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Interaction of achiral host and guest in a chiral solvent as studied by circular dichroism spectroscopy. Complexation of esters and ethers with calix[4]resorcarene in limonene

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When dissolved in limonene as a chiral hydrocarbon solvent, calix[4]resorcarene exhibits induced circular dichroism (CD). The CD intensities become weaker in the presence of increasing amounts of an ester or ether as a guest. This is due to the formation of an achiral host-guest complex, which competes with the chiral host-solvent interaction. Analysis of the CD data allowed characterization of the host-guest complexes in terms of binding constants and stoichiometries. The major driving force of the complexation is host-guest hydrogen-bonding. Dimethyl dicarboxylates and diacetoxyalkanes form expectedly more stable complexes than the corresponding monoesters; diesters are capable of multiple host-guest hydogen-bonding. The affinities of monoesters are remarkably dependent on the chain-lengths of the alkyl moieties; this provides further evidence for the importance of guest-host CH-π or van der Waals interactions. Diesters having an appropriate chain-length exhibit a 2:1 (host to guest) stoichiometry. The complexation of higher homologs of ethyleneglycol dimethyl ether shows a similar 2:1 or 3:1 stoichiometry. These results strongly suggest that the host molecules cluster around a diester or an oligoether guest in a highly cooperative manner via host-host hydrogen-bonding. The potentiality of the present CD method for the evaluation of achiral host-guest interaction, especially that in a hydrocarbon solvent, is discussed.

INTRODUCTION

Calix[4]resorcarene (**1**, Chart I; four circles represent hydrogen-bonding sites composed of a pair of hydrogen-bonded OH groups) forms hydrogen-bonded complexes with a variety of hydroxyl guests such as mononols and polyols,[1–3] including sugars[4] and carboxylic acids.[5] The complexation processes can be conveniently followed by either ^{1}H NMR[1,3–5] or CD (circular dichroism) spectroscopy.[2,3] The NMR method is far less successful for non-hydroxyl guests such as esters and ethers, which give only complexation/decomplexation-averaged signals. The CD method, on the other hand, is applicable to both hydroxylic and non-hydroxylic guests including hydrocarbons, provided that they are chiral. The present work is concerned with the use of limonene as a chiral hydrocarbon solvent. We report here that the complexation of achiral esters and ethers in this particular solvent can be followed very conveniently by the CD method. A highlight of the present work is that diesters and oligoethers form stable 2:1 or 3:1 (host to guest) complexes.

