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Enhanced Sugar-Binding Ability of Deprotonated Calix[4]resorcarene in Water: Balance of CH-π Interaction and Hydrophobic Effect

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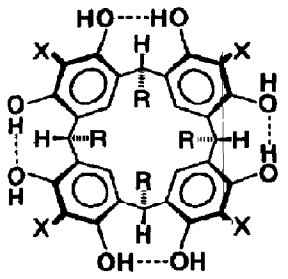
Abstract: *The complexation of calix[4]resorcarene as host and sugar (fucose) as guest in water can be significantly facilitated upon deprotonation of the OH groups of the host. The enhanced sugar-binding ability of the resulting anionic host having a more electron-rich and less hydrophobic aromatic cavity seems to result from a better sugar-host CH-π interaction.*

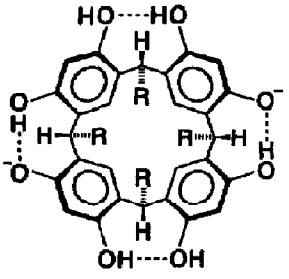
The complexation of highly polar molecules in water is an important but unexplored area of molecular recognition. We have recently shown that a water-soluble tetrasulfonate derivative of calix[4]resorcarene (resorcinol cyclic tetramer, **1**; X = H, CH_3, or OH) binds polyols including relatively hydrophobic sugars.[2] Based on the effects of substituents, especially the OH groups, on the binding abilities of both host[2] and guest,[3] we suggested that the CH-π interaction[4] between C-H bonds of a guest as σ-acids and electron-rich benzene rings of the host as π-bases is at least partially responsible for the present host-guest complexation. This interpretation, however, is not necessarily convincing; the enhanced binding abilities could also be due to host-guest hydrogen-bonding. Such a hydrogen-bonding interaction in water is by no means proved but can not be ruled out, either. Another approach is needed. In the present work, we have investigated the guest-binding properties of deprotonated anionic host. We report here that the complexation of sugars is particularly susceptible to the π-electron density of the host.

Addition of 4-equivalents of OH^- to an aqueous solution of compound **1a** afforded tetra-deprotonated derivative $\mathbf{1a}^{4-}$ having four strong O-H$\cdots$O$^-$ hydrogen bonds.[5] Anionic host $\mathbf{1a}^{4-}$ binds a variety of guest molecules in water in a similar manner as parent host **1a** having a neutral binding site. Three typical guests investigated here are fucose (6-deoxygalactose, **2**), cyclohexanol (**3**), and tetrahydrofuran (**4**) (Chart I). The ^{1}H NMR resonances for a guest undergo significant complexation-induced upfield shifts $\Delta\delta$ (a negative value indicates an upfield shift) as shown for guest **4** with hosts **1a** and $\mathbf{1a}^{4-}$ in Figure 1. The titration data are consistent with a 1:1 host-guest stoichiometry; the binding constants (K, Chart I)[6] and complexation-induced shifts at saturation binding (CIS, vide infra) are obtained according to Benesi and Hildebrand in a usual manner; K's for **2** are for the major β-anomer. In Chart I are also shown the binding constants for di-deprotonated host

$1a^{2-}$ arising from the interaction of **1a** and 2 equivalents of OH^-.[7] The binding sites of anionic hosts $1a^{2-}$ and $1a^{4-}$ are expected to be less hydrophobic than that of **1a**. The former, however, shows larger *K*'s than the latter. The selectivities $K(1a^{2-})/K(1a)$ and $K(1a^{4-})/K(1a)$ are significant for the sugar guest **2** and moderate for more hydrophobic guests **3** and **4**. This can hardly be explained in terms of host–guest hydrogen-bonding. Deprotonated host $1a^{4-}$ is no longer a proton donor. The particular guest **4** has no OH group to donate a proton. The complexation between host $1a^{4-}$ and guest **4** involves neither host-to-guest nor guest-to-host hydrogen bonding. Nevertheless, complex $1a^{4-}\cdot 4$ is of a similar stability as compared with those ($1a^{4-}\cdot 2$ and $1a^{4-}\cdot 3$) derived from hydroxylic guests **2** and **3**. The increase in *K*'s upon changing the hosts may thus most reasonably be ascribed to an electronic effect rather than to a steric effect.[8]

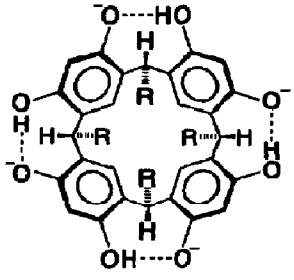


1a : X=H
1b : X=CH_3
1c : X=OH



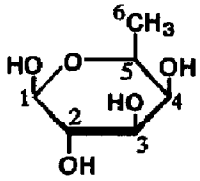
R=$CH_2CH_2SO_3Na$

$1a^{2-}$

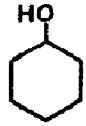


$1a^{4-}$

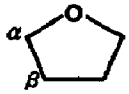
Chart 1



2



3



4

	2	**3**	**4**
K (**1a**) / M^{-1}	2	17	13
K ($1a^{2-}$) / M^{-1}	16	55	58
K ($1a^{4-}$) / M^{-1}	26	20	25

The host–guest complexation in aqueous media is generally promoted by a combination of the hydrophobic force and the van-der-Waals interaction.[9] The present CH–π interaction appears to be a kind of (induced) dipole–dipole interaction between a C–H bond of a guest as σ–acid and an aromatic cavity of the host as π–base. In this respect, it may belong to the general category of the van-der-Waals interaction. Upon deprotonation of the OH groups, the aromatic cavity of the host becomes more electron-rich and less hydrophobic.

