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Calix Crowns Derived from *para*-Bridged Calix[4]arenes

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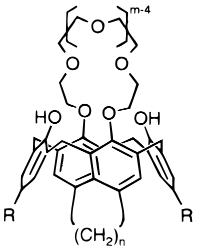
ABSTRACT



5a-d

n = 5, 8 m = 5, 6

Two calix[4]arenes, bridged by aliphatic chains of five and eight carbon atoms spanning two opposite *para* positions, have been converted into their 1,3-crown ether derivatives by reaction with tetraethylene and pentaethylene glycol ditosylates. Of the two possible 1,3-crown derivatives, only the formation of those isomers is observed in which the phenolic units connected at the *para* positions are etherified. This has been established in one case by a single-crystal X-ray analysis. Preliminary results for the extraction of selected alkali and alkaline-earth metals are reported.

Numerous ionophores have been synthesized by the attachment of various ligating functions to calixarenes as a basic skeleton.[1] Often these ligands show unique complexation properties and selectivities.[2] For example tetraesters, -amides, or -ketones **1**, in the cone conformation, are selective ligands for Na^+ cations[3] used in various sensors. 1,3-Crown ethers **2**, fixed in the 1,3-alternate conformation, show for $m = 5$ the highest K^+/Na^+ selectivity of artificial receptors,[4] better even than valinomycin, while the crown-6 compounds ($m = 6$) show exceptionally high Cs^+/Na^+ selectivities,[5] useful for the extraction of Cs from high-salinity nuclear waste.[6] Their efficiency could be further increased in analogous benzo crown ether derivatives.[7]

Tetraester derivatives **3**, derived from *para*-bridged calix[4]arenes **4**, show higher complexation constants for Na^+ than **1a** if $n \geq 8$, while these constants drastically decrease for $n < 7$. This was convincingly explained by a distortion of the perfect cone conformation necessary for an efficient interaction with the complexed cation.[8] We were interested, therefore, to determine whether the length of the connecting

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(1) For recent reviews on calixarenes see for example: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745; (b) Gutsche, C. D. *Calixarenes Revisited*; RSC Monographs in Supramolecular Chemistry; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, U.K., 1998.

(2) For reviews on calixarene-derived ionophores see: McKervey, M. A.; Schwing-Weill, M.-J.; Arnaud-Neu, F. In *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Pergamon: Oxford, U.K., 1996; Vol. 1, p 537.

(3) Schwing-Weill, M.-J.; Arnaud-Neu, F.; McKervey, M. A. *J. Phys. Org. Chem.* **1992**, *5*, 496−501.

(4) Casnati, A.; Pochini, A.; Ungaro, R.; Bocchi, C.; Ugozzoli, F.; Egberink, R. J. M.; Struijk, H.; Lugtenberg, R.; de Jong, F.; Reinhoudt, D. N. *Chem. Eur. J.* **1996**, *2*, 436−445.

(5) Ungaro, R.; Casnati, A.; Ugozzoli, F.; Pochini, A.; Dozol, J.-F.; Hill, C.; Rouquette, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1506−1509.

(6) Dozol, J.-F.; Simon, N.; Lamare, V.; Rouquette, H.; Eymard, S.; Tournois, B.; De Marc, D.; Macias, R. M. *Sep. Sci. Technol.* **1999**, *34*, 877−909.

(7) (a) Hill, C.; Dozol, J.-F.; Lamare, V.; Rouquette, H.; Eymard, S.; Tournois, B.; Vicens, J.; Asfari, Z.; Bressot, C.; Ungaro, R.; Casnati, A. *J. Incl. Phenom.* **1994**, *19*, 399−408; (b) Sachleben, R. A.; Urvoas, A.; Bryan, J. C.; Haverlock, T. J.; Hay, B. P.; Moyer, B. A. *Chem. Commun.* **1999**, 1751−1752.

