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Conformational Templation in a Singly Bridged Calix[7]arene Derivative Induced by Alkali Metal Cations

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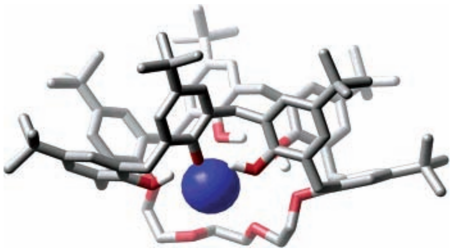
ABSTRACT



The first examples of alkali metal cation conformational templation of a calix[7]arene derivative were found in the alkali salts of 1,4-calix[7]-crown-4, which were obtained by its treatment with the corresponding alkali metal carbonates. Competitive experiments showed that potassium and rubidium cations give the most effective templation, with a slight preference for the former. Experimental results and Monte Carlo conformational searches indicated that the cation interacts with all O-atoms including those of the crown-4 bridge.

The conformational templation of calixarene[1] systems by means of specific interactions with alkali metal cations is a well-documented phenomenon in their multifaceted chemistry.[2] It is considered the main factor controlling the regio- or stereochemical outcome in some O-alkylation reactions.[3] In addition, it can influence the equilibrium composition or the interconversion rate of conformationally mobile derivatives.[4] Furthermore, this templation may also affect the recognition properties[5] or the self-assembly equilibria[6] of specific calixarene hosts.

The majority of these examples has been found in the calix[4]arene series,[2−6] and they are more limited for the corresponding hexameric homologues.[7] Regarding the larger calix[8]arenes, we have recently described an interesting example of solution-state preorganization of poorly functionalized 1,5-bridged derivatives induced by alkali metal cation templation.[8]

In the case of the intermediate calix[7]arene macrocycle, no examples of cation templation have been so far described,

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[2] For a general review with a focus on cation recognition and templation, see: Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713.

[3] (a) Shinkai, S. *Tetrahedron* **1993**, *40*, 8933. (b) Yamamoto, H.; Sakaki, T.; Shinkai, S. *Chem. Lett.* **1994**, 469.

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[5] (a) Ohseto, F.; Yamamoto, H.; Matsumoto, H.; Shinkai, S. *Tetrahedron Lett.* **1995**, *36*, 6911. (b) Jurgen, S.; van Duynhoven, J. P. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1009. (c) Ikeda, A.; Suzuki, Y.; Yoshimura, M.; Shinkai, S. *Tetrahedron* **1998**, *54*, 2497. (d) Nabeshima, T.; Saiki, T.; Iwabuchi, J.; Akine, S. *J. Am. Chem. Soc.* **2005**, *127*, 5507.

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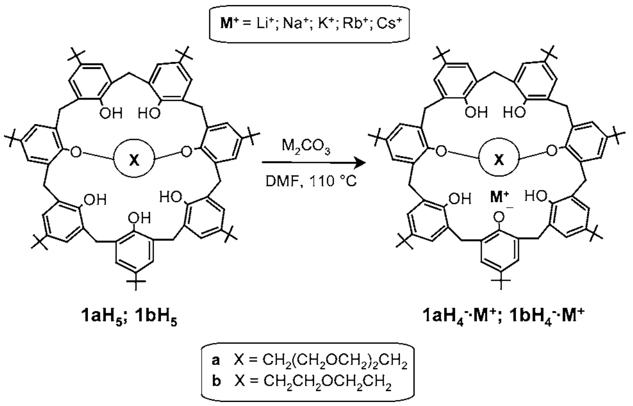
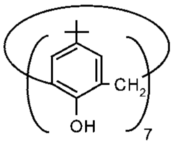
probably as a consequence of the yet limited number of investigations devoted to the chemistry of this calixarene family.[9] Here we report the first example of conformational templation of a calix[7]arene derivate induced by alkali metal cations.

