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endo-Cavity Complexation and Through-the-Annulus Threading of Large Calixarenes Induced by Very Loose Alkylammonium Ion Pairs

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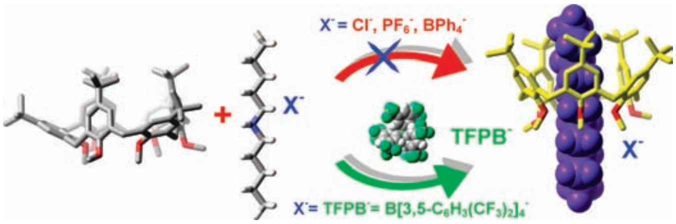
ABSTRACT



A general mode to obtain *endo*-complexation and through-the-annulus threading of scarcely efficient macrocyclic hosts was obtained by exploiting the inducing effect of the weakly coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (TFPB) anion that gives free "naked" cations. This method works very well with simple, conformationally mobile calix[6−7]arene ethers, which give conformationally blocked *endo*-calix or [2]pseudorotaxane complexes.

Over the past two decades calix[*n*]arenes have gained a prominent position in the field of supramolecular chemistry thanks to their wide range of different applications.[1] In contrast with other macrocyclic hosts such as cyclodextrins,[2] crown ethers,[3] and cucurbiturils,[4] which readily give *endo*-complexation with native unsubstituted derivatives,[5] calixarenes often require an extensive chemical modification to give similar results,[6] and more frequently they act as simple scaffolds to construct podand-like receptors where the calix cavity very often remains unexploited.[1]

From another point of view, simple ethers of calixarenes can be seen as modified crown ethers,[3] and in principle they should be able to give *endo*-complexation of organic cations in a similar way. Unfortunately, with the notable exception of some calix[5]arene derivatives,[7] simple ethers of calixarenes do not give such kind of complexation because they are too small in the case of calix[4]arenes or because they are not well preorganized in the case of larger calix[6−8]arenes. Thus, for example, it is well-known that hexamethoxy-*p*-*tert*-butylcalix[6]arene **1a** (Figure 1) is conformationally mobile and does not complex halide, hexafluorophosphate, or tetraphenylborate salts of organic ammonium cations.[8]

On the other hand, the through-the-annulus threading of dialkylammonium or bipyridium cations to give pseudorotaxane structures, which is very popular with large crown

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[1] Gutsche, C. D. *Calixarenes, An Introduction*; Royal Society of Chemistry: Cambridge, U.K., 2008.

[2] Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743.

[3] Gokel, G. W. *Crown Ethers and Cryptands*; Royal Society of Chemistry: Cambridge, U.K., 1991.

[4] Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844.

[5] Ogoshi, T.; Kanai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5022.

[6] Coquière, D.; de la Lande, A.; Martì, S.; Parisel, O.; Prangé, T.; Reinaud, O. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 10449, and references therein.

[7] Garozzo, D.; Gattuso, G.; Notti, A.; Pappalardo, A.; Pappalardo, S.; Parisi, M. F.; Perez, M.; Pisagatti, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 4892, and references therein.

[8] See Supporting Information for further details.

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ethers such as [24]crown-8 or [34]crown-10,[9] respectively, to obtain interlocked rotaxane and catenane topologies,[10] is very rare in the calix[*n*]arene series. In fact, the very few examples regard the threading of viologen derivatives through the annulus of calix[6]arene hosts in which the anion coordinating ability of their ureido groups is exploited to favor the ion-pair dissociation.[11] Instead, to the best of our knowledge, no examples of threading through conformationally mobile, larger calix[6−7]arene annuli by dialkylammonium cations are currently known.[12]

Here, we wish to report on how both problems of *endo*-cavity complexation and through-the-annulus threading of large calix[6−7]arenes can be solved in a general mode by exploiting the inducing effect of a weakly coordinating anion.

