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Remarkable Alkali Cation Template Effect in 1,5-Bridged Calix[8]arenes

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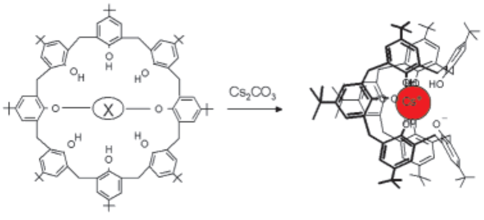
ABSTRACT



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Treatment of 1,5-bridged calix[8]arenes 2–4 with alkali metal carbonates produces salts in which an included cation acts as a conformational template. This induces the folding of calix[8]arene skeleton in a conformation in which the triads of contiguous OH-bearing rings adopt a 3/4-cone conformation with all hydroxyls converging toward the same center. The template effect requires the presence of short bridges (ethylene, tetramethylene, diethylene glycol) and became stronger by increasing the cation dimension up to that of Cs^+.

The template effect is a well-documented phenomenon, today masterfully used in the so-called “template-directed” or “supramolecularly assisted” synthesis of macrocyclic or interlocked molecules.[1] Several templating interactions (including metal cation coordination,[2] π-donor–acceptor,[3] π-stacking,[4] and H-bond[5]) have been exploited for the specific preassembling of reacting species.[6] It has been demonstrated that template effect may affect reversible conformational or self-assembly equilibria.[7]

In calix[4]arene chemistry,[8] the template effect has been invoked to explain the regiochemical or atropisomeric outcome in *O*-alkylation reactions.[9] It has also been used to alter the equilibrium distribution or to reduce the conformational mobility of rapidly interconverting derivatives.[10,11]

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(1) Hoss, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 375. *Templated Organic Synthesis*; Diederich, F., Stang, P. J.; Eds.; Wiley-VCH: Weinheim, 1999.

(2) Dietrich-Buchecker, C.; Rapenne, G.; Sauvage, J.-P.; De Cian, A.; Fischer, J. *Chem. Eur. J.* **1999**, *5*, 1432. Rapenne, G.; Dietrich-Buchecker, C.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1999**, *121*, 994.

(3) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, 3349.

(4) Tjivikuana, T.; Ballester, P.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 1249. Nowick, J. S.; Feng, Q.; Tjivikuana, T.; Ballester, P.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8831.

(5) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599.

(6) It has been demonstrated that even less specific host–guest interactions strongly affect the formation of carcerand structures: Makeiff, D. A.; Pope, D. J.; Sherman, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 1337.

(7) Castellano, R. K.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1996**, *41*, 10002. Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278. It has been proved that template effect can influence product distribution in a dynamic combinatorial library: Cousins, G. R. L.; Furlan, R. L. E.; Ng, Y.-F.; Redman, J. E.; Sanders, J. K. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 423.

(8) For comprehensive reviews on calixarenes see: Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens J., Eds.; Kluwer: Dordrecht, 2001.

(9) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933. Yamamoto, H.; Sakaki, T.; Shinkai, S. *Chem. Lett.* **1994**, 469.

(10) For example, the conformers distribution of mobile tetramethoxycalix[4]arenes is influenced by the nature of metal cation (Iwamoto, K.; Ikeda, A.; Araki, K.; Harada, T.; Shinkai, S. *Tetrahedron* **1993**, *49*, 609), as well as by nitric oxide guest (Rathore, R.; Lindeman, S. V.; Rao, K. S. S. P.; Sun, D.; Kochi, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2123).

(11) For a review see: Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713.

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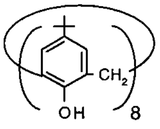
As regards the larger calix[6]arenes, only a few examples exhibiting their guest-induced preorganization are reported.[11,12] In the case of the even larger calix[8]arenes, no clear examples of guest-templation have been so far described,[13] probably as a result of their higher conformational mobility.



