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Inherent Chirality in Calix[8]arenes Exploiting the Steric Constraint of Two Intercrossing Polyether Chains

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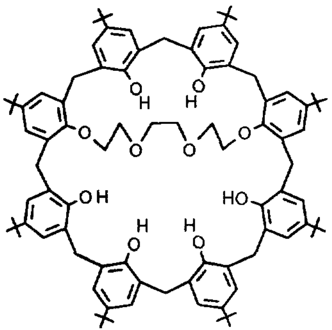
Abstract: The first example of covalently linked, inherently chiral calix[8]arene, 1,4-2,5-calix[8]bis-crown-4 **3**, has been obtained from either 1,4-calix[8]crown-4 **1** or *p-tert*-butylcalix[8]arene by alkylation with triethylene glycol ditosylate. The inherent chirality of **3**, due to the steric constraint of the two intercrossing crown bridges, is evidenced by signal splitting in the ^{1}H NMR spectrum after addition of Pirkle's reagent. Copyright © 1996 Elsevier Science Ltd

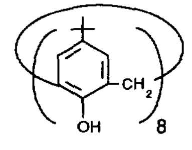
Chiral discrimination using calixarene-based hosts[1] is a challenging research field in which only a few but impressive results have been obtained just very recently.[2] The desired chiral compounds can be prepared either by simply attaching chiral groups at the macrocyclic framework[2,3] or eliminating any symmetry plane or inversion center in their three-dimensional structure, thus producing inherently chiral calixarenes.[4] Examples of these last compounds have been obtained for calix[n]arenes with n up to 6 by generating asymmetry or dissymmetry upon proper substitution with achiral groups at the lower and/or upper rim (including the *meta* position).[4] For the larger calix[8]arenes the few known examples of inherently chiral derivatives are dimetalla complexes in which, however, the chirality is imposed by the coordination geometry of the metal centers.[5]



1

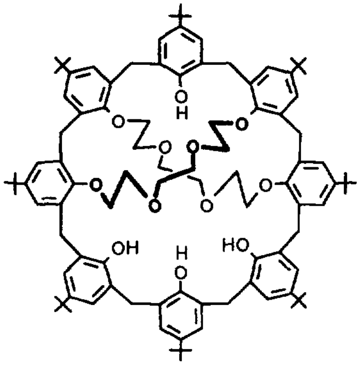
In order to obtain inherently chiral calix[8]arenes with conventional covalent linkages the problem of conformational interconversion has to be overcome and this implies the intramolecular bridging as a mandatory step.[6] The bridges can be used as simple scaffolding elements, in conjunction with other monofunctional substituents arranged asymmetrically at the remaining positions, or themselves as source of asymmetry or dissymmetry. Here we wish to report the first example of covalently linked, inherently chiral calix[8]arene whose dissymmetry is due to the steric constraint of two identical polyether chains.

The availability of a synthetic procedure for the preparation of 1,4-calix[8]crowns[7] by direct alkylation of *p-tert*-butylcalix[8]arene induced us to explore multiple bridging as source of inherent chirality. Thus, when compound **1**[7] was reacted for 5.5 h with 1 equiv of triethylene glycol ditosylate in the presence of Cs_2CO_3 in acetone and the crude product subjected to column chromatography, calix[8]bis-crowns **3** and **4** were isolated in 38% and 14% yield, respectively.[8] In an analogous preparation in which Cs_2CO_3 was replaced by KH in THF/DMF, small amounts (7%) of bis-crown **5** was obtained.[8]



2

Further experiments showed that **3** can be conveniently prepared by direct alkylation of *p-tert*-butylcalix[8]arene **2** with 3 equiv of triethylene glycol ditosylate in acetone in the presence of excess Cs_2CO_3 (13-18% yield), while from the same starting material using NaH as the base and THF/DMF as the solvent compound **4** is obtained in 12-15% yield.



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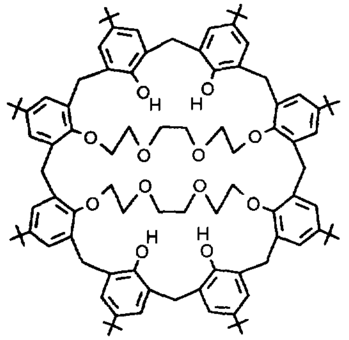

5

FAB(+) mass spectra of the regioisomeric bis-crowns **3-5** were almost identical, with a base peak at 1547 *m/z* corresponding to the $(M + Na)^+$ ion, thus proving the presence of two crown bridges in each of them. Since **3-5** were obtained from compound **1**, which already possesses a 1,4-crown bridge, they must each have one of the nine bridging patterns depicted in Figure 1.

