Headline Articles

C–H···π Hydrogen Bonding between Electron-Rich Benzene Rings and Polarized C–H Bonds: Selectivity in the Complexation of Highly Hydrophilic Guest Molecules with Calix[4]resorcarene Hosts in Water

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Tetrasulfonate derivatives of calix[4]resorcarene (calix[4]arene derived from resorcinol) (**1**) form 1:1 complexes with highly hydrophilic guest molecules, such as ethers, alcohols, ketones, and sulfoxides, in water. The affinities of three types of the guests increase in the order CH_3–X–CH_3 < (–CH_2CH_2–X–)$_2$ < CH_3–X–CH_2CH_2–X–CH_3 (X=O, CH(OH), C=O, or S=O), reflecting the importance of multiple host-guest interactions. The binding constants (K) with respect to X increase in the order O<CH(OH)<C=O<S=O or CH(OH)<O<C=O<S=O. As for the effects of substituents Y on 2-C of the benzene rings of the host, both **1b** (Y=CH_3) and **1c** (Y=OH) exhibit higher binding capabilities than does the parent host **1a** (Y=H). Thus, the present complexation is promoted by electron-withdrawing residue (X) in the guests and electron-donating substituents (Y) in the host. The binding of CH_3–X–CH_3 (X=C=O or S=O) to hosts **1a**—**c** is characterized by favorable enthalpy changes and unfavorable entropy changes. These results, coupled with NMR data, indicate that the driving force of the present complexation is a C–H···π *interaction* between C–H bonds of a guest as soft acids and benzene rings of the host as soft bases.

Complexation of electrically neutral, but highly hydrophilic, molecules in water is an important, yet unexplored, area of molecular recognition.[1] Strategies based on hydrophobic forces and/or hydrogen-bonding interactions are of only limited uses here. On the other hand, van der Waals interactions generally play an important role in the binding of apolar guest molecules. Their significance, however, is often obscured by concurrent hydrophobic effects. The roles of polar functional groups in apolar van der Waals interactions is not well-understood, either.

We have recently shown that tetrasulfonate derivatives of calix[4]resorcarene (calix[4]arene derived from resorcinol) (**1**) bind polyols,[2a,2b] including sugars,[2a] nucleotides and nucleosides,[2b] amino acids,[2c] methylammonium salts,[2b] and aromatic compounds[2b] in water. Based on the effects of substituents in host **1**, we suggested the importance of the guest–host CH–π interaction.[2] Such an interaction was also claimed to make a substantial contribution to the formation of hydrogen-bonded complexes between alcoholic guests and calix[4]resorcarene host in chloroform[3,4] as well as in the vapor phase.[5] Diederich and his associates reported that the complexation of their cyclophane hosts with aromatic guests in water is enthalpically driven.[6] Dougherty and his co-workers[7] and later Shinkai and his group[8] attributed the facile complexation of alkylammonium salts with their cyclophane and calixarene hosts to the cation–π interaction, which is also enthalpic in origin.[7g] Meanwhile, Collet and his associates reported on the formation of van der Waals complexes of the cryptophane hosts in apolar organic media.[9] Encapsulation of small guest molecules in the cavitand and carcerand hosts has been extensively studied by a group led by Cram[10] as well as by the Reinhoudt's group.[11] It is interesting to note that all of the host molecules mentioned above have electron-rich hydroxy-substituted aromatic rings in common; essential aspects of host–guest complexation may also be closely related to each other.

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The object of this work was to better characterize the CH–π interaction.[12] We investigated the complexation of host **1** with a series of otherwise closely related water-miscible guest molecules having different extents of C–H polarization. We report here that the present complexation is, in fact, driven by a CH–π interaction or C–H···π hydrogen bonding between electron-rich benzene rings of the host as soft bases and polarized C–H bonds of a guest as soft acids.

Results

2-Propanol, Acetone, and DMSO. Tetrasulfonate derivatives of calix[4]resorcarene **1a**—**c** form well-defined 1:1 complexes with 2-propanol (**2**), acetone (**3**), and dimethyl sulfoxide (DMSO, **4**) (Chart 1) in D_2O. The complexation was followed by ^1H NMR spectroscopy, as before,[2] i.e., by monitoring either the guest-induced downfield shifts of the aromatic 5-H of the host (2 mM, 1 M=1 mol dm^{-3}) or the host-induced upfield shifts of the methyl protons of the guest (2 mM), as typically shown for the complexation of host **1a** and guest **4** in Fig. 1. The 1:1 host–guest stoichiometry was confirmed by continuous-variation (Job) plots in the usual manner.

In Table 1 are summarized the binding constants at 298 K obtained by a Benesi–Hildebrand analysis[13] and the complexation-induced shifts (CIS, negative value indicates an upfield shift) of the methyl proton resonances of guests at saturation binding to host **1a** or **1c**. The binding constants increase in the order **1a**<**1c**<**1b** and **2**<**3**<**4** with respect to the hosts and guests, respectively. In spite of a big span in the K's (0.50—56.5 M^{-1}), the CIS's for the methyl groups of guest **2**, **3**, or **4** are rather constant at (1.9—2.4) ppm. This is especially so when host is **1c**.

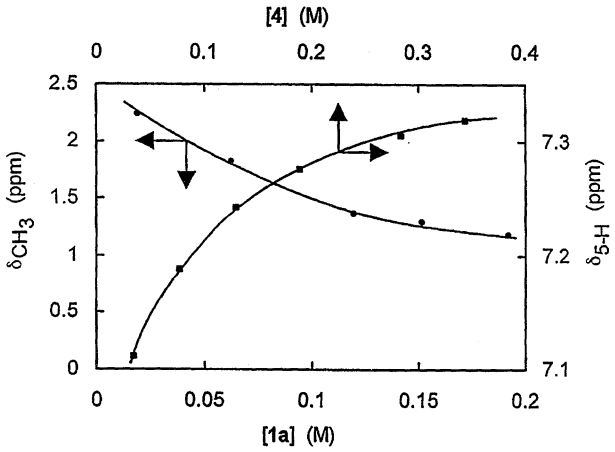


Fig. 1. Chemical shifts for aromatic 5-H of host **1a** (2 mM) as a function of [**4**] and those for methyl protons of guest **4** (2 mM) as a function of [**1a**] in D_2O at 298 K.