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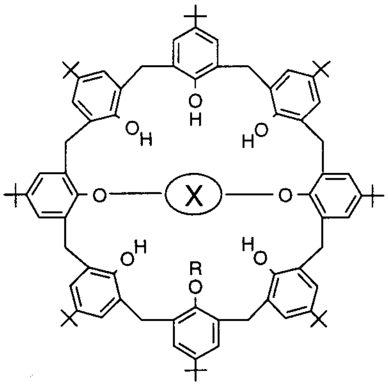

2 R = H; X = $CH_2CH_2CH_2CH_2$
2a R = Me; X = $CH_2CH_2CH_2CH_2$
3 R = H; X = CH_2CH_2
4 R = H; X = $CH_2CH_2OCH_2CH_2$
5 R = H; X = $CH_2(CH_2OCH_2)_2CH_2$

Here we wish to report the first example of solution-state preorganization of a poorly functionalized calix[8]arene induced by alkali cation template effect.

In the course of an investigation on the two-step synthesis of 1,5:3,7-doubly bridged calix[8]arenes,[14] we isolated the intermediate 1,5-singly bridged calix[8]arene **2**,[15] which can be obtained in 90% yield by alkylation in DMF of *p-tert*-butylcalix[8]arene **1** with 1,4-diiodobutane (2 equiv) in the presence of Cs_2CO_3 as base.[16] As expected by the analogy with other singly bridged calix[8]arenes,[16] 1,5-tetramethylene-bridged calix[8]arene **2** showed broad signals in its room temperature ^{1}H NMR spectrum (Figure 1a), indicating a conformational mobility comparable to the NMR time scale. In duplicating the preparation of compound **2**, we serendipitously observed a quite different ^{1}H NMR spectrum with unexpected sharp signals (Figure 1b) for the obtained material.[15] In particular, the presence of two AX systems (δ 3.28 and 4.10, $J = 12.7$ Hz; δ 3.41 and 4.55, $J = 14.7$ Hz) for diagnostic $ArCH_2Ar$ groups clearly indicated a blocked conformation on the NMR time scale. On the basis of the cesium-encapsulating ability of the related 1,5:3,7-doubly bridged calix[8]arenes,[14,17] we formulated this new material as a salt of **2** with an included cesium cation acting as a conformational template.

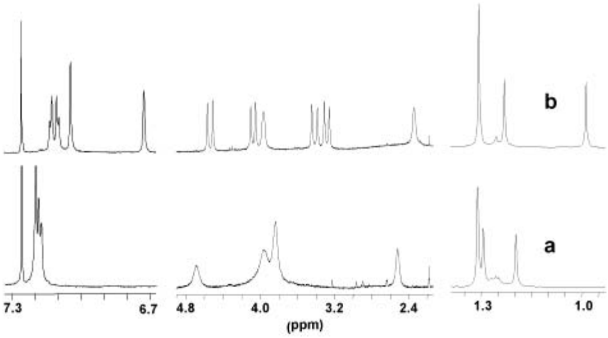

Figure 1. ^{1}H NMR spectrum (250 MHz, $CDCl_3$, 295 K) of 1,5-tetramethylene-bridged calix[8]arene **2** (a) and its cesium salt, $\mathbf{2^-{\cdot}Cs^+}$ (b).

The first proof of this hypothesis came from FAB(+) MS measurements, which showed the calculated [MH^+] molecular ion peak at m/z 1351 for compound **2**, whereas an intense peak at m/z 1484 corresponding to the [MCs^+] ion was observed for the new material.

An additional proof of the saline nature of $\mathbf{2^-{\cdot}Cs^+}$ material was obtained by acidic treatment with diluted HCl, which afforded **2** identified by its characteristic broad spectrum. On the other hand, when **2** was treated with Cs_2CO_3 in DMF at 70 °C or in acetone at room temperature, $\mathbf{2^-{\cdot}Cs^+}$ was readily obtained.[15,18]

A confirmation of the presence of a monoanionic species in $\mathbf{2^-{\cdot}Cs^+}$ was also obtained by its treatment with an excess of MeI (in DMF), which selectively afforded derivative **2a** monomethylated at position 3.[15] This also indicates the preferential charge localization at position 3 in $\mathbf{2}^-$ stabilized by two flanking H-bonds with proximal OH groups.

