

Alkylammonium Guest Induced Fit Recognition by a Flexible Dihomooxacalix[4]arene Derivative

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Abstract: The conformationally mobile tetramethoxy-dihomooxacalix[4]arene **1c** is able to interact with linear and branched alkylammonium guests through an induced fit process mainly driven by H-bonds and cation- π interactions. Thus, while free **1c** adopts a 1,4-alternate conformation in solution, in the presence of linear *n*-BuNH₃⁺ and branched *s*-BuNH₃⁺ and *i*-PrNH₃⁺ guests, it preferentially forms *endo*-complexes in a cone conformation through an adaptive structural change in response to the presence of the ammonium guests. In accordance with previous results, the DFT-optimized structures of the complexes indicate that they are mainly stabilized by H-bonding interactions between the guest ammonium group and the host CH₂OCH₂ ethereal bridge.

Introduction

The recognition of ammonium guests is of significant importance in many living processes and in this context,^[1] in recent years, several studies have established that secondary interactions such as hydrogen bonds^[2] and cation- π ^[3] interactions play a special role in the stabilization of ammonium/receptor complexes. For example, cation- π and H-bonding interactions are essential in the biological recognition of nicotine^[1a] or of the smoking cessation drug cytosine^[1c] by α 4 β 2 neuronal receptor.

Inspired by biological recognition motifs for charged ammonium substrates,^[4] the design and development of artificial ammonium receptors represent a fascinating area of research in supramolecular chemistry. Consequently, a particular attention has been devoted to the recognition of ammonium guests by macrocycles such as calixarenes,^[5] pillararenes,^[6] crown

ethers,^[7] cucurbiturils,^[8] and biphen[*n*]arenes.^[9] In this scenario, the *endo*-complexation properties of dihomooxacalix[4]arene derivatives,^[10] calix[4]arene analogues in which one CH₂ bridge is replaced by one CH₂OCH₂ group, have remained largely less studied.

Very recently,^[5k] we reported a complete study on the complexation of primary and secondary (di)alkylammonium cations by conformationally blocked, cone-shaped *p*-*tert*-butyl-dihomooxacalix[4]arene derivatives **1a–b** in the presence of the weakly coordinating Tetrakis[3,5-bis(triFluoromethyl)Phenyl]Borate (TFPB[−]) “superweak anion” (Figure 1).^[11]

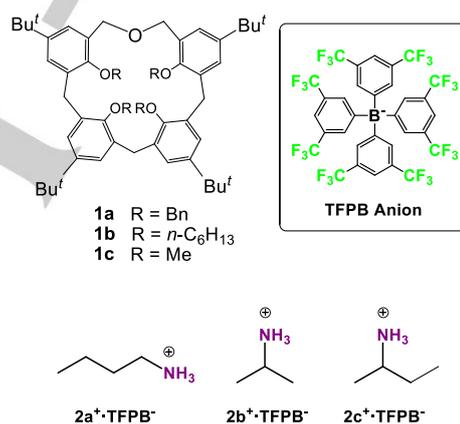


Figure 1

In that study we showed that the cone-shaped dihomooxacalix[4]arenes **1a–b** were able to host linear and branched primary alkylammonium guests inside their aromatic cavities in the presence of the “superweak” TFPB anion. The *endo*-complexes were mainly stabilized by the H-bonding interaction between the ammonium group of the guest and the O-atom of the CH₂OCH₂ bridge of the host.

In natural systems, the induced fit mechanism is the basis of many molecular recognition processes; in these cases, a rigid guest induces an adaptive structural change of the natural receptor in order to adopt a binding site complementary to the guest. As evidenced recently by Fujita,^[12b] are still uncommon the examples of biomimetic artificial hosts able to give adaptive structural changes during the interaction with substrates.^[12] Regarding the calix[4]arenes, for example, four basic conformations are possible for the tetramethoxy derivative (cone, partial-cone, 1,2-alternate, and 1,3-alternate),^[5a] while it adopts

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a cone conformation after addition of Li⁺ or Na⁺ guest,^[12a] with the oxygen atoms at the lower rim close to cationic guest.

In this regard, the dihomooxalix[4]arene macrocycles are particularly promising, thanks to their conformational mobility. In fact, it is well known^[10] that tetramethoxy-dihomooxalix[4]arene **1c** can exist in six basic conformations: cone, partial-cone-1, partial-cone-3, 1,2-alternate, 1,4-alternate, and 1,3-alternate (Figure 2), but at the best of our knowledge, no examples of adaptative conformational changes have been observed for this class of hosts in response to the presence of guests.

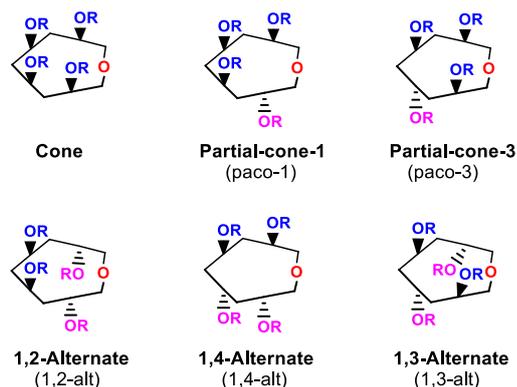


Figure 2. Possible basic conformations of dihomooxalix[4]arenes.

Thus, we decided to investigate the binding abilities of the conformationally flexible tetramethoxy-dihomooxalix[4]arene derivative **1c** toward ammonium guests and we report here the results of our studies.

Results and Discussion

Conformations of tetramethoxy-dihomooxalix[4]arene derivative 1c. The six main conformers of dihomooxalix[4]arenes (cone, partial-cone-1, partial-cone-3, 1,2-alternate, 1,4-alternate, and 1,3-alternate, Figure 2)^[10] can be distinguished by ¹H NMR in accordance with their symmetry elements. In particular, cone and 1,2-alternate possess a symmetry plane, 1,4-alternate and 1,3-alternate have a C₂ symmetry axis, while both partial-cone-1 and -3 have no symmetry elements.

Previous ¹H VT NMR^[10c] and X-ray crystallographic studies^[10e] showed that **1c** mainly exists in the 1,4-alternate conformation (Figure 2) both in solution and in the solid state. Interestingly, DFT^[13] calculations performed in the present work at the MPW1PW91^[14]/6-31G(d) level of theory were in full agreement with these results. In fact, the following stability order was found: **1c**^{1,4-alt} > **1c**^{cone} > **1c**^{1,2-alt} > **1c**^{paco-3} (Figure S10), with relative energies of 0.00, 0.80, 1.31, and 3.56 kcal/mol, respectively, while the two remaining conformations, **1c**^{1,3-alt} and

1c^{paco-1}, were found at energies higher than 4.0 kcal/mol. On the basis of these relative energies, a Boltzmann population at 298 K of 72.2%, 18.7%, 8.6%, and 0.2% can be calculated for **1c**^{1,4-alt}, **1c**^{cone}, **1c**^{1,2-alt}, and **1c**^{paco-3}, respectively. Thus, both theoretical and experimental studies clearly indicated that tetramethoxy-dihomooxalix[4]arene **1c** mainly adopts the 1,4-alternate conformation in solution.

