Does the Calixarene Cavity recognise the Size of Guest Molecules? On the 'Hole-size Selectivity' in Water-soluble Calixarenes

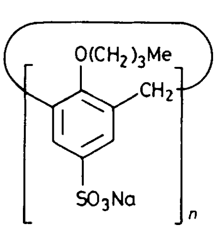
Seiji Shinkai,* Koji Araki, and Osamu Manabe

Department of Industrial Chemistry, Faculty of Engineering, Nagasaki University, Nagasaki 852, Japan

The binding constants of three *p*-sulphonatocalix[*n*]arenes (n = 4, 6, and 8) for neutral guest molecules were determined in an aqueous system; the results established that the calixarene cavity can recognise the size of guest molecules.

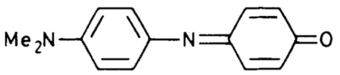
Calixarenes are cyclic oligomers made up of benzene units as cyclodextrins are made up of glucose units.[1,2] Thus, the calixarene cavity may recognise the size of guest molecules on the basis of the 'hole-size selectivity' when they form host–guest-type complexes in solution. Several groups have reported on the ion selectivity of calixarenes which have ether, ester, and/or carboxylate groups on the edge of the cylindrical architecture.[3—7] In contrast, the selectivity of the calixarene cavity for neutral guest molecules is not understood. To answer the question as to whether the calixarene cavity is able to recognise the size of guest molecules, we have synthesised three water soluble calixarenes with different cavity sizes (CX_4, CX_6, and CX_8) and have systematically estimated their binding constants for Phenol Blue (PB) and Anthrol Blue (AB). The butyl group was introduced to add moderate hydrophobicity to the calixarene cavity. We have found for the first time that the calixarene cavity is capable of molecular recognition on the basis of the 'hole-size selectivity'.

CX_4, CX_6, and CX_8 were synthesised in a manner similar to that described previously[8] and identified by i.r. and n.m.r. spectroscopy and by elemental analysis. Since the purpose of the present study was related to the molecular recognition, it was necessary to carry out measurements below the c.m.c.s (critical micelle concentrations) of these calixarenes. We thus determined the c.m.c.s by electric conductance[8] (30 °C, $[CX_n]$ = 2.60×10^{-3} mol dm^{-3}) and ^1H n.m.r.[9] spectroscopy (20.9 °C, D_2O). Figure 1 shows plots of the ^1H n.m.r. chemical shift *vs.* CX_4 concentration. Above 2.5×10^{-3} mol dm^{-3} some protons are shifted to higher field with increasing CX_4

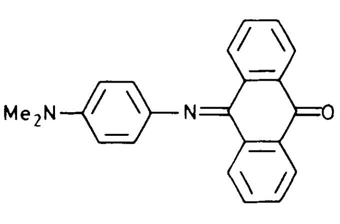


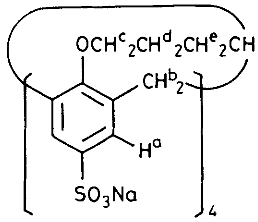
CX_n

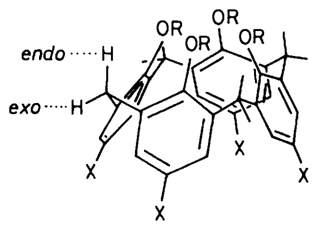
PB :



AB :







R = Bu^n
X = SO$_3$Na

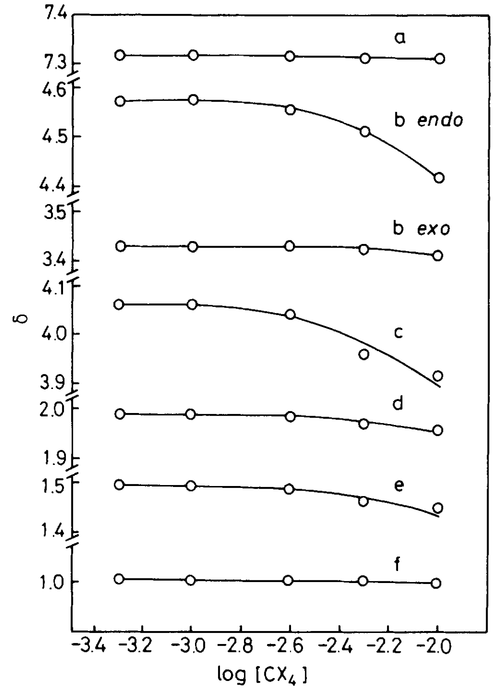
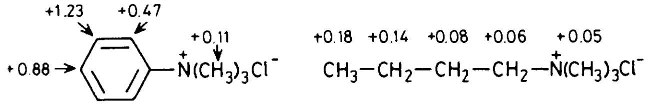