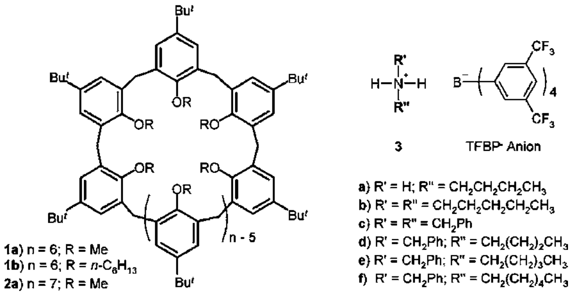

Figure 1

As part of our ongoing program concerning the supramolecular chemistry of large calixarene macrocycles,[13] we decided to investigate the complexing ability toward organic ammonium cations of some simple ether derivatives. Not surprisingly, we found that in addition to hexamethoxy-**1a**, both hexahexyloxy-**1b** and heptamethoxy-*p*-*tert*-butylcalix[7]arene **2a** (Figure 1) also gave no appreciable interactions upon titration with chloride, hexafluorophosphate, or tetraphenylborate salts of organic ammonium cations.[8] This can be ascribed to the sum of two unfavorable effects, namely, the scarce preorganization of conformationally mobile derivatives **1a,b** and **2a** (Figure 1) and the free energy necessary to separate a tight ion pair.[11,14,15]

Therefore, to minimize the latter effect we decided to use a weakly coordinating hydrophobic anion able to give a very loose ion pair. An useful anion in this respect is tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (TFPB$^-$) (Figure 1), which is known to be noncoordinating (or very weakly coordinating) to metal ions and therefore is referred to as a "superweak" anion.[16]

The addition of TFPB salt of *n*-butylammonium cation **3a** (n-$BuNH_3^+ \cdot TFPB^-$) to a $CDCl_3$ solution of hexahexyloxy derivative **1b** gave dramatic changes in its ^1H NMR spectrum (Figure 2a,b). The most evident ones were the sharpening of all signals, the appearing of *n*-butyl resonances in the upfield negative region of the spectrum (−0.87 and −1.07 ppm), and the formation of a well-defined AX system (4.48 and 3.48 ppm, J = 14.4 Hz) for $ArCH_2Ar$ groups (Figure 2b). This is a clear indication that the conformationally mobile calix[6]arene host **1b** became blocked in the NMR time scale in a cone conformation and that the *n*-butylammonium cation **3a** gave an *endo*-calix complexation with the alkyl chain shielded by the aromatic rings.

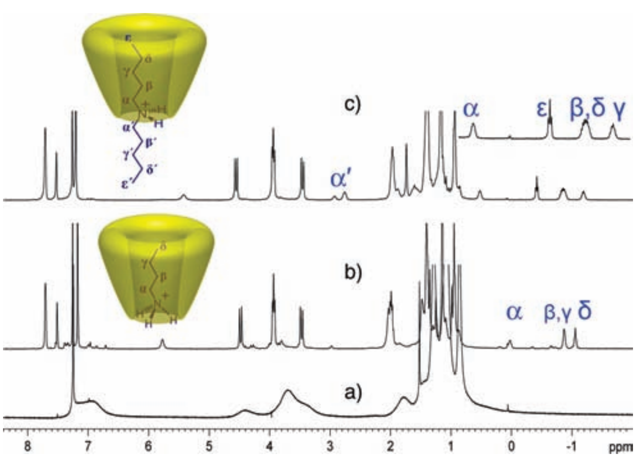

Figure 2. ^1H NMR spectra ($CDCl_3$, 400 MHz, 298 K) of (a) **1b**, (b) equimolar solution (3 mM) of **1b** and *n*-butylammonium TFPB$^-$, (c) equimolar solution (3 mM) of **1b** and di-*n*-pentylammonium TFPB$^-$.

Complex formation was also confirmed by the ESI(+) mass spectrum, which gave as the base peak a value of 1553 m/z corresponding to supermolecular ion n-$BuNH_3^+ \subset$**1b**.[8] The presence of *n*-butylammonium cation inside the calix cavity of **1b** was proved by a 2D NOESY spectrum.[8]

This binding mode was confirmed by the lowest Amber-energy structure of the complex n-$BuNH_3^+ \subset$**1b** (Figure 3a), obtained with the program MacroModel-9.0,[17] where it is possible to observe the position of the nitrogen atom sitting

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(9) Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 1643.

(10) *Molecular Catenanes, Rotaxanes and Knots: A Journey Through the World of Molecular Topology*; Sauvage, J. P., Dietrich-Buchecker, C., Eds.; Wiley-VCH: Weinheim, 1999.

(11) Arduini, A.; Ferdani, R.; Pochini, A.; Secchi, A.; Ugozzoli, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3453.

