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Neutralization of a *sec*-Ammonium Group Unusually Stabilized by the "Rotaxane Effect": Synthesis, Structure, and Dynamic Nature of a "Free" *sec*-Amine/Crown Ether-Type Rotaxane

Kazuko Nakazono and Toshikazu Takata*[a]

Abstract: A fifteen-year riddle has been settled: neutralization, the most popular chemical event, of a crown ether/*sec*-ammonium salt-type rotaxane has been achieved and a completely nonionic crown ether/*sec*-amine-type rotaxane isolated. A [2]rotaxane was prepared as a typical substrate from a mixture of dibenzo[24]crown-8 ether (DB24C8) and *sec*-ammonium hexafluorophosphate (PF_6) with a terminal hydroxy group through end-capping with 3,5-dimethylbenzoic anhydride in the presence of tributylphosphane as a catalyst in 90% yield. A couple of approaches to the neutralization of the ammonium rotaxane were investigated to isolate the free *sec*-amine-type rotaxane by decreasing the degree of thermodynamic and kinetic stabilities. One approach was the counteranion-exchange method in which the soft counterion PF_6^- was replaced with the fluoride anion by mixing with tetrabutylammonium fluoride, thus decreasing the cationic character of the ammonium moiety. Subsequent simple washing with a base allowed us to isolate the free *sec*-amine-type rotaxane in a quantitative yield. The other approach was a synthesis based on a protection/deprotection protocol. The acylation of the *sec*-ammonium moiety with 2,2,2-trichloroethyl chloroformate gave an *N*-carbamated rotaxane that could be deprotected by treating with zinc in acetic acid to afford the corresponding free *sec*-amine-type rotaxane in a quantitative yield. The structure of the free *sec*-amine-type rotaxane was fully confirmed by spectral and analytical data. The generality of the counteranion-exchange method was also confirmed through the neutralization of a bisammonium-type [3]rotaxane. The mechanism was studied from the proposed potential-energy diagram of the rotaxanes with special emphasis on the role of the PF_6^- counterion.

Keywords: crown compounds · kinetics · neutralization · rotaxanes · supramolecular chemistry

Introduction

Neutralization is a very popular chemical event that occurs very quickly between an acid and a base. An ammonium salt, a complex derived from a pair that consists of a strong acid and an amine base, usually acts as a weak acid and is quickly neutralized with a base stronger than its conjugate base. However, it is possible to have an ammonium salt that is never converted into its neutralized form: *sec*-ammonium moieties that are placed in the cavities of crown ethers (especially 24-membered species; see **1**·PF_6; Scheme 1). It is well known that once such a *sec*-ammonium moiety becomes part of a rotaxane, the rotaxane no longer affords the corresponding neutralized *sec*-amine-type rotaxane by treatment with any base.[1] The large stabilization is a common effect in various rotaxane architectures.[2–4] However, the strong resistance of such rotaxanes to neutralization has long been troublesome, thus preventing the application of rotaxanes to functional devices and materials. Although low solubility due to their ionic structure makes the formation of higher-order rotaxanes difficult, strong intramolecular interactions effectively limit the circumrotational and translational mobility of their components, which are the most characteristic feature of the rotaxane structure. This problem is the largest to be solved in the study of crown ether-based rotaxanes, which are the most easily accessible rotaxanes.[5] Therefore, many scientists have long been eager to synthesize *sec*-amine-type nonionic rotaxanes from *sec*-ammonium salt-type rotaxanes, which are the most easily accessible. The unprecedented large stabilization of the *sec*-ammonium moiety when it is used as the axle component of the rotaxane structure might be called the rotaxane effect.

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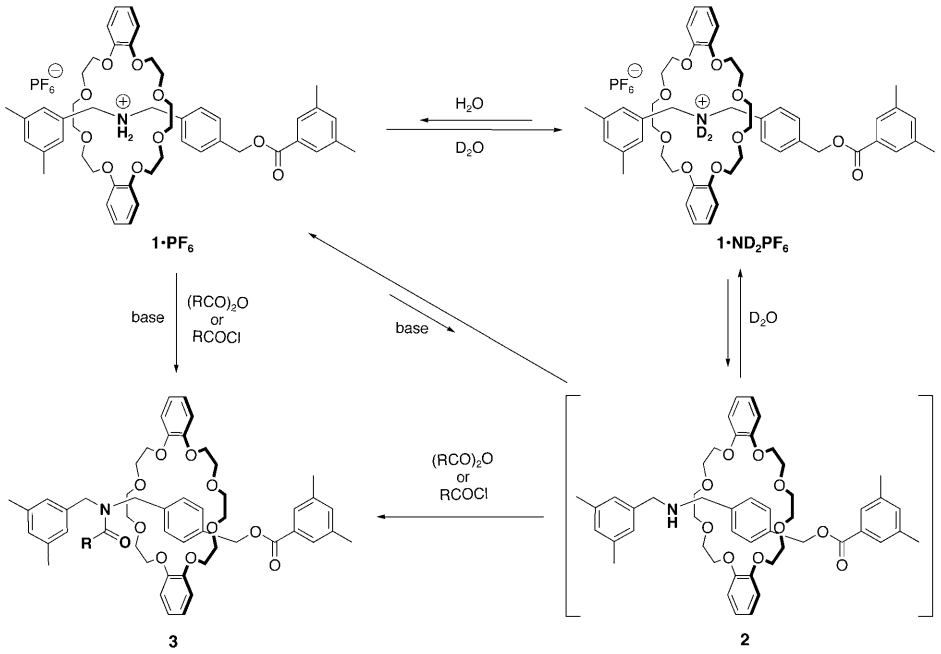


Scheme 1. The formation of a free *sec*-amine-type rotaxane as an intermediate in *N*-acylation and H/D exchange reactions of **1·PF$_6$**.

It is possible to obtain rotaxanes with neutral amine moieties from ammonium salt-type rotaxanes in some special cases. The first approach involves the introduction of a second cation station for the metastable state on the axle. When the axle component of a rotaxane can hold an additional cationic moiety other than the ammonium salt moiety, such as a bipyridinium group, treatment with an appropriate amine base can briefly neutralize the ammonium moiety to yield a rotaxane with a free amine moiety. By moving the crown ether wheel to the second cation station, the free ammonium salt that is not stabilized by the crown ether is readily neutralized, as reported by Stoddart and co-workers.[6] However, they also reported that a [2]rotaxane with two *sec*-ammonium centers could not deprotonate on one ammonium side, even when four equivalents of amine base were used.[7a] Leigh and Thomson also reported this behavior.[7b] Another approach involves a removable second cation station. Tokunaga et al. could neutralize the ammonium moiety by treatment with alkali metal cations capable of binding to the ligand moiety on the axle as a metastable state.[8,9] For a simple rotaxane without any additional cationic station, we reported that *N*-acylation of the ammonium moiety could yield a neutral rotaxane that possesses good component mobility,[10] although *N*-acylation was slow, even with the use of excess amine and electrophiles.[1,11] However, these successful neutralization reactions provided no essential progress toward the synthesis of *sec*-amine-type rotaxanes. Nonetheless, we must note the important fact that a free amine-type rotaxane must be formed as an intermediate during *N*-acylation. This approach seems to present a clear possibility for developing free amine-type rotaxanes.

