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Proton NMR Study on the Complexation of Organic Molecules with Cyclotetra-5-sulfonatotropolonylene in Aqueous Solution

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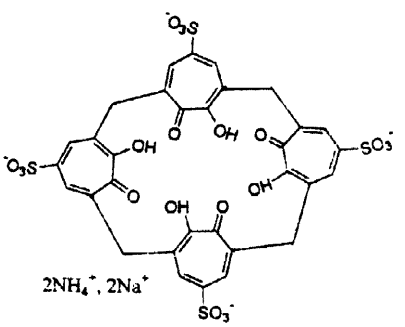
Abstract: The complexation of aromatic (phenols and monosubstituted benzenes) and aliphatic (alcohols) organic molecules by the macrocycle, cyclotetra-5-sulfonatotropolonylene, in an aqueous medium was studied by proton nmr spectroscopy. The aromatic molecules formed moderately strong complexes whereas the aliphatic molecules formed weak complexes.

Synthetic water-soluble macrocycles containing a hydrophobic cavity are a useful model for the hydrophobic pockets of enzymes. They were used to complex with organic molecules in an aqueous medium to gain an understanding of the two important interactions, π-π and CH-π, which occur in the biological system.[1-5] Recently,[6] we synthesized another water-soluble macrocycle **1** which we have named cyclotetra-5-sulfonatotropolonylene. Macrocycle **1** was found to be a good host to the polyaromatic hydrocarbons in water.[7] As a furtherance to our work, we were interested to know the ability of **1** to complex with other organic molecules. This paper reports the results of our proton nmr study on the complexation of several aromatic (phenols and monosubstituted benzenes) and aliphatic (alcohols) organic molecules by **1** in an aqueous medium at 25^{0}C.



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RESULTS AND DISCUSSION

Complexation of phenols

The complexation of six phenols, *p*-XC_6H_4OH, with **1** was carried out in D_2O at pD 7.0 (to keep the phenols as neutral molecules). That the phenols were included in the hydrophobic cavity of **1** was indicated by the upfield shifts of their proton chemical shifts (Table 1). The change in the proton nmr spectrum of the phenolic guest in the presence of **1** is illustrated by *p*-cresol (X = CH_3) in Figure 1.

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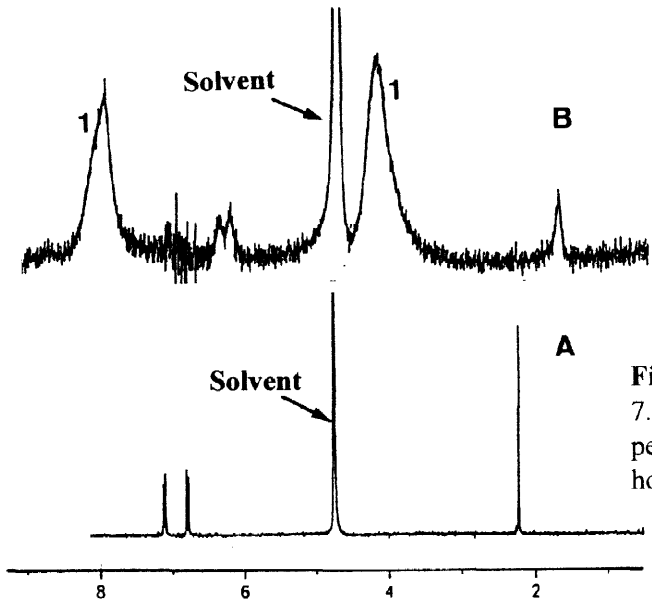


Figure 1. 300 MHz proton nmr spectra in D_2O, pD 7.0 at 25°C of $1.78x10^{-2}$ M of *p*-cresol (solvent peak at 4.80 ppm as internal reference); (**A**) no host, (**B**) in the presence of $5.24x10^{-2}$ M of **1**.

Table 1. Proton NMR Chemical Shifts of Phenols, *p*-XC_6H_4OH, and Stability Constant K of their 1:1 Complexes with **1** in D_2O, pD 7.0 at 25° C.

