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Selective Amine Recognition Driven by Host–Guest Proton Transfer and Salt Bridge Formation

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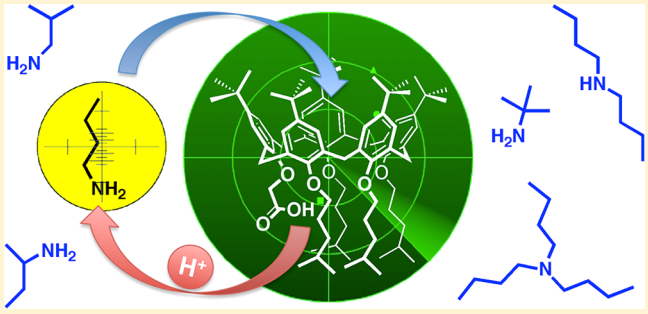
Supporting Information

ABSTRACT: The stepwise synthesis of ionizable *p-tert*-butylcalix[5]arenes **1a**·H and **1b**·H, featuring a fixed *cone* cavity endowed with a carboxyl moiety at the narrow rim, is described. Single-crystal X-ray analyses have shown that in the solid state **1a**·H and **1b**·H adopt a *cone-out* conformation with the carboxylic OH group pointing in, toward the bottom of the aromatic cavity, as a result of a three- or two-center hydrogen-bonding pattern between the carboxyl group and the phenolic oxygen atom(s). The affinity of amines for calix[5]arene derivatives **1a**·H and **1b**·H was probed by ^{1}H NMR spectroscopy and single-crystal X-ray diffraction studies. These carboxylcalix[5]arenes are shown to selectively recognize linear primary amines—over branched, secondary, and tertiary amines—by a two-step process involving a proton transfer from the carboxyl to the amino group to provide the corresponding alkylammonium ion, followed by binding of the latter inside the cavity of the ionized calixarene. Proton transfer occurs only with linear primary amines, that is, when the best size and shape fit between host and substrate is achieved, while the other amines remain in their noncompeting unprotonated form. The role of the solvent in the ionization/complexation process is discussed. Structural studies on the *n*-BuNH$_2$ complexes with **1a**·H and **1b**·H provide evidence that binding of the in situ formed *n*-BuNH$_3^+$ substrate to the cavity of the ionized macrocycle is ultimately secured, in the case of **1a**·H, by the formation of an unprecedented salt-bridge interaction.



INTRODUCTION

Ion-pair association is one of the main obstacles a neutral receptor has to overcome to efficiently bind charged substrates. This phenomenon is particularly pronounced in low-polarity organic solvents, where both receptor and counterion compete for the same ionic species. As a result of this competition, which contributes to the overall complexation equilibrium, the apparent host–guest association constant is often substantially lower than expected.[1]

Over the years, several strategies have been devised to bypass this problem. Earlier approaches relied on the use of weakly coordinating counterions to minimize the effect of ion pairing and hence provide more "naked" ionic species readily available for complexation.[2,3] More recently, receptors for ion-pair recognition based on multisite hetero(poly)topic molecules capable of binding the entire salt species—as either separated or contact ion pairs—have been developed.[4] In parallel, the so-called "dual host" strategy, reliant on the simultaneous and synergic action of two independent receptors with opposite affinities, has also been successfully pursued.[5] A conceptually different way of circumventing the effects of ion pairing relies on the use of "ionizable" macrocycles (e.g., crown ethers, azacrown ethers, calix[4]arenes).[6] This approach was originally suggested by Bartsch and co-workers[7] to improve liquid–liquid extraction of alkali-metal cations from the aqueous to the organic phase by an ion-exchange mechanism and then widely used to target other metal ions.[8] Rather surprisingly, however, the potential of ionizable macrocycles, other than crown ethers,[9,10] to simultaneously behave as host molecules and as counterions of protonated amino-containing organic analytes has scarcely been investigated.[11]

RESULTS AND DISCUSSION

Inspired by the clever extraction strategy outlined above as well as by nature, which makes ample use of salt bridges and other close-range electrostatic interactions,[12] it was decided to develop a new family of receptors for primary amines[13]—based on carboxylcalix[5]arenes[14]—in consideration of the known affinity of these macrocycles for linear alkylammo-

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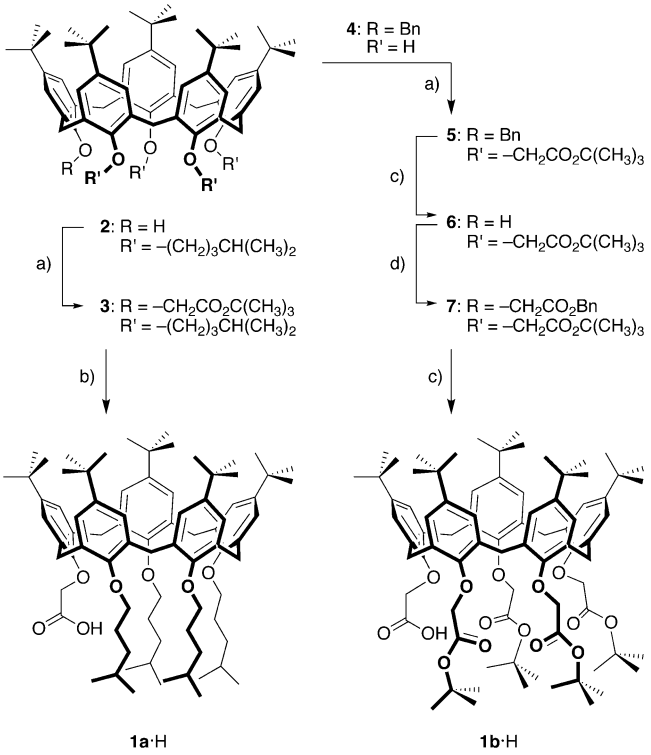
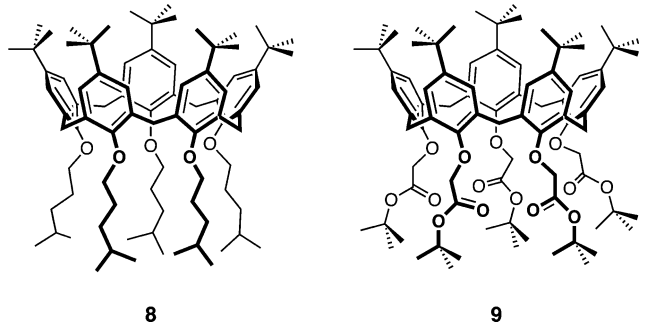
nium[15] and alkanediyldiammonium[16] ions.[17,18] These ionizable calixarenes were expected to selectively form "internal" (*endo* cavity) ion-pair complexes with appropriately sized and shaped amines as a result of the spontaneous transfer of a proton from the host to the guest (vide infra). To this end, calix[5]arenes **1a**·H and **1b**·H (Scheme 1)—bearing a carboxyl group at their narrow rim—were selected as synthetic targets, as they derive from the two most efficient calix[5]arene-based linear alkylammonium receptors known to date, namely penta-*tert*-butylpentakis(4-methylpentyloxy)calix[5]arene[15d] (**8**) and penta-*tert*-butylpentakis(*tert*-butoxycarbonylmethoxy)calix[5]-arene[19] (**9**).[20]