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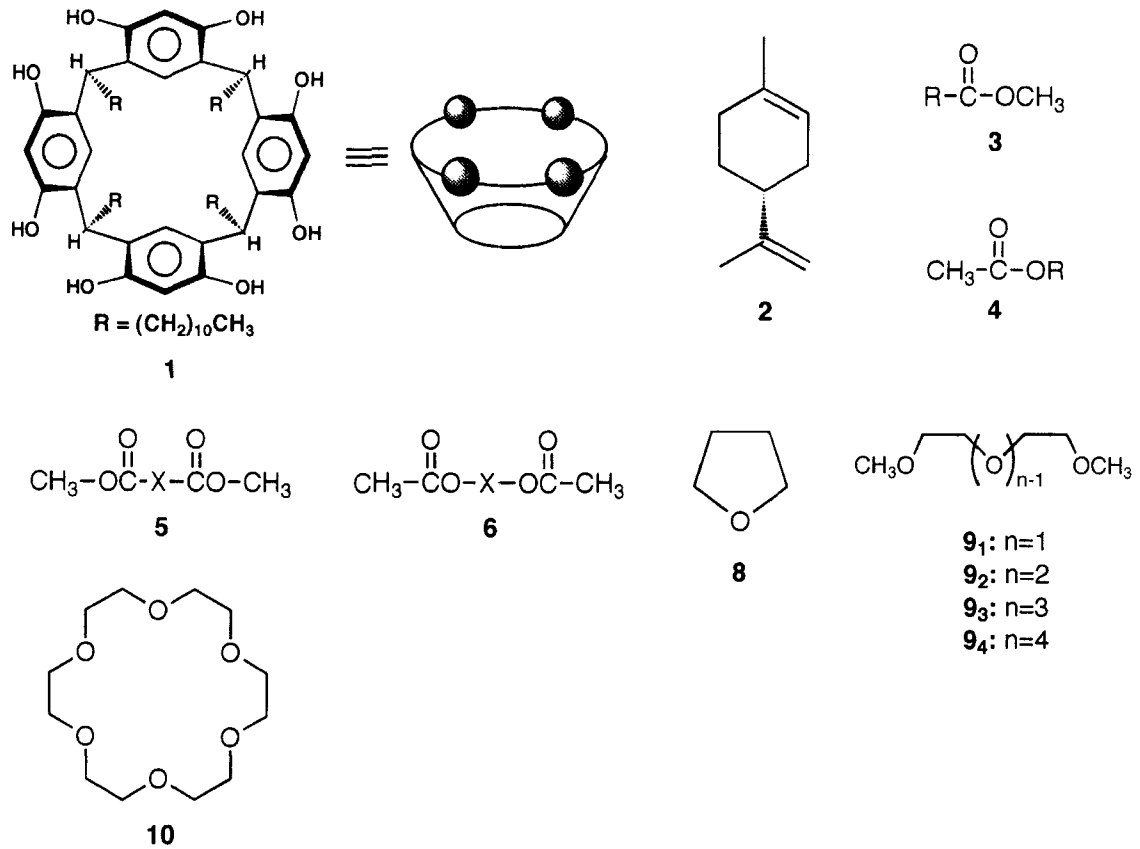
RESULTS AND DISCUSSION

Complexation of Esters in Limonene As a Chiral Hydrocarbon Solvent

Limonene (**2**) is a terpenoid hydrocarbon. When dissolved in this solvent, host **1** (1 mM) exhibits CD with a positive Cotton effect at 303 nm, whose intensities become weaker in the presence of a monoester (methyl carboxylate (**3**) or alkyl acetate (**4**)) or diester (dimethyl



dicarboxylates (**5**) or diacetoxyalkane (**6**)), as typically shown in Figure 1 for hexyl acetate. In Figure 2 are shown the CD intensities (observed ellipticities) as plotted against [ester] for six representative esters, i.e., methyl hexanoate and hexyl acetate as monoesters, dimethyl succinate and 2,3-diacetoxybutane as short-chain diesters, and dimethyl glutarate and 1,4-diacetoxybutane as long-chain diesters. All the titration curves exhibit a saturation behavior. On the other hand, diesters are much more effective in lowering the CD intensities than monoesters. The concentrations of the esters ([ester]$_{1/2}$) which cause a 50% inhibition of the CD intensities are summarized in Tables I (monoesters) and II (diesters).

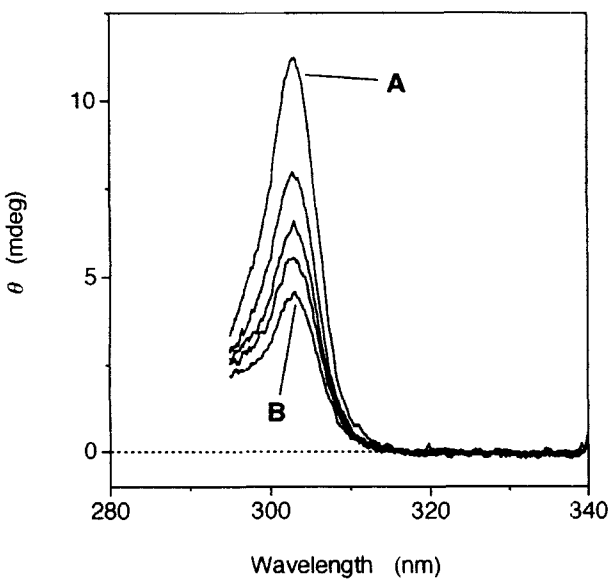


Figure 1. CD spectra for solutions of host **1** (1.0 mM) and varying amounts of hexyl acetate in limonene at 25 °C; [ester] = 0, 20, 40, 60, and 90 mM, read from A to B.

