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Contribution of Guest-Host CH-π Interaction to the Stability of Complexes Formed from Cyclotetrachromotropylene as Host and Alcohols and Sugars as Guests in Water

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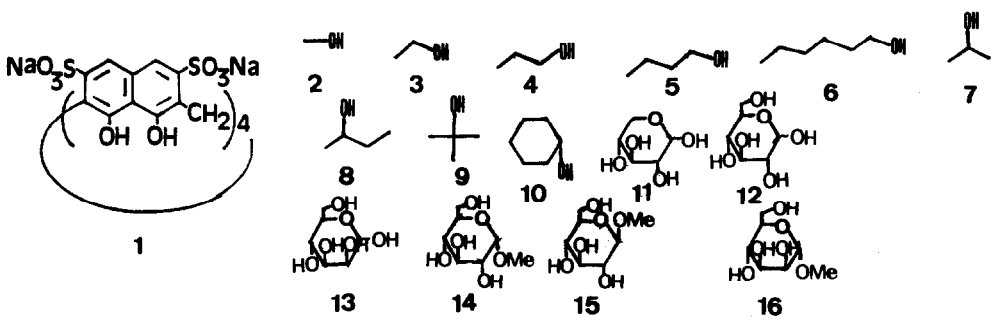
Abstract: The stability constants K of the 1:1 host to guest complexes formed between the cyclic tetramer, cyclotetrachromotropylene, and alcohols and sugars in water at 25° C were determined by ^{1}H nmr spectroscopy. The results indicate that the interaction between the aromatic π-bonds of the host and the C-H bonds of the guests is the major factor responsible for the complexation. The variation of K, in the case of the alcohols as guests, was correlated with the number of C-H bonds interacting with the hydrophobic host cavity.

The binding of carbohydrates by proteins plays a very important role in several biological processes. The two major forces[1,2] involved in the binding are (1) hydrogen bonding between the carbohydrate hydroxyl groups and oxygen and nitrogen atoms of the protein and (2) hydrophobic interaction between the carbohydrate C-H bonds and the aromatic π-bonds of the protein. We are interested to have a better understanding of the latter force as , we believe, it will be useful in the design of synthetic macrocycles for molecular recognition of sugars in water. Molecular recognition of sugars in water is an area of growing interest.[3] In this work, we chose the cyclic tetramer, cyclotetrachromotropylene, 1, as host to provide the aromatic π-bonds, and the alcohols 2-10 and sugars 11-16 as guests to provide the aliphatic C-H bonds. The binding of these alcohols and sugars by 1 in water was studied using proton nmr spetroscopy.



RESULTS AND DISCUSSION

Complexation of alcohols

The proton chemical shifts of the alcohols are shifted upfield by a large amount upon complexation with 1 (Table 1), indicating that the guest molecules are included in the host cavity. This deduction is supported by the absence of any effect of chromotropic acid, disodium salt (the monomer of 1) on the proton chemical shifts of the same alcohols (for example, when the concentration of chromotropic acid, disodium salt was sixteen times that of ethanol, there was no change in the methyl and methylene proton chemical shifts of the latter). The change on the proton nmr spectrum of the guest in the presence of 1 is illustrated by 1-propanol in Figure 1.

