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Regioselective Synthesis of Calix[8]crowns by Direct Alkylation of *p-tert*-Butylcalix[8]arene

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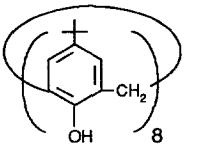
Abstract: Direct alkylation of *p-tert*-butylcalix[8]arene with oligoethylene glycol ditosylates affords calix[8]crowns-n with a bridging pattern dependent on the nature of the base used. Alkali metal hydrides (NaH or KH) afford mainly 1,4-calix[8]crowns $\mathbf{2}_n$ in yield up to 46%, while K_2CO_3 and Cs_2CO_3 with triethylene glycol ditosylate give the 1,3-crown $\mathbf{4}_4$ and its 1,5-isomer $\mathbf{5}_4$ as the main product, respectively. Appreciable amounts of 1,2-calix[8]crowns $\mathbf{3}_4$ are formed with all bases but NaH. At room temperature the ^{1}H NMR spectra of compounds $\mathbf{2}_n$-$\mathbf{5}_4$ show broad signals indicative of hampered conformational mobility. Copyright © 1996 Elsevier Science Ltd

Among the variety of calixarene[1] derivatives synthesized in the last decade calixcrowns[2] undoubtedly occupy a prominent position due to their complexing properties toward several cations, often with very remarkable selectivity,[3] leading to several practical applications.[4] Although the greatest attention has been paid to calix[4]crowns, interesting results have recently been obtained also with calix[5]crowns[5] and calix[6]crowns.[6] Concerning calix[8]crowns, we have recently shown that the introduction of polyether chains in 1,3,5,7-tetra-*O*-benzylated derivatives originates compounds conformationally preorganized in the 220-415 K range.[7] In that study, preliminary attempts at the direct regioselective introduction of polyether chains in the parent *p-tert*-butylcalix[8]arene (**1**) had given unsatisfactory results.[7] Further experiments have now allowed us to find that **1** reacts under appropriate conditions with oligoethylene glycol ditosilates to give the desired calix[8]crowns in satisfying yields.



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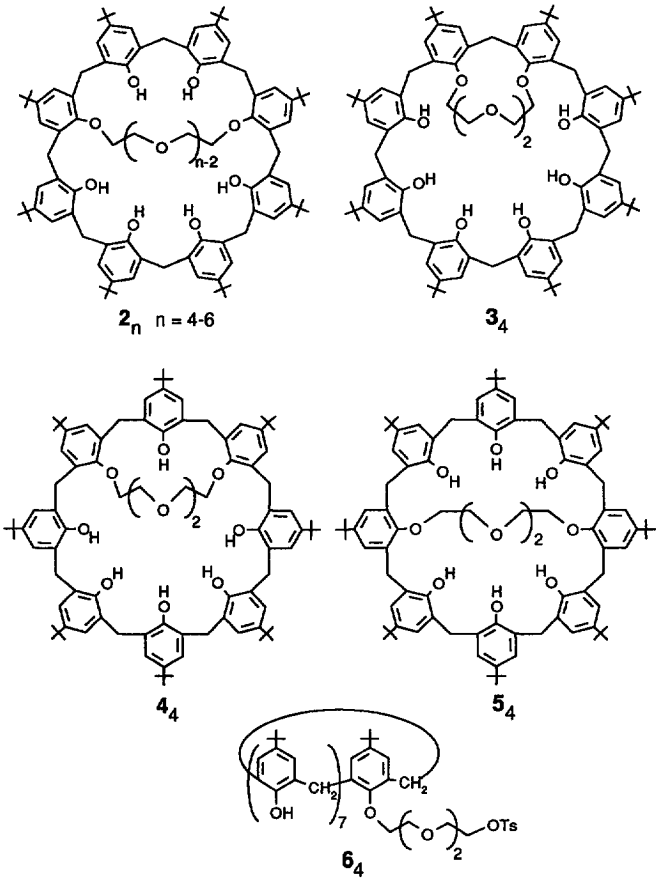
When triethylene glycol ditosylate (1 equiv) and NaH (6-10 equiv) were added to a solution of **1** in THF/DMF (10:1, v/v) and the mixture refluxed for 3-17 h a crude product was obtained from which 1,4-calix[8]crown-4 $\mathbf{2}_4$ was isolated by column chromatography in yield up to 46% (entries 1-2, Table 1).[8] The reaction was extended to tetra- and pentaethylene glycol ditosylates to afford 1,4-calix[8]crown-n $\mathbf{2}_5$ and $\mathbf{2}_6$ in 31 and 25% yield respectively (entries 3-4, Table 1).[8] The use of KH in place of NaH under identical conditions resulted in the formation of 1,2-calix[8]crown-4 $\mathbf{3}_4$ (entry 5, Table 1), in addition to $\mathbf{2}_4$.[8] Weaker bases such as alkali metal carbonates required longer reaction time in order to give appreciable amounts of crowned calix[8]arenes. In fact, after 47 h the reaction using K_2CO_3 as a base afforded monotosylpolyether $\mathbf{6}_4$ in appreciable yields besides 1,2-crown $\mathbf{3}_4$, while the main product was the 1,3-crowned calix[8]arene $\mathbf{4}_4$ (entry 6, Table 1).[8] Cs_2CO_3 in similar conditions yields 1,5-isomer $\mathbf{5}_4$ as the main product (entry 7, Table 1).[8]