Thermodynamic Parameters and H/D Isotope Effects. The binding constants for guests **3** and **4** were determined at various temperatures over the range 278—338 K. The results are summarized in Table 2. Van't Hoff plots of $R\ln K$ vs. $1/T$ are approximately linear for host **1c**, but not for hosts **1a** and **1b** (Fig. 2), as is often the case for related complexation processes using cyclophane hosts. This is because of non-zero heat capacity changes, $\Delta C_p^\circ = \partial \Delta H^\circ / \partial T$.[6,7g,14] The relevant relations are shown in Eqs. 1, 2, 3, and 4. The combination of these equations leads to Eq. 5. The complexation enthalpy and entropy at 0 K (ΔH_0 and ΔS_0) and ΔC_p°

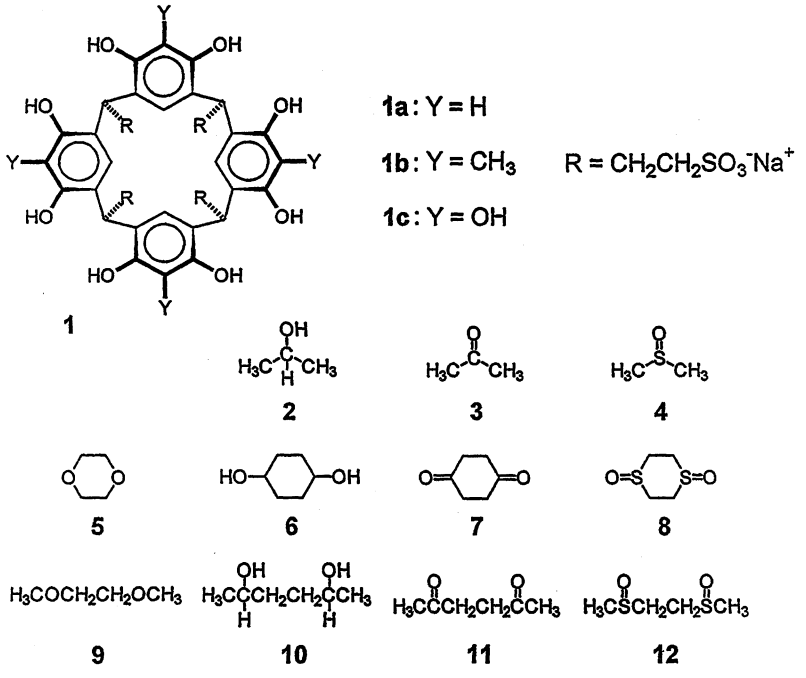


Chart 1.

Table 1. Binding Constants (K)[a] for Host–Guest Complexes in D_2O at 298 K and NMR Data, Hydrophobicities, Substituent Constants, Dipole Moments, Calculated Charges, and pK_a's for Guests and Dimethyl Ether

	Guest (CH_3–X–CH_3)			
	H_3COCH_3[b]	**2**	**3**	**4**
$K_{\mathbf{1a}}/M^{-1}$		0.50	4.40	12.4
CIS[c]/ppm		−2.39	−1.93	−2.02
$K_{\mathbf{1b}}/M^{-1}$		7.79	23.2	56.5
$K_{\mathbf{1c}}/M^{-1}$		7.33	14.7	49.0
CIS[d]/ppm		−2.28	−2.25	−2.26
log P[e]		0.00	−0.24	−2.03
σ_m[f] for X-CH_3	0.12	−0.07[m]	0.38	0.52
σ_I[g] for X-CH_3	0.25	−0.05[m]	0.28	0.52
σ_i[h] for X-CH_3	0.185	−0.045[m]	0.21	0.38
μ[i]/D	1.40	1.66	2.88	3.96
δ_H[j] for CH_3/ppm	3.30	1.13	2.07	2.49
δ_C[k] for CH_3/ppm	60.9	25.1	30.6	40.6
q[l]	0.062	0.045	0.049	0.055
pK_a for CH_3		42.0[n,o]	20.0[o]	31.3[o]

a) The accuracy of the binding constants (K) is within ±10% and never exceeds ±15% in every case. b) See Ref. 30. c) Complexation-induced ^{1}H NMR shifts for guests bound to host **1a**. d) Complexation-induced ^{1}H NMR shifts for guests bound to host **1c**. e) P is partition coefficient of guest between 1-octanol and water.[20] f) Hammett meta substituent constants.[21] g) Taft substituent constants.[22] h) Yukawa–Tsuno substituent constants.[23] i) Dipole moment.[24] j) ^{1}H NMR chemical shifts for guests in the absence of host. k) ^{13}C NMR chemical shifts for guests in the absence of host. l) Calculated partial positive charges on the methyl hydrogen atoms.[25] m) For substituent CH_2CH_3. n) For ethane. o) Ref. 49.

were obtained by nonlinear data fitting to Eq. 5. Then, the complexation enthalpy and entropy at ambient temperatures ($\Delta H°$ and $\Delta S°$) were obtained according to Eqs. 3 and 4. The numerical values at $\Delta H°$, $\Delta S°$, and $\Delta G° = \Delta H° - T\Delta S°$ are shown in Tables 3, 4, 5, 6, 7, and 8. Those at 298 K and the $\Delta C_p°$ values are listed in Table 9. Figures 3 and 4 show how $\Delta H°$, $-T\Delta S°$,

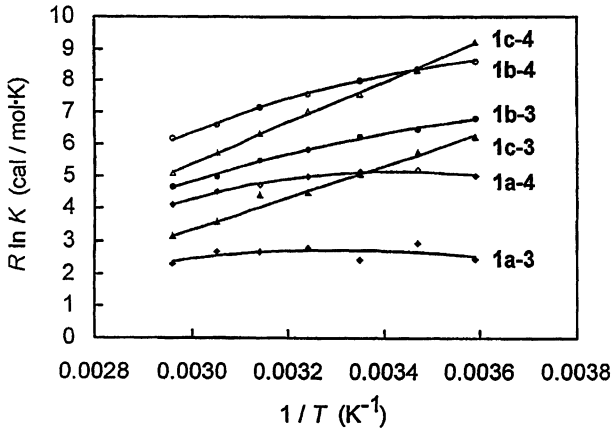


Fig. 2. Van't Hoff plots of $R \ln K$ vs. $1/T$ for the complexation of host **1a**, **1b**, or **1c** with guest **3** or **4** in D_2O. Solid lines are theoretical ones based on Eq. 1 using calculated $\Delta G°$ values.

and $\Delta G°$ change with T for the complexation of guests **3** and **4**, respectively, with hosts **1a**—**c**. The solid lines in Fig. 2 are theoretical ones based on Eq. 1 using the thus calculated $\Delta G°$ values. As in the case for related complexation phenomena,[6,7,15] $\Delta H°$ and $-T\Delta S°$ compensate with each other. Although both terms change with T significantly, the $\Delta G°$ values remain rather constant. There is, in fact, an excellent isoequilibrium relationship for $\Delta H°$ and $\Delta S°$, as shown in Fig. 5, which includes 42 sets of data for every combination of 3 hosts and 2 guests at 7 temperatures; $\Delta S° = 2.77\Delta H° + 3.75$ (correlation coefficient, 0.963).

