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An Unusual Conformation of α-Haloamides Due to Cooperative Binding with Zincated Porphyrins

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CD and NMR spectroscopic evidence of cooperative binding between an α-halogen atom and a carboxamide group with a zinc porphyrin leads to an unprecedented conformation for the determination of the absolute stereochemistry of α-haloamides (α-halocarboxylic acids derivatized with 1,4-phenylenediamine) through the use of exciton-coupled circular dichroism (ECCD). With the use of chiral lactams, whose rotomeric contributions are minimized, both ECCD and NMR spectroscopy demonstrate that the porphyrin favors binding to the side of the sterically more demanding halogen atom as compared to the smaller hydrogen atom. In all, the data is strongly suggestive of an unusual conformation not observed before for α-chiral amides. A mnemonic for determining the absolute stereochemistry of α-halogenated carboxylic acids is provided.

Introduction

Application of Exciton Coupled Circular Dichroism (ECCD)[1,2] as a non-empirical method for absolute stereochemical determinations of chiral organic molecules has parlayed into a number of methodologies that address the configurational assignment of a wide variety of compounds including polyols and carbohydrates,[3–5] monoamines and monoalcohols,[6,7] diamines and amino acids,[8,9] amino alcohols,[10] hydroxy acids,[11] and vicinal diamines and diols[12] and epoxy alcohols[13] (see recent reviews for an overview of the methodology[14–16]). Briefly, ECCD is observed between two or more independently conjugated chromophoric systems that interact through space in a chiral fashion. Stereochemical information is obtained from the interacting electric dipole transition moments (edtm) of the chromophores. The absolute orientation of the two chromophores results in a predicted sign of the ECCD couplet; i.e., a clockwise orientation of two interacting chromophores yields a positive couplet and vice versa.[1,2] Thus, the sign of an ECCD spectrum can be directly related to the orientation of the interacting chromophores, which in turn can lead to the assignment of helicity and subsequently the absolute stereochemistry of the system. The chromophores used for the stereochemical determination either preexist in the system or can be introduced through chemical derivatization[3,17–21] or non-covalent binding. The latter mode of binding has been explored by the use of bis-porphyrin "tweezer" systems as the chromophoric hosts, pioneered by Nakanishi, Berova and co-workers (Figure 1).[8,22–24] Incorporation of a metal atom in the porphyrin core enables binding of the two porphyrins (the host) with a chiral substrate (the guest) that possesses two suitable sites of attachment and allows for the formation of a porphyrin tweezer–chiral substrate complex. For instance, incorporation of a Zn^{II} atom into the porphyrin core allows for binding of substrates containing amino groups,[7,8] whereas exchange of Zn for Mg enables the direct binding of hydroxy group containing substrates.[25] The stereochemistry of the bound chiral substrate induces a helical twist within the porphyrin tweezer complex based on the steric interactions between the porphyrin rings and the substituents at the chiral center. It is believed that the porphyrin ring closest to the chiral center sterically differentiates between the substituents at the chiral center, thus sliding away from the large group and towards the smaller group in order to alleviate steric clash. This movement leads to a "chiral twist" of the porphyrins relative to each other, detected as an exciton CD couplet, the sign of which directly reflects the absolute orientation of the two chromophores and, therefore, the absolute stereochemistry of the bound guest molecule.

The porphyrin tweezer method, however, is not directly applicable to chiral compounds with only one site of attachment, because the two porphyrin groups cannot be oriented relative to each other. To solve this problem chiral substrates are derivatized with small, achiral molecules (carriers) that contain within them the two necessary sites of attachment. In this manner, the derivatized carrier accomplishes the binding of the chiral guest with the por-

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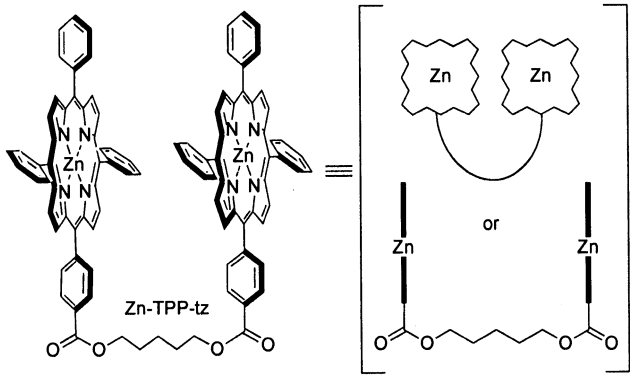


Figure 1. Zn-TPP-tz [two zinc 5-(4-carboxyphenyl)-10,15,20-triphenylporphyrins linked through a 1,5-pentanediol] and its schematic representations.

phyrin tweezer and, if chosen well, should present the chiral center towards the porphyrin for steric differentiation. Utilizing this method, the stereochemistry of derivatized chiral monoamines, monoalcohols and α-chiral carboxylic acids has been determined in a non-empirical fashion according to the sign of the obtained ECCD spectra.[6,7,23,24] The present report describes an unusual experimental observation noted during the development of methodologies for the absolute stereochemical determination of α-chiral carboxylic acids, thus requiring a brief overview of the system in question.

For complexation to the porphyrin tweezer, chiral α-alkyl(alkoxy)carboxylic acids were derivatized with 1,4-phenylenediamine as the carrier molecule.[23] Addition of the derivatized carboxylic acids to a host zinc bis-TPP-porphyrin tweezer system [two zinc-5-(4-carboxyphenyl)-10,15,20-triphenyl porphyrins connected through a 1,5-pentanediol linker, Zn-TPP-tz] yields the tweezer–substrate complex shown in Figure 2. The formation of this chiral complex results in a bisignate ECCD spectrum, the sign of which directly reflects the relative orientation of the two porphyrin rings. In this system, the induced helicity within the porphyrin tweezer is governed by the major conformation around the $C_{C=O}$–C_{α} bond.

A series of ECCD data obtained for various chiral α-alkyl(alkoxy) amides led to the proposition of a mnemonic that predicts the expected ECCD sign for a given amide based on the size of the substituents on the chiral center (the relative size of the substituents on the chiral center is determined according to their reported A-values[26]). It should be noted that Nakanishi and co-workers utilize a different carrier, and thus have arrived at a different mnemonic for derivatized α-chiral carboxylic acids.[24] Consider-

