Cation encapsulation within a ten-oxygen spheroidal cavity of conformationally preorganized 1,5-3,7-calix[8]bis-crown-3 derivatives

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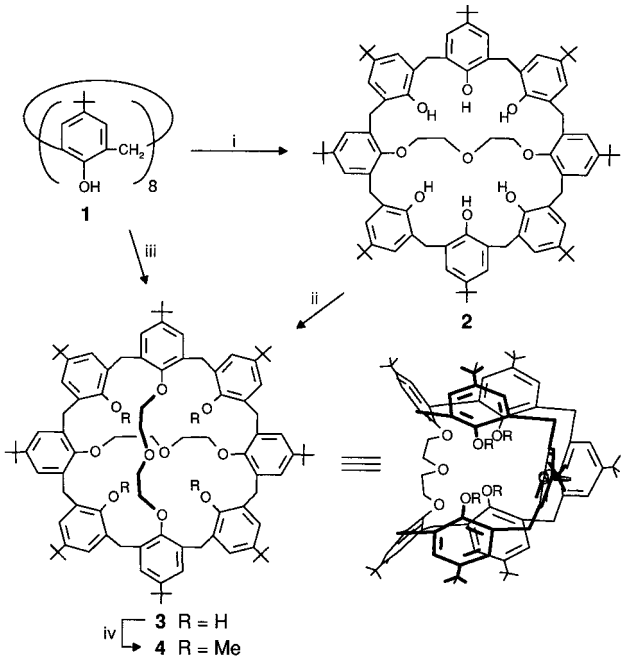
Conformationally preorganized, D_{2d}-symmetrical 1,5-3,7-calix[8]bis-crown-3 derivatives have been synthesized which are able to encapsulate cations with a size dependent selectivity.

In recent years remarkable host properties have been reported for functionalized calix[4]arenes.[1,2] In contrast, calix[8]arenes have shown no complexing abilities worthy of note,[1] apart from the remarkable case of buckminsterfullerene complexation.[3] This can be explained in terms of the preorganization principle[4] and by considering the floppy nature of the larger macrocycle.[5] In order to circumvent this problem, rigidification of calix[8]-arenes has been actively investigated by our[6] and other research groups,[7] giving particular attention to the preorganization by intramolecular bridging. However, notwithstanding the interesting results obtained in this direction,[6–7] to the best of our knowledge no complexing abilities have been registered so far. Here we report the first example of calix[8]arenes that by virtue of their conformational preorganization are able to encapsulate cations with a size-dependent selectivity.

As an extension of our previous studies on the synthesis of calix[8]crowns[6b,d,e] we envisaged that the use of one or more short polyether chains (diethylene glycol) could lead to a better preorganization of the macrocycle.[8] To achieve this aim, we reacted *p-tert*-butylcalix[8]arene **1** with diethylene glycol ditosylate in DMF in the presence of Cs_2CO_3 obtaining 1,5-crown-3 derivative **2** in 78% yield (Scheme 1), in accordance with the previously observed regioselectivity under analogous conditions.[6d] Further alkylation of **2** in the presence of NaH in THF–DMF (10 : 1, v/v) resulted in the introduction of another bridge with very high regioselectivity, thus affording 1,5-3,7-calix[8]bis-crown-3 **3** in 85% yield.† Interestingly, direct alkylation of *p-tert*-butylcalix[8]arene **1** in the presence of NaH, under conditions previously found to be well suited for 1,4-bridging with longer chains (tri- to penta-ethylene glycol),[6d] also gave **3** in 10% yield. This result is in line with the observations of Ikeda *et al*., who reported that intrabridging of **1** with bis(bromomomethyl)arenes under similar conditions results in 1,4-bridging with longer and 1,5-bridging with shorter reagents.[7c]



Scheme 1 *Reagents and conditions*: i, $TsO(CH_2CH_2O)_2Ts$, Cs_2CO_3, DMF, 70 °C; ii, $TsO(CH_2CH_2O)_2Ts$, NaH, THF–DMF (10 : 1, v/v), reflux; iii, $TsO(CH_2CH_2O)_2Ts$, NaH, THF–DMF (10 : 1, v/v), reflux; iv, MeI, NaH, DMF, 70 °C

The presence of a single or double bridge in **2** and **3**, respectively, was deduced by FAB(+) mass spectra, while the bridging pattern was assigned on the basis of the molecular symmetry evidenced in NMR spectra. Thus, the presence of three *tert*-butyl signals in the ^{1}H NMR spectrum ($CDCl_3$, 330 K) of **2** at δ 1.24, 1.28 and 1.31 (1 : 2 : 1) is clear evidence of a calix[8]arene molecule bisected by two orthogonal 2-fold symmetry elements and hence of the 1,5-bridging pattern. Similarly, the presence in the spectrum of **3** [Fig. 1(*a*)] of two equal intensity *tert*-butyl singlets at δ 1.20 and 1.21 coupled with a single AX system for $ArCH_2Ar$ (δ 3.45 and 4.26, J = 14.6 Hz) is compatible, among the 22 possible isomers, only with the most symmetrical 1,5-3,7-bis-crown structure.

