The Proton Cryptate of Hexaethylenetetramine**

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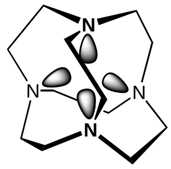
Highly symmetrical molecules have always been fascinating targets for synthetic chemists.[1] Hexaethylenetetramine (**1**) has been our goal ever since 1,4,7-triazacyclononane (**2**) was first synthesized in our laboratory,[2] not just because of its beauty as a *T*-symmetric molecule, but because the electron density of its molecular cavity was expected to be exceptionally high as a result of accumulation of the four nitrogen lone pairs at the center of the small cage. The latter is in sharp contrast to the case for the well-known hexamethylenetetramine (**3**), where the lone pairs are directed outward in the T_d-symmetric adamantane structure.



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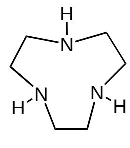

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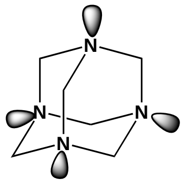

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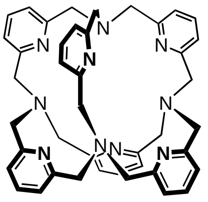

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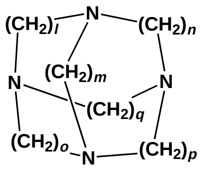

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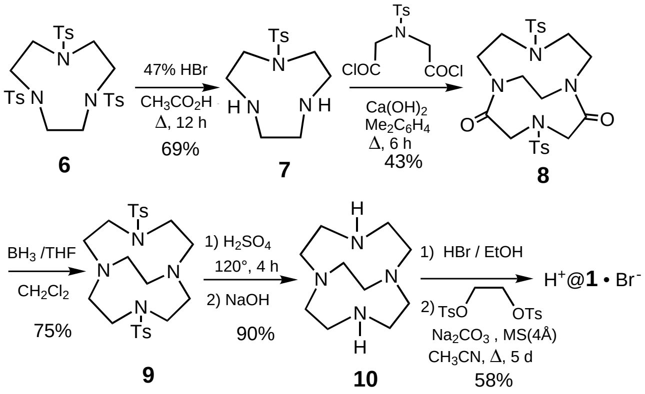
While **3** forms easily upon simple mixing of ammonia and formalin, our synthetic approaches to **1** ended in failure for many years due to its significant strain[3] and the weakness of C–N bonds. Although a highly electron rich cavity could be realized with **4**,[4] which is also *T*-symmetric, we have been all the more fascinated by the smaller and simpler **1**. Springborg et al. have reported the synthesis of **5** ($l = 3$, $m = n = o = p = 2$, $q = 3$),[5] which is larger than our target molecule by only two carbon atoms.[6] Here we report that the synthesis of **1** has been achieved, though as the proton cryptate $H^+@\mathbf{1}\cdot Br^-$, by utilization of the method of Springborg et al. in the final cyclization.



Scheme 1. Synthesis of $H^+@\mathbf{1}\cdot Br^-$. Ts = tosyl = toluenesulfonyl.

The synthetic route to the penultimate tetramine **10** is rather conventional (Scheme 1), but required special caution in each step. Two of the tosyl groups in **6** were removed by heating under reflux in 47 % HBr/CH_3CO_2H (2/1) for 5 h; the bis(hydrogen bromide) salt of **7** crystallized out of the solution.[7] Treatment of the salt with solid KOH in refluxing benzene with azeotropic removal of water gave **7** as a pale yellow solid in 69 % yield. The most critical step of the synthesis was the coupling of **7** with *N*-(*p*-tosyl)iminodiacetyl chloride to give the bicyclic diamide **8**. Presumably to overcome the build-up of strain in going from **7** to **8**, use of high-boiling xylene as the solvent for the reaction under high dilution conditions was essential to obtain **8** in acceptable yields of 30–43 %.[8] The side reactions of the base-sensitive acid chloride, particularly at the high reaction temperature, could be minimized by use of $Ca(OH)_2$ as a mild and nonvolatile base together with 4-Å molecular sieves as a scavenger of the water formed.