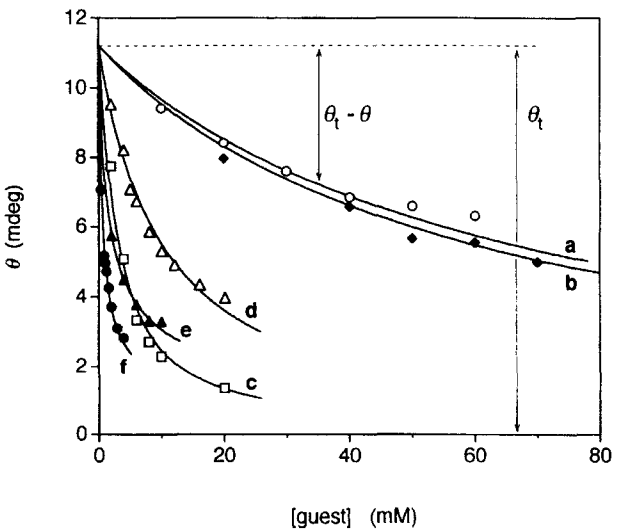


Figure 2. Correlation of observed ellipticities (θ) with [guest] at 25 °C for the complexation of host **1** (1.0 mM) with methyl hexanoate (a), hexyl acetate (b), dimethyl succinate (c), 2,3-diacetoxybutane (d), dimethyl glutarate (e), and 1,4-diacetoxybutane (f).

TABLE I Relative Inhibition Abilities ($[guest]_{1/2}$) and Binding Constants (K) for Complexes **1·3** and **1·4** in Limonene at 25°C

entry	R in **3**	$[guest]_{1/2}$ (mM)[a]	K (M^{-1})	entry	R in **4**	$[guest]_{1/2}$ (mM)[a]	K (M^{-1})
1	CH_3CH_2	390	2.6	10	$CH_3(CH_2)_2$	130	7.5
2	$CH_3(CH_2)_2$	190	5.2	11	$CH_3(CH_2)_3$	72	14
3	$(CH_3)_2CH$	170	6.0	12	$(CH_3)_2CHCH_2$	120	8.2
4	$CH_3(CH_2)_3$	77	13	13	$CH_3(CH_2)_4$	77	13
5	$(CH_3)_2CHCH_2$	140	7.3	14	$(CH_3)_3CCH_2$	110	8.8
6	$CH_3(CH_2)_4$	63	16	15	$CH_3(CH_2)_5$	56	18
7	$CH_3(CH_2)_5$	91	11	16	$CH_3(CH_2)_9$	180	5.7
8	$CH_3(CH_2)_8$	140	7.3	17	$CH_3(CH_2)_{17}$	420	2.4
9	$CH_3(CH_2)_{16}$	370	2.7				

a) Concentrations which cause a 50% inhibition of the CD intensity.

The appearance of CD is a consequence of chirality induction[2] in otherwise achiral host **1** upon interaction with a chiral solvent limonene. This host-solvent interaction, may it be in the form of chiral solvation or formation of a chiral complex, is subject to a competitive inhibition by more potential ester guests, as shown below.

Stoichiometries of Host-Ester Complexation

The host-guest stoichiometry can be conveniently obtained by continuous-variation (Job) plots. Figure 3 shows the observed ellipticities (θ) as plotted against mole fractions of the host (f_1) under conditions $[1]_t + [G]_t = 2$ mM (t = total and G is guest) for four diesters. If there were no host-guest complexation, we would expect ellipticities on the dashed line in Figure 3. The differences between observed and hypothetical ellipticities ($\Delta\theta$) then correspond to the formation of host-guest complexes. Continuous variation (Job) plots of $\Delta\theta$ vs f_1 are shown in Figure 4. For short-chain diesters (dimethyl succinate and 2,3-diacetoxybutane), a maximum occurs at $f_1 = 0.5$, indicating a 1:1 host-guest stoichiometry. Long-chain diesters (dimethyl glutarate and 1,4-diacetoxybutane), on the other hand, show a maximum at $f_1 = 0.67$. They thus form 2:1 (host to guest) complexes, whose structures will be discussed later.