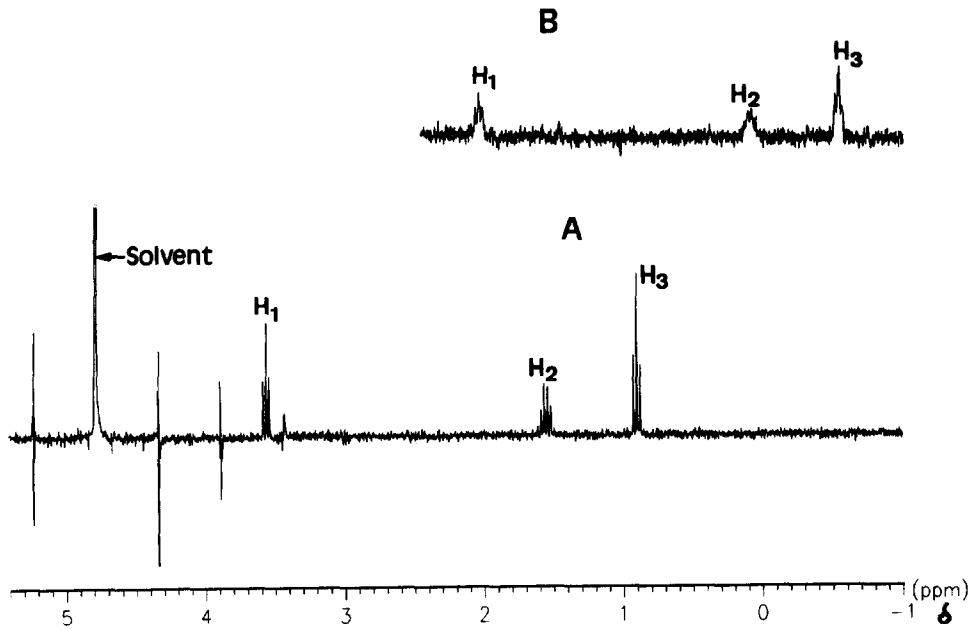


Figure 1. 300 MHz ^1H nmr spectra in D_2O at 25°C of 1.02×10^{-2} M of 1-propanol (solvent peak at 4.80 ppm as internal reference); (A) no host, (B) in the presence of 1.28×10^{-2} M of 1. The methylene and aromatic proton peaks of 1 not shown.

All the proton chemical shift titration curves show the two tangents meeting at a point where the molar ratio of host to guest is unity, indicating that the complexes are of 1:1 host to guest stoichiometry.[4-6] A typical example is shown in Figure 2 for the methyl protons of 1-propanol.

Table 1. Proton NMR Chemical Shifts of Alcohols and Stability Constant K of their 1:1 Complexes with 1 in D_2O at 25°C.

Alcohol	Proton	δ_u[a], ppm	$\Delta\delta$[b], ppm	K[c], M^{-1}	sd[d], ppm
Methanol	H_1	3.36	-	2[e]	-
Ethanol	H_1	3.59	1.59	32	0.07
	H_2	1.13	1.53	32	0.07
1-Propanol	H_1	3.52	2.00	700	0.07
	H_2	1.51	1.91	700	0.06
	H_3	0.84	1.87	700	0.06
1-Butanol	H_1	3.54	1.68	3000	0.06
	H_2	1.45	1.95	3000	0.07
	H_3	1.28	2.08	3000	0.09
	H_4	0.84	1.89	3000	0.07
1-Hexanol	H_1	3.60	1.71	2500	0.09
	H_2–H_4[f]	1.54	2.04	2500	0.11
	H_5	1.30	2.19	2500	0.13
	H_6	0.87	1.46	2500	0.10
2-Propanol	H_2[g]	1.10	1.60	13	0.03
2-Butanol	H_1	3.69	1.82	290	0.07
	$H_2(CH_3)$	1.09	1.14	290	0.04
	$H_2(CH_2)$	1.40	1.82	290	0.07
	H_3	0.82	1.65	290	0.06
2-Methyl-2-propanol	H_2	1.18	1.08	9	0.02
Cyclohexanol[h]	H_1	3.63	0.66	700	0.07
	H_2,eq	1.87	0.62	700	0.05
	H_2,ax	1.31	0.82	700	0.06
	H_3,eq	1.71	1.22	700	0.09
	H_3,ax	1.24	1.37	700	0.10
	H_4,eq	1.55	1.50	700	0.13
	H_4,ax	1.15	1.70	700	0.13

[a]Chemical shift of free alcohol. [b]Difference between the chemical shifts of free and complexed alcohol; positive indicates upfield shift. [c]Calculated by non-linear regression fitting. [d]Standard deviation between experimental and calculated chemical shifts. [e]Estimated value. [f]Appear as a single peak. [g]Signal for H_1 too small to be observed. [h]The symbols eq and ax denote equatorial and axial respectively.