Binding ability of dihomooxalix[4]arene derivative 1c toward linear *n*-butylammonium guest 2a⁺. When the TFPB salt of *n*-butylammonium **2a**⁺ was added to a CDCl₃ solution of **1c** drastic changes were observed in its ¹H NMR spectrum (400 MHz, 298 K) (Figure 3). In particular, a new set of slowly-exchanging signals appeared, including the *n*-BuNH₃⁺ < **1c** complex formation (Figure 3). This is a clear indication that the linear *n*-butylammonium cation **2a**⁺ gave an *endo*-cavity complexation with the alkyl chain shielded by the aromatic rings.^[5g] Complex formation was also confirmed by an ESI(+) mass spectrum which gave as the base peak a value of 809 m/z corresponding to supramolecular ion *n*-BuNH₃⁺ < **1c**.

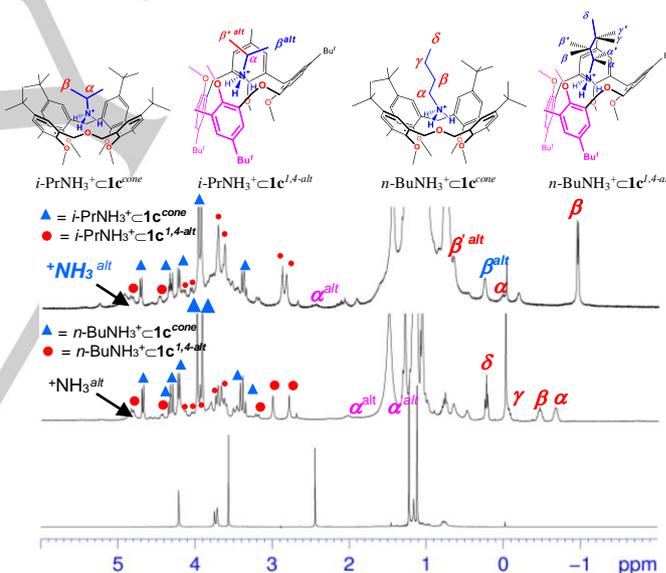


Figure 3. Significant portions of the ¹H NMR spectra (400 MHz, CDCl₃, 298 K) of (bottom) **1c**; (middle) 1:1 mixture of **1c** and **2a**⁺ (3 mM); (top) 1:1 mixture of **1c** and **2b**⁺ (3 mM).

A COSY-45 spectrum (Figure 4) allowed a complete confident assignment of all *n*-BuNH₃⁺ resonances. Thus, the NH₃⁺ signal at 4.24 ppm correlated with α -protons at -0.64 ppm, which showed a coupling with β -methylene group at -0.43 ppm, which in turn presented a cross-peak with γ -protons at -0.02 ppm, finally coupled with δ -methyl at 0.30 ppm. A close inspection of the methylene region of the ¹H NMR spectrum of the 1:1 mixture of **1c** and **2a**⁺ revealed the presence of two intense AX systems (COSY in Figure 4, top) in a 1:2 ratio at 3.40/4.37 ppm ($\Delta\delta = 0.97$ ppm) and 3.44/4.34 ppm ($\Delta\delta = 0.90$

ppm), which correlated in the HSQC spectrum with ^{13}C signals at 30.8 (b in Figure 4, bottom) and 30.4 ppm (a in Figure 4, bottom), respectively.

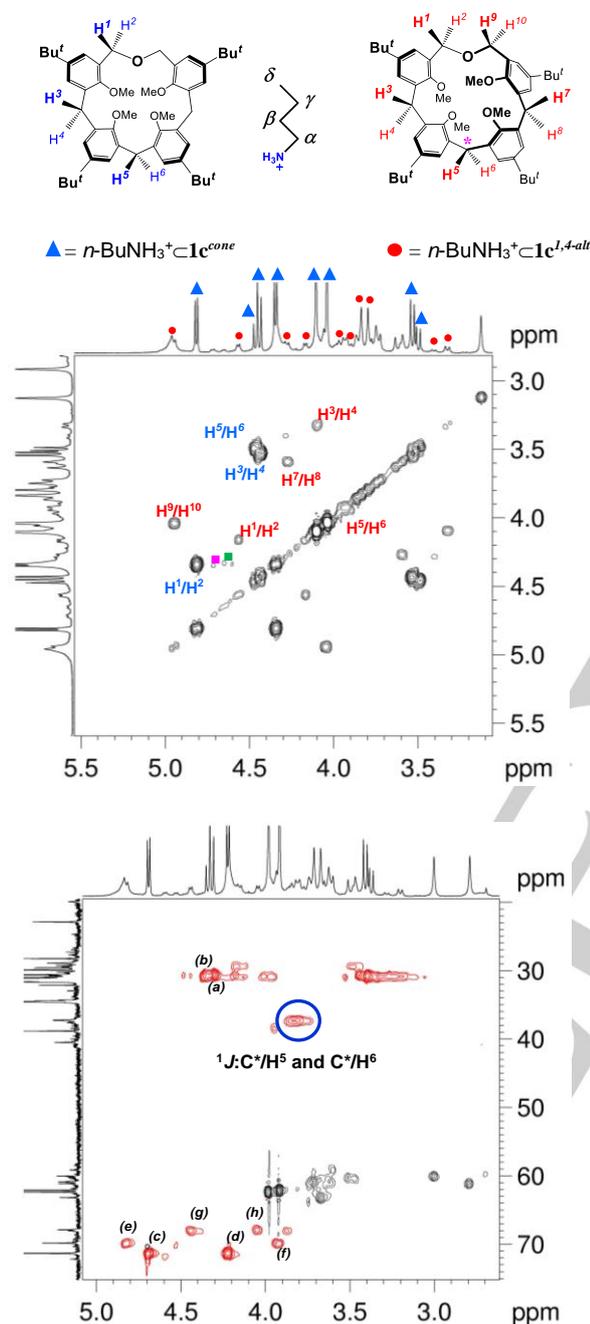


Figure 4. Expansions of the 2D COSY (top) and HSQC (bottom) spectra (600 MHz, CDCl_3 , 298 K) of a 1:1 mixture of **1c** and **2a**.

In addition, an AB system (COSY) was present at 4.25/4.72 ppm relative to CH_2OCH_2 group, which was HSQC-correlated (c and d in Figure 4, bottom) with a carbon at 71.0 ppm. By application of the known Gutschke's and de Mendoza's rules,^[15] these data

were only compatible with a $n\text{-BuNH}_3^+\text{-1c}$ complex in which the tetramethoxy-dihomooxalix[4]arene **1c** was in a cone conformation ($n\text{-BuNH}_3^+\text{-1c}^{\text{cone}}$). Thus, while free **1c** adopts in solution a 1,4-alternate conformation,^[10c,d] in the presence of $n\text{-BuNH}_3^+$ guest it preferentially converts to a cone conformation, through an adaptive structural change.