$$\Delta G° = -RT \ln K \tag{1}$$

$$\Delta G° = \Delta H° - T\Delta S° \tag{2}$$

$$\Delta H° = \Delta H_0 + T\Delta C_p° \tag{3}$$

$$\Delta S° = \Delta S_0 + \Delta C_p° \ln T \tag{4}$$

$$R \ln K = -(\Delta H_0/T) + \Delta C_p° \ln T + (\Delta S_0 - \Delta C_p°) \tag{5}$$

Table 2. Binding Constants (K) for Host–Guest Complexes in D_2O at Various Temperatures[a]

T/K	Guest					
	3			**4**		
	$K_{\mathbf{1a}}/M^{-1}$	$K_{\mathbf{1b}}/M^{-1}$	$K_{\mathbf{1c}}/M^{-1}$	$K_{\mathbf{1a}}/M^{-1}$	$K_{\mathbf{1b}}/M^{-1}$	$K_{\mathbf{1c}}/M^{-1}$
278	3.46	30.8	23.1	12.5	77.0	104
288	4.42	26.1	18.1	13.7	68.0	65.7
298	4.40	23.2	14.7	12.4	56.5	49.0
308	4.05	18.8	9.59	12.2	45.7	34.4
318	3.87	15.8	7.50	10.8	37.0	24.1
328	3.84	12.4	6.10	9.74	27.7	17.9
338	3.22	10.5	4.89	7.87	22.4	12.9

a) The accuracy of the binding constants in within ±10% for most case and never exceeds ±15% in every case.

Table 3. Thermodynamic Parameters for the Complexation of Host **1a** with Guest **3** in D_2O

T	ΔH°	ΔS°	$-T\Delta S^\circ$	ΔG°
K	kcal mol^{-1}	cal mol^{-1} K^{-1}	kcal mol^{-1}	kcal mol^{-1}
278	1.38	7.51	−2.09	−0.71
288	0.81	5.49	−1.58	−0.77
298	0.24	3.54	−1.05	−0.82
308	−0.33	1.65	−0.51	−0.84
318	−0.91	−0.18	0.06	−0.85
328	−1.48	−1.95	0.64	−0.84
338	−2.05	−3.66	1.24	−0.81

Table 4. Thermodynamic Parameters for the Complexation of Host **1b** with Guest **3** in D_2O

T	ΔH°	ΔS°	$-T\Delta S^\circ$	ΔG°
K	kcal mol^{-1}	cal mol^{-1} K^{-1}	kcal mol^{-1}	kcal mol^{-1}
278	−2.04	−0.54	0.15	−1.89
288	−2.53	−2.25	0.65	−1.87
298	−3.01	−3.90	1.16	−1.85
308	−3.49	−5.49	1.69	−1.80
318	−3.98	−7.04	2.24	−1.74
328	−4.46	−8.53	2.80	−1.66
338	−4.94	−9.98	3.38	−1.57

Table 5. Thermodynamic Parameters for the Complexation of Host **1c** with Guest **3** in D_2O

T	ΔH°	ΔS°	$-T\Delta S^\circ$	ΔG°
K	kcal mol^{-1}	cal mol^{-1} K^{-1}	kcal mol^{-1}	kcal mol^{-1}
278	−5.13	−12.2	3.38	−1.75
288	−5.06	−11.9	3.43	−1.63
298	−4.99	−11.7	3.48	−1.51
308	−4.92	−11.4	3.52	−1.40
318	−4.84	−11.2	3.56	−1.28
328	−4.77	−11.0	3.56	−1.17
338	−4.70	−10.7	3.63	−1.06

Table 6. Thermodynamic Parameters for the Complexation of Host **1a** with Guest **4** in D_2O

T	ΔH°	ΔS°	$-T\Delta S^\circ$	ΔG°
K	kcal mol^{-1}	cal mol^{-1} K^{-1}	kcal mol^{-1}	kcal mol^{-1}
278	1.31	9.75	−2.71	−1.40
288	0.32	6.25	−1.80	−1.48
298	−0.68	2.86	−0.85	−1.52
308	−1.67	−0.42	0.13	−1.54
318	−2.66	−3.59	1.14	−1.52
328	−3.66	−6.67	2.19	−1.47
338	−4.65	−9.65	3.26	−1.39

Table 7. Thermodynamic Parameters for the Complexation of Host **1b** with Guest **4** in D_2O

T	ΔH°	ΔS°	$-T\Delta S^\circ$	ΔG°
K	kcal mol^{-1}	cal mol^{-1} K^{-1}	kcal mol^{-1}	kcal mol^{-1}
278	−2.00	1.47	−0.41	−2.41
288	−2.69	−0.97	0.28	−2.41
298	−3.38	−3.32	0.99	−2.39
308	−4.07	−5.60	1.73	−2.34
318	−4.76	−7.81	2.48	−2.28
328	−5.45	−9.94	3.26	−2.19
338	−6.14	−12.0	4.06	−2.08

Table 8. Thermodynamic Parameters for the Complexation of Host **1c** with Guest **4** in D_2O

T	ΔH°	ΔS°	$-T\Delta S^\circ$	ΔG°
K	kcal mol^{-1}	cal mol^{-1} K^{-1}	kcal mol^{-1}	kcal mol^{-1}
278	−6.32	−13.5	3.77	−2.55
288	−6.34	−13.6	3.92	−2.41
298	−6.35	−13.6	4.07	−2.28
308	−6.36	−13.7	4.22	−2.15
318	−6.38	−13.7	4.37	−2.01
328	−6.39	−13.8	4.52	−1.87
338	−6.41	−13.8	4.67	−1.73

An inspection of Figs. 3 and 4 reveals that the present host–guest complexation is driven by favorable (negative) enthalpy changes, while the entropy changes are unfavorable (negative), except for the weakest binder **1a** at lower temperatures. This feature for hosts **1a** and **1b** is more pronounced at higher temperatures, since the heat capacities (ΔC_p°) are negative (Table 9) in reference to Eqs. 3 and 4. More impor-

Table 9. Binding Constants (K)[a] and Thermodynamic Parameters at 298 K and Heat Capacity Changes (ΔC_p°) for Host–Guest Complexation in D_2O

Guest	Host	K_{298}	ΔH°_{298}	ΔS°_{298}	$-T\Delta S^\circ_{298}$	ΔG°_{298}	ΔC_p°
		M^{-1}	kcal mol^{-1}	cal mol^{-1} K^{-1}	kcal mol^{-1}	kcal mol^{-1}	cal mol^{-1} K^{-1}
	1a	4.40	0.24	3.54	−1.05	−0.82	−57.2
3	**1b**	23.2	−3.01	−3.90	1.16	−1.85	−48.4
	1c	14.7	−4.99	−11.7	3.48	−1.51	7.30
	1a	12.4	−0.68	2.86	−0.85	−1.52	−101
4	**1b**	56.5	−3.38	−3.32	0.99	−2.39	−69.1
	1c	49.0	−6.35	−13.6	4.07	−2.28	−1.40

a) The accuracy of the binding constants is within ±10% for most case and never exceeds ±15% in every case.