(12) Very recently, an example of threading through the conformationally blocked pentakis(*tert*-butoxycarbonylmethoxy)-*p*-*tert*-butylcalix[5]arene derivative has been reported: Gattuso, G.; Notti, A.; Parisi, M. F.; Pisagatti, I.; Amato, M. E.; Pappalardo, A.; Pappalardo, S. *Chem.—Eur. J.* **2010**, *16*, 2381.

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(15) Cafeo, G.; Gattuso, G.; Kohnke, F. H.; Notti, A.; Occhipinti, S.; Pappalardo, S.; Parisi, M. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 2122.

(16) (a) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927. (b) Hirochika, N.; Suzuki, H.; Norob, J.; Kimura, T. *Chem. Commun.* **2005**, 2963. (c) Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600. (d) Blight, B. A.; Camara-Campos, A.; Djurdjevic, S.; Kaller, M.; Leigh, D. A.; McMillan, F. M.; McNab, H.; Slawin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 14116.

(17) Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. MacroModel-9.0/Maestro-4.1 program. *J. Comput. Chem.* **1990**, *11*, 440.

(at a distance of 0.76 Å) above the mean plane of the calixarene oxygens.

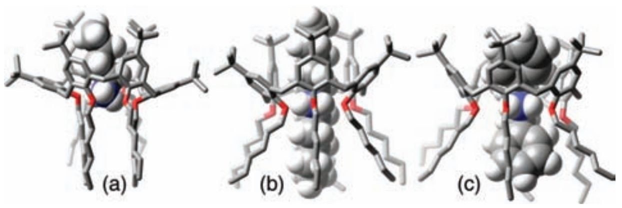

Figure 3. Lowest AMBER-energy structures of (a) n-BuNH$_3^+$$\subset$**1b**, (b) ($n$-Pent)$_2NH_2^+$$\subset$**1b**, and (c) Bn$_2NH_2^+$$\subset$**1b** complexes obtained by Monte Carlo conformational searches. Hydrogen atoms of calix[6]arene hosts **1b** are omitted for clarity.

Three hydrogen bonds are present between $^+$NH$_3$ protons and ethereal calixarene *O*-atoms. The lowest energy structure is asymmetrical, and therefore time-averaging is observed in the NMR time scale to give the observed C_{6v} symmetry.

It is noteworthy that no hint of complexation of **3a**·TFPB$^-$ was observed for hexamethoxycalix[6]arene **1a** and heptamethoxycalix[7]arene **2a**. This implies that upon complexation *n*-butylammonium cation induces the fitting of the host that became effective only when sufficiently bulky groups are present at the lower rim to give a minimal partial preorganization.

To extend the validity of this "weakly-coordinating anion" approach, we tested the complexation of TFPB salts of di-*n*-alkylammonium cations. Thus, the addition of di-*n*-pentylammonium **3b** salt [(n-Pent)$_2$NH$_2^+$·TFPB$^-$] to a CDCl$_3$ solution of calix[6]arene host **1b** again caused dramatic changes in its ^{1}H NMR spectrum[8] (Figure 2c), similar to those discussed above, with the typical signature at highfield negative values and the emergence of the ArCH$_2$Ar AX system (4.40 and 3.51 ppm, $J = 13.6$ Hz).[8,18] Complex formation was also confirmed by a ESI(+) mass spectrum,[8] which gave as the base peak a value of 1637 *m*/*z* corresponding to supermolecular ion (n-Pent)$_2$NH$_2^+$$\subset$**1b**.[8] A 2D ROESY[8] spectrum confirmed the presence of the di-*n*-pentylammonium guest **3b** inside the calix[6]arene cavity.

Monte Carlo conformational searches[8] confirmed a pseudorotaxane structure with the formation of two NH···O hydrogen bonds. In particular, the lowest Amber-energy structure of (n-Pent)$_2$NH$_2^+$$\subset$**1b** shows (Figure 3b) that the secondary ammonium nitrogen is slightly above the mean plane of the six calixarene O-atoms at a distance of 0.34 Å, significantly lower than that observed for n-BuNH$_3^+$$\subset$**1b** complex (0.76 Å).