In addition, we had already determined the kinetic acidity of a *sec*-ammonium salt-type rotaxane by means of an H/D exchange experiment.[1] The acidity of the ammonium salt-type rotaxane derived from the half-lifetime was certainly much lower than that of the corresponding ammonium salt without the rotaxane structure (i.e., the axle component) and lower than those of ethanol and pyrrole (pK_a = 15.9 and 17.5, respectively). The occurrence of a H/D exchange also reveals that a free amine-type rotaxane should be formed as an intermediate, similar to the case of *N*-acylation (Scheme 1). In general, the use of a stronger base with ammonium salts should give free amines, even though their acidity is very low. However, many rotaxane chemists have never succeeded in isolating free amine-type rotaxanes, even when using very strong bases, as far as we know.[1,7] Why can no one obtain free amine-type rotaxanes from ammonium salt-type rotaxanes? Herein, we present a general answer and propose a method by reporting the first successful synthesis of a free nonionic *sec*-amine-type rotaxane from the corresponding *sec*-ammonium-type rotaxane and describing the properties of the *sec*-amine-type rotaxane. In other words, this study refers to the special rotaxane effect in which a functional group placed on the axle component under the strong influence of the wheel component is unusually well protected by the wheel component in a thermodynamic fashion that depends on the mobility of the wheel component in a kinetic fashion. Therefore, this rotaxane effect may be called dynamic protection. The discovery of an efficient neutralization protocol will greatly expand the applicability of crown ether/*sec*-ammonium-type rotaxanes as the most easily available rotaxanes. This report answers a very difficult riddle that has been unsolved for 15 years since the first crown ether/*sec*-ammonium salt rotaxane was reported by Kolchinski et al.[12a] and Ashton et al.[12b]

Results and Discussion

Outline of the neutralization of a *sec*-ammonium salt-type rotaxane and a strategy for the isolation of *sec*-amine-type rotaxane: In addition to the above discussion, the following facts are also relevant: 1) A pseudorotaxane is never formed from a *sec*-ammonium axle with a chloride counteranion[13] and 2) the *tert*-ammonium salt-type rotaxane **4** is relatively easily neutralized by common bases.[14] The situation is com-

plicated because the complex interaction between the ammonium and crown ether moieties disappears when the wheel leaves the ammonium moiety. Namely, the thermodynamic property of the acidity of the ammonium moiety depends strongly on the kinetic property of the translation of the wheel; therefore, once the ammonium moiety is liberated from the protection of the crown ether wheel, it is no longer as special.[1,6–8,15]

The reason why a free *sec*-amine-type rotaxane has never been isolated despite the fact that it is known to form as an intermediate in *N*-acylation and H/D exchange reactions is clearly because the *sec*-ammonium salt-type rotaxane is much more stable than the corresponding free *sec*-amine-type rotaxane, although this is not a typical relationship. The degree of stabilization is remarkably large in the case of **1·PF$_6$** (Scheme 1), enough to make the isolation of **2** impossible. The relative stability of each substance proposed in the present discussion can be summarized in the potential-energy diagram in Figure 1.

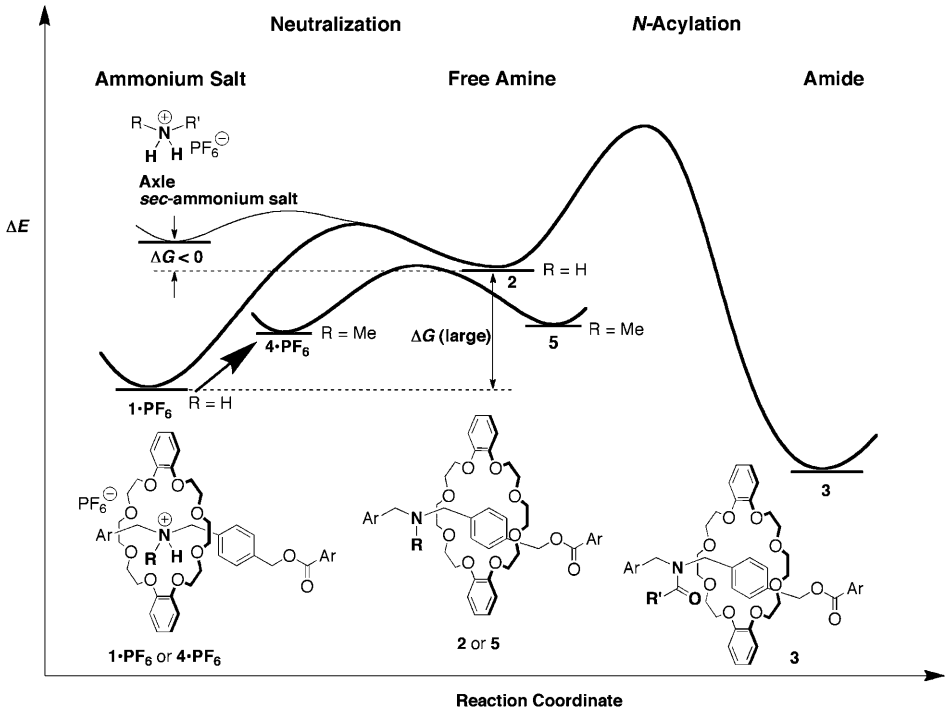


Figure 1. Potential energy diagram of various rotaxane derivatives including **1·PF$_6$** (Scheme 1). Stability of *N*-modified forms of each rotaxane system (R = H, Me) can be qualitatively compared.