Binding Constants

Full analysis of the present complexation requires a detailed knowledge about the **1**-solvent interaction. However, this is not a particular aspect of the present system. Homogeneous host-guest complexation always involves a competition between guest and solvent molecules for the binding site of the host. For the sake of simplicity, solvent molecules are usually not explicitly taken into account. Along this line, the present complexation may be expressed as in eq 1, where H* and HG are solvent-accompanied chiral host and an achiral host-guest complex, respectively. Such being the case, the binding constants can be exressed in terms of ellipticities in reference to Figure 2 (eq 2, t = total). When n = 1, rearrangement of eq 2 leads to a linear Benesi-Hildebrand relationship (eq 3) in a usual manner. For monoesters and short-chain diesters, the inhibition data, as shown in Figure 2, gave a consistent value of K when put in eq 2 (n = 1) and yielded an excellent straight line when treated according to the Benesi-Hildebrand type relation (eq 3) in every case.[6] For long-chain diesters, such plots of $1/(\theta_t - \theta)$ vs $1/[G]_t$ gave a significant curvature. The inhibition data for these guests were satisfactorily analyzed in terms of a 2:1 (host to guest) stoichiometry (eq 1, n = 2) and gave consistent results when treated according to eq 2 (n = 2). The stoichiometries (either 1:1 or 2:1) thus evaluated show a complete agreement with those independently determined from the Job plots. All the binding constants are summarized in Tables I and II. The solid lines in Figure 2 are calculated lines based on K's obtained.

$$n\mathrm{H}^* + \mathrm{G} \underset{\rightleftharpoons}{K} \mathrm{nH{\bullet}G} \tag{1}$$

$$K = \frac{[\mathrm{nH{\cdot}G}]}{[\mathrm{H}^*]^n[\mathrm{G}]} = \frac{\theta_t - \theta}{\theta^n[\mathrm{G}]_t} \tag{2}$$

TABLE II Relative Inhibition Abilities ($[guest]_{1/2}$) and Binding Constants (K) for Complexes **1·5** and **1·6** in Limonene at 25°C

entry	guest	$[guest]_{1/2}$ (mM)[a]	1:1 complex K (M^{-1})	2:1 complex K (M^{-2})
18	**5**; X = $-CH_2-$	4.2	2.7×10^2	
19	**5**; X = $-(CH_2)_2-$	3.1	3.8×10^2	
20	**5**; X = $-(CH_2)_3-$	2.3		5.0×10^5
21	**5**; X = $-(CH_2)_4-$	3.1		3.5×10^5
22	**5**; X = $-(CH_2)_8-$	19	5.5×10	
23	**6**; X = $-(CH_2)_2-$	2.7	4.5×10^2	
24	**6**; X = $-CH(CH_3)CH(CH_3)-$	9.6	1.1×10^2	
25	**6**; X = $-CH(CH_3)CH_2CH_2-$	3.4		3.2×10^5
26	**6**; X = $-(CH_2)_4-$	0.81		1.8×10^6
27	**6**; X = $-(CH_2)_5-$	3.6		3.0×10^5
28	**6**; X = $-(CH_2)_6-$	12		8.5×10^4

a) Concentrations which cause a 50% inhibition of the CD intensity.

