Selective *endo*-Calix Complexation of Linear Alkylammonium Cations by Functionalized (1,3)-*p*-*tert*-Butylcalix[5]crown Ethers

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Synthetic host molecules having neutral organic cavities capable of accommodating molecular guests are of current interest as a structural basis for constructing synzymes.[1] Calixarenes have been widely used as three-dimensional molecular platforms for the construction of ionophores and carriers with specific properties.[2] Although calixarenes are able to form inclusion complexes with several organic neutral guest molecules in the solid state, evidence for host−guest complexes in solution is very limited.[2]

Here we report the synthesis of (1,3)-*p*-*tert*-butylcalix[5]crown-6 derivatives **2a**−**f** in a conelike conformation, and the ability of **2c**−**f** to selectively form 1:1 *endo-calix complexes* with linear primary alkylammonium cations. This is, to the best of our knowledge, the first direct evidence for *endo*-calix complexes in solution.[3]

By using a slight modification of Böhmer's procedure,[4] *p*-*tert*-butylcalix[5]arene (**1**)[5] was reacted with penta(ethylene glycol) ditosylate or 2,2′-bis[2-[(toluene-*p*-sulfonyl)ethoxy]ethoxy]-1,1′-binaphthalene[6] and CsF in dry MeCN to afford regioselectively (1,3)-crown-6−2,4,5-triol derivatives **2a** (65%)[4] and **2b** (72%), respectively, which were in turn subjected to exhaustive alkylation with an excess of CH_3I/NaH in THF or PicCl·HCl/K_2CO_3 in DMF, to give triether derivatives **2c** (85%)[4] and **2d** (80%), **2e** (68%) and **2f** (64%), respectively (Scheme 1).[7]

The overall cone conformation for all new compounds is corroborated by their NMR spectra, showing the $ArCH_2Ar$ protons as three pairs of doublets in the ratio 2:2:1 (five pairs of doublets in the ratio 1:1:1:1:1 for racemic 2,2′-binaphthyl derivatives **2b**, **2d**, and **2f**) with a $\Delta\delta$ separation between geminal protons around 1 ppm and the pertinent methylene carbon resonances in the range 29.2 ± 1.5 ppm.[8,9] The high-field resonances of methoxy groups in trimethyl ether derivatives **2c,d** (δ in the range 1.99−2.93 ppm) are suggestive of a *cone-out* conformation (with methoxy groups pointing into the ring cavity and relevant *p*-*tert*-butyl substituents directed away from it). Conversely, tripicolyl derivatives **2e,f** adopt preferentially a *cone-in* conformation, with the *p*-*tert*-butylphenyl moiety bearing the "isolated" picolyloxy substituent canted inward in the calix cavity, as substantiated by the upfield resonances of the *tert*-butyl and aryl protons [δ 0.49 and 6.31 ppm in **2e**, and 0.42, 6.21 and 6.28 (ABq, J = 2.3 Hz) ppm in **2f**, respectively].

Table 1. Shieldings Observed for *n*-$BuNH_3^+$ Guest upon *endo*-Cavity Complexation with Calix[5]arene Hosts 2[a−c]

host	α-CH_2	β-CH_2	γ-CH_2	CH_3
2c	3.86	3.29	1.94	1.19
2d	3.87	3.33	1.99	1.22
2e	3.26	3.54	2.56	1.59
2f	3.67	3.62	2.44	1.51

[a] In $CDCl_3$−CD_3OD (9:1, v/v). [b] $\Delta\delta$ shieldings (ppm) were calculated as the difference between the resonances of pertinent protons of free and complexed guest. [c] Assignments of signals to the respective protons follow from decoupling experiments.

