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Control of Alkali Cation Complexation in Bridged Calix[4]arene Esters Induced by Small Conformational Changes

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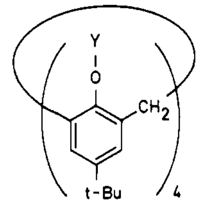
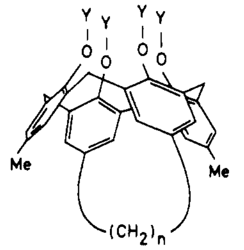
Summary: Tetraester derivatives of calix[4]arenes in which polymethylene chains span two opposite para positions show a sharp change in complexation ability toward alkali cations in going from chain length $n = 6$ to $n = 7$. While the compounds with longer chains behave like the analogous derivatives of unbridged calix[4]arenes, no extraction of picrates is found for compounds with shorter chains. This observation is interpreted in terms of different conformational flexibility.

Several calix[4]arene tetraesters,[1] tetraketones,[2] and tetraamides[3] of the type 1 have a high affinity for alkali metal cations. Stability constant and phase-transfer measurements reveal a pronounced selectivity for Na^+ cation.[4] A series of bridged calix[4]arenes (2) has recently been reported in which polymethylene bridges of length n = 5–16 span two para positions in a diagonal arrangement.[5] The length of the bridge has a profound effect on the conformational mobility of the calixarene as a whole. All members of this series possess stable cone conformations over a wide temperature range, unlike the parent, unbridged calix[4]arenes which, though possessing the cone conformation, are fluxional at ordinary temperatures. The effect of bridging in 2 is most pronounced with chain length $n = 5$ and can be analyzed in the solid state by X-ray analysis.[5-7] The two aromatic rings spanned by the bridge are almost parallel whereas the unbridged rings are constrained to lie at an angle of 109°. This constraint results in an upward movement of two hydroxyl groups and a downward movement of the other two with respect to the mean plane of the macrocyclic ring defined by the positions of the four conjoining methylene carbons. Similarly distorted cone conformations exist in the unbridged tetraester/amide/ketone derivatives 1 as revealed by several X-ray analyses.[1a,c,2-4] On complex formation between tetraamide 1c and KSCN, the ligand assumes regular 4-fold symmetry for the ligating groups (four phenolic and four carbonyl oxygen atoms) about the metal cation.[3] Consequently, the calixarene receptor as a whole acquires 4-fold symmetry. These observations suggest a correlation between calixarene shape and mobility and complexation affinity for alkali cations.



1

a: Y = CH_2CO_2R
b: Y = $CH_2C(O)R$
c: Y = $CH_2C(O)NR_2$



2

a: Y = H
b: Y = CH_2CO_2Et

Table I. Extraction of Alkali Metal Picrates (% *E* Values[a]) from Neutral Aqueous Solution[b] into Dichloromethane at 20 °C

	1a	2b, $n = 5$	2b, $n = 6$	2b, $n = 7$	2b, $n = 9$
Li^+	7	0.0	0.0	4	14
Na^+	29	0.0	0.0	20	38
K^+	5	0.0	0.0	5	19
Rb^+	4	0.0	0.0	3	16
Cs^+	6	0.0	0.0	4	19

[a] Values are 5%. [b] Calixarene and picrate concentrations 2×10^{-4} M.

We have converted four members of the bridged series 2a, viz. n = 5–7 and 9, into tetraethyl esters (2b) and have studied their complexation behavior in a preliminary semiquantitative way using Pedersen's alkali picrate extraction technique[8] (Table I). We have observed that a sharp change in complexation ability occurs in going from $n = 6$ to $n = 7$. In fact, within the detection limits, compounds 2b with $n = 5$ and 6 show no extraction for any of the alkali cations whereas for $n = 7$ and 9 there is extensive extraction, revealing a selectivity for Na^+ which is virtually identical (Table I) with unbridged tetraesters (1a) having four *p-tert*-butyl substituents. The observation that 2b ($n = 9$), which of course is more flexible than 2b ($n = 7$), is even better extracting than 1a needs further elucidation and should not be overinterpreted in the moment.

We interpret this abrupt change in complexation in terms of the varying abilities of the four systems to adapt conformationally to the dimensions favorable to guest cation reception. In $n = 5$ and 6, the methylene bridge is of insufficient length to permit the flexing of all four ligating side arms into the 4-fold symmetry which is apparently required.[9] In contrast, the transition from $n = 6$ to $n = 7$ is obviously the precise elongation of the methylene bridge that is necessary for the conformational change to 4-fold symmetry. According to the X-ray data

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[9] Differences in the flexibility of bridged calixarenes are reflected also by their photo-CIDNP spectra; see: Böhmer, V.; Goldmann, H.; Kaptein, R.; Zetta, L. *J. Chem. Soc., Chem. Commun.* **1987**, 1358.

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for the free phenols[5,7] (**2a**, $n = 6$ and 7), the difference in the distance between carbon 1 and n of the polymethylene bridge in $n = 6$ and 7 is 1.3 Å. Thus we can now quantify the optimum topology for this change in complexation.