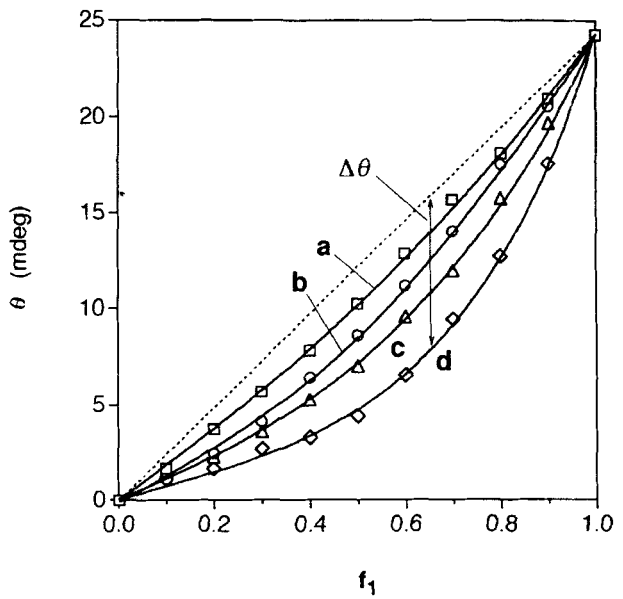


Figure 3. Correlations of observed ellipticities (θ) (solid lines) with mole fractions of host **1** (f_1) at 25 °C for the complexation of **1** and dimethyl succinate (a), 2,3-diacetoxybutane (b), dimethyl glutarate (c), or 1,4-diacetoxybutane (d) under conditions of $[\mathbf{1}]_t + [\text{guest}]_t = 2$ mM and hypothetical ellipticities (dashed line) in the absence of host-guest complexation.

$$\frac{1}{\theta_t - \theta} = \frac{1}{\theta_t}\frac{1}{K}\frac{1}{[G]_t} + \frac{1}{\theta_t} \qquad (3)$$

Selectivity

The binding constants of monoesters (Table I) are dependent on the alkyl groups. Those of methyl alkanecarboxylates (entries 1–9) increase with increasing chain-lengths up to hexanoate (entry 6). Further elongation of the alkyl groups results in reduction in K's. Alkyl acetates exhibit a similar chain-length dependence (entries 10–17), where maximum occurs at the hexyl ester (entry 15). We have previously demonstrated that there is a substantial contribution of the guest-host CH-π interaction to the formation of *hydrogen-bonded* complexes between alcoholic guests and host **1** in chloroform.[3] Such a binding mode must be true also in the complexation of esters. The hydrogen-bonding and the CH-π interactions may be balanced to give an optimal binding at around C_6. Figure 5 shows a CPK molecular model for the complex between host 1 and methyl hexanoate.

Short-chain diesters, either dimethyl dicarboxylates (entries 18 and 19 in Table II) or diacetoxyalkanes (23 and 24) form significantly stabler 1:1 complexes than the corresponding monoesters (Table I), in a similar manner as dicarboxylic acids[5] and diols[1] do so as compared with monoacids and monools. This is readily understandable on the basis of multiple host-guest hydrogen-bonding. The formation of 2:1 (host to guest) complexes from long-chain diesters (entries 20, 21, and 25–28) suggest that the two ester groups in the guest interact with different hosts. The stability in terms of $[\text{guest}]_{1/2}$ and cooperativity in such a ternary complex is far from evident and may be explained by assuming that the two host molecules bridged by a diester guest are hydrogen-bonded with each other, as schematically shown in structure **7** (dashed lines represent hydrogen bonds). This

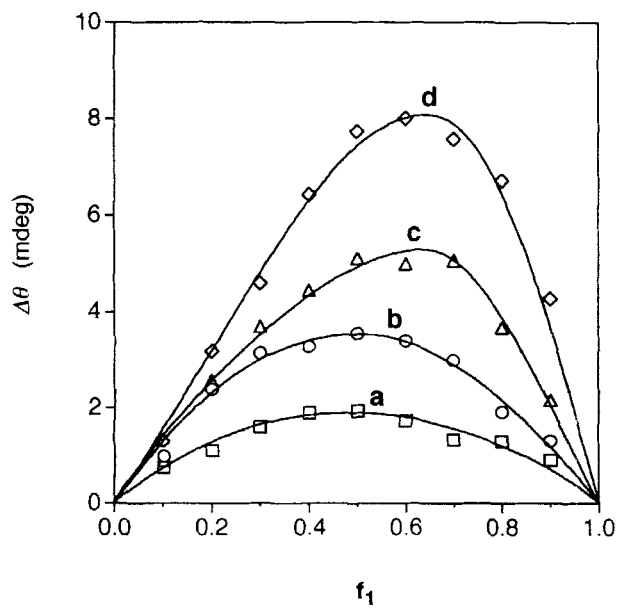


Figure 4. Job plots of Δθ vs f_1 for the complexation of **1** and dimethyl succinate (a), 2,3-diacetoxybutane (b), dimethyl glutarate (c), or 1,4-diacetoxybutane (d) under conditions of $[\mathbf{1}]_t + [\text{guest}]_t = 2$ mM.