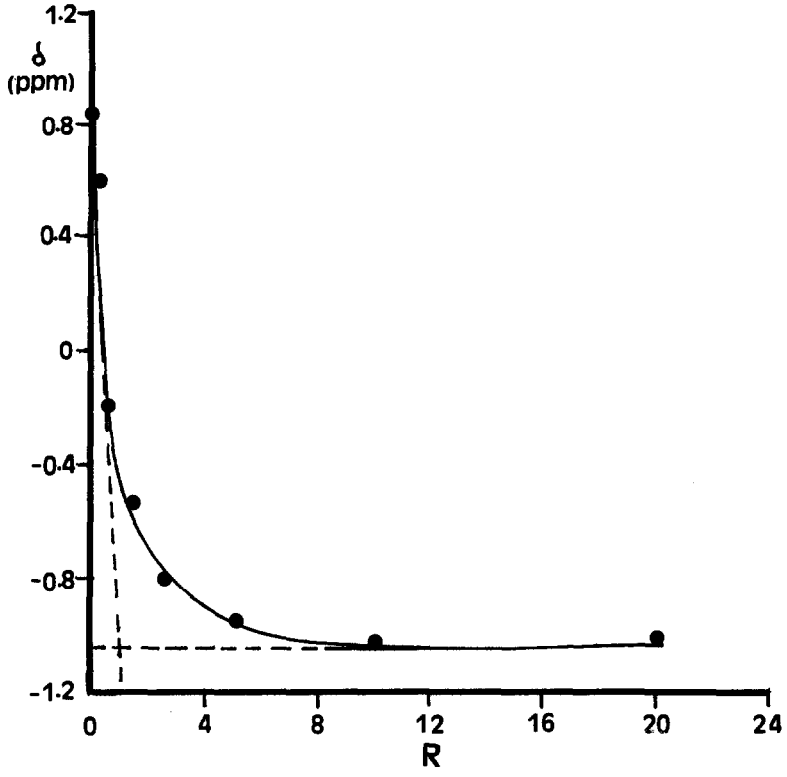
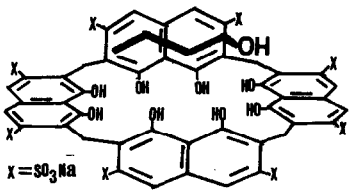


Figure 2. Variation of methyl proton chemical shift of 1-propanol (1.02×10^{-2} M) with the molar ratio (R) of the host (1) to guest used in D_2O at 25^0C.

The almost equal changes in the chemical shifts of the different kinds of protons in each of the linear alcohols (Table 1) indicate that the alcohol molecules lie horizontally in the host cavity (17 depicts the inclusion of 1-butanol in the cavity of the chair conformation[7] of 1). For examples, the upfield shifts, in ppm, are 1.59 and 1.53 respectively for H_1 and H_2 of ethanol (the subscript in H indicates the carbon bonded to the proton, the carbon atom with the hydroxyl group is numbered 1), 2.00, 1.91, and 1.87 respectively for H_1, H_2 and H_3 of 1-propanol, and 1.68, 1.95, 2.08, and 1.89 respectively for H_1, H_2, H_3 and H_4 of 1-butanol. In the case of 1-hexanol, the



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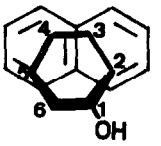

