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Configurational assignment of α-chiral carboxylic acids by complexation to dimeric Zn–porphyrin: host–guest structure, chiral recognition and circular dichroism†

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A circular dichroic (CD) exciton chirality method based on host–guest chiral recognition has been developed to determine the absolute configuration of carboxylic acids with an α-stereogenic center; an amide C = O→Zn coordination, identified by infrared spectroscopy and computations, is involved in this complexation.

Chiral carboxylic acids are often found in nature in non-racemic forms. In the following we describe a microscale chiroptical protocol that determines absolute configurations of carboxylic acids connected directly to a stereogenic center carrying no other derivatizable functionalities.

As shown in Fig. 1a, the chiral substrate is derivatized with the achiral carrier **1** to give a bifunctional amide conjugate that forms a 1 : 1 host–guest complex with a CD sensitive 'receptor', the zinc porphyrin tweezer **2**. The two porphyrins in this complex adopt a preferred helicity (Fig. 1c) dictated by the substituents, L and M according to their relative steric sizes,[1] at the stereogenic center. The exciton coupling between the intense and red-shifted porphyrin Soret transitions,[2] with effective polarization along 5,15 and 5′,15′ directions (Fig. 1b),[3] gives rise to exciton split CD couplets, the signs of which are diagnostic of the absolute configuration of the substrate.

The configurational assignment of chiral carboxylic acids by CD has so far been achieved through correlations based on Cotton effects associated with the n–π* transition of the carboxyl chromophore[4] or by the exciton chirality method.[5] The latter has been applied to α-hydroxy acids[6] and to carboxylic acids carrying a pre-existing chromophore.[7]

Based on the complexation between bidentate derivatives of chiral substrates and the tweezer host **2** through a two-point zinc–nitrogen coordination, we have developed methods to determine the configurations of α,ω-diamines, *prim*-α-substituted amines, *sec*-mono alcohols, and *sec*-monoamines.[8] In order to extend this protocol to carboxylic acids, the hydrazino carrier molecule **3** with two amino nitrogens for binding to the tweezer host **2**, was considered. The conjugate **3–7**[9] formed from (*S*)-naproxen **7** (Table 1) and carrier **3** did exhibit the expected bisignate CD curve upon complexation with tweezer **2** (see ESI†); but with other substrates, carrier **3** gave weak CD couplets with inconsistent signs.

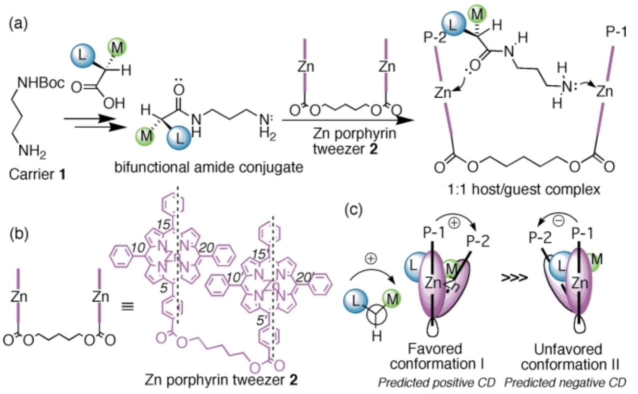
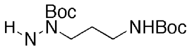


Fig. 1 (a) Formation of a 1 : 1 complex between the bidentate conjugate (formed by a chiral carboxylic acid and carrier **1**) and tweezer **2** (commercially available from TCI, Japan). (b) Schematic representation of 5,15 and 5′,15′ directions. (c) Intra-porphyrin twist adopted according to the substituent relative steric size.[1]

Although oxygen nucleophiles are weaker axial ligands of Zn porphyrins than nitrogen ones,[10] it is known that the coordination between neutral amide groups and metal ions occurs through the oxygen atom.[11] Therefore, we tested *tert*-butyl-*N*-(3-aminopropyl) carbamate **1** as the carrier, in which the amide carbonyl of conjugates formed from carboxylic acids could serve as a second anchoring point to P-2 in the complex following coordination of the *prim*-amino group to Zn in P-1 (Fig. 1a). An intense exciton coupled CD with the expected sign was indeed observed for complex **1–7/2**[9] (see ESI† and Table 1). The modification of carrier **1** to carriers **4** to **6** to give conjugates **4–7** to **6–7** simply gave rise to weaker CD amplitudes, and did not improve the stereodifferentiation (see ESI†); this is most likely due to less favorable steric and/or