Figure 1. ^{1}H N.m.r. chemical shift (p.p.m.) *vs.* CX_4 concentration (20.9 °C, D_2O).

concentration. This indicates that CX_4 forms an aggregate at this concentration.[9] Electric conductance gave an almost identical c.m.c. value (2.5×10^{-3} mol dm^{-3}) although the measurement temperature was somewhat higher than that for the ^{1}H n.m.r. results. In a similar manner, we determined the c.m.c.s for CX_6 (1.0×10^{-3} mol dm^{-3}) and CX_8 (7.0×10^{-4} mol dm^{-3}).

The inclusion phenomena of cyclophanes have been frequently estimated by ^{1}H n.m.r. studies in D_2O since the chemical shift of the guest molecule was found to move to higher field on inclusion.[9,10] This is also the case in calixarene complexes since the ring current of the benzene rings induces a significant upfield shift. We have found that the chemical shift of organic ammonium cations is especially sensitive to this effect. For example, aromatic protons in trimethylanilinium chloride moved to higher field by 0.47—1.23 p.p.m. in the presence of an equimolar amount of CX_4 (20.9 °C, $[CX_4] = 1.01 \times 10^{-3}$ mol dm^{-3}, [guest] $= 1.00 \times 10^{-3}$ mol dm^{-3} (Scheme 1). Since the shift for N^+–CH_3 is relatively small, the ammonium cation is 'anchored' on the sulphonate edge (*i.e.*, upper rim) of the calixarene cavity and the phenyl group is included in the centre of the aromatic ring cavity. Much smaller shifts are found for trimethylbutylammonium chloride.



Scheme 1. Upfield ^{1}H n.m.r. shifts (p.p.m.) in the presence of an equimolar quantity of CX_4.

$$\begin{tikzcd} PB + CX_n \arrow[r, shift left, "K^0"] \arrow[d, shift right, "H^+ K_a^0"'] & PB{\cdot}CX_n \arrow[l, shift left] \arrow[d, shift right, "H^+ K_a"'] \\ PBH^+ + CX_n \arrow[u, shift right, "-H^+"'] \arrow[r, shift left, "K^+"] & PBH^+{\cdot}CX_n \arrow[l, shift left] \arrow[u, shift right, "-H^+"'] \end{tikzcd}$$

Scheme 2

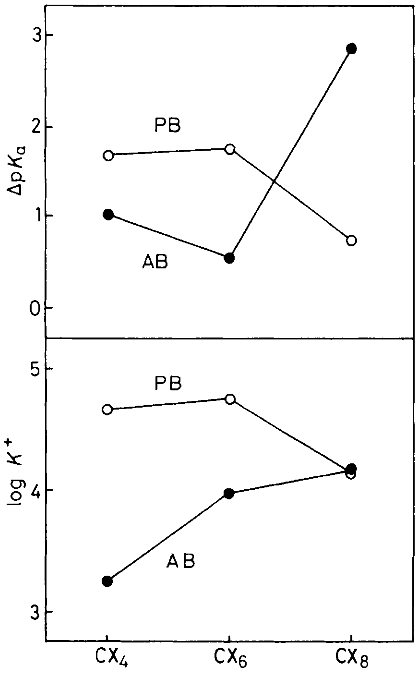


Figure 2. ΔpK_a and log K^+ (data taken from Table 1).

In order to evaluate the 'hole-size selectivity' in CX_n we chose PB and AB as guest molecules, their binding constants being easily determined by the colour change from blue to pink. This occurs owing to the stabilisation of the included protonated species (PBH^+, ABH^+) by the sulphonate groups.[8] The total scheme for the complex formation (*e.g.*, with PB) is illustrated in Scheme 2.