Reduction of the diamide **8** proceeded smoothly in 75 % yield by means of $BH_3\cdot THF$ in dichloromethane. Detosylation of **9** in H_2SO_4 at 120 °C, followed by treatment with KOH, provided **10** as colorless crystals (m.p. 97–99 °C after sublimation at 50 °C/20 Torr) in 90 % yield.

The final ring closure was carried out under the conditions of Springborg et al., except that ethylene glycol di-*p*-tosylate was used for the ethylene bridging instead of trimethylene glycol di-*p*-tosylate. Thus, a mixture of $\mathbf{5}\cdot 3HBr$, the di-*p*-tosylate, Na_2CO_3, and powdered 4-Å molecular sieves in acetonitrile was heated under reflux with stirring for five days. Filtration of the reaction mixture, evaporation of acetonitrile, and crystallization of the residue from chloroform gave colorless rectangular plates which readily lost the solvent of crystallization and deliquesced in the air. On the basis of the following analytical and spectroscopic data, the product proved to be the proton cryptate of the target compound **1** with, in spite of the use of the di-*p*-tosylate in the cyclization, Br^- as the counterion and may be represented as $H^+@\mathbf{1}\cdot Br^-$. A yield as high as 58 % could be obtained if due precautions

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were taken for the considerable sensitivity of $H^+@\mathbf{1}\cdot Br^-$ toward acid, air, light, and heat, particularly in solution.

The FAB mass spectrum of the product showed the parent ion peak at *m*/*z* 225.3, which is assignable to $H^+@\mathbf{1}$. The elemental analysis found for a vacuum-dried sample (C 46.16, H 7.94, N 17.37) is satisfactory if residual chloroform is taken into account (calcd for $C_{12}H_{24}N_4\cdot HBr\cdot 0.09\,CHCl_3$: C 45.95, H 8.00, N 17.73).

The most definitive proof for the structure of the cryptate $H^+@\mathbf{1}\cdot Br^-$ came from X-ray crystallographic analysis. A crystal grown in chloroform was sealed in a capillary and held at −120 °C for collection of reflection data by means of an area detector to minimize radiation damage.[9] As shown in Figure 1, the cage is slightly deformed from the expected *T* symmetry. Unfortunately, the encrypted proton could not be located on the difference Fourier map. However, one of the four nitrogen atoms, N4, is different from the others in several respects: 1) The N⋯N distances to the other nitrogen atoms are almost equal (N4⋯N1 2.650, N4⋯N2 2.598, N4⋯N3 2.603 Å) and shorter than those between the other nitrogen atoms (N1⋯N2 2.857, N1⋯N3 2.860, N2⋯N3 2.827 Å), 2) the N–C bonds at N4 are all relatively long (N4–C7 1.491, N4–C6 1.455, N4–C12 1.484 Å), and 3) the N–C bonds at the "ends" of the chains radiating from N4 are all unusually short (C8–N1 1.372, C5–N3 1.376, C11–N2 1.393 Å). Therefore, the encrypted proton should be present in the neighborhood of N4 in the solid state due to electrostatic interactions with the counterion.

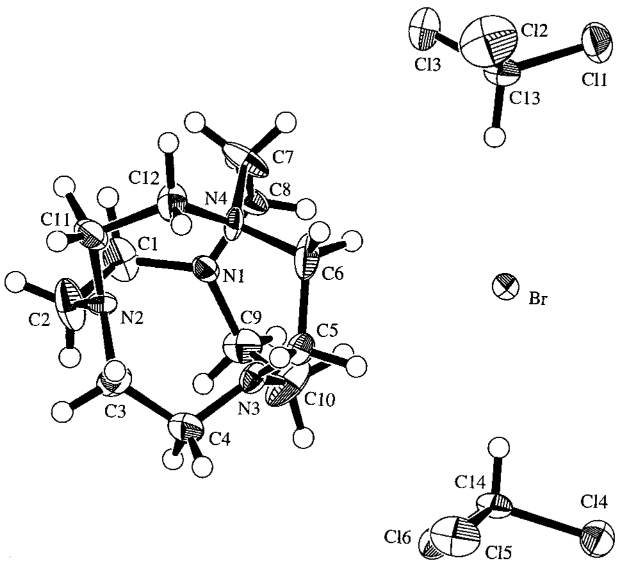

Figure 1. ORTEP representation of $H^+@\mathbf{1}\cdot Br^-\cdot 2\,CHCl_3$ (thermal ellipsoids are drawn at the 50 % probability level).