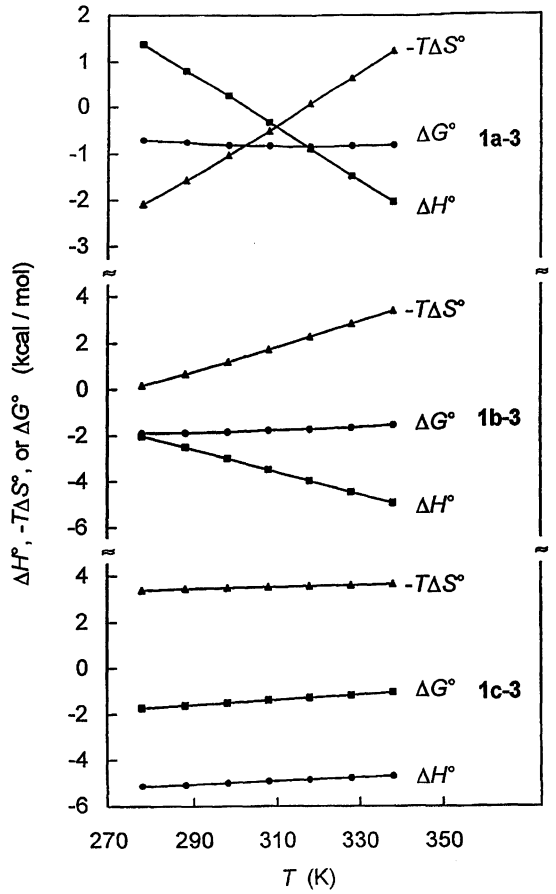


Fig. 3. Thermodynamic parameters ($\Delta H°$, $-T\Delta S°$, and $\Delta G°$) as functions of temperatures for the complexation of host **1a**, **1b**, or **1c** with guest **3** in D_2O.

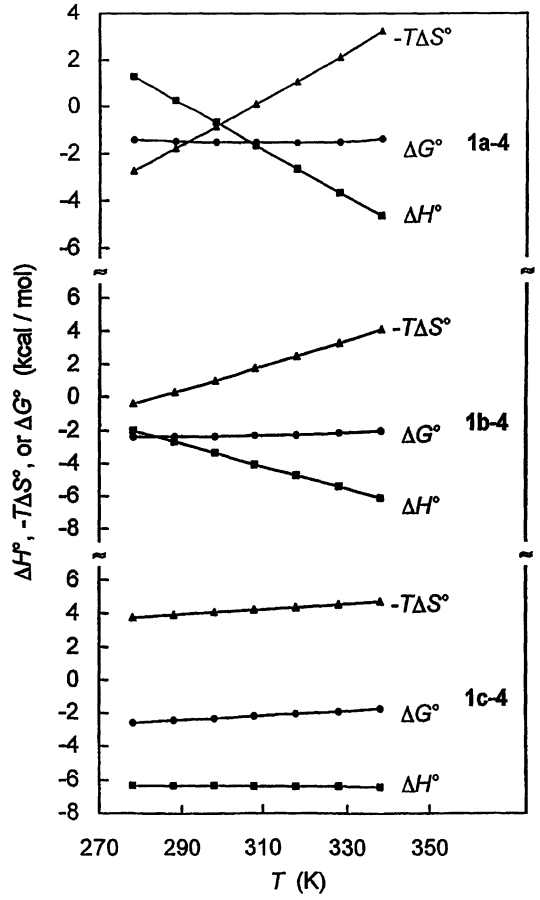


Fig. 4. Thermodynamic parameters ($\Delta H°$, $-T\Delta S°$, and $\Delta G°$) as functions of temperatures for the complexation of host **1a**, **1b**, or **1c** with guest **4** in D_2O.

tantly, the enthalpic driving force of the complexation becomes more pronounced in the order **3**<**4** for any host and **1a**<**1b**<**1c** for each guest (Table 9). Negative heat capacity changes are common for molecular association processes,[6,7g] including biological phenomena[16] in aqueous media. The magnitudes found for hosts **1a** and **1b** are within a typical range.[6,7g] As for the guests, DMSO (**4**) has larger negative $\Delta C_p°$ than dose acetone (**3**). This may be interpreted in terms of a higher hydration of the former (dipole moment, 3.96 D, 1 D=3.335×10^{-30} C m), as compared with the latter (2.88 D). As for the hosts, the magnitudes of $|\Delta C_p°|$ decrease in the order **1a**>**1b**>**1c** for reason(s) which are not clear at present.

The complexation of perdeuterated derivatives of guests **3** and **4** with hosts **1a** and **1c** was readily monitored. The binding constants of **3**-d_6 and **4**-d_6 together with those of perprotiated **3** and **4** are shown in Table 10. There are small, but distinct, H/D isotope effect of $K_H/K_D\simeq1.1$, which remain rather constant with changes in the hosts and guests.

Cyclic and Acyclic Diethers, Diols, Diketones, and Disufoxides. Hosts **1a** and **1c** also form 1:1 complexes with 1,4-cyclohexanediol (**6**, cis/trans≃1), 1,

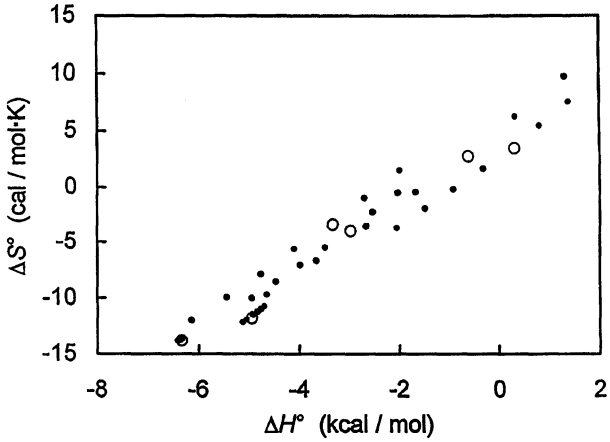


Fig. 5. Isoequilibrium relationship for $\Delta H°$ and $\Delta S°$ of the complexation of host **1a**, **1b**, or **1c** with guest **3** or **4** at various temperatures in D_2O. Six open circles represent the values at 298 K, referring to the data in Table 9.

