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Inherently Chiral Derivatives of Calix[5]crowns

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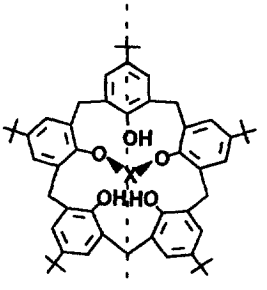
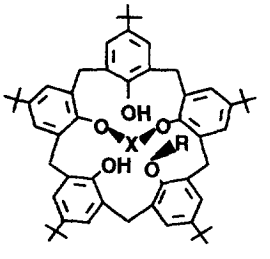
Abstract: Complementary synthetic routes to the chiral (1,3)- and (1,2)-calix[5]crown ethers **2** and **3**, respectively, are described. The regio- and stereochemical arrangement of the O-alkyl residues is deduced by NMR, and further supported by a single-crystal X-ray analysis of crown-5 derivative **3b**.

Chiral recognition and discrimination is one of the main goals in areas like host-guest chemistry or biomimetic chemistry, or simply in analytical chemistry. Since calixarenes[1] or suitable derivatives are widely used as host molecules or building blocks for the construction of sophisticated supra molecules,[1,2] it is not surprising that various attempts have been made to obtain chiral calixarenes. In addition to the simple attachment of chiral groups, their non-planar molecular structure offers the possibility to obtain inherently chiral derivatives.[3] One way consists of the attachment of at least two different residues to the phenolic oxygens of calix[4]arenes while simultaneously fixing the cone conformation.[4,5] While some inherently chiral derivatives have been also prepared from calix[6]arenes,[3] we describe here the first examples of inherently chiral O-alkyl derivatives of calix[5]crown ethers.[6]



1

$X = CH_2(CH_2OCH_2)_{m-2}CH_2$



2

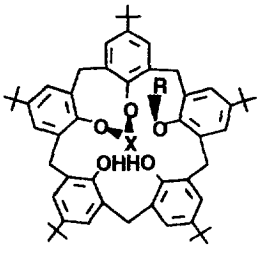
$X = CH_2(CH_2OCH_2)_3CH_2$

2a $R = CH_3$

2b $R = CH_2CO_2Et$

2c $R = COEt$

2d $R = CO\text{-}3,5(NO_2)_2Ph$



3

$X = CH_2(CH_2OCH_2)_{m-2}CH_2$

3a $R = CH_2\text{-Py}$; $m = 4$

3b $R = CH_2\text{-Py}$; $m = 5$

3c $R = CH_2\text{-Py}$; $m = 6$

Achiral crown ether derivatives (crown-5 to -7) are easily obtained in yields higher than 50% from *tert*-butylcalix[5]arene by reaction with suitable oligoethylene glycol ditosylates in the presence of CsF.[7] Under these conditions the 1,3-isomer **1** is formed nearly exclusively and the 1,2-isomer (**3** with R = H) is obtained only in the case of crown-7 as a minor product. The only symmetry element in molecules **1** is a mirror plane and therefore they can be desymmetrized by O-alkylation or O-acylation of one of the two adjacent hydroxy groups. One of these OH groups should be most acidic, due to the stabilization of the monoanion by an intramolecular O-H···O$^-$ hydrogen bond.

Accordingly, acylation or alkylation of **1** in the presence of weak bases (CsF in THF, for acetylation also Hünig's base[8]) leads to the asymmetric compounds **2a-d** in yields of 65-85%. Further asymmetric compounds should be available by exhaustive O-alkylation of monoesters **2c,d** and subsequent hydrolysis. The asymmetry of compounds **2** follows unambiguously from their ^{1}H NMR spectra, which show 5 singlets for *tert*-butyl groups and 5 AB systems (10 doublets) for the aromatic protons (compare Figure 1).

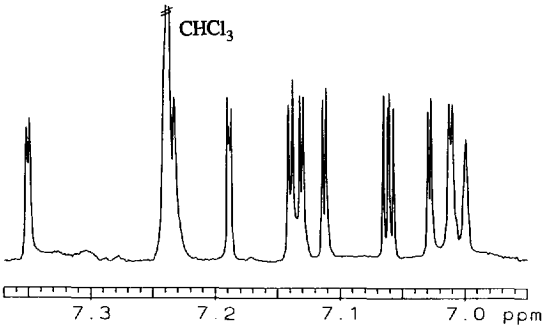


Fig. 1. Section of the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **2a**, showing ten doublets for aromatic protons (one being superimposed by the solvent) and two singlets for OH groups at 7.00 and 7.19 ppm (proved by H-D exchange).

This proves also the presence of a single stereoisomer, although for the larger residues which cannot pass the calixarene annulus it is not unambiguously clear if the newly introduced residue is *syn* or *anti* with respect to the crown ether portion. Signals for all the methylene carbons at ≤ 33 ppm[9] suggest an overall cone conformation, however.