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upfield shift of the terminal methyl protons (H_6, 1.46 ppm) is significantly smaller than those of the preceeding eight methylene protons (about 2.1 ppm). This is consistent with the fact that the vertical naphthalene wall of the cavity is wide enough to interact with only four fully extended methylene units in a horizontal position, as indicated by CPK molecular models. As a result, the terminal methyl protons are relatively further away from the naphthalene wall and experience less shielding effect. The changes in the proton chemical shifts of the acyclic branched alcohols are also consistent with horizontal inclusion. For example, the methine, methylene and methyl (C_3) protons of 2-butanol have similar chemical shift changes (1.82, 1.82 and 1.65 ppm respectively). It is observed that the H_2 protons of the methylene unit are significantly more shielded (1.82 ppm) than the H_2 protons of the methyl unit (1.14 ppm) in 2-butanol. We suggest that the guest molecule lies horizontally in the host cavity with the hydrophilic hydroxyl group away from the hydrophobic naphthalene wall (see 18 for illustration), and the longer ethyl unit (instead of the shorter methyl unit) faces the naphthalene wall for greater hydrophobic attraction. The results for cyclohexanol are also consistent with the guest molecule sitting horizontally in the host cavity, with the C_2-C_5 segment closer to the naphthalene wall, as shown in 19.

The stability constant K of each 1:1 host to guest complex was obtained by a non-linear regression fitting procedure.[6] The K values obtained from different protons of the same alcohol are in good agreement with one another (Table 1). Some representative calculated titration curves togethter with the experimental chemical shifts are shown in Figure 3. Methanol forms a weak complex with 1 as shown by the small change in its chemical shift (a molar ratio of host to guest of 21.1 gave an upfield shift of only 0.22 ppm to the methyl protons). We have to assume a value for the maximum upfield shift in order to estimate the K value of the complex. Using a value of 1.5 ppm, similar to that of ethanol, the estimataed K value is 2 M^{-1}. Our stability constants are the largest compared with those reported for the same alcohols with other macrocyclic hosts.[8-9]