The presence of an AX system for the $ArCH_2Ar$ protons of **3** is clear proof of a strong reduction of the conformational mobility of the macrocycle. This was confirmed by dynamic NMR studies in $CDCl_2CDCl_2$, which showed no hint of coalescence for these signals when raising the temperature up to 380 K, indicating the absence of conformational interconver-

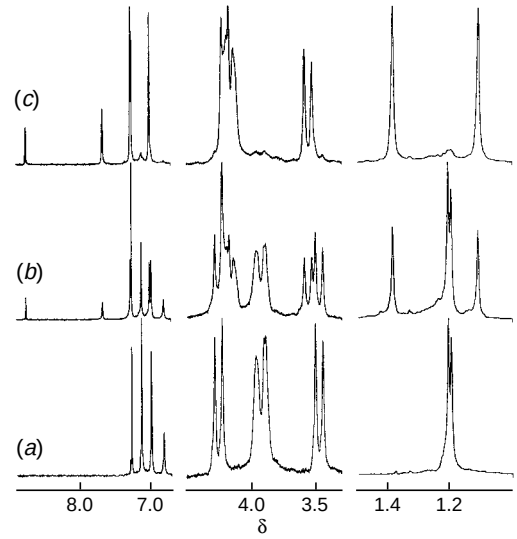


Fig. 1 Caesium cation encapsulation by 1,5-3,7-bis-crown **3**. ^{1}H NMR spectra (250 MHz, $CDCl_3$) of free ligand **3** (*a*), 24 h (*b*) and 48 h (*c*) after addition of solid caesium picrate

sion. The large chemical shift separation of the two doublets of the $ArCH_2Ar$ protons ($\Delta\delta$ = 0.81 ppm) indicates a *syn* orientation of each couple of vicinal aromatic rings with a geometry very similar to that of calix[4]arenes in the cone conformation. This was confirmed by the ^{13}C NMR chemical shift value of δ 32.1 for the $ArCH_2Ar$ groups.

In order to get an insight into the conformation adopted by **3** we undertook a Monte Carlo conformational search using the MacroModel ver.4.5 program[9] and imposed the symmetry equivalences evidenced by NMR. An idealized molecular model was thus obtained (Fig. 2) to be considered as the average structure in solution and possessing four different clefts, each with a structure closely reminiscent of a calix[4]arene cone depleted of an aryl ring ($\frac{3}{4}$ cone). This structure possesses a D_{2d} symmetry and is very similar to that proposed by Ikeda *et al*. for a calix[8]arene 1,5-3,7-doubly-bridged with *ortho* xylene units.[7c] However, this idealized structure does not correspond to an energy minimum and, indeed, its unconstrained full-matrix minimization as well as an independent unconstrained Monte Carlo search originates unsymmetrical geometries with large distortions of the $\frac{3}{4}$ cone units. These deformations can be described as a combination of C_{4v} to C_{2v} transitions typical of calix[4]arene cone[8] for each subunit of the structure.

In the idealized structure the ten oxygens are symmetrically located delimitating a polyhedral, almost spheroidal cavity. The four hydroxylic oxygens describe a planar square with an average diagonal of 6.3 Å, while the central oxygens of the crowns are symmetrically situated at *ca*. 4.1 Å above and below this square. These geometrical features are reminescent of the structure of cryptands, compounds well known as strong complexing agents for alkali metal cations.[10] On the basis of this analogy, we tested the complexing abilities of compound **3**. Thus, preliminary ^1H NMR experiments showed that immediately after the addition of solid caesium picrate to a $CDCl_3$ solution of **3** no appreciable changes can be observed in the spectrum, but after standing for 24 h at room temp. a new set of signals appeared, due to the complex $Cs^+\subset$**3** formation [Fig. 1(*b*)]. A further 24 h standing led to complete complexation [Fig. 1(*c*)]. In the homogeneous phase (CD_3CN–$CDCl_3$, 9 : 1 v/v) completion of the reaction required only a few minutes. The 1 : 1 stoichiometry was confirmed by signal integration in the spectrum. In the complex $Cs^+\subset$**3** the cation appears to be encapsulated inside the ten-oxygen spheroidal cavity, as indicated by the substantial downfield shift experienced by the protons of the crown chains, the aromatic rings and the hydroxy groups. Downfield shifts were also observed in the ^{13}C NMR spectrum for the pertinent carbon signals.