Scheme 1. Synthesis of Calix[5]arenes 1a·H and 1b·H[a]



[a]Legend: (a) $BrCH_2CO_2C(CH_3)_3$, K_2CO_3, CH_3CN, reflux, 24 h; (b) TFA, $CHCl_3$, room temperature, 4 h; (c) H_2, Pd/C, AcOEt, room temperature, 5-6 h; (d) $BrCH_2CO_2Bn$, K_2CO_3, CH_3CN, reflux, 24 h.



8 **9**

Key information for their design was gathered from earlier DFT calculations[21] and single-crystal XRD data[15a] on the inclusion complexes of calix[5]arene pentaester **9** with *n*-hexylammonium and *n*-butylammonium ions, respectively. Specifically, these studies had revealed that one of the (*tert*-butoxycarbonyl)methoxy substituents, present at the narrow rim, points toward the bottom of the calixarene cavity, bringing the carbonyl oxygen atom within hydrogen-bond distance of the included alkylammonium guest. "Removal" of that *tert*-butyl group (i.e., conversion of the ester moiety into a carboxyl one) was then conceived as a convenient way to generate a smart receptor capable, in principle, of undergoing an acid–base reaction with an amine substrate and then firmly holding the resultant alkylammonium cation inside its cavity, by taking advantage of the additional stabilization provided by electrostatic ion-pairing interactions.

Carboxylcalix[5]arenes **1a**·H and **1b**·H were synthesized from penta-*tert*-butyl-tetrakis(4-methylpentyloxy)calix[5]-arene[22] (**2**) and penta-*tert*-butyl(benzyloxy)calix[5]arene[23] (**4**), respectively, as depicted in Scheme 1. Accordingly, alkylation of tetraether **2** with *tert*-butyl bromoacetate, in the presence of K_2CO_3 as a base, provided the monoester derivative **3** (92% yield). Removal of the *tert*-butyl group by TFA treatment yielded **1a**·H (66%). Calix[5]arene **1b**·H, on the other hand, was synthesized in four steps starting from monoether **4**, which was exhaustively alkylated with *tert*-butyl bromoacetate in the presence of K_2CO_3 to afford tetraester **5** in 81% yield. Catalytic hydrogenolysis (Pd/C) of the benzyl protecting group provided hydroxycalix[5]arene **6** (89%), which was alkylated with benzyl bromoacetate/K_2CO_3 to yield the mixed pentaester **7** (80%). Finally, debenzylation with H_2 and Pd/C provided the acid derivative **1b**·H in 94% yield.

The two monoacid derivatives were characterized by NMR spectroscopy and single-crystal XRD analysis. Both molecules display ^{1}H NMR spectra consistent with a C_s-symmetric *cone-out* conformation.[15a,24] This nonregular *cone* conformation[23] is substantiated by downfield resonances for the hydrogen atoms of the *tert*-butylphenoxy ring bearing the carboxyl moiety (relative to those of the remaining aryl units) which, together with the presence of a carboxyl hydrogen peak (δ 10.2 and 10.1 ppm for **1a**·H and **1b**·H, respectively), suggest the likely presence of an intramolecular hydrogen bonding between the carboxyl group and the phenolic oxygen atoms of **1a**·H and **1b**·H (vide infra).

Single-crystal X-ray analyses of **1a**·H and **1b**·H (from $CHCl_3/CH_3CN$) fully support the structural assignments carried out in solution (Figure 1, see also Figure S1 and Table S1 in the Supporting Information). In the solid state both derivatives adopt similar *cone-out* conformations,[15a,24] wherein three *tert*-butylphenoxy rings are leaning outward with respect to the cavity of the macrocycle, whereas the remaining two (namely, B and B′ for **1a**·H and C and B′ for **1b**·H) are nearly perpendicular to the calixarene reference plane passing through the five bridging methylene groups (see Table S2 in the Supporting Information for the relevant dihedral angles). In both cases, the calixarene aromatic cavity is filled by an acetonitrile solvent molecule, held inside the macrocycle by a number of CH–π interactions (Figure 1a and Table S3 (Supporting Information)). The four pendant groups at the narrow rim take on an extended conformation, and the carboxyl OH group points in, toward the bottom of the aromatic cavity. Close comparison of the two structures reveals that ring A of **1a**·H is more markedly tilted away from the axis of the cavity than the corresponding ring of **1b**·H (151.4(1) and 132.68(6)° for **1a**·H and **1b**·H, respectively) (Figure S1 in the Supporting Information). This conformational difference is associated with a different H-bond pattern involving the carboxyl group (Figure 1b). While in **1a**·H the carboxyl group forms a strong three-center intramolecular hydrogen bond with the phenolic oxygen

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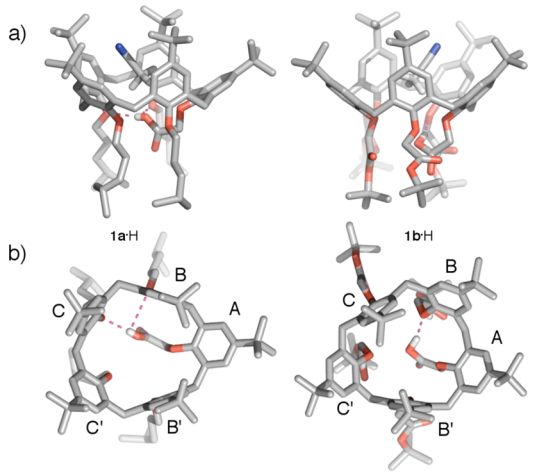

Figure 1. Crystallographic structures of calix[5]arenes **1a**·H and **1b**·H: (a) side views showing the presence of an acetonitrile solvent molecule filling the cavity; (b) top views displaying the presence of intramolecular H bond(s) between the carboxyl group and the phenolic oxygen atom(s) (the acetonitrile molecule has been omitted for clarity).

atoms linked to rings B and C (O···O distances 2.625(9) and 2.874(9) Å), in the case of **1b**·H a weaker two-center hydrogen bond, between the corresponding carboxyl group and the phenolic oxygen of ring B (O···O = 2.995(3) Å), is observed (Figure 1b). The different H-bond strengths and consequently the closer proximity of the oxymethylenecarboxyl moiety to the bottom of the cavity and the wider outward inclination of ring A, may reflect a superior H-bond acceptor ability of the phenolic oxygen atoms present in **1a**·H with respect to those of **1b**·H (linked to 4-methylpentyl and *tert*-butoxycarbonylmethyl pendant moieties, respectively). The distance of the hydroxyl oxygen atom from the calixarene reference plane of −1.712(8) and −2.614(2) Å for **1a**·H and **1b**·H, respectively, quantifies the major conformational difference between the two macrocycles.