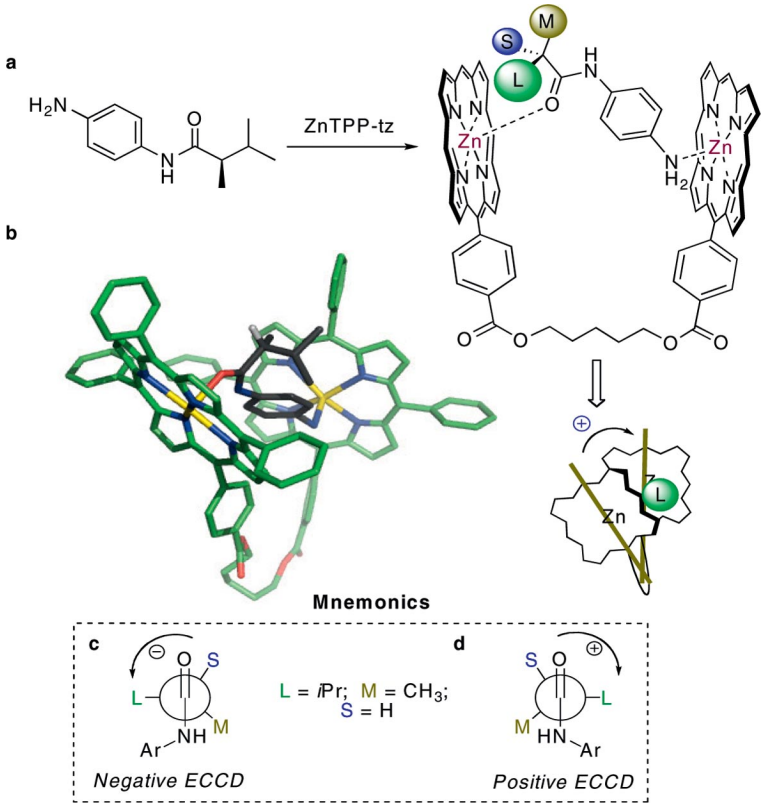


Figure 2. Stereochemical determination of chiral α-alkyl(alkoxy)carboxylic acids derivatized with 1,4-phenylenediamine (carrier) with Zn-TPP-tz as the chromophoric host. (a) Complexation of derivatized (*R*)-2,3-dimethylbutyric acid yields a positive ECCD spectrum; (b) model of the tweezer–chiral amide complex (molecular mechanics, force field MMFF94), dashed box depicts the mnemonic for the absolute stereochemical determination of α-chiral carboxylic acids derivatized with 1,4-phenylenediamine; (c) counterclockwise orientation of chromophores yielding a negative ECCD, and (d) clockwise orientation giving rise to a positive bisignate. The substituents at the asymmetric center are oriented in a way that small and large groups face the porphyrin that is coordinated to the carbonyl oxygen atom.

ing an orientation such that the large group is almost perpendicular to the carbonyl group with the small group pointed toward the porphyrin plane and the medium group staggered with respect to the amide proton (Figure 2, dashed box), the expected ECCD sign can be determined by taking into account the rotation from the large through the medium and towards the small group. A clockwise orientation would translate into a positive ECCD bisignate signal, and vice versa. This mnemonic was proven reliable for chiral carboxylic acids with a variety of alkyl, alkoxy and aryl groups on the α-carbon atom. In all cases, the observed ECCD sign was in agreement with the expected sign as derived from the mnemonic, considering the size of the substituents on the chiral center, based on A-values.[26] We found that use of A-values leads to consistent determination of stereochemistry. It is noteworthy, that Lightner values[27] are also consistent with our results. Nonetheless, because Lightner values of halogen atoms are not reported, we will resort to using A-values in our discussions.

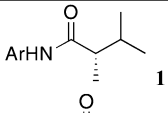
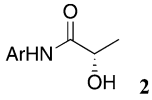
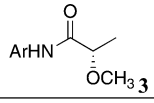
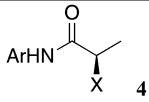
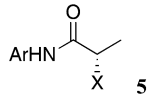
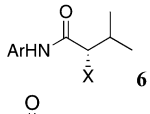
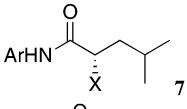
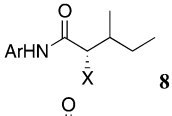
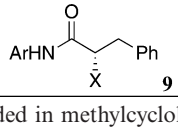
In the course of further studies we have observed that carboxylic acids bearing a halogen atom at the asymmetric center do not follow the rules determined previously and produce ECCD spectra of an unexpected sign. Similar deviation from the mnemonic has been previously observed in the stereochemical determination of α-halogenated chiral carboxylic acids derivatized with 1,3-diaminopropane.[24]

The latter discrepancy has prompted an investigation into the origins of the observed change in the ECCD. Below we detail our studies that lead us to believe that an α-halogen atom, present at the asymmetric center, in addition to the carbonyl group, is involved in cooperative binding with the Zn-porphyrin. Interestingly, we find that only α-halogenated amides, and not other halogenated systems, enjoy the presumed cooperative binding with zincated porphyrin. The bidentate coordination of α-haloamides leads to an ECCD-active conformation that differs from the one proposed for the non-halogenated analogs. Herein, we present CD and NMR spectroscopic data in support of the bidentate model with a number of α-chiral carboxylic acids derivatized with an amine carrier. In addition, a new mnemonic operating for this class of substrates is proposed.

Results and Discussion

As was mentioned above, the observed ECCD sign for carrier-derivatized α-halogenated amides did not match the

Table 1. ECCD data for 1,4-phenylenediamine-derivatized α-halocarboxylic acids with Zn-TPP-tz.[a]

	Substrate	λ, nm, (Δε)	A	*ee*, %	λ, nm, (Δε)	A	*ee*, %	λ, nm, (Δε)	A	*ee*, %
1	 **1**	428 (-43) 418 (+41)	–84	98	---	---	---	---	---	---
2	 **2**	430 (-58) 419 (+65)	–123	99	---	---	---	---	---	---
3	 **3**	430 (-67) 418 (+72)	–139	99	---	---	---	---	---	---
	X =	Br			Cl			F		
4	 **4**	430 (-236) 421 (+136)	–372	99	---	---	---	---	---	---
5	 **5**	429 (+116) 421 (-130)	+246	90	429 (+25) 42 (-38)	+63	99	428 (+34) 419 (-31)	+65	50
6	 **6**	429 (+103) 421 (-91)	+194	90	428 (+132) 421 (-82)	+214	90	428 (+114) 420 (-93)	+207	64
7	 **7**	429 (+107) 421 (-75)	+182	90	429 (+24) 421 (-30)	+54	90	428 (+31) 420 (-30)	+61	80
8	 **8**	429 (+94) 421 (-81)	+175	80	429 (+108) 421 (-124)	+232	80	429 (+96) 420 (-66)	+162	80
9	 **9**	429 (+47) 421 (-43)	+90	90	429 (+22) 421 (-19)	+41	75	428 (+28) 419 (-22)	+50	56

[a] Spectra were recorded in methylcyclohexane at 0 °C and at a 1:20 tweezer/ligand ratio (1 μM Zn-TPP-tz final concentration).

previously developed mnemonic. Entries 1–3 in Table 1 illustrate the data from reported derivatized α-chiral carboxylic acids that produce an ECCD couplet consistent with the previously established mnemonic.[23] For example, in the case of carrier-derivatized (*S*)-2,3-dimethylbutyric acid **1**, where isopropyl is considered as the large group and methyl as the medium group, the expected ECCD sign is negative according to the binding mode described in Figure 2. Indeed, a negative ECCD of high amplitude (–84) is observed, verifying that in the presence of alkyl substituents on the chiral center, the steric factor defines the helicity of the porphyrin tweezer (Table 1, Entry 1).[23] As shown in Figure 3, the predicted ECCD sign, according to the established mnemonic, for the amide derivative of (*S*)-2-bromo-3-methylbutyric acid complexed with the porphyrin tweezer would be negative. This is arrived at by considering that *i*Pr behaves as the large group and Br as the medium-size group on the chiral center as their corresponding A-values indicate (2.2 for *i*Pr and 0.58 for Br; in all cases the halogen atom is the medium-size group according to the reported A-values). Nonetheless, the experimentally obtained ECCD revealed a positive couplet with a large amplitude (+194, Entry 6), suggestive of the presence of a dominant orientation. This discrepancy from the previously proposed mnemonic led to a thorough investigation of carboxylic acids that bear different halogen groups at the asymmetric center. All α-halocarboxylic acids used in the present study were synthesized according to previously reported procedures[28] and were derivatized without incident with 1,4-phenylenediamine to provide chiral amides. A stock solution of Zn-TPP-tz in dichloromethane (c = 1 mM) was diluted with methylcyclohexane to a final concentration of 1 μM, and the appropriate derivatized α-chiral carboxylic acid was added as a 1 mM solution in dichloromethane. Methylcyclohexane was found to be the best solvent for complexation of amides with the porphyrin tweezer providing the largest ECCD amplitudes. Spectra were obtained at tweezer/substrate ratios from 1:1 to 1:40 equiv., and the data collected at 1:20 are reported below.