To assess the effectiveness of the Cs^+ templation, dynamic NMR studies were conducted on both **2** and $\mathbf{2^-{\cdot}Cs^+}$. In the

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(12) Otsuka, H.; Araki, K.; Shinkai, S. *Tetrahedron* **1995**, *51*, 8757. Wang, Y.; Alvarez, J.; Kaifer, A. E. *Chem. Commun.* **1998**, 1457.

(13) An exception could be given by the yet undefined conformational change induced by C_{60}-fullerene complexation: Raston, C. L.; Atwood, J. L.; Nichols, P. J.; Sudria, I. B. N. *Chem. Commun.* **1996**, 2615. It is also known that in lanthanide−calix[8]arene complexes the macrocycle adopts a well-defined solution conformation imposed by the strong coordination geometry of the metal centers: Bunzli, J.; Harrowfield, J. *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991; pp 211−231.

(14) Geraci, C.; Chessari, G.; Piattelli, M.; Neri, P. *Chem. Commun.* **1997**, 921. Geraci, C.; Bottino, A.; Piattelli, M.; Gavuzzo, E.; Neri, P. *J. Chem. Soc., Perkin Trans. 2* **2000**, 185.

(15) Satisfactory microanalytical and spectral data were obtained for all new compounds. ^{1}H NMR spectra were taken at 250 MHz in $CDCl_3$. Compound **2**: ^{1}H NMR (330 K) δ 1.21, 1.31, 1.32 [s, $(CH_3)_3$, 18 H, 18 H, 36 H], 2.50 (bs, OCH_2CH_2, 4 H), 3.85, 3.98 (bs, $ArCH_2Ar$, 8 H each), 4.64 (bs, OCH_2CH_2, 4 H), 7.19, (bs, ArH, 16 H). Salt $\mathbf{2^-{\cdot}Cs^+}$: ^{1}H NMR (295 K) δ 1.01, 1.22, 1.32 [s, $(CH_3)_3$, 18 H, 18 H, 36 H], 2.34 (bs, OCH_2CH_2, 4 H), 3.28, 4.10 (AX, $J = 12.7$ Hz, 8 H), 3.41, 4.55 (AX, $J = 14.7$ Hz, $ArCH_2Ar$, 8 H), 3.97 (bs, OCH_2CH_2, 4 H), 6.73, 7.05, (s, ArH, 4 H each), 7.12, 7.13 (AB, $J = 2.5$ Hz, ArH, 4 H each). Compound **2a**: ^{1}H NMR (295 K) δ 1.12, 1.18, 1.25, 1.27, 1.34 [s, $(CH_3)_3$, 9 H, 18 H, 18 H, 9 H, 18 H], 2.48 (bs, OCH_2CH_2, 4 H), 3.83 (bs, $ArCH_2Ar$, 16 H), 3.94 (s, OCH_3, 3 H), 4.59 (bs, OCH_2CH_2, 4 H), 6.98 (s, ArH, 2 H), 7.04−7.18 (overlapped, ArH, 12 H), 7.19 (s, ArH, 2 H).

(16) For further details on a similar procedure, see: Geraci, C.; Piattelli, M.; Chessari, G.; Neri, P. *J. Org. Chem.* **2000**, *65*, 5143.

(17) Ikeda, A.; Akao, K.; Harada, T.; Shinkai, S. *Tetrahedron Lett.* **1996**, *37*, 1621. Ikeda, A.; Suzuki, Y.; Akao, K.; Shinkai, S. *Chem. Lett.* **1996**, 963.