Interestingly, hexamethoxycalix[6]arene **1a** (Figure 4) and heptamethoxycalix[7]arene **2a**,[8] which previously gave no *endo*-complexation with n-BuNH$_3^+$, both gave through-the-annulus threading with di-*n*-pentylammonium cation **3b** in CDCl$_3$ (Figure 4b). This demonstrates that the through-the-annulus threading tolerates a larger cavity and that the *exo*-oriented pentyl chains in pseudorotaxane (n-Pent)$_2$NH$_2^+$$\subset$**1a** and ($n$-Pent)$_2NH_2^+$$\subset$**2a** positively contributed to the stabilization of calixarene cone conformation, which would be faster interconverting because of the small OMe groups. Clearly, with n-BuNH$_3^+$ cation this extra stabilization is missing because only a single alkyl chain would be present.

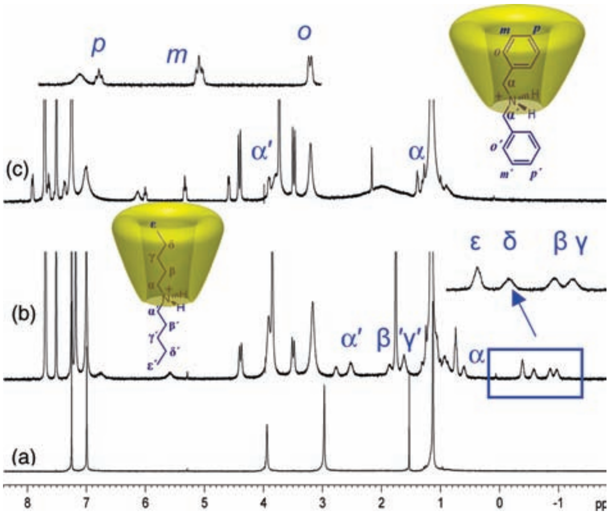

Figure 4. ^{1}H NMR spectra (CDCl$_3$, 400 MHz, 298 K) of (a) **1a**, b) equimolar solution (3 mM) of **1a** and di-*n*-pentylammonium TFPB$^-$, **3b**, (c) equimolar solution (3 mM) of **1a** and dibenzylammonium TFPB$^-$, **3c**.

Additional interesting through-the-annulus threadings were obtained with dibenzylammonium salt **3c** (Bn$_2$NH$_2^+$·TFPB$^-$) and calix[6]arenes **1a** (Figure 4c), **1b**,[8] or calix[7]arene **2a** in CDCl$_3$.[8] In the ^{1}H NMR spectra of these pseudorotaxanes two sets of unshielded and shielded benzyl signals can be always observed corresponding to their *exo*- or *endo*-cavity disposition. The most shielded signals were in the order benzylic-CH$_2$ ($\Delta\delta = 2.77 - 2.78$), *ortho*-BnH ($\Delta\delta = 2.60 - 2.61$), *meta*-BnH ($\Delta\delta = 2.10 - 2.34$), and *para*-BnH ($\Delta\delta = 1.49 - 1.64$).[8] The lowest AMBER-energy geometry of complex Bn$_2$NH$_2^+$$\subset$**1b**, (Figure 3c) evidenced a pseudorotaxane structure with the formation of two NH···O hydrogen bonds. Clearly, the position of dibenzylammonium cation **3c** is averaged on the NMR time scale over the six equivalent *O*-atoms.

The apparent association constants for the above-mentioned complexes (Table 1) were determined by integration of ^{1}H NMR spectra of their 1:1 titration mixture in CDCl$_3$, which showed slowly exchanging signals for both free and complexed guests.[19] In the case of complexes n-BuNH$_3^+$$\subset$**1b**, Bn$_2NH_2^+$$\subset$**1b**, and Bn$_2NH_2^+$$\subset$**2a** the signal of the free guest was below the acceptable limit to allow a reliable direct determination of their association constant.[19]

To overcome this latter problem and to compare the different stability of the complex formed by a given host with different

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(18) Interestingly, a scalar *J*-coupling was observed in the COSY-45[8] spectrum between the $^+$NH$_2$ ammonium protons (5.42 ppm) and their linked α (0.53 ppm) and α′ (2.75 ppm) methylene groups, making straightforward the entire assignment.[8] Thus, two different pentyl chains were observed in the complex (n-Pent)$_2$NH$_2^+$$\subset$**1b**: one strongly shielded and inside the cavity (with ε, δ, γ, β, and α protons resonating at −0.42, −0.87, −1.20, −0.88, and 0.53 ppm, respectively) and the other, at more normal values of chemical shift (with ε', δ', γ', β', and α′ protons resonating at 0.94, 1.15, 1.63, 1.88, and 2.75 ppm, respectively), outside the cavity.