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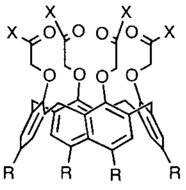
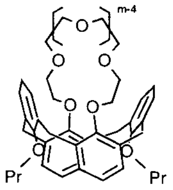


1

a X = O-C$_2$H$_5$

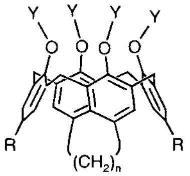
b X = N(Et)$_2$

c X = CH$_3$



2

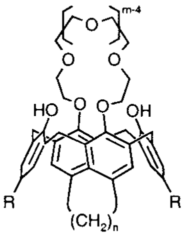
R = C(CH$_3$)$_3$

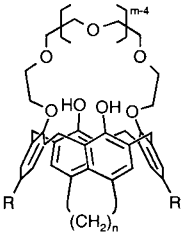


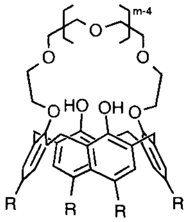
3 Y = CH$_2$-C(O)-O-C$_2$H$_5$

4 a Y = H, n = 5

b Y = H, n = 8







5 a m = 5, n = 5

b m = 6, n = 5

c m = 5, n = 8

d m = 6, n = 8

6

R = C(CH$_3$)$_3$

7

chain would similarly influence the complexation of cations by crown ethers derived from **4**. Reaction of bridged calix[4]arenes **4a**,**b**[9] with the ditosylates of tetraethylene and pentaethylene glycol was carried out in dry acetonitrile under reflux in the presence of CsF.[10] A single reaction product was observed by TLC (in addition to starting materials and minor side products), which was isolated by flash chromatography and further purified by recrystallization.[11] Calixcrowns **5a**–**d** were thus obtained in (nonoptimized) yields of 45–55%. Their purity was checked mainly by ^{1}H NMR spectroscopy (in addition to TLC), and their structure was further confirmed by FD-MS.

The ^{1}H NMR spectra of **5a**–**d** show one singlet for OH, two singlets for Ar H, one pair of doublets for Ar–CH$_2$–Ar, and one singlet for *tert*-butyl protons, in agreement with the C_{2v}-symmetrical structure. However, in principle the regioisomeric structure **6** cannot be unambiguously excluded in this way, although we know from other examples[12] that the 1,3-dialkylation of bridged calix[4]arenes of type **4** occurs at those phenolic units connected also at the *para* positions. Obviously they are conformationally more exposed by the (slight) distortion caused by this *para* bridge.

An unambiguous proof by single-crystal X-ray analysis[13] was also found in the present case. Figure 1 shows the expected molecular structure and conformation of **5a**. The two phenolic residues connected by the pentamethylene chain are nearly parallel and perpendicular to the calixarene reference plane defined by the four benzylic methylene carbons (Ar–CH$_2$–Ar), while the unconnected phenolic units are bent away from the cavity. The angles which the two doubly bridged phenolic units make with the reference plane (91.2, 91.2°) are nearly identical with those of a pentamethylene-bridged calix[4]arene bearing methyl groups instead of *tert*-butyl groups (91.8, 92.2°).[14]