(18) **Procedure for the preparation of the salts of compounds 2−5.** A suspension of 0.014 mmol of compound **2** (or **3**−**5**) and 0.14 mmol of alkali metal carbonate in DMF (2 mL) was maintained overnight at 70 °C under stirring. The mixture was dried under vacuum, and then H_2O (5 mL) was added. The suspension was filtered to recover the solid salt, which was washed (×4) with H_2O (5 mL) and dried (90−95% yield). Analytically pure samples were obtained by crystallization from CH_2Cl_2/MeOH.

first instance sharp signals corresponding to a fast conformational interconversion were observed at temperatures higher than 315 K. Upon cooling a coalescence of $ArCH_2$-Ar signals can be ascertained at 276 K, while the freezing-out of a 2-fold symmetrical conformation of **2** can be observed down to 215 K. From these data an energy barrier of 13.9 kcal/mol can be estimated. In the case of $\mathbf{2^{-}{\cdot}Cs^{+}}$ no significant spectral changes were observed in the 220−355 K range, while a coalescence of $ArCH_2Ar$ AX systems takes place at about 370 K in $C_2D_2Cl_4$. In this instance an energy barrier higher than 17.1 kcal/mol can be evaluated. Comparison of the two barrier values leads to a difference of about 3 kcal/mol, which can be mainly attributed to the conformational stabilization brought by the cesium template effect.

A better understanding of this template effect in $\mathbf{2^{-}{\cdot}Cs^{+}}$ can be achieved on geometrical grounds. In fact, the presence of two well-spaced AX systems for $ArCH_2Ar$ groups ($\Delta\delta$ = 0.82 and 1.14) in its 2D COSY NMR spectrum clearly points to a *syn* relative orientation of each couple of calix[8]arene aromatic rings. This requirement can be adequately satisfied assuming a folded conformation of the calix[8]arene skeleton (depicted in Figure 2) in which the two triads of contiguous OH-bearing rings (at positions 2,3,4 and 6,7,8, respectively) adopt a 3/4-cone conformation with all hydroxyls converging toward the same center.

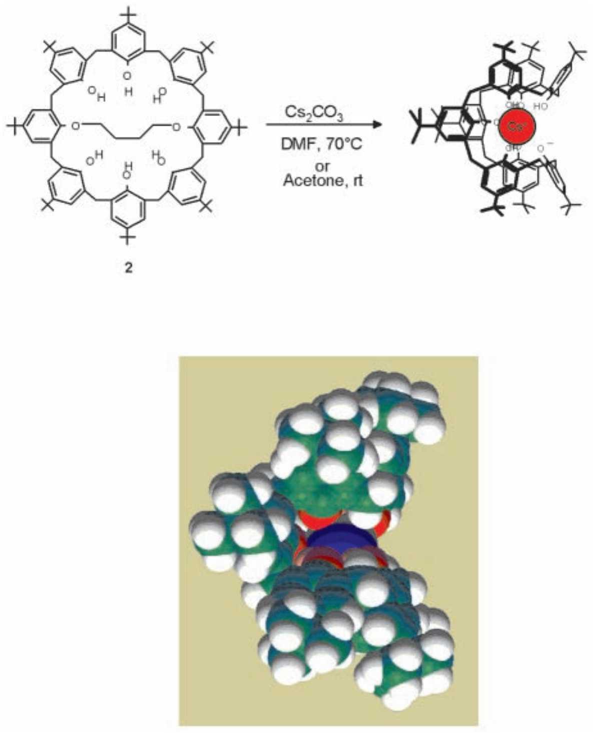

Figure 2. Formation of the cesium template in the $\mathbf{2^{-}{\cdot}Cs^{+}}$ salt (top) and its CPK computer model (bottom).

The overall geometry of the calix[8]arene macrocycle has to be very similar to the D_{2d} structure of related cesium-selective 1,5:3,7-doubly bridged calix[8]arene ionophores.[14,17] In analogy to them, the cesium cation in $\mathbf{2^{-}{\cdot}Cs^{+}}$ would sit at the center of the structure surrounded by the eight oxygens. In this way Cs^+ cation blocks the folded conformation because of its interaction with O atoms with the aid of ion-pairing electrostatic stabilization.

