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Novel 1,2-Bridged Calix[4]crowns in the 1,2-Alternate Conformation[1]

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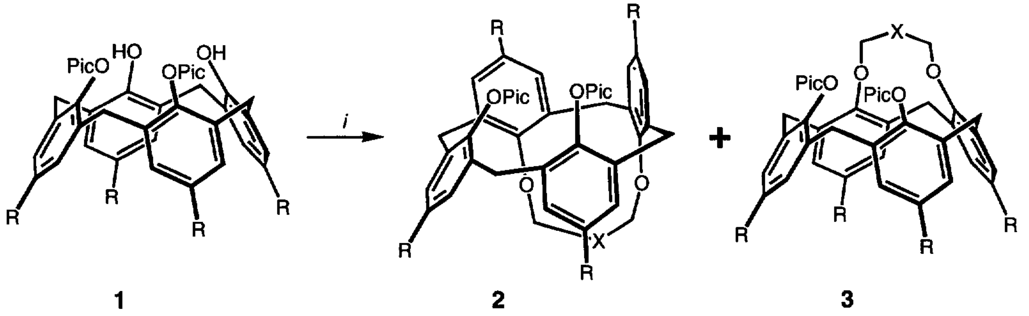
Abstract: Treatment of 1,2-di[(2-pyridylmethyl)oxy]calix[4]arenes **1** (R = *t*-Bu, H) with tri- to pentaethylene glycol ditosylates in anhydrous toluene in the presence of *t*-BuOK affords a mixture of 1,2-alternate and cone (1,2)-calix[4]crown conformers **2** and **3** in a 55-70% overall yield. The conformational features of **2** have been deduced by NMR, and further confirmed by single-crystal X-ray analysis on crown-5 derivative **2e**. Copyright © 1996 Elsevier Science Ltd

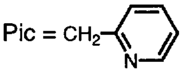
The term calixcrowns refers to the family of macropolycyclic molecules in which a monocyclic calixarene structure is linked - via its phenolic oxygens - to a cyclic polyether moiety. Since the first report by Ungaro,[2] the design and synthesis of the various conformers of (1,3)-calix[4]crowns (cone, partial cone and 1,3-alternate) have developed very rapidly, owing to their proclivity to selectively bind alkali and alkaline earth metal cations.[3] Conversely, synthetic methodologies leading to (1,2)-bridged calix[4]crowns have not kept pace with their (1,3)-regioisomers,[4] and the only structures reported so far [(1,2)-calix[4]crowns,[5] (1,2)-calix[4]biscrowns,[6] and inherently chiral (1,2)-calix[4]crowns[7]] all adopt a fixed cone conformation. We felt that readily available 1,2-di-O-alkylated calixarenes[8,9] could represent pivotal starting materials for the attainment of (1,2)-calix[4]crowns other than cone, and in this paper we wish to report the first examples of (1,2)-calix[4]crown ethers in a fixed 1,2-alternate conformation.

The slow addition of oligoethylene glycol ditosylate (1.1 equiv) in toluene to a dilute solution of 1,2-di[(2-pyridylmethyl)oxy]calix[4]arenes **1** (R = *t*-Bu, H) in anhydrous toluene at 70 °C in the presence of *t*-BuOK (2.2 equiv) afforded a mixture of 1,2-alternate and cone calix[4]crown ethers **2** and **3** in a 55-70% overall yield,[10,11] which were isolated by column chromatography (Scheme 1).

A likely reaction pathway to account for product formation in the cyclization of **1** is depicted in Scheme 2. Deprotonation of **1** with 2 equivalents of the strong base *t*-BuOK affords two dianionic conformers, cone $[\mathbf{C\text{-}1}]^{2-}$ and partial cone $[\mathbf{PC\text{-}1}]^{2-}$, in equilibrium. Upon cyclization with oligoethylene glycol ditosylate, $[\mathbf{C\text{-}1}]^{2-}$ can afford the cone conformers **3** (path a), whereas $[\mathbf{PC\text{-}1}]^{2-}$ can yield **3** and the 1,2-alternate conformers **2** (paths b and c, respectively), subsequent to interconversion of the residual phenoxide group on the initial tosylated intermediate. Our results show that the bulkiness of the *para*-substituent (R = *t*-Bu, H) plays an important role in product distribution, with the 1,2-alternate prevailing over cone conformers (ratio ca. 3:1) when *t*-Bu groups are absent.