For compound **3**, a symmetry element bisecting opposite aromatic rings (Ar—Ar symmetry) was evidenced by the presence of five *tert*-butyl signals at δ 1.19, 1.21, 1.25, 1.28, 1.35 (2:2:1:2:1) in the ^1H NMR spectrum, as well as by ten resonances for quaternary aromatic carbons bearing oxygen or *tert*-Bu groups (δ 141.4, 142.8, 143.1, 146.5, 147.0, 148.3, 148.7, 150.6, 151.1, 151.6) in the ^{13}C NMR spectrum. A glance at Figure 1 discloses that only the 1,4-2,5-bridging pattern is compatible with these data, thus allowing to assign the 1,4-2,5-calix[8]bis-crown-4 structure to compound **3**. Accordingly, three singlets were seen in the ^1H NMR spectrum attributable respectively to the isolated phenolic hydroxyl at position 3 (7.59 ppm, 1 H), the symmetry-related hydroxyls at positions 6 and 8 involved in a single H-bond (8.51 ppm, 2 H) and to the doubly-H-bonded hydroxyl at position 7 (8.92 ppm, 1 H).

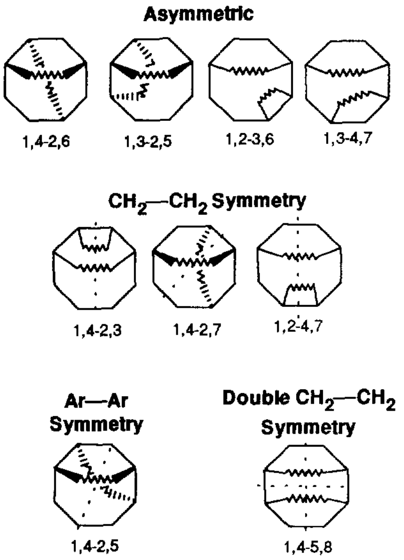

Fig. 1. Schematic representation of the possible bis-crown-4 derivatives attainable from 1,4-calix[8]crown-4.

The presence of a single C_2 symmetry axis in the 1,4-2,5-bis-crown structure of **3** and the steric requirement of the two crossing polyether chains make this compound dissymetric and hence inherently chiral. In principle the two enantiomers could racemize only by interchanging the two crown chains *via* their passage over the *t*-Bu groups. On the basis of computer molecular modeling this route does not appear feasible, indicating a practicable resolution of racemic **3**. Indeed, this compound possesses a somewhat rigid structure, as revealed by the presence of one AB and three AX systems for the $ArCH_2Ar$ groups in the 2D COSY NMR spectrum.[8] In DMSO-d_6 these signals undergo a small shift upon heating but no hint of coalescence was observed up to 385 K, thus confirming the conclusion of modeling study. Evidence for the inherently chiral nature of **3** was provided by the addition of excess Pirkle's reagent [(*S*)-(+)-(9-anthryl)-2,2,2-trifluoroethanol] to a $CDCl_3$ solution, which caused the doubling of many signals in the ^1H NMR spectrum and in particular of the *tert*-butyl resonance at 1.35 ppm (see Figure 2).

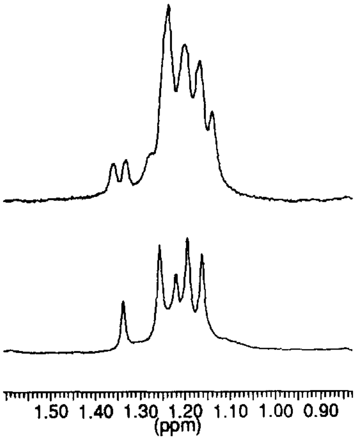

Fig. 2. *tert*-Butyl region of the ^1H NMR spectrum ($CDCl_3$, 260 K) of **3** in the presence (top) or in the absence (bottom) of Pirkle's reagent

Considerations similar to those used for **3** allowed to assign the 1,4-5,8-calix[8]bis-crown-4 structure to **5**.[8] In particular, the high symmetry of the molecule (double CH_2—CH_2 symmetry, Figure 1) was indicated by the presence in the ^1H NMR spectrum of two *tert*-Bu signals of equal intensity at 1.23 and 1.30 ppm and a single OH resonance at 7.93 ppm (4 H). Moreover, that the molecule contains aromatic rings of only two kinds is clearly evidenced by the presence in the ^{13}C NMR spectrum of just two signals for the oxygen-bearing (δ 151.0, C-OR; 149.5, C-OH) and two for the *t*-Bu-bearing aromatic carbons (δ 146.9 and 142.0 for the alkylated and unsubstituted rings, respectively). 1,4-5,8-Calix[8]bis-crown-4 **5** is conformationally mobile since at 330 K three clear singlets (δ 4.14, 3.99 and 3.96, 1:2:1) for the $ArCH_2Ar$ groups can be seen in the ^1H NMR spectrum. This suggest that intercrossing of two polyether chains is required for the inhibition of the flipping motion of aromatic rings.[9]