The previous experience with alkali salts of singly bridged calix[8]arenes[8] prompted us to verify if a similar alkali metal cation templation could occur also in the calix[7]arene series. Therefore, we decided to study the alkali salts[10] of the known 1,4-calix[7]crown-4 **1aH$_5$**[11] (Scheme 1), obtainable in good yields by Cs_2CO_3-promoted direct alkylation of *p-tert*-butylcalix[7]arene **2**. Thus, **1aH$_5$** was treated with potassium carbonate (10 equiv) in DMF at 100 °C for 17 h. Then, the solvent was removed under vacuum and the crude product washed with water, to give **1aH$_4^-$·K$^+$**.[12]

Scheme 1



The composition of **1aH$_4^-$·K$^+$** was confirmed by elemental analysis and mass spectrometry. In fact, ESI(+) MS measurements showed a very intense [MK$^+$] ion peak at *m*/*z* 1287, whereas the starting material **1aH$_5$** only gave the [MH$^+$] molecular ion peak at *m*/*z* 1249. The saline nature of **1aH$_4^-$·K$^+$** was confirmed by acidic treatment with a diluted HCl solution, which afforded the parent **1aH$_5$**.



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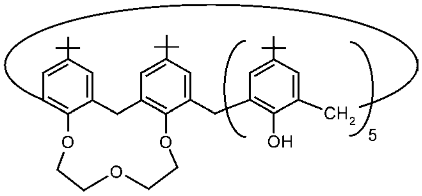

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As envisaged, the ^{1}H NMR spectrum of the **1aH$_4^-$·K$^+$** salt showed sharp signals at room temperature, in clear contrast with the parent singly bridged calix[7]arene **1aH$_5$**, which gave broad resonances indicative of a conformational mobility comparable to the NMR time scale (Figure 1). The 2D COSY-45 spectrum of **1aH$_4^-$·K$^+$** evidenced four AX systems for ArCH$_2$Ar groups (δ 3.24/3.76, $J = 13.0$ Hz; 3.30/4.22, $J = 14.0$ Hz; 3.36/4.13, $J = 12.9$ Hz; 3.50/4.37, $J = 16.8$ Hz),[12] clearly indicating a blocked conformation on the NMR time scale.

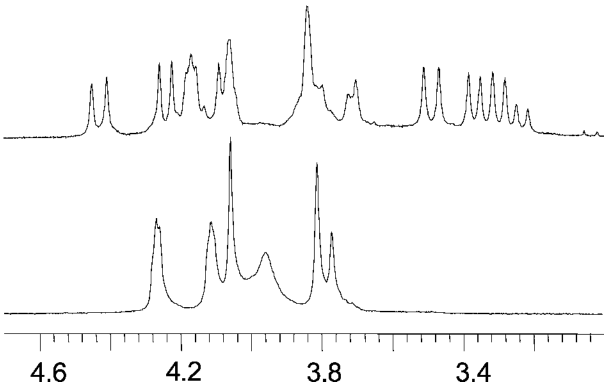

Figure 1. Comparison of the methylene region of the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of 1,4-calix[7]crown-4 **1aH$_5$** (bottom) and its potassium salts **1aH$_4^-$·K$^+$** (top).

This behavior is very similar to that of 1,5-bridged calix[8]arenes,[8] where X-ray crystallography proved that alkali metal cations can act as a conformational template, folding their skeleton in a blocked *tub-shaped* conformation.[8b] Therefore, in analogy, we propose a comparable conformational templation of the calix[7]arene skeleton induced by the K$^+$ cation.

The effectiveness of this templation was evaluated by means of dynamic NMR studies. In fact, the broad signals of ArCH$_2$Ar groups of **1aH$_5$** gave a coalescence at 233 K, corresponding to an energy barrier of 11.0 kcal/mol for its conformational interconversion. On the other hand, no hint of coalescence could be observed up to 363 K for the AX systems of the **1aH$_4^-$·K$^+$** salt, which implies an energy barrier certainly higher than 16.5 kcal/mol. Consequently, a minimum difference of 5.5 kcal/mol between the two values can be considered as a direct consequence of the K$^+$ conformational templation. This value is comparable to those found for similar salts of calix[8]-[8] and -[6]arenes,[7b] whereas no significant lowering of the rate of conformational inversion was observed for the calix[4]arene analogues.[7b]

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[9] For a review on the chemistry of calix[7]arenes, see: (a) Martino, M.; Neri, P. *Mini-Rev. Org. Chem.* **2004**, *1*, 219.