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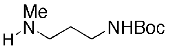

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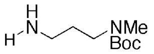

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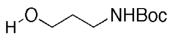

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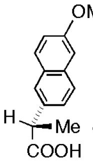
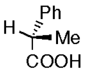
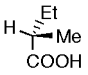
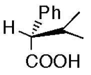
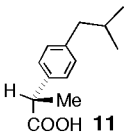
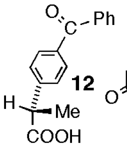
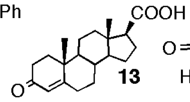
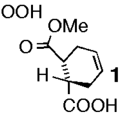
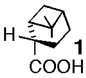
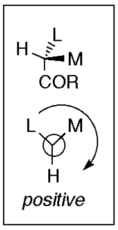
Table 1 Structures and schematic representation of carboxylic acid from **7** to **15** and observed CD data of their conjugate in MCH with carrier **1** after complexation with tweezer **2** (tweezer, 1 μM; conjugate, 40 μM). For all substrates the predicted CD couplet is positive (frame)

	7	**8**	**9**	**10**	**11**
					
λ nm **(Δε)**	431 nm (+134) 424 nm (- 109)	431 nm (+ 198) 423 nm (- 154)	430 nm (+ 40) 421 nm (- 35)	431 nm (+ 181) 422 nm (- 150)	430 nm (+ 143) 421 nm (- 64)
A_{CD}	+243	+352	+75	+331	+207

	12	**13**	**14**	**15**
				
λ nm **(Δε)**	430 nm (+ 60) 420 nm (- 13)	431 nm (+ 108) 423 nm (- 76)	430 nm (+ 54) 420 nm (- 20)	430 nm (+ 203) 421 nm (- 130)
A_{CD}	+73	+184	+74	+333



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† Electronic supplementary information (ESI) available: spectroscopic data for compounds **1–7/2** and **3–7/2** to **6–7/2**; UV-Vis spectra and binding curves for titration of **2** with **1–8**; Job plot for **1–8/2**; computational and experimental sections. See http://www.rsc.org/suppdata/cc/b2/b204554k/

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electronic factors. Thus carrier **1** has been employed in the studies described here.

The stoichiometry of the complex was determined by titrating tweezer **2** with conjugate **1–8** (see ESI†). Upon binding, a characteristic red shift of the zinc porphyrin Soret band occurs in the UV-Vis (from 419 to 422 nm, see ESI†). The association constant K_a of the complex was calculated to be $4.65 \cdot 10^5$ M^{-1}, through a non-linear fitting (see ESI†) of the absorbance values at 422 nm and assuming a 1 : 1 stoichiometry. The formation of a 1 : 1 complex for **1–8/2** was also confirmed by a Job plot analysis followed by CD (see ESI†).

In order to prove the C=O→Zn binding, IR spectra of host–guest complex **1–8/2** were measured in CH_2Cl_2. It was expected that after complexation, the amide C=O stretching frequency (amide I band) would decrease.[12] The amide I band of the free conjugate **1–8** occurs at 1666 cm^{-1} while the ester carbonyl C=O stretching of the tweezer is observed at 1714 cm^{-1} (Fig. 2a). Subtraction of the free tweezer IR from that of the complex, shows the amide I band for the complex to be at 1658–1661 cm^{-1} (Fig. 2b). This *ca.* 8 cm^{-1} shift to lower frequencies upon complexation suggests that a Zn ligation occurs at the carbonyl oxygen in this complex.

The structure of the complex was further studied by molecular modeling using Monte Carlo (MC) conformational searches with Merck Molecular Force Field (MMFFs), and treating the ligand/Zn coordination within a non-bonded model.[13] In the lowest energy structure calculated by MC/MMFFs for complex **1–8/2**, as well for all minimum energy conformations within 50 kJ mol^{-1}, the ligation between the conjugate and the Zn on P-2 always occurs through the carbonyl oxygen (Fig. 3).