NMR data (400 MHz) for **2b** ($n = 9$) and its Na^+ complex in solution support this conclusion.[10] While **2b** ($n = 9$) displays two singlets for the ArH protons (6.901 and 6.181 ppm), two singlets for the OCH_2CO protons (5.032 and 4.428 ppm) and two quadruplets for the OCH_2CH_3 protons (4.231 and 4.114 ppm, $J_{AB} = 7.2$ Hz), its sodium complex displays only one (or nearly so) of each of these signals (6.925 6.912 for ArH; 4.427, 4.423 for OCH_2CO; 4.346 ppm for OCH_2CH_3), which demonstrates clearly that differences in chemical shifts are not caused by substituent effects. Furthermore, with the exception of the 1 and 9 methylene protons, all the protons of the bridge appear between 1.1 and 1.3 ppm, with no signals at higher field, whereas in the Na^+ complex two pentuplets, each for two methylene groups, appear at 0.551 and 0.408 ppm. This shows that in going to 4-fold symmetry the polymethylene chain is pulled into the more shielded zone of the cavity defined by the aromatic moieties. Clearly, the free ligand has the characteristic C_2 symmetry of a distorted calix[4]arene in the cone conformation, while the Na^+ complex requires the more regular C_4 symmetry. When this arrangement is prohibited by the shorter bridges in **2b**, $n = 5$ and 6, cation complexation is closed down under the experimental conditions of picrate extraction.

This sharp discontinuity in complexation associated with very minor conformational restrictions induced by polymethylene bridging suggests the possibility of designing host molecules in which conformation flexing in a reversible fashion may be coupled with the selective reception and release of guest cations. This complexation of metal ions between the ether/ester groups may be related also to the complexation of a suitable host within the hydrophobic cavity and vice versa, leading to very simple models for allosteric effects.

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Supplementary Material Available: Characterization and ^1H NMR spectra for compounds **26** ($n = 5$–7, 9) (6 pages). Ordering information is given on any current masthead page.

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[10] ^1H NMR (400 MHz) [**2b** ($n = 9$), $CDCl_3$] δ 6.901 (s, 4 H, ArH), 6.181 (s, 4 H, ArH), 5.032 (s, 4 H, OCH_2CO), 4.786 (d, 4 H, $ArCH_AH_BAr$, $J_{AB} = 13.2$ Hz), 4.428 (s, 4 H, OCH_2CO), 4.231 (q, 4 H, OCH_2CH_3, $J_{AB} = 7.2$ Hz), 4.114 (q, 4 H, OCH_2CH_3, $J_{AB} = 7.2$ Hz), 3.120 (d, 4 H, $ArCH_AH_BAr$, $J_{AB} = 13.2$ Hz), 2.315 (s, 6 H, $ArCH_3$), 2.05 (m, 4 H, $ArCH_2CH_2$), 1.292 (t, 6 H, OCH_2CH_3, $J_{AB} = 7.2$ Hz), 1.229 (t, 6 H, OCH_2CH_3, $J_{AB} = 7.2$ Hz), 1.25 (br m, 8 H, $CH_2CH_2CH_2$), 1.15 ppm (br m, 6 H, $CH_2CH_2CH_2$). After shaking this solution with solid NaSCN the spectrum of the Na^+ complex is obtained: δ 6.925 (s, 4 H, ArH), 6.912 (s, 4 H, ArH), 4.427 (s, 4 H, OCH_2CO), 4.423 (s, 4 H, OCH_2CO), 4.346 (q, 8 H, OCH_2CH_3, $J_{AB} = 7.1$ Hz), 4.168 (d, 4 H, $ArCH_AH_BAr$, $J_{AB} = 12.2$ Hz), 3.311 (d, 4 H, $ArCH_AH_BAr$, $J_{AB} = 12.2$ Hz), 2.40 (m, 4 H, $ArCH_2CH_2$), 2.084 (s, 6 H, $ArCH_3$), 1.388 (t, 12 H, OCH_2CH_3, $J_{AB} = 7.1$ Hz), 1.3 (br m, 6 H, $CH_2CH_2CH_2$), 0.551 (br p, 4 H, $CH_2CH_2CH_2$, $J_{AB} = 7.2$ Hz), 0.408 ppm (br p, 4 H, $CH_2CH_2CH_2$, $J_{AB} = 7.3$ Hz).

4-Siloxy-α-bromocrotonate: A New Reagent for [2 + 3] Annulation Leading to Oxygenated Cyclopentenes at Low Temperatures

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Summary: The lithium dienolate of 4-siloxy-2-bromocrotonate was condensed with several enones to afford silyl enol ether terminated vinylcyclopropanes, which were rearranged at low temperatures under various conditions to the corresponding oxycyclopentenes. The conditions, unoptimized yields, and the initial results regarding the stereochemical course of this new rearrangement are reported. An application of this methodology to the synthesis of highly functionalized oxygenated cyclopentanoids such as the iridoids is suggested.

Oxygenated cyclopentanes are found in such natural products as iridoids, prostaglandins, and sesquiterpenes.[2] A number of approaches to cyclopentanoid compounds have been reported,[3] including our efforts in the area of [4 + 1] and [2 + 3] annulations.[4] We considered an efficient and a general approach to oxygenated cyclopentanoids under conditions that would tolerate a higher degree of oxygenation and substitution than permitted by the currently used thermolytic rearrangements. A methodology was envisioned that would provide oxygenated cyclopentenes such as **2** by the enantiocontrolled [2 + 3] annulation of enone **3**, derived optically pure from toluene,[5] with a zwitterion such as **1** (Figure 1), provided such a synthon could be easily prepared.

A two-step procedure for the synthesis of fused cyclopentene esters of type **7** (Figure 2) has been realized via either thermolysis or nucleophilic opening rearrangements of vinylcyclopropanes **6**.[6] We now report the use of γ-

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