Chiral Recognition by CD-Sensitive Dimeric Zinc Porphyrin Host. 2. Structural Studies of Host−Guest Complexes with Chiral Alcohol and Monoamine Conjugates

Tibor Kurtán,[§] Nasri Nesnas,[§] Frank E. Koehn,[‡] Yuan-Qiang Li,[§] Koji Nakanishi,*[,§] and Nina Berova*[,§]

Contribution from the Department of Chemistry, Columbia University, New York, New York 10027, and Department of Discovery, Analytical Chemistry, Wyeth Ayerst Research, 401 North Middletown Road, Pearl River, New York 10965

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Abstract: A structural study of complexes formed between a dimeric zinc porphyrin tweezer (host) and chiral monoalcohols and monoamines derivatized by a bidentate carrier molecule (guest) confirmed that their CD couplets arise from the preferred porphyrin helicity of 1:1 host−guest complexes. NMR experiments and molecular modeling of selected tweezer complexes revealed that the preferred conformation is the one in which the L (larger) group protrudes from the porphyrin sandwich; this preferred helicity of the complex determines the CD of the complexes. It was found that the porphyrin ring-current induced ^{1}H chemical shifts and molecular modeling studies of the complex lead to the assignments of relative steric size of the L (large)/M (medium) substituents attached to the stereogenic center. The assignments, in turn, are correlated with the sign of the CD exciton couplet that establishes the absolute configuration at the stereogenic center. Variable-temperature NMR experiments proved that the observed increase in CD amplitude at lower temperatures derives from conformational changes in the preferred offset geometry between two porphyrin rings.

Introduction

In the preceding paper,[1] a new microscale approach was described for absolute configurational assignments of secondary monoalcohols and primary monoamines based on the exciton-coupled CD method. The chiral alcohols and monoamines **4** were derivatized with a bidentate carrier molecule **1** that enabled the resulting conjugates with general formulas **19** to complex with an achiral CD sensitive "receptor", the zinc porphyrin tweezer **2** (Figure 1; compound numbering follows that of the preceding paper). The host−guest complex **3** exhibits a positive or negative exciton couplet depending on the absolute configuration of the substrate and conformation of the complex. In the preferred conformation **I** that determines the CD couplet sign, the larger group (L) points away from P-2 and protrudes out of the complex sandwich, while the medium group (M) is closer to P-2 (Figure 1).

The experimental CD of complexes **3** and their correlation with the absolute configuration of the starting monoalcohol or monoamine were reported in the preceding paper.[1] The studies described here are aimed at clarifying the conformational aspects of host−guest complexes and the origin of the observed CD exciton couplets in more detail. Here UV−VIS, low-temperature CD and NMR measurements, microcalorimetric titrations, and molecular modeling of the host−guest complexes will be discussed. It is shown that NMR and conformational analysis of the host−guest complex **3** can lead to the assignments of the relative steric size of the substituents linked to the stereogenic center. In conjunction with the sign of the CD exciton couplet, this then determines the absolute configuration at the stereogenic center. This NMR/modeling approach becomes particularly critical when the relative steric size assignment of substituents based on conformational *A* values is ambiguous.

Results and Discussion

UV−VIS Properties of the Porphyrin Tweezer Complex 3. The most intense UV−VIS transition of zinc porphyrin tweezer **2** is the Soret band with λ_{max} 419 nm, ϵ 890 000 in dichloromethane, and λ_{max} 417 nm, ϵ 640 000 in methylcyclohexane. The strong UV−VIS absorption of the Soret band greatly simplifies the CD analysis because, along with other factors, it significantly enhances the CD sensitivity (large A_{CD} amplitude)[2] and provides Cotton effects not complicated by overlap with other absorptions below 350 nm. The amine/zinc porphyrin coordination shift of the Soret band to longer wavelength has been reported previously. In studies of the binding of DABCO (1,4-diazabicyclo[2.2.2]octane) to mono tetraalkyl zinc porphyrins, Sanders[3] observed maxima at 402 and 415 nm, respectively, before and after binding (in dichloromethane). However, when DABCO was bound as a bidentate ligand to the zinc porphyrin dimer, the observed maximum was blue-shifted to 409 nm due to exciton coupling between the two porphyrins that adopt an offset geometry.[3]

* To whom correspondence should be addressed. E-mail: kn5@columbia.edu and ndb1@columbia.edu.
[§] Columbia University.
[‡] Wyeth Ayerst Research.

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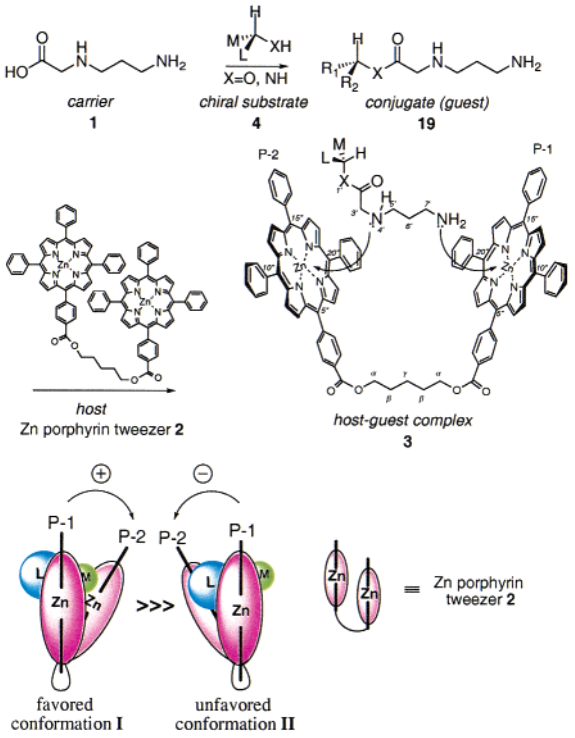

Figure 1. Carrier **1** is linked to the chiral alcohol or amine substrate **4** to provide conjugate **19** that becomes the guest. The guest is then treated with the host, zinc porphyrin tweezer **2**, yielding the host−guest complex **3**. Two conformers are conceivable for the sandwich complex. In favored conformation I the larger group L protrudes from the sandwich while the medium group M is clamped between the sandwich. In the unfavored conformation II the M group protrudes from the sandwich while L is between the sandwich. Upon complex formation, the *primary* amine of the conjugate coordinates with the Zn in one of the porphyrin rings P-1, and this is followed by coordination of the *secondary* amine with the other porphyrin ring P-2 in a manner that reflects the absolute configuration at the stereogenic center.

