Molecular Design of a "Molecular Syringe" Mimic for Metal Cations Using a 1,3-Alternate Calix[4]arene Cavity

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A 1,3-alternate calix[4]arene bearing a nitrogen-containing crown cap at one side and a bis(ethoxyethoxy) group at another side has been synthesized. ^{1}H NMR spectroscopic studies showed that Ag^+ is bound to the crown-capped side (log $K_{ass.}$ = 9.78: CD_2Cl_2:CD_3OD = 4:1 v/v, 30 °C), and the dissociation of Ag^+ from this cavity is very slow. When the nitrogen atom in the crown ring is protonated with trifluoroacetic acid, Ag^+ is pushed out to the bis(ethoxyethoxy) side through a π-basic tube of the 1,3-alternate calix[4]arene. The dissociation of the complex from the bis(ethoxyethoxy) side occurs relatively fast. On the other hand, when the nitrogen·H^+ in the crown ring is deprotonated with Li_2CO_3 and diazabicycloundecene, Ag^+ is sucked back to the crown-capped side through the π-basic tube. These chemically-switchable actions well imitate the function of a "syringe", using the π-basic tube as a pipette and the crown ring as a rubber cap. We believe that this prototype of a "molecular syringe" is a novel molecular architecture for the action of metal cations.

Introduction

Selective recognition of alkali metal cations is one of the central research interests not only in biological systems but also in artificial chemical systems. This is now possible by the use of either naturally-occurring ionophores or synthetic, polyether-type macrocylic receptors, e.g., crown ethers.[1−5] Over the last decade, it has been demonstrated that ionophoric cavities constructed from calix[4]arenes frequently show Na^+ selectivity superior to that observed for crown ethers.[6−11] It is also noteworthy that the stereochemistry of calix[4]arenes has made remarkable progress: it is now possible to freeze the rotation of phenyl units in calix[4]arene by introducing bulky substituents onto OH groups[12−19] or by cross-linking two phenyl uints.[20−24] This progress has enabled us to selectively synthesize and isolate four possible calix[4]arene conformers: that is, cone, partial-cone, 1,2-alternate, and 1,3-alternate.[12−19] By applying these advanced synthetic methods, one can now design various ionophoric calix[4]arenes which show various metal selectivities. For example, certain rigidified calix[4]arenes such as calixcrowns and calixspherands can form kinetically stable complexes with alkali metal cations.[20b] These results demonstrate that conformationally-rigidified calix[4]arenes are very useful for designing ionophoric cavities with the desired size and shape.

We recently found that in certain 1,3-alternate conformers of calix[4]arene the metal cation is bound nonsymmetrically to one of two cavity edges.[25] Since one

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(1) Raymond, K. N.; Carrano, C. J. *Acc. Chem. Res.* **1979**, *12*, 183.
(2) Choy, E. M.; Evans, D. F.; Cussler, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 7058.
(3) Cram, D. J. *Science* **1983**, *219*, 1177 and references cited therein.
(4) Lehn, J.-M. *Science* **1985**, *227*, 849 and references cited therein.
(5) Gokel, G. W. In *Crown Ethers & Cryptands*; Royal Society of Chemistry: Cambridge, 1991.
(6) (a) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *Tetrahedron* **1986**, *42*, 2089. (b) Andreetti, G. D.; Calestani, G.; Ugozzoli, F.; Auduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *J. Incl. Phenom.* **1987**, *5*, 123.
(7) Chang, S.-K.; Cho, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 211.
(8) McKervey, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B.; Harris, S. *J. Chem. Soc., Chem. Commun.* **1985**, 388.
(9) Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E.; Ruhl, B. L.; Schwing Weill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 8681.
(10) Arimura, T.; Kubota, M.; Matsuda, T.; Manabe, O.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1674.
(11) (a) Shinkai, S.; Otsuka, T.; Fujimoto, K.; Matsuda, T. *Chem. Lett.* **1990**, 835. (b) Yamamoto, H.; Shinkai, S. *Ibid.* **1994**, 1115. (c) Yamamoto, H.; Ueda, K.; Sandanayake, K. R. A. S.; Shinkai, S. *Ibid.* **1995**, 497. (d) Yamamoto, H.; Ueda, K.; Suenaga, H.; Sakaki, T.; Shinkai, S. *Ibid.* **1996**, 39.
(12) For comprehensive reviews see (a) Gutsche, C. D. In *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) Vicens, J.; Böhmer, V., Eds. In *Calixarenes*; Kluwer Academic Press: Dordrecht, 1991. (c) Shinkai, S. *Bioorg. Chem. Front.* **1990**, *1*, 161. (d) *Idem. Tetrahedron* **1993**, *49*, 8933. (e) Böhmer, V. *Angew. Chem., Ind. Ed. Engl.* **1995**, *34*, 713.
(13) (a) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955. (b) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1161. (c) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325.
(14) Shinkai, S.; Fujimoto, K.; Otsuka, T.; Herman, H. L. *J. Org. Chem.* **1992**, *75*, 1516.
(15) Iwamoto, K.; Shinkai, S. *J. Org. Chem.* **1992**, *57*, 7066.
(16) Gutsche, C. D.; Reddy, P. A. *J. Org. Chem.* **1991**, *56*, 4783.
(17) See, K. A.; Fronczek, F. R.; Watson, W. H.; Kashyap, R. P.; Gutsche, C. D. *J. Org. Chem.* **1991**, *56*, 7256.
(18) Iqbal, M.; Mangiafico, T.; Gutsche, C. D. *Tetrahedron* **1987**, *43*, 4917.
(19) Verboom, W.; Datta, S.; Asfari, Z.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 5394.
(20) (a) Dijkstra, P. J.; Brunink, J. A. J.; Bugge, K.-E.; Reinhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567. (b) Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; El-Fadl, A. A.; Reinhoudt, D. N. *Ibid.* **1990**, *112*, 6979. (c) van Loon, J.-D.; Groenen, L. C.; Wijmenga, S. S.; Verboom, W.; Reinhoudt, D. N. *Ibid.* **1991**, *113*, 2378.
(21) (a) Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1075. (b) Arduini, A.; Casnati, A.; Dodi, L.; Pochini, A.; Ungaro, R. *Ibid.* **1990**, 1597. (c) Arduini, A.; Casnati, A.; Fabbi, M.; Minari, P.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Supramol. Chem.* **1993**, *1*, 235.
(22) Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, *57*, 4527.
(23) (a) Böhmer, V.; Goldmann, H.; Vogt, W. *J. Chem. Soc., Chem. Commun.* **1985**, 667. (b) Goldmann, H.; Vogt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811. (c) Böhmer, V.; Vogt, W.; Goldmann, H. *J. Org. Chem.* **1990**, *55*, 2569.
(24) (a) Araki, K.; Akao, K.; Otsuka, H.; Nakashima, K.; Inokuchi, F.; Shinkai, S. *Chem. Lett.* **1994**, 1251. (b) Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032. (c) Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032. (d) Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 4271.