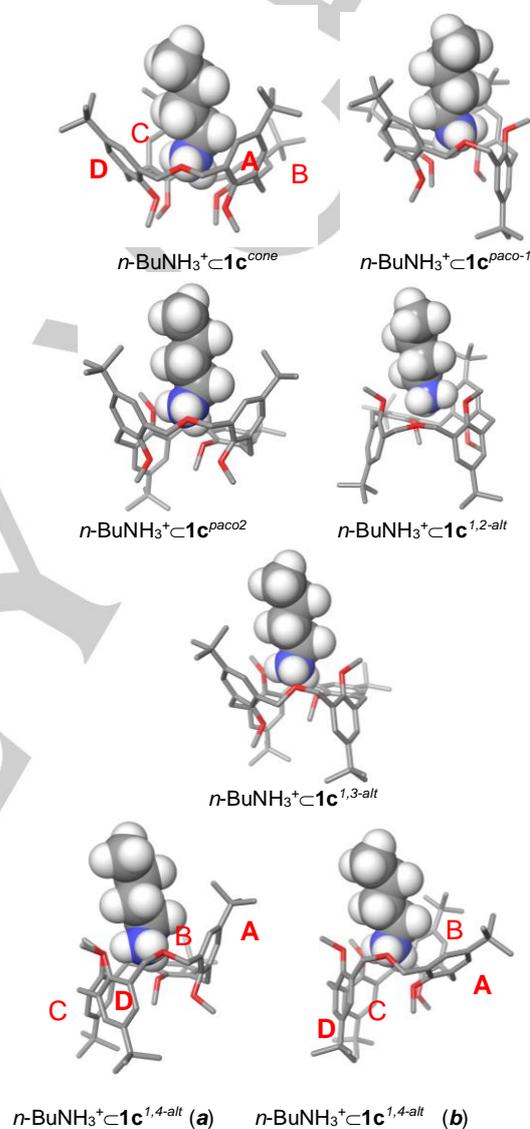


Figure 5. Optimized Structure of the $n\text{-BuNH}_3^+\text{-1c}$ complexes with **1c** in different conformations (MPW1PW91^[14] DFT calculations, 6-31G(d) basis set).

A further analysis of the $\text{ArCH}_2\text{OCH}_2\text{Ar}$ region of the ^1H NMR, 2D COSY, and HSQC spectra (Figures 3 and 4) reveals the presence of two AB systems at 4.04/4.56 and 4.17/4.94 ppm, corresponding to another specie in a 0.35 ratio with respect to the most abundant $n\text{-BuNH}_3^+\text{-1c}^{\text{cone}}$ complex (as determined by integration of their respective ^1H NMR signals). These AB systems correlate in the HSQC spectrum with oxygenated CH_2

carbons at 67.8 (*g* and *h* in Figure 4, bottom) and 69.7 ppm (*e* and *f* in Figure 4, bottom), respectively. In addition, two ArCH₂Ar AX systems can be seen at 3.32/4.10 and 3.60/4.28 ppm, which are HSQC-correlated with ArCH₂Ar carbons at 30.7 and 29.1 ppm, respectively, typical of *syn*-oriented aromatic rings, while an AB system was presents at 3.79/3.98 ppm, which is HSQC-correlated with ArCH₂Ar carbons at 37.1 ppm, typical of *anti*-oriented aromatic rings.

A more careful analysis of the 2D COSY spectrum evidenced the presence of two further, very weak, ArCH₂OCH₂Ar AB systems (indicated by pink and green squares in Figure 4) at 4.22/4.57 and 4.20/4.51 ppm, corresponding to a third specie in a 0.021 ratio with respect to the most abundant *n*-BuNH₃⁺⊂**1c**^{cone} complex (as determined by integration of their respective ¹H NMR signals). On the other hand, the HSQC spectrum showed cross-peaks between a ¹H resonance at 3.95 ppm and one pertinent carbon signal at 38.1 ppm, which can be assigned to ArCH₂Ar groups between *anti*-oriented aromatic rings.

Table 1. MPW1PW9/6-31G(d) Energy Data and Room Temperature Boltzmann Populations for the Six *n*-BuNH₃⁺⊂**1c** Complexes in Figure 3.

	ΔE^1 kcal/mol	Z_i	Fractional Population
cone	0.0000	1.000000	0.757
1,4-alt	0.74	0.28	0.210
paco-1	2.08	0.029	0.022
paco-3	2.58	0.013	0.0098
1,2-alt	4.65	0.00038	0.000287
1,3-alt	5.03	0.00020	0.000151

¹Obtained by single point calculations starting from optimized structures of the complexes at MPW1PW9/6-31G(d) level of the theory.

In conclusion, all the above data clearly evidenced the presence of two additional *n*-BuNH₃⁺⊂**1c** complexes in which the tetramethoxy-dihomooxalix[4]arene **1c** was in a conformation different than the cone one (Figure 5).

In order to clarify the conformational distribution of *n*-BuNH₃⁺⊂**1c** complexes, we decided to undertake a DFT study on the six possible conformers. Single-point DFT^[13] calculations on the optimized structures of the complexes (Figure 5) at the MPW1PW9^[14]/6-31G(d) level of theory indicated the following stability order: *n*-BuNH₃⁺⊂**1c**^{cone} > *n*-BuNH₃⁺⊂**1c**^{1,4-alt} > *n*-BuNH₃⁺⊂**1c**^{paco-1} > *n*-BuNH₃⁺⊂**1c**^{paco-3} with the relative energies of 0.00, 0.74, 2.08, and 2.58 kcal/mol, while the two other possible alternate conformations, *n*-BuNH₃⁺⊂**1c**^{1,3-alt} and *n*-BuNH₃⁺⊂**1c**^{1,2-alt}, were found at energies higher than 4.5 kcal/mol. In correspondence to the MPW1PW9/6-31G(d) relative energies of

the *n*-BuNH₃⁺⊂**1c** complexes, a Boltzmann population at 298 K of 75.7% and 21.0% for *n*-BuNH₃⁺⊂**1c**^{cone} and *n*-BuNH₃⁺⊂**1c**^{1,4-alt}, respectively, can be calculated, in addition to minor conformers (Table 1).

On this basis and by a close inspection of the methylene region of the ¹H NMR spectrum (Figures 3 and 4), we can assign to the *n*-BuNH₃⁺⊂**1c**^{1,4-alt} complex the ArCH₂OCH₂Ar signals at 4.94/4.17 and 4.56/4.04 ppm, the ArCH₂Ar systems at 3.32/4.10, 3.79/3.98, and 3.60/4.28 ppm, and the OMe singlets at 2.80, 3.02, 3.69, and 3.73 ppm, corresponding to the experimentally determined 0.35 ratio with respect to the most abundant *n*-BuNH₃⁺⊂**1c**^{cone} complex.

A careful examination of the DFT-optimized structure of the *n*-BuNH₃⁺⊂**1c**^{cone} complex (Figure 5) reveals the existence of three hydrogen-bonds between the ammonium group of **2a**⁺ and the O-atom of the CH₂OCH₂ bridge of **1c** (N⁺⋯O distance of 2.80 Å), and the OMe groups of rings B (N⁺⋯O distance of 2.84 Å) and D (N⁺⋯O distance of 2.89 Å). In addition, the distances between the positive N-atom of **2a**⁺ and the centroids of the aromatic rings A and C (Figure 5) of **1c** were 3.50 and 3.70 Å, respectively, compatible with the existence of cation-π interactions.^[1,3]

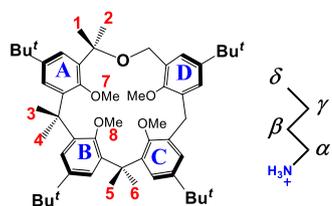
Regarding the *n*-BuNH₃⁺⊂**1c**^{1,4-alt} complex, a distance of 2.80 Å was measured between the O-atom of the CH₂OCH₂ bridge of **1c** and the N-atom of **2a**⁺. In addition, two other H-bonds were present between the ammonium group of **2a**⁺ and the O-atoms of the inverted C and D rings (Figure 5). Finally, a distance of 3.60 Å was measured between the centroid of the aromatic ring B of **1c** and ammonium group of **2a**⁺ compatible with the existence of a cation-π interaction.