First, we confirmed that PB and AB form 1:1 complexes with these calixarenes on the basis of a continuous variation method {30 °C, [PB (or AB)] + $[CX_n] = 1.92 \times 10^{-5}$ mol dm^{-3}}. Based on the phototitration of PB (at 660 nm) and AB (at 560 nm) in the absence and the presence of CX_n and the computer assisted curve-fitting of the plots of the absorbance (660 nm and pH 6.4 for PB; 560 nm and pH 5.5 for AB) *vs.* $[CX_n]$, we could determine the pK_a^0, pK_a, and K^+ independently.† The results are shown in Table 1 and Figure 2.

---

† Further details of this analytical method will be reported elsewhere together with results on related systems. The K^0 values, which are smaller by 1—2 orders of magnitude than K^+, are not determined accurately in the present method.

Table 1. pK_a Shifts and binding constants (K^+) for the calixarene complexes (30 °C).

Guest		Calixarene		
		CX_4	CX_6	CX_8
PB[a]	ΔpK_a[c]	1.68	1.75	0.73
	$10^{-3}\,K^+/(dm^3\,mol^{-1})$	47.2	55.7	13.5
AB[b]	ΔpK_a[c]	1.02	0.54	2.84
	$10^{-3}\,K^+/(dm^3\,mol^{-1})$	1.82	9.30	15.0

[a] pK_a^0 (in the absence of CX_n) = 4.60. [b] pK_a^0 (in the absence of CX_n) = 4.34. [c] $\Delta pK_a = pK_a$ (in the presence of CX_n) $-pK_a^0$ (in the absence of CX_n).

Examination of these results reveals that the K^+ values are sensitive to changes in the cavity size. PB (small guest molecule) shows the selectivity order of $CX_6 > CX_4 > CX_8$, while AB (large guest molecule) shows the selectivity order of $CX_8 > CX_6 > CX_4$. The results suggests that PB can fit the cavity of CX_4 and CX_6 while AB is too large to be included in the cavity of these calixarenes. Thus, the largest difference in K^+ (31-fold) was attained between CX_6–PB (largest K^+, 5.57×10^4 dm^3 mol^{-1}) and CX_4–AB (smallest K^+, 1.82×10^3 dm^3 mol^{-1}). The pK_a shift is roughly correlated with log K^+, indicating that the apparent basicity of strongly bound guest molecules is efficiently strengthened. On the basis of X-ray studies[1] and Corey–Pauling–Koltun molecular models, the upper-rim diameters of calix[4]arene and calix[6]arene are estimated to be 3.8 and 5.0 Å, respectively. Therefore, the molecular recognition pattern of calix[6]arene and its derivatives would be comparable to that of β-cyclodextrin (diameter 5.5—5.9 Å) which favourably binds benzene analogues. On the other hand, the cavity of CX_8, the size of which cannot be estimated precisely because of a conformational fluctuation called 'transannular pinching,'[1] would be too large to include benzene analogues. These findings consistently support the idea that the calixarene cavity is capable of molecular recognition on the basis of 'hole-size selectivity.'

In conclusion, the present study indicates that the 'hole-size selectivity' does exist in host–guest type complexation with calixarenes. The finding suggests that calixarenes would act as a new, potential building block to design enzyme mimics in totally synthetic systems.

Received, 6th October 1987; Com. 1458

References

1 C. D. Gutsche, *Acc. Chem. Res.*, 1983, **16**, 161.
2 S. Shinkai, *Pure Appl. Chem.*, 1987, **59**, 425.
3 S.-K. Chang, *Chem. Lett.*, 1984, 477.
4 R. Ungaro, A. Pochini, and G. D. Andreetti, *J. Inclusion Phenom.*, 1984, **2**, 199.
5 M. A. McKervey, E. M. Seward, G. Ferguson, B. Ruhl, and S. J. Harris, *J. Chem. Soc., Chem. Commun.*, 1985, 388.
6 S. Shinkai, H. Koreishi, K. Ueda, and O. Manabe, *J. Chem. Soc., Chem. Commun.*, 1986, 233.
7 S. Shinkai, H. Koreishi, K. Ueda, T. Arimura, and O. Manabe, *J. Am. Chem. Soc.*, 1987, **109**, 6371.
8 S. Shinkai, S. Mori, H. Koreishi, T. Tsubaki, and O. Manabe, *J. Am. Chem. Soc.*, 1986, **108**, 2409.
9 G. Schürmann and F. Diederich, *Tetrahedron Lett.*, 1986, **17**, 4249.
10 C.-F. Lai, K. Odashima, and K. Koga, *Tetrahedron Lett.*, 1985, **26**, 5179, and references cited therein.