[10] For additional studies on alkali salts of calixarenes, see ref 7 and: (a) Gutsche, C. D.; Iqbal, M.; Nam, K. S.; See, K.; Alam, I. *Pure Appl. Chem.* **1988**, *60*, 483. (b) Harrowfield, J. M.; Ogden, M. I.; Richmond, W. R.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1991**, 1159. (c) Bock, H.; John, A.; Nather, C.; Havlas, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9367. (d) Abidi, R.; Baker, M. V.; Harrowfield, J. M.; Ho, D. S.-C.; Richmond, W. R.; Skelton, B. W.; White, A. H.; Varnek, A.; Wipff, G. *Inorg. Chim. Acta* **1996**, *246*, 275. (e) Wipff, G.; Engler, E.; Guilbaud, P.; Lauterbach, M.; Troxler, L.; Varnek, A. *New J. Chem.* **1996**, *20*, 403. (f) Nam, K. C.; Kim, D. S.; Kim, J. M. *Bull. Korean Chem. Soc.* **1997**, *18*, 636. (g) Murayama, K.; Aoki, K. *Inorg. Chim. Acta* **1998**, *281*, 36. (h) Nachtigall, F. F.; Vencato, I.; Lazzarotto, M.; Nome, F. *Acta Crystallogr.* **1998**, *C54*, 1007. (i) Clague, N. P.; Clegg, W.; Coles, S. J.; Crane, J. D.; Moreton, D. J.; Sinn, E.; Teat, S. J.; Young, N. A. *Chem. Commun.* **1999**, 379. (j) Thuéry, P.; Asfari, Z.; Vicens, J.; Lamare, V.; Dozol, J.-F. *Polyhedron* **2002**, *21*, 2497. (k) Guillemot, G.; Solari, E.; Rizzoli, C.; Floriani, C. *Chem.−Eur. J.* **2002**, *8*, 2072. (l) Hanna, T. A.; Liu, L.; Zakharov, L. N.; Rehingold, A. L.; Watson, W. H.; Gutsche, C. D. *Tetrahedron* **2002**, *58*, 9751. (m) Gueneau, E. D.; Fromm, K. M.; Goesmann, H. *Chem.−Eur. J.* **2003**, *9*, 509. (n) Bergougnant, R. D.; Robin, A. Y.; Fromm, K. M. *Cryst. Growth Des.* **2005**, *5*, 1691.

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[12] See the Supporting Information for additional details.

The interaction of the potassium cation with the 1,4-calix[7]crown-4 system can be understood by considering the following. First, on the basis of the well-known preferential formation of doubly H-bonded monoanions in the weak base-promoted regioselective O-alkylation of calixarenes,[1,7b,8a,13] a preferential negative charge localization at position 6 in $\mathbf{1aH_4}^-\cdot\mathbf{K}^+$ can be confidently assumed. Second, the well-spaced AX systems for $ArCH_2Ar$ groups point to a syn orientation of each couple of proximal aromatic rings. This could be accounted for by a geometry very similar to that of the *double-cone pinched* conformation of *p-tert*-butylcalix[7]arene, previously found by X-ray crystallography[14] and MM3 calculations,[15] which is characterized by a syn combination of tetrameric (conelike) and trimeric (3/4-conelike) substructures.