X	Proton	δ_u[a], ppm	$\Delta\delta$[b], ppm	K[c], M^{-1}	sd[d], ppm
H	H_o	6.94	0.44 (0.75)[e]	17	0.008
	H_m	7.34	0.52 (1.03)	12 (17)[f]	0.007
	H_p	7.02	0.47 (0.72)	22	0.009
OMe	H_o	6.94	0.63 (1.17)	14	0.025
	H_m	6.97	0.73 (1.23)	18 (15)	0.021
	CH_3	3.85	0.46 (0.93)	12	0.019
Me	H_o	6.84	0.66 (1.00)	23	0.017
	H_m	7.16	0.85 (1.39)	19 (21)	0.025
	CH_3	2.26	0.58 (0.93)	20	0.019
Br	H_o	6.83	0.77 (1.26)	20	0.024
	H_m	7.42	1.18 (1.91)	20 (20)	0.037
NO_2	H_o	6.93	0.50 (0.98)	14	0.023
	H_m	8.21	0.73 (1.59)	11 (13)	0.014
SO_3Na	H_o	7.03	0.09	g	
	H_m	7.74	0.07		

[a]Chemical shift of the free guest. [b]Induced upfield chemical shift observed at host to guest molar ratio of 10.0, 6.7, 5.5, 9.1, 4.9 and 12.9 for X = H, OMe, Me, Br , NO_2 and SO_3Na respectively. [c]Calculated by non-linear regression fitting. [d]Standard deviation between experimental and calculated chemical shifts. [e] Values in parentheses are the differences between the chemical shifts of free and complexed guests (the chemical shift of the latter obtained from non-linear regression fitting).[f]Average value in parentheses. [g]Weak complexation.

The complexation-induced chemical shifts in Table 1 show that the phenolic molecules penetrate axially into the hydrophobic cavity of the host **1** from their more hydrophobic end (H, OMe, Me, Br and NO_2 instead of OH) since the chemical shift changes of H_m are larger than those of H_o (H_o, H_m and H_p refer to the hydrogens *ortho*, *meta* and *para* to the OH group of the phenol respectively). The shallow penetration of *p*-sulfonatophenol is also from the more hydrophobic end (OH instead of SO_3^-), as indicated by the larger change in the chemical shift of H_o compared to that of H_m. Axial inclusion of phenols and other substituted benzenes was also reported for similar macrocycle hosts, such as cyclophanes[2-4] and calix[4]arenes.[8]

The complexation-induced chemical shifts of the methyl protons of X = OMe and Me are smaller than those of their aromatic protons, indicating that the methyl group is located further away from the cavity in the complex as shown in **2** for *p*-methoxyphenol (only one tropolone wall of the cavity is shown for clarity).

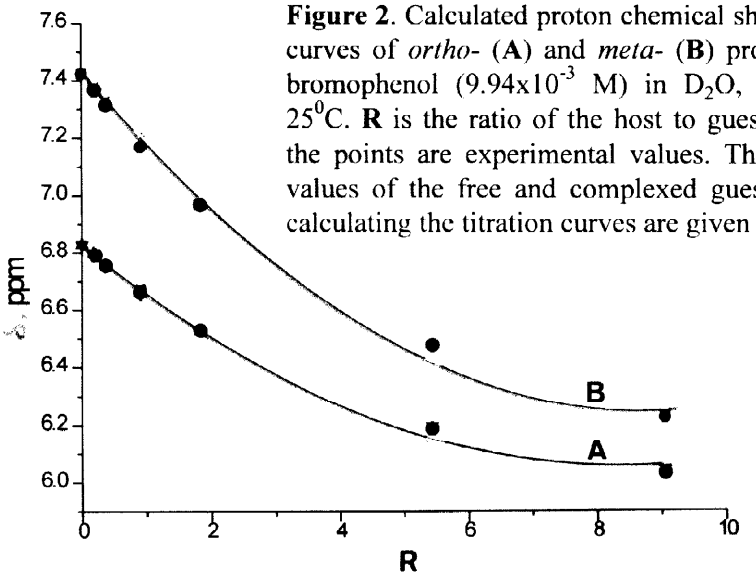
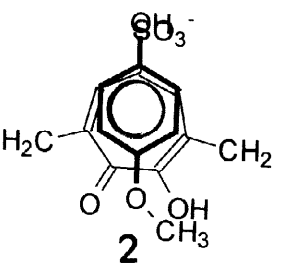


