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C-H Acidity Effect of Guest Molecules on the Complexation with Monomethyl Ether of Monodeoxycalix[4]arene

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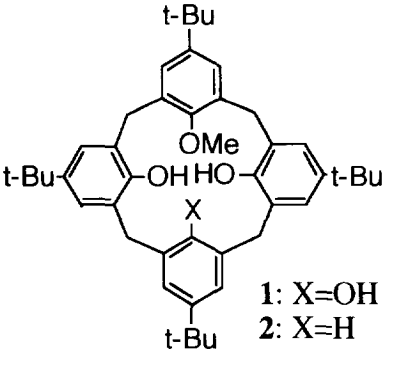
Abstract Monomethyl ether of monodeoxycalix[4]arene (**2**) is found to be a good receptor of small neutral organic guest molecules in carbon tetrachloride solution. The host has an open-ended narrow necked cone shape so that the solvent inaccessible cavity facilitates the inclusion of the guests. Since the guest with highly acidic C-H bonds binds strongly in the cavity, the C-H acidity of the guests rather than van der Waals interaction plays a dominant role in the stability of the complexes.

Noncovalent interaction between aromatic rings and neutral molecules is important in determining the structures and properties of molecular complexes in host-guest chemistry. Calixarenes,[1] which are macrocyclic compounds containing cavities composed of aromatic walls, are interesting because they are able to form inclusion complexes with several organic neutral guest molecules in the crystalline state.[2] The three dimensional arrangement of these compounds has been elucidated by X-ray diffraction studies. However, studies of complexation in solution are limited because of solubility problems of the host compounds.[3] Weak host-guest interaction for these compounds is another problem. We found that monoalkyl ethers of calix[4]arenes (**1**)[4] and its monodeoxy derivatives (**2**)[5] are soluble in the usual organic solvents. These compounds are known to adopt cone conformations in solution.[6] In order to reserve enough space for guest molecules, bulky *tert*-butyl groups were placed at the "upper rim" of the calixarenes. When dissolved in CCl_4 these host molecules can bind small neutral organic molecules in their cone cavities. CCl_4 is too large to reside in the cavity of this host molecule and hence, it does not compete with the small guest molecules for their binding sites. In this paper we present the complexation of X-CH_2-Y type molecules with the monomethyl ether of monodeoxycalix[4]arene (**2**) and discuss the important function of the C-H acidity of the guests in the formation of host-guest complexes.



1: X=OH
2: X=H

A standard titration experiment was carried out by ^{1}H-NMR spectroscopy. To a solution of a guest in CCl_4 was added the solution of the host in the same solvent. The NMR signal of the guest showed gradual upfield shift with the increase in host concentration. The complexation induced

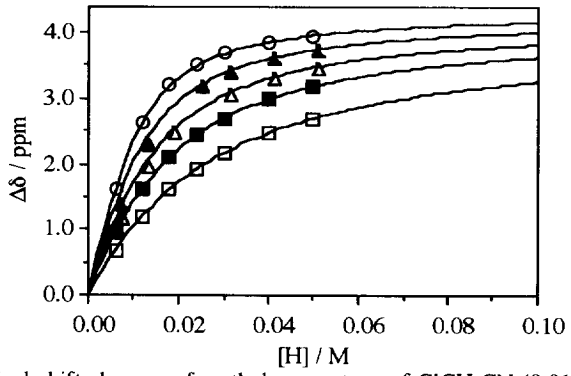


Fig. 1. Chemical shift changes of methylene protone of $ClCH_2CN$ (0.010 M) in the presence of various amounts of host **2**; □ at 25 °C; ■ at 10 °C; Δ at 0 °C; ▲ at -10 °C; O at -20 °C.

shifts of the CH_2 signal of the guest were monitored (Fig. 1). Stoichiometry of the complex was analyzed by a continuous variation method[7] and found to be 1 : 1 in all cases. The association constants at various temperatures were obtained by a non-linear least squares curve fitting program using Gauss-Newton algorithms.[8] The same curve fitting analysis gave the complexation induced shift (CIS) for the completely bound guest in a 1 : 1 complexes at each temperature. The observed CIS values for each guest did not show any large temperature dependence and had small standard deviation. From the association constants we could estimate the free energy of complexation at each temperature. Regression analysis of the free energy versus temperature gave thermodynamic parameters for these complexation phenomena. The results are summarized in Table 1.

