CH-π Interaction as an Important Driving Force of Host–Guest Complexation. Further Evidence for the Selective Incorporation of Alkyl Groups in the Polyhydroxy Aromatic Cavity of Calix[4]resorcarene Host

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The complexation of a calix[4]resorcarene host (2,8,14,20-tetraundecylcalix[4]arene-4,6,10,12,16,18,22,24-octol) with borneol in benzene or alkylbenzene was investigated by circular dichroism (CD) spectroscopy. The binding constants are dramatically solvent-dependent and decrease with respect to the substituents on the benzene ring in the order H>methyl>ethyl>propyl>butyl. The complexation of the same host with alkyl benzoates in limonene as a chiral hydrocarbon solvent was readily monitored by following their competitive inhibition effects on the CD intensities, reflecting the chiral host-solvent interaction. The binding constants for alkyl benzoates were again highly dependent on the alkyl groups, and changed in the order decyl<hexyl<methyl<propyl≈pentyl≪butyl. There is thus an optimal chain length at butyl. These results provide further evidence for the selective incorporation of alkyl groups in the polyhydroxy aromatic cavity of the host.

We have recently demonstrated that the formation of hydrogen-bonded complexes between calix[4]resorcarene (2,8,14,20-tetraundecylcalix[4]arene-4,6,10,12,16,18,22,24-octol (**1**), Chart 1) and alcoholic guests in chloroform actually involves a substantial contribution of the CH-π interaction between the alkyl groups of the guest and the polyhydroxy aromatic cavity of the host.[1] The present work was concerned with the roles of the alkyl groups in aralkyl molecules. Circular dichroism spectroscopy[2] with inhibition techniques allowed us to characterize the interaction between host **1** and the alkyl groups in alkylbenzenes as solvents and those in alkyl benzoates as guests. We report here that the incorporation of alkyl groups in the cavity is dramatically dependent on the nature, especially the chainlengths, of the alkyl groups.

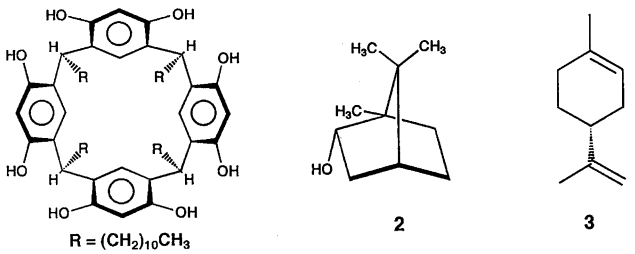

Chart 1.

Results and Discussion

Effects of Benzene and Alkylbenzene Solvents on the Complexation of (−)-Borneol. (−)-Borneol (**2**, Chart 1) is a typical monool whose complexation with host **1** in chloroform ($K = 54\ M^{-1}$ at 25 °C, 1 M = 1 mol dm^{-3}) can be studied by CD.[1] The borneol complex **1**·**2** in benzene or an alkylbenzene as a solvent exhibits a negative Cotton effect at 304 nm in a similar manner as in chloroform. In Fig. 1 are plotted the observed ellipticities (θ) as functions of [**2**] under conditions of [**1**] = 1.0 mM at 25 °C for two typical solvents, i.e., benzene and ethylbenzene. Figure 1 immediately suggests that the complexation is solvent-dependent. Otherwise, the titration curves exhibit a similar saturation behavior in all cases and are consistent with a 1 : 1 host–guest complexation. Benesi–Hildebrand treatment (Eq. 1) of the data gave an excellent straight line in every case, as shown in Fig. 2 for the complexation in ethylbenzene. In the following equation, $[\mathbf{1}]_t = 1.0$ mM and $[\mathbf{2}]_t$ (t = total) and l (0.1 cm) is the light path length:

$$\frac{[\mathbf{1}]_t l}{100\theta} = \frac{1}{K[\theta]}\frac{1}{[\mathbf{2}]_t} + \frac{1}{[\theta]} \quad (1)$$

The binding constants (K) and molar ellipticities ($[\theta]$) obtained from the slopes and intercepts are summarized in Table 1. As shown, the binding constants are dramatically dependent on otherwise closely related solvents. Host **1** and guest **2** form a more stable complex in benzene than in chlo-