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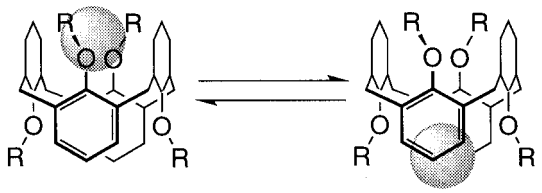
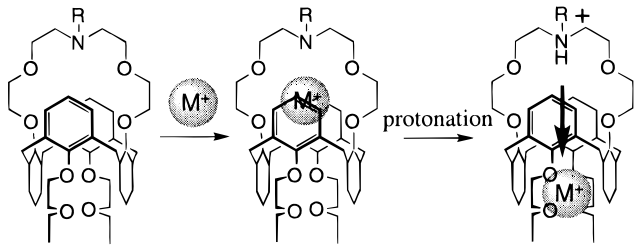


Figure 1. Schematic representation of the metal-tunneling through a π-basic tube of 1,3-alternate calix[4]arene.

cavity edge is composed of two phenolic oxygens and two benzene rings, this metal-binding mode is considered to be an example for the participation of the "cation-π interaction".[26−29] Dynamic ^{1}H NMR spectroscopy at low temperature showed that the metal cation alternates intramolecularly between the two cavity edges through a π-basic hole of 1,3-alternate calix[4]arenes (Figure 1).[25] To the best of our knowledge, this is the first direct evidence for metal cation-tunneling across an aromatic cavity and has important implications with regard to the metal cation−π interaction expected for metal transport through ion channels, metal inclusion in fullerenes, intercalation of metal cations into graphites, etc.[27−29] Here, it occurred to us that it might be possible to design a mechanochemical "molecular syringe" for metal cations from a 1,3-alternate calix[4]crown, using the π-basic tube as a "pipette" and the crown-ring as a "rubber cap". We thus synthesized a chemically-switchable compound **1**. Judging from the relative cation-binding ability of two calix[4]arene edges, the crown-capped side should bind metal cations more strongly than the bis(ethoxyethoxy) side. When the nitrogen atom in the crown ring is protonated, the metal cation would be pushed out through the π-basic cavity to the bis(ethoxyethoxy) side because of electrostatic repulsion.[30] We here report spectroscopic data of **1** which support the molecular-syringe-like action.



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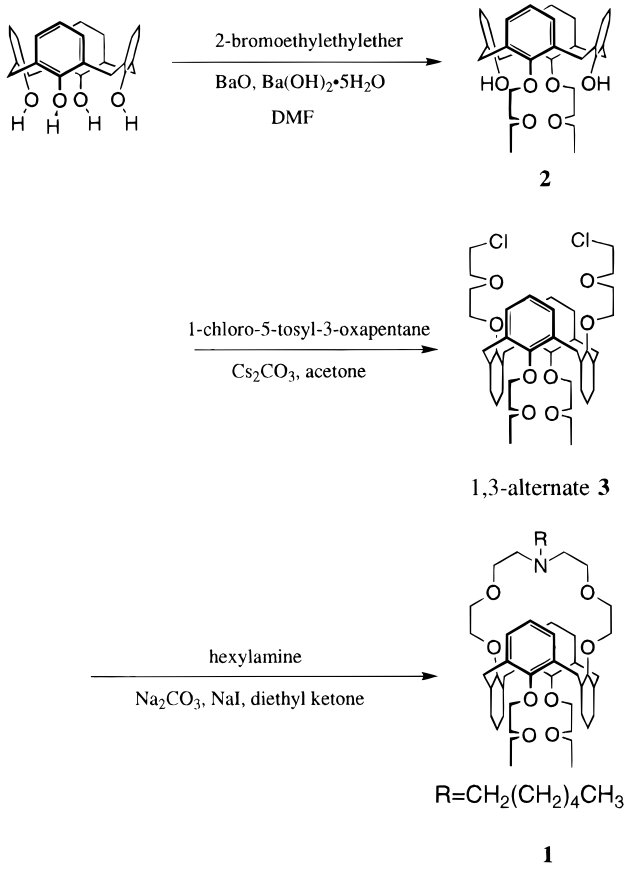
Scheme 1



Results and Discussion

Synthesis. Compound **1** was synthesized from calix[4]arene-25,26,27,28-tetraol via three steps (Scheme 1). Cs_2CO_3, which tends to yield 1,3-alternate calix[4]arenes,[9,13−15,25,31,32] was used as base for the reaction of 1-chloro-5-tosyl-3-oxapentane with **2**. 1,3-Alternate **3** thus obtained was allowed to react with hexylamine under the high-dilution conditions. Compound **1** was obtained from 1,3-alternate **3** in 39% yield. The structure was identified by ^{1}H NMR and mass spectroscopic evidence and elemental analysis (see Experimental Section).

Dynamic ^{1}H NMR Spectra of a 1·Ag$^+$ Complex. For complexation studies, we chose Ag^+ which is known to form stable complexes with 1,3-alternate calix[4]arenes and possesses a metal-tunneling rate comparable with the NMR time-scale.[25,33] In previous examples of 1,3-alternate calix[4]arene·M^+ complexes, the coalescence temperature for the intermolecular metal exchange ($T_{c,inter}$) was always higher than that for the intramolecular metal-tunneling ($T_{c,intra}$).[25] This result implied that the metal cation bound to the calix[4]arene edge tended to move intramolecularly to another edge rather than to dissociate intermolecularly into the solvent. We measured ^{1}H NMR spectra for various mixtures of **1** and

(25) (a) Ikeda, A.; Shinkai, S. *J. Am. Chem. Soc.* **1994**, *116*, 3102. (b) Koh, N. K.; Araki, K.; Shinkai, S.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1995**, *36*, 6095.