(1,3)-Calix[5]crown ethers **2** are potentially heteroditopic receptors, since they combine both a hydrophilic crown ether pocket at the lower rim and a preorganized hydrophobic cone cavity on the opposite side, the latter being well suited for cation−π interactions. In order to prove complementary host−guest interactions and determine the preferred binding sites, ^{1}H NMR titration experiments of **2** with (C_3 and C_4) RNH_3^+ picrate salts (up to 2 equiv) were carried out in $CDCl_3$−CD_3OD (9:1, v/v) by following the spectral changes upon addition of increasing amounts of salt. Our results seem to indicate that the complexation mode and binding geometry of RNH_3^+ by **2** is strongly affected both by the steric encumbrance of substituents at the lower rim and by the shape of the guest cation. For instance, the less hindered compound **2a**, with free OH groups, complexes *n*-$PrNH_3^+$, *n*-$BuNH_3^+$, and *i*-$BuNH_3^+$ (but not *i*-$PrNH_3^+$, *s*-$BuNH_3^+$, or *t*-$BuNH_3^+$), probably *via* hydrogen bonding(s) of the $-NH_3^+$ head with the crown-6 moiety,[10] without apparent selectivity. However, when the OH groups are replaced by the bulkier alkoxy groups (compds **2c**−**f**), no interaction at all occurs with the branched (C_3 and C_4) RNH_3^+ cations, while unprecedented *endo-cavity complexation* is observed with the linear guest cations. This is unambiguously supported by the dramatic upfield shifts ($\Delta\delta$ up to 3.87 ppm) experienced by the resonances of the cavity-included *n*-alkyl chain (see Table 1 for the complexation of *n*-$BuNH_3^+$). Further evidence for host−guest interactions with our systems was provided by the ^{13}C NMR spectrum of **2e**⊂*n*-$BuNH_3^+$ *endo*-complex (obtained by treating **2e** with 20 equiv of picrate salt; see the Supporting Information).

Typical ^{1}H NMR spectra of receptor **2c**, without and with 1 equiv amount of *n*-$BuNH_3^+$ picrate, are shown in Figure 1. The free host and *endo*-cavity complex exchange slowly in the NMR time scale, as shown by the presence in the spectra of distinct signals for the free and complexed species. Consequently, the 1:1 host−guest stoichiometry and association constants (K_{assoc}) for the formation of the *endo*-complexes could be deduced by direct ^{1}H NMR analysis from the peak intensity ratio of equimolar solutions (ca. 5×10^{-3} M) of host and guest in

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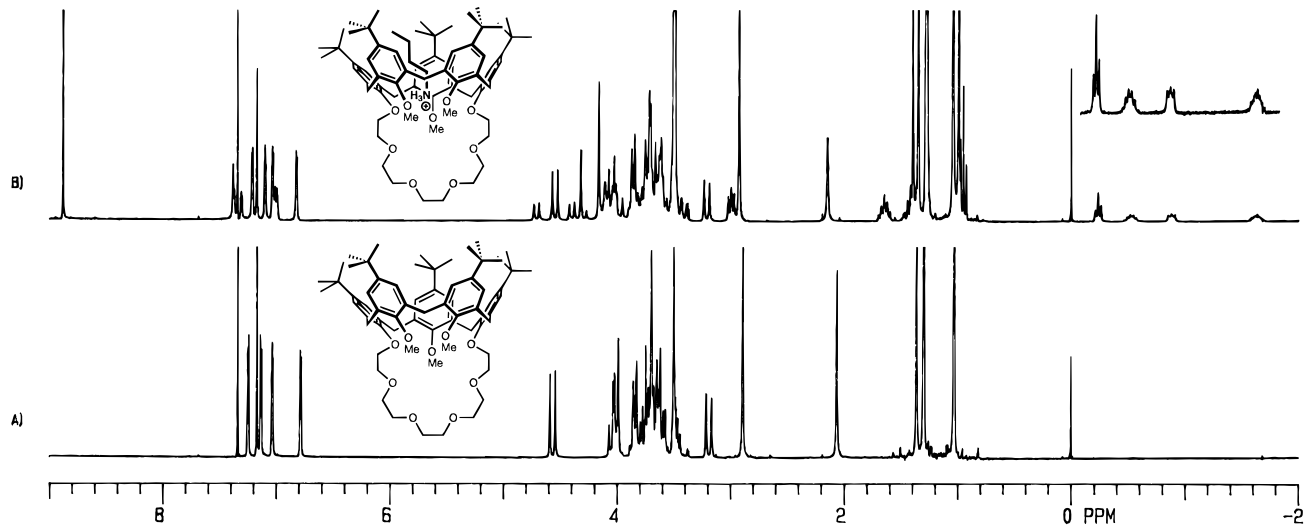
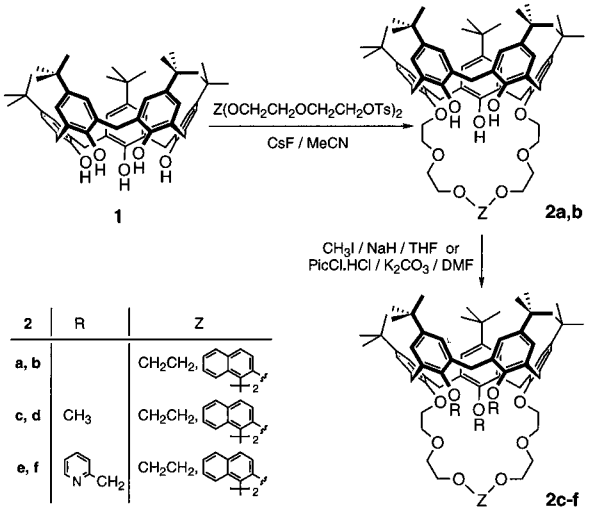