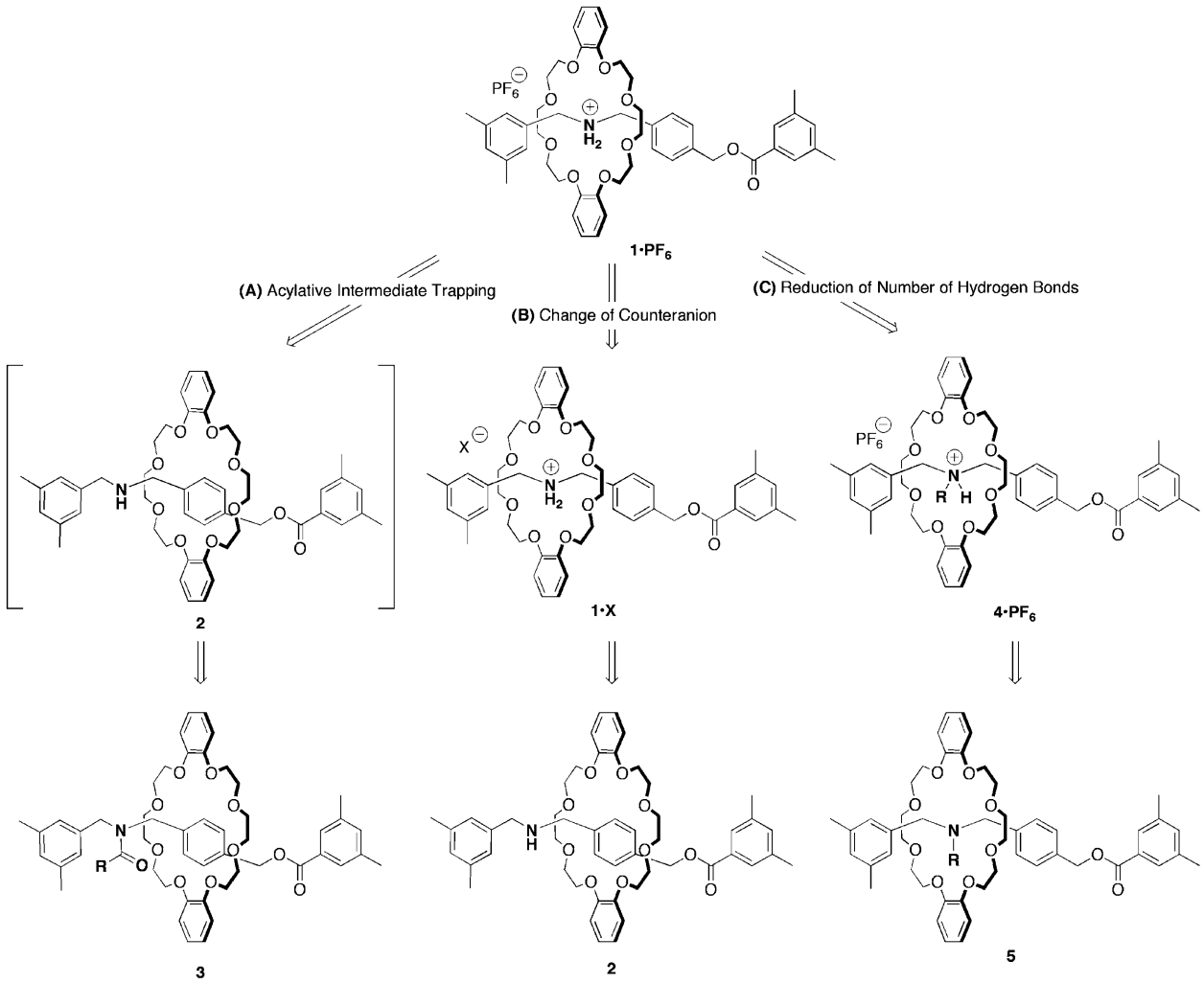
As indicated in Figure 1, the *sec*-ammonium PF_6 salt-type rotaxane **1·PF$_6$** is stabilized to a similar extent as the *N*-acylated rotaxane **3** and much more than the free *sec*-amine rotaxane **2**. The stability of **1·PF$_6$** is also confirmed by the fact that pseudorotaxanes with a *sec*-ammonium axle without end-cap moieties can sometimes be isolated as stable compounds.[16] Thus, a *sec*-ammonium compound incorporated into the crown ether cavity can form an unusually stable complex. It can be concluded that the acidity of the ammonium group of **1·PF$_6$** is unusually lowered, much more than that of a general *sec*-ammonium salt, probably due to highly effective cation charge delocalization through hydrogen bonding by rotaxane complexation. However, we believe an additional effect that lowers the acidity may exist because the degree of decrease in acidity and stabilization of **1·PF$_6$** are unexpectedly large. This effect is a result of kinetic protection against proton abstraction from the ammonium moiety by the crown ether wheel, which acts as a surrounding "bulky" group that suppresses neutralization by a base.[17] In the neutralization of ammonium salts in organic solvents, it seems most likely that neutralization occurs through initial ammonium proton abstraction by a basic nucleophile present in the system, but not through direct dissociation to a proton and free amine, especially in the present system.

From the results and discussion above, we have concluded that the free *sec*-amine-type rotaxane must be isolated from the *sec*-ammonium salt-type rotaxane if the remarkably strong hydrogen bonding between the ammonium moiety on the axle and the crown ether wheel is sufficiently weakened. The decrease in strength of hydrogen bonding can be accomplished by 1) decreasing the number of hydrogen bonds and 2) decreasing the cationic character of the nitrogen atom. That is, both protocols promote the transfer of the crown ether wheel from the ammonium moiety to elsewhere on the axle, thus making neutralization easy.

As a result, we can list the possible synthetic protocols to form neutral rotaxanes, which contain the following three approaches (summarized in Scheme 2):

A) neutralization through *N*-acylation of an intermediary free *sec*-amine-type rotaxane formed in situ under basic conditions;
B) neutralization by decreasing the cationic character of the ammonium moiety by counteranion exchange;
C) neutralization through weakened hydrogen-bonding interactions by decreasing the number of hydrogen atoms capable of participating in bonding.

We have already successfully implemented approach A in Scheme 2 in the selective *N*-acylation of **1·PF$_6$** in the presence of excess electrophile and base to **3**.[1,11] This approach consists of trapping a very small amount of "unstable" intermediate **2** formed in equilibrium with **1·PF$_6$** with an electrophile. We have also recently succeeded in obtaining a free



Scheme 2. Possible synthetic protocols to form neutral rotaxanes.

tert-amine-type rotaxane by decreasing the number of hydrogen bonds from two to one.[14] Specifically, *N*-methylation of **1·PF$_6$** yielded the *tert*-ammonium salt-type rotaxane **4·PF$_6$** (R = H), which turned out to be easily neutralizable to the *tert*-amine-type rotaxane **5** (R = H) by treatment with a typical amine base (approach C in Scheme 2). The weakened hydrogen bonding in **4·PF$_6$** was confirmed by the fact that a much less appreciable amount of the inclusion complex (pseudorotaxane) was formed between the *tert*-ammonium salt axle and dibenzo[24]crown-8 ether (DB24C8).[14] The activation energy from the *N*-methylated *tert*-ammonium PF_6-type rotaxane **4·PF$_6$** to free *tert*-amine-type rotaxane **5** should be much smaller than that from **1·PF$_6$** to **2**, as judged from its ease of neutralization (Figure 1). The small activation energy is supported by the fact that reversible acidification/neutralization of **5** has been attained.[14]

Although the isolation of the genuinely free amine-type rotaxane **2** remained a major target, the neutralization successfully proceeded to give **2** in a quantitative yield through approach B by decreasing the cationic character of the *sec*-ammonium group (described later in detail).

Synthesis of *sec*-amine-type rotaxane 2 by neutralization through counteranion exchange: As mentioned above, the difficulty of neutralization, that is, the unusual stabilization of **1·PF$_6$**, should come from not only delocalization of the cationic charge through hydrogen bonding, but also the steric-protection effect of the crown ether wheel against proton abstraction in an organic solvent. The former is thermodynamic stabilization, whereas the latter is kinetic stabilization. This type of kinetic stabilization may be due to the exceptionally specific circumstances seen in interlocked systems, such as rotaxanes. We previously reported that *N*-acylation with a bulky electrophile causes wheel migration to the less-crowded side of the axle in the resulting rotaxane.[1,11] This behavior indicates that the acylating agent attacks exclusively from the more-crowded side.[15d] By considering the possibility of ammonium proton abstraction with a base in **1·PF$_6$**, basic species must slowly attack the proton on the lower charged cation, probably from the more-crowded side, to move the wheel to the less-crowded side. Therefore, the attack should take place more slowly than reverse protonation of the free *sec*-amine-type rotaxane product **2**. Thus,

we first examined neutralization by using a small nucleophilic base to cause the crown ether wheel to migrate from the ammonium salt center. An attempted neutralization with a hydride ion as the smallest nucleophilic base, namely, the treatment of **1·PF$_6$** with $NaBH_3CN$ or $NaBH(OAc)_3$, yielded no corresponding neutralized *sec*-amine-type rotaxane **2**, only **1·PF$_6$**. The hydride donor did not work adequately as a scavenger of HPF_6, nor could it remove the PF_6^- ion, with original as discussed later.

From the unsuccessful results with the hydride donor, we turned our attention to anion exchange for the successful removal of the PF_6^- ion from the reaction system. A small, hard anion was selected as a new partner counteranion for **1·PF$_6$**, which would be capable of forming a hydrogen bond with the ammonium moiety instead of the crown ether wheel, because it is known that small, hard anions can directly connect to the ammonium group through hydrogen bonding.[13] If the introduction of a small, hard counteranion removes the strong interaction between the crown ether and the ammonium group to eject the crown ether wheel to elsewhere on the axle, the resulting ammonium salt should become an ordinary acid that is weak enough to be neutralized with typical bases. The degree of dissociation equilibrium of an anion/ammonium complex can be explained by the HSAB rule: the harder the anion is, the more strongly it interacts with ammonium hydrogen atoms. Thus, anion exchange seems to be an effective way to decrease the kinetic acidity of the ammonium salt.