4-cyclohexanedione (**7**), 1,4-dithiane 1,4-dioxide (**8**, as an essentially pure stereoisomer),[17] 2,5-hexanediol (**10**, *dl*/*meso*≃1), 2,5-hexanedione (**11**), and 1,2-bis(methylsulfonyl) ethane (**12**, *dl*/*meso* or *meso*/*dl*≃7 : 3)[17] (Chart 1).[18] Continuous-variation (Job) plots for the

Table 10. Binding Constants (K)[a] for Host–Guest Complexes in D_2O at 298 K and ^1H NMR Data for Guests

Guest	Host									
	1a				**1c**					
			CIS/ppm				CIS/ppm		δ_H[b]/ppm	
	K_{1a}/M^{-1}	K_H/K_D	CH_3	CH_2	K_{1c}/M^{-1}	K_H/K_D	CH_3	CH_2	CH_3	CH_2
3	4.40		−1.89		14.7±0.4		−2.25		2.07	
3-d_6					13.6±0.2	1.08				
4	12.4±0.6		−2.02		49.0±1.6		−2.26		2.49	
4-d_6	11.5±0.3	1.08			43.7±1.3	1.12				
5	3.50			−1.46	17.3			−1.68		3.79
6	7.26				38.0					
7	10.7			−1.67	40.0			−1.86		2.72
8	33.9			−1.58	142			−1.91		3.55, 3.21
9	18.2		−1.11	−2.01	49.9		−1.20	−2.26	3.41	3.65
10	4.27				11.3				1.21	1.54
11	70.0		−0.99	−2.28	140		−1.03	−2.46	2.26	2.85
12	87.1		c)	c)	273		c)	c)	2.83	3.32

a) The accuracy of the binding constants for guests **5**—**12** is within ±10% for most case and never exceeds ±15% in every case. b) ^1H NMR chemical shifts for guests in the absence of host. c) CIS's for a 1 : 1 complex for disulfoxide **12** could not be obtained. See Ref. 19.

complexation of host **1a** with guest **11**, as an example, are shown in Fig. 6.[19] Diols **6** and **10**, diketones **7** and **11**, and disulfoxides **8** and **12** may be regarded as being cyclic and acyclic dimers of alcohol **2**, ketone **3**, and sulfoxide **4**. The binding constants for guest **6**—**8** and **10**—**12** together with those for diethers dioxane (**5**) and ethylene glycol dimethyl ether (**9**) are shown in Table 10. The binding affinities increase upon going from host **1a** to **1c** again for any guest, and also on going, except for diols **6** and **10**, from cyclic dimers **5**, **7**, and **8** [$(-CH_2CH_2-X)_2$; X=O, CH(OH), C=O, and S=O] to the corresponding acyclic dimers **9**, **11**, and **12** ($CH_3-X-CH_2CH_2-X-CH_3$) for each host. The binding constants K with respect to residue (X) increase in the order either O<CH(OH)<C=O<S=O, i.e., **5**<**6**<**7**<**8** or CH(OH)<O<C=O<S=O, i.e., **10**<**9**<**11**<**12**.

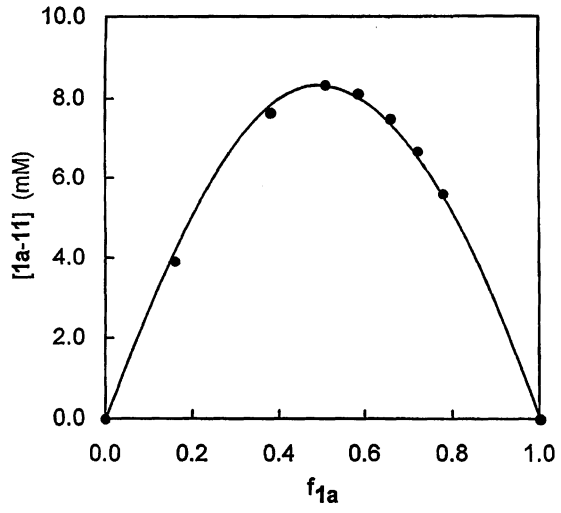


Fig. 6. Continuous variation plots of [**1a**—**11**] vs. mole fraction of **1a** (f_{1a}) for the complexation of host **1a** with guest **11** in D_2O at 298 K under conditions where [**1a**]+[**11**] is maintained at 40 mM.

Complexes derived from guests **5**, **7**, **8**, **9**, and **11** exhibited a single ^1H NMR resonance for the methyl and/or methylene protons. The CIS values are shown in Table 10.

Discussion

CH–π Interaction between Electron-Rich Benzene Rings and Polarized C–H Bonds. All of the guest molecules investigated here are highly hydrophilic; they are miscible with water at any ratio. The hydrophobicity of a compound can be conveniently expressed by its partition coefficient (P, Table 1) between an appropriate organic solvent, such as 1-octanol, and water.[20] Based on this criterion, guests **2**, **3**, and **4** become less hydrophobic in this order, while the K's increase in the same order (Table 1). This is taken as evidence that the hydrophobic effect is not an important factor here for the guests. This is also true for the hosts. Both hosts **1b** (Y=CH_3 which is highly hydrophobic and moderately electron-donating) and **1c** (Y=OH which is highly hydrophilic and highly electron-donating) exhibit enhanced guest-binding capabilities as compared with parent host **1a** (Y=H). The observed substituent effects may be most reasonably explained in terms of an electronic effect, rather than a hydrophobic effect; electron-donating substituents (Y=CH_3 and OH) increase the π-electron density or π-basicity of the benzene rings, and this, in turn, facilitates guest-binding.