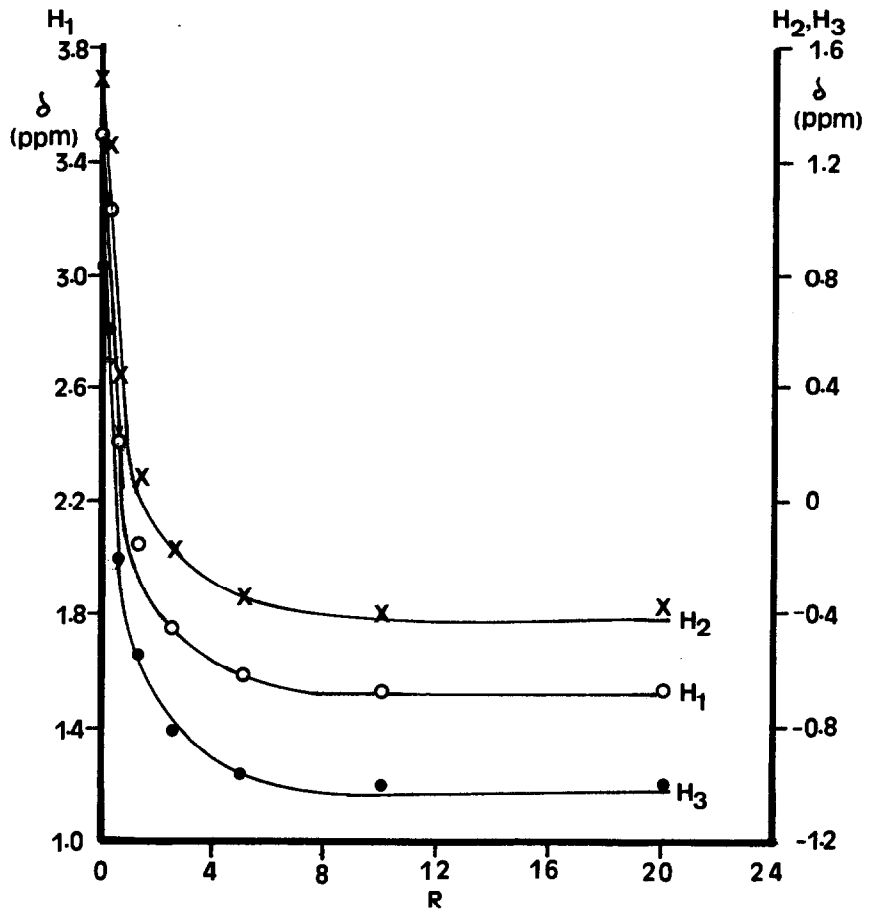

Figure 3. Calculated proton chemical shift titration curves of 1-propanol : D_2O at 25°C. R is the molar ratio of the host to guest used and the points a: experimental values. The K and δ values of the free and complexed guest us(for calculating the titration curves are given in Table 1.

Table 2. Log K of 1:1 Complexes of Alcohols with 1, Log P and N of Alcohols

No.	Alcohol	Log K	Log P[a]	N[b]
2	Methanol	0.3[c]	-0.82	3
3	Ethanol	1.51	-0.32	5
4	1-Propanol	2.85	0.34	7
5	1-Butanol	3.48	0.88	9
6	1-Hexanol	3.40	2.03	8
7	2-Propanol	1.11	0.06	4
8	2-Butanol	2.46	0.61	6
9	2-Methyl-2-propanol	0.95	0.37	3
10	Cyclohexanol	2.85	1.23	8

[a] From ref.10 . [b] Number of C-H bonds interacting with the vertical naphthalene wall. [c] Estimated value.

If hydrophobic attraction is the main driving force in the binding of the alcohols in the hydrophobic cavity of the host, a linear correlation between log K and log P (P is the partition coefficient which measures the hydrophobicity of the substrate[10]) is expected.[8,10] A considerable degree of such linear correlation was reported by Matsui and Mochida[8] for the 1:1 complexes of alcohols with α- and β-cyclodextrin in an aqueous medium. However, a plot of our log K against the reported log P values in Table 2 for the alcohols shows no linear relationship (Figure 4). We attribute the absence of a linear relationship to the lack of a uniform hydrophobic wall enclosing the host cavity. The chair conformation of 1 has only one vertical naphthalene wall to shield the guest molecules. The other vertical naphthalene wall is antiparallel to it and situated about half the height of a naphthalene unit below it. The remaining two naphthalene units are in a horizontal position (see 17). Bearing in mind that the partition coefficient values of the alcohols were determined under the condition in which all the hydrocarbon parts of the alcohol molecules can interact with the hydrophobic solvent (1-octanol), it is not surprising that they are not applicable to our case where, for some alcohols, only part of their hydrophobic structure can interact with the hydrophobic vertical naphthalene wall. In the case of branched and cyclic alcohols, only one hydrocarbon chain can interact with the vertical hydrophobic naphthalene wall at any one moment. In the case of the long chain 1-hexanol, the naphthalene wall is wide enough to interact

with only its middle four methylene units (see above). If our reasoning is correct, the total number of C-H bonds in the hydrocarbon chain interacting with the vertical naphthalene wall is a better measure of hydrophobic interaction between host and guest molecules in our case. There is no ambiguity about which hydrocarbon chain should be chosen in the case of the linear alcohols (for 1-hexanol, the number of C-H bonds is eight and not thirteen since only four methylene units can interact with the naphthalene wall). For the branched alcohol, 2-butanol, the longer three carbon unit