The affinity of amines for calix[5]arenes **1a**·H and **1b**·H was initially probed by adding an equimolar amount of *n*-butylamine to a solution of each of them (1 mM in $CDCl_3$/CD_3OD, 9/1). As expected, protonation of the target amine occurred and inclusion of the latter—as the corresponding alkylammonium ion—inside the calixarene cavity was revealed by ^{1}H NMR spectroscopy (Figure 2).[25]

endo-Cavity inclusion of the *n*-butylammonium ion is unambiguously demonstrated by the appearance, in the high-field region of the spectra (−0.02 to −2.02 and −0.47 to −1.85 ppm for *n*-$BuNH_3^+$⊂**1a**$^-$ and *n*-$BuNH_3^+$⊂**1b**$^-$, respectively), of a set of resonances consistent with an *n*-butyl moiety positioned inside a calix[5]arene cavity and experiencing the shielding effect of the surrounding aryl rings (Figures 2b,d). In line with several other cases of positively charged calix[5]arene/alkylammonium complexes,[15] association/dissociation of the "overall neutral" *n*-$BuNH_3^+$⊂**1a**$^-$ and *n*-$BuNH_3^+$⊂**1b**$^-$ complexes was found to be slow on the NMR time scale, giving rise to distinct sets of resonances for both complexed and free species present at equilibrium. As a result, direct integration of the pertinent peaks provided the association constants for the two complexes (K_a = (3.21 ± 0.3) × 10^4 and (1.13 ± 0.1) × 10^4 M^{-1}, corresponding to ca. 84 and 74% complexation for *n*-$BuNH_3^+$⊂**1a**$^-$ and *n*-$BuNH_3^+$⊂**1b**$^-$, respectively). The higher affinity of *n*-$BuNH_2$ for **1a**·H with respect to **1b**·H was also confirmed by an independent competition experiment (carried out on a 1/1/1 mixture of the amine and the two host molecules) that revealed the preferential formation of *n*-$BuNH_3^+$⊂**1a**$^-$ over *n*-$BuNH_3^+$⊂**1b**$^-$ (ca. 60 to 40%; see Figure S6 in the Supporting Information).

Solvent was found to play a crucial role in the overall ionization/complexation process. Accordingly, the degree of complexation between *n*-$BuNH_2$ and both receptors increases significantly (52, 84, and >99% for **1a**·H; 10, 74, and >99% for **1b**·H) on going from neat $CDCl_3$ to $CDCl_3$/CD_3OD (9/1) and then to $CDCl_3$/CF_3CD_2OD (9/1) (Figures S7 and S8 in the Supporting Information). Most likely, the presence in solution of a protic solvent enhances the acidity of the carboxyl moiety of **1a**·H and **1b**·H. Specifically, CD_3OD and CF_3CD_2OD act as increasingly stronger H-bond donors toward

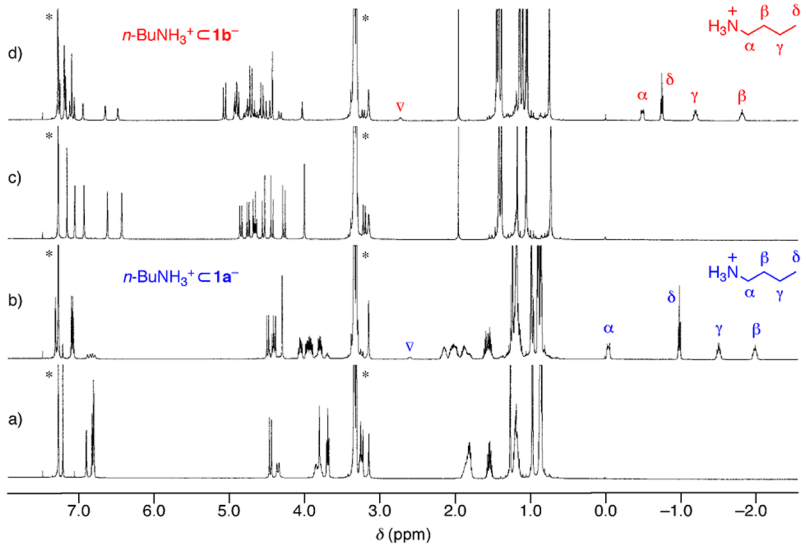

Figure 2. ^{1}H NMR spectra (500 MHz, $CDCl_3$/CD_3OD 9/1 v/v, 25 °C, 1 mM): (a) **1a**·H; (b) *n*-$BuNH_3^+$⊂**1a**$^-$; (c) **1b**·H; (d) *n*-$BuNH_3^+$⊂**1b**$^-$. The symbols ▽ and ∗ indicate the resonances of the α-CH_2 group of the free guest and the residual solvent signals, respectively.

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the carboxyl group, thus facilitating the formation of butylammonium ions. Moreover, the presence of polar protic solvents, such as CD_3OD and CF_3CD_2OD, favors the charge-separation step and contributes at the same time to the stabilization of the ion-pair complex, by efficiently solvating it once it has formed (see X-ray studies below).