The strategy of introducing O-alkyl residues may be inversed. A recent study[10] has shown that monoalkylation of *p-tert*-butylcalix[5]arene with 2-(chloromethyl)pyridine (used as its hydrochloride) can be achieved in 66% yield in the presence of $KHCO_3$. Subsequent reaction with suitable oligoethylene glycol ditosylates in dry DMF in the presence of K_2CO_3 affords a single isolated crown ether derivative **3** (25-40% yield),[11] although four regioisomers with a *syn* arrangement of the O-alkyl group are theoretically possible.[12]

^{1}H NMR data (e.g. 5 singlets for *tert*-butyl groups and 5 AB systems for the aromatic protons of the calixarene) prove that asymmetric compounds are obtained. Contrary to compounds **2**, signals for OH protons at rather low field (two singlets at 8.18 and 6.86 ppm in **3a**, at 7.91 and 6.87 ppm in **3b**, and a broad singlet at 7.70 ppm in **3c**) suggest the occurrence of two adjacent hydroxy groups involved in intramolecular H-bonding. The overall cone conformation of **3a-c** is corroborated by a chemical shift separation of geminal $ArCH_2Ar$ protons of about 1 ppm and by resonances for the pertinent methylene carbons in the range 29-31 ppm.[9,10]

The regio- and stereochemical arrangement of the O-alkyl residues is unambiguously proved for **3b** by a single-crystal X-ray analysis (Figure 2).[13] It shows that two oxygens are crowned which are adjacent to each other and adjacent and *syn* to the O-picolyl residue. The calix[5]arene moiety of **3b** assumes a distorted cone

conformation, as shown in Figure 2, with an acetonitrile molecule of solvation enclathrated within the calix cup. There is also another acetonitrile molecule in the crystal lattice, but this was allowed for after careful examination of difference maps. The conformation of molecule **3b** can be defined by the interplanar angles which the various phenyl rings make with the plane of the methylene carbons (C17, C27, C37, C47, C57) which join them. These values are 94.2(1), 144.0(1), 94.0(1), 132.6(1), and 132.5(1)° for aromatic rings Ci1-Ci6 (n = 1 to 5), respectively. The distances between phenolic oxygen atoms are O1···O2 3.46(1), O2···O3 3.58(1), O3···O4 3.20(1), O4···O5 3.22(1), O5···O1 3.24(1) Å.

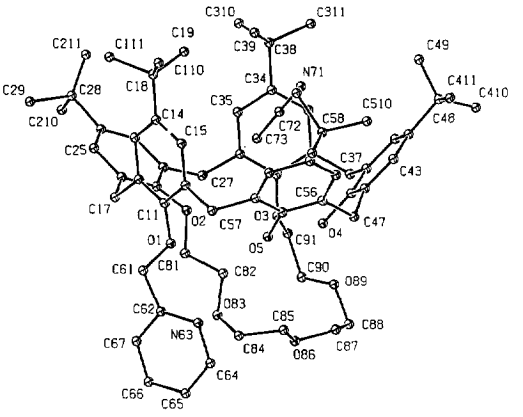


Fig. 2. A view of crown ether **3b** with H atoms omitted for clarity.

Thus, this inverse strategy (monoalkylation of the calix[5]arene and subsequent formation of the 1,2-crown ether) is complementary to the first one (formation of the 1,3-crown ether followed by its monoalkylation), and leads to monoalkyl crown ethers of type **3**. Surprisingly the 1,2-crown ether **3** is also obtained when the reaction of the monoether with the ditosylate is carried out using CsF in acetonitrile, that means under conditions which lead to 1,3-crowns in the case of free calix[5]arenes. At the other hand the monoalkylation of **1** (m = 5, 6) with 2-(chloromethyl)pyridine, attempted under numerous conditions, did not yet achieve a stereoregular derivative of type **2**. Therefore, we have not yet obtained an example for a pair of regioisomers of types **2** and **3**.

Further studies are presently undertaken to find out the scope and the limits of both strategies, to separate the enantiomers thus obtained and to elucidate their potential for chiral recognition.