The anion-exchange experiment was carried out by mixing **1·PF$_6$** with one of several salts with small anions at room temperature in an organic solvent followed by washing the resulting mixture with saturated sodium hydrogen carbonate for neutralization (Scheme 3 and Table 1). Table 1 shows that potassium and cesium fluoride salts were ineffective (Table 1, entries 1 and 2), whereas tetrabutylammonium fluoride (TBAF) resulted in complete neutralization to free *sec*-amine-type rotaxane **2** (100% conversion; Table 1, entry 3). The spectral change on the addition of TBAF to a solution of **1·PF$_6$** in $CHCl_3$ at room temperature was monitored and clearly suggested the formation of the ammonium fluoride-type rotaxane **1·F** by the emergence of new signals that were different from those of **1·PF$_6$**, which agreed well with the structure of **2**. The conversion of the anion exchange from **1·PF$_6$** into **1·F** was 100% with the use of TBAF, in good accordance with our expectations, whereas it clearly depended on the kind of halide counteranion used, which is consistent with the HSAB theory. Namely, the conversion yield decreased proportionally on the order of ion size (i.e., $100 > 80 > 44\%$ for $F > Cl > Br$, respectively), which was determined from the signals observed by ^{1}H NMR spectroscopic analysis and that were assigned to the oxybenzylic proton signal h at $\delta = 5$–6 ppm.

Table 1. One-pot neutralization of *sec*-ammonium rotaxane **1·PF$_6$** with various salts.[a]

Entry	Anion-exchanging agent (equiv to rotaxane)	Conditions		Conversion yield[b] [%]
1	KF (50)	THF/H_2O (5/1)	70 °C	0
2	CsF (2.4)	DMF	RT	0
3	TBAF (1.2)	THF	RT	100
4	TBACl (1.2)	THF	RT	80
5	TBABr (1.2)	THF	RT	44
6[c]	TBAF (3.0)	THF	RT	97[d]
7	TBAOH (2.0)	10% H_2O/[D_6]DMSO	RT	–[e]

[a] Each anion exchange agent (or its solution) was added to the *sec*-ammonium PF_6 salt-type rotaxane **1·PF$_6$** (50 μmol) dissolved in 0.5 mL of solvent. Each mixture was then washed well with aqueous Na_2CO_3. [b] The conversion ratio was determined by ^{1}H NMR spectroscopic analysis. [c] The *sec*-ammonium fluoride-type rotaxane **1·F** that formed was isolated by directly pouring the reaction mixture into diethyl ether (97% yield). [d] Yield of the isolated product. [e] Starting material **1·PF$_6$** was gradually decomposed. Free crown ether was confirmed by the ^{1}H NMR spectrum.

1·PF$_6$ **2**

Scheme 3. Neutralization through counteranion exchange.

However, we could not isolate **2** from the reaction mixture by typical isolation procedures, such as chromatographic purification and recrystallization, even though the counteranion exchange of **1·PF$_6$** followed by neutralization of **1·F** was successfully achieved, as seen by ^{1}H NMR spectroscopy (see above). The final product obtained in hand was always **1·PF$_6$**. We eventually concluded that the present phenomenon must result from the much higher stability of **1·PF$_6$** relative to **2** or **1·F**. Therefore, we examined the isolation of **2** after the complete removal of PF_6^- ions in the form of $TBAPF_6$. When a reaction mixture that contains the products **1·F** and $TBAPF_6$ along with excess TBAF was poured directly into a large quantity of diethyl ether, rotaxane **2** could be isolated in 97% yield as the sole soluble substance. As an alternative method, initial filtration of the reaction mixture with celite followed by washing with aqueous Na_2CO_3 was also effective enough to give pure **2** in 97% yield.

The structure of **2** was determined by ^{1}H NMR and IR spectroscopy and a titration experiment (the details are given later). In relation to the ^{1}H NMR spectra of **1·PF$_6$** and **2**, the disappearance of the broad signal assigned to the NH_2

group and large upfield shift of the N–CH_2 signals due to deprotonation of the ammonium salt moiety were confirmed. Other signals were easily assigned to those expected for **2**, which were comparable with those of the *tert*-amine-type rotaxane **5**. Furthermore, the typical absorptions of the P–F bond at $\tilde{\nu}=841$ and 557 cm^{-1} completely disappeared in the IR spectrum. Finally, rotaxane **2** was treated with HPF_6, and the resulting product showed a ^1H NMR spectrum fully coincident with that of **1**·PF_6.

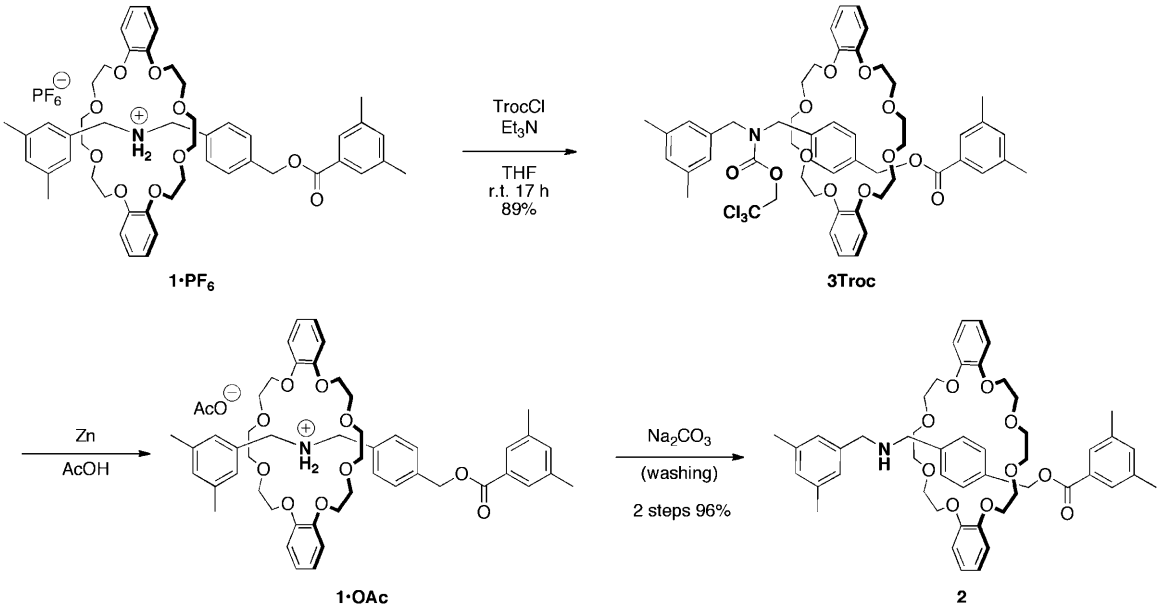
To rule out the possibility of direct neutralization with TBAOH formed in situ as the decomposition product of TBAF, **1**·PF_6 was treated with an equimolar amount of TBAOH (0.4 M in HO) in ([D_6]DMSO) at ambient temperature. An ^1H NMR spectrum of the reaction mixture after 10 minutes indicated the formation of not only the *sec*-amine-type rotaxane **2** but also free DB24C8 as a decomposition product of **1·PF$_6$**. Further addition of TBAOH induced a significant increase in the ratio of free DB24C8, thus indicating competitive decomposition of the axle moiety of **1·PF$_6$**, possibly through hydrolysis. This result, along with the quantitative formation of **2** by the use of TBAF, rules out the participation of TBAOH.