Many other studies agree with this trend. Namely, when the two porphyrin moieties are oriented in a parallel manner, the $\pi-\pi$ interactions lead to hypsochromic shifts of the Soret band in comparison to the porphyrin monomer.[3−6] Two opposing effects are conceivable for the changes in the Soret band. While coordination of zinc porphyrin to nitrogen in general leads to a large bathochromic shift as compared to free zinc porphyrin, the parallel or acute angular geometry leads to hypsochromic shifts in the absorption maxima due to $\pi-\pi$ interactions. This trend is also seen in the dimeric zinc porphyrin tweezer **2**. The complex formed between tweezer **2** and the monodendate isopropylamine showed a Soret band at 429 nm in dichloromethane.[7] In this case the random orientation of the two porphyrins reduces the magnitude of the $\pi-\pi$ interaction, and hence a bathochromic shift due to monodentate amine coordination prevailed.[7] However, upon binding of bis-amine conjugates **19** to zinc porphyrin tweezer **2**, the Soret band of complex **3** moves to 423 nm in dichloromethane and to 422 nm in

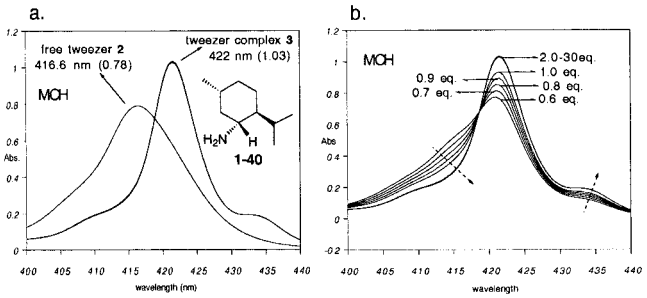

Figure 2. (a) UV−VIS of the free porphyrin tweezer **2** and its complex **3** with 30 equiv of conjugate **1-40**. (b) Isosbestic point in the UV−VIS titration of tweezer **2** with 0.6−30 equiv of conjugate **1-40**, in methylcyclohexane. (See Figure 5 for structures of conjugate **1-40** and their complex with tweezer **2**.)

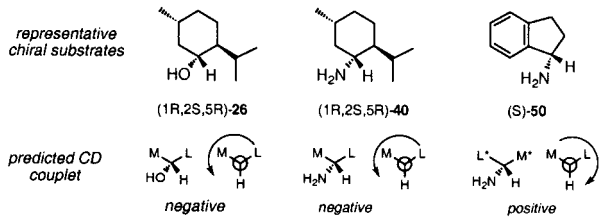

Figure 3. Representative chiral substrates employed in the present studies. Their esters or amides with carrier **1** are denoted conjugates **1-26**, **1-40**, and **1-50**, while their complexes with host tweezer **2** are denoted **1-26**/tweezer **2** complexes, etc.

methylcyclohexane. Here obviously the large bathochromic complexation shift is partially compensated by exciton coupling between the two porphyrin rings that adopt a twist orientation as evidenced from the observed CD couplets. The half-bandwidth of the Soret band of tweezer **2** also decreases after complexation in **3**, most likely as a result of diminished conformational flexibility of the complex (see Figure 2a). These results corroborate the data reported by Hunter et al., who found that in similar cases the reduced conformational freedom leads to a narrower distribution of the excited-state vibrational levels, and hence to a narrower Soret band.[5]

Determination of Binding Constants and Stoichiometry of the Complex. The changes in the position of the Soret band after complexation (Figure 2a) can be used to determine the association constant of the conjugate by titration. Earlier studies have shown that the donor−acceptor coordination of basic bidentate nitrogen ligands to the zinc atoms incorporated into covalently linked bisporphyrins usually leads to strong binding.[3,8−12] Titration of the zinc porphyrin tweezer **2** (1 μM in methylcyclohexane) with conjugate **1-40** (Figure 3), monitored by UV, showed a sharp isosbestic point at 0.6−30 equiv of conjugate (Figure 2b). The binding curve was analyzed by taking into account three parameters, i.e., absorption coefficients of the complexed and free porphyrin tweezer, and a single binding constant. This led to a binding constant of 1×10^6 M^{-1} for the complex **1-40**/tweezer **2** (in methylcyclohexane) as determined by nonlinear curve fitting at 422 nm (Table 1). Such binding

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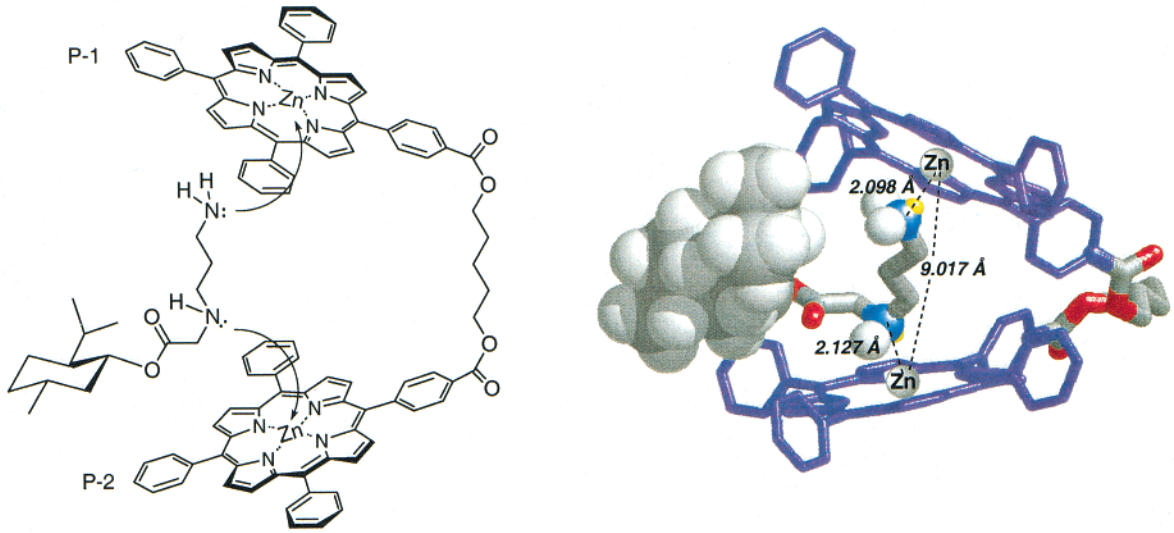

Figure 4. Schematic representation of complex formation between conjugate **1-40** and tweezer **2**, clarifying the IMPACT minimization giving optimal Zn−N distances.

Table 1. Association Constants (K_a) of Zinc Porphyrin Tweezer **2** with Various Bidendate Guests

Amine	K_a ($dm^3\ mol^{-1}$)	Solvent
H_2N NH_2 **13**	3.8×10^8 [a]	*methylcyclohexane*
conjugate **1-40**	1.0×10^6 [a]	*methylcyclohexane*
	7.6×10^5 [b]	*toluene*
conjugate **6-39**	4.5×10^5 [a]	*methylcyclohexane*

[a] Determined by UV titration. [b] Determined by microcalorimetric titration.

constants are observed in similar cases where two zinc porphyrin residues, connected by various linkers, bind to bispyridines[10] or alkyldiamines.[12] The value of $1 \times 10^6\ M^{-1}$ is somewhat larger than that for the complex **6-39**/tweezer **2** which was $4.5 \times 10^5\ M^{-1}$ (measured in the same solvent). The binding constant of diaminopropane **13** (Table 1) with tweezer **2** was also 2 orders of magnitude larger[7] than that of **1-40**. Most likely this difference reflects the steric interactions with the P-2 of the *secondary* amine group in conjugate **1-40**, in contrast to the *primary* amine in diaminopropane **13**.