Table 1. C-H acidity (pKa), van der Waals volume (V_{vdw}) and polarizability (α) of guests and free energy at 298K ($\Delta G_O(298)$), enthalpy (ΔH_O), entropy (ΔS_O), and CIS for complexation of **2** with guests.

Guest	pKa	V_{vdw} [Å^3]	α [Å^3]	$\Delta G_O(298)$ [kcal mol^{-1}]	ΔH_O [kcal mol^{-1}]	ΔS_O [cal mol^{-1} K^{-1}]	CIS [ppm]
$ClCH_2Cl$	35	60.2	6.33	-0.95±0.06	-4.35±0.25	-11.3±0.9	3.97±0.25
$ClCH_2CN$	26	62.1	6.17	-2.30±0.01	-5.72±0.06	-11.4±0.2	4.15±0.05
CH_3CH_2CN	31	63.7	6.06	-1.67±0.02	-5.06±0.09	-11.4±0.3	3.42±0.02
$BrCH_2Cl$	38	69.2	7.79	-1.00±0.37	-4.08±0.49	-10.3±1.9	3.65±0.12
$BrCH_2Br$	41	75.9	8.45	-1.10±0.43	-3.96±0.57	-9.8±2.1	3.20±0.12
$BrCH_2CN$	29	71.0	7.63	-2.12±0.02	-5.12±0.03	-10.1±0.1	3.85±0.06

Large observed CIS values (3.2 ~ 4.2 ppm) suggested that the guest molecules reside deep within the cavity and the methylene protons of the guests are fairly close to the aromatic walls of the host. This idea is supported by the molecular structure of the crystalline inclusion complex of CH_2BrCl (Fig. 2),[9] the guest of which has CIS value close to the average of all the guests. In this structure the methylene protons are facing the deoxy ring of the host though their exact position cannot be determined because of a positional disorder of the halogen atoms. Host-guest type inclusion complexes for similar guests in an organic solvent have been reported by Collet and his coworkers using cryptophane as the host molecules.[10] They applied ball shape

cavities so that their hosts showed excellent shape-selectivity in the inclusion complexation.[11] Since our host has an open-ended narrow necked cone shape it does not show any shape-selectivity. It also shows neither "V" shape nor linear correlation with the free energies of complexation versus the volume of guests.[12] The same is true for the relation between the enthalpies of complexation and the volume of the guests.

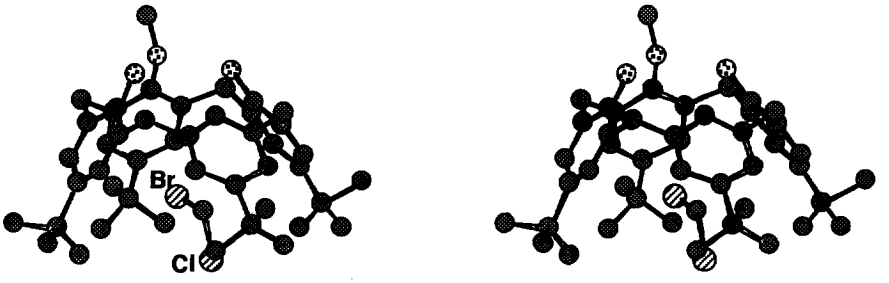


Fig. 2. A stereoview of molecular structure of **2** with $BrCH_2Cl$ in crystal.

Van der Waals interaction is one of the most important driving forces for the formation of inclusion complexes. Polarizability (α) of molecules is known to be related to the extent of van der Waals attractive interaction.[13] The guest molecules were selected to have a rather narrow range of polarizability to exclude the possibility of many different orientations for them within the cone cavity of the host. It is not unreasonable to assume that each guest has a similar orientation within the host cavity because the CIS value of each guest stays within a rather narrow range (3.7 ± 0.5 ppm). Van der Waals interaction for these complexes, however, is found not to be the influential factor in this case because the polarizability of the guests does not give a good correlation with either the free energies or the enthalpies of complexation.