(26) For the π-donor participation (to the metal-binding) see (a) Iyoda, M.; Kuwatani, Y.; Yamauchi, T.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1988**, 65. (b) Leookes, R.; Vögtle, F. *Chem. Ber.* **1983**, *116*, 215. (c) Pierre, J.-L.; Baret, P.; Chautemps, P.; Armand, M. *J. Am. Chem. Soc.* **1981**, *103*, 2986. (d) Kang, H. C.; Hanson, A. W.; Eaton, B.; Boekelheide, V. *Ibid.* **1985**, *107*, 1979. (e) Heirtzler, F. R.; Hopf, H.; Jones, P. G.; Bubenitschek, P.; Lehne, V. *J. Org. Chem.* **1993**, *58*, 2781. (f) Gano, J. E.; Subramaniam, G.; Birnbaum, R. *Ibid.* **1990**, *55*, 4760.

(27) (a) Dougherty, D. A.; Stauffer, D. A. *Science* **1990**, *250*, 1558. (b) Dougherty, D. A. *Ibid.* **1996**, *271*, 163 and references cited therein.

(28) Kim, K. S.; Lee, J. Y.; Lee, S. J.; Ha, T.-K.; Kim, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 7399.

(29) Inokuchi, F.; Miyahara, Y.; Inazu, T.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1364.

(30) The similar idea with a switch function has been applied to a molecular shuttle: Bissell, R. A.; Cordova, E.; Kaifer, A. E.; Stoddart, J. F. *Nature* **1994**, *369*, 133.

(31) Ungaro, R.; Casnati, A.; Ugozzoli, F.; Pochini, A.; Dozol, J.-F.; Hill, C.; Rouquette, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1506.

(32) Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud, F.; Fanni, S.; Schwing, M.-J.; Egberink, R. J. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 2767.

(33) For other examples for calixarene-based Ag^+ ionophores see (a) Iwema, W. I.; Verboom, W.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1994**, 71. (b) Perez-Adelmar, J. -A.; Abraham, H.; Sanchez, C.; Rissanen, K.; Prados, P.; de Mendoza, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1009.

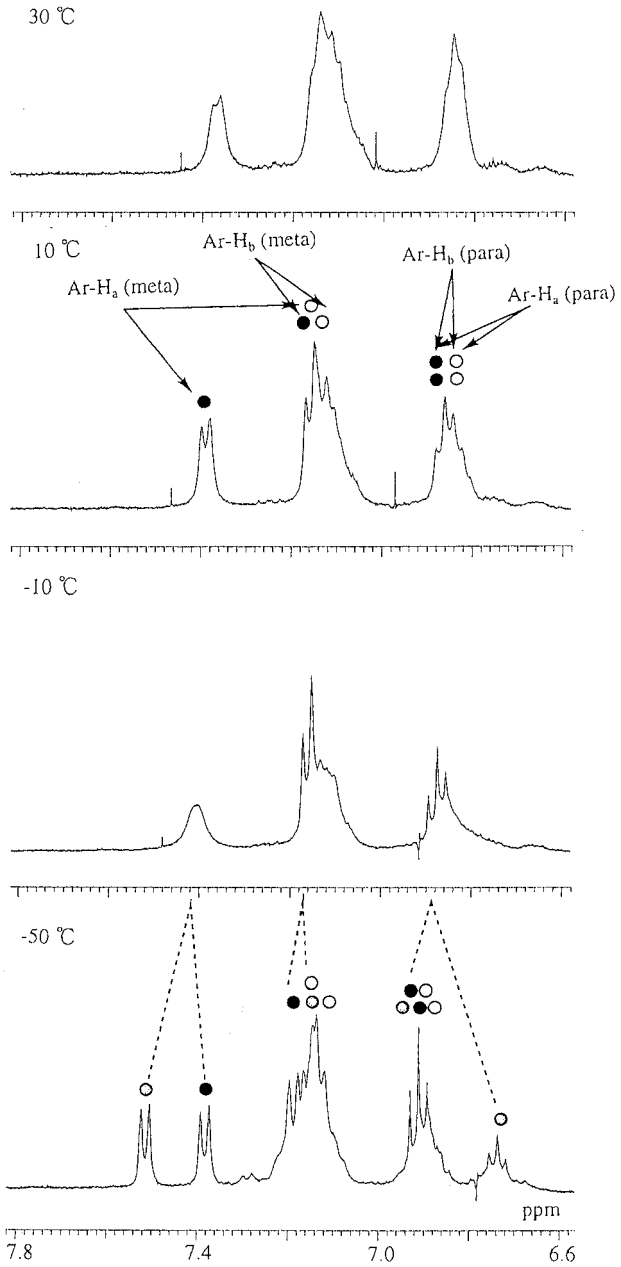


Figure 2. Partial ^{1}H NMR spectra of a **1**-Ag^+ system: 400 MHz, CD_2Cl_2:CD_3OD = 4:1 v/v, [**1**] = 5.00 mM, [CF_3SO_3Ag] = 2.50 mM. Ar-H_a and Ar-H_b denote the aromatic protons at crown-capped side and those at bis(ethoxyethoxy) side, respectively. Open and solid (or shaded) circles denote the signals for free **1** and those for the **1**·Ag^+ complex, respectively.

CF_3SO_3Ag in CD_2Cl_2:CD_3OD = 4:1 v/v at eight different temperatures (between −85 and 30 °C). The typical spectra for [CF_3SO_3Ag]/[**1**] = 0.5 are shown in Figure 2. It is seen from Figure 2 that the peaks for the **1**·Ag^+ complex appear separately from those for free **1** even at 30 °C although they are somewhat broadened compared with those at 10 °C. The result indicates that the $T_{c,inter}$ is higher than 30 °C under these measurement conditions. As the measurement temperature was lowered the peaks coalesced at −20 °C and then split into pairs again. To corroborate that this coalescence is assignable to the $T_{c,intra}$, we examined the influence of the Ag^+ concentration on the coalescence temperature because the $T_{c,inter}$ reflects an intermolecular event and therefore is concentration-dependent whereas the $T_{c,intra}$ reflects an intramolecular event and therefore is concentration-independent.[25] As shown in Figure 3, the coalescence temperature observed at around −20 °C is concentration-independent for [CF_3SO_3Ag]/[**1**] = 0.5 to 5.0. This result clearly supports the view that this coalescence temperature can be assigned to the $T_{c,intra}$. In general, the $T_{c,inter}$ drops with increasing metal concentration.[25] In the present system, however, the $T_{c,inter}$ could not be observed even at [CF_3SO_3Ag]/[**1**] = 5.0 (the upper limit of the CF_3SO_3-Ag solubility). The high $T_{c,inter}$ value implies that the intermolecular metal exchange is considerably slow.