The increasing K's in the order **2**<**3**<**4** can be correlated with the electron-withdrawing inductive effects of residue X (O, CH(OH), C=O, or S=O), as expressed by the Hammett-type substituent constants (σ_m (Hammett),[21] σ_I (Taft),[22] or σ_i (Yukawa–Tsuno)[23])

for substituents X–CH_3 (Table 1). This table also shows the dipole moments (μ)[24] of the guests and the ^1H and ^{13}C NMR chemical shifts for the methyl groups of the guests in the absence of host **1** (δ_H and δ_C). The dipole moments reflect the dipolar character of residue X (CH(OH), C=O, or S=O), and increase in the order **2**<**3**<**4**. The chemical shifts provide a direct measure of the electron deficiency of the C–H moieties, which become more pronounced (downfield shifted) in the same order. The calculated positive changes (q)[25] on the terminal H atoms also follow the same order (Table 1). These results demonstrate that the primary driving force of the present complexation is a CH–π *interaction* between electron-rich benzene rings of the host and electron-deficient or polarized C–H bonds of a guest.[26] The requisite CH–π proximity is independently evidenced by the large CIS's for the guest proton resonances in the upfield direction as a result of ring-current effects of the host benzene rings (Table 1).[27]

Thermodynamic Characterization of the CH–π Interaction and Hydrophobic Contribution Hydrophobic association, as in micelle formation, is based on the structuring of solvent water molecules, and is thermodynamically characterized by a favorable entropy change ($\Delta S^\circ > 0$ and $\Delta H^\circ \simeq 0$).[28,29] Except for host **1a** at lower temperatures, this is not the case; the complexation is driven by favorable enthalpy changes accompanied by unfavorable entropy changes as the result of enthalpy–entropy compensation (Fig. 5). The enthalpy changes become more negative (more favorable) upon going from guest **3** to **4**, and also with respect to the hosts in the order **1a**<**1b**<**1c**, while K or $-\Delta G^\circ$ increases in the order **1a**<**1c**<**1b** (Table 9). These results indicate that (1) the host–guest *interaction*, in fact, promotes their association to give tight complexes and (2) the strength of this interaction can be correlated with the C–H acidities of the guests and electron-donating abilities of the substituents Y in the hosts; the Hammett σ_p values for H, CH_3, and OH are 0, −0.17, and −0.37, respectively. An apparent electrostatic or charge-transfer interaction, found for cyclophane-arene[6] and cyclophane-cation[7] complexations, is also evident in the present case of complexation between cyclophane **1** and substituted alkanes. Host **1a** binds guest **3** and, to a lesser extent, also **4** due to favorable entropy changes at lower temperatures (Table 9). The stronger guest-binding to host **1b** than to **1c** is not of an enthalpic, but of an entropic, origin (Table 9). These can be taken as a good sign of hydrophobic contribution in the case of hydrophobic hosts **1a** and **1b**.

Modest Affinities of Ethers: Unsuccessful Correlation with Electron Densities of the C–H Bonds. The ether oxygen residue, when free from resonance effect, is moderately electron-withdrawing by an inductive effect, as judged by the σ_m, σ_I, and σ_i values for the OCH_3 group (Table 1).[30] The NMR data (δ_H and δ_C in Tables 1 and 10) show that the oxy residue in ethers is highly effective in lowering the electron density of the adjacent C–H bonds; δ_H and δ_C are shifted farthest downfield. What effect does an ether moiety have on the acidity (pK_a) of adjacent C–H bonds? We could so far never encounter any information in the literature describing pK_a's for ethers. The oxy-substituted carbanion may be either stabilized by an electron-withdrawing effect of oxygen, or destabilized due to a repulsion between a pair of electrons on carbon and lone-pair electrons on oxygen. Ethers, such as diethyl ether and tetrahydrofuran, are frequently used as solvents for reactions involving organometallic species, such as Grignard reagents and alkyllithiums. This indicates that proton transfer from ether to an unstabilized carbanion is slow (reaction 6). From a kinetic point of view, ethers may be weaker acids, even than hydrocarbons.

$$-\text{O}-\text{C}-\text{H} + -\text{C}^- \xrightarrow{\text{slow}} -\text{O}-\text{C}^- + -\text{C}-\text{H} \qquad (6)$$

Thus, the effects of residue X (O, CH(OH), C=O, or S=O), on the *acidities* of adjacent C–H bonds on three criteria are not consistent with each other. Substituent constants (σ_m, σ_I, or σ_i) as a measure of the electron-withdrawing ability increase in the order CH(OH)<O<C=O<S=O. NMR chemical shifts (δ_H or δ_C) as a measure of the electron deficiency or partial positive charge of the C–H bonds follow the order CH(OH)<C=O<S=O<O. On the other hand, thermodynamic acid dissociation constants (K_a) for the C–H bonds may increase (with decreasing pK_a) in the order O<CH(OH)<S=O (Table 1).[31]

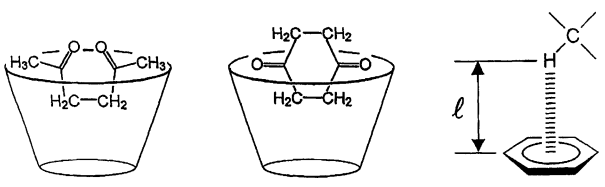
The binding constants shown in Table 10 increase in the order **5**<**6**<**7**<**8** and **10**<**9**<**11**<**12**, i.e., with respect to residue (X) in the order O<CH(OH)<C=O<S=O or CH(OH)<O<C=O<S=O, respectively. The order of residues CH(OH), C=O, and S=O is the same as that for the monofunctional series CH_3–X–CH_3 (**2**—**4**). Although the order of O and CH(OH) is reversed for the cyclic and acyclic series, there is no doubt that ethers show only modest affinities. The binding constants are thus best correlated with substituent constants (σ_m, σ_I or σ_i) and possibly with pK_a when ketonic guests are excluded,[31] but not with NMR chemical shifts (δ_H and δ_C). We paid particular attention to the effect of the oxy functionality which characterizes polyols and related compounds. The present finding is rather disappointing in this regard. Sugars, for example, have many C–H bonds which are apparently highly polarized by an adjacent OH group. They may, however, only poorly be bound to hydroxy-substituted aromatic hosts via CH–π interactions.

Significance of Multiple CH–π Interaction. When compared among guests having the same residue X (O, CH(OH), C=O, or S=O), the binding constants increase in the order (**2**—**4**)<(**5**—**8**)<(**9**—**12**), except for diols **6** and **10** (Tables 1 and 10). This order demon-

strates the importance of the multiple CH–π interaction. The two equivalent CH_2 moieties of acyclic bifunctional guests **9** and **11** exhibit larger CIS's (2.0—2.5 ppm) than do the two equivalent CH_3 groups, whose CIS's are still significantly large (1.0—1.2 ppm) (Table 10). The complexation geometry consistent with these results is schematically shown in structure **13** (Chart 2) for diketone guest **11**. In this way, all 10 protons can be in contact with the aromatic rings of the host. This is, however, not the case for cyclic and hence rigid bifunctional guests **5**—**8**. When two adjacent CH_2 moieties are deeply bound, the remaining two CH_2 groups are forced to stay away from the cavity, as shown in structure **14** (Chart 2). Actually, bound guests **5**—**8** must be rapidly turning round to give an averaged CIS (1.4—1.9 ppm) for the four equivalent CH_2 groups.