A better insight into the geometry of the cation templation in $\mathbf{1aH_4}^-\cdot\mathbf{K}^+$ was obtained by Monte Carlo conformational searches using the MacroModel-9.0 program[16] [OPLS (optimized potentials for liquid simulations) force field, $CHCl_3$ solvent]. Several starting structures were used, which were built on the basis of the most common conformations adopted by the calix[7]arene skeleton as found in the X-ray crystal structures.[9] In accordance with the above considerations, the location of the phenoxide anion at the 6 position always led to a lower energy with respect to all the other ones. Therefore, all conformational searches were conducted on this anion. One point of particular interest concerns the possibility that oxygen atoms of the crown-4 bridge may be involved or not in cation interactions. The lowest OPLS energy configuration found by these means is depicted in Figure 2a. In this structure, the K^+ cation is located approximately in the center of a *double-cone pinched* calix[7]arene skeleton in close contact with the phenoxide anion. It appears to be also interacting with all the remaining eight O-atoms including those of the crown-4 bridge. The structure is asymmetrical; therefore, a fast exchange between two mirror image geometries has to be invoked to explain the C_s symmetry observed in its ^1H NMR spectrum.

A significantly less stable symmetrical structure was also obtained (Figure 2b), which can be considered as a good representation of the averaged conformation compatible with the NMR spectra. Other configurations in which cation−bridge interactions were absent or in which the K^+ ion gave cation−π interactions[7b,10b,10l] were found at substantially higher OPLS energies.

The above results induced us to extend the study to other alkali metal cations. Thus, $\mathbf{1aH_5}$ was treated with alkali metal carbonates in DMF under the above conditions, to give the corresponding salts $\mathbf{1aH_4}^-\cdot\mathbf{M}^+$. Interestingly, these materials showed different ^1H NMR spectra. Thus, the cesium salt $\mathbf{1aH_4}^-\cdot\mathbf{Cs}^+$ (Figure 3) showed some broad AX systems in the methylene region, indicative of a reduced conformational mobility, although with a less effective cation templation with respect to the K^+ analogue. On the contrary, the rubidium cation presents a similar strong templation as indicated by a very similar ^1H NMR spectrum with four well-separated AX systems for $ArCH_2Ar$ groups (Figure 3). On the other hand, the lithium and sodium salts showed broad ^1H NMR spectra indicating a weaker conformational templation with respect

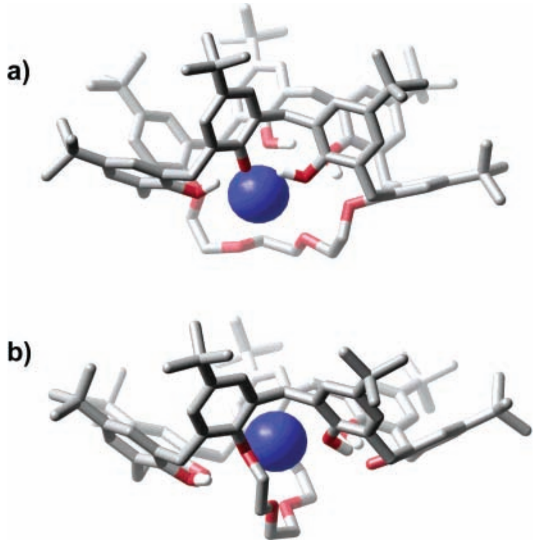

Figure 2. Computer models of the asymmetrical lowest OPLS energy conformation (a) and of the averaged symmetrical structure (b) of the $\mathbf{1aH_4}^-\cdot\mathbf{K}^+$ salt found by Monte Carlo conformational searches.

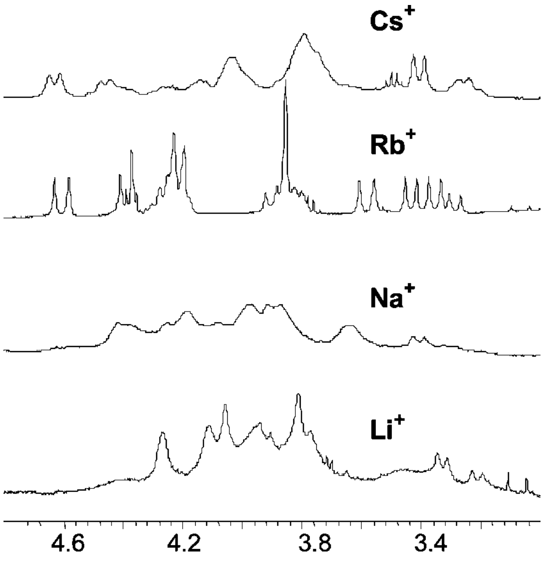

Figure 3. Comparison of the methylene regions of the ^1H NMR spectra (400 MHz, $CDCl_3$, 298 K) of the alkali salts $\mathbf{1aH_4}^-\cdot\mathbf{M}^+$ ($M^+ = Cs^+$, Rb^+, Na^+, and Li^+).