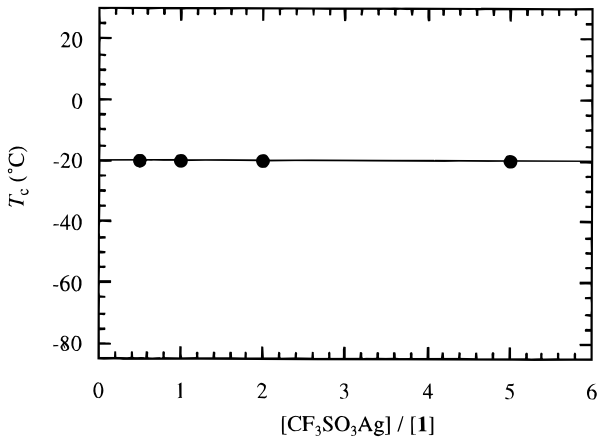


Figure 3. Concentration dependence of $T_{c,intra}$: [**1**] = 5.00 mM, CD_2Cl_2:CD_3OD = 4:1 v/v. The concentration of **1** was maintained constant while the concentration of CF_3SO_3Ag was varied.

We first considered that this $T_{c,intra}$ should be attributed to the metal-tunneling between two cation-binding sites in **1** because the $T_{c,intra}$ values for 1,3-alternate calix[4]-arenes frequently appear at this temperature region.[25] We noticed, however, that the integral intensity below the $T_{c,intra}$ always appears in a 1:1 ratio. This implies that Ag^+ is distributed equally between both binding sites. This partition seems rather unlikely judging from the cation-binding ability of each site. Thus, we carefully analyzed the ^{1}H NMR spectra using 2D COSY and NOE methods. Firstly, we assigned all peaks by 2D COSY. The methylene protons (8-H and 9-H) adjacent to the nitrogen atom appear separately from other protons (at 3.09 ppm). We measured the NOE spectrum with respect to these protons at −50 °C (below $T_{c,intra}$). As shown in Figure 4A, different NOE signals were observed for the aromatic 1-H and 2-H protons which appeared below $T_{c,intra}$ but the aromatic 3-H and 4-H protons on the opposite side remained as one peak. On the basis of this finding, one can conclude that in the present system the $T_{c,intra}$ is not due to the metal-tunneling as in the previous systems[25] but due to the flip-flop-type, rope-jumping motion of a nitrogen-containing crown loop (as shown in Figure 5). This conclusion reasonably explains why the integral intensity of 1-H and 2-H always appears in a 1:1 ratio. Of course, such a flip-flop-type motion of the crown loop is also expected for free **1**. However, the aromatic 1-H and 2-H signals in free **1** did not split even at −85 °C. Presumably, the flip-flop-type motion in the **1**·Ag^+ complex is suppressed by Ag^+ sitting in the small calix[4]crown cavity: that is, the ring cannot provide a satisfactory inner space to fully include Ag^+ but rather perches Ag^+ on the crown loop. In such a Ag^+-binding mode, the structure of the **1**·Ag^+ complex becomes nonsymmetrical, and the exchange between two forms on an NMR time-scale creates a peak-coalescence phenomenon. This view is also supported by the chemical

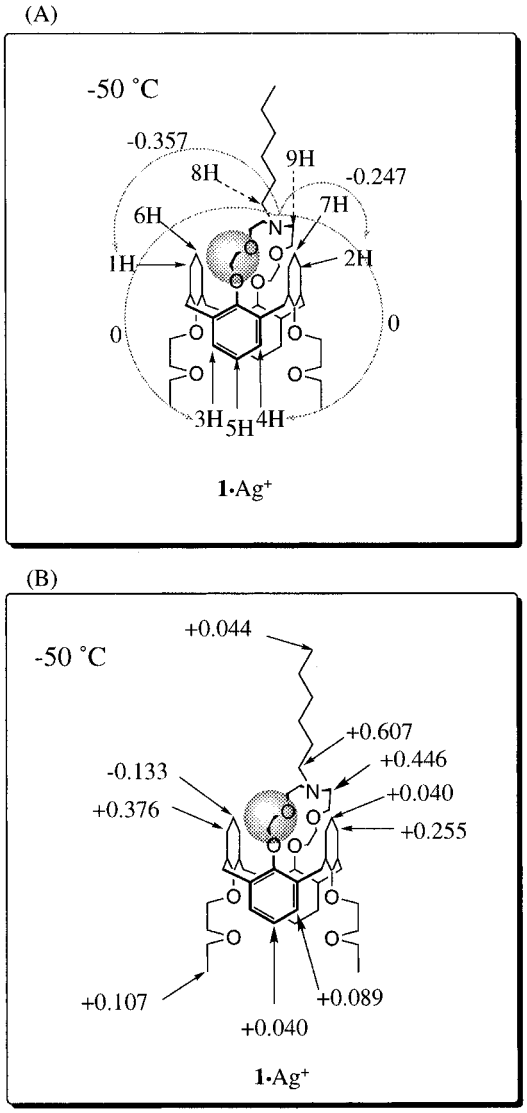


Figure 4. (A) Assignment of chemical shifts for selected protons in the **1**·Ag^+ complex by 2D COSY and NOE signal intensities with respect to 8-H and 9-H: −50 °C, CD_2Cl_2:CD_3OD = 4:1 v/v, [**1**] = 5.00 mM, [CF_3SO_3Ag] = 10.0 mM. (B) Changes in the ^1H NMR chemical shift of **1** induced by added Ag^+: the measurement conditions are the same as A. A plus sign (+) denotes a shift to lower magnetic field, whereas a minus sign (−) denotes a shift to higher magnetic field.