Characterization of the CH–π Interaction As C–H···π Hydrogen Bonding. There seems to be no good reason why the present CH–π interaction should not belong to a kind of polar interaction.[32] The present interaction, however, is not a simple charge effect or a dipole interaction, since there is no correlation between the binding constants and the partial positive charges on the C–H moieties. Another fundamental question is why guest–host OH–π[33] (in the case of alcoholic guests **2**, **6**, and **10**) and CH–O interactions[34] are not important in the present case,[35] even though the O–H group is a stronger acid than C–H and an oxygen base is stronger than a π-system. These may be explained in terms of hardness/softness of acids and bases.[36] Charge or dipole characterizes hard acids and hard bases. They interact with each other as in usual Z–H···Z hydrogen bonding (Z=O or N) in apolar organic media. Otherwise, they are stabilized via an interaction with highly dielectric and dipolar solvent water, which is a hard acid as well as a hard base. Consequently, charge–charge, charge–dipole, and dipole–dipole interactions are not effective in water, as is well-known.

Aromatic rings having conjugated π-electrons are softer bases than the conventional nitrogen and oxygen bases having lone-pair electrons. On the other hand, C–H moieties are softer acids than H^+ and $Z\text{–}H^{\delta+}$ (Z=O or N). What is characteristic about soft acids and soft bases is not the intrinsic charge, but the polarizability.[37] The present CH–π interaction may be viewed as being a polarization-induced dipole interaction, possibly of a charge-transfer character,[38] between a soft acid and a soft base. In contrast to the charge densities as a ground-state property, Hammett-type substituent constants and pK_a's refer to how developing charges are either stabilized or destabilized. In this regard, a better correlation of the binding constants (K) with σ_m, σ_I, or σ_i is consistent with the present mechanism involving the polarization of soft acid and soft base. Dynamic polarization is also consistent with the isotope effects $K_H/K_D \simeq 1.1$ (Table 10) observed for guests **3** and **4**. It is known that the polarizabilities of deuterated derivative are slightly larger than those of the corresponding nondeuterated compounds.[39]



13 14 15

Chart 2. Structure **13**—**15**.

It is interesting here to note the CIS data for the methyl groups of guests **2**—**4**. They are roughly constant at (1.9—2.4) ppm, irrespective of the hosts (**1a** or **1c**) and guests (Table 1). This is especially so in the case of the stronger binder **1c**. At first glance, this is surprising in view of a big span of the binding constants (0.50—49.0 M^{-1}). The methylene protons in guests **5**, **7**, and **8** and the methyl and methylene protons in guests **9** and **11** exhibit similar behaviors (Table 10). The magnitude of CIS is a function of the H–π proximity.[40] The above results, on this basis, indicate that the guest–host H···π distance depends on the geometrical types (**2**—**4**, **5**—**8**, or **9**—**12**) of X–C–H, but remains rather constant with a change in X. In the case where a proton undergoing a CIS of 2 ppm is located right above one benzene ring, the distance between them (referring to structure **15**), according to Johnson and Bovey,[40] is $l \simeq 2.8$ Å,[41] which is very close, or somewhat shorter, than the sum (2.9 Å) of van der Waals radii of the benzene ring (1.7 Å, i.e., half of the π-electron thickness (3.4 Å)) and the hydrogen atom (1.2 Å). There are numerous examples which show the CH–π proximity in organic crystal structures including host–guest complexes derived from calixarenes[42] and calix[4]resorcarene-based cavitands.[42] A newest report[43] shows that the CH_2Cl_2 complex of a calix[4]resorcarene derivative is stabilized by host–guest π-arene···H–C hydrogen bonds with a ring centroid···H distance of 2.84 Å, which is very close to that (ca. 2.8 Å) estimated above based on NMR data.

There is now good reason why the present CH–π interaction can be regarded as C–H···π hydrogen bonding. The acid-base interaction of a more or less fixed H···π distance is accompanied by a concomitant weakening of the C–H bond, in a similar manner as in the usual hydrogen bonding, such as O–H···O. Conventional hydrogen bonding is essentially a dipole interaction between a hard acid ($N\text{–}H^{\delta+}$ and $O\text{–}H^{\delta+}$) and a hard base (N and O),[44] and is hence effective only in apolar organic media. The C–H···π hydrogen bonding, on the other hand, is essentially an induced-dipole interaction between a soft acid (C–H) and a soft base (aromatic ring), and is effective in not only organic, but also aqueous media.

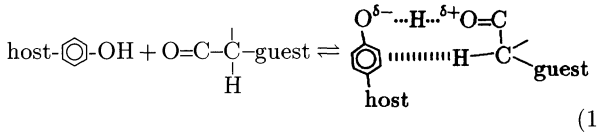
Possible Collaboration of Soft Acid-Base and

Hard Acid-Base Hydrogen Bonding Interactions. We should also pay attention to the possible roles of polar functional groups. The OH groups attached to soft aromatic bases in the host are hard acids. They are hydrated by or hydrogen-bonded to solvent water in such a way as to result in a partial deprotonation of the former (Eq. 7). The residue X (O, CH(OH), C=O, or S=O), adjacent to the soft C–H acids in a guest is a hard base. It would also interact with water so as to be partially protonated (Eq. 8 in the case of ketonic guest). There might also be direct hydrogen-bonding interaction between the OH groups of the host and residue X (O, CH(OH), C=O, or S=O), of the guest (Eq. 9). Such a proton transfer involving a hard acid and a hard base would make the soft aromatic rings of the host and soft C–H acids of the guest more basic and more acidic, respectively, thus resulting in a stronger C–H···π hydrogen bonding (Eq. 10).

$$\text{host-OH} + \text{OH}_2 \rightleftharpoons \text{host-O}^{\delta-}\cdots\text{H}\cdots^{\delta+}\text{OH}_2 \quad (7)$$

$$\text{guest-C=O} + \text{H}_2\text{O} \rightleftharpoons \text{guest-C=O}^{\delta+}\cdots\text{H}\cdots^{\delta-}\text{OH} \quad (8)$$

$$\text{host-OH} + \text{O=C-guest} \rightleftharpoons \text{host-O}^{\delta-}\cdots\text{H}\cdots^{\delta+}\text{O=C-guest} \quad (9)$$



(10)

There are numerous examples of at least apparent collaboration of polar and apolar interactions in the biological systems. A best example is the double helical structure of DNA, where nucleobases are in-plane hydrogen-bonded and π–π stacked.[45]. A protein-substrate interaction, particularly protein–sugar complexation[46] provides another good example. The C–H bonds of a bound sugar are often in contact or hydrogen-bonded with aromatic rings, such as indole and phenol moieties of Trp and Tyr, respectively. There is also an extensive hydrogen-bonded network involving the N–H group of the indole or the O–H group of the phenol in concern as a proton donor and the sugar O–H groups as proton acceptors. Such a cooperation (referring to Eq. 10) of hard acid-base hydrogen bonding (Z–H···Z; Z=O or N) and soft acid-base hydrogen bonding (C–H···π) may be an essential aspect of the biological complexation and molecular recognition therein, and is also one of next subjects of the present work.