As can be seen from Entries 4–9 in Table 1, the observed sign was consistent for all α-chiral halocarboxylic acid derivatives submitted for ECCD analysis (Br, Cl, and F; although not shown, derivatized α-iodocarboxylic acids did also lead to the same results, however, their considerable instability did not lend themselves to full characterization and thus they are omitted from discussion), with enantiomeric acids resulting in opposite ECCD signs [that is all acids with (*R*) configuration produced negative ECCD spectra and vice versa].

As expected, enantiomeric amides **4-Br** and **5-Br** resulted in opposite ECCD signs (Table 1, Entries 4 and 5). As can be seen from Entries 5–8 (methyl: A-value = 1.74; isopropyl: A-value = 2.2; *sec*-butyl: A-value = 2.4) changing the size of the alkyl substitution does not greatly affect the amplitude of the spectrum. The presence of the benzyl group (Entry 9, A-value = 1.76) also indicates that the ECCD-active conformation is not affected by aromatic substitution. In all cases, however, the presence of a halogen

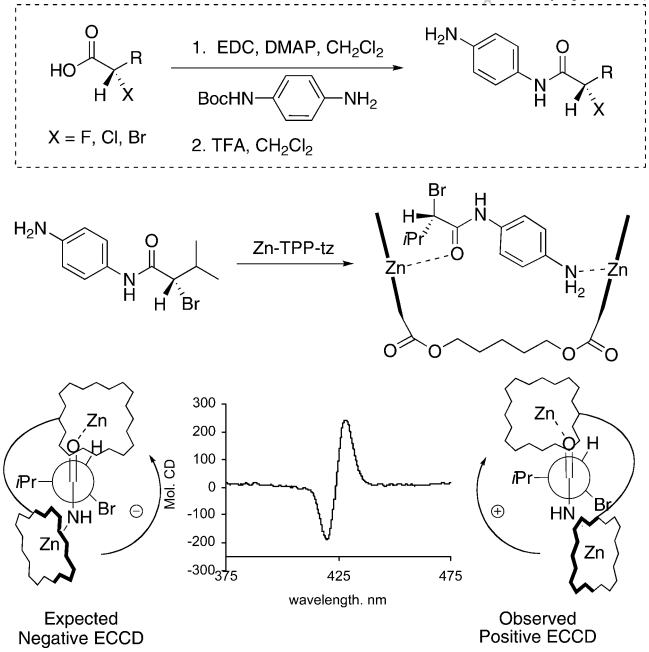


Figure 3. Unexpected positive ECCD observed with (*S*)-2-bromo-3-methylbutyric acid carrier conjugate (spectrum in methylcyclohexane at 20 equiv. of chiral guest).

atom on the α-carbon atom significantly alters the conformation of the complex and results in ECCD signs that are opposite to those anticipated. Interestingly, as demonstrated in Table 1, the observed ECCD sign does not depend on the nature of the α-halogen atom present. Consistent results were obtained for all Br-, Cl- and F-substituted α-haloamides, suggesting that the ECCD-active conformation is not directly affected by the halogen size.

Based on these observations one can assume that the presence of a halogen atom at the chiral center of the derivatized α-chiral carboxylic acid appears to induce a different mode of binding with the porphyrin tweezer, which in turn translates into a different ECCD-active conformation. Considering the possible electronic interaction between the halogen atom and the aromatic plane of the porphyrin it is plausible to assume that a halogen–π interaction is favored in the complex. There are a number of reports that address the nature, magnitude and practical applications of halogen–π (C–X···π) interactions.[29,30] Increasing experimental evidence indicates that halogen atoms are involved in noncovalent, dipolar protein–ligand interactions and thus contribute significantly to the binding affinity during molecular recognition.[31–33] C–X···π interactions are rather common in a variety of supramolecular structures, host–guest systems, and two-dimensional networks.[29,30] Halogenation of amino acid residues can also lead to additional stabilization in peptide folding and interstrand binding.[34–36] A favorable interaction between chlorine atoms and aromatic amino acids is found 78 times in 52 protein structures in different families.[37] Recent computational studies have also identified Cl/Br···π interactions as a key factor for the development of new pharmacological agents.[38] In particu-

lar, it has been shown that a suitably positioned halogen can experience van der Waals interactions with a π-system, which dominate over the electrostatic repulsion between the partial negative charges at the halogen atom and the π-cloud.[39] Based on ECCD results and corroborating literature precedents, we assume that the major ECCD-active conformation must reflect a C–X···π interaction contributing to the binding of the α-haloamides to the Zn-porphyrin tweezer.

Conformational Analysis of α-Halocarboxylic Acids

Figure 4 depicts a set of conformational possibilities for a derivatized chiral α-halocarboxylic acid [in this case (*S*)-2-chloropropionic acid] when complexed with zinc-tetraphenylporphyrin (Zn-TPP, the second porphyrin ring of the porphyrin tweezer coordinated to the aniline nitrogen atom of the carrier is not shown for clarity). Taking into consideration the conformational flexibility of the $C_{C=O}$–C_α bond, there are four possible ECCD-active rotomers. Conformation **A** follows the mnemonic previously established for α-alkyl(alkoxy)amides placing the large group (Me) perpendicular to the carbonyl group, whereas the small group (H) is pseudo-*syn* and the medium group (Cl) is *anti*-periplanar. In this case the differentiation will occur between the small and the large group resulting in a predicted negative ECCD spectrum. As shown in Table 1, a positive ECCD spectrum was obtained upon coordination of (*S*)-2-chloropropionic acid **5-Cl** with the porphyrin tweezer. Thus, conformation **A**, favored for non-halogenated α-chiral amides, can be excluded from consideration. Conformations **B** and **C** are derived from the predicted geometries for carbonyl systems bearing electronegative substitution, according to the polar Felkin–Anh rules.[40,41] Both **B** and **C** lead to the observed positive ECCD sign. Conformation **B** maintains the small group (H) *syn* to the carbonyl group, placing the medium group (Cl) perpendicular, and the large group (Me) *anti*-periplanar. With such a disposition, the differentiation will take place between the small hydrogen atom and the medium halogen group, resulting in a positive ECCD couplet. Although the sign of the observed ECCD couplet would be in agreement with experimentally observed data, this conformation is not expected to be favored due to the substantial $A_{1,3}$ strain between the large Me group and the amide N–Ar group. In conformation **C**, the large group is *syn* to the carbonyl group, whereas the small group is *anti* to the carbonyl group (reduced $A_{1,3}$). This is expected to be an energetically more favorable arrangement as compared to conformation **B**, and thus is considered as a plausible contributor to the observed ECCD. Considering that upon complexation to the porphyrin tweezer, the alkyl group in conformation **C** may experience steric interaction with the chromophore, one can envision additional rotation along the $C_{C=O}$–C_α bond, giving rise to conformation **D**, the bidentate model, which would also yield the observed ECCD.