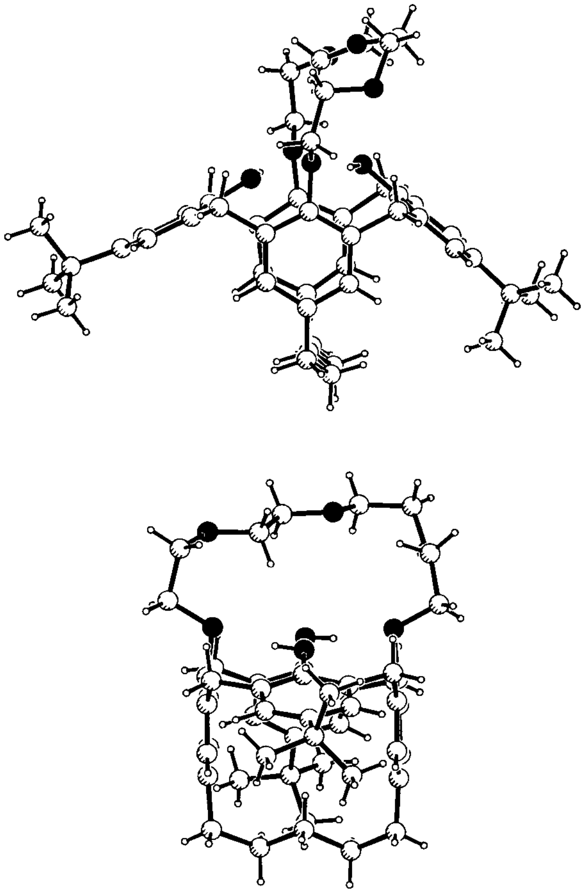


Figure 1. Molecular conformation of compound **5a** seen from two different orthogonal directions.

This demonstrates that the conformation of the calixarene part is mainly determined by the short pentamethylene chain. The inclination of the free phenolic units (137.5, 155.0°) shows a somewhat larger deviation from the former structure (141.7, 145.9°), which may be due to differences in the intramolecular hydrogen bonds (2.869 and 2.871 Å, respectively) of the hydroxy groups with the ether oxygens in comparison to the cyclic array of O–H···O–H hydrogen bonds of the *para*-bridged calixarene with four free OH groups (O–O distances: 3.04, 2.90, 2.86, and 2.90 Å). Packing effects in connection with the polyether chain bent to one side of the calixarene skeleton may be another reason.

The crown-6 derivatives **5b** and **5d** were checked for their extraction[15] ability toward selected alkali-metal and alkaline-earth-metal cations from water (c(M(NO$_3$)$_n$) = 10^{-4} M) to

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(8) Arnaud-Neu, F.; Böhmer, V.; Guerra, L.; McKervey, M. A.; Paulus, E. F.; Rodriguez, A.; Schwing-Weill, M.-J.; Tabatabai, M.; Vogt, W. *J. Phys. Org. Chem.* **1992**, *5*, 471–481.

(9) Goldmann, H.; Vogt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811–6817.

(10) Reinhoudt, D. N.; de Jong, F.; Tomassen, H. P. M. *Tetrahedron Lett.* **1979**, *20*, 2067–2070. Compare also: Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; Abu El-Fadl, A.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1990**, *112*, 6979–6985.

chloroform (c(ligand) = 5×10^{-3} M). In the presence of picric acid ($c = 5 \times 10^{-3}$ M) at pH = 5.2 (NaOAc/HCl buffer)[16] both compounds as well as *tert*-butylcalix[4]arene crown-6 (**7**), studied for comparison, are selective for Cs^+ (Figure 2). The efficiency decreases in the order **5b** > **7** > **5d**. It is tempting to explain the higher percent extractability for **5b** by a change to the 1,3-alternate conformation facilitated by the short aliphatic chain, but ^1H NMR studies give no indication of such a conformational change.

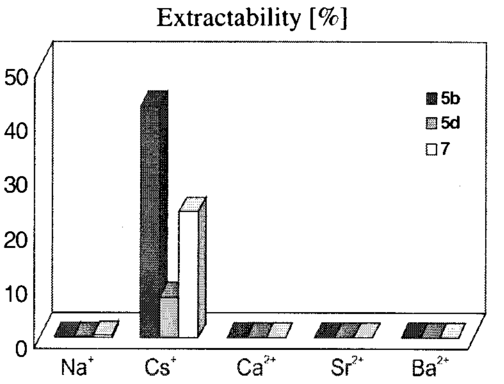

Figure 2. Extractability of selected alkali-metal and alkaline-earth-metal cations by ligands **5a**, **5d**, and **7** from water to chloroform.