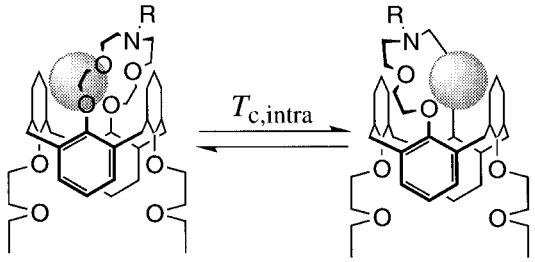


Figure 5. Schematic representation of a rope-jumping motion in the **1**·Ag^+ complex.

shift changes induced by Ag^+ complexation (Figure 4B). While the chemical shifts for the aromatic protons in the bis(ethoxyethoxy) side are scarcely changed, those in the crown-capped side are strongly affected. In particular, the signals for *meta*-protons largely shift to lower magnetic field whereas those for *para*-protons are scarcely affected or inversely shift to higher magnetic field. In the preceding examples for 1,3-alternate calix[4]arene·Ag^+ complexes, Ag^+ most strongly interacts with *para*-carbons, and therefore the largest downfield shift in ^1H NMR spectroscopy is always observed for *para*-protons.[25] In the present system, it is likely that Ag^+ cannot occupy the central position flanked by two *para*-carbons because of the smaller cavity for Ag^+ but rather leans on *meta*-carbons.

The foregoing ^1H NMR spectroscopic studies consistently indicate that Ag^+ is entirely bound to the crown-capped side: that is, Ag^+ has been deposited in a rubber cap of a calix[4]arene-based "molecular syringe" (although it can slowly leak into the solvent by an intermolecular path).[34] Consequently, we tried to estimate the equilibrium constant for the association ($K_{ass.}$) of **1** and CF_3SO_3Ag. When the ^1H NMR peaks for the complex appear separately from the ligand, one can directly calculate the $K_{ass.}$ from the ratio of the integral intensities. In the present system, however, the integral intensity of **1**·Ag^+ was always equal to the amount of added CF_3SO_3Ag (at [**1**] = [CF_3SO_3Ag] = 0.100 to 2.00 mM). This implies that the $K_{ass.}$ is too large to determine by a ^1H NMR method. Thus, the $K_{ass.}$ was estimated by a conductivity method, which is very sensitive and therefore suitable to the determination of large association constants.[35,36] A plot of Λ vs [**1**]/[CF_3SO_3Ag] gave a saturation curve, which was analyzed by the nonlinear least-squares method.[36,37] We thus obtained log $K_{ass.}$ = 9.76: this value is much greater than the $K_{ass.}$ values for 1,3-alternate calix[4]-crowns without the nitrogen atom.[25b,32] Conceivably, the nitrogen in the crown ring significantly contributes to the Ag^+-binding in addition to the cation−π interaction with the aromatic rings and the electrostatic interaction with the crown oxygens.

Chemical Switching by Protonation and Deprotonation of the Crown Nitrogen. To protonate the nitrogen atom in the crown loop we used 600 mM of CF_3COOD (TFA-*d*). The ^1H NMR signals in the absence and the presence of Ag^+ were assigned using 2D COSY and NOE methods. The peaks assignable to protonated **1** (**1**H^+) did not appear separately from those of free **1** even at −85 °C. To confirm that **1** (5.00 mM) is fully converted to **1**H^+, the ^1H NMR spectra were measured as a function of the TFA-*d* concentration. The δ_{m-H} (7.10 ppm in CD_2Cl_2:CD_3OD = 4:1 v/v at 30 °C in the absence of TFA-*d*), used as a marker peak, shifted to lower magnetic field with increasing TFA-*d* concentration and was saturated at 7.16 ppm above [TFA-*d*]/[**1**] = 20. One may thus regard that the ^1H NMR spectrum measured in the presence of TFA-*d* (600 mM) is entirely attributable to **1**H^+. The difference in the chemical shift between **1** and **1**H^+ is shown in Figure 6A. It is seen from Figure 6A that the methylene protons adjacent to the NH^+ are shifted to lower magnetic field (by 0.42−0.45 ppm); whereas the other protons are shifted by a smaller amount.

When TFA-*d* was added to **1** in the presence of CF_3SO_3Ag, the largest downfield shift was observed for *meta*-

(34) In compound **1**, the metal cation included in the crown cap can leak out directly as an intermolecular path. The ^1H NMR spectral data indicate, however, that this path occurs incomparably more slowly than the intramolecular metal-tunneling path. One can consider, therefore, that upon protonation of the ring nitrogen the metal cation moves to the another side *predominantly* via the calix[4]arene tube.

(35) Takeda, Y.; Yano, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1720.
(36) Shinkai, S.; Inuzuka, K.; Miyazaki, O.; Manabe, O. *J. Am. Chem. Soc.* **1985**, *107*, 3950.
(37) Shinkai, S.; Araki, K.; Manabe, O. *J. Am. Chem. Soc.* **1988**, *110*, 7214.

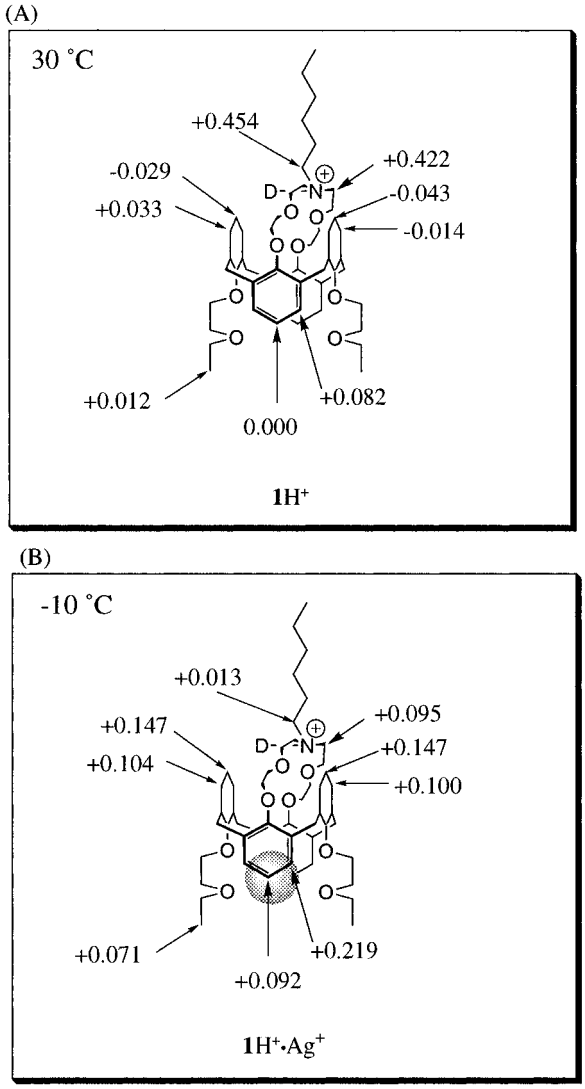


Figure 6. (A) Assignment of chemical shifts for selected protons in $\mathbf{1}H^+$ and changes from those in **1**:30 °C, [**1**] = 5.00 mM, [TFA-*d*] = 600 mM, CD_2Cl_2:CD_3OD = 4:1 v/v. (B) Changes in the ^1H NMR chemical shift of $\mathbf{1}H^+$ induced by added Ag^+ ([CF_3SO_3Ag] = 10.0 mM): the measurement conditions are the same as A. A plus sign (+) denotes a shift to lower magnetic field, whereas a minus sign (−) denotes a shift to higher magnetic field.