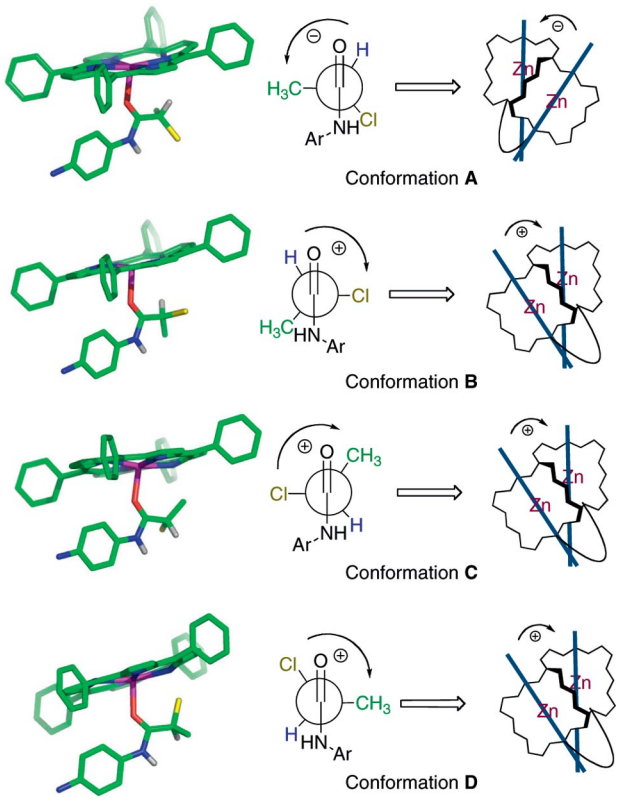


Figure 4. Possible ECCD-active conformations (conformational search, molecular mechanics, force field MMFF94) of (*S*)-2-chloropropionic acid derivative **5-Cl** when bound to zinc porphyrin.

To summarize thus far, the obtained ECCD data suggests that derivatized α-halo chiral carboxylic acids exist in a unique ECCD-active conformation, not previously observed for α-alkyl(aryl)- or α-alkoxy(aryloxy)carboxylic acids, upon binding to the porphyrin tweezer. The suggested conformation **D** places the halogen atom pseudo-*syn* or *syn* to the carbonyl group, regardless of its greater A-value as compared to the hydrogen atom. This preference does not appear to depend on the size of the halogen atom, and therefore, must be due to their particular electronic properties. Nonetheless, at this point none of the conformations **B**, **C** or **D** can be excluded. In order to gain further insight into the current system and the observed binding anomaly several NMR spectroscopic experiments were designed and performed.

NMR-Based Conformational Analysis of α-Halogenated Amides Complexed with Zn-TPP

As it has been widely discussed in literature the aromatic core of porphyrins generates a large shielding cone.[42–44] Thus, when a substrate binds to the metal atom incorporated within the porphyrin core, the strong diamagnetic anisotropy of the porphyrin ring induces an upfield shift of the protons (shielding). The magnitude of this effect depends on the distance of the substrate from the porphyrin, its position relative to the center of the ring and the binding

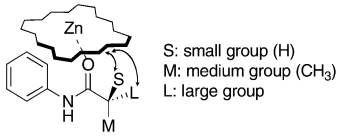
constant. In particular, protons located closer to the porphyrin plane and closer to the center of the shielding cone experience larger upfield shift. Therefore, the anisotropic shift of the protons of a chiral substrate bound to the metal center of the porphyrin can assist in mapping the disposition of the substituents relative to the porphyrin plane within the shielding cone, and consequently, the orientation of the substituents relative to the carbonyl group.

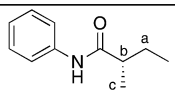
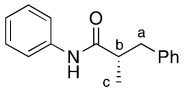
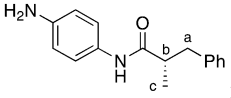
A similar approach was successfully used for the conformational analysis of porphyrin tweezer complexes with different chiral guests.[45] In the present study we followed a simplified approach, utilizing a mono-porphyrin (Zn-TPP) bound to aniline derivatives of chiral carboxylic acids for NMR spectroscopic studies, instead of the full Zn-TPP-tz. Because the major contribution to the observed conformation in the tweezer-chiral guest complex is determined by the porphyrin coordinated closer to chiral center, we opted to use the carbonyl-porphyrin coordination to monitor the effect of porphyrin shielding onto the relative shifts of the substituents at the asymmetric center. Exclusion of the second porphyrin, coordinated to the aryl amino group of the carrier greatly simplified the analysis of the observed NMR spectra. As a control experiment to judge whether or not binding of the mono-porphyrin (Zn-TPP) yields reliable and accurate information with regard to the orientation of the bound chiral amide with respect to the porphyrin plane (similar to the ECCD-active conformation observed with Zn-TPP-tz complex previously established)[23] the relative shielding of substituents **10** and **11a** were measured (Table 2). Based on the data obtained it is clear that the degree of shielding produced by the porphyrin on each substrate follows a similar trend. The relative shielding correlates with the position of the substituents relative to the porphyrin plane and agrees with the conformation represented by the established working mnemonic.[23] Namely, the smallest shift is observed for the medium group, oriented away from the porphyrin, whereas the large and small groups that point to the plane of the porphyrin ring yield larger upfield shifts. [Note: As shown in Table 2 the same trend is observed when the binding of **11b** to Zn-TPP-tz is monitored by NMR spectroscopy. This result verifies that the simplified approach of using mono-porphyrin Zn-TPP for NMR spectroscopic analysis is valid.] Having in hand a valid control for NMR spectroscopic experiments, a similar analysis was performed for the halogenated amides.[46]

Based on the changes in the chemical shift between the free and the bound form of the chiral amide, we expect to gather conformational information regarding the effect of an α-halogen atom on the overall binding, as well as the relative position of the substituents on the chiral center with respect to the plane of the porphyrin ring, when the amide is complexed with the Zn-porphyrin. Table 3 lists the changes in chemical shift ($\Delta\delta = \delta_{complex} - \delta_{free}$, $\Delta\delta$ in ppm) for a series of α-halocarboxylic acids derivatized with aniline, upon coordination with Zn-TPP. A more negative $\Delta\delta$ value indicates that the corresponding proton has a longer residency (tighter binding) and/or is closer to the porphyrin plane. For example, the methyl protons of aniline-derivatized α-bromopropionic acid **13** (Table 3) resonate at δ = 1.955 ppm. Upon addition of Zn-TPP, the same signal shifts upfield to δ = 1.862 ppm ($\Delta\delta$ = –0.093 ppm) indicating that the protons lie within the porphyrin's shielding cone. Although the differences in ^{1}H NMR chemical shift are small, they are reproducible and are in the range that is acceptable for stereochemical assignment using Mosher ester analysis.[47–50] The strong shielding field provided by the porphyrin is counterbalanced by the relatively weak binding of amide carbonyl groups with the zincated chromophore (note that with porphyrin tweezer the binding is stronger due to the presence of a free amine group in the carrier that binds strongly with the metalloporphyrin). It is important to note the difference in the shift of the α-protons (Hb) vs. the methyl protons (Ha). As expected, both sets of protons are more shielded when the molecule is complexed to Zn-TPP. However, the larger shift of the signal of the Hb protons upon complexation is due to the inherent difference in distance from the porphyrin center (Hb protons are closer to the center), and not due to the conformation adopted upon complexation. Particularly noticeable is the change in the chemical shift of the signals of the aryl protons (Hc–He). Although rather far away from the coordination site, the aromatic protons appear to experience enhanced deshielding in the presence of an α-halogen atom, possibly due to tighter binding.