The host–guest complexes were characterized by X-ray analysis of single crystals obtained in the presence of *n*-$BuNH_2$ from trifluoroethanol (TFE) solutions of **1a**·H and **1b**·H, respectively.[26] Both crystal structures show the formation of a supramolecular host–guest salt (that is, an "internal" ion-paired host–guest complex) having a *n*-$BuNH_3^+$ cation bound inside the cavity of the ionized carboxylate-calixarene (Figure 3). The

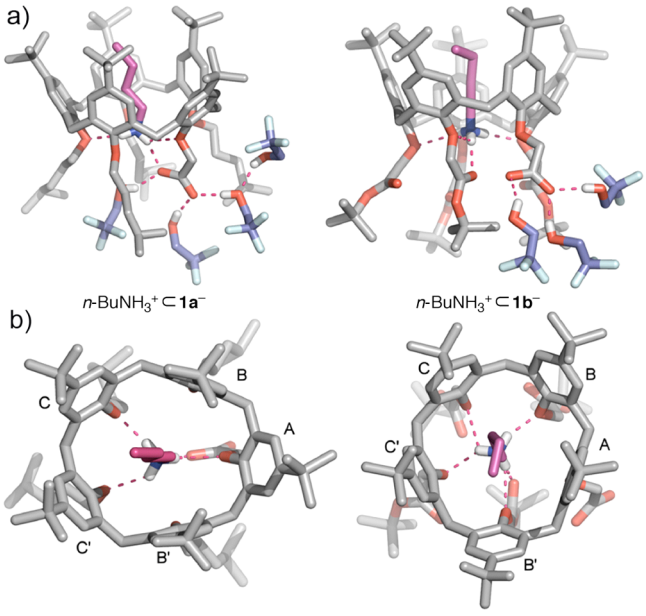

Figure 3. Crystallographic structures of the *n*-$BuNH_3^+$⊂**1a**$^-$ and *n*-$BuNH_3^+$⊂**1b**$^-$ complexes: (a) side views showing the different orientation of the carboxylate group in the two complexes and the presence of a salt bridge interaction only in the case of *n*-$BuNH_3^+$⊂**1a**$^-$; (b) top views highlighting the presence of intermolecular H bonds between host and guest. In both structures the carboxylate moiety is surrounded by hydrogen-bonded TFE solvent molecules. The carbon atoms of the guest and the solvent molecules are depicted in magenta and blue, respectively.

proton transfer from the carboxyl moiety of **1a**·H to the amino group of *n*-$BuNH_2$ with the formation of a salt bridge (similar to those commonly found in proteins[27] and in other supramolecular systems[28]) is clearly confirmed by the residual electron density maps reported in Figure 4. In comparison to previously reported crystallographic structures of calix[5]arene/*n*-$BuNH_3^+$ ion complexes, in the case of *n*-$BuNH_3^+$⊂**1a**$^-$ the positively charged nitrogen atom is seen well below the macrocycle reference plane (distances −0.938(1), −0.616(6), 0.133(3), and −0.13(5) [−0.55(2)] Å for *n*-$BuNH_3^+$⊂**1a**$^-$, *n*-$BuNH_3^+$⊂**1b**$^-$, *n*-$BuNH_3^+$⊂**8**,[15b] and *n*-$BuNH_3^+$⊂**9**,[15a] respectively). These data emphasize the key role played by a salt-bridged carboxylate/ammonium ion pair in the stabilization of the *endo*-cavity complex *n*-$BuNH_3^+$⊂**1a**$^-$.

In *n*-$BuNH_3^+$⊂**1a**$^-$, the *n*-butylammonium ion is held in place by a network of four intermolecular H-bond interactions involving the NH_3^+ group of the guest and three phenolic oxygen atoms (N···O distances in the 2.868(4)–2.934(4) Å

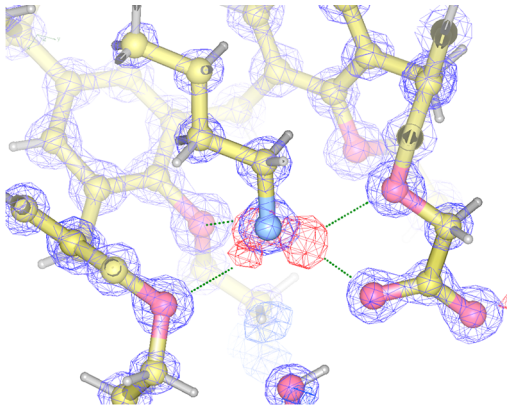

Figure 4. Section of the electron density map ($2F_o - F_c$, contour level 1.4 σ, purple) and the residual electron density map ($mF_o - DF_c$, contour level 3 σ, red) observed for the *n*-$BuNH_3^+$⊂**1a**$^-$ complex, showing the position of the hydrogen atoms involved in H bonds (green dashed line).

range; see Figure 3 and Table S3 (Supporting Information)) as well as the carboxylate moiety of the host (N···O distance 2.779(5) Å). Additional CH–π interactions[29] are also observed between the α- and β-CH_2 groups of the *n*-$BuNH_3^+$ ion and rings B, B′, C, and C′ of the host (Table S3).[15a,b,17a] Three TFE solvent molecules surround the carboxylate group and interact with it via hydrogen bonds (Figure 3). In contrast with the *n*-$BuNH_3^+$⊂**1a**$^-$ structure, no salt bridge interaction is observed in the crystallographic structure of the *n*-$BuNH_3^+$⊂**1b**$^-$ complex. In this case, the cationic guest is anchored inside the cavity by H bonds with four phenolic oxygen atoms (N···O distances in the 2.805(8)–2.949(8) Å range) and an additional carbonyl oxygen from the ester moiety linked to ring B′ (N···O distance 2.786(9) Å; see Figure 3 and Table S3). The carboxylate group is pointing away from the cavity (N···O distance 5.41 Å) and is solvated by three TFE molecules.

Unlike the case for previously reported calix[5]arene host molecules (e.g., **8** and **9**) that show no detectable affinity for amines,[20] the new generation of ionizable calix[5]arenes—selectively derivatized with a single carboxyl moiety at the narrow rim—takes advantage of both molecular (acid–base) and supramolecular (host–guest) interactions to optimize matching with their specific substrates. Calixarenes **1a**·H and **1b**·H play an active role in the complexation process, by generating their own substrate in situ. That is, amines are the species present in solution, but alkylammonium ions are the substrates that internally bind to the ionized macrocycle. In practical terms, the stoichiometric proton transfer from the built-in carboxyl group to the amine provides an ammonium ion—devoid of an "external", and hence competitive, counter-ion—readily available for ion pairing with the anionic host. The effectiveness of this recognition/binding behavior is notably confirmed by a control complexation experiment carried out, under conditions identical with those used above, between calixarenes **1**·H and *n*-butylammonium picrate (Figure S9 in the Supporting Information). When calixarenes **1a**·H and **1b**·H are asked to act as nonionized receptors for a salt species, they retain their affinity for butylammonium ions but, lacking the additional stabilizing contribution provided by the electrostatic interaction of ion pairing, only succeed in binding 60 and 52% of the available guest (apparent $K_a = (3.82 \pm 0.2) \times 10^3$ and $(2.22 \pm 0.2) \times 10^3$ M^{-1} for *n*-$BuNH_3^+$⊂**1a**·H and *n*-$BuNH_3^+$⊂**1b**·H, respectively).