In order to corroborate the 1.00/0.35 cone/1,4-alt conformational assignment for the *n*-BuNH₃⁺⊂**1c** complexes, we performed DFT based GIAO NMR calculations at the MPW1PW91/6-311++(d,p) level of theory with the aim to predict the NMR chemical shifts of the two complexes and to compare them with the experimental ones, following a protocol already reported.^[15c-d,16] At this regards, we focused our attention to the chemical shift of the host ¹H-nuclei which can be considered useful conformational probes, such as the ArCH₂Ar and OMe groups. These calculations were also extended to the *endo*-complexed *n*-BuNH₃⁺ guest in order to gain additional structural informations.

Regarding the *n*-BuNH₃⁺⊂**1c**^{cone} complex, the calculated data reported in Table 2 show an acceptable agreement with the experimental ones. In detail, for the ArCH₂OCH₂Ar H-1/2 atoms the calculated ¹H $\Delta\delta$ value is 0.52, perfectly matching the experimental one (0.52 ppm). Analogously, for the ArCH₂Ar H-3/4 and H-5/6 couples (Table 2) the calculated ¹H $\Delta\delta$ values are 0.82 and 1.37 ppm in acceptable agreement with those observed experimentally (0.90 and 0.97 ppm, respectively). Clearly, these data are well compatible with the cone conformation of the dihomooxalix[4]arene host in the *n*-BuNH₃⁺⊂**1c** complex. This agreement also holds for the OMe groups (experimental at 3.94 and 4.01 ppm, versus calculated at 3.95 and 4.19 ppm, respectively). In addition DFT-based GIAO NMR chemical shift calculations predict quite well the ¹H δ

values of the $n\text{-BuNH}_3^+$ guest shielded by the aromatic walls of host **1c**. In fact, the experimental δ value of -0.64 ppm of the α H-atoms of $n\text{-BuNH}_3^+$ was well predicted by the DFT one at -0.43 ppm. Analogously, the experimentally observed shielding order ($\alpha > \beta > \gamma > \delta$) of $n\text{-BuNH}_3^+$ guest was also well reproduced. All these data clearly indicated that the most

Table 2. Calculated and Experimental ^1H δ of the $n\text{-BuNH}_3^+\text{-1c}^{\text{cone}}$ Complex.



	^1H δ_{calcd}^1	^1H δ_{exp}^2	^1H $\Delta\delta_{\text{calcd}}^1$	^1H $\Delta\delta_{\text{exp}}^2$
1	4.45	4.25	0.52	0.52
2	4.97	4.72		
3	3.85	3.44	0.82	0.90
4	4.67	4.34		
5	3.60	3.40	1.37	0.97
6	4.97	4.37		
7	3.95	3.94		
8	4.19	4.01		
α	-0.45	-0.64		
β	-0.14	-0.43		
γ	0.52	-0.024		
δ	0.60	0.30		
$^+\text{NH}_3$	4.83	4.24		

¹For NMR shift calculations of $n\text{-BuNH}_3^+\text{-1c}^{\text{cone}}$ complex, the indicated atoms were treated at the MPW1PW91/6-311++(d,p) level of theory, in chloroform as solvent. The structure of the $n\text{-BuNH}_3^+\text{-1c}^{\text{cone}}$ complex was initially minimized with MM3 and successively optimized at MPW1PW91/6-31G(d) level of theory. ²Experimental ^1H NMR chemical shifts were measured in CDCl_3 and referred to the TMS as internal standard (600 MHz, 298 K).

abundant specie in solution was $n\text{-BuNH}_3^+\text{-1c}$ complex with the dihomooxalix[4]arene in a cone conformation.

Regarding the $n\text{-BuNH}_3^+\text{-1c}^{1,4\text{-alt}}$ complex, a Monte Carlo search (MM3 Force Field, GB/SA CHCl_3 model solvent)^[17] revealed the existence of a second structure (complex **b** in Figure 5) which differs with respect to that already shown in Figure 5 (complex **a**) mainly for the different orientation of ring B of **1c**. In fact, in the complex **a** ring B assumes an out inclination to facilitate the formation of a H-bond between its O-atom and the ammonium group of the guest, with a $^+\text{N}\cdots\text{OMe}$ distance of 2.80 Å. In the complex **b**, the inclination of ring B is almost

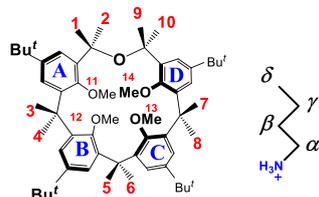
perpendicular to the mean plane of the ArCH_2Ar groups, which lengthens the $^+\text{N}\cdots\text{OMe}$ distance to a value of 4.22 Å.

Thus, we decided to perform a MPW1PW91/6-31G(d) geometry optimization of both structures (Figure 5). The single point energy calculations revealed that conformer **a** was more stable by 0.70 kcal/mol with respect to conformer **b**, which should be very quickly exchanging in solution. Therefore, the experimental δ values must be compared with the weighted sum of the theoretical MPW1PW91/6-311++(d,p) δ values of both **a** and **b** conformers of $n\text{-BuNH}_3^+\text{-1c}^{1,4\text{-alt}}$ complex (Table 3).

Another important point to be considered is related to the expected number of resonances. In fact, due to the presence of the $n\text{-BuNH}_3^+$ guest in the slowly exchanging $n\text{-BuNH}_3^+\text{-1c}^{1,4\text{-alt}}$ complex, the C_2 symmetry axis is lost with respect to the free state. This justifies the presence of four singlets relative to OMe groups, three AX systems relative to ArCH_2Ar bridges, two AX/AB systems relative to $\text{ArCH}_2\text{OCH}_2\text{Ar}$ groups, and finally the presence of diastereotopic protons relative to the guest butyl chain (Figures S1 and S2).

As concerns ^1H $\Delta\delta$ values of the ArCH_2Ar bridge between *anti*-oriented B and C rings (Table 3), the calculated value of 0.39 ppm is in agreement with the experimental datum of 0.19 ppm. Naturally, on the basis of the Gutsche's and de Mendoza's rules,^[15] this ArCH_2Ar ^1H $\Delta\delta$ of 0.19 ppm is indicative of an *anti*-orientation between the pertinent aryl rings B and C, in accordance with the 1,4-alternate conformation of **1c** in the complex. In a similar way, the ArCH_2Ar bridging groups between *syn* oriented A/B and C/D rings, gave calculated ^1H $\Delta\delta$ of 0.78 and 0.71 ppm, respectively, which are very close to the experimental ones of 0.78 and 0.68 ppm. In addition, the calculated δ values of OMe groups at 2.22, 3.73, 3.88, and 3.31 ppm were also in agreement with the observed ones at 2.80, 3.69, 3.73, and 3.02 ppm.

