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Synthesis of Two Calix[4]arenes Constrained to a 1,3-Alternate Conformation by Di-Aza-Benzo Crown Ether Bridging.

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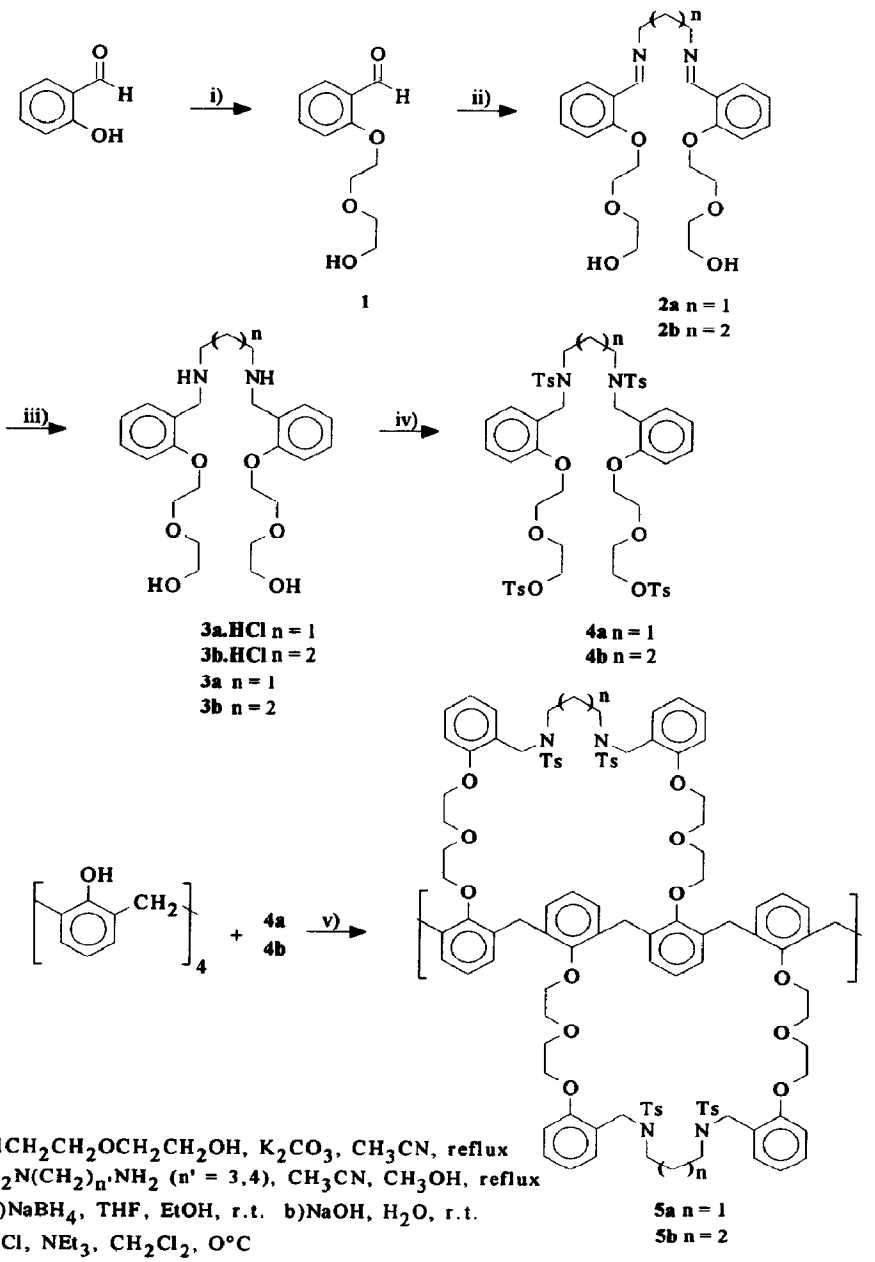
Abstract: We report the synthesis of two calix[4]arenes constrained to a 1,3-alternate conformation by di-aza-benzo crown ether bridging. Preliminary binding properties of one of them is also described.

Aza macrocycles are well-known for their binding properties towards inorganic or organic cations, anions and neutral molecules. It has become interesting to study in the same way N-tosyl aza macrocycles for their complexation properties. For example, Bottibo et al.[1] described the synthesis of N-tosyl aza macrocycles with the TsNHNa method as an easy entry to symmetrical N-tosyl aza macrocycles. Burguete et al. [2] have studied the conformational behaviour of N-tosyl polyaza[4](1,4)naphthalenophanes and concluded that the tosyl groups play an important role in the interconversion barrier of the potential receptors. Failla et al. [3] synthesised a N,N'-ditosyl-8,19-dimethoxy-2,5-diaza-[6 1]-naphthyl-cyclophane which can include one molecule of chloroform in the crystal lattice. Hamilton and Kazanjian[4] prepared a molecular ditopic receptor consisting of a diaza crown linked to a tetraaza cyclophane in which two opposite nitrogens are protected as N-tosyl groups. This receptor was shown to complex primary alkylammonium and tetraalkylammonium picrates.[4]