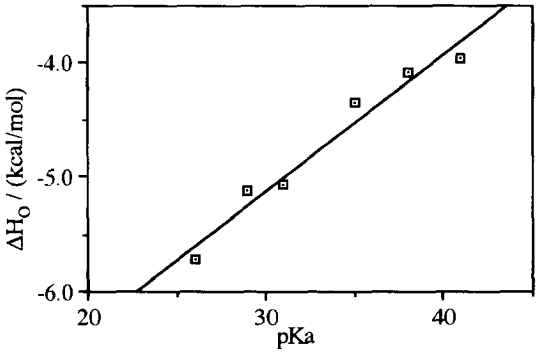


Fig. 3. Correlation between ΔH_O for the complexation and pKa of the guests.

The C-H acidity[14] of the guests, on the other hand, gives an excellent linear correlation with the enthalpy of complexation (Fig. 3) by regression analysis whose correlation coefficient (R^2) is high (0.961). This good correlation is quite interesting and it shows that the more acidic guest binds more strongly to the host by an acid-base type attractive interaction with aromatic π base. This acid-base type attractive interaction is supported by the molecular structure of the above mentioned crystalline inclusion complex. In that structure the methylene protons are on the π surface of one of the aromatic rings. Importance of this interaction for these guests is

further supported by the fact that all the inclusion complexes have a similar structure. Thus the acid-base type attractive interaction between the guest protons and π base of the host is shown to be the dominant factor for the stability of these inclusion complexes in solution. Further experimental support for the importance of this type of interaction in the formation of such complexes in solution is now being sought in our laboratory using monomethyl ether of calix[4]arene (**1**).

REFERENCES AND NOTES

1. Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989.
2. (a) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005. (b) Coruzzi, M.; Andreetti, G. D.; Bocchi, V.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2.* **1982**, 1133. (c) Ungaro, R.; Pochini, A.; Andreetti, G. D.; Domiano, P. *ibid.* **1985**, 197
3. ref. 1, pp. 75-79.
4. (a) Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1075. (b) Casnati, A.; Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *Tetrahedron* **1991**, 47, 2221.
5. (a) Fukazawa, Y.; Deyama, K. and. Usui, S *Tetrahedron Lett.* **1992**, 33, 5803. (b) Ting, Y.; Verboom, W.; Groenen, L. C.; van Loon, J.-D. and Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1990**, 1432. (c) Grynszpan, F.; Goren, Z. and Biali, S. B. *J. Org. Chem.* **1991**, 56, 532
6. Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, 119, 335.
7. Job, P. *Ann. Chim.* **1928**, 9, 113.
8. (a) Connors, K. A. *Binding Constants*; John Wiley & Sons: New York, 1987. (b) Legget, D. J. *Modern Inorganic Chemistry Series, Computational Methods for the Determination of Formation Constants*; Plenum Press: New York; London, 1985.
9. The crystallographic data of **2**-$BrCH_2Cl$ complex is as follows: $C_{46}H_{60}O_3BrCl$, FW=776.30, Monoclinic, space group $P2_1/n$, a=15.893(5)Å, b=22.107(8)Å, c=12.693(5)Å, β=98.32(3)°, Z=4, V=4413(3)Å^3, Dc=1.17g/cm^3, The measurement was performed with Mac Science MXC18; radiation MoKα (λ=0.71073); unique reflections 7769, observed 2549 with $|F| > 4.0\sigma(|F|)$, R=0.176.
10. (a) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1986**, 108, 4230. (b) Garel, L.; Dutasta, J-P.; Collet, A. *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1169
11. Canceill, J.; Cesario, M.; Collet, A.; Guilhem, J.; Lacombe, L.; Lozach, B.; Pascard, C. *ibid.* **1989**, 28, 1246.
12. These values are van der Waals volume calculated by MacroModel (Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem*, **1990**, 11, 440).
13. Diederich, F. *Cyclophanes*, Royal Society of Chemistry: Cambridge, 1991, pp. 254-263.
14. The pKa values in DMSO are calculated by the method reported: Gushurst, A. J.; Jorgensen *J. Org. Chem.* **1986**, 51, 3513.

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