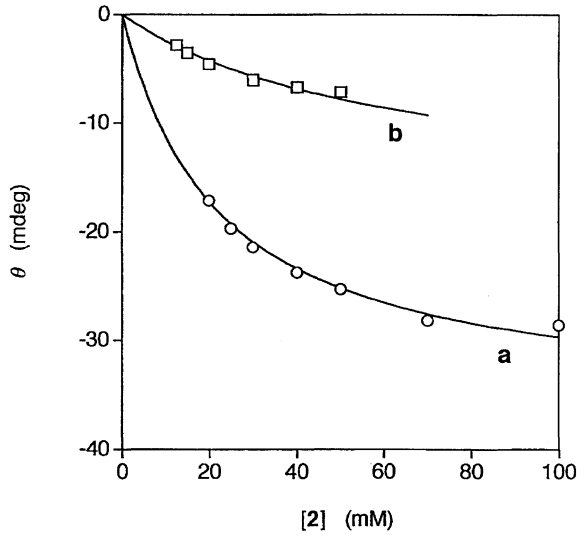

Fig. 1. Correlations of observed ellipticities (θ at 304 nm) with [**2**] at 25 °C for the complexation of host **1** (1.0 mM) and guest **2** in benzene (a), and ethylbenzene (b).

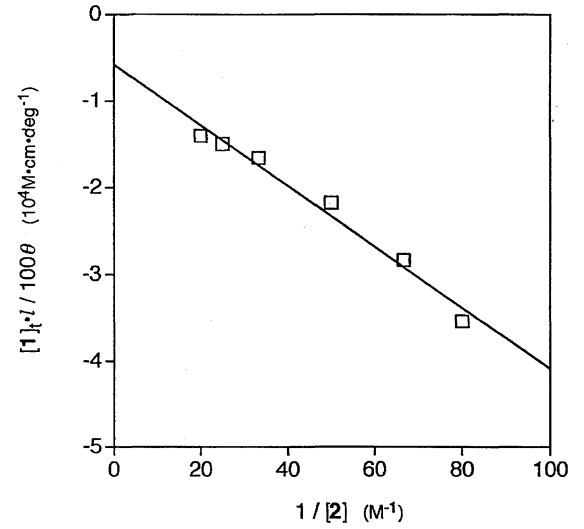

Fig. 2. Benesi–Hildebrand plots for the complexation of host **1** and guest **2** at 25 °C in ethylbenzene.

roform (Entries 0 and 1). Changing the solvent from benzene to toluene results in a significant reduction in K (Entry 2). In addition, the binding constants sharply decrease with increasing chainlengths of the alkyl groups in alkylbenzene solvents, from methyl through ethyl to propyl (Entries 2—4). In butylbenzene, the complexation has just been detected (Entry 6).

The complexation between host **1** and guest **2** in chloroform is based on both hydrogen bonding and CH-π interactions.[1] The former involves the OH groups of the host and guest and the latter the highly branched aliphatic moiety of the guest and the electron-rich aromatic cavity of the host. The relatively high binding constant observed (K=54 M^{-1}), as compared with those for simpler secondary alcohols, suggests that the CH-π interaction makes a larger contribution than does the hydrogen bonding in this particular case of guest **2**.[1] The complexation-promoting effect of benzene, itself, may be consistent with the view that hydrogen bonding is stronger in less-polar benzene (dielectric constant is ε=2.284) than in more-polar chloroform (ε=4.806). On the other hand, the inhibitory effects of alkylbenzenes compel us to assume that the alkyl groups compete with the aliphatic skeleton of guest **2** for the aromatic cavity of the host.[3] The more pronounced inhibitory effects of the longer alkyl chains would reflect the better cavity packing therewith. Figure 3 shows a CPK molecular model for the CH-π complex of host **1** with butylbenzene, where the resorcinol ring of the host in the front side is omitted for clarity. In marked contrast, branching in alkyl groups lowers the affinity thereof to the cavity. This is clearly shown by the less pronounced inhibitory effects of isopropyl-, isobutyl-, *s*-butyl-, and *t*-butylbenzene as compared with their open-chain analogs (Entries 5 and 7—9 vs. 4 and 6). The actual energetics of CH-π interaction would be subject to a delicate balance between high-efficiency cavity packing and unfavorable steric interactions. The latter seems to be the governing factor in the case of branched alkyl groups.