A microcalorimetric titration of conjugate **1-40** with tweezer **2** in toluene resulted in an inflection point at 1 equiv of conjugate. This clearly indicates a 1:1 host−guest stoichiometry of binding, in accordance with previous studies on similar systems.[3,10,11] The binding constant obtained was $7.6 \times 10^5\ M^{-1}$ in toluene (Table 1), which was only slightly lower than that obtained by UV titrations in methylcyclohexane, most likely due to solvent effects. Toluene was used as solvent since the solubility of tweezer **2** in methylcyclohexane was not adequate for microcalorimetric titrations.

Geometry of Porphyrin Tweezer Complex and Ring-Current Effect. X-ray studies on tetraphenyl porphyrins have shown that due to steric interactions with the pyrrole rings, the phenyl rings are approximately perpendicular to the plane of the porphyrin core.[6,13] Such a geometry is expected to enhance the chiral recognition of the conjugate by tweezer complexation. An IMPACT molecular mechanics minimization carried out with a zinc porphyrin tweezer complex[14] (**1-40**, Figure 4) revealed the distance between the two coordinating zinc atoms to be 9.02 Å. This enables tweezer **2** to sandwich relatively large molecules. The calculated distances from primary and secondary amine nitrogens in the **1-40**/tweezer **2** complex to the zinc atoms were found to be 2.09 and 2.13 Å, respectively. Both values are close to the Zn−N distance of 2.07 Å obtained by Collins and Hoard from X-ray analysis of five-coordinated monopyridine zinc tetrapyridylporphyrin; the authors also reported that the zinc atom lies ca. 0.33 Å out-of-plane toward the axial pyridine ligand.[15] It should also be mentioned that prior to complexation the secondary nitrogen undergoes rapid inversion at room temperature, whereas upon coordination to zinc the nitrogen configuration becomes fixed. The preferred side that the lone pair adopts is dependent on the side from which P-2 approaches, which in turn is governed by the chirality of the stereogenic center in the substrate. The tendency of porphyrins to induce large upfield ring-current effects on groups located in close proximity is described in detail by Abraham et al. and Cross and Crossley.[16,17] These studies revealed that the porphyrin ring-current effect is a through space phenomenon affecting protons several bonds away from the zinc−amine binding site. Furthermore, the studies describe the ring-current effects of tetraphenyl porphyrin monomers on the ligand as a function of distance and orientation from the center of the porphyrin.[16,17] The ring-current shift decreases with increasing

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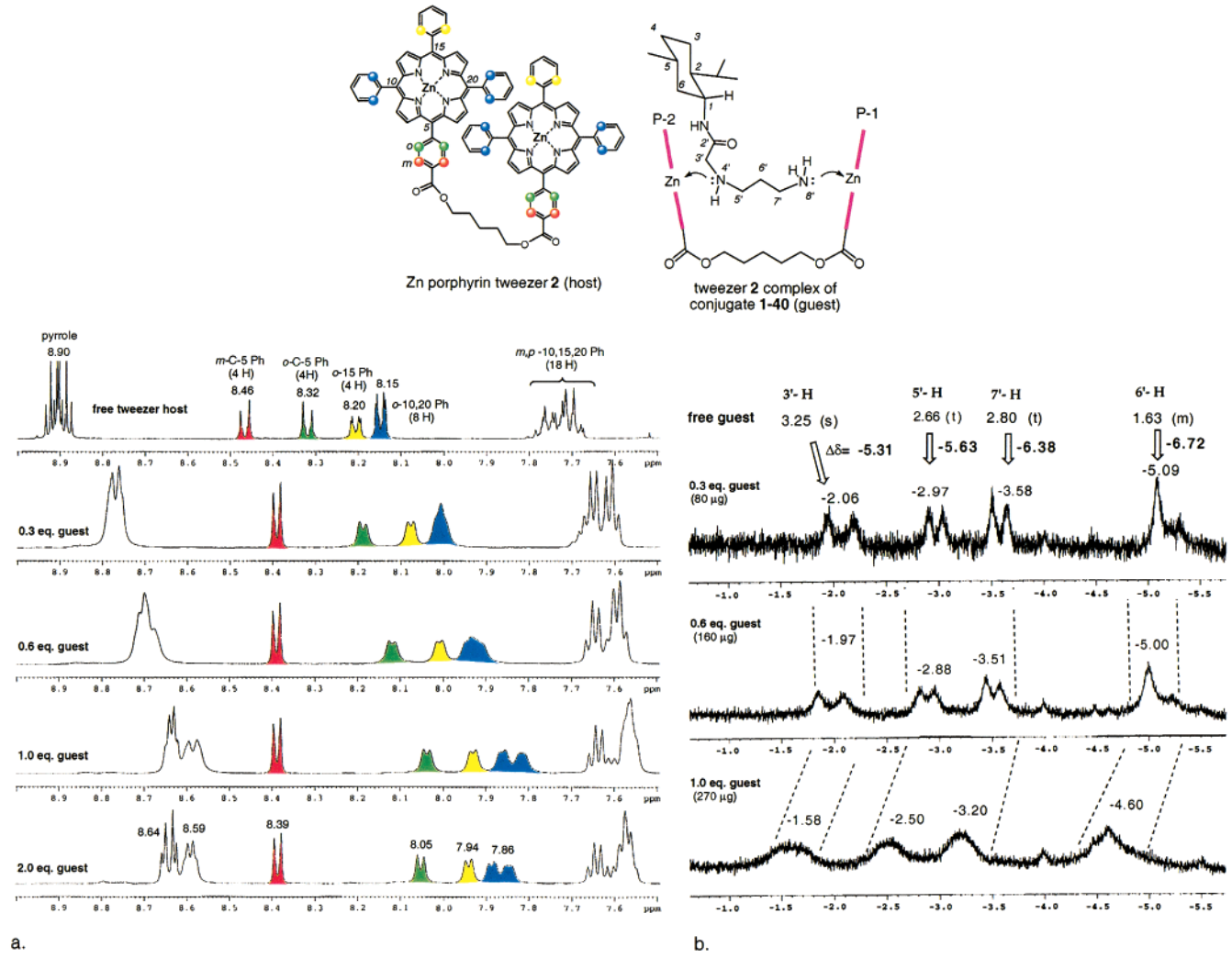

Figure 5. (a) Change in the aromatic signals of tweezer **2** with increasing amounts of conjugate **1-40**, in $CDCl_3$. (b) Change in the upfield shifted signals of **1-40**/tweezer complex with increasing concentrations of conjugate **1-40**, in $CDCl_3$.

distance from the center of the porphyrin and at the periphery of the tetraphenyl porphyrin; the phenyl ring-current also opposes the main porphyrin ring-current shift. This implies that the bidentate conjugate located within the two porphyrins in complex **3** will be exposed to the ring-current effects of both porphyrin rings and that the NMR signals of the guest will be shifted upfield depending on the spatial orientations.