Concluding Remarks

The characterization of *apolar interaction* is often clouded by concurrent hydrophobic forces in water or hard acid-base hydrogen bonding in apolar organic media. The present work demonstrates that there is a hydrogen bond-like attractive interaction between aromatic rings as soft bases and C–H bonds as soft acids. This interaction is based on neither dispersion forces nor charge or dipole interactions. In the context of van der Waals interactions, it may best be represented as an induced dipole interaction.[1i,32] The general advantages of this interaction are as follows: (1) Despite its apparently polar character, it is applicable to host–guest complexation, not only in apolar organic media, but also in water. (2) In the choice of organic guest molecules, an almost unlimited variation is allowed; organic molecules usually have carbon-bound hydrogen atoms. (3) It is particularly suited for the binding and recognition of multifunctional, and, hence, generally complex guests; they have many hydrogens so as to allow multiple interactions. Highly polar and water-miscible guest molecules **2**—**4**, **5**—**8**, and **9**—**12** can thus be bound to host **1** in water with remarkably varying affinities (0.50—273 M^{-1} at 298 K) depending on the electronic and geometrical properties. In addition, there is possibly an entropic advantage of the C–H···π hydrogen bonding. The observation of a single ^{1}H NMR resonance for the complexes of guests **2**—**4** suggests that the methyl groups are rapidly rotating while forming C–H···π hydrogen bonds with benzene rings of the host. On the other hand, a conventional Z–H···Z hydrogen bond (Z=O or N) must be formed at the sacrifice, or an entropy cost of freezing motional freedom of the three atoms.

The interaction of the present type must be kept in mind whenever dealing with an aromatic host or guest. Examples that may have relevance include the so-called π–π interaction, the cation–π interaction,[7] the binding of aromatic guests to cyclodextrins, the formation of hydrogen-bonded complexes in apolar organic media, and the structures and substrate-binding properties of proteins and organic crystals. Particular comments are as follows: (1) The arene–arene interaction of the type not only edge-to-face,[47] but also face-to-face[48] has CH–π proximity. In addition, arenes are stronger acids (e.g., $pK_a=37$ for benzene) than alkanes (e.g., $pK_a=45$ for cyclohexane).[49] (2) The cation–π interaction probably belongs to the general category of the CH–π interaction. The relatively strong binding of tetramethylammonium iodide to host **1a** in water ($K=280$ M^{-1}) is primarily due to a multiple CH–π interaction, and not due to a cationic charge effect. The binding constant of dimethylammonium iodide for the same host ($K=6.00$ M^{-1}) is not particularly large, as compared with those for related neutral-dimethyl analogs **2**–**4** (Table 1).[50] (3) Cyclodextrins generally prefer aromatic guests than the corresponding aliphatic counterparts.[51] Furthermore, α-cyclodextrin binds less hydrophobic, but more basic phenoxide anions ($K_D=4.0\times10^{-4}$ M for *p*-nitorophenoxide at 25 °C) more strongly do than the corresponding phenols ($K_D=5.3\times10^{-2}$ M for *p*-nitorophenol at 25 °C) which are more hydrophobic but less basic.[51] (4) Although the solvent dependence of the CH–π interaction remains to be investigated,[52] there is no reason to believe that it should not be effective in apolar organic media. The only problem here is that the CH–π interaction in such a medium is often clouded or ren-

dered unvisible by the more visible host–guest hydrogen bonding. Actually, the former may be facilitated by the latter, owing not only to an entropic effect, but also to a more essential collaboration between them, as discussed in the last paragraph of the discussion section. We have previously shown that the formation of hydrogen-bonded complexes between host **1a** and alcoholic guests in chloroform actually involves a substantial contribution of the CH–π interaction.[3e] (5) Multiple CH–π interaction may be most effective in macromolecular or aggregate systems such as proteins and organic crystals. There are in fact numerous examples of CH–π proximity there. Such an interaction may represent an essential force of protein folding and crystal packing.

Experimental

General Procedure. ^{1}H NRM spectra at 400 MHz were taken with a JEOL JNM-EX 400 spectrometer; HDO (δ_H 4.80) in D_2O (Nippon Sanso Corporation, 99.9% isotopic purity) was used as an internal standard and temperatures were controlled (±0.5 °C) with a JEOL NM-EVS 3 thermocontroller. Host **1** was prepared as described.[2a] All of the guests except for **8** and **12**, were commercial products of the highest grades. 1,4-dithiane-1,4-dioxides (**8**) and 1,2-bis(methylsulfonyl) ethane (**12**) were prepared according to literature methods.[17]

Binding Constants, Complexation-Induced Shifts, Continuous-Variation Plots and Thermodynamic Parameters. ^{1}H NMR spectra were taken for a series of solutions containing host **1** (2 mM) and varying amounts (0.2—1.2 M) of a guest in D_2O at 298 K. The binding constants (K) were obtained by the Benesi–Hildebrand analysis of the chemical shifts changes for the aromatic 5-H of the host. Double-reciprocal plots of $1/\Delta\delta_{5\text{-H}}$ vs. $1/[\text{guest}]_t$ (t=total) gave a straight line with an excellent linearity (correlation coefficient≥0.99) in every case. At least three runs were carried out for each guest; the average values of K's obtained are listed in Tables 1 and 10. The accuracy in K's is within ±10% in most cases, and never exceeds ±15% in every case.

The complexation-induced ^{1}H NMR upfield shifts (CIS) for guests were obtained by the Benesi–Hildebrand analysis of the NMR data for a series of solutions of a fixed amount of guest (2 mM) and varying amounts of host. Those for guests **2** and **3** with host **1a** were determined by a nonlinear curve-fitting method.

Sample solutions for continuous variation plots contained host **1** and a guest where $[\mathbf{1}]_t+[\text{guest}]_t$ was kept constant at 40 mM. Except for the case of disulfoxide **12**, plots of the [complex] vs. mole fraction of host **1** (f_1) gave a maximum at $f_1=0.5$, indicating a 1 : 1 host–guest stoichiometry; [complex] was evaluated according to the relation $[\text{complex}]=[\text{guest}]_t(\Delta\delta_{obsd}/\Delta\delta_{CIS})$, where $\Delta\delta_{obsd}$ and $\Delta\delta_{CIS}$ are observed and saturation shifts, respectively, for an appropriate guest proton resonance.

Thermodynamic parameters were obtained by nonlinear data fitting to Eq. 5 of the binding constants at various temperatures by using a semi-Newton method.

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