Regarding the resonances of the guest butyl chain in the $n\text{-BuNH}_3^+\text{-1c}^{1,4\text{-alt}}$ complex, a close inspection of the 2D COSY spectrum (Figure S1) revealed the presence of a correlation between a broad signal at 4.88 ppm relative to the ammonium protons and two diastereotopic signals relative to α -methylene H-atoms at 2.05 ppm and 1.59 ppm (AB system), which correlated in the 2D HSQC spectrum with a carbon resonance at 40.4 ppm (Figure S2). Interestingly, diastereotopic resonances relative to β - and γ -methylene groups of the guest were found at 1.21/1.00 and 0.82/0.70 ppm, which correlated in the HSQC spectrum with carbon resonances at 37.3 and 28.9 ppm, respectively (Figure S2). As expected, the calculated chemical shifts values of the guest butyl chain in the $n\text{-BuNH}_3^+\text{-1c}^{1,4\text{-alt}}$ complex were in good agreement with the experimental ones (Table 3). It is worth pointing out that these values were in the positive region of the spectrum and far away from those of the corresponding protons in the $n\text{-BuNH}_3^+\text{-1c}^{\text{cone}}$ complex. Clearly, this lower upfield shift is due to the lower number of shielding Ar rings (two) in $n\text{-BuNH}_3^+\text{-1c}^{1,4\text{-alt}}$ with respect to those (four) of $n\text{-BuNH}_3^+\text{-1c}^{\text{cone}}$.

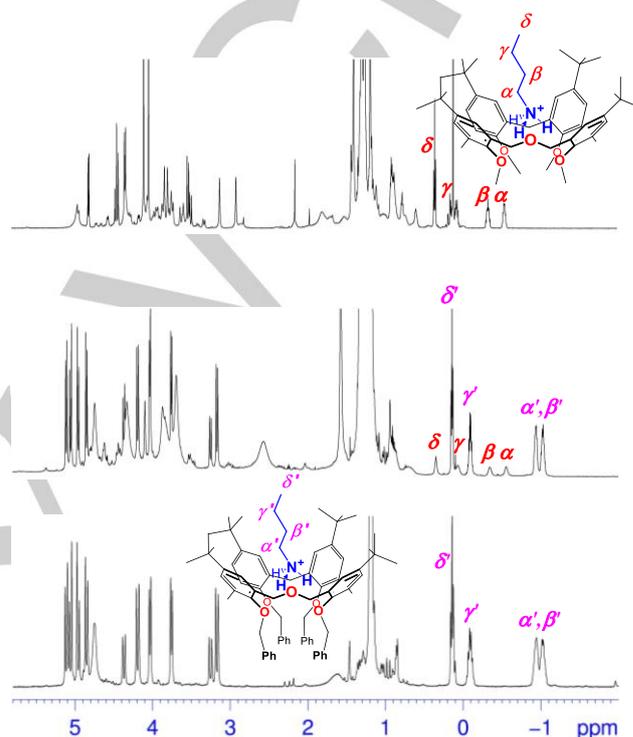
Table 3. Calculated (weighted sum) and Experimental ^1H δ values of the $n\text{-BuNH}_3^+\text{-}1\text{c}^{1,4\text{-alt}}$ Complex.

	δ_{calcd}^1	δ_{exp}^1	$\Delta\delta_{\text{calcd}}$	$\Delta\delta_{\text{exp}}$
1	4.33	4.04	0.75	0.52
2	5.08	4.56		
3	3.59	3.32		
4	4.37	4.10	0.78	0.78
5	3.89	3.79		
6	4.28	3.98	0.39	0.19
7	4.51	4.28		
8	3.80	3.60	0.71	0.68
9	5.25	4.94		
10	4.43	4.17	0.82	0.77
11(OMe) ¹	2.22	2.80		
12(OMe) ¹	3.73	3.69		
13(OMe) ¹	3.88	3.73		
14(OMe) ¹	3.31	3.02		
⁺ NH ₃	5.39	4.88		
α	1.87	2.05		
α'	1.08	1.59		
β	1.56	1.21		
β'	1.48	1.00		
γ	1.14	0.82		
γ'	1.18	0.70		
δ	1.06	0.80		

¹ Due to the presence of the $n\text{-BuNH}_3^+$ guest in the 1,4-alternate conformation of **1c**, it loses the C_2 symmetry axis with respect to the free state.^{10c} This justifies the presence of four singlets relative to OMe groups, three AX systems relative to ArCH_2Ar bridges, two AX/AB systems relative to $\text{ArCH}_2\text{OCH}_2\text{Ar}$ groups, and finally the presence of diastereotopic protons relative to the guest butyl group.

In conclusion, the conformationally mobile tetramethoxy-dihomooxalix[4]arene **1c** host is able to complex $n\text{-BuNH}_3^+$ guest in the presence of TFPB counter-ion and 1D and 2D NMR studies, corroborated by GIAO NMR chemical shift prediction and single-point energy calculations, indicates that the most

abundant species in solution were $n\text{-BuNH}_3^+\text{-}1\text{c}$ complexes with the dihomooxalix[4]arene in a cone and 1,4-alternate conformations. At this point the third species hardly seen in solution at a 0.021 ratio with respect to $n\text{-BuNH}_3^+\text{-}1\text{c}^{\text{cone}}$ complex can be serenely assigned to $n\text{-BuNH}_3^+\text{-}1\text{c}^{\text{paco-1}}$ complex, which follows in energy order (Table 1). Of course, its complete NMR study is precluded by the very low signal intensities, which are very close to the detection limit.

**Figure 6.** Significant portions of the ^1H NMR spectra (600 MHz, CDCl_3 , 298 K) of: (bottom) 1:1 mixture of **1a** and **2a*** (3 mM); (middle) 1:1:1 mixture of **1a**, **1c**, and **2a*** (3 mM each one); (top) 1:1 mixture of **1c** and **2a*** (3 mM).

Interestingly, a competition experiment (Figure 6) was performed by mixing 1 equiv of $n\text{-BuNH}_3^+\text{-TFPB}^-$ **2a*** in CDCl_3 with a mixture of two different hosts, namely cone-shaped tetrabenzoyloxy-dihomooxalix[4]arene **1a**^[5k] and tetramethoxy-dihomooxalix[4]arene **1c** (1 equiv each). Thus, it was evidenced that $2\text{a}^+\text{-}1\text{a}$ is preferentially formed over $2\text{a}^+\text{-}1\text{c}^{\text{cone}}$ in a 5:1 ratio (by integration of their n -butyl resonances in the upfield negative region of the spectrum). This is probably due to the greater preorganization of conformationally blocked tetrabenzoyloxy-dihomooxalix[4]arene **1a** with respect to mobile tetramethoxy **1c**. On the basis of the previously reported association constant for $2\text{a}^+\text{-}1\text{a}$ ($K_{\text{ass}} = 5.5 \times 10^6 \text{ M}^{-1}$),^[5k] a significantly lower K_{ass} value of $2.2 \times 10^5 \text{ M}^{-1}$ was calculated for $2\text{a}^+\text{-}1\text{c}^{\text{cone}}$ complex.^[18] In a similar way, a K_{ass} of $7.7 \times 10^4 \text{ M}^{-1}$ was calculated for the $2\text{a}^+\text{-}1\text{c}^{1,4\text{-alt}}$ complex.^[19]