Figure 2. Calculated proton chemical shift titration curves of *ortho*- (**A**) and *meta*- (**B**) protons of *p*-bromophenol (9.94×10^{-3} M) in D_2O, pD 7.0 at 25^0C. **R** is the ratio of the host to guest used and the points are experimental values. The K and δ values of the free and complexed guest used for calculating the titration curves are given in Table 1.



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Two assumptions have to be made to calculate the stability constant K of the complexes. First, we assume that the complexes are of 1:1 host to guest stoichiometry since the method of drawing tangents to the proton chemical shift titration curve to determine the stoichiometry is not reliable when K is small.[9] This assumption is reasonable since the cavity size of **1** is between those of calix[4]arenes (cavity diameter ~ 3.8 Å for upper rim[10] and ~2 Å for lower rim[11]) and cyclophanes with cavity diameters[4] ~ 4.3 Å which form complexes of 1:1 host to guest stoichiometry with phenols and other substituted benzenes.[3,4,8] Second, we assume that all the three conformers of **1** (cone, 1,2-alternate and 1,3-alternate in equal population[6]) complex with the phenolic guests equally well. The latter assumption, though weak, will only affect the magnitude of K but not the trend needed in our discussion below (for example, the K values would be three times larger if the 1,3-alternate conformer is the only one complexing with the phenolic molecules[7]). The values of K, obtained

from the chemical shifts of different protons of the same guest molecule are in satisfactory agreement with one another. Figure 2 shows the calculated titration curves together with the experimental chemical shifts for the *ortho* and *meta* protons of *p*-bromophenol.

With the exception of X = SO_3Na, the values of K are practically independent of the substituent X (ranging from a strong electron-donor OMe to a strong electron-withdrawer NO_2), indicating that any electronic effect from the substituent is small. There is also no significant contribution from CH-π interaction for X = OMe and Me, consistent with the deduction that the OMe and Me groups are away from the aromatic walls of the host shown in **2**. In the case of X = SO_3Na, only shallow penetration is observed because both the OH and SO_3^- groups are hydrophilic and do not like the hydrophobic cavity of the host.

Complexation of monosubstituted benzenes

The complexation of five monosubstituted benzenes, XC_6H_5, with **1** in D_2O was carried out. The

Table 2. Proton NMR Chemical Shifts of Monosubstituted Benzenes, XC_6H_5, and Stability Constant K of their 1:1 Complexes with **1** in D_2O at 25^0 C.

X	Proton	δ_u[a], ppm	$\Delta\delta$[b], ppm	K[c], M^{-1}	sd[d], ppm
H	H^e_{arom}	7.45	0.47 (0.62)[f]	25	0.005
OMe	CH_3	3.83	0.40 (0.54)	36	0.005
	H_o	7.04	0.68 (0.91)	40 (37)[g]	0.004
	H_m	7.39	0.58 (0.81)	33	0.006
	H_p	7.08	0.56 (0.76)	38	0.006
Me	CH_3	3.86	0.31 (0.45)	29	0.004
	H_m	7.41	0.39 (0.55)	31 (30)	0.007
	$H^e_{o,p}$	7.05	0.35		
CHO	CHO	10.02	0.36 (0.50)	36	0.009
	H_o	8.02	0.50 (0.69)	34 (36)	0.016
	H_m	7.70	0.46 (0.66)	35	0.009
	H_p	7.84	0.40 (0.56)	39	0.010
NO_2	H_o	8.27	0.56 (0.85)	24	0.009
	H_m	7.65	0.44 (0.66)	26 (26)	0.004
	H_p	7.83	0.40 (0.61)	27	0.007