The above observations are consistent for derivatized halocarboxylic acids **13**–**15** bearing either a Br, Cl, or F atom (Table 3). However, in the absence of an α-halogen atom (derivatized α-methylpropionic acid **12**, Table 3) the corresponding $\Delta\delta$ values observed for each proton are signifi-

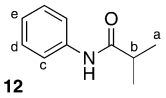
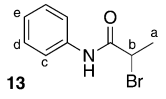
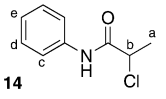
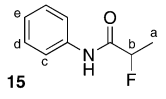
Table 2. Change in chemical shifts of α-alkylamides upon addition of Zn-TPP.[a]



Substrate	$\Delta\delta = \delta_{complex} - \delta_{free}$ Ha	Hb	Hc
 **10**	–0.047	–0.112	–0.061
 **11a**	–0.089	–0.124	–0.102
 **11b**[b]	–0.153	–0.231	–0.138

[a] The reported numbers refer to a $\Delta\delta$ value for each proton ($\Delta\delta = \delta_{complex} - \delta_{free}$, ppm). Spectra were measured in $CDCl_3$ at a 1:1.2 Zn-TPP/ligand ratio (18 mM Zn-TPP final concentration). [b] Spectra were measured in $CDCl_3$ at a 1:1.2 Zn-TPP-tz/ligand ratio (18 mM Zn-TPP final concentration).

Table 3. Change in chemical shifts of haloamides upon addition of Zn-TPP.[a]

Substrate	$\Delta\delta = \delta_{complex} - \delta_{free}$				
	Ha	Hb	Hc	Hd	He
 **12**	–0.019	–0.084	–0.068	0	0
 **13**	–0.093	–0.177	–0.104	–0.036	–0.024
 **14**	–0.080	–0.162	–0.095	–0.022	–0.017
 **15**	–0.092	–0.156	–0.104	–0.021	–0.016

[a] The reported numbers refer to a $\Delta\delta$ value for each proton ($\Delta\delta = \delta_{complex} - \delta_{free}$, ppm). Spectra were measured in $CDCl_3$ at a 1:1.2 Zn-TPP/ligand ratio (18 mM Zn-TPP final concentration).

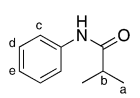
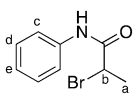
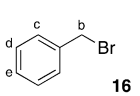
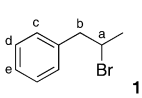
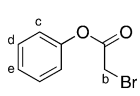
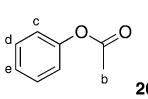
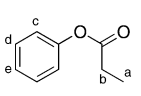
cantly lower, indicating that the binding of non-halogenated amides with Zn-TPP is weaker than what is observed when an α-halogen atom is present. These results directly suggest that the presence of an α-halogen atom promotes a tighter binding between the derivatized acid and the zincated porphyrin, thus supporting the proposal for a carbonyl–halogen cooperative binding.

On the other hand one has to consider that because the latter analysis is based on complex formation, the observed result must also depend on the binding affinity between the constituents of the complex. Because NMR spectroscopic analysis reports an average signal, the observed difference in shielding between non-halogenated and halogenated substrates might also be attributed to the enhanced binding affinity of the latter due to additional interaction between the porphyrin core and the halogen atom. To further investigate this supposition the binding affinity of Zn-TPP-tz with carrier-derivatized alkylcarboxylic acid **1** and halocarboxylic acid **6-Cl** were measured by UV titration,[12] and the following association constants were obtained: $K_a = 4.37 \times 10^4\ M^{-1}cm^{-1}$ with non-halogenated substrate **12** and $K_a = 1.01 \times 10^5\ M^{-1}cm^{-1}$ with halogenated substrate **14**. Based on the latter binding affinities it is clear that the presence of a halogen atom on the asymmetric center enhances the complexation, and the observed shielding of the halogenated substrates might be attributed to the larger amount of the complexed species present in the solution of Zn-TPP and halogenated carboxylic acids.

To further probe the effect of the α-halogen substitution on amide binding with zincated porphyrins, $\Delta\delta$ values were calculated for a series of compounds bearing possible coordinating functional groups of different types on the α-carbon atom. The results, as summarized in Table 4, reveal that porphyrin binding evidently decreases when either the halogen atom or the amide moiety is removed from the molecule. Removal of the α-halogen atom (substrates **12**, **17**, **20** and **21**) results in significantly decreased $\Delta\delta$ values for all the protons, supporting the suggestion that the α-halogen atom assists in the porphyrin binding. Similar results were observed when the amide functionality is removed, while the halogen atom is maintained in the molecule (substrates **16**, **18** and **19**). The calculated $\Delta\delta$ values for **16** and **18** are much lower indicating that the sole presence of a halogen atom in the molecule cannot account for the tighter binding observed for α-haloamides. Interestingly, it appears that α-haloamides constitute a special case, because the same level of binding is not observed for either esters **20** and **21** or α-haloester **19**. These additional ^1H NMR spectroscopic results further support the suggestion that there is a cooperative binding between the amide carbonyl group and the α-halogen atom with the metal center of the porphyrin core.

With the above ^1H NMR spectroscopic data in hand, a reevaluation of the postulated conformers depicted in Figure 4 is in order. As discussed before, conformations **C** and **D** position the halogen atom (medium group according to A-values) either *syn* or perpendicular to the amide carbonyl group in a manner that enables cooperative interaction with the porphyrin (the porphyrin ring either slides towards the halogen atom in **C** or cooperatively binds both the carbonyl group and the halogen atom in **D**). However, conformation **B**, which also leads to the observed ECCD sign, does not invoke cooperative binding of the halogen atom (the por-

Table 4. Chemical shift changes for various molecules with Zn-TPP.[a]

H	 **12**	 **13**	 **16**	 **17**	 **18**	 **19**	 **20**	 **21**
a	–0.019	–0.093	----	----	0	----	----	–0.005
b	–0.084	–0.177	–0.023	–0.003	–0.004	–0.014	–0.029	–0.011
c	–0.068	–0.104	n.d.	–0.005	–0.008	–0.017	–0.028	–0.017
d	0	–0.036	n.d.	n.d.	n.d.	–0.013	–0.015	–0.012
e	0	–0.024	n.d	n.d.	n.d.	–0.010	–0.013	–0.008

[a] The reported numbers refer to a $\Delta\delta$ value for each proton ($\Delta\delta = \delta_{complex} - \delta_{free}$, ppm). Spectra were measured in $CDCl_3$ at a 1:1.2 Zn-TPP/ligand ratio (18 mM Zn-TPP final concentration).

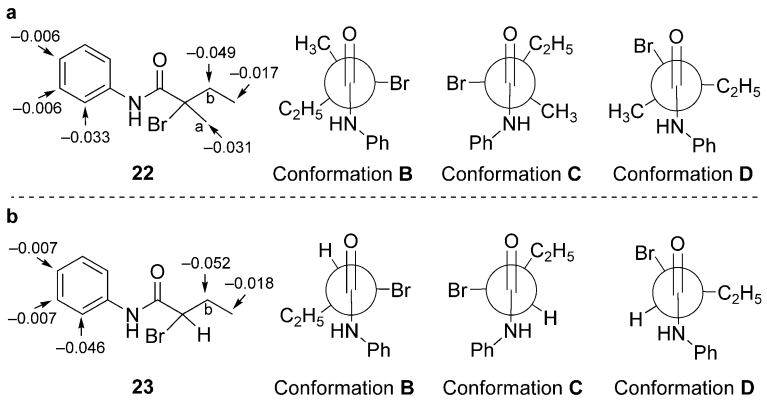


Figure 5. Chemical-shift changes and corresponding conformations of (a) 2-bromo-2-methyl-*N*-phenylbutanamide (**22**) and its Newman projection when bound to Zn-TPP; (b) 2-bromo-*N*-phenylbutanamide (**23**) and its Newman projection when bound to Zn-TPP.

phyrin slides away from the halogen atom towards the smaller hydrogen atom), and thus is less likely to be operative. Further evidence to exclude conformation **B** is provided below.