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[14] Andreetti, G. D.; Ugozzoli, F.; Nakamoto, Y.; Ishida, S.-I. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, *10*, 241.

[15] Harada, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2231.

[16] *MacroModel*, version 9.0; Schrödinger, LLC: New York, 2005. Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

to both Rb^+ and K^+. This demonstrates that cations of intermediate dimensions are more effective to generate a cation template in 1,4-bridged calix[7]crown-4 **$1aH_5$**. This result is in clear contrast with that of 1,5-bridged calix[8]-arenes where cations of larger dimensions (Cs^+) were more effective.[8] In these instances, the size complementarity between the cation and the macrocycle clearly plays a crucial role.

Competition experiments were performed by treating **$1aH_5$** with a mixture of two alkali carbonates in equivalent excess. Thus, treatment of 1,4-calix[7]crown-4 with a mixture of cesium and rubidium carbonates resulted in the formation of the rubidium salt **$1aH_4^-{\cdot}Rb^+$**, whereas no formation of cesium salt was observed. This is indicative of a higher stability of the Rb^+ over the Cs^+ template.

Analogous treatment of **$1aH_5$** with a mixture of potassium and sodium carbonates only gave the **$1aH_4^-{\cdot}K^+$** salt. The competitive experiments with rubidium and potassium carbonates were very interesting, which afforded a mixture of **$1aH_4^-{\cdot}K^+$** and **$1aH_4^-{\cdot}Rb^+$**. In particular, the ^1H NMR spectrum of this mixture (Figure 4) showed distinct resonances easily assignable to each of the two salts. Thus, integration of the aromatic signals at 6.35 and 6.38 ppm of potassium and rubidium salt, respectively, clearly evidenced a slightly higher stability of K^+ over Rb^+ templation (3:2 ratio of intensity).

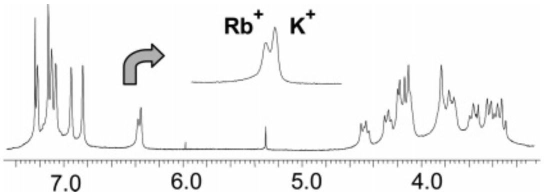

Figure 4. Methylene and aromatic region of the ^1H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of **$1bH_5$** after the competitive treatment with an equivalent excess of rubidium and potassium carbonates.

The presence of the bridge is of fundamental importance for conformational blockage. In fact, alkali metal salts of *p-tert*-butylcalix[7]arene **2**, obtained under the same conditions, showed broad ^1H NMR spectra, indicative of a conformational mobility comparable to the NMR time scale. The nature and position of the bridge also plays a fundamental role; in fact, no conformational blockage was observed after heating 1,4-calix[7]crown-3 **$1bH_5$** and 1,2-calix[7]crown-3 **3** with alkali metal carbonates. These results clearly confirm the direct involvement of the crown bridge evidenced by the above-discussed molecular mechanics calculations.

In conclusion, the present work reports on the first examples of conformational templation of a singly bridged calix[7]arene induced by alkali metal cations. Different from a similar case observed in calix[8]arene chemistry, in this instance a higher effectiveness of templation was given by cations of intermediate size (K^+ and Rb^+), with the direct involvement of the polyether bridging moiety.

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Supporting Information Available: Synthetic details, ^1H/^{13}C and 2D NMR data, and OPLS energy-minimized structures for the **$1aH_4^-{\cdot}K^+$** salt. This material is available free of charge via the Internet at http://pubs.acs.org.

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