

Direct determination of absolute configuration of carboxylic acids by cyclooctapyrrole†

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Octaphyrin **O1** has been found to be an effective sensor for the direct determination of absolute configuration of a variety of carboxylic acids at mM concentrations at room temperature based on CD exciton chirality method.

Facile methods for the determination of molecular chirality will help understanding better the role of chirality in natural phenomena and medicine and aid the development of new intelligent materials. Based on the circular dichroism (CD) exciton chirality method,¹ the supramolecular chirality induction (supramolecular chirogenesis) has been successfully used for the absolute configuration determination of chiral monoalcohols,² dialcohols,³ amines and aminoalcohols,⁴ amino acid derivatives,⁵ diamines⁶ and bifunctional amide conjugates.⁷ In these cases, the host–guest interactions are typically based on the metal coordination or acid–base binding. A somewhat tedious two-phase extraction technique was used for the absolute configuration determination of a pair of potassium monocarboxylate salts by crown ether-bis porphyrin.⁸

Metal free octaphyrins, which are known to exist in a chiral figure eight type conformation,⁹ possess a relatively spacious cavity with basic pyrrole nitrogen atoms able to bind Lewis and protic acids. Further, depending on the number of the π -electrons or the nature of the β -pyrrole and *meso*-carbon substituents, the octaphyrins can possess enough structural flexibility to undergo the chirality interconversion.^{9,10}

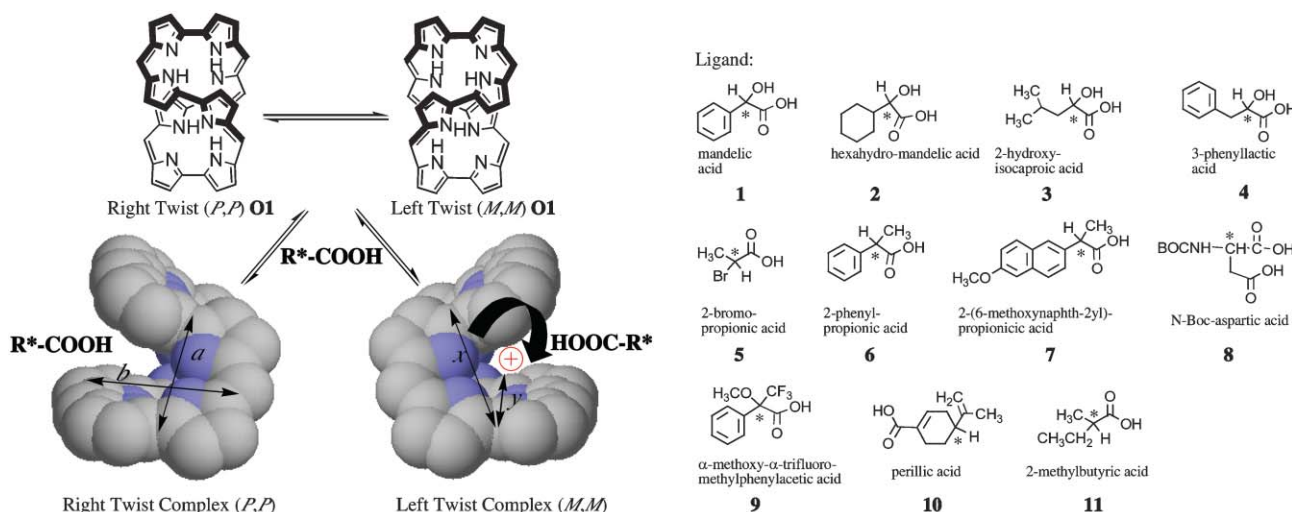
Herein, we report the use of 2,3,6,7,11,12,15,16,20,21,24,25,29,30,33,34-hexadecaethyl-9,18,27,36-tetraphenyl[32]octaphyrin-(1.0.1.0.1.0.1.0) **O1** (C₉₂H₁₀₄N₈) (Scheme 1) for the direct determination of absolute configuration of a variety of carboxylic acids at sub mM concentrations and room temperature based on the CD exciton chirality method.¹