The ^{1}H NMR spectroscopic experiments presented so far have focused on identifying additional stabilization of the porphyrin–substrate complex due to the presence of a halogen atom at the asymmetric center. These ^{1}H NMR spectroscopic data support a preference for rotamers **C** and **D** as major ECCD-contributing conformers. However, unambiguous identification of conformer **C**, **D** vs. **B** would be possible only through a direct correlation between the shielding of an alkyl group (R) on the chiral center with either X (halogen) or H (hydrogen). Nonetheless, as it was mentioned earlier, the ^{1}H NMR spectroscopic studies reported in Tables 3 and 4 do not allow for the direct correlation between the shielding of the large group and α-hydrogen atom on the chiral center, because of the intrinsically larger shift of the signal of the α-hydrogen atom due to its closer proximity to the center of the shielding cone of the porphyrin, as compared to the shift of the signal of the β-hydrogen atoms of the large substituent. This problem can be alleviated by substituting the α-hydrogen atom with an alkyl group, such that a 3° chiral amide is used for complexation with Zn-TPP. For example, amide **22**, (Figure 5) with a methyl substituent in place of the α-hydrogen atom, enables the direct comparison of groups of different size by comparing the β-hydrogen atoms on the large ethyl and the medium methyl substituents (according to the A-values the bromine atom here is the small substituent). The relative shielding of these two sets of β-hydrogen atoms upon complexation with Zn-TPP is a direct consequence of their relative distance to the porphyrin plane, and thus should yield information with regard to the rotomeric disposition of the $C_{C=O}$–C_α bond.

Figure 5 depicts the results obtained upon complexation of **22** and **23** with Zn-TPP along with the rotomers that correspond to conformations **B**, **C**, and **D** based on the size of the substituents. In the case of 2-bromo-2-methylbutyric acid (**22**), conformations **B** and **C** place the Br atom perpendicular to the carbonyl group, with either the medium group (methyl) or large group (ethyl) pointing towards the porphyrin ring. Based on the data in Figure 5a, conformation **B** can be excluded, because the β-hydrogen atoms of the larger ethyl group experience a larger shielding ($\Delta\delta$ = –0.049 ppm) as compared to the β-hydrogen atoms of the methyl substituent ($\Delta\delta$ = –0.031 ppm). The NMR spectroscopic data supports the presence of rotomers **C** or **D**, because in both cases the ethyl group is situated closer to the plane of the porphyrin ring as compared to the methyl group. Nonetheless, the fact that a halogen effect is observed in binding of α-haloamides with Zn-TPP, and the larger anticipated steric demand of the large ethyl group if directly pointed towards the porphyrin ring, argues against conformation **C** and favors conformation **D**.

Interestingly, the $\Delta\delta$ value calculated for the β-hydrogen atoms of the ethyl group in 2-bromobutyric acid conjugate **23** (Figure 5b) is similar ($\Delta\delta$ = –0.052 ppm) to the observed shielding of the ethyl group in **22** ($\Delta\delta$ = –0.049 ppm), thus suggesting that both molecules bind in a similar manner and similar affinity to Zn-TPP. Note that in the case of compound **23**, the halogen atom would be considered as the medium group and, therefore, if sterics were guiding the rotomeric distributions one would not expect similar results for both **22** and **23**. The observed similarity points to the fact that electronic factors override steric considerations with α-haloamides, such that the ethyl group in both structures **22** and **23** is situated in a similar orientation with respect to the plane of the porphyrin ring. This provides further proof for the suggestion of cooperative binding. It is also important to note that in both cases the $\Delta\delta$ values experienced by the aromatic protons are similar, suggesting that the overall binding remains the same.

Ring-Locked Systems: α-Halolactams

Although the NMR spectroscopic results support the premise for a halogen effect with regard to binding of α-halo-substituted amides with zincated porphyrins, the free rotation along the $C_{C=O}$–C_α bond can lead to multiple coexisting conformations. Any or a combination of each pop-

ulation can result in a host–guest complex that can be CD-active. In order to obviate the possibility of having multiple conformations (as a result of different rotomeric conformations), α-chiral lactams were pursued such that the $C_{C=O}$–C_α bond could not rotate and the substituents at the asymmetric carbon atom would adopt a defined geometry relative to the carbonyl group. Thus, by using α-chiral lactams the position of both the α-halogen atom and the α-hydrogen atom relative to the amide carbonyl group is locked (both the halogen atom and the hydrogen atom are forced to always be *gauche* to the carbonyl group). As shown in Figure 6, with the latter constraints in place, the bound porphyrin will have to choose between the hydrogen atom (small group) and the halogen atom (large group). As illustrated with (*R*)-α-chlorolactam, if the stereodifferentiation solely depends on sterics, the porphyrin should prefer to slide toward the smaller hydrogen atom, resulting in a negative ECCD. On the other hand, if there is an interaction between the halogen atom and the porphyrin, a positive ECCD spectrum should be observed.

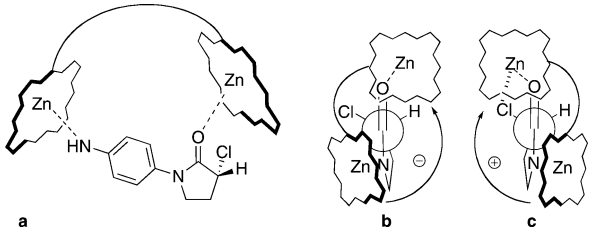
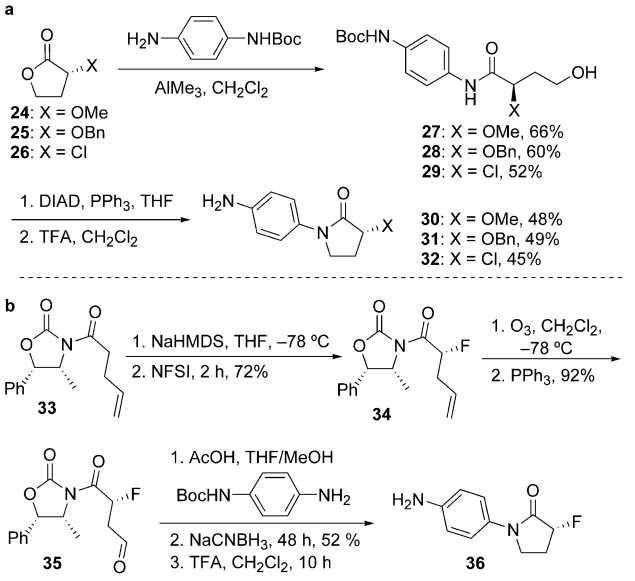


Figure 6. (a) Mode of binding of Zn-TPP-tz to butyrolactams; (b) negative ECCD in the absence of halogen–π interaction in (*R*)-2-chlorobutyrolactam (**32**); (c) positive ECCD due to C–X···π interactions in (*R*)-2-chlorobutyrolactam.

Prior to the CD analysis of α-halogenated lactams, several α-alkoxybutyrolactams were synthesized and complexed with Zn-TPP as controls for establishing the behavior of non-halogenated systems. This was done to verify that the previously established rules, i.e. the fact that the helicity of the porphyrin tweezer results solely from the steric differentiation at the chiral center, were operational.