Earlier studies by Fuhrhop et al. describing that porphyrin monomers are prone to aggregate in nonpolar solvents[18,19] prompted us to analyze first the solution of free porphyrin tweezer **2** in $CDCl_3$ at NMR concentrations of 10^{-3} M. The observed sharp ^{1}H NMR signals (Figure 5a, top) suggest that under these conditions, similar to the case of cage porphyrin dimers studied by Sanders and co-workers,[18] the free tweezer **2** is not aggregated and its two porphyrin residues adopt a syn orientation.

The fact that the tweezer **2** molecule exists in a nonaggregated state at NMR concentrations can most likely be attributed to intramolecular $\pi-\pi$ interactions between the two linked porphyrins that compensate for the intermolecular $\pi-\pi$ interactions noted by Sanders in the aggregation of monoporphyrins.[18] Furthermore, according to other studies, metalation with zinc generally increases the $\pi-\pi$ interaction by enhanced polarization of the porphyrin ring.[20] This promotes the attractive forces between the two covalently linked porphyrin residues and hence their syn orientation. The syn conformation of the free porphyrin tweezer **2** is also in agreement with the UV and NMR data of syn oriented rigid porphyrin dimers[21] and the conformation of ethylene linked porphyrin dimers.[22]

NMR Titration of Porphyrin Tweezer: Changes in the Porphyrin Host NMR Signals (Figure 5a). To confirm the 1:1 stoichiometry obtained from UV and microcalorimetric studies, an NMR titration was also carried out. A $CDCl_3$ solution of 1.3 μM tweezer **2** was titrated with menthylamine conjugate **1-40** and the changes in chemical shifts were followed by NMR. The top spectrum in Figure 5a shows the aromatic protons of the free porphyrin tweezer **2** before complexation. The four spectra that follow show the changes in the aromatic signals of tweezer **2** accompanying the increase in the amount of conjugate **1-40** from 0.3 to 2.0 equiv. Addition of 0.3 equiv of conjugate to tweezer **2** leads to upfield shifts and signal broadening. Since the orientation of the two zinc porphyrin rings was originally

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syn before complexation, the upfield shifts of aromatic protons accompanying the increase in the guest ratio can be ascribed to decrease in the distance between the two connected porphyrin rings upon complexation. Further increase in the amount of guest induces further upfield shifts with changes in the shape, except for the 8.46 ppm benzoate meta protons (shown in red in Figure 5a) that do not display any changes from 0.3 to 2.0 equiv of guest. Since the 8.46 ppm meta protons are situated closest to the points of attachment to the pentanediol linker, and in contrast to the ortho protons, are far from the core of the porphyrins, they are the least sensitive to the effect of complexation. The 1:1 stoichiometry of the complex is corroborated by the fact that the aromatic signals do not undergo further changes in host/guest ratios exceeding 1:1. The pyrrole protons are no longer equivalent above 1 equiv of guest and hence split into two multiplets, supporting the offset orientation of the porphyrin rings expected on the basis of exciton-coupled CD.

Changes in the Guest Molecule NMR Signals (Figure 5b). The ^{1}H NMR spectrum of porphyrin tweezer **2** (c = 2.0 mM) with <1 equiv of menthylamine conjugate **1-40** revealed that protons of the propane diamine chain, 5′-H, 6′-H, and 7′-H, are shifted upfield by at least 5 ppm. Furthermore, the 6′-methylene group situated halfway between two complexing porphyrin rings showed the largest shift (Figure 5b). Since these protons are located between the centers of the two porphyrin rings they are exposed to considerable ring-current effects. Their broad signals suggest that the free and complexed conjugate molecules are in fast equilibrium, and that at a guest concentration of 1 equiv and above, the free and bound conjugate coalesce and cannot be observed separately. The proton assignments based on TOCSY cross-peaks between the adjacent methylenes and DEPT-HSQC experiments also provide evidence for the 1:1 host−guest complexation. This is in accordance with the previous UV and microcalorimetric titration. The numerous examples in the literature dealing with the ring-current shift of bidentate ligands sandwiched between dimeric zinc porphyrins[3,6,8,10,12,21,23] clearly show that the observed ring-current shifts of the methylene protons in conjugate **1-40** arise from additive shielding effects of the two porphyrin rings. The large shift of 3′-H (−5.31 ppm) and the fact that 6′-H located in the middle of the chain experiences the largest shift of −6.72 ppm also proves that both amine nitrogens are coordinated to zinc atoms. Complex formation with a single nitrogen would result in substantially smaller upfield shifts, especially for the protons farther from the coordination site.

It is noteworthy that the geminal C-3′, C-5′, and C-7′ protons that were equivalent in the free conjugate **1-40** (Figure 5b) become nonequivalent in the complex. The signals of these methylene protons underwent slight downfield shifts when the host-to-guest ratio was increased from 0.3 to 0.6 equiv and coalesced when the ratio became 1.0. Above 1 equiv of conjugate (guest), the coalesced signals underwent further downfield shifts due to the increase in the amount of the free guest, the protons of which are located at much lower fields (see chemical shifts of free guest before complexation in Figure 5b).

Molecular Modeling. Molecular modeling calculations were performed on an O_2 Silicon Graphics workstation using MacroModel 7.0.[24] Monte Carlo conformational searches were performed using MM2 force field. Since the nonoptimized zinc force field parameters were not appropriate for our purposes, zinc was not included in the minimized structure. To compensate for the absence of the zinc atom, the distances between the four pyrrole nitrogens and the lone pairs of the conjugate's primary and secondary nitrogens were constrained to 2.83 and 2.88 Å, respectively. These values were derived from a molecular modeling minimization with IMPACT (using OPLS-AA force field; see also the previous section above) and were also in agreement with values obtained from the X-ray of five coordinated zinc porphyrins.[15] This is a reasonable approximation since the effect of the zinc is to complex the conjugate amino groups and confine them to fixed distances maintaining the overall clamshell shape of the tweezer. The main interest behind the conformational search was to determine the preference of porphyrin helicity which is derived from rotation about the pentamethylene carbons of the tweezer, as well as the optimal orientation of the conjugate within the complex. Therefore the pentamethylene chain of the tweezer linker and the acyclic portion of the conjugate were allowed to freely rotate in the conformational search, thus allowing for the generation of the optimal conformation. The structures shown below are the most stable conformations with the preferred porphyrin helicity that is common to all conformations within 1 kcal/mol (Figures 6b and 9b).