Structure assignment for compounds $\mathbf{2}_n$ relied essentially on spectral analysis. Thus, the molecular masses were determined by FAB(+) mass spectroscopy, while the bridging pattern was inferred from extensive NMR analysis. At room temperature the ^{1}H NMR spectra of calix[8]crown $\mathbf{2}_n$ show broad signals indicating that conformational motion is hampered. Thus, the spectrum of $\mathbf{2}_4$ at rt in $(CD_3)_2CO$ shows broad, shapeless signals in the methylene region. The presence of four equal intensity signals at 1.17, 1.97, 1.22, and 1.25 ppm for the *t*-Bu groups is indicative of the presence in the molecule of a symmetry axis passing through two diametrical $ArCH_2Ar$ groups.[8] This was confirmed by the appearance in the ^{13}C NMR spectrum of eight signals due to aromatic carbons bearing either an oxygen atom or a *t*-Bu-group (140-155 ppm region), as well as two signals at δ 133.4 and 133.6 for the *C*-CH_2 carbons of alkylated phenolic rings. Discrimination between the two possible bridging patterns (1,2 or 1,4) compatible with the observed symmetry was achieved by a combination of 2D HETCOR and long-range HETCOR NMR experiments performed in C_6D_6 at 310 K in order to have sufficiently resolved methylene signals. The presence of cross-peaks between the bridgehead aromatic carbons and two $ArCH_2Ar$ singlets of 4 H intensity (δ 4.04 and 4.08) clearly indicated the 1,4-bridging. Structure assignment for the other 1,4-calix[8]crown $\mathbf{2}_5$ and $\mathbf{2}_6$ was based on similar arguments.

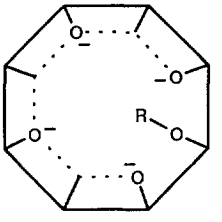
At this point the structure of 1,2-calix[8]crown-4 could be immediately assigned to $\mathbf{3}_4$, that possesses the same symmetry as $\mathbf{2}_4$ (four 18 H singlets for *t*-Bu groups at 1.19, 1.20, 1.208, and 1.213 ppm are present in its ^{1}H NMR spectrum in $(CD_3)_2CO$, as well as eight signals for quaternary aromatic carbons are seen in the 140-155 ppm region of the ^{13}C NMR spectrum).[8] Interestingly, the chemical shift values for the three 2 H hydroxyl groups in the 1,2- and 1,4-isomers, $\mathbf{2}_4$ and $\mathbf{3}_4$, are a sensitive structural probe. Indeed, in the spectrum of $\mathbf{2}_4$ these resonances appear at δ 8.35, 8.85, and 9.05, and are to be attributed respectively to a singly-H-bonded hydroxyl, a singly-H-bonded hydroxyl in a semicircular array and a doubly-H-bonded hydroxyl. In contrast, the spectrum of $\mathbf{3}_4$ contains a signal at δ 8.69, attributable to an OH single-H-bonded in a semicircular array, and two resonances at δ 8.97 and 9.13 for doubly-H-bonded OH groups.

