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Chiral information transfer by solid–solid interaction: application for absolute configuration assignment†

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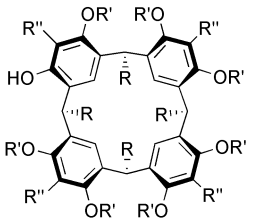
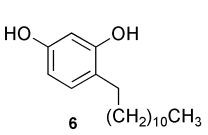
Host–guest complexes of calix[4]resorcarene with chiral molecules were efficiently formed by solid–solid grinding and exhibited CD Cotton effects reflecting the absolute configuration of the guest.

Calixarenes are macrocycles capable of accommodating a rather small molecule as a guest and thus are widely utilized as host molecules.[1] The host–guest complexation involving calixarenes generally takes place in solution, thus allowing the process to be followed by means of solution spectroscopy such as NMR, absorption, and emission spectra. Herein we report that calix[4]resorcarene (**1**) efficiently forms a host–guest complex with a polar molecule by solid–solid reaction.[2,3] If the guest is chiral, solid-state circular dichroism (CD) spectra of the complexes exhibit induced Cotton effects reflecting stereochemistry of chiral guests.[4,5] The solid-state complexation and subsequent CD measurement is therefore applicable to predicting the absolute configuration of chiral guest molecules.



1a: R = $CH_3(CH_2)_{10}$, R' = H, R'' = H
1b: R = $CH_3(CH_2)_6$, R' = H, R'' = H
1c: R = $CH_3(CH_2)_4$, R' = H, R'' = H
2 : R = $CH_3(CH_2)_{10}$, R' = CH_3CO-, R'' = H
3 : R = $CH_3(CH_2)_{10}$, R' = H, R''= OH
4 : R = $CH_3(CH_2)_{10}$, R' = H, R''= CH_3



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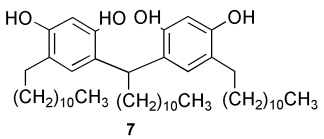

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We have previously demonstrated that **1** in apolar organic solvents could form a 1 : 1 complex with a polar molecule, such as carboxylic acids and sugars, *via* hydrogen-bonding interactions.[6] The affinity of host **1** for the guests varied widely depending on the guest molecules: carboxylic acids and sugars were strongly (K_a = 10^3–10^5/l mol^{-1}) and moderately (K_a = 10^1/l mol^{-1}) bound,[6] while aminoacids were scarcely bound to **1**. Here we have found that **1** forms host–guest complexes by solid-state grinding when, in a typical example, 2.8 mg (2.5×10^{-3} mmol) of **1a** and an equimolar amount of a guest were ground in an agate pestle and mortar for a few minutes. Powder X-ray diffraction patterns of the original **1a** and guest disappeared after grinding together whereas those of **1a** and guest were virtually invariant after grinding independently. The IR spectra of the ground mixture of **1a** and a di- or monocarboxylic acid guest, such as glutaric, 2-methylglutaric, and 2-phenylbutyric acids in a Nujol mull or KBr pellet gave a ν_{OH} signal at 3193 cm^{-1} for **1a** and a $\nu_{C=O}$ at 1713 cm^{-1} for glutaric acid, whereas before grinding the values were at 3372 and 1730 cm^{-1}, respectively, indicating that hydrogen bond formation between OH groups in **1a** and guest carboxyl groups occurred.‡ The hydrogen bond formation was also confirmed by solid-state ^{13}C NMR spectra.§ A ground mixture of **1a** and methyl-β-D-glucopyranoside or aminoacids readily dissolves in $CDCl_3$ and exhibits a typical ^1H NMR spectrum of the **1a**·guest complex: for example, the proton resonances from the glycoside C–H and O–H are largely shifted to high fields ($\Delta\delta \sim 3$ ppm) due to the ring current of the aromatic rings in **1a**.[7]¶ On the other hand, the mixture without grinding is not completely soluble in $CDCl_3$ and only shows the proton resonances of **1a**. These spectroscopic results indicate that the complexation of **1a** with guests through hydrogen bonding interactions took place by solid-state grinding and the complex structures were identical to those of the **1**·guest complexes from solution.[8]‖ Complexes were easily formed from **1a** and an equal or slight excess (1–10 fold) of a variety of carboxylic acids, alcohols, amino acids, and even esters, aldehydes, and ketones, some of which were negligibly bound to **1** in solution. These results indicate complex formation occurred much more efficiently in the solid-state than in solution.