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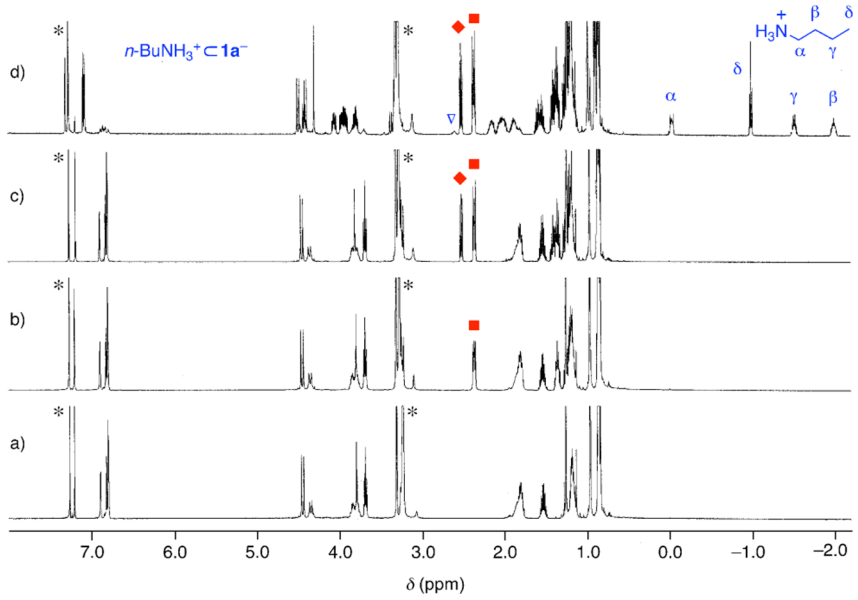

Figure 5. ^{1}H NMR spectra (500 MHz, $CDCl_3/CD_3OD$ 9/1 v/v, 25 °C): (a) [**1a**·H] = 1 mM; (b) [**1a**·H] = [*n*-Bu_3N] = 1 mM; (c) [**1a**·H] = [*n*-Bu_3N] = [*n*-Bu_2NH] = 1 mM; (d) [**1a**·H] = [*n*-Bu_3N] = [*n*-Bu_2NH] = [*n*-$BuNH_2$] = 1 mM. The symbols ■, ◆, ▽, and ∗ indicate the resonances of the α-CH_2 group of *n*-Bu_3N, *n*-Bu_2NH, and *n*-$BuNH_2$ and the residual solvent signals, respectively.

To investigate the binding selectivity of calixarene **1a**·H, different (tertiary, secondary, and primary) potential amine substrates were progressively added to a solution ($CDCl_3/CD_3OD$, 9/1 v/v) of the receptor and ^{1}H NMR spectra were regularly taken after each addition (Figure 5). Titration of a 1 mM solution of **1a**·H with 1 equiv of *n*-Bu_3N did not result in any guest *endo*-cavity inclusion and, surprisingly, produced no evidence in favor of amine protonation (Figure 5b).[30] Similarly, subsequent addition of 1 equiv of the secondary amine *n*-Bu_2NH again resulted in no inclusion or protonation (Figure 5c).[30] On the other hand, final addition to the solution of 1 equiv of *n*-$BuNH_2$ induced proton transfer from the carboxyl moiety of **1a**·H to the primary amine, producing the expected *endo*-cavity inclusion complex (Figure 5d).

In a similar fashion, selectivity of **1a**·H for *n*-$BuNH_2$ vs isomeric *iso*-, *sec*-, and *tert*-butylamine was tested by an analogous NMR titration experiment (Figure S11 in the Supporting Information). Branched amines such as *s*- and *t*-$BuNH_2$ were neither protonated[30] nor included in the cavity of **1a**·H, whereas addition of the less hindered *i*-$BuNH_2$ led to the formation of ca. 13% of the corresponding *i*-$BuNH_3^+$⊂**1a**$^-$ complex. However, when *n*-$BuNH_2$ was added to the mixture, *i*-$BuNH_3^+$ ions were extruded from the cavity of **1a**$^-$ (as *i*-$BuNH_2$ molecules) and the more stable *n*-$BuNH_3^+$⊂**1a**$^-$ complex was formed (ca. 80%).

Assuming that in a $CDCl_3/CD_3OD$ solution the carboxylic hydrogen atom of **1a**·H is held within the cavity by an intramolecular hydrogen bond network, similar to that observed in the solid state (Figure 1b), the inability of its carboxyl group to donate a proton to *n*-Bu_2NH or *n*-Bu_3N suggests that proton transfer from the calixarene to the amine is prevented by an unfavorable energy trade between hydrogen bond breakage and simple "*exo*-cavity" salt formation. This experiment demonstrates that, regardless of the basicity of the amine used, proton transfer from **1a**·H to the substrate only occurs when formation of a salt bridge stabilizing the "internal" ion-pair complex is allowed (i.e. *n*-$BuNH_3^+$⊂**1a**$^-$). According to these data, the formation of a salt-bridged complex acts as a potential well, promoting proton transfer exclusively when size and shape complementarity between host and guest matches. Given that the only acidic protons available to the pool of amines tested derive from the carboxyl group of the calixarene, the stoichiometric matching allows only the best-fitting substrate to be protonated, leaving the other amine(s) in their noncompeting, unprotonated form. The combination of these findings indicates that the overall recognition/protonation/binding process of *n*-$BuNH_2$ by **1a**·H is highly selective.

■ CONCLUSION

In conclusion, calix[5]arene receptors have been equipped with a carboxyl group at their narrow rim to allow selective complexation of linear primary amines. This functionalization converts a class of receptors specific only for cationic species into new derivatives able to capture neutral molecules. Carboxylcalix[5]arenes show remarkable binding properties, being capable of recognizing linear primary amines and selectively promoting them to alkylammonium ion guests by means of a proton transfer mechanism that turns "dormant" substrates into "active" ones. By this mechanism, the mere presence of the calixarene cavity and the driving force provided by the *endo*-cavity inclusion of a suitable guest directs protonation only toward the best-fitting substrate(s). Formation of overall neutral ion-paired host−guest complexes is secured by a number of hydrogen-bonding and CH−π interactions as well as—in the case of **1a**·H—an unprecedented salt bridge, acting as an additional close-range electrostatic interaction. We are currently investigating the possibility of assembling molecular capsules from diamines and ionizable (bis)calixarene receptors.