[a]Chemical shift of the free guest. [b]Induced upfield chemical shift observed at host to guest molar ratio of 7.3, 9.5, 15.9, 5.4 and 8.1 for H, OMe, Me, CHO and NO_2 respectively. [c]Calculated by non-linear regression fitting. [d]Standard deviation between experimental and calculated chemical shifts. [e]Aromatic protons appear as a singlet. [f] Values in parentheses are the differences between the chemical shifts of free and complexed guests (the chemical shift of the latter obtained from non-linear regression fitting). [g]Average value in parentheses.

complexation-induced chemical shifts are given in Table 2. Again, they indicate that the guest molecules penetrate axially into the hydrophobic cavity of the host from their more hydrophobic end (OMe, CHO and NO_2 instead of H) since the chemical shift changes are $H_o > H_m > H_p$ (H_o, H_m, and H_p refer to the protons *ortho*, *meta* and *para* to the substituent respectively). The smaller induced chemical shifts of the methyl protons of anisole and toluene, compared to those of the aromatic protons, indicate that they are located further away from the host cavity in the complexes, analogous to **2**.

Based on the two assumptions given above, the K values for the 1:1 host to guest complexes were calculated by a non-linear regression fitting and given in Table 2. Again, the K values are practically independent of the substituent on the guest molecule.

Complexation of alcohols

The complexation of seven aliphatic alcohols with **1** in D_2O was investigated. The complexation-induced proton chemical shifts of six short chain alcohols are small, even at a host to guest molar ratio of about ten used (0.02 to 0.08 ppm for ethanol, *n*-propanol, *i*-propanol, *n*-butanol, *s*-butanol and *t*-butanol; these values are too small for obtaining reliable K values), indicating that the complexes are weak. The calculated K value for 1:1 stoichiometry[5] for *n*-hexanol is only 7 M^{-1}. Thus, aliphatic molecules form weak complexes with **1**. Aliphatic molecules were also reported[5,13] to form weak complexes with similar macrocycles with cavity walls formed from benzene units. Stronger complexation with aliphatic molecules was observed when the cavity walls have a much larger surface for CH-π interaction.[1]

Table 3. Proton NMR Chemical Shifts of n-Hexanol and Stability Constant K of its 1:1 Complexes with **1** in D_2O at 25^0 C.

Proton	δ_u[a], ppm	$\Delta\delta$[b], ppm	K[c], M^{-1}	sd[d], ppm
H_1	3.61	0.134 (0.44)[e]	7.1	0.003
H_2	1.55	0.204 (0.69)	6.6 (7)[f]	0.004
H_3-H_5	1.31	0.272 (0.83)	7.7	0.004
H_6	0.88	0.195 (0.63)	6.9	0.003

[a]Chemical shift of the free guest. [b]Induced upfield chemical shift observed at host to guest molar ratio of 9.3. [c]Calculated by non-linear regression fitting. [d]Standard deviation between experimental and calculated chemical shifts. [e]Values in parentheses are the differences between the chemical shifts of free and complexed guests (the chemical shift of the latter obtained from non-linear regression fitting). [f]Average value.

EXPERIMENTAL

Materials. The synthesis of **1** was reported earlier.[6] All other chemicals were commercial samples.

Proton nmr spectra in D_2O at 25^0C were recorded with a 300 MHz Bruker AC300 Superconducting NMR spectrometer. The solvent peak (unaffected by the concentration variation of the host and guest compounds) at 4.80 ppm was used as the internal reference. In all the chemical shift titrations, the concentration of the phenols, monosubstituted benzenes and alcohols was kept constant at about $1x10^{-2}$ M while the concentration of the host **1** varied. The concentration range ($2.7 x10^{-3}$ to $6.6x10^{-2}$ M) of **1** used was below the critical aggregation concentration since the proton chemical shifts of **1** did not change. The relatively broad proton resonance peaks of **1** makes it unsuitable to carry out chemical shift titrations of the host protons with variation of guest concentration.

Calculations of the stability constant K of the 1:1 host to guest complexes using the non-linear regression fitting of the proton chemical shift titration curves were carried out as reported earlier.[12]

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