The transformation of **1·PF$_6$** into **2** or the isolation of **2**, which has been long believed to be impossible, was first accomplished in this study by changing the counteranion of the ammonium salt unusually stabilized by the crown ether wheel to the common ammonium salt uncovered by the crown ether wheel. This exchange was carried out by an initial counteranion exchange with fluoride anions followed by neutralization with a typical alkali and skillful removal of the PF_6^- ions.

Synthesis of 2 through a protection/deprotection protocol: The above-mentioned synthesis of **2** requires the complete removal of PF_6^- ions from the system due to the fast reverse conversion of **2** into **1·PF$_6$** owing to its extraordinary stability. The most effective and easy method for removing PF_6^- ions should be the acylation of **1·PF$_6$** (Scheme 2) because of the high stability of product **3**, as discussed previously (Figure 1). Therefore, we adopted the synthesis of **2** based on the carbamate protection/deprotection protocol as an alternative. Roxtane **1·PF$_6$** was transformed into *N*-trichloroethylcarbamoyl derivative **3**Troc in 89% yield by treatment with 2,2,2-trichloroethyl chloroformate (TrocCl) and triethylamine in THF at room temperature (the protection step; Scheme 4).[15d] Derivative **3Troc** was deprotected with active zinc in acetic acid to give *sec*-ammonium acetate **1·OAc**, which was washed with aqueous Na_2CO_3 to afford **2** in 96% overall yield, similar to that of the anion-exchange method mentioned above. The present synthetic method for the neutral rotaxane might be useful in various systems because neutral intermediate rotaxanes can be isolated.

The structures of the intermediate rotaxanes **3Troc** and **1·OAc** were determined from various spectroscopic analyses. Figure 2 shows the NMR spectra of four rotaxanes related to the *sec*-amine-type rotaxane **2** in Scheme 4. The top spectrum of **2** agreed well with the spectrum of **2** obtained from counteranion exchange as described above. Spectra (b) and (c) in Figure 2 correspond to the precursors **1·OAc** and **3Troc**, respectively, and are reasonably assignable. In particular, **1·OAc** was almost the same as **1·PF$_6$**, although **1·OAc** can be deprotonated by Na_2CO_3. This difference is invisible in the spectra. However, a large difference in the intramolecular dissociation equilibrium of the crown ether and ammonium moiety can be observed.

Structural study of *sec*-amine-type rotaxane: One of the most interesting things about neutral rotaxane **2**, prepared



Scheme 4. The synthesis of **2** based on carbamate protection/deprotection.

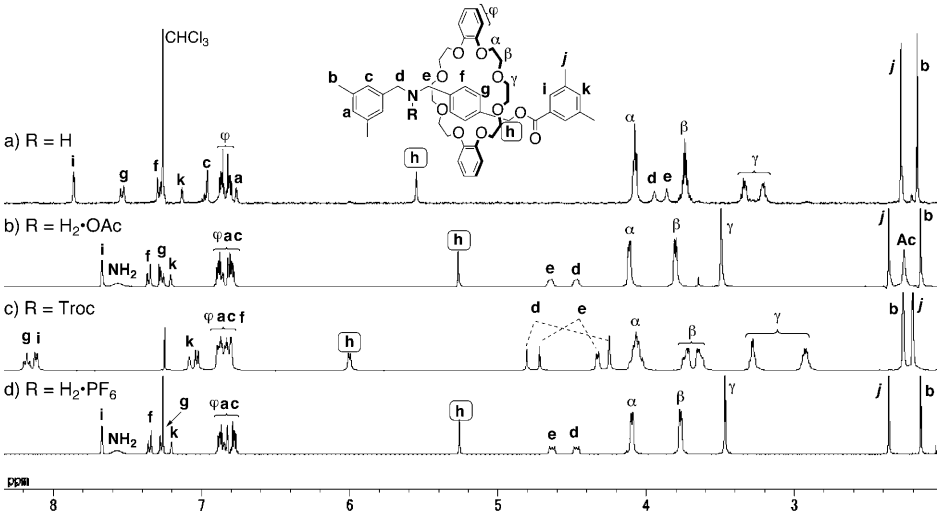


Figure 2. ^{1}H NMR spectra of rotaxanes a) **2** , b) **1·OAc**, c) **3Troc**, d) **1·PF$_6$** (400 MHz, $CDCl_3$, 298 K).

first in this study, is the relative positions of its components. Here, the structure and position or mobility of the components of **2** are discussed relative to a few related rotaxanes by using NMR spectroscopy. The ^{1}H NMR spectrum of **2** is shown in Figure 3b along with other rotaxanes.

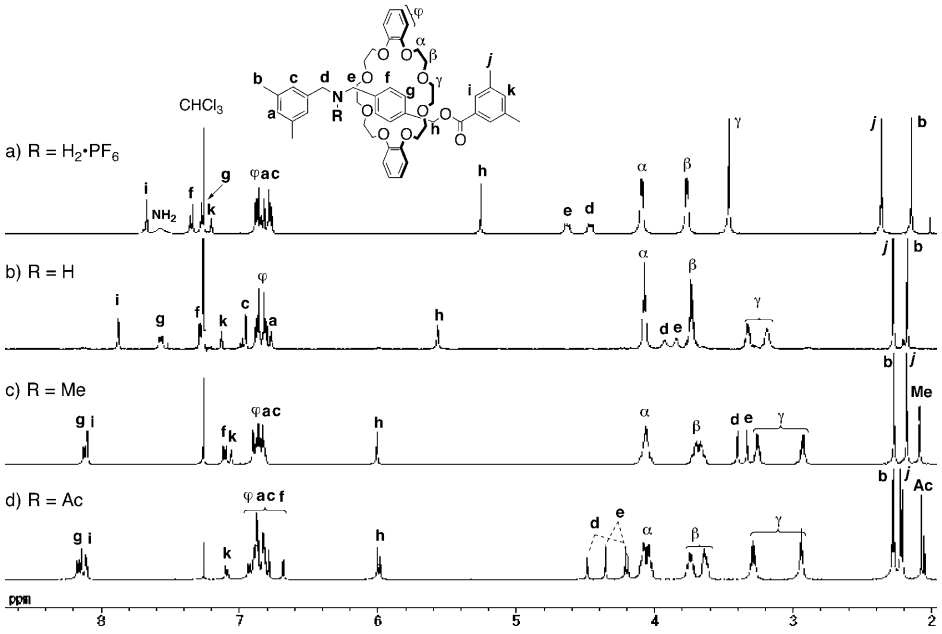


Figure 3. ^{1}H NMR spectra of rotaxanes a) **1**·PF_6, b) **2**, c) **5**, d) **3Ac** (400 MHz, $CDCl_3$, 298 K).