It is interesting that the crystal contains two molecules of chloroform which are hydrogen-bonded to the bromide ion (C13⋯Br 3.553, C14⋯Br 3.627 Å), and the atoms C13, Br, and C14 are aligned almost in a straight line (175.7°). In agreement with the X-ray results, a chloroform-containing sample of $H^+@\mathbf{1}\cdot Br^-$ in Nujol mull showed an absorption at 2450 cm^{-1} in the IR spectrum (Figure 2C). This absorption was absent when the same sample was measured in CH_2Cl_2 or when the included $CHCl_3$ was removed (Figure 2B). The pronounced shift of the C–H stretching band to lower frequency compared to that for free $CHCl_3$ (3040 cm^{-1}) should be due to the presence of hydrogen bonding.

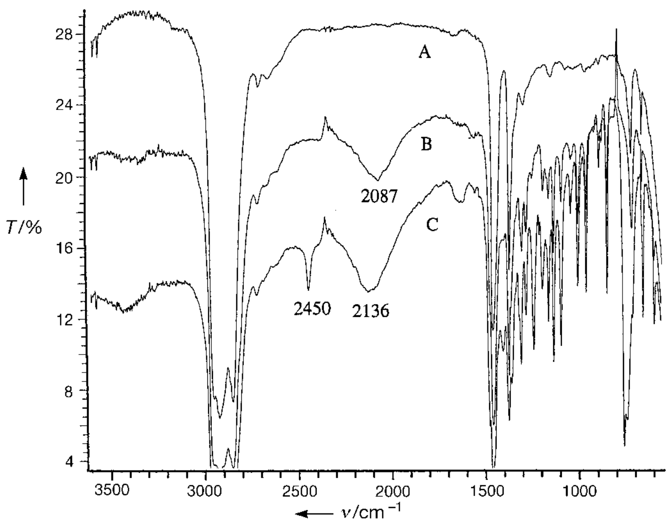

Figure 2. IR spectra of Nujol (A), $H^+@\mathbf{1}\cdot Br^-$ in Nujol (B), and $H^+@\mathbf{1}\cdot Br^-\cdot 2\,CHCl_3$ in Nujol (C). *T* = transmittance.

The most noticeable feature of the IR spectra, however, is the occurrence of a broad but distinctive band at about 2100 cm^{-1}. The shape and position of this band were almost unaffected when the measurements were carried out in CH_2Cl_2 (2132 cm^{-1}), suggesting that it is isolated from external effects. Extensive studies by Alder et al. on intra-bridgehead hydrogen-bonded ions in bicyclic diamines have shown that the position of the stretching band for hydrogen-bonded N–H groups ranges from 2450 cm^{-1} for systems with a N–H⋯N angle of 130° down to 1400–1900 cm^{-1} for a highly hydrogen bonded linear N–H⋯N system.[10] Thus, the present system shows favorable hydrogen-bonding interactions even with the less favorable tetrahedral bond angles of 109°, under the assumption that the encapsulated proton is at the center of the cage.

As expected, NMR spectroscopy provided more information on the structure of $H^+@\mathbf{1}\cdot Br^-$. In contrast to the complex multiplets observed for the CH_2 protons of **10** and its salts, the ^1H NMR spectrum (400 MHz) of $H^+@\mathbf{1}\cdot Br^-$ in $CDCl_3$ is very simple. It consists of a singlet at $\delta = 15.00$ for the included proton and a sharp signal at $\delta = 3.04$ for the CH_2 protons in a ratio of 1:24, and it is free from characteristic *p*-tosyl peaks. Most significantly, the CH_2 proton signal is not a singlet, but a narrow doublet separated by 1.0 Hz. That this splitting is caused by coupling with the included proton was confirmed by a decoupling experiment with irradiation at $\delta = 15.00$. The appearance of only one peak at $\delta = 48.05$ in the ^{13}C NMR spectrum of $H^+@\mathbf{1}\cdot Br^-$ also indicates a symmetrical structure.