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5. One type of residue is sufficient when conformations different from cone are fixed. For a survey see: Böhmer, V.; Kraft, D.; Vogt, W. *Supramol. Chem.* **1994**, *3*, 299-301.
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8. In a typical procedure, a mixture of *p-tert*-butylcalix[5]crown-5 (1 mmol) and CsF (2 mmol) in THF was stirred for 30 min at room temperature. Then 3,5-dinitrobenzoylchloride (1.1 mmol) was added. After 5 h the reaction mixture was acidified with 1 M HCl (30 mL) and extracted with $CHCl_3$. After usual workup the product was finally purified by flash chromatography ($CHCl_3$:CH_3OH / 9:1); yield 85% of **2d**; mp: 217-219 °C (decomp.); ^1H NMR (400 MHz, $CDCl_3$): δ 0.02, 1.18, 1.23, 1.31, 1.34 (s, $C(CH_3)_3$, 9 H each), 3.27, 3.33, 3.34, 3.39, 3.46 (d, *J* = 13.9, 15.7, 13.6, 15.5, and 13.9 Hz, respectively, *exo*-$ArCH_2Ar$, 1 H each), 3.35-4.23 (m, *endo*-$ArCH_2Ar$ and -OCH_2CH_2O-, 19 H), 4.35, 4.47 (d, *J* = 14.2 and 13.8 Hz, respectively, *endo*-$ArCH_2Ar$, 1 H each), 5.81, 6.84 (br s, Ar-OH, 1 H each), 7.04 (d, *J* = 2.3 Hz, ArH, 2 H), 7.05, 7.07, 7.15, 7.22 (d, *J* = 2.3, 2.2, 2.3, and 2.2 Hz, respectively, ArH, 1 H each), 7.28 (d, J = 2.3 Hz, ArH, 2 H), 7.33, 7.41 (d, J = 2.1 and 2.4 Hz, respectively, ArH, 1 H each), 9.32 (d, J = 2.1 Hz, 4-$(NO_2)_2$-ArH, 1 H), and 9.50 (d, J = 2.1 Hz, 2,6-$(NO_2)_2$-ArH).
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11. In a typical procedure, a solution of monopicolyl-*p-tert*-butylcalix[5]arene (0.45 g, 0.5 mmol) in DMF (20 mL) was slowly added to a stirred solution of tetraethylene glycol ditosylate (1 equiv) in DMF (30 mL) in the presence of K_2CO_3 (10 equiv) under N_2. The mixture was kept at 60 °C under stirring for 2 days. Usual workup, followed by column chromatography (eluent cyclohexane-AcOEt 5:1, v/v) afforded **3b** (132 mg, 25%) as fine needles, mp 265-268 °C (CH_2Cl_2-MeOH); ^1H NMR δ 0.25, 1.06, 1.24, 1.33, 1.40 [s, $C(CH_3)_3$, 9 H each], 3.20-3.49 (m, *exo*-$ArCH_2Ar$, 5 H), 3.52-4.19 (m, overlapped OCH_2CH_2O, 16 H), 4.31-4.67 (m, *endo*-$ArCH_2Ar$, 5 H), 5.04 (s, OCH_2Py, 2 H), 6.09, 6.23 (ABq, *J* = 2.2 Hz, ArH, 2 H), 6.87 (s, OH, 1 H), 6.92, 7.03 (ABq, *J* = 2.2 Hz, ArH, 2 H), 7.10 (t, *J* = 2.9 Hz, ArH, 2 H), 7.16, 7.20 (ABq, *J* = 2.3 Hz, ArH, 2 H), 7.24 (m, 5-PyH, 1 H), 7.31 (t, *J* = 2.4 Hz, ArH, 2 H), 7.77 (td, *J* = 7.6, 1.7 Hz, 4-PyH, 1 H), 7.88 (d, *J* = 7.9 Hz, 3-PyH, 1 H), 7.91 (s, OH, 1 H), and 8.59 (d, *J* = 4.1 Hz, 6-PyH, 1 H); ^{13}C NMR δ 28.85 (t, $ArCH_2Ar$), 30.44, 31.18, 31.45, 31.67 [q, $C(CH_3)_3$], 33.45, 33.78, 33.91, 34.06, 34.21 [s, $C(CH_3)_3$], 67.85, 69.10, 69.96, 70.26, 71.30, 72.21, 74.66 (t, OCH_2), 120.95, 122.38, 122.97, 123.14, 124.74, 125.11, 125.55, 126.86, 127.00 (d, 3,5-Py and Ar), 126.06, 127.48, 131.80, 132.33, 132.83, 133.26, 134.24, 135.30 (s, bridgehead-C), 136.85 (d, 4-Py), 142.33, 142.54, 145.72, 145.98, 146.62 [s, $C_{sp}2$-$C(CH_3)_3$], 148.96 (d, 6-Py), 148.18, 149.57, 150.28.151.26, 152.93 (s, $C_{sp}2$-O), and 158.36 (s, 2-Py); FAB (+) MS, *m/z* 1060 (100, MH^+).
12. Assuming the O-picolyl residue in 1-position, 2,3-, 2,4-, 2,5- and 3,4-mono crowns are possible, from which the latter two are achiral.
13. Crystal data for **3b**: $C_{69}H_{89}NO_8 \cdot 1.6(C_2H_3N)$, M_r = 1126.3, monoclinic, *a* = 30.600(3), *b* = 20.522(3), *c* = 23.487(4) Å, β = 112.405(12)°, *V* = 13636(3) $Å^3$. Space group *C2/c*, *Z* = 8, *F*(000) = 4874, d_{calc} = 1.097 g cm^{-3}, μ = 0.07 mm^{-1}. The crystals did not diffract well; of the 8363 reflections measured, 8105 were unique (R_{int} = 0.039) and only 2252 were "observed" at the 2σ(*I*) level. Structure solution using SHELXS86[14] and refinement using NRCVAX[15] and SHELXL-93[16] with all 8105 F^2 data. Final R(F^2) = 0.125. The analysis was complicated by disorder of the pendant O-picolyl and crown-ether moieties as well as the *tert*-butyl methyl groups; this was allowed for in the refinements. There is an acetonitrile molecule (with unit occupancy) enclathrated within the calix[5]arene cup and another (with occupancy 0.6) in what would have been a void in the crystal lattice between calix[5]arene molecules.
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