Table 1. Binding Constants (K) and Molar Ellipticities ([θ]) for Complex **1**·**2** in Various Solvents at 25 °C

Entry	Solvent	K/M^{-1}	[θ]/deg·M^{-1}·cm^{-1}
0	$CHCl_3$	54	-1.3×10^4
1	C_6H_5–H	240	-3.6×10^4
2	C_6H_5–CH_3	75	-1.5×10^4
3	C_6H_5–CH_2CH_3	17	-1.7×10^4
4	C_6H_5–$(CH_2)_2CH_3$	ca. 1	-9.1×10^5
5	C_6H_5–$CH(CH_3)_2$	110	-1.4×10^4
6	C_6H_5–$(CH_2)_3CH_3$	<1	—
7	C_6H_5–$CH_2CH(CH_3)_2$	7	-1.7×10^5
8	C_6H_5–$CH(CH_3)CH_2CH_3$	3	-3.9×10^4
9	C_6H_5–$C(CH_3)_3$	55	-2.8×10^4

Effects of Alkyl Benzoates on the Complexation of Limonene. Limonene (**3**, Chart 1) is a chiral terpenoid hydrocarbon. A limonene solution of host **1** exhibits a CD with a positive Cotton effect at 303 nm, which becomes weaker in the presence of an alkyl benzoate. When plotted against [al-

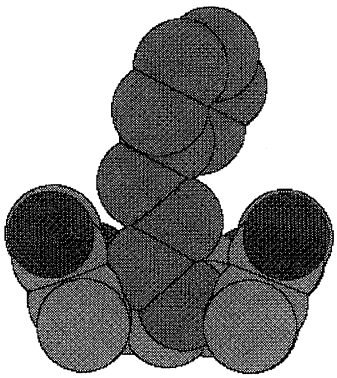

Fig. 3. A CPK molecular model for the CH-π complex of host **1** and butylbenzene. The resorcinol ring of the host in the front side is omitted for clarity.

kyl benzoate], the CD intensities (observed ellipticities, θ) decrease with a saturation behavior, as shown in Fig. 4 for methyl, butyl, and decyl benzoate. The appearance of CD is a consequence of chirality induction in an otherwise achiral host **1** upon an interaction with a chiral solvent limonene.[2] The interaction would be more appropriately viewed as a host-solvent complexation, rather than as a simple chiral solvation. There are a couple of reasons for this: (1) We have already demonstrated that some rigid hydrocarbons in fact form complexes with host **1**.[1] (2) The present host-solvent interaction is subject to a competitive inhibition by more potential guests, as shown below.

Stoichiometry. The host–guest stoichiometry can be conveniently obtained by continuous-variation (Job) plots. Figure 5 shows the observed ellipticities (θ), as plotted against mole fractions of the host (f_1) under the conditions $[\mathbf{1}]_t+[\text{guest}]_t=4$ mM (t=total) for butyl bezoate as a typical example. If there were no host–guest complexation, we would expect ellipticity on the dashed line in Fig. 5. The difference between the observed and expected ellipticities ($\Delta\theta$) corresponds to the formation of the host–guest complex. Continuous variation (Job) plots of $\Delta\theta$ vs. f_1 are shown in the inset of Fig. 5. In every case, the maximum occurs at $f_1=0.5$. This is consistent with a 1 : 1 host–guest stoichiometry.