NMR Assignment of Conjugates 1-26 and 1-40 upon Complexation to Tweezer 2. This section deals with NMR proton assignments of complexes **1-26** and **1-40** with tweezer **2** using TOCSY, DEPT-HSQC, and ROESY experiments. Supporting results from MM2 Monte Carlo conformational search for the conformation of the **1-26**/tweezer complex that dictates the sign of CD couplet are also presented. The NMR measurements were carried out on ca. 1 mM porphyrin tweezer solution in the presence of 0.9 equiv of conjugate. Although these conditions are different from those used for CD measurements where 30 equiv of the conjugate is added for maximal CD amplitudes, the isosbestic point in the UV titration described above clearly indicates that the same complex form is present between 0.6 and 30 equiv of the conjugate. The CD of the **1-26**/tweezer **2** complex recorded with 0.5 equiv of the former differed only slightly in the CD couplet magnitude. The chemical shift differences in the conjugate, before and after complexation, reflect the changes in its conformation as well as the ring-current and other anisotropic effects arising from the sandwiching tweezer (Figure 6a). The conspicuous chemical shift differences, summarized below, are all in good agreement with molecular modeling results as depicted in Figure 6b.

(1) The menthyl protons in the complex (Figure 6a) undergo a much smaller upfield shift in comparison to the carrier methylenes, 3′-H, 5′-H,and 7′-H, clearly indicating that the menthyl moiety protrudes from the sandwich. The methylene and amine protons of the carrier moiety were assigned from the TOCSY spectrum (Figure 7), which also revealed that 3′-H, 5′-H, and 7′-H are nonequivalent as was the case for the conjugate **1-40**/tweezer **2** complex (Figure 5).

(2) 6-H_{eq} and 6-H_{ax}, distinguished by the NOE between 6-H_{eq} and 1-H, experience considerable upfield chemical shifts of 0.90 ppm for 6-H_{eq} and 0.59 ppm for 6-H_{ax}. The 6-H_{eq} also showed strong NOE with the pyrrole protons.

(3) 5-Me (or 9-H) shifts from 0.90 to 0.72 ppm, i.e., a 0.18 ppm upfield shift.

(4) 2-H shifts from 1.37 to 0.84 ppm, i.e., a 0.53 ppm upfield shift.

(5) 7-H shifts from 1.83 to 0.79 ppm, i.e., a 1.04 ppm upfield shift.

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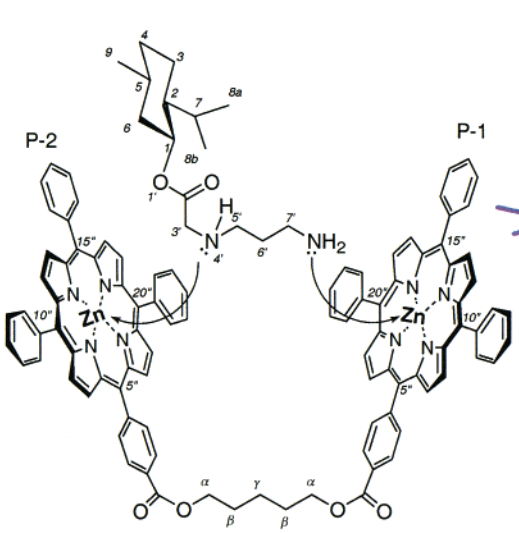
Proton	Conjugate **1-26** δ / ppm	Tweezer **2** complex of conjugate **1-26** δ (Δδ) / ppm	
2-H	1.37	0.84 (-0.53)	
6-H_{eq}	1.99	1.09 (-0.90)	(-0.75)
6-H_{ax}	0.98	0.39 (-0.59)	
9-H	0.90	0.72 (-0.18)	
7-H	1.83	0.79 (-1.04)	
8-H_a	0.89	0.69 (-0.20)	(-0.38)
8-H_b	0.75	0.18 (-0.57)	

a.



b.

Figure 6. (a) Selected NMR chemical shifts of free conjugate **1-26** and its complex, in $CDCl_3$. (b) Optimal conformation obtained from an MM2 conformational search. The zinc atoms are only shown for clarity, but were not included in the calculation (see text). The yellow balls represent the lone pair electons on the nitrogens. The light purple porphyrin ring is P-1 and is pointing away from the viewer, while the dark purple porphyrin ring is P-2 and is pointing out toward the viewer, hence resulting in a negative twist.

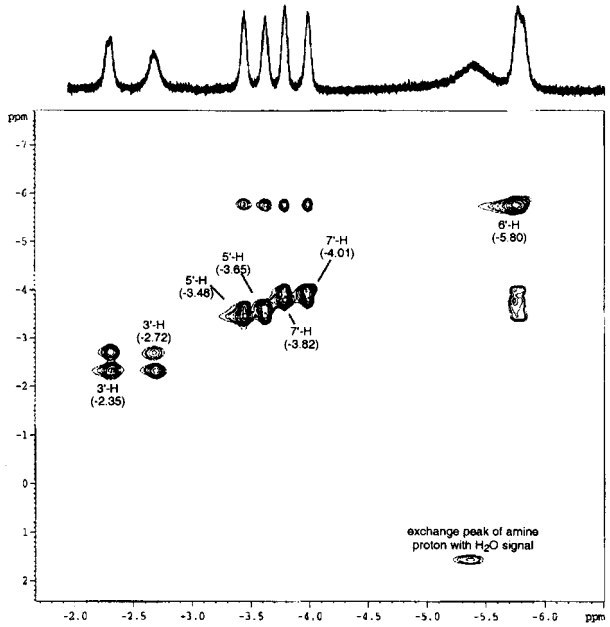


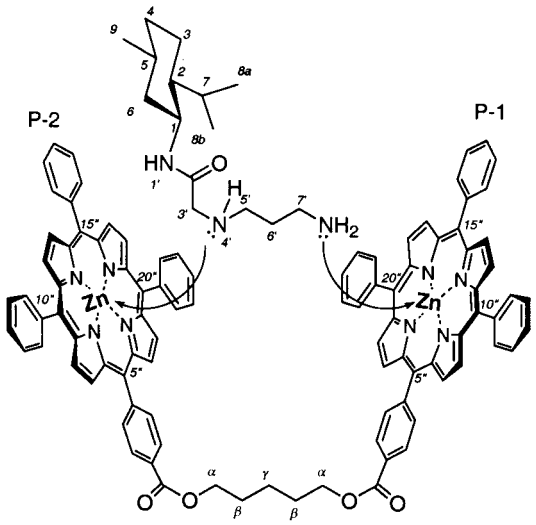
Figure 7. TOCSY spectrum of the upfield protons in the **1-26**/tweezer **2** complex, in $CDCl_3$. The spectrum was recorded with 1.3 mM tweezer **2** and 0.9 equiv (400 μg) of conjugate **1-26** with 20 ms NMR mixing time.