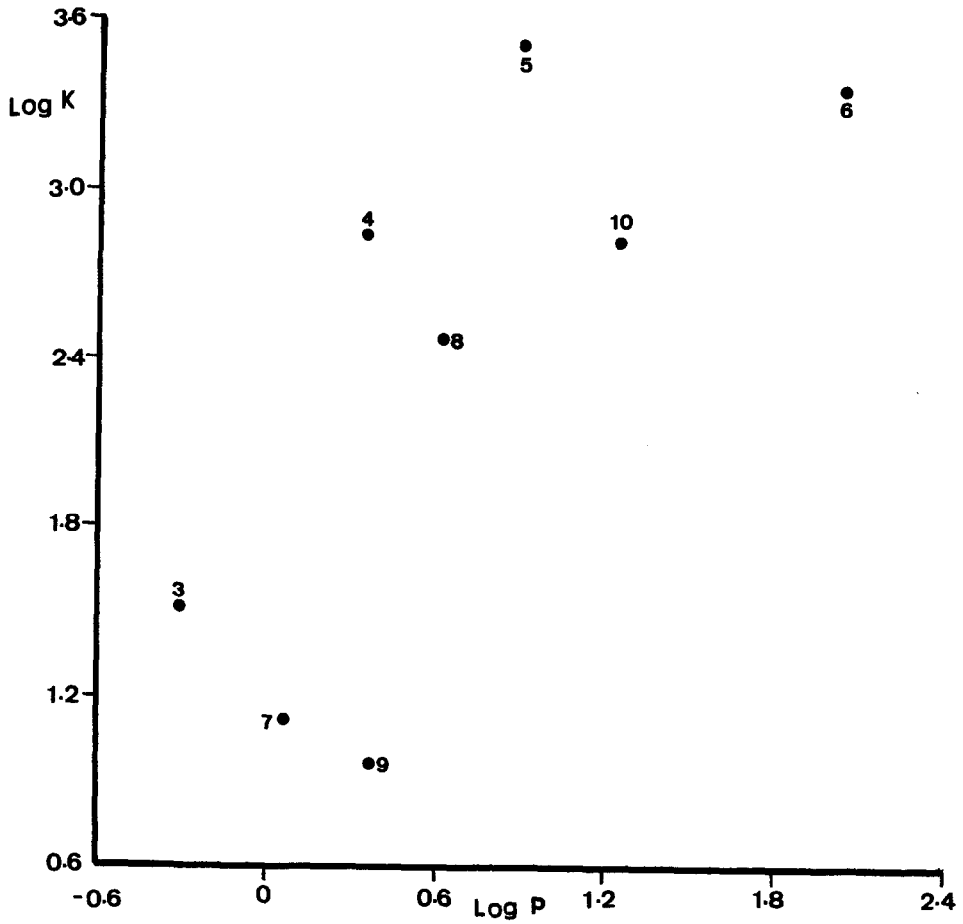

Figure 4. A plot of log K versus log P. The numbers refer to the alcohols given in the text.

chain (six C-H bonds) is chosen over the two carbon unit chain, consistent with 18 above. Similarly, the number of C-H bonds for cyclohexanol is eight (C_2 to C_5).The total number of C-H bonds (N) for the alcohols are given in Table 2. Indeed, a good linear relationship is obtained when log K is plotted against N (Figure 5, correlation coefficient 0.974 for eight alcohols). This linear plot indicates that hydrophobic interaction is the main driving force in the inclusion of alcohols into the cavity of 1.