Figure 1. *Endo-calix* complexation of *n*-$BuNH_3^+$ cation by calix[5]crown ether **2c**. ^1H NMR spectrum (300 MHz, $CDCl_3-CD_3OD$ 9:1, 293 K) of (A) the free host and (B) spectral changes after addition of 1 equiv of picrate salt.

Scheme 1



the stated solvent mixture. The K_{assoc} at 293 K for the *endo*-calix complexation of *n*-$BuNH_3^+$ with **2c**−**f** are 86, 65, 83,[11] and 48 M^{-1}, respectively.

The unique ability of compounds **2c**−**f** to discriminate between linear and branched primary alkylammonium cations can be ascribed to a remarkable steric and electronic complementarity between the preorganized π-rich hydrophobic cavity of the calix[5]arene skeleton and the shape of the guests. It seems reasonable to assume that other noncovalent interactions, including hydrogen bonding between the cavity-included $-NH_3^+$ head and the ethereal oxygen(s) and/or pyridine nitrogen(s) of the host, may contribute to the stabilization of these *endo*-complexes, whereas the presence of *tert*-butyl substituents at the upper rim, which sterically interfere with the branched alkylammonium guests, may favor selectivity. These results are interesting because no calixarene derivative exhibiting such an enzyme-like specificity for *n*-$BuNH_3^+$ over other butylammonium cations has been reported so far, even though a number of calixarene-type host molecules for butylammonium recognition have been synthesized.[13]

An estimate of how deeply the *n*-$BuNH_3^+$ cation is accommodated into the cavity of calix[5]arene derivatives **2** can be deduced from the observed shieldings for the included *n*-butyl chain (Table 1). A scrutiny of Table 1 reveals that the most effective shieldings for γ-methylene protons ($\Delta\delta \sim 2.4-2.6$ ppm) are observed for crown ether derivatives **2e,f** carrying α-picolyl pendant groups. This may imply that the $-NH_3^+$ head of the cation penetrates the cavity more deeply, because of additional hydrogen bonding with the pyridine ring nitrogen(s).

Further elaboration of calix[5]arene-based hosts and their molecular recognition properties toward biologically active alkylammonium guests are currently being investigated.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, ^1H NMR spectra of equimolar solution of hosts **2d**−**2f** and *n*-$BuNH_3^+$ picrate, and the ^{13}C NMR spectrum of **2e**⊂*n*-$BuNH_3^+$ *endo*-complex (9 pages).

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(11) The ^1H NMR spectra of equimolar amounts of **2e** and *n*-$BuNH_3^+$ showed the presence of additional signals of low intensity, which were assigned to protonated host (~10%) by comparison with the spectrum obtained after protonation of **2e** with TFA. The enhanced basicity[12] of the "isolated" picolyl substituent, which is almost completely protonated even by 1 equiv of L-Phe-OMe·HCl, is believed to be associated with the juxtaposition of the polyether bridge that stabilizes the pyridinium cation by self-complexation. Subsequent to protonation, compound **2e** assumes a more open cone conformation, as suggested by the resonance of the "isolated" *p-tert*-butyl substituent, which is shifted downfield ($\Delta\delta$ 0.95 ppm).

(12) Preliminary results of the acid−base behavior of **2e** (L) in MeOH have shown the following log *K* of protonation: log K_1 ($L + H^+ = LH^+$) = 8.6; log K_2 ($LH^+ + H^+ = LH_2^{2+}$) = 4.1; log K_3 ($LH_2^{2+} + H^+ = LH_3^{3+}$) = 3.3.

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