The synthesis of chiral α-alkoxybutyrolactams **30** and **31**, and α-chlorobutyrolactam **32** commenced with the Lewis acid mediated amidation of α-substituted chiral lactones **24**–**26** to yield amides **27**–**29** (Scheme 1a). Mitsunobu lactamization of the latter amides and subsequent deprotection of the arylamine Boc protecting group furnished the desired lactams **30**–**32**. The (*R*)-2-fluorolactam **36** was accessed through Evans auxiliary controlled asymmetric fluorination of compound **33** (Scheme 1b),[51] followed by ozonolysis,[52] to afford aldehyde **35**. Reductive amination of **35** with mono-Boc-protected 1,4-phenylenediamine provided the corresponding secondary amine, which cyclizes in situ and upon treatment with TFA yields lactam **36**.[53] The (*R*)-2-iodolactam **37** was obtained directly from **36-Boc** by Finkelstein reaction.[54]

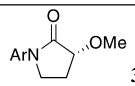
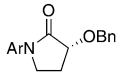
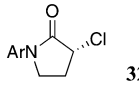
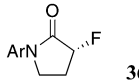
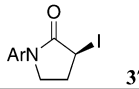


Scheme 1. (a) Synthesis of chiral α-alkoxy- and α-chloro-γ-butyrolactams **30**–**32**; (b) synthesis of α-fluoro-γ-butyrolactam **36**; NFSI: *N*-fluorobenzenesulfonimide.

Table 5 summarizes the ECCD data obtained for butyrolactams **30**–**32**, **36**, and **37** upon complexation with Zn-TPP-tz. The (*R*)-alkoxy butyrolactams **30** and **31** represent the control cases in which the substituents are not expected to interact directly with the porphyrin system, thus leading to observed helicity only as a result of steric differentiation. As depicted in Figure 7b, the observed negative sign for the ECCD of **30** and **31** bound with Zn-TPP-tz can be rationalized based on the anticipated disposition of the substituents on the chiral center as they are projected towards the coordinating porphyrin ring, such that size-based differentiation between the alkoxy group and the hydrogen atom leads to a counterclockwise orientation of the chromophores. This result mimics the previously reported behavior of the corresponding α-alkoxy chiral carboxylic acids derivatized with the 1,4-phenylenediamine carrier.[23,24]

In comparison with **30** and **31**, the halogen-substituted lactams **32** and **36** (Table 5, Entries 3 and 4) retain the same stereochemistry and relative size distribution of the substituents, yet the latter two lactams yield positive ECCD signs upon complexation with Zn-TPP-tz. Because the $C_{C=O}$–C_α bond rotation is restricted in these substrates, the observed change in the sign of ECCD suggests that the porphyrin coordinated with the carbonyl oxygen atom slides towards the halogen atom and away from the smaller hydrogen atom (Figure 7c). These results are consistent with the presence of a halogen–carbonyl cooperative binding with the zincated porphyrin ring and support the proposition that α-halogenated chiral carboxylic acids derivatized as amides interact with the porphyrin tweezer in a manner suggested in conformation **D** (Figure 4). The mode of binding appears the same regardless of the nature of the halogen atom present, as evident by the ECCD obtained upon binding of α-iodolactam **37** with Zn-TPP-tz. In this case, the ECCD sign

Table 5. ECCD data of α-chiral lactams in the presence of Zn-TPP tweezer.[a]

Entry	Substrate	Zn-TPP tweezer λ, nm, (Δε)	A
1	 **30**	429 (-57) 421 (+53)	–110
2	 **31**	429 (-45) 421 (+55)	–100
3	 **32**	427 (+25) 419 (-36)	+61
4	 **36**	429 (+27) 418 (-21)	+48
5	 **37**	429 (-15) 420 (+12)	–27

[a] Spectra recorded in methylcyclohexane at 0 °C and at a 1:20 tweezer/ligand ratio (1 μM Zn-TPP-tz final concentration).

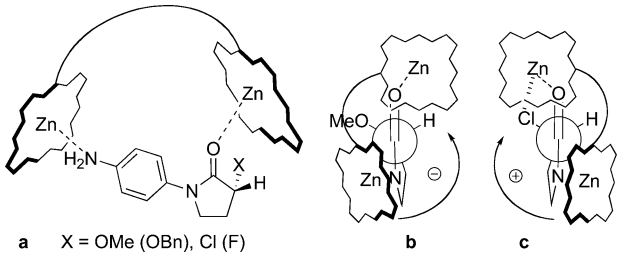


Figure 7. (a) Mode of binding of porphyrin tweezer to butyrolactams; (b) negative ECCD detected for (*S*)-2-alkoxybutyrolactam (**30** or **31**); (c) positive ECCD detected for (*R*)-2-halobutyrolactam (**32** or **36**) due to C–X···π interaction.

is opposite to that obtained for lactams **32** and **36** due to the inversion of the stereochemistry during the Finkelstein reaction.

NMR-Based Conformational Analysis of α-Halolactams Complexed with Zn-TPP

Having in hand chiral lactams **30**–**32** and **36** enabled us to perform NMR spectroscopic analysis for the characterization of their mode of binding with zincated porphyrins. Considering that the binding of the chiral lactams with the metalloporphyrin, and the subsequent interaction with the chiral center (either due to steric differentiation or the postulated halogen–π interaction) leads to the porphyrin ring tilting to one side of the lactam ring, anisotropic shielding of the protons on one face of the lactam ring would suggest closer proximity to the porphyrin ring. This, in turn, could reveal the position of the porphyrin ring bound to the chiral lactams relative to either the alkoxy or the halogen substituent.

The ^{1}H NMR spectra of α-chiral halolactams and alkoxylactams exhibit two distinct sets of diastereotopic protons for β- (Figure 8, Ha_1 and Ha_2) and γ-methylene groups (Figure 8, Hb_1 and Hb_2).[55] Protons Ha_1 and Hb_1 reside on the same side of the lactam ring, *cis* to the hydrogen atom on the chiral center, whereas Ha_2 and Hb_2 are *cis* with the larger substituent. It is anticipated that a bound porphyrin that slides to the side of the smaller hydrogen atom should more effectively shield Ha_1 and Hb_1 relative to Ha_2 and Hb_2 (Figure 8b) in contrast to the porphyrin sliding towards the larger X group (Figure 8a). Hence, monitoring of the relative shifts of the signals of the β- and γ-hydrogen atoms should map out the position of the bound metalloporphyrin relative to the substituents at the asymmetric center.

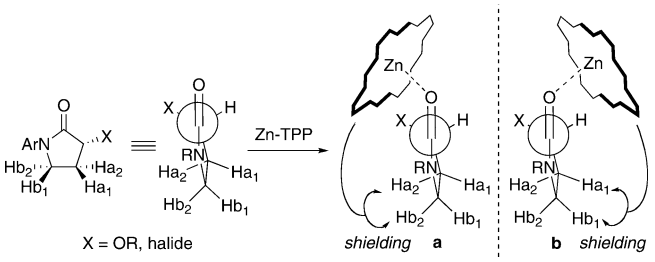
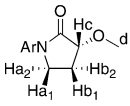
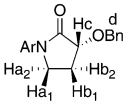
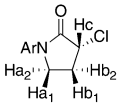
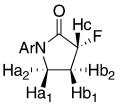


Figure 8. NMR-based conformational analysis of α-alkoxy and α-halogenated lactams complexed with Zn-TPP. (a) C–X···π interactions leading to larger shielding of diastereotopic hydrogen atoms Ha_2/Hb_2; (b) absence of C–X···π interactions leading to a larger shift of the signals of the protons Ha_1/Hb_1.