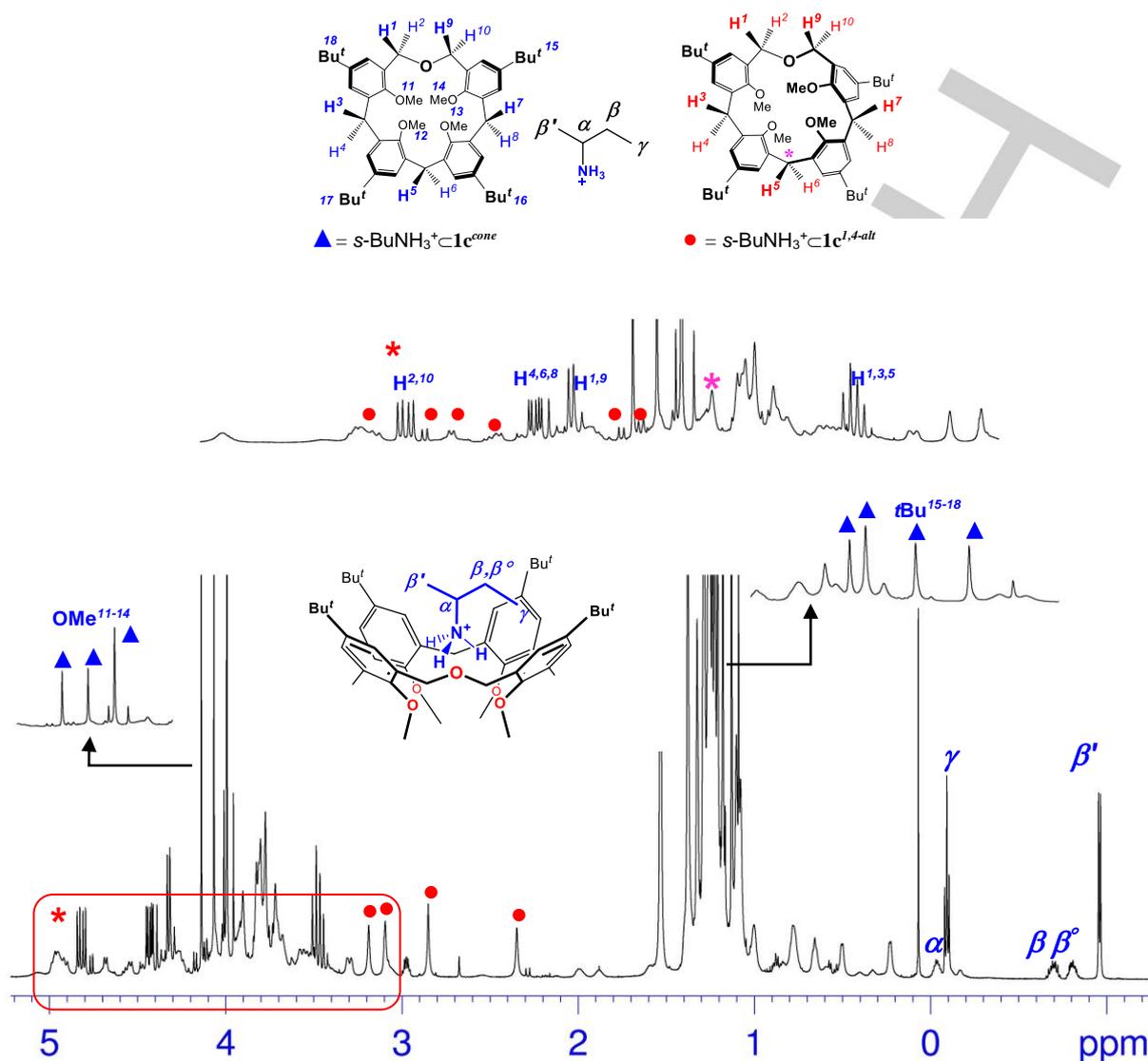


Figure 7. Significant portion of the ^1H NMR spectrum (600 MHz, CDCl_3 , 298 K) of a 1:1 mixture of **1c** and **2c⁺** (3 mM).

Binding ability of dihomooxalix[4]arene derivative **1c toward branched *i*-propylammonium guest **2b⁺**.** The extension of complexation studies to *i*-propylammonium **2b** guest revealed a behavior very similar to that of **2a**. In fact, a close inspection of the methylene region of the ^1H NMR spectrum of a 1:1 mixture of **1c** and *i*-PrNH $_3^+$ ·TFPB $^-$ salt in CDCl_3 (Figure 3), evidenced the presence of two AX systems (COSY spectrum, Figure S3) in a 2:1 ratio at 3.50/4.44 ppm ($\Delta\delta = 0.94$ ppm) and 3.49/4.47 ppm ($\Delta\delta = 0.90$ ppm), which correlated in the HSQC spectrum (Figure S4) with signals at 30.7 and 30.8 ppm, respectively, relative to carbon atoms between *syn*-oriented aryl rings. In addition, an AB system

(COSY spectrum) was present at 4.34/4.84 ppm relative to ArCH $_2$ OCH $_2$ Ar group which correlated with a carbon at 71.4 ppm. By application of the above mentioned Gutsche's and de Mendoza's rules, these data were indicative of a cone conformation of **1c** in the *i*-PrNH $_3^+$ ·**1c^{cone}** complex. In accordance, shielded signals relative to *i*-PrNH $_3^+$ guest inside the aromatic cavity of **1c** were observed at 0.13 [–CH(CH $_3$) $_2$] and –0.82 [–CH(CH $_3$) $_2$] ppm. Analogously to *n*-BuNH $_3^+$ ·**1c^{cone}** complex, two singlets relative to OMe groups of **1c** in the *i*-PrNH $_3^+$ ·**1c^{cone}** complex were observed at 4.09 and 4.05 ppm.

Interestingly, additional signals for ArCH $_2$ OCH $_2$ Ar protons were present at 4.05/4.95 and 4.18/4.59 ppm, which can be confidently assigned to *i*-PrNH $_3^+$ ·**1c^{1,4-alt}** complex, in which **1c**