Variation of the ligand concentration ($c_L = 5 \times 10^{-4} - 5 \times 10^{-3}$ M) leads to log/log c_L plots with a slope of 1, suggesting a 1:1 stoichiometry for the extracted complex. Surprisingly, the extractability for Cs^+ nearly disappears (2%) in the absence of picrate at pH 12 ($c(LiNO_3) = c(LiOH) = 0.1$ M). Among the cations studied, Ba^{2+} is best extracted (8.4%) by **5b**, which corresponds to results with homocalixarene systems.[17] This may be due to the strong interaction of the divalent barium cations with the phenolate formed in the alkaline solution.

In conclusion, there is an influence of the length n of the aliphatic chain on the extraction of Cs^+. In contrast to the tetraester derivatives **3**, compound **5b** with the shorter chain is more effective than **5d**. It is also better than the nonbridged crown ether **7**, but the effects are not as strong.

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Supporting Information Available: Crystal data, structure refinement details, and CIF file for *para*-bridged **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) General procedure for the synthesis of crown ethers **5a**−**d**: a solution of the bridged calixarene **4** (0.5 mmol) in 30 mL of dry acetonitrile was refluxed with 2 mmol of CsF for 1 h to give a clear solution. Then 0.5 mmol of the corresponding glycol ditosylate, dissolved in 20 mL of acetonitrile, was added slowly over a period of 4 h and reflux was continued for 24 h (or longer if TLC control showed still the presence of unreacted **4**). The solvent was evaporated (oil pump) and the residue distributed between chloroform and water saturated with NaCl. The organic phase was dried over $MgSO_4$ and evaporated again, and the crude product was purified, as indicated for the single compounds. For **5a**, repeated column chromatography (chloroform/acetone 5:1) gave 31% of a white product, mp 215 °C dec, from which single crystals were obtained by recrystallization from cyclohexane. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.06, 6.26 (two s, each 4H), 6.23 (s, 2H), 4.35 (d, J = 13.4 Hz, 4H), 4.03 (br d, 8H), 3.95, 3.76 (two t, J = 6 Hz, each 4H), 3.22 (d, J = 13.4 Hz, 4H), 2.14 (br t, 4H), 1.34 (s, 18H), 0.93 (br t, 4H), −0.46 (br t, 2H). FD-MS: m/z 763.6 (100, M, calcd for $C_{49}H_{62}O_7$ 762.45). For **5b**, flash chromatography (chloroform/acetone 5:1) gave 57% of a white product, which after recrystallization from n-hexane showed mp 208 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.05, 6.24 (two s, 4H each), 5.65 (s, 2H), 4.38 (d, J = 13.5 Hz, 4H), 4.00, 3.92, 3.85, 3.76 (four m, each 4H), 3.72 (s, 4H), 3.22 (d, J = 13.6 Hz, 4H), 2.13 (br t, 4H), 1.34 (s, 18H), 0.95 (br t, 4H), −0.351 (br t, 2H). FD-MS: m/z 807.0 (100, M, calcd for $C_{51}H_{66}O_8$ 806.47). For **5c**, flash chromatography (chloroform/acetone 5:1) gave 44% of a white product, mp 295 dec. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (s, 2H), 7.03, 6.63 (two s, each 4H), 4.35 (d, J = 12.8 Hz, 4H), 4.05 (ps s, 8H), 3.95, 3.85 (two t, J = 5 Hz, each 4H), 3.27 (d, J = 12.9 Hz, 4H), 2.30 (br t, J = 6 Hz, 4H), 1.26 (s, 18H), 1.12, 0.69, 0.16 (three br t, each 4H). FD-MS: m/z 804.6 (100, M, calcd for $C_{52}H_{68}O_7$ 804.49). For **5d**, column chromatography (chloroform/acetone 1:1) gave 51% of a white product, mp 243−244 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.15 (s, 2H), 7.02, 6.64 (two s, each 4H), 4.31 (d, J = 12.8 Hz, 4H), 4.10, 3.99, 3.95, 3.86 (four m, each 4H), 3.73 (s, 4H), 3.27 (d, J = 12.9 Hz, 4H), 2.30 (br t, 4H), 1.26 (s, 18H), 1.11, 0.68, 0.15 (three br t, each 4H). FD-MS m/z 849.2 (100, M, calcd for $C_{54}H_{72}O_8$ 848.52).