Table 6 summarizes the $\Delta\delta$ NMR shifts obtained upon complexation of chiral lactams **30**–**32** and **36** with 2.2 equiv. of Zn-TPP in $CDCl_3$ for protons Ha_1, Ha_2, Hb_1, and Hb_2. As anticipated, upon complexation of the metalloporphyrin with α-alkoxylactams **30** and **31**, the observed $\Delta\delta$ value for Ha_1 and Hb_1 (*cis* to the small group on the chiral center) is larger than that for Ha_2 and Hb_2. The latter result supports the claim that upon steric differentiation, the zincated porphyrin slides away from the bulkier alkoxy group in preference to the smaller hydrogen atom. Gratifyingly, complexation of Zn-TPP with either α-halolactam **32** or **36** leads to the greater shielding of Ha_2 and Hb_2 (protons that are *cis* to the halogen atom) as compared to Ha_1 and Hb_1. This result provides strong support for the supposition that the metalloporphyrin resides primarily to the side of the bulkier halogen group, thus suggesting the presence of an interaction that energetically compensates for the greater steric arrangement.

The data obtained thus far from CD and NMR spectroscopic experiments indicate that the presence of a halogen atom α to an amide carbonyl group enhances its binding to Zn-TPP-tz, suggesting a direct interaction between the halogen atom and the porphyrin system. The exact nature of this interaction can be either a bidentate-type of coordination of the haloamides (both the carbonyl oxygen atom and the halogen atom) to the zinc atom in the porphyrin core or a direct interaction between the halogen atom and the aromatic system of the porphyrin (halogen–π interac-

Table 6. ^{1}H NMR shift observed upon complexation of butyrolactams with Zn-TPP.[a]

H	$\Delta\delta = \delta_{complex} - \delta_{free}$, ppm			
				
	30	**31**	**32**	**36**
a_1	**–0.130**	**–0.102**	–0.038	–0.061
a_2	–0.081	–0.076	**–0.046**	**–0.071**
b_1	**–0.110**	**–0.091**	–0.034	–0.045
b_2	–0.074	–0.054	**–0.048**	**–0.056**
c	–0.220	–0.252	–0.141	–0.108
d	–0.123	–0.183	----	----

[a] The reported numbers refer to a $\Delta\delta$ value for each proton ($\Delta\delta = \delta_{complex} - \delta_{free}$, ppm). Spectra were measured in $CDCl_3$ at a 1:1.2 Zn-TPP/ligand ratio (18 mM Zn-TPP final concentration).

tion). Based on ECCD and NMR spectroscopic results, and corroborating literature precedents, we propose that the major ECCD-active conformation must reflect a C–X···π interaction contributing to the binding of the α-haloamides to the Zn-porphyrin tweezer.

Conclusions

We believe that the series of experiments described in this manuscript support the presence of a halogen–π interaction between the α-halogen atom of chiral amides and the porphyrin of the Zn-TPP-tz. Such binding results in a conformation that does not agree with the one previously observed for amide-derivatized chiral α-alkyl- and α-alkoxycarboxylic acids. On the basis of the newly established ECCD-active conformation, we propose a new mnemonic device for determining the absolute stereochemistry of α-halocarboxylic acids derivatized with 1,4-phenylenediamine, by using ECCD. As shown in Figure 9, due to the cooperative binding, the halogen atom is placed pseudo-*syn* to the amide carbonyl group, whereas the large group (L) is perpendicular and the small group (S) staggered. The expected ECCD sign can be predicted by determining the sense of rotation originating from the large group through the small group and towards the halogen. A clockwise orientation would translate into a positive ECCD bisignate signal, and vice versa.

More significantly, this study demonstrates that α-haloamides constitute a special category of substrates with enhanced interactions between the halogen atom and the zincated porphyrin. The source of this interaction, and more specifically, the reason why it is observed solely with amides is currently under investigation.

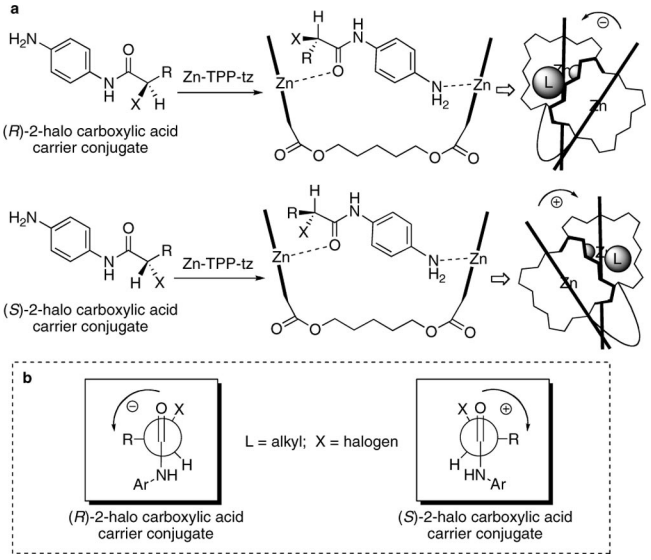


Figure 9. General mnemonic for stereochemical determination of 1,4-phenylenediamine-derivatized chiral α-halogenated carboxylic acids with Zn-TPP-tz.

Experimental Section

General Experimental Procedures: Anhydrous CH_2Cl_2 was dried with CaH_2 and distilled. The solvents used for CD measurements were purchased from Aldrich and were of spectral grade. All reactions were performed in dried glassware under nitrogen. Column chromatography was performed by using SiliCycle silica gel (230–400 mesh). ^{1}H NMR spectra were obtained with a Varian Inova 300 MHz or 500 MHz instrument and are reported in parts per million [ppm] relative to the solvent resonances (δ), with coupling constants (J) in Hertz [Hz]. IR studies were performed with a Galaxy series FTIR 3000 instrument (Matteson). UV/Vis spectra were recorded with a Perkin–Elmer Lambda 40 spectrophotometer and are reported as λ_{max} [nm]. CD spectra were recorded with a JASCO J-810 spectropolarimeter, equipped with a temperature controller (Neslab 111) for low-temperature studies, and are reported as λ [nm] ($\Delta\varepsilon_{max}$ [$mol^{-1}\,dm^3cm^{-1}$]). Optical rotation was measured with a Perkin–Elmer Polarimeter 341 (microaperture, 1 mL cell) at 20 °C.

General Procedure for CD Measurements: Zn-TPP tweezer (1 μL, 1 mM solution in anhydrous CH_2Cl_2) was added to methylcyclohexane (1 mL) in a 1.0 cm cell to obtain 1 μM tweezer solution. The background spectrum was recorded from 550 nm to 350 nm with a scan rate of 100 nm/min at 0 °C. The prepared solution of porphyrin tweezer **1** was titrated with a solution of the carrier/chiral acid conjugate (1 mM) from a ratio of 1:1 to 1:40. The ECCD data obtained with 10 or 20 equiv. of chiral substrate are reported. The CD spectra were measured immediately (minimum of four accumulations). The resultant spectra were recorded in millidegrees and normalized on the basis of the tweezer concentration and presented in $\Delta\varepsilon/\lambda$ [nm] units.

Supporting Information (see footnote on the first page of this article): Experimental procedures for synthesis of compounds **1**–**36** and CD measurements of all complexes.

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[55] See Supporting Information for synthetic details and NMR spectroscopic analysis.

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