Figure 3b shows signals easily assigned to the structure of the free *sec*-amine-type rotaxane **2**. For example, two aryl methyl signals appear at around $\delta = 2.2$ and 2.3 ppm, whereas the crown ether methylene signals (α–γ) are observed at $\delta = 2.9$–4.1 ppm with split γ proton signals. Characteristic signals are the benzylic proton signals d, e, and h, which are shifted considerably relative to **1·PF$_6$** in accordance with the structural change. In spectrum (a) of **1·PF$_6$**, a couple of multiplet signals at around $\delta =$ 4.5 ppm (i.e., d and e) are characteristic of benzylic proton signals of the *sec*-ammonium moiety encapsulated by the crown ether wheel through hydrogen bonding (Figure 3a).[6,18] Therefore, both $N-CH_2$ signals (i.e., d and e) of **1·PF$_6$** are shifted by approximately $\Delta\delta =$ 0.7 ppm upfield in **2** as a result of neutralization. Such a big shift corresponds to the loss of cationic charge at the nitrogen atoms, thus indicating cancellation of the attractive interaction with the crown ether wheel. A further upfield shift of signals d and e to around $\delta = 3.4$ ppm is confirmed in spectrum (c) of the *tert*-amine-type rotaxane **5** (R = Me), which is consistent with the electron-donating effect of a methyl group (Figure 3c). This shift is also consistent with the above discussion that a rather large downfield shift of proton signals d and e is confirmed for the acetamide-type rotaxane **3Ac** (R = Ac), although *syn–anti* stereoisomerism around the amide moiety of **3Ac** causes splitting of all signals (Figure 3d).

It is important to note the deshielding effect of the crown ether wheel, which seems to be a good probe for its position on the axle of the rotaxane.[11,19] We noticed a singlet signal at around $\delta = 5$–6 ppm assignable to the *O*-benzyl protons (signal h). As shown by the spectra (a–d) in Figure 3, a significant chemical-shift difference for signal h can be confirmed, even though no big chemical change is conceived of at this position far from the nitrogen atom. The difference obviously corresponds to the difference in the deshielding effect of the wheel component toward the *O*-benzyl moiety. Therefore, the downfield shift of signal h means that the crown ether wheel is localized around the *O*-benzyl moiety to some extent.[11] Comparison of the ^{1}H NMR spectra of the *tert*-amine- and amide-type rotaxanes **5** and **3Ac** (Figure 3c,d, respectively) with **2** seems to suggest the presence of weak hydrogen bonding of NH···O, which explains some of the upfield shift

of signal h in **2** relative to **5** and **3Ac**. This discussion is based on the fact that the crown ether wheel is localized at the *O*-benzyl moiety in the X-ray crystal structure analyses of **5**[14] and **3Ac**,[11] in which weak interactions such as C–H···π and C–H···O are probably operative, in accordance with the NMR results.

From the above discussion, we can conclude in simple terms that the crown ether wheel has the highest probability of existing at a position on the axle with which it has the strongest attractive interaction. The position evaluated by NMR spectroscopy, therefore, should be a mean position that results from fast translation on the axle. Thus, the wheel of **2** might possess a few stations as local minima on the axle; therefore, the chemical shift of signal h in **2** in the NMR spectra appears between those of **1·PF$_6$** and **5** or **3Ac**, thus suggesting the wheel component is localized at the phenylene moiety of the axle component.

Dynamic nature of *sec*-ammonium-type rotaxane 2: A variable-temperature (VT) NMR spectroscopic study of **2** was carried out to examine the dynamic nature of the free amine-type rotaxane in detail (Figure 4). An interesting feature of signal h was confirmed: the signal was shifted downfield by cooling and finally shifted to $\delta = 6$ ppm at −50 °C. On the other hand, the signal moved to $\delta = 5.5$ ppm with heating to 50 °C. Here, the chemical species involved in the system should be single because each signal was quite sharp over the temperature range examined. The wheel component is likely to be localized at a thermodynamically stabilized position, that is, the *O*-benzyl moiety, at a lower temperature, whereas it becomes free from interactions at the *O*-benzyl moiety and translates to the amine moiety in a rapid equilibrium at a higher temperature. The chemical shift of signal h was shifted upfield with an increase in the degree of wheel translation to the amine moiety. The translation reached thermal equilibrium at above 50 °C, and the chemical shift settled at approximately $\delta = 5.5$–5.4 ppm. In the control VT-NMR experiments, both the *sec*-ammonium salt-type rotaxane **1·PF$_6$** and *tert*-amine-type rotaxane **5** showed no such temperature-dependent behavior. Thus, the present VT-NMR spectroscopic studies clearly demonstrated an excellent dynamic property of the *sec*-amine-type rotaxane, thus strongly suggesting the significance of the neutralization of *sec*-ammonium-type rotaxanes or the synthesis of *sec*-amine-type rotaxanes.

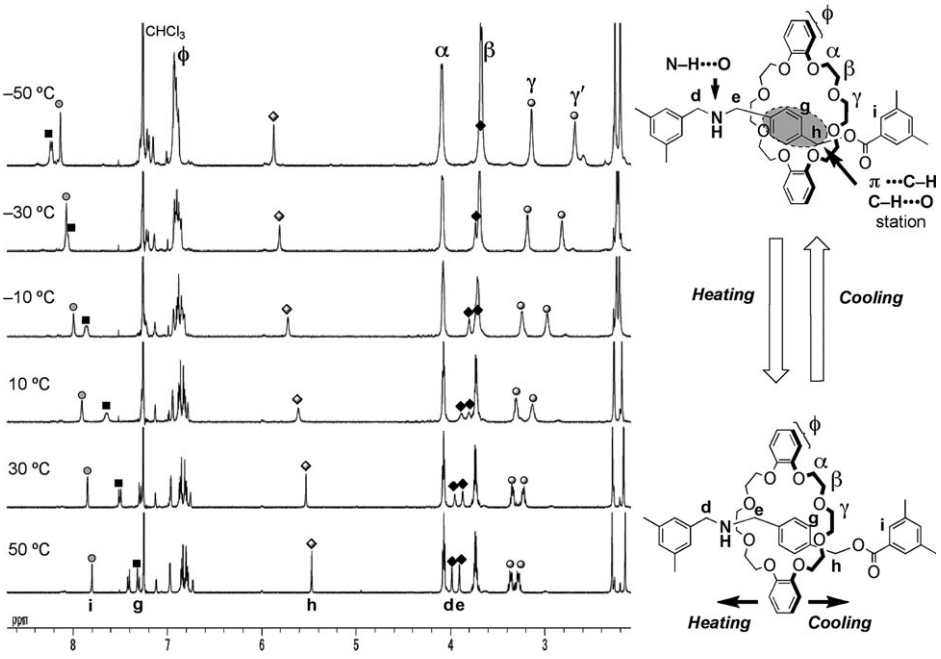
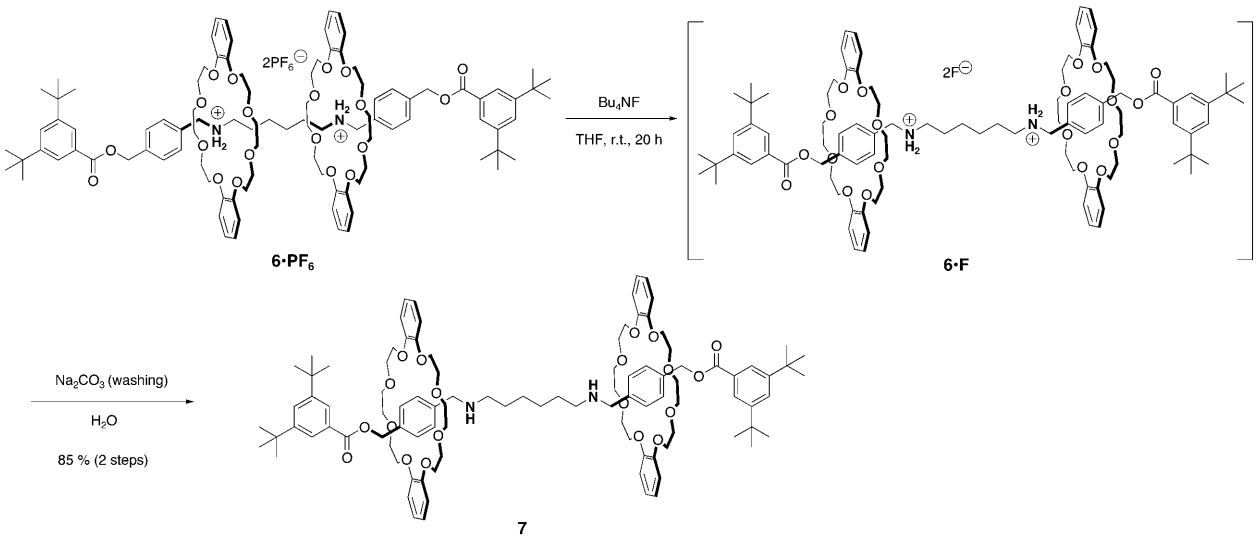


Figure 4. VT-NMR spectrum of rotaxane **2** (^{1}H NMR, 400 MHz, $CDCl_3$).