When a guest was chiral the solid-state circular dichroism spectrum (CD) of the complex exhibited induced CD possessing split Cotton effects at the absorption band of aromatic rings of **1a**.[9] The sample preparation for CD measurement is simple: the complex (0.1–0.2 mg) obtained by solid-state grinding was suspended in liquid paraffin (10 mg) and the suspension obtained was pasted onto a KBr plate or was injected into a NaCl liquid cell. **1a**and the chiral guests themselves are otherwise CD silent in this region since **1a** is inherently achiral and the guests are non-chromophores. For example, the CD of **1a**·(*R*)- and **1a**·(*S*)-2-phenylbutyric acid complexes are illustrated in Fig. 1, the enantiomeric complexes giving a pair of spectra which are mirror images of each other. Upon complexation of (*S*)-2-phenylbutyric acid to **1a**, it is possible that the two adjacent benzene rings in **1a** make a clockwise movement from front to back as shown in *p*-**8** in Fig. 2 due to steric repulsion between the right benzene ring and the phenyl group as the larger substituent. In accordance with exciton-coupled circular dichroism, the clockwise orientation of the two equivalent benzene rings (positive chirality) gives rise to the first half (the longer wavelength half) of the split Cotton effect curve positive and second half negative.[10] Thus, the positive or negative first

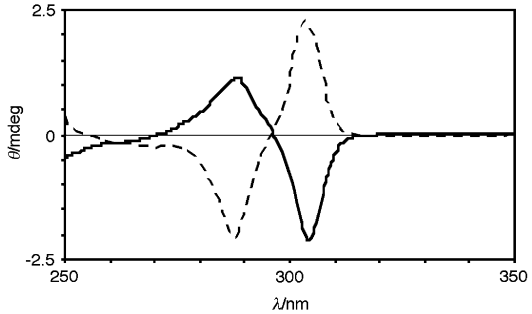

Fig. 1 Solid-state CD spectra of **1a**·*R*- (solid line) and **1a**·*S*-2-phenylbutyric acid (dotted line) complexes in a Nujol mull.

† Electronic supplementary information (ESI) available: IR and ^1H NMR spectra. See http://www.rsc.org/suppdata/cc/b2/b209281f/

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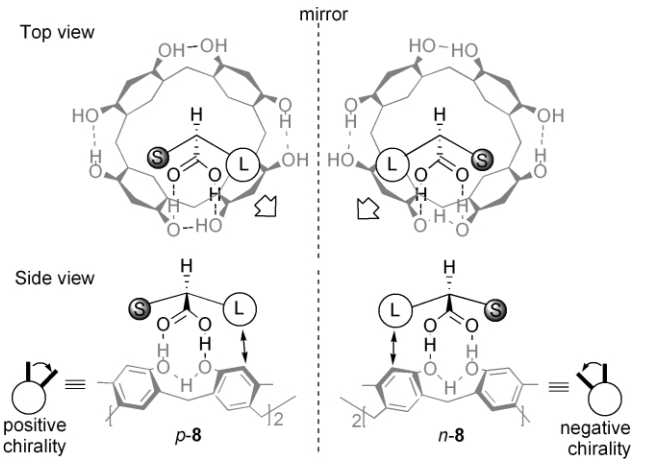

Fig. 2 Schematic representation of chiral induction in **1** (gray drawing) upon complexation with *S*- and *R*-2-phenylbutyric acids (black drawing), in which L and S stand for the larger (phenyl) and smaller (ethyl) substituents.

Cotton effect was observed when the larger substituent was situated on the right or left, respectively, with respect to the stereogenic center such as in *p*-**8** and *n*-**8**. The relationship between the stereochemistry of the chiral guests and the signs of induced CD are interpreted in the same way and they are highly correlated (Table 1). When the two substituents in a chiral guest possessed an identical size, such as CH_3 and NH_2 (in Table 1, L- and D-alanine) the chiral information transfer failed to provide an induced CD. The generality of the observations is suggestive of a rule which is practically applicable to the determination of absolute configurations.