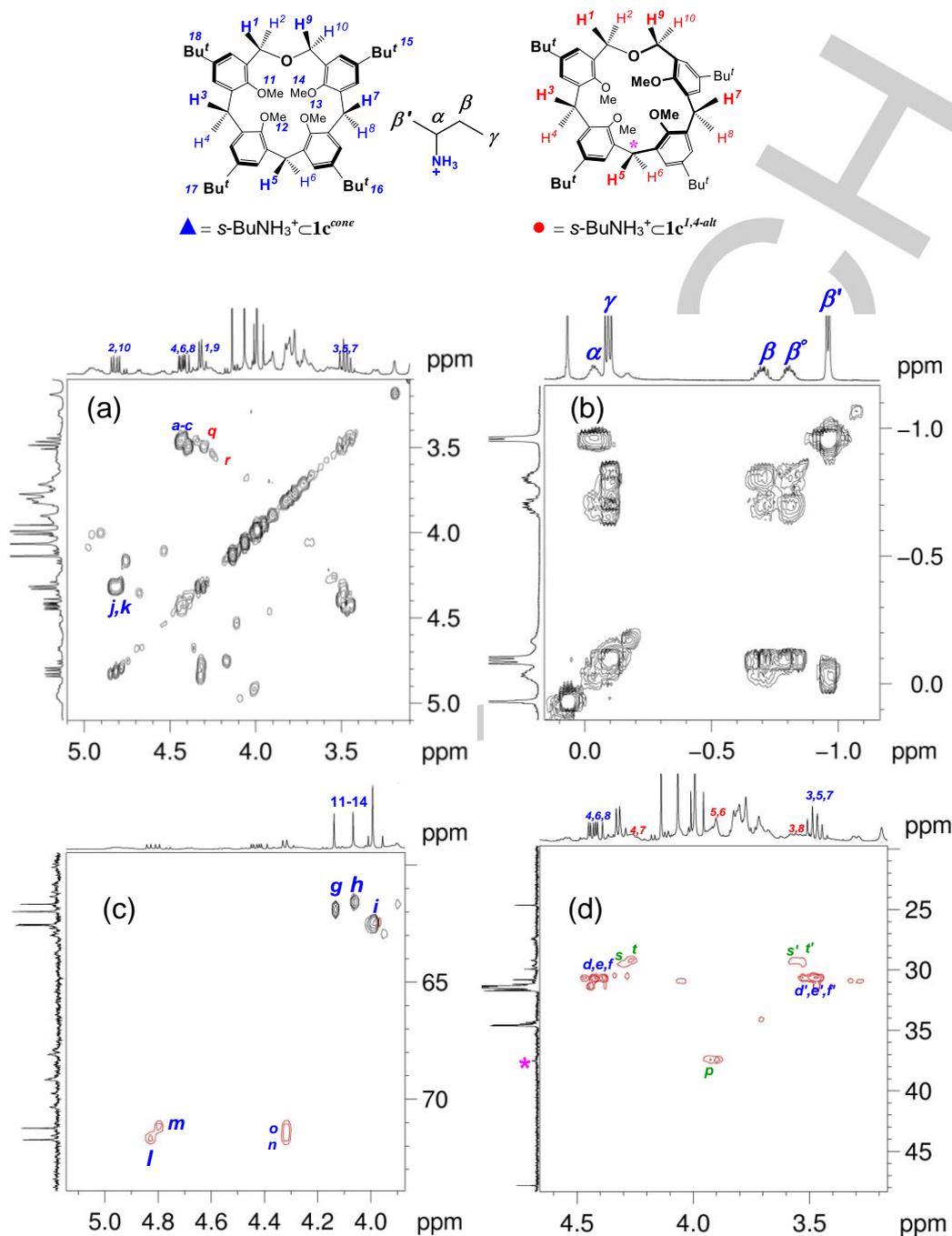


Figure 8. Significant portions of COSY [(a) and (b)] HSQC [(c) and (d)] spectra (600 MHz, CDCl₃, 298 K) of a 1:1 mixture of **1c** and **2c*** (3 mM).

host is in the 1,4-alternate conformation. This conformation was confirmed by three AX/AB ArCH₂Ar systems at 3.57/4.28, 3.32/4.09, and 3.86/3.96 ppm, which correlated in the HSQC spectrum with carbon signals at 29.2, 30.5, and 37.2 ppm. Finally, the four OMe groups of the *i*-PrNH₃⁺**1c**^{1,4-alt} complex resonated at 2.96, 3.01, 3.75, and 3.84 ppm and correlated in the HSQC spectrum with carbon signals at 61.3, 60.2, 60.8, and

60.7 ppm.

Regarding the resonances of the guest isopropyl chain in the *i*-PrNH₃⁺**1c**^{1,4-alt} complex, a close inspection of the 2D COSY spectrum (Figure S3) revealed the presence of a correlation between a broad signal at 4.95 ppm relative to the ammonium protons and a broad signal relative to the α-hydrogen at 2.05 ppm, which correlated in the 2D HSQC

spectrum with a carbon resonance at 44.5 ppm (Figure S4). Interestingly, the α -hydrogen correlated with two signals at 0.28 and 0.65 ppm relative to β and β' methyl groups of the guest, which correlated in the HSQC spectrum with carbon resonances at 19.4 and 20.2 ppm (Figure S4). The presence of two diastereotopic β and β' methyl groups of the guest in the i -PrNH₃⁺⊂**1c**^{1,4-alt} complex is consistent with what discussed above for the corresponding n -BuNH₃⁺ complex and is justified by a close inspection of its energy-minimized structure (Figure S11). In fact, one of the two methyl group (blue in Figure S11) of the **2b**⁺ guest is pointing toward two aromatic rings of **1c**, while the other one (red in Figure S11) is oriented toward the OMe groups of the two inverted Ar rings.

Integration of ArCH₂OCH₂Ar ¹H NMR signals relative to i -PrNH₃⁺⊂**1c**^{cone} and i -PrNH₃⁺⊂**1c**^{1,4-alt} revealed that the two complexes were present in a 1:1 ratio. Interestingly, a competition experiment (Figure S8) was performed by mixing 1 equiv of i -PrNH₃⁺·TFPB⁻ **2b**⁺ in CDCl₃ with the mixture of cone-shaped tetrabenzoyloxy-dihomooxalix[4]arene **1a**^[5k] and tetramethoxy-dihomooxalix[4]arene **1c** (1 equiv each). Thus, it was evidenced that **2b**⁺⊂**1a** is preferentially formed over **2b**⁺⊂**1c**^{cone} in a 4:1 ratio (by integration of guest methyl resonances in the upfield negative region of the spectrum). Therefore, on the basis of the known $K_{\text{ass}} = 7.65 \times 10^4 \text{ M}^{-1}$ for **2b**⁺⊂**1a**,^[5k] a K_{ass} of $4.1 \times 10^3 \text{ M}^{-1}$ was calculated for **2b**⁺⊂**1c**^{cone} complex, in accordance with its lower preorganization.

Binding ability of dihomooxalix[4]arene derivative 1c toward sec-butylammonium guest 2c⁺. Previously,^[5k] we have showed that the *endo*-cavity complexation of racemic s -BuNH₃⁺ guest **2c**⁺ by achiral cone-shaped tetrabenzoyloxy-dihomooxalix[4]arene **1a** results in a s -BuNH₃⁺⊂**1a** complex which is asymmetric on the NMR time-scale, giving rise to a chiral s -BuNH₃⁺⊂**1a** supramolecule. Interestingly, this transfer of chirality^[20] from chiral guest to achiral host is rather uncommon on the NMR timescale and must be due to a restricted motion of the branched s -BuNH₃⁺ guest inside the narrow oxalix cavity of **1a**. On this basis, we extended the complexation study of racemic (\pm)- s -BuNH₃⁺·TFPB⁻ **2c**⁺ by conformationally mobile tetramethoxy-dihomooxalix[4]arene **1c**. A close inspection of the methylene regions of 1D (Figure 7) and 2D (Figure 8) NMR spectra (600 MHz, CDCl₃, 298 K) of the 1:1 mixture of **1c** and **2c**⁺ revealed the presence of three AX systems in a 1:1:1 ratio relative to ArCH₂Ar groups at 3.53/4.47, 3.50/4.43, and 3.48/4.46 ppm (*a*-*c* in Figure 8a), which correlate in the HSQC spectrum with carbon resonances at 30.5, 30.5, and 31.2 ppm (*d*-*f* and *d'*-*f'* in Figure 8d), respectively. These data, in accordance with the Gutsche's and de Mendoza's rules, are compatible with a cone conformation of **1c**. The presence of three ArCH₂Ar AX systems for **1c** in the s -BuNH₃⁺⊂**1c**^{cone} complex was consistent with an asymmetric structure of the complex in which a chirality transfer took place on the NMR time scale from chiral **2c**⁺ guest to achiral **1c** host. This was confirmed by four *t*-butyl ¹H singlets at 1.25, 1.26, 1.29, and 1.31 ppm (Figure 7), which correlated in the HSQC spectrum with carbon resonances at 31.1, 31.1, 31.2, and 31.18 ppm, respectively. In addition, four ¹J correlations were present in the

HSQC spectrum (Figure 8c) relative to OMe groups at 4.02/62.28, 4.02/62.31, 4.10/61.4, and 4.17/61.7 ppm (*g*-*i* in Figure 8c).