Octaphyrin **O1** was obtained by using the method developed recently by our group.¹¹ Extensive variable temperature (VT) NMR studies^{9,10} reveal that **O1** and a similar [32]octaphyrin possess a fast chiral interconversion equilibrium at room temperature therefore being a suitable host compound under CD spectrometric conditions. The UV-vis absorption spectrum of **O1** in dichloromethane shows one major band (570 nm) at longer wavelength region (Fig. 1a). Addition of a chiral carboxylic acid into the CH₂Cl₂ solution containing **O1** caused a clear bathochromic shift of the Soret band, which is induced by the formation of carboxylic acid-ligated **O1** absorbing at *ca.* 645 nm (Fig. 1a). This shift is due to the formation of a protonated octaphyrin. Similar bathochromic shift can be observed when **O1** is titrated with a strong protic acid, such as hydrochloric acid

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Scheme 1 Chirality induction in octaphyrin **O1** upon binding of chiral carboxylic acids. The X-ray structure of the racemic free base **O1** is shown as a space filling model omitting the pyrrole β -ethyl substituents, *meso*-phenyl substituents, and two diethyl ether solvates for clarity.

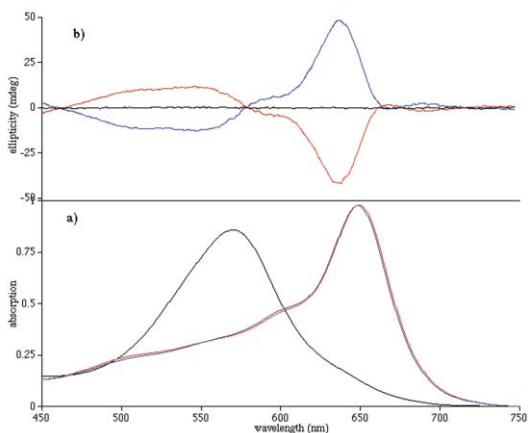


Fig. 1 (a) UV-vis spectra and (b) CD spectra of **O1** in the absence (black) and presence (100 eq.) of (*S*)-(+)-hexahydromandelic acid **2** (red) or (*R*)-(-)-hexahydromandelic acid **2** (blue) in CH_2Cl_2 at 298 K.

(HCl) (Fig 2). Upon addition of HCl up to 2 equivalents, the intensity decrease of the 570 nm band stops whereas the intensity increase of the 630 nm band stops. The plot of Δabs at 630 nm vs. concentration of HCl does not fit to the nonlinear optimization of 1 : 1 binding model therefore verifying that the absorption band at 630 nm originates from both mono and diprotonated **O1**. Addition of HCl more than 2 equivalents causes a gradual disappearance of the 630 nm band and a new band formation at 586 nm. The growth of the intensity of this band saturates when 7.0 equivalents of HCl is added. By considering the fact that the octaphyrins can accommodate maximum of four protons,¹² it becomes clear that the absorption band at 586 nm originates from tri and tetra protonated **O1**.

The CD spectrum is silent for **O1**, whereas the 1st Cotton effect of the bisignate CD signal band at 639 nm arises upon complexation of the chiral carboxylic acid (Fig. 1b). The titration of **O1** with (*R*)-(-)-**1** shows that this band represents both 1 : 1 and 1 : 2 complexes which have the same chirality (see ESI[†]). The sign of this induced Cotton effect is determined solely by the absolute configuration of the carboxylic acid. The plausible mechanism for the generation of the CD signal is shown in ligand free X-ray structure in Scheme 1. This is based on the finding that the X-ray structures reported for the free base and the

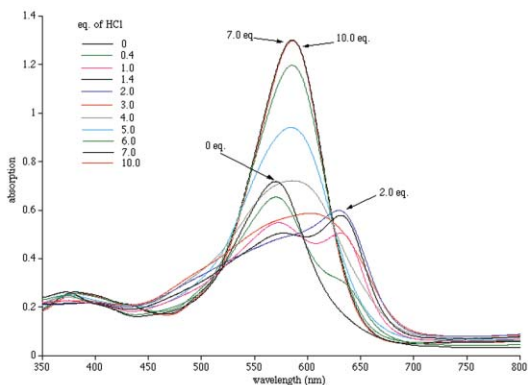


Fig. 2 UV-vis spectral changes of **O1** (5.83×10^{-6} M in CH_2Cl_2) upon addition of HCl (3.50×10^{-4} M in MeOH) at 293 K.

dihydrochloride complex of [36]octaphyrin(2.1.0.1.2.1.0.1) showed a similar figure eight structure to that of **O1**.¹² The X-ray crystallography of **O1** indicated the racemic structure with figure eight trajectory of the π -system where planar dipyrromethene moieties were stabilized by the intramolecular NH–N hydrogen bondings.