protons in the bis(ethoxyethoxy) side (Figure 6B). Although the chemical shifts for those protons in the crown-capped side also move to lower magnetic field, the magnitude is much smaller than that induced by the Ag^+-binding to **1** (compare with those in Figure 4B). Thus, these small chemical shift changes can be reasonably explained by the inductive effect caused by the Ag^+-binding to the opposite bis(ethoxyethoxy) side.[25] These findings support the view that Ag^+ is now trapped by the bis(ethoxyethoxy) side. At [CF_3SO_3Ag]/[$\mathbf{1}H^+$] = 0.50 the measurement temperature to −85 °C. Although the peaks gradually broadened with lower temperature, no peak splitting between $\mathbf{1}H^+$ and $\mathbf{1}H^+$·Ag^+ was observed. One can thus consider that the intermolecular metal exchange with the bis(ethoxyethoxy) side in $\mathbf{1}H^+$ is much faster than that with the crown-capped side in **1**. Figure 7 shows a plot of $\Delta\delta_{m-H}$ (averaged chemical shift change in *meta*-protons in the bis(ethoxyethoxy) side against CF_3SO_3Ag concentration). From this plot the $K_{ass.}$ was

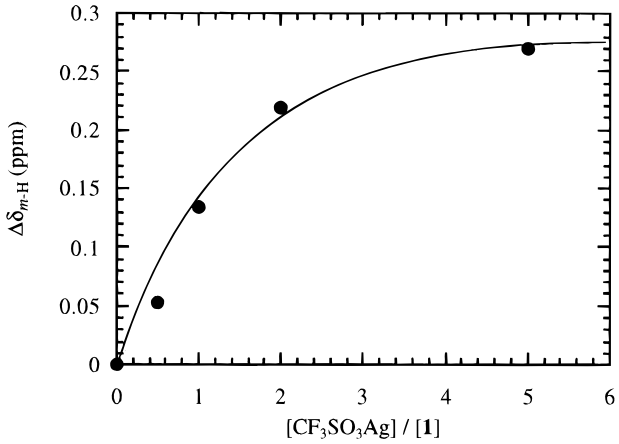


Figure 7. Chemical shift change in δ_{m-H} of $\mathbf{1}H^+$ induced by added CF_3SO_3Ag: 30 °C, [**1**] = 5.00 mM, [TAF-*d*] = 600 mM, CD_2Cl_2:CD_3OD = 4:1 v/v.

estimated to be 220 M^{-1}: a value smaller by 2.7 × 10^7-fold than that for the crown-capped side of **1**.

On the basis of the above results, it is proposed that Ag^+ bound to the crown-capped side in **1** is pushed out to the opposite bis(ethoxyethoxy) side through a π-basic 1,3-alternate calix[4]arene tube only when the nitrogen atom in the crown ring is protonated. In order to move Ag^+ to the crown-capped side again, one must deprotonate $\mathbf{1}H^+$ to **1**. To remove excess TFA-*d*, we first treated the solution with solid Li_2CO_3 (in a separate study, it was confirmed that Li_2CO_3 is scarcely soluble in a mixed solvent of CD_2Cl_2:CD_3OD = 4:1 v/v and Li^+ is not bound to **1**). By this treatment one can remove TFA-*d* without polluting the reaction system. After removing precipitated CF_3COOLi and unreacted Li_2CO_3 by filtration, we added diazabicycloundecene (DBU, 1.0 equiv to $\mathbf{1}H^+$) and measured the ^1H NMR spectrum at various temperatures (between −85 and 30 °C). Except several peaks assignable to protonated DBU, the resultant ^1H NMR spectrum totally coincided with the initial spectrum containing **1** and CF_3SO_3Ag. The finding allows us to conclude that Ag^+ has shifted from the bis(ethoxyethoxy) side to the opposite crown-capped side through a π-basic 1,3-alternate calix[4]arene tube. These reversible metal-tunneling processes can be illustrated as in Figure 8.

Conclusion

The design of a "molecular syringe" mimic reported herein was modeled by combining the idea of using a chemically-switchable molecular shuttle[30] with our previous finding that certain metal cations can enjoy the intramolecular tunneling through the π-basic 1,3-alternate calix[4]arene cavity.[25] We considered that if one could fix a switch-functionalized, strong metal-binding site to one calix[4]arene edge and a relatively weak metal-binding site to another edge, the resultant molecular architecture should behave like a "syringe" for metal cations. In this article, the molecular design has been realized using a chemically-switchable nitrogen-containing crown ring for one side and a bis(ethoxyethoxy) group for the other side. Syringelike, ion-pumping processes have been fully characterized by ^1H NMR spectroscopy. The residual problem is to suppress the intermolecular path (direct Ag^+-leakage from the azacrown cap). We believe that the novel findings reported herein are particularly useful in helping to understand many dy-

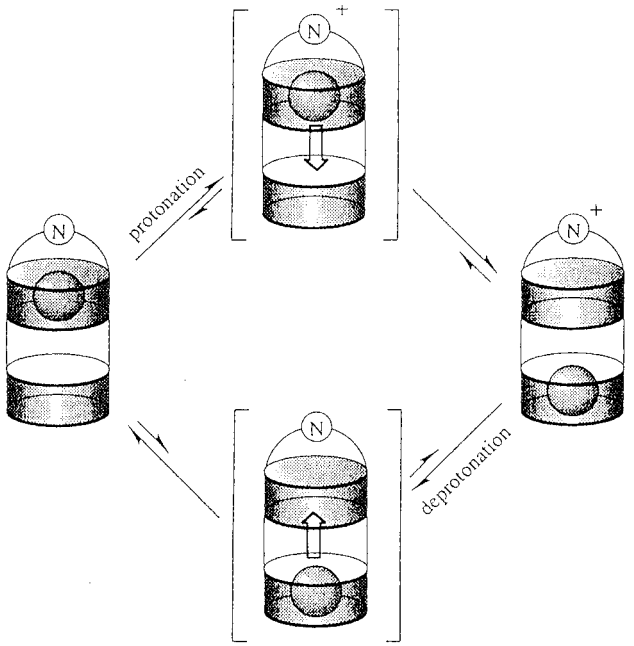


Figure 8. Schematic representation of a reversible metal pumping in a microscopic "molecular syringe" **1** designed from 1,3-alternate calix[4]arene.

namic metal transport systems such as metal transport across ion channels, metal deposition on the molecular assembly surfaces, and metal cation scavenging in solution.