Binding Constants. Eq. 2 shows the simplest equilibrium for the present complexation, where H, G, S* represent host **1**, and alkyl benzoate guest, and a chiral solvent limonene, respectively. Solvent molecules play an essential role. This is, however, not necessarily particular here. Host–guest complexation in homogeneous solutions always involves a competition between the solvent and guest molecules for the binding site of the host. In deriving the binding constants, however, solvent molecules are usually not taken into account for the sake of simplicity. Along this line, Eq. 2 may be simplified to Eq. 3, where H* and HG stand for the solvent-accompanied chiral host and an achiral host–guest complex, respectively. The binding constants are $K=[\text{HG}]/[\text{H}^*][\text{G}]\fallingdotseq([\text{H}^*]_t-[\text{H}^*])/[\text{H}^*][\text{G}]_t$ where $([\text{H}^*]_t-[\text{H}^*])$ and $[\text{H}^*]$ are proportional to $(\theta_t-\theta)$ and $(\theta-\theta_\infty)$, respectively, in reference to Fig. 4 (θ_∞ is the ellipticity at $[\text{G}]_t=\infty$). Rearrangement Results in a Benesi–Hildebrand Type Relation (Eq. 4). The inhibition data, such as that shown in Fig. 4, were satisfactorily analyzed according to Eq. 4. Polts of $1/(\theta_t-\theta)$ vs. $1/[\text{G}]_t$ gave an excellent straight line. From the slope and intercept were obtained θ_∞ and K. The former (θ_∞) turned out to be ca. 0 in every case, as expected. The binding constants (K) are summarized in Table 2. The solid lines in Fig. 4 are the calculated ones based the on the thus-obtained K's.

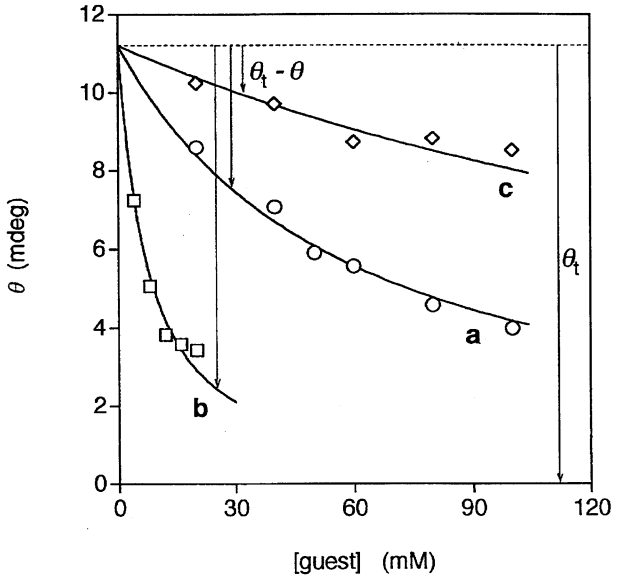

Fig. 4. Correlation of observed ellipticities (θ) with [guest] at 25 °C for the complexation of host **1** (1.0 mM) and methyl benzoate (a), butyl benzoate (b), or decyl benzoate (c) in limonene.

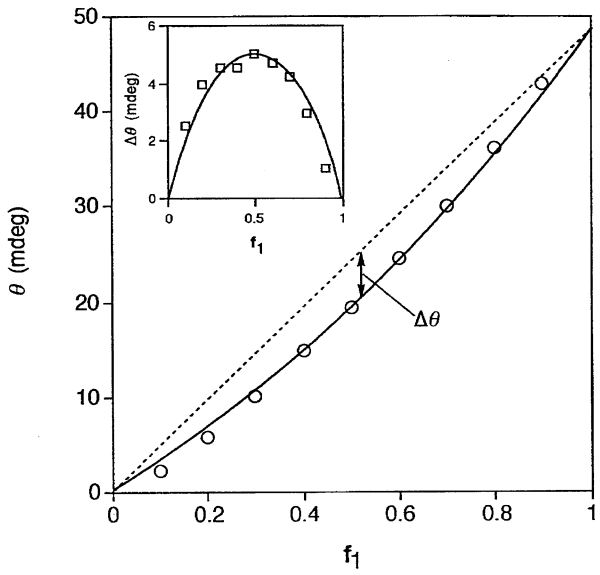

Fig. 5. Correlation of observed ellipticities (θ) (solid line) with mole fractions of host **1** (f_1) at 25 °C for the complexation of **1** and butyl benzoate under conditions of $[\mathbf{1}]_t+[$butylbenzoate$]_t=4$ mM and hypothetical ellipticities (dashed line) in the absence of host–guest complexation. Inset; Job plots of $\Delta\theta$ vs. f_1.