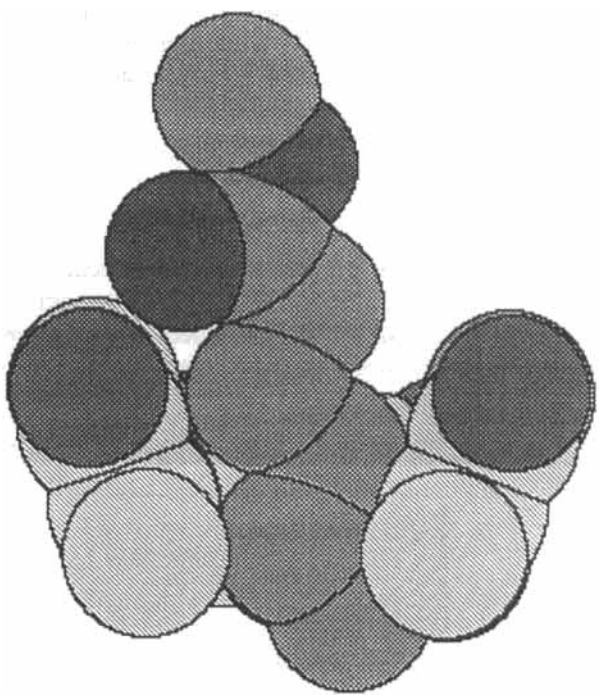
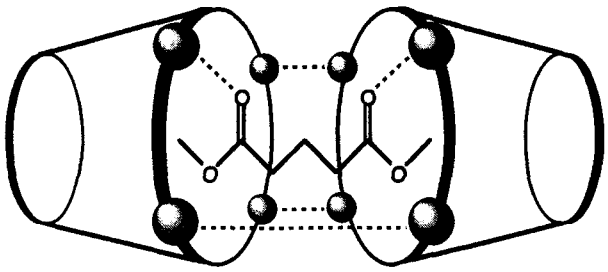


Figure 5. A CPK molecular model for complex **1**·(methyl hexanoate).



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interpretation may be supported by the failure of dimethyl sebacate (entry 22) to form a 2:1 complex. It only forms an apparently 1:1 complex, indicating that separation of the two ester groups in this guest is so long that they are practically independent of each other.

Complexation of Ethers

Ethers are another type of molecules which serve only as hydrogen-bond acceptors. The ethers investigated here are tetrahydrofuran (**8**; entry 29 in Table III) and ethyleneglycol dimethyl ether ($\mathbf{9}_1$, entry 30) together with its linear ($\mathbf{9}_{2-4}$, entries 31–33) and cyclic (**10**, entry 34) homologues (Chart I). Typical titration curves are shown in Figure 6. The effects of multifunctionality are dramatic here again. The efficiencies in terms of $[guest]_{1/2}$ in inhibiting CD intensities become more pronounced with respect to the polyether skeletons in **9** in the order $\mathbf{9}_1$ (ethylene glycol) < $\mathbf{9}_2$ (diethylene glycol) < $\mathbf{9}_3$ (triethylene glycol) < $\mathbf{9}_4$ (tetraethylene glycol) <18-crown-6 (**10**) (Table III).