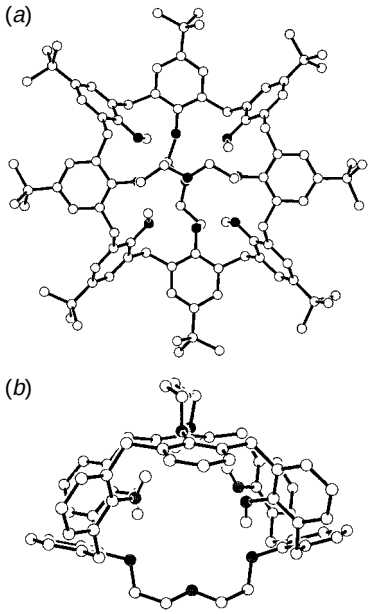


Fig. 2 Computer model of idealized conformation of **3**: (*a*) top view (H atoms omitted); (*b*) side view (H atoms and *tert*-butyl groups omitted)

The selectivity of complexation was investigated by standard two-phase picrate extraction experiments.[11] Thus, it was shown that different cations can be encapsulated besides Cs^+ with the following equilibrium constants: K_e ($dm^6\ mol^{-2}$) = 3.7×10^4 for Na^+, 11×10^4 for K^+, 10×10^4 NH_4^+, 640×10^4 for Rb^+ and 5200×10^4 for Cs^+. The $K_e(Cs^+)/K_e(Na^+)$ selectivity factor is therefore 1400, thus confirming the cation/cavity size complementarity expected for the encapsulation process.‡

It is to be expected that chemical modifications of **3** can have a profound influence on the complexing properties. We prepared the tetramethyl derivative **4** (MeI–NaH–DMF, 80% yield), whose complexing properties toward caesium cations do not differ substantially from that of **3**. Interestingly, an upfield shift from δ 3.44 to 2.84 is observed, upon Cs^+ complexation, for the OMe groups in the ^1H NMR spectrum of **4** (CD_3CN–$CDCl_3$, 9 : 1 v/v) indicating that they are forced to point inside the shielding $\frac{3}{4}$ cone aromatic cavities. However, the determination of picrate extraction equilibrium constants [K_e ($dm^6\ mol^{-2}$) = 1.3×10^4 for Na^+, 3.9×10^4 for K^+, 4.0×10^4 for NH_4^+, 16×10^4 for Rb^+ and 87×10^4 for Cs^+] revealed a reduced $K_e(Cs^+)/K_e(Na^+)$ selectivity factor (67). A more detailed investigation of the complexation properties of **3**, **4** and other analogues is currently carried out in our laboratory.

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Footnotes

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† Satisfactory microanalytical and spectral data were obtained for all new compounds.

‡ This selectivity factor cannot be directly compared to the Cs^+/Na^+ selectivity [$S = \beta(Cs^+)/\beta(Na^+)$] calculated as the ratio of stability constants (β) and usually reported for caesium-selective 1,3-alternate calix[4]crowns [for which $S \geqslant 10^5$, refs. 2(*a*), (*b*)].

References

1 V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 713 and references cited therein.
2 (*a*) A. Casnati, A. Pochini, R. Ungaro, F. Ugozzoli, F. Arnaud, S. Fanni, M.-J. Schwing, R. J. M. Egberink, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1995, **117**, 2767; (*b*) Z. Asfari, J. M. Harrowfield, A. N. Sobolev and J. Vicens, *Aust. J. Chem.*, 1994, **47**, 757; (*c*) H. Yamamoto and S. Shinkai, *Chem. Lett.*, 1994, 1115; (*d*) Y. Kubo, S. Maeda, S. Tokita and M. Kubo, *Nature*, 1996, **382**, 522.
3 C. L. Raston, J. L. Atwood, P. J. Nichols and I. B. N. Sudria, *Chem. Commun.*, 1996, 2615.
4 D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1009.
5 C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.*, 1985, **107**, 6059; G. M. L. Consoli, F. Cunsolo, M. Piattelli and P. Neri, *J. Org. Chem.*, 1996, **61**, 2195.
6 (*a*) F. Cunsolo, M. Piattelli and P. Neri, *J. Chem. Soc., Chem. Commun.*, 1994, 1917; (*b*) C. Geraci, M. Piattelli and P. Neri, *Tetrahedron Lett.*, 1995, **36**, 5429; (*c*) F. Cunsolo, G. M. L. Consoli, M. Piattelli and P. Neri, *Tetrahedron Lett.*, 1996, **37**, 715; (*d*) C. Geraci, M. Piattelli and P. Neri, *Tetrahedron Lett.*, 1996, **37**, 3899; (*e*) 7627.
7 (*a*) A. Arduini, A. Pochini, A. Secchi and R. Ungaro, *J. Chem. Soc., Chem. Commun.*, 1995, 879; (*b*) M. Mascal, R. T. Naven and R. Warmuth, *Tetrahedron Lett.*, 1995, **36**, 9361; (*c*) A. Ikeda, K. Akao, T. Harada and S. Shinkai, *Tetrahedron Lett.*, 1996, **37**, 1621.
8 A. Arduini, W. M. McGregor, D. Paganuzzi, A. Pochini, A. Secchi, F. Ugozzoli and R. Ungaro, *J. Chem. Soc., Perkin Trans. 2*, 1996, 839.
9 F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.
10 B. Dietrich, P. Viout and J.-M. Lehn, *Macrocyclic Chemistry*, VCH, Weinheim, 1993, pp. 241–356.
11 A. Arduini, A. Pochini, S. Reverberi, R. Ungaro, G. D. Andreetti and F. Ugozzoli, *Tetrahedron*, 1986, **42**, 2089.

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