(6) Average shifts of the two 7-Me groups (8-H_a and 8-H_b) are from 0.82 to 0.44 ppm, i.e., a 0.38 ppm upfield shift. Although P-2 complexes from the side of the 6-methylene (M), this orients the i-Pr group (L) toward P-1, as shown by NOE between one of its methyl groups and the 10″, 15″, 20″-phenyl protons (of P-1). These chemical shifts observed upon complexation of **1-26** with tweezer **2** clarify the orientation of the conjugate within the complex (Figure 6a). This is clearly represented by molecular modeling simulation that led to the preferred conformation shown in Figure 6b. In the stick model in Figure 6b generated from an MM2 Monte Carlo conformational search, the dark purple porphyrin (P-2) represents the porphyrin pointing toward the viewer, while the light purple porphyrin (P-1) represents the porphyrin pointing away from the viewer. Accordingly, P-2 approaches the conjugate from the side of the 6-methylene, i.e., the medium group (M), which results in the two porphyrins adopting a negative sense of twist; this is corroborated by the negative CD exciton couplet and NMR data (discussed in the previous paper;[1] see also Figure 3). Furthermore, the secondary nitrogen adopts a configuration that enables complexation to occur from the side of the 6-methylene (M). Alternate conformers obtained from the conformational search, that were within 1 kcal/mol, had the same sense of twist.

Thus NMR chemical shifts induced by the porphyrin ring-currents, along with ROESY experiments, lead to a prediction for the orientation of the conjugate within the complex. The moiety that appears to be closer to porphyrin P-2 is the medium group M, while the other moiety, pointing away from P-2, is the larger group L. Thus in cases where the M and L assignments cannot be determined from conformational *A* values, the described NMR approach can be utilized as an alternative means of assigning M and L to the substituents flanking the stereogenic center.

The proton signals of the homochiral amide analogue of **1-26**, namely **1-40**, undergo similar NMR changes after complexation to tweezer **2** (Figure 8). This suggests that the orientation of amide conjugate **1-40** resembles that of the ester conjugate **1-26** in agreement with their similar CD spectra.[1]

The analysis performed with the tweezer complex of conjugate (*S*)-**1-50** showed that the two porphyrin rings have positive helicity resulting in a positive CD couplet (Figure 9). The proton assignments of conjugate (*S*)-**1-50** in the complex were also based on TOCSY, DEPT HSQC, HMBC, and ROESY experiments (Figure 9a). The methylene protons in the diaminopropyl side-chain, 3′-H, 5′-H, and 7′-H, showed similar upfield shifts as in the tweezer complex of the conjugates **1-26** and **1-40** (not shown), the 6′-methylene situated halfway between the two porphyrin rings giving the largest ring-current shift (−6.84 ppm). The carbon signals of the side-chain methylenes also experienced large upfield shifts (up to 12.9 ppm). However, in contrast to the proton chemical shift differences, the carbon chemical shift differences originate not only from the ring-current but also from the complexation to zinc which was shown to be the major contributor by Abraham et al.[16]



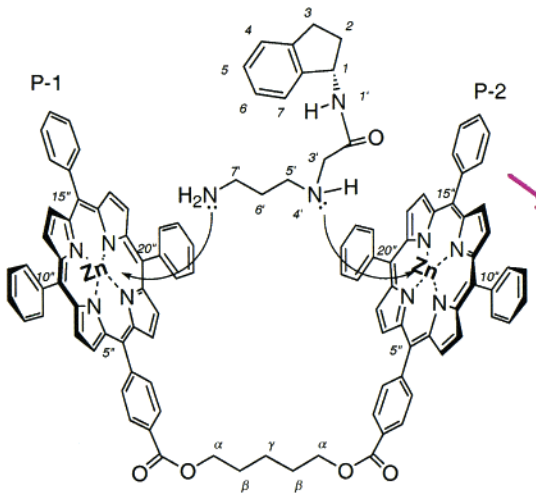
Proton	Conjugate **1-40** δ / ppm	Tweezer **2** complex of conjugate **1-40** δ (Δδ) / ppm	
2-H	1.10	0.47 (-0.63)	
6-H_{eq}	1.94	1.15 (-0.79)	(-0.70)
6-H_{ax}	0.81	0.21 (-0.60)	
9-H	0.87	0.73 (-0.14)	
7-H	1.84	0.80 (-1.04)	
8-H_a	0.90	0.63 (-0.27)	(-0.45)
8-H_b	0.79	0.15 (-0.64)	
1'-NH	6.97	3.38 (-3.59)	

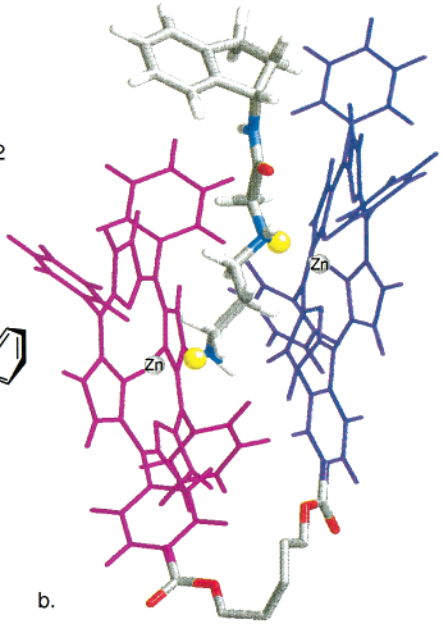
Figure 8. Selected NMR chemical shifts of free conjugate **1-40** and its complex, in $CDCl_3$.

As one moves away from the complexing 4′-NH toward the indane ring, a substantial decrease in chemical shifts is seen, i.e., the amide 1′-NH is shifted by −3.70 ppm, while 1-H of the indane ring is shifted by only −1.16 ppm (Figure 9a). The 2-methylene protons were upfield shifted by 0.73 and 0.61 ppm, and exhibited NOE with both the pyrrole protons and the 10″-, 15″-, and 20″-phenyl ortho protons. The 3-methylene protons also exhibited NOE with the 10″,15″,20″-phenyl meta,para protons, and accordingly their shifts were smaller. The 4-H and 5-H phenyl protons showed virtually no ring-current effect, indicating that they are protruding from the complex, as is also evidenced from molecular modeling calculations shown in Figure 9b. The 7-H is shifted upfield by 0.77 ppm and shows NOE with the pyrrole and 10″,15″,20″-phenyl ortho protons. These data suggest an orientation of the aminoindane in which the C-2 (M group) is pointing toward the P-2 porphyrin ring and the phenyl (L group) is pointing away from P-2. This causes the 7-H and 6-H to point toward the center of the complex and to be exposed to the ring-current effect of P-1 as well. Although the aromatic signals from P-1 and P-2 cannot be distinguished, the NOEs of 7-H with the pyrrole and 10″,15″,20″-phenyl ortho protons most likely derive from P-1. The assignment of 7-H is based on HMBC measurements that clarified the correlation between 7-H and C-1. Moreover, 7-H also gave an NOE with both the amide 1′-NH and the indane 1-H.