■ EXPERIMENTAL SECTION

General Considerations. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$, at 500 and 125 MHz, respectively. Chemical shifts are reported in ppm and are referenced to the residual solvent (δ_H 7.26 ppm and δ_C 77.0

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ppm). Where present, ^{1}H NMR peak assignments follow from COSY experiments. ^{13}C NMR spectra were acquired with the attached proton test (APT) technique. Mass spectra were measured on an ion trap electrospray instrument. Anhydrous solvents were either obtained commercially or dried by standard methods prior to use, while other chemicals were reagent grade, used without further purification. Column chromatography was performed on silica gel (Merck, 230−400 mesh). All reactions were carried out under an argon atmosphere. 5,11,17,23,29-Pentakis(1,1-dimethylethyl)-35-hydroxy-31,32,33,34-tetrakis(4-methylpentyloxy)calix[5]arene[22] (**2**), and 5,11,17,23,29-pentakis(1,1-dimethylethyl)-31-benzyloxy-32,33,34,35-tetrakis-(hydroxy)calix[5]arene[23] (**4**) were synthesized according to published procedures.

Synthetic Procedures. *5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31-tert-butoxycarbonylmethoxy-32,33,34,35-tetrakis(4-methylpentyloxy)calix[5]arene (**3**).* A stirred mixture of calix[5]arene **2** (350 mg, 0.305 mmol), *tert*-butyl bromoacetate (178 mg, 0.915 mmol), and K_2CO_3 (126 mg, 0.915 mmol) in CH_3CN (50 mL) was heated to reflux for 24 h. After evaporation of the solvent, the solid residue was partitioned between $CHCl_3$ (50 mL) and aqueous 0.1 M HCl (30 mL). The organic layer was washed with water (2 × 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield, after recrystallization from MeOH/CH_2Cl_2, ester **3** (354 mg, 92%) as a colorless solid: mp 177−181 °C; ^{1}H NMR δ 0.95 (d, J = 6.9 Hz, 24H), 0.96, 1.07, 1.08 (3 × s, 2:1:2 ratio, 45H), 1.31−1.37 (m, 8H), 1.45 (s, 9H), 1.62 (septet, J = 6.9 Hz, 4H), 1.81−1.95 (m, 8H), 3.26, 3.29 (2 × d, J = 14.7 and 16.0 Hz, 3:2 ratio, 5H), 3.52−3.73 (m, 8H), 4.54, 4.56, 4.69 (3 × d, J = 13.7, 15.1, and 14.2 Hz, 2:1:2 ratio, 5H), 4.54 (s, 2H), 6.81 and 6.83, (AB system, J = 2.0 Hz, 4H), 6.94 (s, 2H), 6.97 and 6.99 (AB system, J = 2.0 Hz, 4H) ppm; ^{13}C NMR δ 22.80, 22.81, 22.88, 28.1, 28.21, 28.24, 28.3, 28.4, 29.46, 29.53, 30.3, 31.3, 31.4, 31.5, 33.92, 33.96, 33.98, 35.2, 71.0, 74.1, 74.3, 80.8, 125,16, 125.20, 125.4, 125.9, 133.38, 133.41, 133.7, 133.9, 134.0, 144.50, 144.54, 144.8, 152.6, 152.7, 152.8, 168.9 ppm; ESI-MS m/z 1284.4 [M + Na]$^+$, 1300.4 [M + K]$^+$. Anal. Calcd for $C_{85}H_{128}O_7$: C, 80.90; H, 10.22. Found: C, 80.69; H, 10.45.

*5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31-carboxymethoxy-32,33,34,35-tetrakis(4-methylpentyloxy)calix[5]arene (**1a**·H).* A solution of **3** (330 mg, 0.262 mmol) was dissolved in $CHCl_3$/CF_3CO_2H (1/1, v/v, 6 mL) and stirred for 4 h at room temperature. Solvents were removed under reduced pressure and the crude product crystallized from MeOH/CH_2Cl_2 to afford **1a**·H (208 mg, 66%): mp 97−101 °C; ^{1}H NMR δ 0.91, 0.94 (2 × d, J = 6.8 Hz, CH(CH_3)$_2$, 24H), 0.92, 1.01, 1.32 (3 × s, 2:2:1 ratio, C(CH_3)$_3$, 45H), 1.21−1.27 (m, OCH$_2$CH$_2$CH$_2$, 8H), 1.56−1.66 (m, CH(CH_3)$_2$, 4H), 1.85−1.99 (m, OCH$_2$CH$_2$, 8H), 3.30 (d, J = 13.9 Hz, ArCH$_2$Ar, 5H), 3.73−3.80 (m, OCH$_2$CH$_2$, 4H), 3.84−3.95 (m, OCH$_2$CH$_2$, 4H), 3.90 (s, OCH$_2$CO, 2H), 4.45, 4.50, 4.51 (3 × d, J = 14.0, 13.8, and 14.2 Hz, 2:2:1 ratio, ArCH$_2$Ar, 5H), 6.79 and 6.84 (AB system, J = 2.3 Hz, ArH, 4H), 6.82 and 6.91 (AB system, J = 2.3 Hz, ArH, 4H), 7.27 (s, ArH, 2H), 10.20 (br s, CO_2H, 1H) ppm; ^{13}C NMR δ 22.6, 22.67, 22.69, 27.79, 27.81, 27.9, 28.0, 29.3, 29.9, 30.0, 31.2, 31.4, 31.6, 33.9, 34.2, 34.86, 34.92, 69.7, 75.5, 75.6, 124.7, 125.2, 125.5, 126.0, 126.6, 133.1, 133.3, 133.6, 134.1, 134.2, 145.2, 145.4, 146.1, 150.9, 152.1, 152.5, 170.2 ppm; ESI-MS m/z 1206.6 [M + H]$^+$, 1228.5 [M + Na]$^+$, 1244.4 [M + K]$^+$. Anal. Calcd for $C_{81}H_{120}O_7$: C, 80.68; H, 10.03. Found: C, 80.52; H, 10.18.