As concerns compound **4**, four equal intensity *t*-Bu signals in the ^1H NMR spectrum and eight resonances for *C*-Bu^t and *C*-O aromatic carbons in the ^{13}C NMR spectrum evidenced a symmetry element bisecting $ArCH_2Ar$ groups (CH_2—CH_2 symmetry), thus limiting the possible structure to 1,4-2,3-, 1,4-2,7-, or 1,2-6,7-calix[8]bis-crown (see Figure 1).[8] Among them, the 1,4-2,7-calix[8]bis-crown structure is expected to be somewhat rigid and inherently chiral because of the two intercrossing bridges. Although a reduced conformation mobility, revealed by the presence in the COSY NMR spectrum of two AX and three AB systems for $ArCH_2Ar$, and a splitting of signals (particularly evident for those attributable to the *tert*-Bu groups) after addition of (*S*)-α-methylbenzylamine speak in favour of the 1,4-2,7-calix[8]bis-crown structure, we consider necessary to wait for a more direct, unambiguous evidence. In fact, it is known that symmetrical achiral compounds can also show signal splitting after addition of chiral reagents.[10]

In conclusion, we have synthethized the first example of covalently linked, inherently chiral calix[8]arene exploiting, for the first time in the calixarene family, the steric constraint of two identical polyether chains. The direct resolution of this racemate by enantioselective HPLC methods is currently under investigation in our laboratory. In addition, this work demonstrates the possibility of achieving sophisticated bridging patterns with good regioselectivity and paves the way for the preparation of topologically more intriguing calix[8]arene-based molecules.

Acknowledgements. Thanks are due to Mr. R. Rapisardi (I.C.T.M.P., C.N.R., Catania) for measurement of FAB MS spectra.

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8. Satifactory microanalytical and spectral data were obtained for compounds **3-5**. Compound **3**: FAB(+) MS 1547 $(M + Na)^+$; ^1H NMR ($CDCl_3$, 295 K) δ 1.19, 1.21, 1.25, 1.28, 1.35 [s, $(CH_3)_3$, 18 H, 18 H, 9 H, 18 H, 9 H], 3.39 and 4.55 (AX, J = 14.1 Hz, $ArCH_2Ar$, 4 H), 3.53 and 4.32 (AX, J = 13.9 Hz, $ArCH_2Ar$, 4 H), 3.56 and 4.25 (AX, J = 13.8 Hz, $ArCH_2Ar$, 4 H), 4.06 and 4.17 (AB, J = 15.5 Hz, $ArCH_2Ar$, 4 H), 3.60-4.05 (overlapped, OCH_2CH_2O, 24 H), 6.95-7.25 (overlapped, ArH, 16 H), 7.59, 8.51, 8.92 (s, OH, 1 H, 2 H, 1 H). Compound **4**: FAB(+) MS 1547 $(M + Na)^+$; ^1H NMR ($CDCl_3$, 295 K) δ 1.14, 1.24, 1.26, 1.28 [s, $(CH_3)_3$, 18 H each], 3.38 (d, J = 14.0 Hz, $ArCH_2Ar$, 1 H), 3.39-4.24 (overlapped, OCH_2CH_2O and $ArCH_2Ar$, 36 H), 4.29 (d, J = 15.0 Hz, $ArCH_2Ar$, 2 H), 5.09 (d, J = 15.5 Hz, $ArCH_2Ar$, 1 H), 6.95 (bs, ArH, 4 H each), 6.90-7.20 (overlapped, ArH, 12 H), 8.60, 8.80 (bs, OH, 2 H each). Compound **5**: FAB(+) MS 1547 $(M + Na)^+$; ^1H NMR ($CDCl_3$, 330 K) δ 1.23, 1.30 [s, $(CH_3)_3$, 36 H each], 3.78, 3.83 (m, OCH_2CH_2O, 8 H each), 3.87 (bs, OCH_2CH_2O, 8 H), 3.96, 3.99, 4.14 (bs, $ArCH_2Ar$, 4 H, 8 H, 4 H), 7.09 and 7.17 (AB, J = 3.2 Hz, ArH, 8 H), 7.13 (bs, ArH, 8 H), 7.93 (s, OH, 4 H).
9. In accordance, 1,3-5,7-calix[8]bis-crowns, which also lack intercrossing chains, are conformationally mobile: Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1995**, *36*, 5429.
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