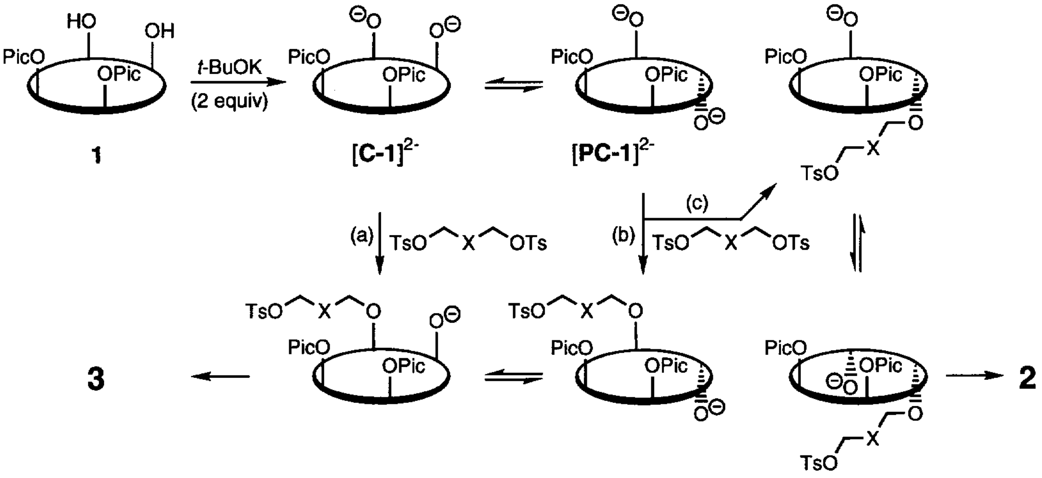


1	R
a	H
b	*t*-Bu



2-3	X	R
a	$(CH_2OCH_2)_2$	H
b	$(CH_2OCH_2)_3$	H
c	$(CH_2OCH_2)_4$	H
d	$(CH_2OCH_2)_2$	*t*-Bu
e	$(CH_2OCH_2)_3$	*t*-Bu
f	$(CH_2OCH_2)_4$	*t*-Bu

Scheme 1. Reagents and conditions: *i*) $TsOCH_2(CH_2OCH_2)_nCH_2OTs$ (n = 2-4) (1.1 equiv), *t*-BuOK (2.2 equiv), toluene, 70 °C, 24-36 h.



Scheme 2

For the less polar components the 1,2-alternate structures **2** were unambiguously assigned by distinctive NMR spectral patterns of the calix[4]arene framework. Apart from the two obvious resonances for the *t*-Bu groups, the ^1H NMR spectra display two AX systems (J = 12.4±0.3 Hz) and an AB quartet (J = 17.2±0.5 Hz) in the ratio 1:1:2 for the $ArCH_2Ar$ groups, and two pairs of doublets for the *t*-butylated or two pairs of double doublets and two triplets for the deterbutylated aromatic rings, respectively. The 1,2-alternate conformation is further substantiated by the presence, in the ^{13}C NMR spectra, of two resonances in the range 28-30 ppm and a resonance of double intensity at 37-39 ppm for the bridging methylene carbons, in full agreement with the single rule for the determination of calix[4]arene conformations.[12] On the other hand, the more polar cone conformers **3** exhibit the expected proton and carbon NMR spectral patterns for a bis-*syn*-proximal functionalization at the lower rim of calix[4]arenes (in particular, a set of three AX systems for $ArCH_2Ar$ in the ratio 1:2:1 and three resonances for the pertinent carbons at δ 29-31 ppm).[8,9]

A comparison of the ^1H NMR spectra of **2** and **3** reveals strong upfield shifts for a pair of symmetrical β-oxyethylene protons and for the pyridyl protons of **2**, which are respectively exposed to the diamagnetic shielding effect of two pairs of aryl rings (one above and one below the mean methylene-containing plane). The dramatic upfield shift experienced by H3 (Δδ ca 1.7 ppm) and to a lesser extent by H4 (Δδ ca 0.8 ppm) pyridyl protons further suggests that (a) the heteroaromatic pendant groups alternate in filling the pocket created by the two facing aryl rings, and (b) the ring nitrogen is *exo* to the calix cup and *anti* oriented with respect to the phenolic oxygen. The uniformity of the spectra of the entire series of **2** clearly indicates that these compounds in solution adopt the same conformation.

The 1,2-alternate conformation was unambiguously proven by single-crystal X-ray structure determination of **2e** (Figure 1).[13] The conformation of **2e** can be defined by the interplanar angles which the various phenyl rings make with the plane of the methylene carbons (C7A, C7B, C7C, C7D) which join them. These values are 42.4(2), 86.7(2), 79.9(2), and 60.9(2)° for aromatic rings A-D, respectively. The intramolecular O···O distances are O1A···O1B 3.449(6), O1A···O1C 4.694(7), O1A···O1D 3.162(7), O1B···O1C 4.465(7), O1B···O1D 5.488(7), O1C···O1D 3.450(6) Å.

The topology of these receptors is such that cone conformers **3** are expected to behave as monotopic ligands, while 1,2-alternate dipyridino-(1,2)-calix[4]crown ethers **2** could act (at least in principle) as ditopic ligands, since they contain potential binding sites above and below the mean plane containing the four bridging methylenes. The metal ion selectivities and binding mode of these new classes of ligands towards alkali metal cations are currently under investigation.