The apparent T_d symmetry of $H^+@\mathbf{1}\cdot Br^-$ is evidently derived from averaging of signals on the NMR time scale. ^1H NMR studies (400 MHz) at various temperatures revealed that, as the temperature was lowered, the closely spaced doublet for the CH_2 protons collapsed to a broad singlet and, below the coalescence temperature of $-65\,^{\circ}C$, split to an AA′BB′ system (Figure 3) in a similar fashion as the signals for axial and equatorial protons in cyclohexane.

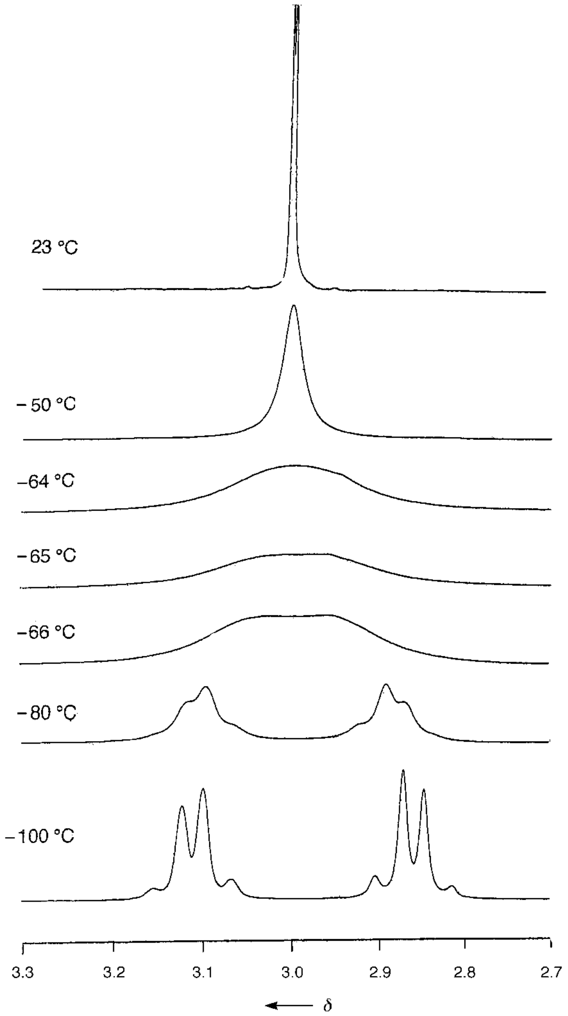

Figure 3. ^1H NMR spectra (400 MHz) of $H^+@\mathbf{1}\cdot Br^-$ in CD_2Cl_2/CS_2 (3/2).

As shown in Figure 4, the most interesting features of $H^+@\mathbf{1}$ as a *T*-symmetric species are its chirality and the interconversion of its enantiomers. When the chiral shift agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol was added to a solution of $H^+@\mathbf{1}\cdot Br^-$ in CD_2Cl_2 at room temperature and the ^1H NMR spectrum was measured immediately at $-90\,^{\circ}C$, the peaks for the encapsulated proton and one of the CH_2 protons split into two peaks of roughly equal intensity (Figure 5). The activation energy ΔG_{208} for the process was estimated to be about $9.8\ kcal\,mol^{-1}$ from the difference in chemical shift at $-100\,^{\circ}C$ and a line-shape analysis based on the AA′BB′ spin system.

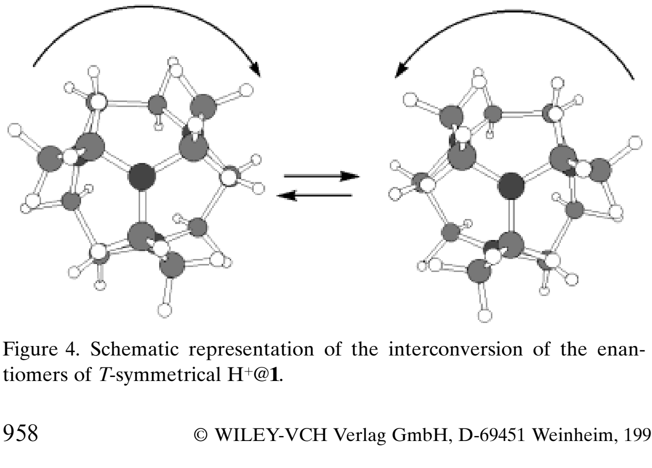

Figure 4. Schematic representation of the interconversion of the enantiomers of *T*-symmetrical $H^+@\mathbf{1}$.

