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Inherently Chiral Calix[4]crown Ethers

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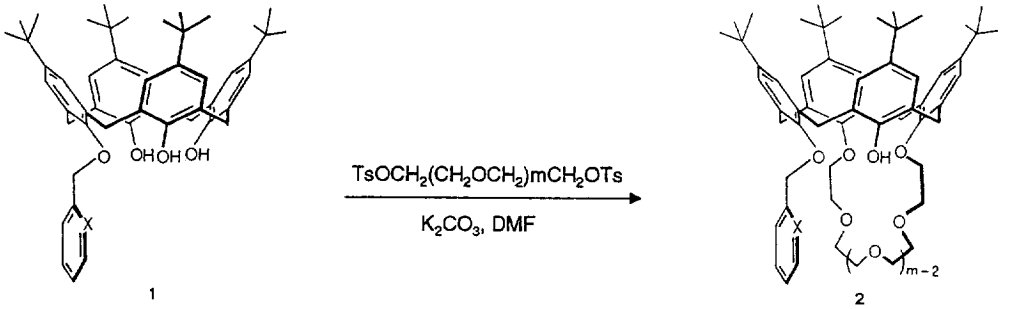
Abstract: The first inherently chiral calix[4]crown ethers **2** have been obtained by the base-catalysed reaction of mono-alkylated *p-tert*-butylcalix[4]arenes **1** with oligoethylene glycol ditosylates. Preliminary ^{1}H NMR studies suggest the ability of these receptors to bind either chiral alkylammonium or Zn^{2+} guest species within the hydrophilic pocket generated by the O-alkyl residues at the lower rim.

Calixarenes have been widely used as three-dimensional building blocks for the construction of artificial molecular receptors capable of recognizing neutral molecules, cations, and more recently anions.[1] The design and synthesis of conformationally preorganized achiral calix[4]crown ethers of different topology (1,2-calix[4]crowns,[2] 1,3-calix[4]crowns,[3] 1,2-calix[4]-bis-crowns,[2a,4] 1,3-calix[4]-bis-crowns,[3b,5] double calixarenes,[6] and double 1,3-calix-bis-crowns[7]) have developed very rapidly in the last few years, owing to their proclivity to bind alkali and primary ammonium cations.

Following previous studies on the creation of molecular asymmetry by modulation of the substitution pattern at the lower rim,[8] we report here the first examples of inherently chiral 1,2-calix[4]crown ethers **2** in the cone conformation, and preliminary complexation studies with chiral alkylammonium and Zn^{2+} guest species.



1

a: X = N
b: X = CH

2

aa: X = N; m = 2
ab: X = N; m = 3
ac: X = N; m = 4
ad: X = $^+$NH; m = 4
bc: X = CH; m = 4

Scheme

Racemic 1,2-calix[4]crown ethers **2** were obtained in 30-40% yield by dropwise addition of a DMF solution of mono-alkylated calix[4]arene **1** to a DMF solution of oligoethylene glycol ditosylate (1 equiv) in the presence of anhydrous K_2CO_3 (10 equiv) (see Scheme).[9,10] In agreement with the general mechanism of alkylation of calix[4]arenes with weak bases,[11] the presence of regioisomeric achiral mono-alkylated 1,3-calix[4]crown ethers was not detected (TLC) in the reaction mixtures.

Attempts to prepare by the same strategy analogous inherently chiral calix[4]crown ethers endowed with larger (3,5-dinitrobenzyl, 2-naphthylmethyl, or 2-quinolylmethyl) pendant groups failed, owing to the deleterious role played by the bulkiness of such substituents during the crucial crown ether cyclization step.

The asymmetry of structures **2** follows unambiguously from their ^1H NMR spectra, which show 4 singlets for *tert*-butyl groups, 4 partly overlapped AX systems for the bridging methylenes, 3 AB systems and a (pseudo) singlet for the aromatic protons of the calix[4]arene skeleton. The cone conformation of **2** is corroborated by a chemical shift difference ($\Delta\delta$) > 1 ppm (J = 12.5-14.0 Hz) between the four pairs of signals due to the bridging methylene protons (CH_{exo} and CH_{endo}),[12] and by the presence of the pertinent methylene resonances in the expected region of the ^{13}C NMR spectrum (30.9 ± 0.55 ppm).[13]

Evidence of chirality for the compounds synthesized was provided by titration experiments of $CDCl_3$ solutions of **2** (containing one drop of CD_3OD) with enantiomerically pure alkylammonium cations [(*R*)- and (*S*)-α–methylbenzylammonium picrates]. Whereas the ^1H NMR spectra of compounds **2aa** and **2ab** (m = 2,3) did not show any appreciable change upon titration with one equiv of the chiral salt, splitting and doubling of signals occurred in *every region* of the spectra of **2ac** and **2bc** (m = 4) from the addition of the first aliquot (0.25 equiv) of each chiral salt. Illustrative regions of the ^1H NMR spectrum of receptor **2ac**, without and with increasing amounts of the (R)-salt, are shown in Figure 1.