The CH–π interaction would be strengthened and the hydrophobic association weakened as a consequence. The data in Chart I seem to show how these two opposing factors balance with each other and how this balance depends on the nature of the guests. Both factors would make comparable contributions in the binding of moderately hydrophobic guests **3** and **4**; they are bound to hosts **1a** and $\mathbf{1a}^{4-}$ with similar *K*'s. The highest binding ability of the di–deprotonated host $\mathbf{1a}^{2-}$ may be explained in terms of a cooperation of the CH–π interaction and the hydrophobic force. In the binding of a more hydrophilic and hence more polarized sugar guest **2**, the CH–π interaction would play a more important role than the hydrophobic force. This may be why there is significant increase in *K*'s for this particular guest on going from host **1a** through $\mathbf{1a}^{2-}$ to $\mathbf{1a}^{4-}$. It is also interesting to see the binding constants in terms of the selectivities of the hosts. The more hydrophobic and less electron–rich host **1a** discriminates the guests on the basis of their hydrophobicities (**3**, **4** > **2**). The less hydrophobic and more electron–rich host $\mathbf{1a}^{4-}$, however, is remarkably nondiscriminate in this respect; it binds three guests with similar *K*'s.

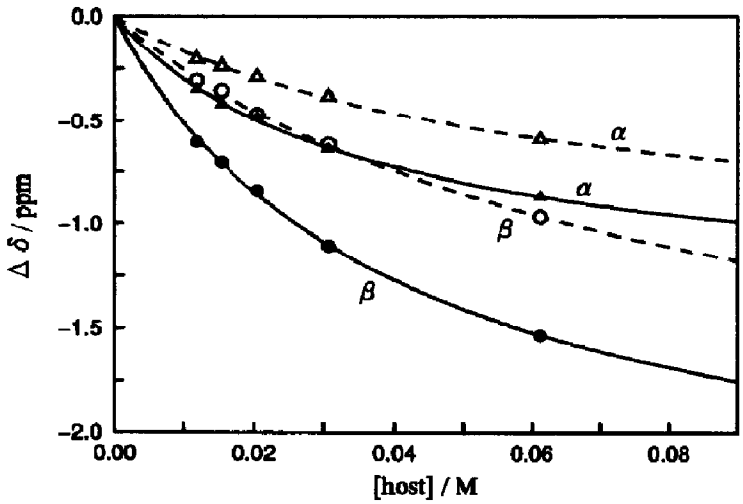


Fig. 1. The changes of the chemical shifts of α–H and β–H of guest **4** (2mM) in the presence of varying amounts of host **1a** (– – –) and $\mathbf{1a}^{4-}$ (——) in water at 25℃.

It is interesting at this point to refer to the CIS data, which support the above view. The complexation–induced upfield shifts for guest **4** decrease in the order β–H > α–H (referring to Figure 1); the CIS's in ppm at saturation binding are –2.10 (β–H) and –1.18 (α–H) with host **1a** and –2.52 (β–H) and –1.40 (α–H) with host $\mathbf{1a}^{4-}$. Whichever host is used, this moderately hydrophobic guest is bound with the most hydrophobic β–CH_2 moiety pointing to the aromatic cavity and the hydrophilic oxygen functionality being exposed to bulk water. In the case of sugar guest **2**, the CIS's are host–dependent. When host is **1a**, the methyl group of bound **2** exhibits a large CIS (–2.01 ppm), as compared with small CIS's for the hydroxymethine protons, e.g., –0.19 ppm for 1–H.[10] Changing the hosts from **1a** to $\mathbf{1a}^{4-}$ results in a significant decrease in the CIS of the methyl group to a value of –0.93 ppm and a compensating increase in those for the hydroxymethine–protons, 1–H in particular,

for which the CIS is –0.28 ppm.[10] There must be a significant change in the complexation geometries upon changing the hosts. The aromatic cavity of host **1a** most strongly binds the hydrophobic methyl group of **2**. That of host $\mathbf{1a}^{4-}$ also prefers the hydrophilic *H*–*C*–OH moieties, especially the most acidic 1–H; the C–H bonds polarized by an OH group would allow a better CH–π interaction with the electron-rich aromatic cavity of $\mathbf{1a}^{4-}$.[3]

In summary, the CH–π interaction cooperates with the hydrophobic force in water. They are compensating with respect to the polarities of the guests. This is especially important in the design of more elaborate artificial sugar-receptors. The present work also shed more light on the roles of aromatic amino acids in the sugar-binding proteins.[11] In order to get deeper insight into the detailed nature of the CH–π interaction, attention should also be directed to a systematic change in the guest structures, especially those having different C–H acidities. Further work is now under way in this laboratory under these lines.

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6. Titrations were carried out for solutions of a fixed amount of guest (2 mM) and varying amounts of host at 25℃. The Benesi-Hildebrand plots for a particular proton of a guest gave an excellent straight line (correlation coefficient, $r \geq 0.995$) and the accuracy of K obtained was ±10% in every case. Analysis of different protons of a guest gave essentially the same K. The binding constant K=2 M^{-1} of host **1a** for fucose (**2**) is in excellent agreement with K=1.8 M^{-1} obtained under conditions of constant **[1a]** and varying **[2]**.[2]
7. Host $\mathbf{1a}^{2-}$ having a dianionic binding site gave single ^{1}H–NMR signals for the aromatic 2–H (6.19) and 5–H (7.26), indicating the equivalence of the four benzene rings.
8. Even host **1a** has a very rigid guest-binding site (polyhydroxy aromatic cavity) doubly linked via methine bridges and O–H···O–H hydrogen bonds.[2] It seems less likely that the change in molecular geometries among host **1a**, $\mathbf{1a}^{2-}$, and $\mathbf{1a}^{4-}$ is big enough to be responsible for the observed variation in K's.
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10. Only 1–H can be readily assigned.
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