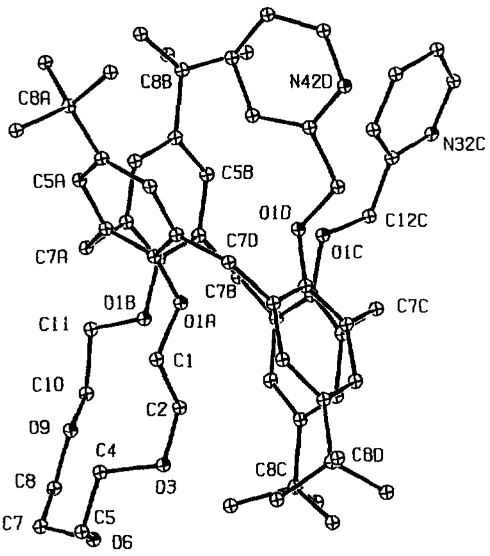


Fig. 1. A view of **2e** with an indication of our numbering scheme. For clarity, H atoms are omitted and all other atoms are shown as small spheres of an arbitrary size.

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References and Notes

1. Dedicated to Prof. Mario Piattelli on the occasion of his 70th birthday.

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10. Satisfactory microanalytical and spectral data were obtained for all new compounds.
11. In a typical procedure, a solution of pentaethylene glycol ditosylate (300 mg, 0.55 mmol) in dry toluene (30 mL) was added dropwise over 3 h to a stirred solution of **1b** (415 mg, 0.5 mmol) and *t*-BuOK (123 mg, 1.1 mmol) in dry toluene (50 mL) under N_2 at 70 °C. The stirred mixture was kept at 70 °C for 24 h. Usual workup, followed by column chromatography (neutral alumina, 2:1 cyclohexane-AcOEt) gave **2f** (21%) and **3f** (35%). **2f**: mp 252-254 °C; ^1H NMR ($CDCl_3$) δ 1.11, 1.37 [s, $C(CH_3)_3$, 18 H each], 2.55 (dt, *J* = 9.7, 7.1 Hz, $ArOCH_2C(H)\underline{H}O$, 2 H), 3.09-3.16 (m, OCH_2CH_2O, 2 H), 3.16, 3.21 (d, *J* = 12.2 and 12.4 Hz, respectively, *exo*-$ArCH_2Ar$, 1 H each), 3.39-3.63 (overlapped, OCH_2CH_2O, 16 H), 3.84, 3.90 (ABq, *J* = 17.2 Hz, $ArCH_2Ar$, 4 H), 4.17, 4.46 (d, *J* = 12.3 and 12.1 Hz, respectively, *endo*-$ArCH_2Ar$, 1 H each), 4.54, 4.59 (ABq, *J* = 13.9 Hz, OCH_2Py, 4 H), 6.14 (d, *J* = 7.7 Hz, 3-PyH, 2 H), 6.76 (d, *J* = 2.5 Hz, ArH, 2 H), 6.78 (td, *J* = 7.7, 1.9 Hz, 4-PyH, 2 H), 6.87 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 5-PyH, 2 H), 7.12, 7.19, 7.37 (d, *J* = 2.4, 2.5 and 2.4 Hz, respectively, ArH, 2 H each), and 8.28 (ddd, *J* = 4.8, 1.8, 0.8 Hz, 6-PyH, 2 H);); FAB (+) MS, *m/z* 1033 (100, MH^+). **3f**: mp 270-272 °C (dec); ^1H NMR δ 1.08, 1.09 [s, $C(CH_3)_3$, 18 H each], 3.10, 3.12 (d, *J* = 12.6 Hz, ratio 3:1, *exo*-$ArCH_2Ar$, 4 H), 3.48-4.08 (overlapped, OCH_2CH_2O, 20 H), 4.34, 4.43, 4.51 (d, *J* = 12.5, 12.6 and 12.6 Hz, respectively, ratio 2:1:1, *endo*-$ArCH_2Ar$, 4 H), 5.01 (pseudo-s, OCH_2Py, 4 H), 6.80-6.83 (m, ArH, 8 H), 7.17 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 5-PyH, 2 H), 7.59 (td, *J* = 7.6, 1.8 Hz, 4-PyH, 2 H), 7.85 (d, *J* = 7.8 Hz, 3-PyH, 2 H), and 8.53 (dt, *J* = 4.9, 0.9 Hz, 6-PyH, 2 H); FAB (+) MS, *m/z* 1033 (100, MH^+).
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13. Crystal data for **2e**: $C_{64}H_{80}N_2O_7$, Mr = 989.3, triclinic, a = 10.446(13), b = 14.136(3), c = 19.733(2) Å, α = 93.04(2), β = 99.951(12), γ = 101.081(13)°, V = 2810.08(8) Å^3, space group *P-1*, Z = 2, $F(000)$ = 1068, d = 1.169 gcm^{-3}, μ = 0.07 mm^{-1}. The crystals diffracted weakly (only 48% of the data in the 2-20° shell were 'observed' at the $2\sigma(I)$ level. The structure was solved using SHELXS86[14] and NRCVAX94.[15] The methyl carbons of two of the four *t*-Bu groups showed large anisotropy, but no significant changes arose when these methyl C atoms were treated as being disordered over two orientations. R = 0.079 for 2553 observed data.
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