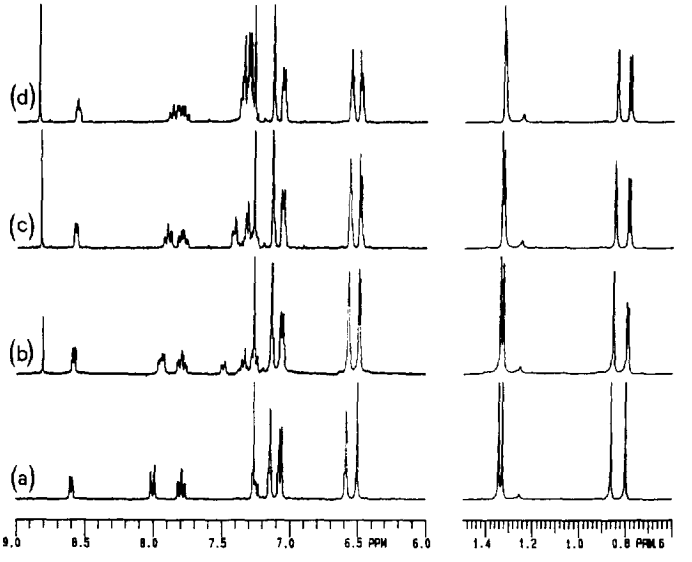


Fig. 1. Aromatic and *tert*-butyl regions of the ^1H NMR spectrum ($CDCl_3$, 300 MHz) of **2ac** (a), and spectral changes upon addition of (b) 0.25 , (c) 0.5, and (d) 1 equiv amount of (*R*)-α-methylbenzylammonium picrate. The two regions are plotted in different scales.

The spectra did not change further by adding an excess of the salt, suggesting that the diastereomeric 1:1 complexes had formed. These results confirm that a crown-6 moiety is a prerequisite for anchoring the NH_3^+ group of the primary ammonium cation into its cavity via N-H···O hydrogen bonds.[14] Compounds **2ac** and **2bc** do not give any diastereomeric interaction with the more encumbered (*R*)- or (S)-α–methyl-*o*-methoxybenzylammonium picrates, which presumably cannot approach in a favourable manner the crown ether portion from either side (*vide infra*).

In order to prove that complexation occurs inside the hydrophilic pocket generated by the substituents attached at the lower rim of the calix[4]arene, a $CDCl_3$ solution of pyridino compound **2ac** was protonated with CF_3COOH (1.2 equiv) to give the corresponding pyridinium salt **2ad** (as testified by a significant to large downfield shift experienced by the pyridinyloxy protons). Upon titration with one equiv of the (R)-salt, the chemical shifts of most protons remained unvaried, with the exception of the *tert*-butyl region which underwent some changes. The two downfield resonances coalesced to a broad singlet, while the remaining two singlets split into two doublets. The invariability of the other signals in the spectrum suggests that the R-NH_3^+ cation is impeded from entering the hydrophilic pocket of **2ad** (*internal approach*), due to a strong electrostatic repulsion with the pendant pyridinium group (switch off by protonation); therefore the interaction with the crown ether moiety necessarily occurs on the side exterior to the hydrophilic cavity (*external approach*).

Receptors **2aa-2ac**, containing a pyridinyl side-arm, can also be viewed as 'lariat' calix[4]crown ethers, and the similarity of the stereochemical features of R-NH_3^+ with tetrahedral transition metal complexes led us to explore the complexation properties of **2ab** towards Zn^{2+}. Addition of solid $Zn(CF_3SO_3)_2$ to a $CDCl_3$ solution of **2ab** caused the immediate evolution of totally new sets of resonances in every region of the ^{1}HNMR spectrum corresponding to the formation of the Zn^{2+} complex. The spectrum remained unchanged after 1d exposure of the $CDCl_3$ solution to an excess of the salt. The oxymethylene and aromatic regions in the ^{1}H NMR spectra of the receptor and of its Zn^{2+} complex are shown in Figure 2. The remarkable shifts experienced by the pyridinyloxy protons and, to a lesser extent, by the crown ether portion of the molecule suggest that the cationic guest is bound *via* favourable electrostatic interactions with the ring nitrogen and the polyether moiety in a tetrahedral arrangement.