Other signals of the axle also shifted reasonably with the temperature change. The phenylene and *ortho*-protons of the dimethylbenzoyl group (i.e., signals g and i, respectively) were shifted upfield by $\Delta\delta = 0.3$–0.7 ppm from approximately $\delta = 8$ ppm with decreasing temperature. The chemical-shift changes are derived from the deshielding effect of the crown ether wheel with attractive interactions with parts of the axle.[10] Protons at the opposite side of the axle, such as *N*-benzyl protons h, were shifted downfield with increasing temperature by $\Delta\delta = 0.2$ ppm from approximately $\delta = 3.8$ ppm with a little splitting. Both upfield and downfield shifts clearly correspond to the movement of the wheel from the *O*-benzyl ester moiety to the phenylene group. In good agreement with the change in the axle proton signal, the wheel proton signals, in particular two split γ proton signals, approached each other, which is consistent with the increasing symmetry of the axle with the movement of the wheel. The present discussion might be reasonably supported by the sharp signals in all the spectra obtained over the temperature range studied, thus suggesting fast translation and circumrotation of the rotaxane wheel (when the axle is fixed).

Neutralization of bis(ammonium salt)-type [3]rotaxane: Neutralization of a bis(ammonium salt)-type [3]rotaxane by a similar procedure was examined to confirm the scope and limitations of the present neutralization protocol. This investigation is very important for obtaining information on applicability to oligo- and polyrotaxanes. The synthesis of [3]rotaxane **6·PF$_6$** was performed according to our previously reported method that employed pseudo[3]rotaxane and 3,5-di-*tert*-butylbenzoic anhydride by using tributylphos-



Scheme 5. Neutralization of a bis(ammonium salt)-type [3]rotaxane.

phine-catalyzed end-capping (Scheme 5).[20] [3]Rotaxane **6·PF$_6$** was similarly treated with 3.0 equivalents of TBAF and worked up according to the optimized conditions mentioned above. As a result, **7** was successfully isolated as a white powder without any other product, such as **6·F**. The structure of **7** was confirmed by ^{1}H NMR spectroscopy (Figure 5). The characteristic signal h of the wheel position was shifted downfield from $\delta = 5.24$ to 5.56 ppm by this neutralization reaction. Other proton signals also indicated the proposed structure of **7**. Thus, the present neutralization protocol involving an initial anion exchange with TBAF followed by washing with an aqueous solution of a base was also useful for neutralizing a more complicated rotaxane, namely, [3]rotaxane.

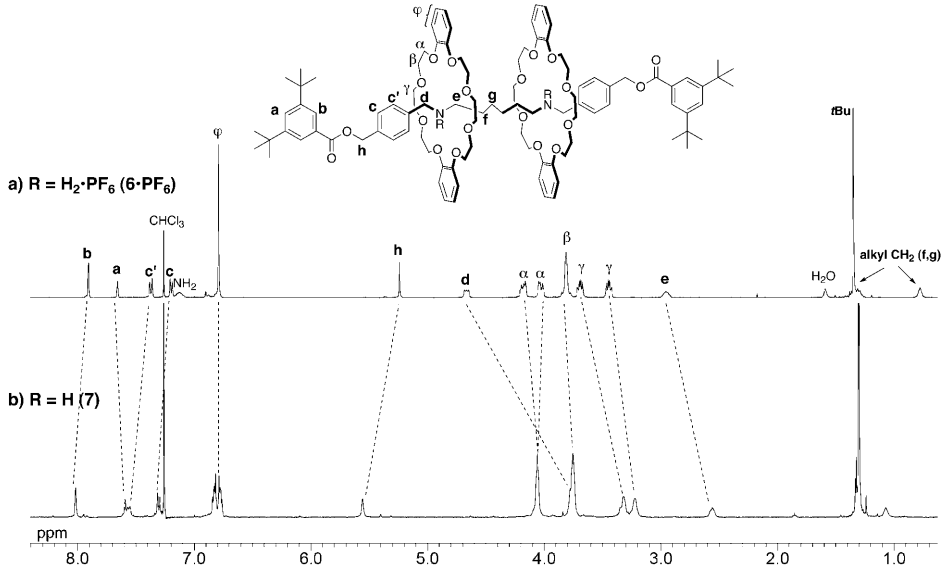
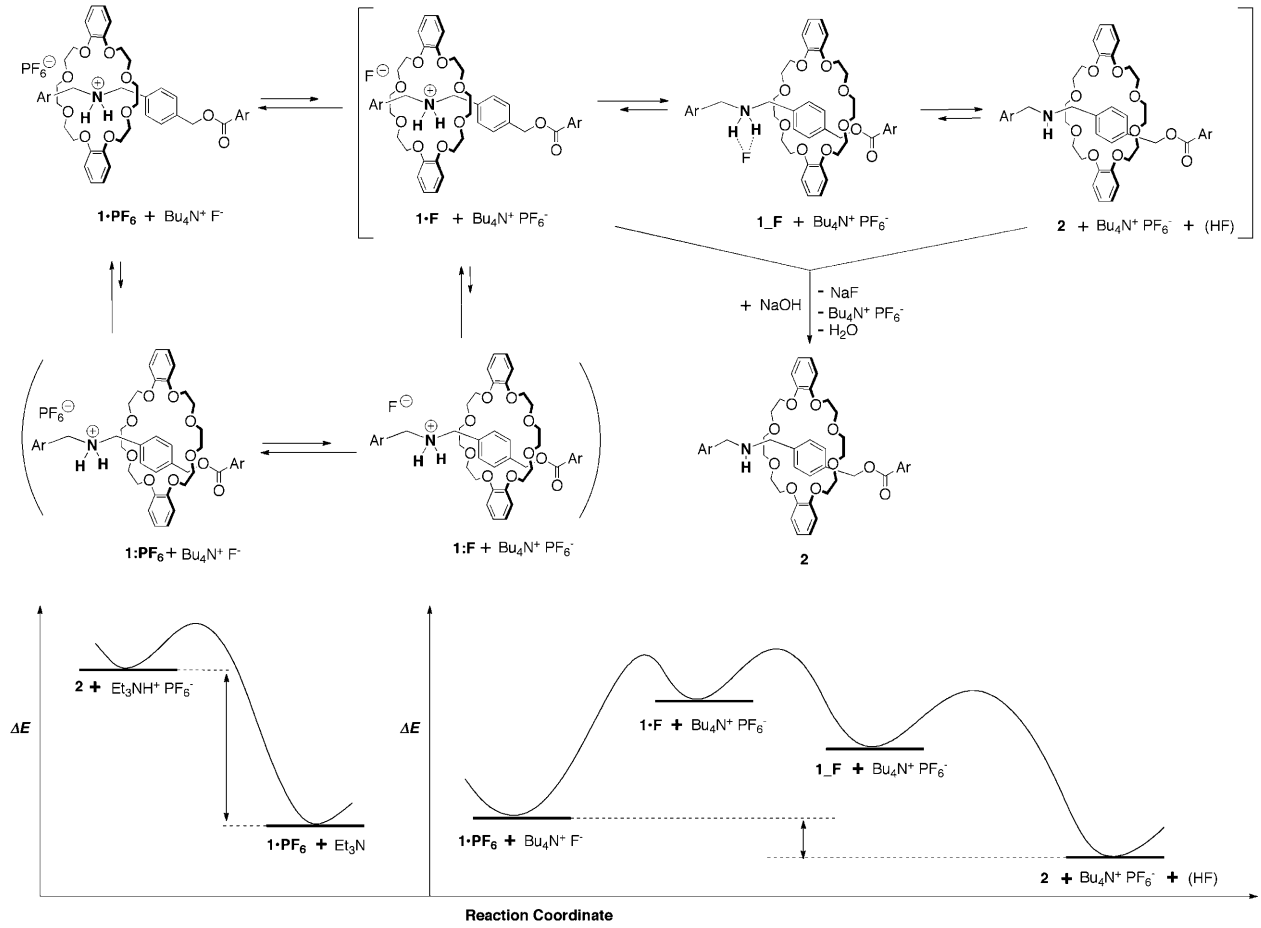