Assignment of the bridging pattern to 1,3-calix[8]crown-4 $\mathbf{4}_4$ was based on the presence of a symmetry element bisecting opposite aromatic rings, as indicated by its ^{1}H NMR spectrum which shows five singlets for *t*-Bu groups (δ 1.18, 1.23, 1.24, 1.26, and 1.27, 1:2:1:2:2) and by the presence in its ^{13}C NMR spectrum of ten resonances in the 140-155 ppm region.[8] Analogously the 1,5-bridging in $\mathbf{5}_4$ was deduced from the presence of three *t*-Bu signals in its ^{1}H NMR spectrum (δ 1.24, 1.32, and 1.35, 2:1:1) and six quaternary carbon resonances in the low-field ^{13}C NMR region.[8]

Table 1. Yield of Calix[8]crown-n in Direct Alkylation of 1 with $TsO(CH_2CH_2O)_mTs$ (1 equiv)

Entry	m	Base	Solvent	Time (h)	Compd (yield %)
1	3	NaH	THF/DMF	17	$\mathbf{2}_4$ (46)
2	3	NaH	THF/DMF	3	$\mathbf{2}_4$ (35)
3	4	NaH	THF/DMF	3	$\mathbf{2}_5$ (31)
4	5	NaH	THF/DMF	3	$\mathbf{2}_6$ (25)
5	3	KH	THF/DMF	17	$\mathbf{2}_4$ (28), $\mathbf{3}_4$ (8)
6	3	K_2CO_3	Me_2CO	47	$\mathbf{3}_4$ (5), $\mathbf{4}_4$ (12), $\mathbf{6}_4$ (6)
7	3	Cs_2CO_3	Me_2CO	22	$\mathbf{2}_4$ (2), $\mathbf{3}_4$ (6), $\mathbf{5}_4$ (13)

The regiochemical outcome observed in the alkylation of **1** with triethylenglycol ditosylate in the presence of various bases deserves a comment. We suggest that the major factor controlling the bridging position is the strength of the base. Thus, in the presence of 6-10 equiv of a strong base (NaH or KH) the closure step of a mono-*O*-alkylcalix[8]arene like $\mathbf{6}_4$ reasonably proceeds through a well defined polyanion, very likely a 2,4,6,8-tetraanion of type **7**, thus leading to 1,4-bridging. The reaction promoted by a weak base (K_2CO_3) proceeds through the formation of a monoanion in which, according to earlier observations,[9] the charge is preferentially localized at position 3, so 1,3-bridged derivatives are preferentially formed. Cs_2CO_3, a base of intermediate strength, is unable to reach the same level of multiple deprotonation as does an alkali metal hydride and gives either a di- or a trianion, with a negative charge preferentially located at position 5. Cation template effect can be invoked to explain the formation of 1,2-bridge with all bases but NaH.[10] In any case, definite conclusions have to await a more systematic study extended to polyethylene glycols of different length.



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The direct regioselective synthesis of calix[8]crowns here described provides a convenient method for the intrabridging of the calix[8]arene macrocycle with different bridging patterns. It is conceivable that a careful extension of this methodology could lead to multiple-crowned calix[8]arenes effectively preorganized to host suitable guests. Moreover, the succession of two or more steps in different conditions should lead to mixed bridging patterns with interesting stereochemical implications.