Finally, to corroborate the asymmetric host structure in s -BuNH₃⁺⊂**1c**^{cone} complex, two AB systems relative to ArCH₂OCH₂Ar groups were present at 4.35/4.86 and 4.35/4.83 ppm (*j*-*k* in Figure 8a), which were HSQC-correlated with carbon resonances at 71.5 and 71.0 ppm (Figure 8c, *l*-*o*)

In accordance with the ¹H NMR data previously reported^{5k} for the s -BuNH₃⁺⊂**1a**^{cone} complex, shielded s -BuNH₃⁺ resonances were present at negative values of chemical shifts (Figure 8b). Thus, α -proton at -0.04 ppm showed COSY cross-peaks (Figure 8b) with both β' -methyl [-0.96 ppm (*d*, $J = 6.8$ Hz)] and diastereotopic β -methylene (-0.70 and -0.80 ppm) groups. Finally, both β -methylene protons were correlated with γ -methyl group at -0.01 ppm (*t*, $J = 8.0$ Hz).

In analogy to the above reported results, a close inspection of the methylene region of the HSQC spectrum revealed the presence of s -BuNH₃⁺⊂**1c**^{1,4-alt} complex in which the host adopts a 1,4-alternate conformation. In fact, a ¹J correlation (*p* in Figure 8d) was present between a broad ¹H singlet at 3.90 ppm and a carbon resonance at 37.4 ppm relative to ArCH₂Ar bridge (*C*^{*}) between *anti*-oriented aryl rings. In addition, two AX systems were present at 3.53/4.29 and 3.56/4.27 ppm (*q* and *r* in Figure 8a) which correlated with carbon resonances at 29.6 and 29.3 ppm, respectively (*s*/*t* and *s*/*t'* in Figure 8d). These data were indicative of a *syn*-orientation between the pertinent Ar rings. Four ¹J correlations relative to OMe groups of s -BuNH₃⁺⊂**1c**^{1,4-alt} complex were present in the HSQC spectrum at 2.34/59.8, 2.85/61.0, 3.09/59.9, and 3.19/61.9 ppm.

Integration of the 1D and 2D NMR signals relative to the s -BuNH₃⁺⊂**1c**^{cone} and s -BuNH₃⁺⊂**1c**^{1,4-alt} complexes revealed that the two supramolecules were present in a 2.8:1 ratio. In analogy to the above reported results, a competition experiment (Figure S9), mixing 1 equiv of s -BuNH₃⁺·TFPB⁻ **2c**⁺ in CDCl₃ with the mixture of cone-shaped tetrabenzoyloxy-dihomooxalix[4]arene **1a**^[5k] and tetramethoxy-dihomooxalix[4]arene **1c** (1 equiv each), evidenced the preferential formation of **2c**⁺⊂**1a** complex over **2c**⁺⊂**1c**^{cone} in a 2.5:1 ratio (by integration of their s -Bu resonances in the upfield negative region of the spectrum). Thus, a K_{ass} of $3.8 \times 10^3 \text{ M}^{-1}$ was calculated for **2c**⁺⊂**1c**^{cone} complex, on the basis of the known K_{ass} for **2c**⁺⊂**1a** ($3.6 \times 10^4 \text{ M}^{-1}$).^[5k]

Conclusions

In conclusion, we have shown that the conformationally mobile tetramethoxy-dihomooxalix[4]arene **1c** is able to recognize linear and branched alkylammonium guests through an induced fit mechanism. Thus, while free **1c** preferentially adopts in solution a 1,4-alternate conformation, in the presence of linear n -BuNH₃⁺ and branched s -BuNH₃⁺ and i -PrNH₃⁺ guests, it preferentially forms *endo*-complexes in cone conformation. In addition, 1D and 2D NMR studies evidenced that other complexes with **1c** in different conformations were also present and characterized. Interestingly, a good agreement was found between the experimental ¹H chemical shift values assigned to

n -BuNH₃⁺⋅**1c**^{cone} and n -BuNH₃⁺⋅**1c**^{1,4-alt} complexes and those predicted by DFT-based GIAO NMR chemical shift calculations, that corroborated the conformational assignment.

Experimental Section

General Experimental Method: ESI(+)-MS measurements were performed on a triple quadrupole mass spectrometer equipped with electrospray ion source, using CHCl₃ as solvent. All chemicals were reagent grade and were used without further purification. Anhydrous solvents were used as purchased from supplier. When necessary compounds were dried *in vacuo* over CaCl₂. Reaction temperatures were measured externally. Derivative **2a-c**^{+,5k} and **1c**^{9d} were synthesized according to literature procedures. NMR spectra were recorded on 400 or 600 MHz spectrometers (TMS as internal standard). The temperature was maintained at 298 K for all NMR spectra. COSY-45 spectra were taken using a relaxation delay of 2 s with 30 scans and 170 increments of 2048 points each. HSQC spectra were performed with gradient selection, sensitivity enhancement, and phase-sensitive mode using Echo/Antiecho-TPPI procedure. A typical experiment comprised 20 scans with 113 increments of 2048 points each. Monte Carlo conformational searches (10000 steps) were performed with MacroModel-9.0/Maestro-4.1 program using CHCl₃ as solvent (GB/SA model). K_{ass} values were determined by ¹H NMR competition experiments in accordance to a literature procedure.^{5k,j}

General procedure for the preparation of alkylammonium complexes. Dihomooxalix[4]arene derivative **1c** (1.23×10⁻³ mmol) and the appropriate alkylammonium TFPB salt **2a-c**⁺ (1.23×10⁻³ mmol) were dissolved in CDCl₃ (0.4 mL, 3.0×10⁻³ M solution). The solution was sonicated for 15 min at room temperature and transferred into a NMR tube for 1D and 2D NMR spectra acquisition.

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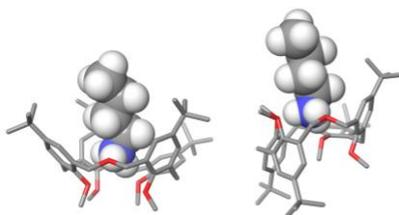
Keywords: homooxalixarene • induced fit • alkylammonium guest • superweak anion • DFT calculations

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The conformationally mobile tetramethoxy-dihomooxalix[4]arene is able to interact with linear and branched alkylammonium guests through an induced fit process mainly driven by H-bonds and cation- π interactions. An adaptive transition from 1,4-alternate to cone conformation is observed upon complexation.



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