The presence of the two repeating subunits dipyrromethene and bipyrrole and their electronic transition dipole moments *a* and *b* (Scheme 1, arrows *a* and *b*), respectively, results in exciton interactions, in which the dipyrromethene exciton couplings¹³ appear at the lowest energy levels. The figure eight conformation of **O1** possesses at least three such exciton couplings of each dipyrromethene chromophore; in a short molecular axis helicene-shape substructure (electronic transitions, arrows *x* and *y*, Scheme 1), a long axis zig-zag structure and a long range through space positioning. Except for the third case which seems to have a negligible effect, the direction of the orientation of the coupling transitions in the first and second cases is the same thus resulting in the intense 1st Cotton effect. The shape of the CD spectra in Fig. 1 suggests that the value differences for the dipyrromethene exciton interaction energies (electronic transition *a*, Scheme 1 arrow *a*) are small, whereas higher energy region CD bands (460–580 nm) are distributed at much wider energy range due to the greater energy differences of the electronic transitions such as *b* of the higher energy coupling chromophores (Scheme 1, arrow *b*). The assignment of the 1st Cotton effects to the particular helical structures shown in Scheme 1 is in agreement with the results found for the close analog [36]octaphyrin-(2.1.0.1.2.1.0.1) and its metal complex,⁹ and the various helicene systems.¹⁴ The ability of sensing the chirality of carboxylic acids by **O1** is remarkable. All the (*S*)-configuration acids examined induce negative and the (*R*)-acids positive chirality (Table 1). The OH group containing **1–3** induces clear CD spectra when added 300-fold excess. Also the positioning of the 1st Cotton effect and UV-vis absorption maxima are similar. The lactic acid derivative **4** and the CF_3 group containing **9** bind

Table 1 CD and UV-vis spectral data for supramolecular chirogenesis upon complexation of octaphyrin **O1** with various chiral carboxylic acids at 298 K in a 1 cm optical cell^a

Ligand	CD data		UV-vis data	
	Sign and λ_{max} (nm) of 1st Cotton effect	λ_{max} /nm	λ_{max} /nm	Relative CD intensity ^f
(<i>R</i>)-(-)- 1 ^b	+(644)	647	647	87
(<i>S</i>)-(+)- 1 ^b	-(644)	647	647	81
(<i>R</i>)-(-)- 2 ^b	+(639)	649	649	55
(<i>S</i>)-(+)- 2 ^b	-(639)	649	649	49
(<i>S</i>)-(-)- 3 ^b	-(642)	647	647	60
(<i>S</i>)-(-)- 4 ^{b,d}	-(644)	636	636	17
(<i>S</i>)-(-)- 5 ^b	-(611)	638	638	11
(<i>R</i>)-(-)- 6 ^c	+(642)	642	642	21
(<i>S</i>)-(+)- 6 ^c	-(642)	642	642	27
(<i>S</i>)-(+)- 7 ^{b,e}	-(644)	636	636	26
L- 8 ^b	-(643)	646	646	17
(<i>R</i>)-(+)- 9 ^{c,d}	+(647)	642	642	19
(<i>S</i>)-(-)- 9 ^{c,d}	-(647)	642	642	15
(<i>S</i>)-(-)- 10 ^{c,e}	-(622)	630	630	12
(<i>S</i>)-(+)- 11 ^{c,e}	-(641)	641	641	6

^a [**O1**] = 6.5×10^{-6} M, [carboxylic acid] = 1.95×10^{-3} M. ^b In CH_3OH . ^c In CH_2Cl_2 . ^d C = 1.95×10^{-4} M. ^e C = 9.75×10^{-3} M. ^f |1st Cotton effect λ_{max} mdeg|/corresponding λ_{max} abs.