On the other hand, a wide variety of N,O-donor macrocycles has been described which contain both polyoxa and polyaza subunits in their framework[5]. A series of oxa-aza macrocycles were synthesised by Fenton[6] to test the selectivity towards transition metals. Attention has also been focused on « compartmental » macrocyclic receptors in which the different donors are located at opposite sides of the same molecule, thus presenting coordination sites with different characteristics.[7,8] With this aim, we previously reported the synthesis and complexing properties of oxa-aza macrocycles containing in their framework *p-tert*-butylcalix[4]arene and Schiff base elements[9,10] and a diaza-benzo crown ether *p-tert*-butylcalix[4]arene hydrogenated derivative.[11]

This paper describes the one step synthesis of 1,3-calix[4]-*bis*-(di-aza-benzo) crown ethers **5**, combining calix[4]arene unit and two diaza-benzo crown ethers in a highly symmetrical way. Preliminary complexation of **5a** with ammonium cations is also reported.



i) $ClCH_2CH_2OCH_2CH_2OH$, K_2CO_3, CH_3CN, reflux
ii) $H_2N(CH_2)_{n'}NH_2$ (n' = 3,4), CH_3CN, CH_3OH, reflux
iii) a)$NaBH_4$, THF, EtOH, r.t. b)NaOH, H_2O, r.t.
iv)TsCl, NEt_3, CH_2Cl_2, O°C
v)K_2CO_3, CH_3CN, reflux

The synthesis of **5**, depicted in Scheme 1, began with the O-alkylation of salicylaldehyde with 1 equiv. 2-(2-chloroethoxy)ethanol in the presence of K_2CO_3 in refluxing acetonitrile for 4 days to produce in 82% yield aldehyde **1**, which was further condensed with 0.5 equiv. of 1,n'-diaminoalkane (n' = 3 and 4 respectively) in a refluxing 1:1 mixture of methanol:acetonitrile for 24 h, leading quantitatively to Schiff bases **2**. Hydrogenation of **2** was carried out with 8 equiv. of $NaBH_4$ in a 1:1 mixture of tetrahydrofuran-ethanol at r.t. for 4 h. Hydrogenation products were obtained in their hydrochloride forms **3.HCl**, which when treated with 8 equiv. of NaOH in water led to pure diamino diols **3**. Total yield for both reactions ranged from 95 to 100 %. Compounds **3** were reacted with 4 equiv of tosylchloride in presence of 5-8 equiv. of NEt_3 in CH_2Cl_2 at 0°C over 8 h for **3a** and 48 h for **3b**. The respective residues were eluted from silica with 97:3 CH_2Cl_2:acetone to afford tetra N-tosylated derivatives **4a** (40%) and **4b** (17%). By means of a procedure already described by us[12] calix[4]arene was condensed with 2 equiv. of **4** in the presence of K_2CO_3 in refluxing acetonitrile for 7 days.[13] Tetrakis N-tosylated products were obtained pure by chromatography on silica with 98:2 CH_2Cl_2/acetone as eluent for **5a** and 95:5 CH_2Cl_2/ethyl acetate for **5b**, in 25% and 17 % yields respectively. Analytical data were in agreement with the proposed structures of **5** consisting of two oxa-aza ether chains attached to one calix[4]arene unit.[13]

The formation of **5** implies a preliminary *distal* 1,3-capping of the calix[4]arene by one oxa-aza ether chain as already observed during the formation of 1,3-calixcrowns.[15,16] The second capping enforces the 1,3-alternate conformation on the calixarene, consistent with the ^{1}H-NMR spectra. One observes a singlet at 4.25 ppm and at 4.35 ppm for the methylene $ArCH_2Ar$ in **5a** and **5b**, respectively. The detection of only one singlet at 2.40 ppm in the spectrum of **5a** and at 2.39 ppm for **5b** for the methyl of the tosyl indicated the high symmetry of the molecules. A similar highly symmetrical arrangement has already been observed for *p-tert*-butylcalix[4]-*bis*-crown-6.[17,18]

Tetrakis N-Ts ligand **5a** was not observed to complex $Zn(ClO_4)_2.6H_2O$, $Ba(ClO_4)_2$, $Cu(ClO_4)_2.4DMSO$ or $Eu(CF_3SO_3)_3$ in a 1:1 mixture of $CDCl_3$:CD_3OD. However extraction of ammonium picrate, $NH_4^+Pic^-$ from the solid into chloroform solution occured with **5a** [19] ^{1}H-NMR indicated the formation of a 1:1 complex as deduced from the integration ratio between the picrate proton singlet and the CH_3 signal of the tosyl residue and mass spectrometry The downfield shifts of 0.19, 0.09 and 0.13 ppm for the respective methylene proton signals OCH_2CH_2O attached to the calixarene and the meta aromatic protons allowed us to locate NH_4^+ nearer of the corresponding oxygen atoms probably by H-bonding[20] The broadening of the signals at 3.43, 3.71 and 4.03 ppm is reminiscent of a metal-ligand exchange as already observed in Ag^+-1,3-alternate calix[4]arenes.[21] Similar experiments with larger tetramethyl and tetraethyl ammonium cations were unsuccessful.