Experimental Section

Materials. Compound **1** was synthesized from calix[4]-arene-25,26,27,28-tetraol according to Scheme 1.

25,27-Bis(ethoxyethoxy)-26,28-dihydroxycalix[4]-arene (2). This compound was synthesized from calix[4]-arene-25,26,27,28-tetraol by the reaction with 2-bromoethyl ethyl ether in the presence of BaO and $Ba(OH)_2$ in DMF in a manner similar to that used for the synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-bis(ethoxyethoxy)-26,28-dihydroxycalix-[4]arene:[38] yield 52%; mp 160.0−161.0 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ 1.28 (t (7.0 Hz), 6H,CH_3), 3.34 (d (13 Hz), 4H, $ArCH_2Ar$), 3.70 (q (7.0 Hz), 4H, $CH_2(CH_3)$), 3.94 (t (4.8 Hz), 4H, CH_2O), 4.18 (t (4.8 Hz), 4H, $ArOCH_2$), 4.40 (d (13 Hz), 4H, $ArCH_2Ar$), 6.62 and 6.76 (t each (7.5 Hz each), 2H each, ArH), 6.88 and 7.04 (d each (7.5 Hz each), 4H each, ArH), 7.83 (s, 2H, ArOH). Anal. Calcd for $C_{36}H_{40}O_6$: C, 76.06; H, 7.04. Found: C, 75.93; H, 7.14.

25,27-Bis(ethoxyethoxy)-26,28-bis[(chloroethoxy)-ethoxy]calix[4]arene (1,3-alternate 3). Compound **2** (3.00 g, 5.37 mmol) and Cs_2CO_3 (28.0 g, 86.0 mmol) were mixed in dehydrated acetone (600 mL), and the mixture was stirred under reflux for 30 min. Then, 1-chloro-5-tosyl-3-oxapentane (15.7 g, 53.7 mmol) was added, and the resultant mixture was stirred under reflux for 4 days. These operations were all carried out under a nitrogen atmosphere. The reaction mixture was filtered, the filtrate being concentrated in vacuo to dryness. The residue was extracted with a mixture of aqueous 1 M HCl solution (50 mL) and chloroform (100 mL). The chloroform layer was separated, washed three times with water, and dried over $MgSO_4$. The solution was evaporated to dryness, the residue being recrystallized from chloroform−hexane: yield 57%; mp 150.0−151.2 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ 1.29 (t (7.5 Hz), 6H, CH_3), 3.56−3.83 (m, 36H, $CH_2(CH_3)$, CH_2O (bis(ethoxyethoxy) side), $ArOCH_2$ (bis(ethoxyethoxy) side), $ArCH_2Ar$, $ArOCH_2$ (bis(chloroethoxyethoxy) side), CH_2O (bis(chloroethoxyethoxy) side), $CH_2(CH_2Cl)$, and $(CH_2)CH_2Cl$), 6.64−6.71 (m, 4H, ArH), 7.05−7.11 (m, 8H, ArH). Since the ^{1}H NMR spectrum could be satisfactorily assigned to the structure of 1,3-alternate **3**, the product was used for the next reaction without further purification.

Compound 1. 1,3-Alternate **3** (0.50 g, 0.640 mmol), hexylamine (0.21 mL, 1.60 mmol), Na_2CO_3 (1.4 g, 12.8 mmol), and NaI (1.8 g, 12.8 mmol) were mixed in diethyl ketone (200 mL). The mixture was refluxed for 5 days. After filtration the filtrate was evaporated to dryness. The residue was extracted with a mixture of water (50 mL) and dichloromethane (100 mL). The organic layer was separated, washed three times with water, and dried over $MgSO_4$. After evaporation to dryness, the residue was purified by column chromatography (silica gel, ethyl acetate:hexane = 1:1 v/v): yield 39%; mp 95.4−96.4 °C; mass (positive SIMS, *m*-nitrobenzyl alcohol) *m*/*z* 810 (M^+); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ 0.91 (t (6.3 Hz), 3H, $CH_3((CH_2)_5)$), 1.19−1.48 (m, 14H, $(OCH_2)CH_3$ and $(CH_3)CH_2$-$CH_2CH_2CH_2(CH_2)N$), 2.46 (t (7.5 Hz), 2H, $(CH_3(CH_2)_4)CH_2N$), 2.60 (t (5.6 Hz), 4H, $O(CH_2)CH_2N$), 3.10 (t (6.4 Hz), 4H, $OCH_2(CH_2)N$), 3.31−3.81 (m, 20H, $OCH_2(CH_3)$ and $ArOCH_2$-CH_2O), 3.81 (brs, 8H, $ArCH_2Ar$), 6.81, and 6.87 (t each, 2H each, ArH), 7.08−7.11 (m, 8H, ArH). Anal. Calcd for $C_{50}H_{67}$-NO_8·0.4 CH_2Cl_2: C, 71.72; H, 8.10; N, 1.66. Found: C, 71.53; H. 8.09; N, 1.72. The peak for 0.4 equiv of CH_2Cl_2 was detected in ^{1}H NMR spectroscopy.