These are all in agreement with molecular modeling calculations leading to the optimal conformation shown in Figure 9b. The stick model representation of the most stable conformer of tweezer **2** complex with (*S*)-**1-50**, generated from the MM2 Monte Carlo conformational search, shows the orientation of the conjugate phenyl moiety within the complex. As noted in earlier conformational studies of conjugate **1-50** prior to complexation (preceding paper), the amide NH-proton prefers to be oriented toward the phenyl moiety, possibly owing to π-hydrogen bond formation between NH and the aromatic π-system. This in turn renders the phenyl moiety perpendicular with respect to the plane of the carrier carbonyl, thus making it behave as the larger group, hence L* (the asterisk denotes assignment made independent of conformational *A* values). As evident from NMR chemical shifts presented above, the larger (L*) phenyl group points away from the P-2 porphyrin ring

Proton	Conjugate **1-50** δ / ppm	Tweezer **2** complex of conjugate **1-50** δ (Δδ) / ppm	
1-H	5.51	4.35 (-1.16)	
2-H_a	1.81	1.08 (-0.73)	(-0.67)
2-H_b	2.60	1.99 (-0.61)	
3-H_a	2.88	2.64 (-0.24)	(-0.26)
3-H_b	2.99	2.72 (-0.27)	
4-H	7.23	7.18 (-0.05)	
5-H	7.23	7.18 (-0.05)	
6-H	7.23	7.00 (-0.23)	
7-H	7.23	6.46 (-0.77)	
1'-NH	7.52	3.82 (-3.70)	





a. b.

Figure 9. (a) Selected NMR chemical shifts of free conjugate (*S*)-**1-50** and its complex with tweezer **2** complex, in $CDCl_3$. (b) Optimal conformation obtained from an MM2 conformational search. The zinc atoms are only shown for clarity, but were not included in the calculation (see text). The yellow balls represent the lone pair electons on the nitrogens. The light purple porphyrin ring is P-1 and is pointing away from the viewer, while the dark purple porphyrin ring is P-2 and is pointing out toward the viewer, hence resulting in a positive twist.

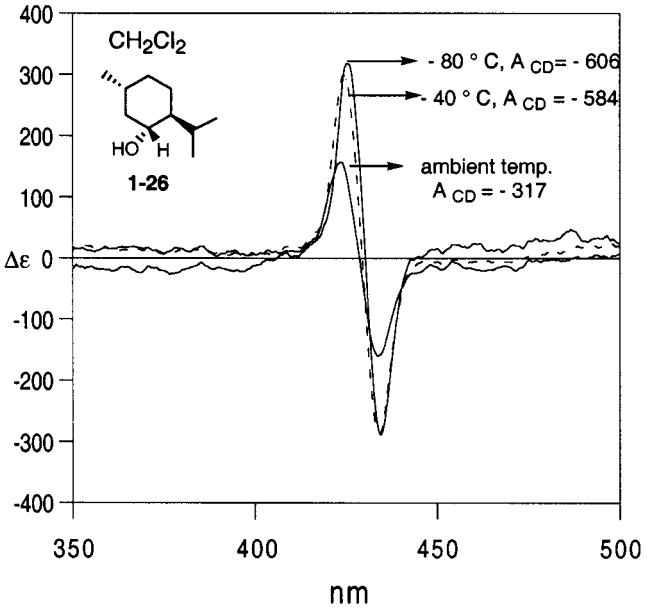


Figure 10. Low-temperature CD measurements of **1**-**26**/tweezer **2** complex, in dichloromethane.

(Figure 9b). This implies that P-2 approaches the conjugate from the side of the 2-methylene, i.e., the medium group (M). This results in a positive sense of twist in the complex as previously observed from CD measurements (previous paper;[1] see also Figure 3), and also depicted in the conformation in Figure 9b. In the stick model depicted, the light purple porphyrin (P-1) represents the porphyrin pointing away from the viewer, while the dark purple porphyrin (P-2) represents the porphyrin pointing toward the viewer. This represents a conformer with positive helicity in accord with the positive CD couplet (Figure 3). Alternate conformers obtained from the conformational search that were within 1 kcal/mol had the same sense of twist.

Calculation of the tweezer **2** complex of the alcohol analogue of (*S*)-**1**-**50**, namely (*S*)-**1**-**44**, led to an optimal conformation (not shown) with a negative helicity that is opposite to that of (*S*)-**1**-**50**.

Low-Temperature CD and NMR. The effect of temperature on conformation and spectral properties of the host/guest complexes were next investigated. The low-temperature CD of the complex of **1**-**26** was measured at −40 and −80 °C in dichloromethane to check the temperature effect on the conformation and porphyrin helicity. Although the offset orientation of the two porphyrin residues is locked in the tweezer complex of conjugate **1**-**26** by coordination to the bidentate conjugate, surprisingly the amplitude of its CD couplet almost doubled upon decreasing the temperature from 25 to −80 °C (Figure 10). In general, along with other factors, the CD exciton-couplet amplitude A_{CD} depends on the distance and projection angle between the interacting electric transition moments. Therefore, the reason for this significant increase in the CD of the **1**-**26** complex can be attributed either to changes in the ratio of conformers **I** and **II** (Figure 1) or to temperature-induced changes in the geometry of the complex, or both (Figure 6). In an attempt to address these questions, variable-temperature NMR measurements were also performed. Unfortunately, since the NMR of the tweezer complex of **1**-**26** was complicated due to overlapping signals of the guest, a close comparison of temperature effects on its CD and NMR was impossible. Instead, variable-temperature NMR measurements were performed at 25 to −20 °C on the tweezer complex of **1**-**50** (Figures 9 and 11).

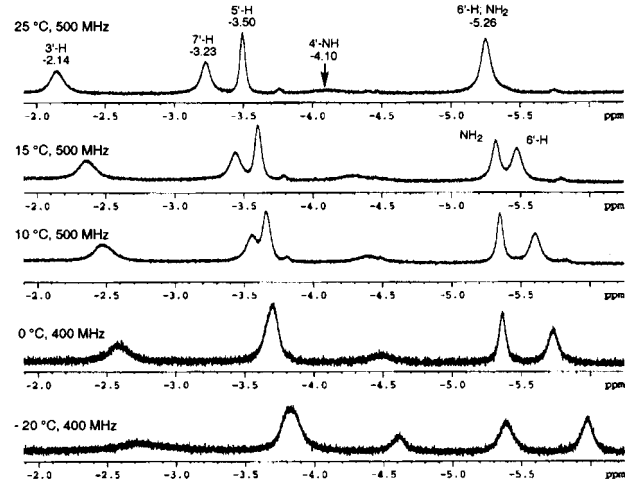


Figure 11. Change in the upfield carrier methylene protons (5′, 6′, and 7′) and amine protons in the (*S*)-**1**-**50**/tweezer complex, with decreasing temperature, in $CDCl_3$. (See also Figure 9 for structures.)