(19) Hirose, K. *J. Incl. Phenom. Macrocycl. Chem.* **2001**, *39*, 193.

Table 1. Association Constants (K_a, M^{-1}) and Percentages of Formation of Butylammonium **3a** and Dialkylammonium **3b,c** Complexes with Calixarene Hosts **1a,b** and **2a** Determined by ^1H NMR Spectroscopy (400 MHz, $CDCl_3$, 25 °C) upon Addition of 1 equiv of Their Corresponding TFPB Salts

	3a	**3b**	**3c**
1a	*a*	4.4×10^2 (42%)[8]	2.5×10^3 (67%)[b]
1b	8.3×10^6[b]	3.5×10^4 (84%)[8]	1.2×10^5[b]
2a	*a*	1.5×10^3 (59%)[8]	4.5×10^3[b]

[a] No complexation takes place. [b] Obtained by competition experiments.[8]

guests, competition experiments[20] were performed by treating 1 equiv of hexahexyloxycalix[6]arene **1b** in $CDCl_3$ with a mixture of two different ammonium TFPB salts (1 equiv each).

Thus, it was evidenced that $Bn_2NH_2^+{\subset}$**1b** is preferentially formed over $(n\text{-Pent})_2NH_2^+{\subset}$**1b** in a ratio of 3:2, probably because the less-flexible benzyl group may give a better conformational templation at the lower rim with respect to the pentyl one. A similar comparison indicated that $n\text{-BuNH}_3^+{\subset}$**1b** is preferentially formed over $Bn_2NH_2^+{\subset}$**1b** in a 9:1 ratio probably because an higher number of hydrogen bonds (3) can be formed in the first complex with respect to the second one (2 H-bonds).[21] From these results the relative stability constants (K_{rel}, Table S1 in Supporting Information) can be calculated, which allowed the indirect determination of association constants for complexes $n\text{-BuNH}_3^+{\subset}$**1b**, $Bn_2NH_2^+{\subset}$**1b**, and $Bn_2NH_2^+{\subset}$**2a** (Table 1).[22]

As a final point, we decided to study the threading of an unsymmetrical dialkylammonium cation that would give rise to two stereoisomeric directional pseudorotaxane complexes.[23] In particular, the addition of *n*-hexylbenzylammonium **3f** $TFPB^-$ salt [$(n\text{-Hex})NH_2^+Bn{\cdot}TFPB^-$] to calix[6]arene host **1b** in $CDCl_3$ clearly evidenced the formation of two distinct diastereoisomeric $(n\text{-Hex})NH_2^+Bn{\subset}$**1b** complexes (Figure 5): one with a shielded *endo*-cavity *n*-hexyl chain resonating at negative values and the other with a shielded *endo*-cavity benzyl moiety resonating in the 3−5 ppm range. Signal integration indicated that the *endo*-hexyl complex is preferentially formed over the *endo*-benzyl stereoisomer in a ratio of 4:1. Interestingly, the same experiment performed with shorter alkyl chains such as pentyl (**3e**) [$(n\text{-Pent})NH_2^+Bn{\cdot}TFPB^-$] and butyl (**3d**) ($n\text{-BuNH}_2^+Bn{\cdot}TFPB^-$) groups led to higher *endo*-alkyl/*endo*-benzyl ratios of 10:1 and 30:1,[8] respectively. Thus, the preference for *endo*-alkyl stereoisomer increases with shorter alkyl chains. All these results can be explained by assuming the above-mentioned better conformational templation of a benzyl group with respect to an alkyl one, in particular when this latter become shorter. An alternative explanation can also be related to different solvation patterns and/or entropic contributions of benzyl versus alkyl group upon *endo*-calix inclusion.

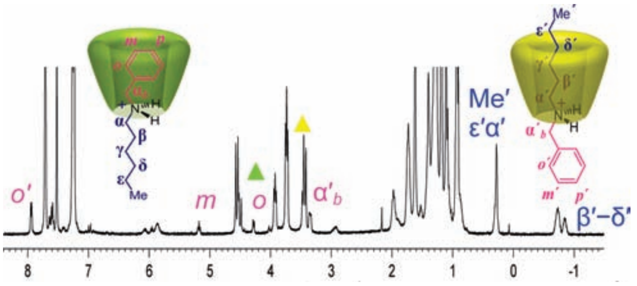

Figure 5. ^1H NMR spectra ($CDCl_3$, 400 MHz, 298 K) of equimolar solution (3 mM) of **1b** and *n*-hexylbenzylammonium $TFPB^-$ **3f**.