^{1}H NMR Spectra of 1·Ag^+ and 1H$^+$·Ag^+ Complexes. Using 2D COSY and NOE methods, the ^{1}H NMR signals for the **1**·Ag^+ complex ([**1**] = 5.00 mM, $[CF_3SO_3Ag]$ = 10.0 mM) were assigned as follows (400 MHz, CD_2Cl_2:CD_3OD = 4:1 v/v, −50 °C) δ 0.92−0.98 (m, 3H, $CH_3((CH_2)_5)$), 1.23−1.50 (m, 14H, $(OCH_2)CH_3$ and $(CH_3)CH_2CH_2CH_2CH_2(CH_2)N$), 3.05−3.17 (m, 6H, $(CH_3(CH_2)_4)CH_2N$ and $O(CH_2)CH_2N$), 3.65−3.85 (m, 16H, $OCH_2(CH_2)N$, $OCH_2(CH_3)$, and $ArOCH_2CH_2O$), 4.00 (brs, 8H, $ArCH_2Ar$), 4.27−4.62 (m, 4H, $ArOCH_2CH_2O$), 6.77 (m, 1H, ArH (crown-capped side)), 6.76−6.94 (m, 3H, ArH (crown-capped side and bis(ethoxyethoxy) side)), 7.19−7.24 (m, 4H, ArH (bis-(ethoxyethoxy) side)), 7.39 (d, 2H, ArH (crown-capped side)), 7.52 (d, 2H, ArH (crown-capped side)). The results support the view that Ag^+ is bound to the crown-capped side of **1**.

Next, we confirmed that **1** is entirely converted to **1**H$^+$ in the presence of 600 mM of TFA-*d*: ^{1}H NMR (400 MHz, CD_2-Cl_2:CD_3OD = 4:1 v/v, −10 °C) δ 0.95−1.00 (m, 3H, CH_3-$((CH_2)_5)$), 1.24−1.50 (m, 14H, $(OCH_2)CH_3$ and $(CH_3)CH_2CH_2$-$CH_2CH_2(CH_2)N$), 2.89−2.95 (m, 2H, $(CH_3(CH_2)_4)CH_2N$), 3.02−4.11 (m, 36H, $O(CH_2)CH_2N$, $OCH_2(CH_2)N$, $OCH_2(CH_3)$, $ArOCH_2CH_2O$ (crown-capped side), $ArOCH_2CH_2O$ (bis(ethoxy-ethoxy) side), and $ArCH_2Ar$), 6.75−6.77 (m, 2H, ArH (crown-capped side)), 6.91 (t (7.5 Hz), 2H, ArH (bis(ethoxyethoxy) side)), 7.07 and 7.15 (d each (7.3 Hz each), 2H each, ArH (crown-capped side)), 7.16−7.18 (m, 4H, ArH (bis(ethoxy-ethoxy) side)). The results support the view that the nitrogen in the crown loop is fully protonated.

According to the similar method, ^{1}H NMR signals for the **1**H$^+$·Ag^+ complex ([**1**] = 5.00 mM, $[CF_3SO_3Ag]$ = 10.0 mM, [TFA-*d*] = 600 mM) were assigned as follows (400 MHz, CD_2-Cl_2:CD_3OD = 4:1 v/v, −10 °C) δ 0.97 (m, 3H, $CH_3((CH_2)_5)$), 1.33−1.51 (m, 14H, $(OCH_2)CH_3$ and $(CH_3)CH_2CH_2CH_2CH_2$-$(CH_2)N$), 2.93−2.95 (m, 2H, $(CH_3(CH_2)_4)CH_2N$), 3.16−4.19 (m, 36H, $O(CH_2)CH_2N$, $OCH_2(CH_2N)$, $OCH_2(CH_3)$, $ArOCH_2CH_2O$ (crown-capped side), $ArOCH_2CH_2O$ (bis(ethoxyethoxy) side), and $ArCH_2Ar$), 6.90−6.92 (m, 2H, ArH (crown-capped side)), 7.05 (t (15 Hz), 2H, ArH (bis(ethoxyethoxy) side)), 7.17 and 7.25 (d each (7.6 Hz each), 2H each, ArH (crown-capped side)), 7.40−7.42 (m, 4H, ArH (bis(ethoxyethoxy) side)). The results support the view that Ag^+ is bound to the bis(ethoxyethoxy) side of **1**H$^+$.

Actions of a "Molecular Syringe" in Response to Protonation and Deprotonation. To protonate the **1**·Ag^+ complex we added TFA-*d* (600 mM) to a CD_2Cl_2:CD_3OD = 4:1 v/v solution containing **1** (5.00 mM) and CF_3SO_3Ag (10.0 mM). The ratio of TFA-*d* vs **1** was the same as that used in ref 30. The ^{1}H NMR spectrum (vide supra) showed that Ag^+ has shifted from the crown-capped side to the bis(ethoxyethoxy) side.

(38) (a) Deng, G.; Sakaki, T.; Nakashima, K.; Shinkai, S. *Chem. Lett.* **1992**, 1287. (b) Deng, G.; Sakaki, T.; Shinkai, S. *J. Polym. Sci., Polym. Chem.* **1993**, *31*, 1915.

To restore Ag^+ back to the crown-capped side one must neutralize TFA-*d*. To avoid pollution of the reaction system, we first treated the solution with Li_2CO_3 which is insoluble in this solution but can neutralize TFA-*d*. Separately, we also confirmed that Li^+ does not interact with **1** by solid (Li_2CO_3)−liquid (CD_2Cl_2:CD_3OD = 4:1 v/v containing **1**) extraction. To a solution (CD_2Cl_2:CD_3OD = 4:1 v/v) containing **1** (5.00 mM), CF_3SO_3Ag (10.0 mM), and TFA-*d* (600 mM) was added Li_2CO_3 (2.0 equiv to TFA-*d*), and the mixture was stirred at 0 °C for 60 min. The precipitate (CF_3COOLi and unreacted Li_2CO_3) was removed by filtration. TFA-*d* could be removed from the solution by this treatment (confirmed by GLC), but the resultant ^1H NMR spectrum showed that the nitrogen in the crown loop is still protonated. Here, we added DBU (1.0 equiv to **1**H^+). The ^1H NMR spectrum showed that it has been deprotonated and Ag^+ has shifted back to the crown-capped side.

Miscellaneous. The routine ^1H NMR measurements were carried out with Bruker AC-250P (250 MHz). On the other hand, the specific ^1H NMR measurements such as temperature-dependence, 2D-COSY, NOE, etc. were carried out with a JEOL GX-400 (400 MHz). The conductivity measurements were carried out in CH_2Cl_2:MeOH = 4:1 v/v at 30 °C with a TOA conductivity Meter, Model CM-20E. A Teflon flask was used for this purpose to avoid the leakage of Na^+ from the glassware wall. The concentration of CF_3SO_3Ag (1.00×10^{-7} mM) was kept constant while that of **1** was varied at ($0.25-4.00$) $\times 10^{-7}$ mM.

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