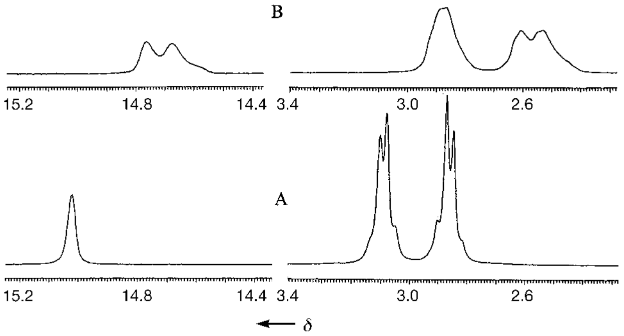

Figure 5. ^1H NMR spectra of $H^+@\mathbf{1}\cdot Br^-$ in CD_2Cl_2 at $-90\,^{\circ}C$ before (A) and after addition of the chiral shift reagent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (B).

The proton signal appearing at such a low field as $\delta = 15.00$ in the NMR spectrum is typical of a hydrogen-bonded proton.[10] Even in the larger **5** ($l=3$, $m=n=o=p=2$, $q=3$; $\delta = 15.2$ in D_2O) the encrypted proton is very strongly held in the cavity by the hydrogen bonds, and could not be removed by treatment with aqueous base.[5] Likewise, the encrypted proton of $H^+@\mathbf{1}\cdot Br^-$ ($\delta = 15.17$ in D_2O) did not show any sign of being removed to form the vacant **1** or of exchanging with an external deuteron in a strongly alkaline solution (3 M NaOD), even after standing at room temperature for 14 days followed by heating at 95 °C for 3 days.

In addition to continued efforts at making proton-free **1**, we are trying to include an alkaline or a transition metal ion in **1**, with encapsulation of a metal atom as our ultimate goal.

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Keywords: cage compounds · cryptates · nitrogen heterocycles

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[3] The steric energy of **1** ($74.7\ kcal\,mol^{-1}$) is considerably higher than that of **10** ($46.9\ kcal\,mol^{-1}$), as calculated by Allinger's MM3(94) molecular mechanics program implemented in a SYBYL molecular modeling package (Tripos Associates). Very recent ab initio calculations on **1** and $H^+@\mathbf{1}$ show that the encrypted proton enters into very strong, four-centered hydrogen bonding in $H^+@\mathbf{1}$ at the center of the cavity: S. T. Howard, I. A. Fallis, *J. Org. Chem.* **1998**, *49*, 7117–7119.

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[6] Springborg et al. mentioned their failure to obtain **10** by their approach: J. Springborg, P. Kofod, C. E. Olsen, I. Søtofte, *Acta Chem. Scand.* **1995**, *49*, 564–570.

[7] J. L. Sessler, J. W. Sibert, V. Lynch, *Inorg. Chem.* **1990**, *29*, 4143–4146.

[8] The yield of **8** increased as the boiling temperature of the solvent was raised on going from benzene to toluene to xylene. In addition, when one of the ethylene bridges in **7** was replaced by a less sterically demanding *o*-phenylene bridge, the cyclization occurred readily at room temperature in 53% yield: Y. Miyahara, K. Handou, T. Inazu, unpublished results.