Figure 7 shows the observed ellipticities under continuous-variation conditions for the complexation of $\mathbf{9}_2$, $\mathbf{9}_3$, and **10**. Figure 8 shows the Job plots derived therefrom. A maximum occurs at $f_1 = 0.67$ for dimer $\mathbf{9}_2$ or 0.75 for higher homologues $\mathbf{9}_3$ and **10**, indicating a 2:1 or 3:1 (host to guest) stoichiometry, respectively. These results suggest again that host molecules cluster around an oligoether guest in a highly cooperative manner as a result of intracomplex host-host hydrogen bonding. The titration data in Figure 5 were satisfactorily analyzed on the basis of eqs 1 and 2 with respective stoichiometries indicated above (n = 1, 2, or 3). The binding constants obtained are shown in Table III. The agreements between

TABLE III. Relative Inhibition Abilities ($[guest]_{1/2}$) and Binding Constants (K) for Complexes **1·8**, **1·9** and **1·10** in Limonene at 25°C

entry	guest	$[guest]_{1/2}$ (mM)[a]	1:1 complex K (M^{-1})	2:1 complex K (M^{-2})	3:1 complex K (M^{-3})
29	**8**	91	11		
30	$\mathbf{9}_1$	24	43		
31	$\mathbf{9}_2$	1.3		1.0×10^6	
32	$\mathbf{9}_3$	0.26			1.5×10^{10}
33	$\mathbf{9}_4$	0.20			4.3×10^{10}
34	**10**	<0.20			$>4.3\times10^{10}$

a) Concentrations which cause a 50% inhibition of the CD intensity.

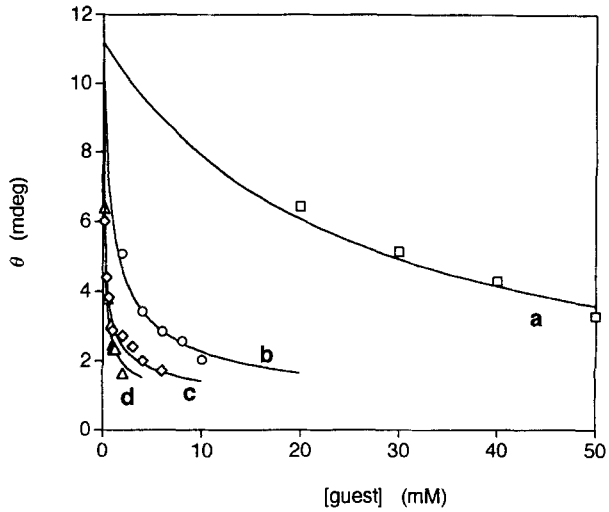

Figure 6. Correlations of observed ellipticities (θ) with [guest] at 25 °C for the complexation of host **1** (1.0 mM) with $\mathbf{9}_1$ (a), $\mathbf{9}_2$ (b), $\mathbf{9}_3$ (c), and $\mathbf{9}_4$ (d).

observed and calculated titration curves in Figure 5 are excellent again.

CONCLUSIONS

The present work may be summarized as follows: (1) The interaction of host **1** and a chiral hydrocarbon solvent limonene is enough to induce a chiral deformation of the multibenzenoid macrocyclic skeleton of the host. This results in induced CD. (2) The complexation

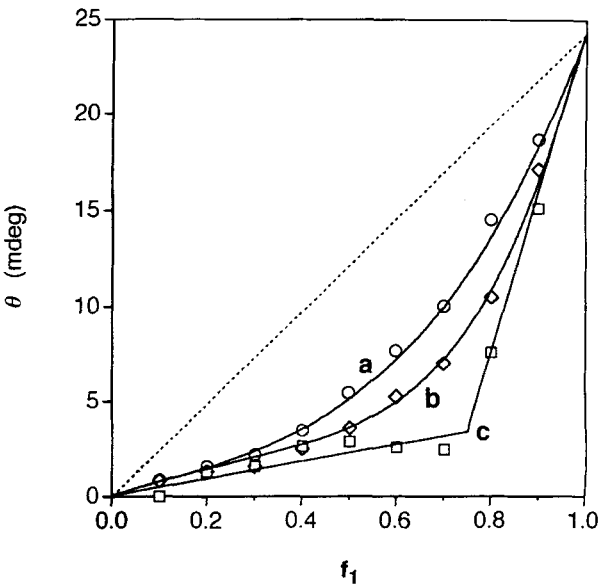

Figure 7. Correlations of observed ellipticities (θ) (solid lines) with mole fractions of host **1** (f_1) at 25 °C for the complexation of **1** and $\mathbf{9}_2$ (a), $\mathbf{9}_3$ (b), or **10** (c) under conditions of $[1]_t + [guest]_t = 2$ mM and hypothetical ellipticities (dashed line) in the absence of host-guest complexation.