Multiple hydrogen-bond binding points (OH groups) having the correct orientation are essential features of the solid-state host. In fact, the octaacetate (**2**) of **1a**, which has no OH groups, and calix[4]arene (**5**), where OH groups adopt an unfavorable orientation, did not function as a solid-state host despite having an aromatic cavity identical to **1a**. On the other hand, the aromatic cavity in **1a** is also an important structural aspect of the host: thus, complexation did not proceed when alkylresorcinol (**6**) and its dimer (**7**), which are constituents of **1a** but lack the aromatic cavity, were used as a host. The length of the alkyl chains in **1**, however, did not affect the binding ability since **1b** and **1c** also form complexes with the guests reported here. When **3** or **4** were adopted as the host instead of **1a**, no or quite weak induced CD were observed probably because the extra four hydroxyl and methyl groups in **3** and **4** inhibited the guest insertion into the cavity.¶ The mechanism of efficient complexation here must be similar to that of the solid reaction recently reported: the intervention of a liquid phase has been claimed to explain the mechanism of an apparent solid–solid reaction.[3] Thus, it is also possible here that a liquid or melt phase is induced as a result of a eutectic or peritectic melt phase occurring at the surface of the host or guest solids by grinding and that the host–guest complexation takes place consecutively in the liquid phase.

The complex formation of **1** with guest molecules by solid–solid grinding allows high efficiency of host–guest complexation and the use of a large excess of chiral guests as well as toxic organic solvents becomes unnecessary. The absolute configuration of the bound guest can be elucidated by solid-state CD measurement from the simple relationship of the signs of the induced CD.[11]

Table 1 Signs of split Cotton effect for **1a**·guest complexes

	Substituents		Cotton effect	
Guest	Left[a]	Right[a]	First	Second
(*S*)-2-methylbutyric acid	ethyl (S)[a]	phenyl (L)[a]	+	−
(*R*)-2-methylbutyric acid	phenyl (L)	ethyl (S)	−	+
(*S*)-2-(6-methoxy-2-naphthyl)propionic acid	methyl (S)	naphthyl (L)	+	−
(*S*)-mandelic acid	hydroxyl (S)	phenyl (L)	+	−
(*R*)-mandelic acid	phenyl (L)	hydroxyl (S)	−	+
L-alanine	amino	methyl	nd[b]	nd[b]
D-alanine	methyl amino	nd[b]	nd[b]	
L-amino acids[c]	amino (S)	residue (L)	+	−
D-amino acids[c]	residue (L)	amino (S)	−	+
L-phenylalanine methyl-ester hydrochloride	amino (S)	benzyl (L)	+	−
L-valine methyl-ester hydrochloride	amino (S)	*iso*-propyl (L)	+	−
(*S*)-2-butanol	methyl (S)	ethyl (L)	+	−
(*R*)-1-phenyl-1-butanol	phenyl (S)	propyl (L)	+	−
(*S*)-1-phenyl-1-butanol	propyl (L)	phenyl (S)	−	+
(*S*)-2-(6-methoxy-2-naphthyl)propanol	methyl (S)	naphthyl (L)	+	−
(*S*)-2-(6-methoxy-2-naphthyl)propanal	methyl (S)	naphthyl (L)	+	−

[a] 'Left' and 'right' stand for the position of the larger (L) or smaller (S) substituents with respect to the stereogenic center in **8**. [b] 'nd' indicates 'not detected'. [c] D- and L-amino acids include 2-phenylglycine, valine, phenylalanine, leucine, isoleucine, and methionine.

Notes and references

‡ The authentic 1:1 complex of **1a** and glutaric acid from a $CHCl_3$ solution for a KBr pellet also indicated a ν_{OH} in **1a** at 3208 cm^{-1} and a $\nu_{C=O}$ in carboxylic acid at 1714 cm^{-1}.

§ The solid-state ^{13}C NMR spectra (CPMAS, 67.5 MHz) showed a downfield shifted C=O carbon resonance for bound glutaric acid at 179.9 ppm (182.3 ppm without **1a**) for both the ground mixture of **1a** and glutaric acid and the authentic 1:1 complex of **1a** and glutaric acid.

¶ The experimental results also indicated that the solid-state complexation was a result of guest insertion into the host cavity rather than intercalation (clathrate formation) of guests into the **1a** crystal lattice. For details of clathrate formation of calixarenes, see reference 1.

‖ The yields of the complexes based on **1a** were estimated from quantitative IR and CD analyses. Calibration curves for the efficiency were obtained from the authentic 1:1 **1a**·guest complexes from $CHCl_3$ solution: **1a**·dicarboxylic acid complexes (quant.), **1a**·monocarboxlic acids (~50%), **1a**·monools (~10%), and **1a**·aminoacid complexes (~5%). All complexes have a melting point of >300 °C.

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