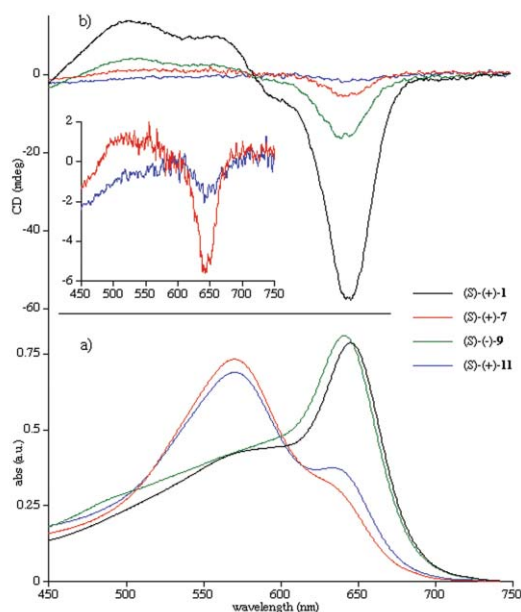


Fig. 3 (a) UV-vis spectra and (b) CD spectra of **O1** (6.5×10^{-6} M) in the presence of (*S*)-(+)-**1** (300 eq.), (*S*)-(+)-**7** (1500 eq.) (also in inset), (*S*)-(-)-**9** (30 eq.) and (*S*)-(+)-**11** (1500 eq.) (also in inset) in CH_2Cl_2 at 298 K.

strongly to **O1** and easily form tri- and tetraprotonated complexes when present more than 30 molar equivalents.

Based on the moderate UV-vis spectral changes (Fig. 3a), weak binding was observed for **7** and **11** most likely due to the guest bulkiness and pK_a factors. Comparison of the UV-vis and CD spectral intensities around 630–650 nm region (Fig. 3a and 3b) reveals that **9** binds more strongly than **1** but yields significantly smaller intensity CD spectrum. This can be explained by the substituent bulkiness order effect around the chiral carbon. The size difference of the chiral center's substituents other than CO_2H is greater in **1** than in **9**; (Ph, OH, H) vs. (Ph, OMe, CF_3), respectively. Similarly, **11** binds more strongly than **7** but yields smaller intensity CD spectrum, which is consistent with the substituent bulkiness order effect. The large size of the naphthyl derivative substituent in **7** is a possible reason for the weak binding thus suggesting that **O1** is not able to complex with even larger size carboxylic acids. Surprisingly the absolute configuration of the remote chiral center in **10** can be read out by **O1**.

Since practically no other chirality probe can sense absolute configuration of carboxylic acids of low concentrations at ambient temperature, the ability and potential of **O1** as a chirality sensor is important and promising. Additionally, the polarity of the solvent for the chiral ligand can be varied without greatly affecting the complexation, therefore the present method should provide effective analysis for a large variety of carboxylic acids.

Hence, we examined a variety of synthetic and natural chiral carboxylic acids, including aliphatic, cyclic and aromatic

carboxylic acids with one chiral center to give the consistent results. In the typical case the absolute configuration of the carbon α to CO_2H is exposed, although the more remote chiral center can be exposed as well. Changing the basicity and the cavity size with these figure eight type structures is of great importance to enlarge the scope of this novel chirality probe, which is now extensively underway in our laboratory.

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Notes and references

[‡] Crystal data for **O1** $\text{C}_{92}\text{H}_{104}\text{N}_8 \cdot 2\text{C}_4\text{H}_{10}\text{O}$, $M = 1470.07$, $T = 300(2)$ K, monoclinic, space group $C2/c$, $a = 20.381(2)$, $b = 19.5758(18)$, $c = 23.321(2)$ Å, $\beta = 108.829(2)^\circ$, $V = 8806.7(15)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 1.109$ g cm⁻³, $\mu(\text{Mo K}\alpha) = 0.066$ mm⁻¹, reflections collected: 23501, unique reflections: 8797 ($R_{\text{int}} = 0.0834$), final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0781$, $wR_2 = 0.2045$, R indices (all data) $R_1 = 0.1518$, $wR_2 = 0.2510$. CCDC reference number 608298.

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