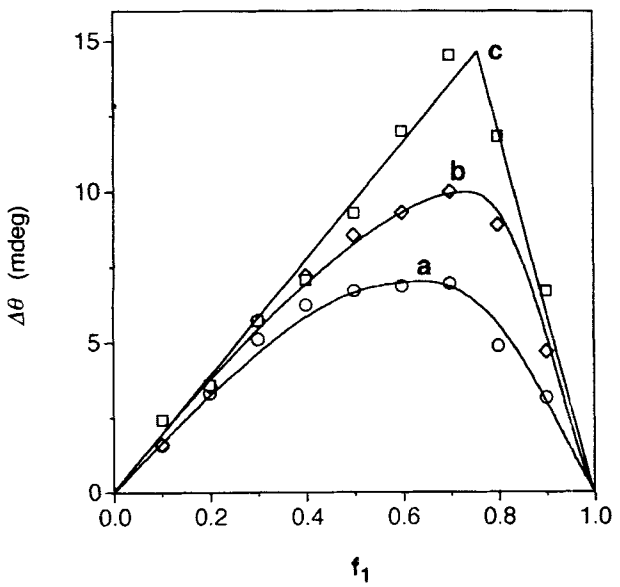

Figure 8. Job plots of $\Delta\theta$ vs f_1 for the complexation of **1** and $\mathbf{9}_2$ (a), $\mathbf{9}_3$ (b), or **10** (c) under conditions of $[\mathbf{1}]_t + [\text{guest}]_t = 2$ mM.

of esters and ethers can be monitored very conveniently by following their competitive inhibition effects on the CD intersities which reflect the host-solvent interaction. (3) The complexation of esters actually involves a cooperation of hydrogen-bonding and CH/π or van der Waals interactions between host and guest. Thus, there are significant selectivities arising from the alkyl moieties, especially their chain-lengths, of the guests. (4) Diesters form stabler complexes than monoesters, since the former allows multiple host-guest hydrogen-bonding. (5) Long-chain diesters having an appropriate chain length form 2:1 complexes, which are strongly suggested to be promoted by cooperative host-host hydrogen-bonding.[7] (6) Such a cooperativity is also pronounced in the complexation of oligoethers having an oxyethylene repetition unit. (7) The present method provides a unique opportunity to study host-guest hydrogen-bonding in a hydrocarbon solvent. Limonene is commercially available and readily dried. Chloroform as an extensively used NMR solvent is more polar and a trace amount of water, which is not readily removed, can make tremendous effects on host-guest hydrogen-bonding.

EXPERIMENTAL SECTION

Host **1** was prepared as described.[4] Commercially aviable limonene (**2**) was purified by column chromatography on silica gel to remove oxygenated impurities. CD spectra were obtained with a JASCO J-500C spectropolarimeter at 25 °C. The CD data were analyzed in a similar manner as reported.[2]

ACKNOWLEDGEMENT

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6 Strictly, θ_t in the right-hand side of eqs 2 and 3 should be $\theta_t - \theta_\infty$, where θ_∞ is the ellipticity at $[G]_t = \infty$. Benesi-Hildebrand analysis of the inhibition data indicated that $\theta_\infty \fallingdotseq 0$; complexes **1** ·guest are CD-inactive as expected.
7 Such a binding mode is also suggested for the formation of a 2:1 (host to guest) complex derived from methyl glucopyranoside as a guest: Kikuchi, Y.; Tanaka, Y.; Sutarto, S.; Kobayashi, K.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 10302.