(12) See for instance: (a) Berger, B.; Böhmer, V.; Paulus, E.; Vogt, W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 96−99. (b) Wasikiewicz, W.; Rokicki, G.; Kielkiewicz, J.; Paulus, E. F.; Böhmer, V. *Monatsh. Chem.* **1997**, *128*, 863−879.

(13) Single crystals of **5a** were obtained by slow evaporation of a cyclohexane solution. Crystal data and refinement details: 25 reflections with $\theta > 10°$ were used to determine the cell constants a = 11.179(1) Å, b = 13.411(2) Å, c = 14.382(1) Å, α = 84.26(1)°, β = 83.38(1)°, γ = 85.51(2)°, V = 2126 Å^3, Z = 2, $C_{49}H_{62}O_7$, M_r = 762.99, D_{exptl} = 1.192 Mg/m^3, $P\bar{1}$, 6629 reflections ($-12 \le h \le 0$, $-15 \le k \le 14$, $-16 \le l \le 16$) were collected, 6327 unique (R_{int} = 0.0373), completeness 99.9%, 2991 reflections $>2\sigma(I)$, computer-controlled four-circle diffractometer (Siemens), Mo Kα radiation, μ = 0.078 mm^{-1}, T = 193 K, all reflections were used for structure analysis, direct methods for solving the phase problem, refinement of the structure parameters (506) by full-matrix least squares on F^2, no restraints were used, weighting scheme w according to the counting statistics $\sigma(I)$, $w = 1/\sigma^2(F_o^2) + (0.0549P)^2$, where $P = (\max(F_o^2, 0) + 2F_c^2)/3$, the coordinates of the H atoms were calculated, extinction coefficient 005(1), S = 0.867, R1($I > 2\sigma$) = 0.0546, wR2($I > 2\sigma$) = 0.1050, R1(all data) = 0.1416, wR2(all data) = 0.1303, largest difference peak and hole in the final electron density synthesis 0.291 and −0.223 e/Å^3. The mean standard deviations are as follows: C−C bond, 0.005 Å; C−O bond, 0.005 Å; C−C−C bond angles, 0.4°, C−C−C−C torsion angles, 0.5°. All calculations were done by a DEC 3000/900 AXP and a Pentium PC computer with the SHELXTL-PLUS programs (Sheldrick, G. M. University of Göttingen, Göttingen, Germany, 1993−1997).

(14) Böhmer, V.; Goldmann, H.; Vogt, W.; Paulus, E. F.; Tobiason, F. L.; Thielman, M. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1769−1775.

(15) Extraction was performed at 25 ± 1 °C in 2 mL micro centrifuge tubes by mechanically shaking 0.5 mL each of the organic and the aqueous phases for 30 min, which was sufficient to reach the extraction equilibrium. All samples were centrifuged after extraction, and the metal concentration in both phases was determined radiometrically by measuring the γ-radiation of ^{22}Na, ^{137}Cs, ^{85}Sr, and ^{133}Ba in a NaI(Tl) scintillation counter (Cobra II; Canberra-Packard) and the β-radiation of ^{45}Ca in a liquid scintillation counter (Tricarb 2500, Canberra-Packard). For further details see ref 17.

(16) Despite the huge excess of sodium (c = 0.2 M) compared to the amount of ligand ($c = 5 \times 10^{-3}$ M), only traces of Na^+ are extracted into the organic phase (%E < 0.5%).

(17) Schmitz, J.; Vögtle, F.; Nieger, M.; Gloe, K.; Stephan, H.; Heitzsch, O.; Buschmann, H.-J. *Supramol. Chem.* **1994**, *4*, 115−119.