Further studies of the complexation properties of **5** are currently under investigation and will be presented in full in due course. We are also investigating binding properties of other receptors of type **5** Our objectives include : a) removing the tosyl groups of **5**; b) studying the complexation of neutral, cationic and anionic species; and c) preparing calixarenic ligands containing both crown ether and polyaza polyoxa crown ether chains to provide allosteric systems.

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13. *A typical procedure is given for* **5a** : In a 250 ml 2-necked round bottom flask, a solution of calix[4]arene[14] (1.274 g - 3.00 mmoles) and potassium carbonate (4.146 g - 30.00 mmoles) in acetonitrile (150 ml) was stirred at r. t. for 20 h. A solution of **4** (3.238 g - 3.00 mmoles) in acetonitrile (15 ml) was added dropwise and refluxed for 2 days. Then, another 1 equiv. of **4** was added dropwise, under similar conditions, to the solution and refluxed for a further 5 days. After evaporation to dryness under reduced pressure, the residue was dissolved in chloroform and potassium carbonate neutralised with 1N HCl. The organic layer was dried over Na_2SO_4 and concentrated to obtain a yellow solid (7.376 g). Pure product **5a** (1.411 g, 25%) was obtained as a white solid after chromatography (SiO_2, Bio-Rad, Bio Sil 40-63, Rf = 0.55, CH_2Cl_2/acetone 98/2). Mp 117-118°C. ^1H NMR ($CDCl_3$, 200 MHz, 25°C): δ 1.50 (m, 4H, CH_2), 2.40 (s, 12H, CH_3), 2.97 (t, J = 7.0 Hz, 8H, CH_2), 3.24 (t, J = 5.5 Hz, 8H, CH_2), 3.60 (s large, 16H, CH_2), 3.79 (s, 8H, CH_2), 3.96 (t, J = 4.9 Hz, 8H, CH_2), 4.25 (s, 8H, CH_2), 6.71-7.62 (m, 44H, arom.). Positive ion FAB, m/z = 1893.4 (M^+, 21%), 1738.3 (M^+ - $C_7H_7O_2S$, 100%). Found: H 6.21, C 67.07; calcd for $C_{106}H_{116}O_{20}N_4S_4$: H 6.17, C 67.21.
Characterization data of **5b** : White solid. Mp. 113-114°C. (SiO_2, Bio-Rad, Bio Sil 40-63, Rf = 0.58, CH_2Cl_2/ethyl acetate 95/5). ^1H NMR ($CDCl_3$, 200 MHz, 25°C): δ 1.70 (m, 8H, CH_2), 2.39 (s, 12H, CH_3), 2.93 (s large, 8H, CH_2), 3.32 (s large, 8H, CH_2), 3.63 (s large, 16H, CH_2), 3.71 (s, 8H, CH_2), 4.01 (t, J = 4 9 Hz, 8H, CH_2), 4.35 (s, 8H, CH_2), 6.64-7.66 (m, 44H, arom.). Positive ion FAB, m/z = 1922.3 (M^+, 45%), 1764.7 (M^+ - $C_7H_7O_2S$, 100%). Found: H 6.38, C 67.36; calcd for $C_{108}H_{120}O_{20}N_4S_4$: H 6.29, C 67.48.
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19. *Preparation of the 1:1 complex* **5a-$NH_4^+Pic^-$** *:* ligand **5a** (0.056 g - 0.03 mmoles) and solid ammonium picrate (0.037g - 0.15 mmoles) were refluxed in chloroform for two days. The unreacted $NH_4^+Pic^-$ was filtered off and the filtrate evaporated to dryness to give a yellowish-brown solid. Quantitative yield ^1H NMR ($CDCl_3$, 200 MHz, 25°C): δ 1.45 (b. s, 4H, CH_2), 2.40 (s, 12H, CH_3), 2.95 (t, J = 6.8 Hz, 8H, CH_2), 3.43 (b. s, 8H, CH_2), 3.71 (s large, 16H, CH_2), 3.78 (s, 8H, CH_2), 4.03 (b. s, 8H, CH_2), 4.26 (s, 8H, CH_2), 6.70-7.17 (m, 28H, arom.), 7.20 (d, J = 7.0 Hz, 8H, Hm), 7.59 (AB system, J = 8.2 Hz, 8H, arom), 8.90 (s, 2H, arom),. Positive ion FAB, m/z = 1911.7 ($M^+ + NH_4^+$, 43%), 1892.9 (M^+, 10%).
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