In order to define the scope and limitations of the method, carboxylic acids with known absolute configurations (**7** to **15**) were tested (Table 1). The absolute configuration is correlated with the CD couplet sign in the following manner. When the stereogenic center is viewed with the carboxylic group in the rear in the Newman projection (Table 1, Fig. 1c), and L (large group), M (medium group)[1] and H are arranged in a clockwise fashion, a positive exciton couplet is observed, and *vice versa*. This is because in the most favored conformation I of the complex (Fig. 1c), group M at the stereogenic center is clamped between the two porphyrins, while group L is extruding out of the intra-porphyrin pocket. In such preferred conformation the two porphyrins adopt a positive helicity. For all substrates investigated, the prediction of the preferred chiral twist agrees with the relative steric size[1] of the substituents. The additional oxygen functionalities in compounds **7**, **12**, **13**, and **14** do not interfere with the amide-carbonyl/Zn complexation because of their distances from the binding site. The presence of different substituents on the aromatic rings (compounds **7**, **8**, **11**, and **12**) does not affect the determination, although the CD amplitudes vary for reasons not well understood. However, when the chiral center carries N, O or halogen, the CD couplet signs are opposite to the predicted (data not shown).

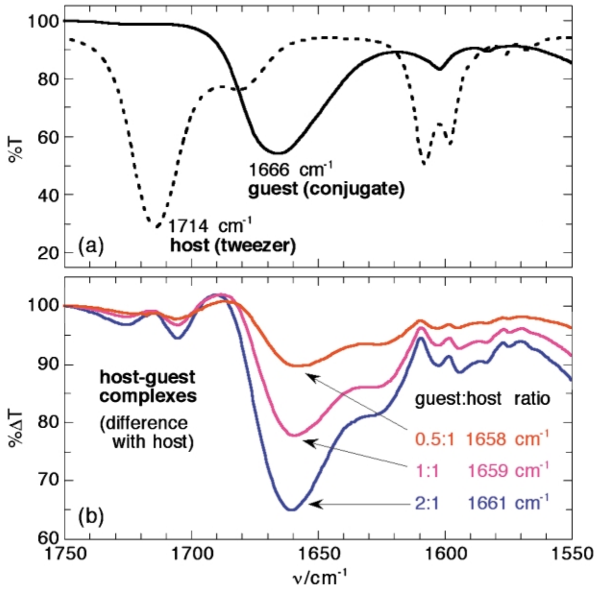

Fig. 2 (a) IR spectra of tweezer **2** (host, dotted line) and conjugate **1–8** (guest, solid line) in CH_2Cl_2. (b) IR difference spectra of complexes **1–8/2** at different host–guest molar ratios in CH_2Cl_2, free host spectrum has been subtracted.

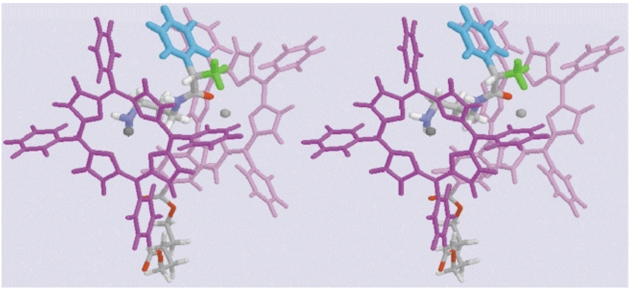

Fig. 3 Stereoview of lowest energy MC/MMFFs structure of **1–8/2**.

The present paper describes a procedure to determine the absolute configuration of α-chiral carboxylic acids through complexation with a Zn porphyrin tweezer. IR and molecular modeling studies demonstrate that in addition to the complexation of the terminal amino function to P-1,[8] a second mode of host–guest binding, a C=O to Zn ligation (of P-2), is present. Studies are ongoing to clarify the nature of the complex formed by the Zn tweezer **2** and derivatives of chiral carboxylic acids carrying heteroatoms at the chiral center. The use of a Mg–porphyrin tweezer with enhanced binding affinity to the amide carbonyl oxygen of a guest molecule is under investigation.

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9 In the text, notation **3–7** refers to the covalent conjugate between carrier **3** and the chiral carboxylic acid **7**, while **3–7/2** refers to the complex between conjugate **3–7** and the tweezer molecule **2**.

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