[9] X-ray structure analysis of $H^+@\mathbf{1}\cdot Br^-$: Measurements were carried out on a colorless prism ($0.3 \times 0.3 \times 0.2$ mm^3) in a sealed capillary at $-120\,^\circ$C; Rigaku RAXIS II instrument with an imaging plate area detector, graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.7107$ Å) up to $2\theta = 54.9^\circ$. Of 5363 total reflections collected, 3733 were observed [$I > 3.0\sigma(I)$]; Lorentz polarization corrections were made. Crystal data: $C_{12}H_{24}N_4\cdot Br\cdot 2CHCl_3$, $M_r = 543.01$, orthorhombic, space group *Pbca* (no. 61), $a = 21.078(3)$, $b = 17.378(3)$, $c = 12.560(3)$ Å, $V = 4600(2)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.57$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 24.95$ cm^{-1}. The structure was solved by direct methods (SHELXS86). All the hydrogen atoms (except the encrypted proton) were found, but refined as fixed at idealized positions. The final residuals $R = 0.051$ and $Rw = 0.025$ were obtained after refinement against $|F|$; min./max. residual electron density $-1.25/1.08$ e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-103234. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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A Potassium Complex of a Fluorine-Containing Macrocyclic Cage Compound: Interactions between Fluorine Atoms and Metal Ions[**]

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Hiroyuki Kariyazono, Teruo Shinmyozu, and
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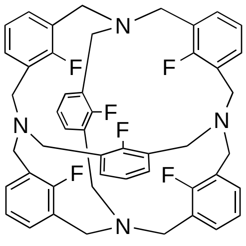
Interactions between covalently bonded fluorine atoms (C–F) and metal cations have been observed in the solid state and discussed based on crystallographic data.[1] Theoretical studies also predict such interactions in solution.[2] On the other hand, few reports are available of experimental elucidation of these interactions.[3] The first attempt to obtain experimental evidence was made in 1984 by Cram and coworkers.[4] However, the fluorinated spherands did not show any complexation phenomena toward alkali metal cations.

Most recently, Plenio et al. synthesized several types of macrocyclic compounds which contain oxygen and fluorine as the donor atoms.[5] Based on ^{13}C and ^{19}F NMR spectral data, X-ray crystallographic analyses, and determinations of stability constants, they concluded that the fluorine atom plays an important role in the complexation of alkali and alkaline earth metal cations. These results are probably the first experimental proof of $C{-}F\cdots M^+$ interactions. However, the molecules contain the ethyleneoxa moiety, and there is no doubt that the oxygen atoms significantly contribute to the trapping of metal cations. Therefore, it is a drawback that the effect of oxygen has to be subtracted from the total cation affinities, and careful handling of each datum is required to discuss the $C{-}F\cdots M^+$ interactions.

Is it possible to observe the interactions with the fluorine atom as the sole donor? To give an unequivocal answer to this question, we began to design a host molecule in which only the fluorine atom acts as a donor. Previously, we reported the simple synthesis of the cage compound **2** and its analogues.[6] The pyridine analogue of **2** is an ideal host molecule for spherical cations because it has a preorganized structure and an "enforced" cavity. Actually, the pyridine analogue showed strong binding phenomena toward alkali metal cations, ammonium ions, and protons. We applied these structures to capture metal cations by fluorine; replacing pyridine or benzene units by fluorobenzene promises a preorganized cavity in which six C–F donor units are pointing toward the cavity (**1**). We now report the synthesis of the host molecule **1** and its ability to complex cations as well as the structure elucidation of the potassium complex of **1**.



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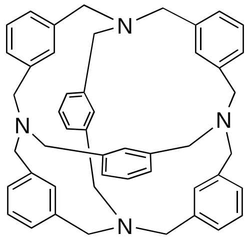

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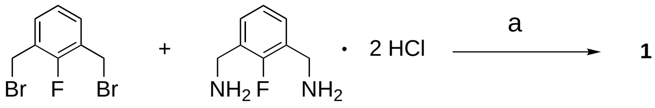
Compound **1** was synthesized in a manner similar to that for **2**.[6f] The reaction of 2-fluoro-1,3-bis(bromomethyl)benzene and 2-fluoro-1,3-bis(aminomethyl)benzene dihydrochloride under phase-transfer conditions (CH_2Cl_2/Bu_4NBr/aq. KOH) afforded **1** in 2.3% yield (Scheme 1). To estimate the complexation ability of **1**, extraction experiments with metal



Scheme 1. Synthesis of cage compound **1**. a) CH_2Cl_2/aq. KOH, Bu_4NBr.

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