*5,11,17,23,29-Pentakis(1,1-dimethylethyl)-35-benzyloxy-31,32,33,34-tetrakis(tert-butoxycarbonylmethoxy)calix[5]arene (**5**).* A mixture of monoether **4** (205 mg, 0.228 mmol), *tert*-butyl bromoacetate (534 mg, 2.736 mmol), and K_2CO_3 (378 mg, 2.736 mmol) in CH_3CN (30 mL) was refluxed for 24 h. After cooling, the inorganic salts present in the reaction mixture were collected by filtration, washed with $CHCl_3$, and disposed, while the combined organic layers were evaporated to dryness. The resulting oily residue was treated with petroleum ether (50 mL), and the additional salts precipitated out removed by suction filtration. The filtrate was washed with water (2 × 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield, upon recrystallization from MeOH/$CHCl_3$, tetraester **5** (251 mg, 81%): mp 187−190 °C; ^{1}H NMR δ 0.83, 1.13, 1.14 (3 × s, 2:1:2 ratio, 45H), 1.38, 1.47 (2 × s, 1:1, 36H), 3.21, 3.33, 3.41 (3 × d, J = 14.2, 14.2, and 15.6 Hz, 2:2:1 ratio, 5H), 4.20 and 4.49 (AB system, J = 15.6 Hz, 4H), 4.33 and 4.44 (AB system, J = 15.7 Hz, 4H), 4.34 (s, 2H), 4.71, 4.74, 4.89 (3 × d, J = 14.2, 14.2, and 15.7 Hz, 2:2:1 ratio, 5H), 6.51 and 6.67 (AB system, J = 2.4 Hz, 4H), 6.98 and 7.12 (AB system, J = 2.4 Hz, 4H), 7.07 (s, 2 H), 7.21 (t, J = 7.3 Hz, 1H), 7.34 (t, J = 7.3 Hz, 2H), 7.49 (d, J = 7.3 Hz, 2H) ppm; ^{13}C NMR δ 28.0, 28.2, 29.4, 31.2, 31.4, 31.5, 33.8, 34.00, 34.03, 70.7, 71.8, 75.2, 80.9, 81.0, 125.49, 125.52, 125.54, 125.7, 126.2, 126.6, 127.6, 128.5, 133.2, 133.26, 133.32, 133.5, 134.0, 139.5, 145.1, 145.2, 145.3, 152.0, 152.2, 152.6, 168.8, 169.2 ppm; ESI-MS m/z 1380.3 [M + Na]$^+$, 1396.8 [M + K]$^+$. Anal. Calcd for $C_{86}H_{116}O_{13}$: C, 76.07; H, 8.61. Found: C, 76.01; H, 8.58.

*5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31,32,33,34-tetrakis-(tert-butoxycarbonylmethoxy)-35-hydroxycalix[5]arene (**6**).* A suspension of **5** (231 mg, 0.170 mmol) and 5% Pd/C (40 mg) in AcOEt (50 mL) was stirred at room temperature in the presence of H_2 for 5 h. The mixture was filtered through Celite, and the filtrate was concentrated to dryness under reduced pressure to give **6** as a colorless solid (192 mg, 89%): mp 192−194 °C; ^{1}H NMR δ 0.65, 1.23, 1.29 (3 × s, 2:2:1 ratio, 45H), 1.50, 1.53 (2 × s, 1:1 ratio, 36H), 3.22, 3.34, 3.42 (3 × d, J = 14.0, 14.2, and 14.5 Hz, 1:2:2 ratio, 5H), 4.13 and 4.49 (AX, J = 15.6, Hz, 4H), 4.32 and 4.74 (AX, J = 15.5 Hz, 4H), 4.61, 4.71, 4.92 (3 × d, J = 14.2, 14.5, and 14.0 Hz, 2:2:1 ratio, 5H), 6.40 and 6.60 (AB system, J = 2.0 Hz, 4H), 6.47 (s, 1H), 7.10 (s, 2H), 7.14 and 7.22 (AB system, J = 2.5 Hz, 4H) ppm; ^{13}C NMR δ 28.2, 28.3, 29.1, 30.0, 31.4, 30.9, 31.5, 31.7, 33.7, 33.9, 34.1, 71.4, 72.2, 81.3, 81.6, 124.6, 124.8, 125.9, 126.0, 126.1, 126.5, 132.3, 132.7, 133.9, 134.1, 141.8, 145.5, 146.0, 150.6, 152.0, 152.1, 168.7, 169.7 ppm; ESI-MS m/z 1290.3 [M + Na]$^+$, 1306.1 [M + K]$^+$. Anal. Calcd for $C_{79}H_{110}O_{13}$: C, 74.85; H, 8.75. Found: C, 75.04; H, 8.84.

*5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31-benzyloxycarbonylmethoxy-32,33,34,35-tetrakis(tert-butoxycarbonylmethoxy)calix-[5]arene (**7**).* A stirred mixture of **6** (183 mg, 0.144 mmol), benzyl bromoacetate (68 μL, 0.432 mmol), and K_2CO_3 (60 mg, 0.432 mmol) in CH_3CN (30 mL) was heated at reflux for 24 h. The mixture was cooled, and the inorganic salts were filtered, washed with $CHCl_3$, and disposed. The combined organic layers were concentrated under reduced pressure, and the residue that was left gave a powdery precipitate after addition of CH_3OH. Crystallization of this solid from MeOH/$CHCl_3$ afforded mixed pentaester **7** in 80% yield (163 mg): mp 196−199 °C; ^{1}H NMR δ 0.94, 1.03, 1.09 (3 × s, 2:2:1 ratio, 45H), 1.41, 1.44 (2 × s, 1:1 ratio, 36H), 3.29, 3.35, 3.38 (3 × d, J = 14.5, 14.5, and 14.7 Hz, 2:2:1 ratio, 5H), 4.47 and 4.53 (AB system, J = 15.6 Hz, 4H), 4.58 (s, 4H), 4.65 (s, 2H), 4.74, 4.80, 4.82 (3 × d, J = 14.5, 15.0, and 14.3 Hz, 2:1:2 ratio, 5H), 5.22 (s, 2H), 6.73 and 6.79 (AB system, J = 2.5 Hz, 4H), 6.87 and 6.92 (AB system, J = 2.5 Hz, 4H) 6.97 (s, 2H), 7.27−7.41(m, 5H) ppm; ^{13}C NMR δ 28.09, 28.12, 30.2, 31.2, 31.28, 31.33, 31.4, 33.8, 33.9, 34.0, 66.1, 70.4, 71.27, 72.33, 80.96, 80.98, 125.56, 125.64, 125.7, 125.9, 126.0, 128.0, 128.3, 128.4, 133.1, 133.2, 133.3, 133.4, 133.7, 136.0, 145.35, 145.36, 145.44, 151.8, 151.9, 152.3, 169.0, 169.2, 170.0 ppm; ESI-MS m/z 1438.5 [M + Na]$^+$. Anal. Calcd for $C_{88}H_{118}O_{15}$: C, 74.65; H, 8.40. Found: C, 74.31; H, 8.56.