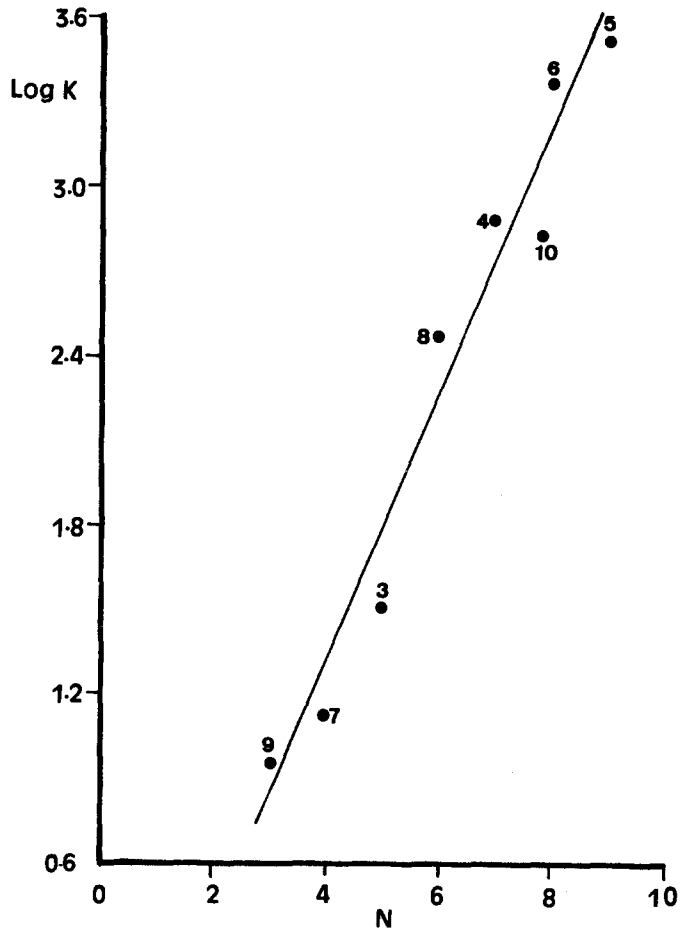

Figure 5. Linear relationship between log K and N (correlation coefficient 0.974, intercept -0.56 and slope 0.46). The numbers refer to the alcohols given in the text.

Complexation of sugars

The proton nmr spectra of D-xylose (11), D-glucose (12), and D-mannose(13) were unaffected by the presence of 1 (no noticeable change was observed even in the presence of a sixteen fold excess of 1), indicating the absence of complexation between them. The CH groups in these sugars are unable to interact with the naphthalene π-bonds of the host because they are situated between the hydrophilic hydroxyl groups which prefer to be away from the hydrophobic naphthalene wall (see the earlier discussion for alcohols).

However, complexation was observed when the hydroxyl group at C_1 of the sugars was replaced by a methoxyl group, such as methyl α-D-glucopyranoside (14), methyl β-D-glucopyranoside (15) and methyl α-D-mannopyranoside (16). Figure 6 shows the methyl and C_1-H proton nmr titration curves of methyl α-D-glucopyranoside.

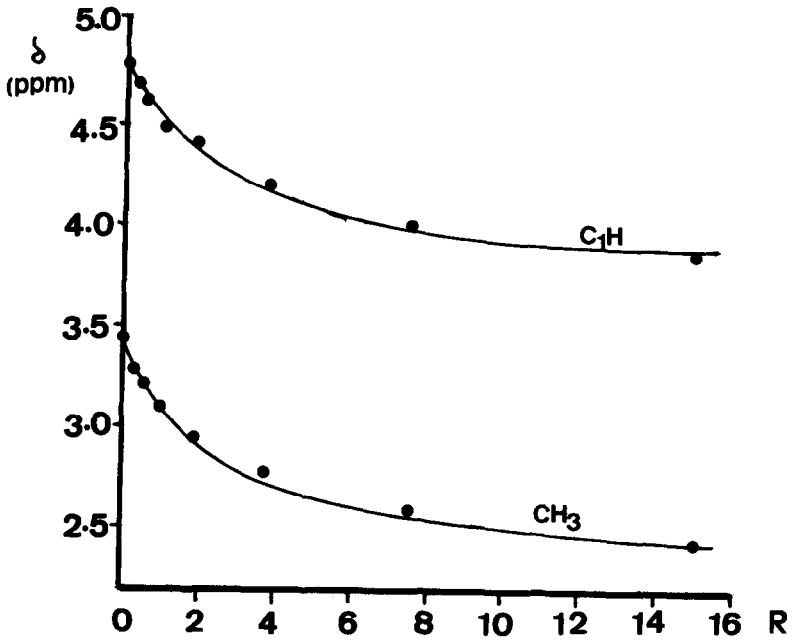

Figure 6. Variation of the chemical shifts of the methyl protons and proton at C_1 of methyl α-D-glucopyranoside (2.13×10^{-2} M) with the molar ratio (R) of host (1) to guest used in D_2O at 25°C. The points are experimental values and the curves calculated by non-linear regression fitting using the K and chemical shift values given in Table 3.