On the basis of above structural features it is conceivable that other alkali cations could give rise to a template effect with different efficiency. Therefore, formation of inclusive salt of **2** was investigated by heating it in DMF with alkali metals carbonates.[18] The material obtained after washing with H_2O showed sharp AX systems in the ^1H NMR spectrum in the case of K^+, Rb^+, or Cs^+ cations, whereas Na^+ gave a broad spectrum (Figure 3).[19] This demonstrates that a cation of larger dimension is required for generation of template effect.

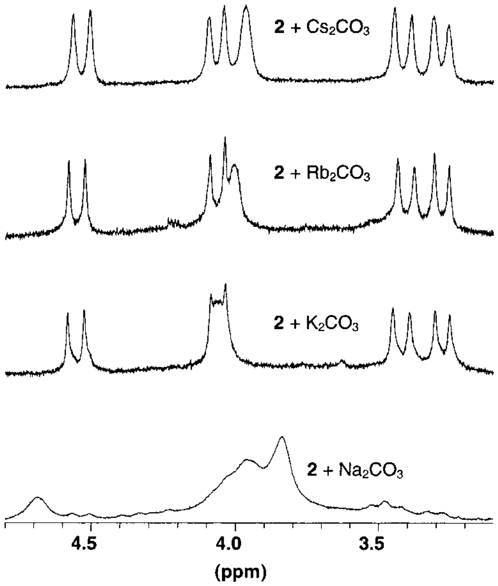

Figure 3. Comparison of the methylene region of the ^1H NMR spectra (250 MHz, $CDCl_3$, 295 K) of **2** after overnight treatment with alkali metal carbonates in DMF at 70 °C.

Interestingly, $\mathbf{2^{-}{\cdot}K^{+}}$, $\mathbf{2^{-}{\cdot}Rb^{+}}$, and $\mathbf{2^{-}{\cdot}Cs^{+}}$ salts gave slightly different ^1H NMR spectra (Figure 3), thus allowing an easy discrimination among them. On this premise, competition experiments were performed by treating **2** with a mixture of two alkali carbonates in equivalent excess. The result of these tests allowed to establish the following stability order: $\mathbf{2^{-}{\cdot}Cs^{+}} > \mathbf{2^{-}{\cdot}Rb^{+}} > \mathbf{2^{-}{\cdot}K^{+}} > \mathbf{2^{-}{\cdot}Na^{+}}$. An additional evidence of this relative stability was obtained from their ^1H NMR spectra acquired in acetone-d_6. In fact, in this solvent both $\mathbf{2^{-}{\cdot}Cs^{+}}$ and $\mathbf{2^{-}{\cdot}Rb^{+}}$ gave sharp AX systems for $ArCH_2Ar$ groups, whereas $\mathbf{2^{-}{\cdot}K^{+}}$ gave broad signals. This is explainable by the lower stability of the K^+ template associated with the higher cation-coordinating ability of

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[19] The salt formation is evidenced by a large increase of solubility with respect to **2**, which is scarcely soluble in common organic solvents.

acetone solvent. Therefore, it can be concluded that cation dimension plays a crucial role in the effectiveness of template effect.

It is worth noting that alkali salts of *p*-*tert*-butylcalix[8]arene (**1^{-}·Cs^{+}**, **1^{-}·Rb^{+}**, and **1^{-}·K^{+}**), obtained with the same procedure, all gave broad ^{1}H NMR spectra. This indicates that 1,5-bridging is a fundamental requirement for template effect. Even the bridge length plays a major role in this respect, since both 1,5-calix[8]crown-2 **3**[16] and 1,5-calix[8]crown-3 **4**[16] display Cs^{+} template effect, whereas 1,5-calix[8]crown-4 **5**[16] does not. Probably, the higher rigidity imposed by a shorter bridge is also an essential requisite for template effect in these calix[8]arene derivatives.

In conclusion, the present work reports on the first examples of conformational preorganization in solution by alkali cation template effect on poorly functionalized 1,5-bridged calix[8]arenes. It is also demonstrated that short bridges are required to give a template effect, which becomes stronger by increasing the cation dimension. The presence of this templation in 1,5-bridged calix[8]arenes could be used to explain the somewhat surprising selectivity observed in the preparation of doubly bridged derivatives.

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