon atoms of the calculated model were omitted for clarity.

stereoselectivity. On the basis of the stereochemical assignment for the enantiomers of the closely related chromophore **15Ni**, we attributed the fraction with the positive Cotton effect at 443 nm to the *P-S,S*-**6g**$^{(+)}$**Ni**-configuration, and the fraction with the negative Cotton effect at this wavelength to the *M-R,R*-**6g**$^{(+)}$**Ni**-configuration.

Acid-induced exchange of the cholesterol moieties for ethoxy groups using a large excess of EtOH proceeded smoothly. This converted the two diastereomers of *M-R,R*- and *P-S,S*-**6g**$^{(+)}$**Ni** to the corresponding pure enantiomers, *M-R,R*-**6bNi** and *P-S,S*-**6bNi**, respectively. The mirror-imaged CD spectra of *M-R,R*-**6bNi** and *P-S,S*-**6bNi** are shown in Scheme 5. Significantly, the diastereomer of **6g**$^{(+)}$**Ni** with a positive Cotton effect at 443 nm also generated the enantiomer of **6bNi** with a positive Cotton effect of identical magnitude at 442 nm. This, in combination with the unchanged relative configuration (according to NMR/NOE), indicated that the stereochemical purity of each chromophore was preserved, that is, no diastereomerization or racemization had taken place in the alkoxy-exchange reaction, certainly a consequence of the conformational rigidity of the chromophore. The same conclusions were derived in an earlier communication, though a different relative stereostructure was implied.[16]

Synthesis and Racemate Resolution of a Doubly-*β*-Carbon-to-*o*-Phenyl-Linked [Morpholinochlorinato]Ni(II) 19Ni. When forming the *β*-carbon-to-*o*-phenyl-fused products **6Ni** from the alkoxy-hydroxymorpholinochlorin Ni(II) complexes **13Ni** under strong-acid catalysis, particularly when using extended reaction times, the formation of one low-polarity side product, **19Ni**, was observed (Scheme 6). It was isolated in yields up to 10%. In all cases, the same product was obtained, irrespective of the alkoxy groups of **13Ni** used. In fact, acid treatment of the alkoxy phenyl-fused products **6bNi**/**6fNi** also resulted in the formation of **19Ni**. Similarly to the monophenyl-fused compound **6Ni**, the ^{1}H NMR spectrum of **19Ni** indicated the presence of a *β*-carbon-to-*o*-phenyl-fusion, but in contrast to **6Ni**, its spectrum had only a half set of proton signals and thus was diagnostic of a compound with either a C_2-symmetry axis or a mirror plane. It furthermore showed that **19Ni** was devoid of any alkoxy side chains. This, and its molecular formula ($C_{44}H_{27}N_4NiO$ for [MH^+] as determined by ESI+ HR-MS), suggested the bis-phenyl-fused structure.

A simple plastic ball-and-stick model that maintains the Ni(II)-induced ruffling strongly suggested a *trans*-relationship between the two phenyl fusions, generating an overall chiral C_2-symmetric molecule, with a conformation similar to that of indaphyrins.[32,34] An HPLC resolution of the two enantiomers of **19Ni** succeeded (Figure 8). Incidentally, the *P-S,S*- and *M-R,R*-enantiomers of this chromophore eluted in an inverse order compared to those of **5bNi** or **15Ni** (Figures 3 and 7). The fact that **19Ni** was separable by HPLC on a chiral phase and that the two peaks obtained gave perfectly mirror-imaged CD curves provided a solid proof for the C_2-symmetric and, thus, chiral relative *trans*-configuration of this porphyrinoid. It excluded the possible *cis*-configuration as this alternative stereostructure of **19Ni** would constitute a CD-silent *meso*-compound. Furthermore, the experimental and computed CD spectra were in good agreement, establishing the absolute configurations for the enantiomers of **19Ni**.

■ CONCLUSIONS

We established a general synthetic methodology for the stepwise replacement of a pyrrole group in *meso*-tetraphenylporphyrin by a morpholine moiety with and without direct *β*-carbon-to-*o*-phenyl linkages. The relative stereostructures and conformations of a range of free-base and Ni(II)

dx.doi.org/10.1021/ja202451t |*J. Am. Chem. Soc.* 2011, 133, 8740–8752

morpholinochlorins with and without β-to-*o*-phenyl linkages were elucidated using NMR spectroscopy and X-ray diffractometry. Steric and stereoelectronic effects rationalized their stereoselective formation and the differences in the relative stereostructures between the free-base macrocycles and their corresponding Ni(II) complexes. All Ni(II) complexes and most free-base compounds exhibited a ruffled macrocycle. The varying conformations in the free bases and the enormous distortion upon Ni(II) insertion highlight the conformational flexibility of this class of pyrrole-modified porphyrins.

The ruffling imposes a rare type of inherent helical chirality onto the macrocycles. In many cases, the chiral resolution of the helicene-like, enantiomeric [morpholinochlorinato]Ni(II) complexes proved possible using classic diastereomer separation methods and/or HPLC on a chiral stationary phase. Crucial for the stereochemical stability was the presence of at least one alkoxy substituent on the morpholino ring or β-carbon-to-*o*-phenyl linkage that locked in the conformation. In the absence of such a "steric lock", no chiral resolution can be achieved, suggesting a low helimeric inversion barrier at room temperature. Quantum mechanical computations of the CD spectra of all resolved enantiomers permitted the assignment of the absolute configurations of the chromophores and provided an estimate for the inversion barrier of the nonsubstituted morpholinochlorins.

This study enables the utilization of the resolved morpholinochlorins in stereoselective molecular recognition systems, asymmetric catalysis, as chiral optical probes, or as components in novel materials with chiroptical properties.

EXPERIMENTAL SECTION

HPLC-CD. Analytical enantiomeric resolution was performed on Jasco HPLC systems (pump PU1580, gradient unit LG-980-025 or LG-2080-04, degasser DG-2080-53 or DG-2080-54, UV detector MD-2010Plus or Erma Cr. Inc. Erc-7215) equipped with Chirex (S)-Val (4.6 × 250 mm; 5 μm) as the chiral phase and coupled to a Jasco 715 spectropolarimeter for the online-CD investigations (scanning rate, 500 nm/min; bandwidth, 0.5 nm; response time, 0.5 s; accumulations, 5−15). All enantiomeric resolutions were carried out at room temperature with a constant flow rate using an isocratic solvent system consisting of CH_2Cl_2 and *n*-hexane (detailed conditions indicated in the corresponding figure captions).

ASSOCIATED CONTENT

Supporting Information. Full experimental details and spectroscopic data of all novel compounds described herein, details concerning the computations, and the X-ray crystallographic determinations of **5aNi**, **5fNi**, **15Ni**, **20f**, **25b**, **26**, and **26Ni** including cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

Dedicated to Siegfried Hünig on the occasion of his 90th birthday. This work was supported by the NSF (CHE-0517782 and CMMI-0730826, both to C.B.), the Degussa Stiftung, and the Studienstiftung des deutschen Volkes e.V. (fellowships to D.C.G.G.). The diffractometer at YSU was funded by NSF grant 0087210, by Ohio Board of Regents grant CAP-491, and by YSU. S.P.F. is grateful to EPSRC for a studentship. The work was also facilitated by the award of a Visiting Fellowship to C.B. by the Ferens Educational Trust, University of Hull.

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