$$\text{H}\cdot n\text{S}^* + \text{G} \rightleftharpoons \text{H}\cdot\text{G} + n\text{S}^* \quad (2)$$

$$\text{H}^* + \text{G} \rightleftharpoons \text{H}\cdot\text{G} \quad (3)$$

$$\frac{1}{\theta_t-\theta} = \frac{1}{\theta_t-\theta_\infty}\frac{1}{K}\frac{1}{[\text{G}]_t} + \frac{1}{\theta_t-\theta_\infty} \quad (4)$$

An inspection of Table 2 reveals that the K's are again significantly dependent on the alkyl groups of the alkyl benzoates. The binding constants increase with increasing alkyl chainlengths up to C_4 (Entries 1, 2, and 4), as in the case of alkylbenzenes (Table 1, Entries 1—4 and 6). Interestingly, any further elongation of the alkyl groups in the alkyl benzoates lowers the affinities (Entries 7, 9, and 11). There is thus an optimal chainlength at C_4. The selectivity among C_3, C_4, and C_5 is remarkable (Entries 2, 4, and 7). Another factor

Table 2. Binding Constants (K) for Complexes **1**·(Alkyl Benzoate) in Limonene at 25 °C

Entry	R in $C_6H_5CO_2R$	K/M^{-1}
1	CH_3	17
2	$(CH_2)_2CH_3$	20
3	$CH(CH_3)_2$	87
4	$(CH_2)_3CH_3$	150
5	$CH_2CH(CH_3)_2$	44
6	$C(CH_3)_3$	11
7	$(CH_2)_4CH_3$	21
8	$CH_2C(CH_3)_3$	5
9	$(CH_2)_5CH_3$	11
10	$CH(CH_2)_5$ (cyclohexyl)	21
11	$(CH_2)_9CH_3$	4

of concern is alkyl branching. Isopropyl benzoate, for example, has a larger binding constant than does that of propyl benzoate (Entries 2 and 3). This is in marked contrast to the host-alkylbenzene interaction discussed above, where alkyl branching is affinity-lowering (Entries 4 and 5 in Table 1).

There is little doubt that the major driving force of the complexation of host **1** and an alkyl benzoate is host–guest hydrogen bonding, which is common for all of the esters. This may be why the effects of the alkyl chainlengths in the complexation of alkyl benzoates are not so dramatic as in the case of the **1**-alkylbenzene interaction. The incorporation of an alkyl group of an alkylbenzene in the cavity of host **1** is an intermolecular process. On the other hand, that of an alkyl group of an alkyl benzoate is essentially an intramolecular process for a hydrogen-bonded **1**-ester adduct.[4]

Concluding Remarks

The present work provides further evidence for the selective incorporation of alkyl groups in the aromatic cavity of host **1**. This incorporation may be simply viewed as being *cavity packing*, to which both an attractive CH-π[5] or van der Waals interaction and an unfavorable steric repulsion contribute, as in the case of crystal packing.[6] Further work should be directed to shed light on how these two opposing factors balance each other.

This work also unambiguously demonstrates that solvent participates in the host–guest complexation in apolar organic media. Chloroform is one of the most frequently used solvents in this area. We have to elucidate how inert or how potential this solvent is as a guest.

Inhibition techniques are not novel at all in studying host–guest complexation in solution. The choice of a chiral solvent, as described here, may be a new technique. This undoubtedly widens the scope and potentiality of the CD spectroscopy,[7] which can now be applied to complexations between an achiral host and a guest.

Experimental

Host **1** was prepared as described.[8] Commercially available limonene was purified by column chromatography on silica gel with hexane as an eluent in order to remove any oxygenated impurities. Alkyl benzoate of higher alcohols (pentanols, hexanols, and decanol) were prepared by the reaction of alcohols and benzoyl chloride in pyridine in yields of 80—90%, and purified by means of column chromatography. All other chemicals were commercial ones and of highest grade. The CD spectra were obtained with a JASCO J-500C spectropolarimeter at 25 °C. The obtained data were treated as in previous studies.[1,2]

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