*5,11,17,23,29-Pentakis(1,1-dimethylethyl)-31-carboxymethoxy-32,33,34,35-tetrakis(tert-butoxycarbonylmethoxy)calix[5]arene (**1b**·H).* A solution of **7** (150 mg, 0.106 mmol) and 5% Pd/C (28 mg) in AcOEt (20 mL) was stirred at room temperature in the presence of H_2 for 6 h. The suspension was filtered through Celite, and the filtrate was evaporated under reduced pressure to give calixarene **1b**·H as a colorless crystalline solid (132 mg, 94%): mp 125−128 °C; ^{1}H NMR δ 0.77, 1.14, 1.25 (3 × s, 2:2:1 ratio, C(CH_3)$_3$, 45H), 1.45, 1.50 (2 × s, 1:1 ratio, OC(CH_3)$_3$, 36H), 3.26, 3.37, 3.46 (3 × d, J = 13.8, 14.3, and 15.9 Hz, 2:2:1 ratio, ArCH$_2$Ar, 5H), 4.09 (s, OCH$_2$CO$_2$H, 2H), 4.29 and 4.82 (AX, J = 16.1 Hz, OCH$_2$CO$_2$*t*Bu, 4H), 4.44 and 4.61 (AB system, J = 15.6 Hz, OCH$_2$CO$_2$*t*Bu, 4H), 4.69, 4.87, 5.01 (3 × d, J = 15.9, 14.3, and 13.8 Hz, 1:2:2 ratio, ArCH$_2$Ar, 5H), 6.45 and 6.65 (AB system, J = 2.5 Hz, ArH, 4H), 6.99 and 7.12 (AB system, J = 2.4 Hz, ArH, 4H), 7.21 (s, ArH, 2H), 10.08 (br s, CO_2H, 1H) ppm; ^{13}C NMR δ 28.1, 28.2, 29.2, 31.4, 31.8, 31.1, 31.4, 31.5, 33.7, 34.0, 34.1, 70.8, 71.4, 72.0, 81.3, 81.5, 125.4, 125.5, 125.7, 126.0, 126.4, 132.0, 133.28,

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133.34, 133.5, 134.1, 145.5, 146.2, 150.5, 152.9, 153.0, 169.2, 169.3, 169.8 ppm: ESI-MS m/z 1348.3 $[M + Na]^+$. Anal. Calcd for $C_{81}H_{112}O_{15}$: C, 73.38; H, 8.52. Found: C, 73.05; H 8.68.

^{1}H NMR Titration Experiments. All spectra were recorded at 500 MHz and at 25 °C. Prior to use, $CDCl_3$ was filtered through neutral aluminum oxide to remove any traces of acid. Percentages of complexation (required for the calculation of the corresponding association constants, K_a) were determined by direct ^{1}H NMR analysis of the peak (host, ArH; guests, α-CH_2) intensity ratio of equimolar solutions. A set of three different equimolar sample solutions was examined for each K_a determination. NMR samples were prepared by adding aliquots of solutions of the relevant amines (8 μL, [amine] = 0.1 M in $CDCl_3$; $CDCl_3/CD_3OD$ 9/1, v/v or $CDCl_3/CF_3CD_2OD$ 9/1, v/v) to a solution of the receptor ($[\mathbf{1}\cdot H] = 1 \times 10^{-3}$ M in $CDCl_3$; $CDCl_3/CD_3OD$ 9/1, v/v or $CDCl_3/CF_3CD_2OD$ 9/1, v/v).

X-ray Diffraction Studies. Colorless crystals of calix[5]arenes **1a**·H and **1b**·H suitable for X-ray analysis were obtained by slow evaporation at room temperature of 5/1 $CHCl_3/CH_3CN$ mixtures. Rodlike crystals of n-$BuNH_3^+\subset\mathbf{1a}^-$ were obtained by slow evaporation of a 2,2,2-trifluoroethanol (TFE) solution containing **1a**·H and n-butylamine in a 1:6 molar ratio. On the other hand, cocrystallization of **1b**·H and n-$BuNH_2$ was carried out by the sitting drop technique, as the evaporation method proved to be unsuccessful. To a solution of **1b**·H in TFE (25 mM) was added n-$BuNH_2$ in a 1:4 molar ratio. The sitting drop contained 4 μL of a **1b**·H/n-$BuNH_2$ solution (30 mg/mL) and 4 μL of a TFE solution containing polyethylene glycol 300 (PEG-300) in the 10−60% (v/v) range. Drops were equilibrated against 1 mL of the TFE-PEG solution (reservoir). Block-shaped colorless crystals grew in 2 months.

Crystals of **1a**·H, **1b**·H, n-$BuNH_3^+\subset\mathbf{1a}^-$, and n-$BuNH_3^+\subset\mathbf{1b}^-$ were all of small dimensions and contained a large amount of solvent molecules; therefore, to improve the intensity of the diffraction pattern, data collections were carried out using synchrotron radiation at the X-ray diffraction beamline of the Elettra Synchrotron, Trieste, Italy, employing the rotating-crystal method with the cryo-cooling technique. Routinely, the crystal dipped in Paratone, as cryo-protectant, was mounted in a loop and flash-frozen to 100 K with liquid nitrogen. In all instances, data were collected under conditions in which the $(\sin\theta_{max})$/wavelength value was slightly lower than 0.550. However, in each of the four cases, the number of combined reflections recorded was sufficient to allow anisotropic refinement of the structure. Diffraction data were indexed and integrated using MOSFLM[31] and scaled with SCALEPACK.[32] The structures were solved by direct methods using SIR2008,[33] and non-hydrogen atoms were anisotropically refined (H atoms at the calculated positions) with bond length and angle restraints by full-matrix least-squares methods on F^2 using SHELXL-97.[34] Crystal data and refinement details are reported in Table S1 (Supporting Information).

The electron density map and the refinement of the **1a**·H structure showed that several *tert*-butyl groups were equally disordered over two sites. Furthermore, restraints were introduced to account for the anisotropic thermal parameters of carbon atoms in the pendant 4-methylpentyl chains (including the severely disordered terminal C4NB atom), using the card SIMU. Disordered solvent molecules reside in the interstitial voids generated between neighboring calixarenes in **1a**·H. To investigate the solvent-containing cavities, the SQUEEZE function of the PLATON program was used.[35] A residual density of 226 electrons/cell, found in the voids of **1a**·H (corresponding to about 12% of the cell volume), was attributed to three chloroform and two acetonitrile molecules. A refinement using reflections modified by the SQUEEZE procedure behaved well, and the R factor was reduced from 26.2 to 16.4%.

■ ASSOCIATED CONTENT

Supporting Information

CIF files, figures, and tables giving crystal data for compounds **1a**·H, **1b**·H, n-$BuNH_3^+\subset\mathbf{1a}^-$, and n-$BuNH_3^+\subset\mathbf{1b}^-$ (CCDC reference numbers 853682, 853681, 871289 and 871290, respectively), additional X-ray plots and ^{1}H and ^{13}C NMR, and IR spectra, and ^{1}H and ^{13}C NMR characterization spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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