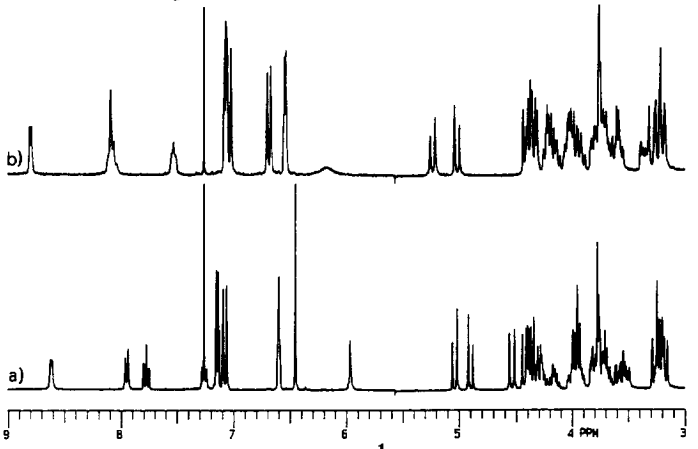


Fig. 2. The 3.0-9.0 ppm region of the ^{1}H NMR spectra ($CDCl_3$, 300 MHz) of (a) receptor **2ab** , and (b) its complex with $Zn(CF_3SO_3)_2$.

The direct separation of the enantiomers of **2** by HPLC using chiral stationary phases, the role in chiral recognition played by the nature of the substituents appended at the lower rim, as well as the discrimination of transition metal cations (based on the preferred geometries of their complexes) are currently being studied.

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9. Satisfactory microanalytical and spectral data were obtained for all new compounds.
10. In a typical procedure, a solution of **1a** (0.74 g, 1 mmol) in DMF (20 mL) was slowly added to a stirred solution of triethylene 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 **2aa** (38%); mp 278-281 °C (MeOH); R_f = 0.34 (cyclohexane-AcOEt 5:1); ^{1}H NMR δ 0.79, 0.88, 1.33, 1.34 (s, $C(CH_3)_3$, 9 H each), 3.17, 3.23, 3.29 (d, J = 12.6, 13.4, and 13.4 Hz, respectively, *exo*-$ArCH_2Ar$, ratio 2:1:1, 4 H), 3.57-4.35 (m, polyether chain, 12 H), 4.26, 4.31, 4.49, 4.50 (d, J = 13.5, 12.7, 13.0, and 12.4 Hz, respectively, *endo*-$ArCH_2Ar$, 1 H each), 4.94, 5.00 (ABq, J = 11.9 Hz, OCH_2Py, 2 H), 5.84 (s, OH, 1 H), 6.48 (s, ArH, 2 H), 6.58, 6.64 (ABq, J = 2.4 Hz, ArH, 2 H), 7.05, 7.08 (ABq, J = 2.4 Hz, ArH, 2 H), 7.14, 7.16 (ABq, J = 2.5 Hz, ArH, 2 H), 7.27 (m, 5-PyH, 1 H), 7.78 (td, J = 7.6, 1.8 Hz, 4-PyH, 1 H), 7.88 (d, J = 7.7 Hz, 3-PyH, 1 H), and 8.62 (d, J = 4.1 Hz, 6-PyH, 1 H); ^{13}C NMR δ 30.4, 31.2, 31.5 (t, $ArCH_2Ar$), 31.0, 31.7 (q, $C(CH_3)_3$), 33.8, 34.1 (s, $C(CH_3)_3$), 69.4, 69.8, 70.2, 71.3, 72.5, 75.3 (t, OCH_2), 78.7 (t, OCH_2Py), 122.8, 123.0 (d, 3,5-Py), 124.8, 125.1, 125.4, 125.6, 125.8 (d, Ar), 128.3, 129.5, 131.6, 131.9, 132.0, 132.7, 135.7, 135.9 (s, bridgehead-C), 136.6 (d, 4-Py), 141.5, 145.3, 145.8 (s, C_{sp^2}-$C(CH_3)_3$), 149.2 (d, 6-Py), 150.4, 150.7, 151.6, 153.5 (C_{sp^2}-O), and 157.6 (s, 2-Py); FAB (+) MS, *m/z* 854 (100, MH^+).
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