In conclusion, we have reported here a general mode to obtain *endo*-cavity complexation and through-the-annulus threading of large calixarene by exploiting the inducing effect of the weakly coordinating TFPB anion. This method works very well with simple calixarene ethers, and no extensive or sophisticated chemical modifications of the parent macrocycles are required. In particular, the obtained pseudorotaxane complexes represent the first examples of threading through larger calixarene annuli by dialkylammonium cations.

Acknowledgment. Thanks are due to Dr. Patrizia Iannece (Dipartimento di Chimica, Università di Salerno) for ESI-MS measurements.

Supporting Information Available: Synthetic details, 1D and 2D NMR spectra, details on molecular modeling, and relative stability constants (K_{rel}). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The formation of the above *endo*-cavity and pseudorotaxane complexes is induced by the very weakly coordinating anion $TFPB^-$, and it can be expected that these complexes can be broken by addition of any specie able to interact competitively with the cation. In fact, we found that the addition of 30 equiv of CD_3CN leads to complete dethreading of the di-*n*-pentylammonium guest from the cavity of calix[6]arene **1a** [$(n\text{-Pent})_2NH_2^+{\subset}$**1a**, 15 mM in $CDCl_3$], whereas 62 equiv of CD_3CN is necessary for breaking the $Bn_2NH_2^+{\subset}$**1a** complex (15 mM in $CDCl_3$). This is in accordance with the higher stability (see Table 1) of $Bn_2NH_2^+{\subset}$**1a** ($K_a = 2.5 \times 10^3\ M^{-1}$) with respect to $(n\text{-Pent})_2NH_2^+{\subset}$**1a** complex ($K_a = 4.4 \times 10^2\ M^{-1}$). Interestingly, the most stable complex $n\text{-BuNH}_3^+{\subset}$**1b** ($K_a = 8.3 \times 10^6\ M^{-1}$) retained its structure even after the addition of 1300 equiv of CD_3CN to its 5 mM solution in $CDCl_3$. On the other hand, under the same conditions the addition of 1.3 equiv of $n\text{-Bu}_4N^+Cl^-$ is sufficient to give a complete decomplexation of the *n*-butylammonium guest of $n\text{-BuNH}_3^+{\subset}$**1b**, thus confirming the impressive effect produced by the ion-pairing tendency of chloride anion. As expected, similar results were also obtained by addition of appropriate amounts of bases.

(22) An alternative way to assess the stability of each complex can be based on the reduction of the host conformational mobility upon complexation. Therefore, VT ^1H NMR studies ($C_2D_2Cl_4$, 400 MHz) were conducted on both **1a** and $(n\text{-Pent})_2NH_2^+{\subset}$**1a**, and a coalescence of $ArCH_2Ar$ signals was ascertained at 278 and 358 K (see Table S2 in Supporting Information), respectively. From these data an energy barrier for conformational interconversion of 12.4 and 16.3 kcal/mol, respectively, can be estimated. Comparison of the two barrier values leads to a difference of about 3.9 kcal/mol, which can be mainly attributed to the host conformational stabilization brought by the ammonium templation. Indeed, this value compares very well with the ΔG of complexation of 3.6 kcal/mol calculated by the experimental association constant ($4.4 \times 10^2\ M^{-1}$, Table 1). A similar favorable result was also obtained in the case of $Bn_2NH_2^+{\subset}$**2a** complex, whose ΔG of complexation of 5.0 kcal/mol calculated by the experimental association constant ($4.5 \times 10^3\ M^{-1}$, Table 1) was in accordance with a difference of energy barriers of 5.8 kcal/mol between complexed and free **2a** estimated by VT ^1H NMR studies (see Table S3 in Supporting Information).

(23) For recent examples diastereoisomeric pseudorotaxanes see: Arduini, A.; Bussolati, R.; Credi, A.; Faimani, G.; Garaudée, S; Pochini, A.; Secchi, A.; Semeraro, M.; Silvi, S.; Venturi, M. *Chem.—Eur. J.* **2009**, *15*, 3230.