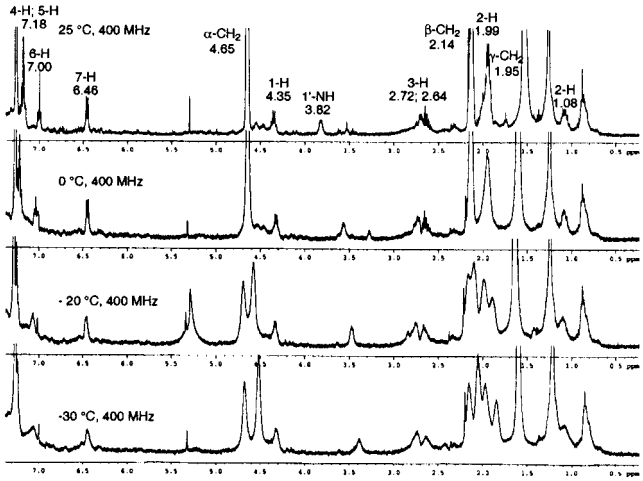


Figure 12. Selected NMR signals of (*S*)-**1**-**50**/tweezer complex showing aliphatic signals of the pentamethylene chain in tweezer **2**, with decreasing temperature, in $CDCl_3$.

As shown in Figure 11, the carrier methylene protons in the range of −2 to −6 ppm, 3′-H, 5′-H, 6′-H, and 7′-H, are sensitive to changes in temperature from 25 to −20 °C, reflecting the relative arrangement of the two porphyrin rings. The assignments at room temperature, based on TOCSY, revealed that the terminal NH_2 protons overlap with the 6′-Hs, while the 4′-NH is at −4.10 ppm. Both NH signals show TOCSY exchange cross-peaks with the water signal at 1.56 ppm. The 7′-H and 5′-H signals move upfield with a decrease in temperature at different rates and overlap at 0 °C. On the other hand, the primary NH_2 and 6′-Hs separated at 15 °C and 6′-H continuously shifted upfield with decreasing temperature. The 6′-H assignment was confirmed by a TOCSY spectrum measured at 3 °C. While the indane 2-H, 3-H, and phenyl signals in the complex did not significantly change, except for line broadening and upfield shift of the amide proton, this was not the case for signals of the tweezer host (Figure 12). At −20 °C, the α, *β*, and *γ* methylenes of the pentanediol linker connecting the porphyrin moieties became nonequivalent. This implies that they are exposed to the ring-current effect of the porphyrin rings to a different extent, and that their offset orientation is enhanced at lower temperature. The aromatic signals of the porphyrin showed extensive line broadening at low temperature; nonetheless, a downfield shift of the pyrrole and some of the *m*,*p*-10″,-

15″, and 20″-phenyl protons as well as signal splitting could be clearly observed at − 20 °C (not shown; see Figure S3 in the Supporting Information). Although the variable-temperature NMR data strongly support a change in the geometry of the complex at lower temperature, a possible temperature-dependent change in the ratio of conformers **I** and **II** (Figure 1) cannot be excluded.

The NMR data for **1-50** thus suggest that the offset porphyrin orientation is temperature dependent. Since lower temperatures favor larger offset orientation of the porphyrins in the complex, perhaps this is the main reason for the increase in CD amplitudes. Hunter et al. found that in the optimal geometry of porphyrin dimers, the pyrrole ring of one porphyrin is directly above the π-cavity at the center of the other, to minimize the $\pi-\pi$ repulsion and maximize attraction between the σ-framework and π-electrons, respectively.[20] In other studies, Sanders and co-workers have suggested that at low temperatures, the bisporphyrins show a trend to increase overlap of the π-systems and decrease interannular separation.[18]

In the complexes of tweezer **2**, the coordination of the bidentate ligand reduces the $\pi-\pi$ interactions between the two porphyrin rings. The presence of a bidentate ligand thus forces the porphyrins to adopt a reduced offset conformation, which at low temperatures further favors $\pi-\pi$ interactions and the two porphyrin rings approach each other. These low-temperature changes are also in agreement with variable-temperature NMR studies by Leighton et al.[18] on caged porphyrin dimers connected by two flexible linkers.

Conclusion

The structure of chiral zinc porphyrin tweezer complexes, suitable for configurational assignments of monoalcohols and monoamines, has been studied by UV−VIS, microcalorimetric titrations, variable-temperature NMR and CD measurements, and molecular modeling. The conjugate/tweezer complex formation was monitored by UV−VIS, NMR, and microcalorimetric titrations which confirmed a 1:1 stoichiometry of the host−guest complex and resulted in determination of binding constants. The observed chemical shift differences between the free and complexed conjugate as well as ROESY experiments and molecular modeling revealed the L group attached to the stereogenic center that points away from the P-2 porphyrin. Once the L and M groups are assigned, the absolute configuration at the stereogenic center can be determined from the observed porphyrin exciton CD chirality of the preferred host−guest complex.

Experimental Section

Materials and General Procedures. ^{1}H NMR spectra were obtained on Bruker DM 400 or 500 MHz spectrometers and are reported in parts per million (ppm) relative to TMS (δ), with coupling constants (J) in hertz (Hz). Two-dimensional NMR spectra of conjugate−tweezer complexes were measured on a Bruker Avance 500 NMR spectrometer equipped with a 5 mm TXI ^{1}H−^{13}C−^{115}N triple resonance CryoProbe. Homonuclear phase sensitive TOCSY spectra were measured in TPPI or States-TPPI mode using MLEV-17 mixing times of 20 and 55 ms. Heteronuclear ^{1}H−^{13}C correlation assignments were made using double inept HSQC and multiplicity edited double inept HSQC in the echo-antiecho TPPI gradient-enhanced mode.[25] Phase-sensitive ROESY TPPI and States-TPPI spectra were measured using a continuous rectangular pulse of 150 and 200 ms duration in the center of the spectrum. HMBC spectra were measured with a long-range evolution time of 55 ms.

Microcalorimetric Titrations. Microcalorimetric titrations were performed on Omega's ultrasensitive titration calorimeter (T115 and Control Module I106) purchased (by Professor Breslow) from MicroCal, Inc., MA. A cell with a volume of 1.346 mL, containing a toluene solution of 0.122 mM of tweezer **2**, was titrated with a toluene solution containing 2.50 mM of conjugate **1-40** from a stirring syringe. The titration involved 40 injections of 3 μL of conjugate injected over 6 s, with 3 min intervals between injections. Stirring was maintained constant at 400 rpm. The reference cell was pre-rinsed and filled with HPLC grade toluene. Raw data (μcal/mol) released from each injection were integrated using Omega's software: Origin and data were fitted to the one binding site equation resulting in a binding constant and stoichiometry for binding.

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Supporting Information Available: Materials and general procedures including low-temperature NMR andNMR spectra of conjugates **1-26**, **1-40**, and **1-50** complexed with zinc porphyrin tweezer **2** in $CDCl_3$; TOCSY spectra of the upfield shifted protons in the tweezer **2** complex of **1-50** at 25 and 3 °C in $CDCl_3$; NMR spectra displaying the change of the aromatic protons of tweezer complex of **1-50** with decreasing temperature in $CDCl_3$; figure showing the low-temperature conformation of zinc porphyrin rings in the tweezer complex; and tables of NMR data of free conjugates **1-26**, **1-40**, and **1-50** and their complexes with tweezer **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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