The methyl protons and the proton at C_1 experience the largest shielding in each case. For example, the upfield shifts are 0.33 (CH_3), 0.31 (C_1H) and 0.11 ppm (C_4H) for methyl α-D-glucopyranoside in the presence of an equal molar of 1. The guest molecule, consistent with the proton nmr results, lies in the host cavity with the CH_3-O-C_1H-C_2H(OH) unit (analogous to 1-butanol in 17) closer to the vertical naphthalene wall, as shown in 20 for methyl α-D-glucopyranoside.

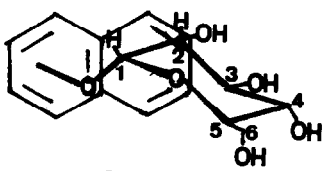

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Table 3. Proton NMR Chemical Shifts (ppm) of Sugars and Stability Constant K of their 1:1 Complexes with 1 in D_2O at 25°C.

Sugar	Proton	δ_u[a]	$\Delta\delta$[b]	K, M^{-1}	sd[c]
14	CH_3	3.42	1.07	28	0.04
	H_1	4.78	0.98	28	0.04
15	CH_3	3.58	1.13	6	0.02
	H_1	4.39	0.84	6	0.02
16	CH_3	3.42	1.67	75	0.05
	H_1	4.75	1.90	75	0.06

[a]Chemical shift of free sugar. [b]Difference between the chemical shifts of free and complexed sugar; positive indicates upfield shift. [c]Standard deviation between experimental and calculated chemical shifts.

Table 3 gives the K values, obtained by a non-linear regression fitting procedure, of the three 1:1 complexes. The K values obtained from the methyl protons and the proton at C_1 are in good agreement with each other (the other protons were excluded because their chemical shifts were smaller and the signals sometimes overlapped with each other). The K value of methyl α-D-mannopyranoside (16, 75 M^{-1}) is larger than that of methyl α-D-glucopyranoside (14, 28 M^{-1}) because the proton at C_2 in the former is closer to interact with the vertical naphthalene wall (see 20, these two sugars differ in the configuration at C_2). Molecular models indicate that, for the CH_3-O-C_1H-C_2H(OH) unit to penetrate the host cavity to the same depth, the ring structure of methyl β-D-glucopyranoside (15) cannot penetrate as deeply into the cavity as that of its α-anomer. Thus, the K value of the former (6 M^{-1}) is smaller than that of the latter. The K values of these three sugars, which have four to five CH protons to interact with the vertical naphthalene wall of the host, are around that of ethanol (32 M^{-1}) which have five CH protons, indicating that CH-π interaction is the major factor responsible for the

complexation of the monomethylated sugars by 1 in water. Until now, t only one study, by Kobayashi and coworkers[3], on the complexation of su synthetic macrocycles in water. They also found that there complexation between D-xylose, D-glucose, D-mannose and the resorcinol tetramers. Weak complexation, due to CH-π interaction, was obser methyl α-D-glucopyranoside and its anomer (K values not more than 2

EXPERIMENTAL

Materials. All the alcohols, sugars and chromotropic acid, disodi were commercial samples. The host 1 was prepared as described earli

^{1}H nmr spectra in D_2O at 25°C were recorded with a 300 MHz Bruke Superconducting NMR spectrometer. The solvent peak (unaffected concentration variation of the host and guest compounds) at 4.80 ppm was as the internal reference. The chemical shift error is 0.01 ppm. In chemical shift titrations, the concentration of the alcohols and sug kept constant at about 1.0×10^{-2} M while the concentration of the varied.

Calculations of the stability constant K of the 1:1 host t complexes using the non-linear regression fitting of the proton c shift titration curves were carried out as reported earlier.[6] The K obtained have an estimated error of 10%.

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