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8. Satifactory microanalytical and spectral data were obtained for compounds $\mathbf{2_n}$-$\mathbf{6_4}$. **Compound $\mathbf{2_4}$:** FAB(+) MS 1411 (MH^+); ^{1}H-NMR [$(CD_3)_2CO$, 295 K] δ 1.17, 1.97, 1.22, 1.25 [s, $(CH_3)_3$, 18 H each], 3.70-4.10 (overlapped, OCH_2 and $ArCH_2Ar$, 28 H), 7.06 (d, J = 2.2 Hz, ArH, 2 H), 7.12 (d, J = 2.2 Hz, ArH, 2 H), 7.16 (d, J = 2.4 Hz, ArH, 2 H), 7.18 (d, J = 2.3 Hz, ArH, 2 H), 7.28 (bs, ArH, 4 H), 7.30 (d, J = 2.5 Hz, ArH, 2 H), 7.34 (d, J = 2.3 Hz, ArH, 2 H), 8.35, 8.85, 9.05 (bs, OH, 2 H each). **Compound $\mathbf{2_5}$:** FAB(+) MS 1455 (MH^+); ^{1}H-NMR ($CDCl_3$, 306 K) δ 1.24, 1.28, 1.32, 1.34 [s, $(CH_3)_3$, 18 H each], 3.84 (bs, OCH_2, 8 H), 3.91, 3.94 (s, $ArCH_2Ar$, 2 H each), 3.95, 4.01, 4.11 (s, $ArCH_2Ar$, 4 H, each), 4.13, 4.36 (bt, OCH_2, 4 H each), 7.06 (d, J = 2.2 Hz, ArH, 2 H), 7.14 (d, J = 2.3 Hz, ArH, 2 H), 7.17 (d, J = 2.1 Hz, ArH, 4 H), 7.20 (d, J = 2.3 Hz, ArH, 4 H), 7.21 (d, J = 2.4 Hz, ArH, 2 H), 7.23 (d, J = 2.4 Hz, ArH, 2 H), 8.20, 9.04, 9.73 (bs, OH, 2 H each). **Compound $\mathbf{2_6}$:** FAB(+) MS 1499 (MH^+); ^{1}H-NMR ($CDCl_3$, 293 K) δ 1.18, 1.23, 1.27, 1.28 [s, $(CH_3)_3$, 18 H each], 3.68 (bs, OCH_2, 4 H), 3.77, 3.83 (bt, OCH_2, 4 H each), 3.86, 3.90, 4.00, 4.10 (s, $ArCH_2Ar$, 4 H each), 4.11, 4.26 (bt, OCH_2, 4 H each), 7.00 (d, J = 1.9 Hz, ArH, 2 H), 7.08 (d, J = 2.5 Hz, ArH, 2 H), 6.95-7.23 (overlapped, ArH, 12 H), 8.20, 9.04 and 9.73 (bs, OH, 2 H each). **Compound $\mathbf{3_4}$:** FAB(+) MS 1411 (MH^+); ^{1}H-NMR ($CDCl_3$, 295 K) δ 1.24, 1.25, 1.26 [s, $(CH_3)_3$, 36 H, 18 H, 18 H], 3.70-4.35 (overlapped, OCH_2 and $ArCH_2Ar$, 28 H), 7.00-7.27 (overlapped, ArH, 16 H), 8.69, 8.97, 9.13 (bs, OH, 2 H each). **Compound $\mathbf{4_4}$:** FAB(+) MS 1411 (MH^+); ^{1}H-NMR ($CDCl_3$, 295 K) δ 1.18, 1.23, 1.24, 1.26, 1.27 [s, $(CH_3)_3$, 9 H, 18 H, 9 H, 18 H, 18 H], 3.65-4.35 (overlapped, OCH_2 and $ArCH_2Ar$, 28 H), 7.04, 7.14 (s, ArH, 2 H each), 7.15-7.18 (overlapped, ArH, 12 H), 7.65, 8.66, 9.01, 9.24 (bs, OH, 1 H, 2 H, 2,H, 1 H). **Compound $\mathbf{5_4}$:** FAB(+) MS 1411 (MH^+); ^{1}H-NMR ($CDCl_3$, 295 K) δ 1.24, 1.32, 1.35 [s, $(CH_3)_3$, 36 H, 18 H, 18 H], 3.65-4.35 (overlapped, OCH_2 and $ArCH_2Ar$, 28 H), 7.12 (bs, ArH, 8 H), 7.17, 7.29 (s, ArH, 4 H each), 8.99, 9.65 (bs, OH, 4 H, 2 H). **Compound $\mathbf{6_4}$:** FAB(+) MS 1585 (MH^+); ^{1}H-NMR ($CDCl_3$, 295 K) δ 1.26, 1.27, 1.29, 1.30 [s, $(CH_3)_3$, 36 H, 18 H, 9 H, 9 H], 2.23 (CH_3Ts, 3 H), 3.30, 3.53 (bt, OCH_2, 2 H each), 3.60-4.23 (overlapped, OCH_2 and $ArCH_2Ar$, 24 H), 6.96-7.36 (overlapped, ArH and TsH, 18 H), 7.68 (d, J = 8.0 Hz, TsH, 2 H), 8.96, 9.22, 9.42 (bs, OH, 2 H, 2H, 3 H).

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