Figure 5. ^{1}H NMR spectra of [3]rotaxanes a) **6·PF$_6$** and b) **7** (400 MHz, $CDCl_3$, 298 K).

Neutralization mechanism: The successful isolation of the *sec*-amine-type[2]rotaxane **2** in this study realized the generation of a crown ether/*sec*-amine-based rotaxane almost free from strong intercomponent interactions. Here, we would like to discuss the mechanism of this neutralization in detail. The fact that **1·F** is readily neutralized to **2** with a simple base, whereas **1·PF$_6$** is never neutralized with any base, raises the question of why **1·F** is so much more unstable than **1·PF$_6$** or why **1·F** has a much higher potential energy than **1·PF$_6$**. The answer can be derived from detailed analysis of the neutralization mechanism (Scheme 6). There are several possible species for the counteranion exchange. Rotaxane **1:PF$_6$**, a structural isomer of **1·PF$_6$** with an uncovered ammonium moiety, is possible, but scarcely plays a role in the equilibrium shown in Scheme 6 because of its instability. From the low acidity of HF relative to HPF_6, not only **1·F** but also **1:F**, with an uncovered ammonium moiety, and nonionic **1 F**, consisting of NH···F hydrogen bonds, are also much more unstable than **1·PF$_6$**. Judging from the fact that neutral *sec*-amine rotaxane **2** is actually observed as the only species in the counteranion-exchange system, even with the use of 1.0 equivalent of TBAF, the product species (i.e., $\mathbf{2} + Bu_4N^+PF_6^- + HF$) should be more stable than the starting species (i.e., $\mathbf{1{\cdot}PF_6} + Bu_4N^+F^-$). However, no such extra stability seems to appear in the product species when compared



Scheme 6. Prospective neutralization mechanism of **1·PF$_6$** to **2** via **1**·F and related species **1:F** and **1_F** in organic solvent.

with the species **1:F**+$Bu_4N^+PF_6^-$, which is clearly inconsistent with the formation of **2**. One possible answer may confirm the experimental findings by assuming a leak process in the equilibrium of Scheme 6. Namely, it is considered that HF can no longer form an adduct with **2**, such as **1·F** and **1:F**, once liberated because HF is a weak acid in DMSO ($pK_a = 15$).[21,22] Thus, the formation of **2** by counteranion exchange can be rationalized by assuming special stabilization of **1·F** that leads to **2** with the liberation of HF. The starting species **1·PF$_6$**+$Bu_4N^+F^-$ becomes more unstable than the product species **2**+$Bu_4N^+PF_6^-$[+HF]. Therefore, the isolation of **1·F** (or **1:F**) as a stable product is impossible in this system. In fact, the ^{1}H NMR spectrum of **1·F** that we first considered was practically the same as **2**.

An excess amount (3 equiv) of TBAF is required because TBAF is used to suppress the highly favorable formation of **1·PF$_6$** with a contaminated source of H^+ ions other than HF, such as water, during the isolation process because PF_6^- ions still remain as $Bu_4N^+PF_6^-$ in the system. Specifically, TBAF would convert some protonic species, such as H_2O into HF, which does not promote the formation of **1·PF$_6$**.

Conclusion

As discussed herein, we have succeeded for the first time in isolating nonionic free *sec*-amine-type rotaxanes from *sec*-ammonium salt-type rotaxanes by using a protocol based on the unique nature of the rotaxanes, although no one had prepared such simple free amine rotaxanes so far. By using energy diagrams, the neutralization can be explained as follows (Figure 1 and Scheme 6): The *sec*-ammonium salt-type rotaxane is highly stabilized toward a base for several reasons. First, the ammonium salt-type rotaxane forms strong hydrogen bonds with the crown ether wheels, which brings about effective delocalization of the cation charge. This behavior results in thermodynamic stabilization. Second, the crown ether wheel that covers the ammonium group acts as a bulky group to largely prevent attack on the proton of the ammonium group or decrease the proton dissociation rate to a large extent in an organic solvent. This behavior results in kinetic stabilization. These two different effects work together in the rotaxane system to provide the extraordinary stability of the ammonium moiety. Therefore, the effect of the counteranion on the stabilization is significantly amplified in organic solvents; we call this the rotaxane effect. Both effects are deeply related and inseparable from each

other. Our present protocol, which involves the counteranion-exchange method in addition to decreasing the number of hydrogen bonds,[13] could solve a significant problem that had remained unsettled for 15 years. Counteranion exchange causes a major structural change in *sec*-ammonium rotaxanes due to the special nature of HF, which was liberated from the system to remarkably enhance the stability of the product species relative to the starting species in the entire equilibrium. As a result, the *sec*-amine-type rotaxane was obtained quantitatively. Not only a [2]rotaxane but also a [3]rotaxane were completely neutralized to the corresponding *sec*-amine-type rotaxanes. This protocol will be applicable to the construction of various rotaxane-based supramolecular and polymer architectures. The rotaxane effect can be regarded as one of the dynamic steric protections often found in interlocked systems.

Experimental Section

Measurements: Melting points were measured on a melting-point apparatus SMP3 instrument (Stuart Scientific). The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL AL-400 NMR spectrometer operating at 400 and 100 MHz, respectively, in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. The NMR chemical shifts were reported in delta units δ. Multiplicity is indicated by s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad). The coupling constants J are reported in Hz. The IR spectra were measured by a JASCO FT/IR-460 plus spectrometer. Preparative HPLC was carried out on a JAI HPLC LC-918 instrument (columns: JASCO Megapack-Gel 201C, Megapack-Gel 201 CP, and JAI JAIGEL-1H; eluent: $CHCl_3$; flow rate: 3.5 mL min^{-1}). The mass spectra were recorded on a JEOL JMS-700 instrument with *meta*-nitrobenzyl alcohol as the matrix. Elemental analyses were carried out on a LECO CHNS-932 instrument.

Materials: All the solvents were distilled before use according to general purification procedures. Commercially available reagents were used without further purification unless otherwise noted. Column chromatography was performed on Wakogel C-400HG. Rotaxane **1**·PF_6 was prepared according to the reported procedures.[10]

Neutralization through an anion-exchange reaction (Table 1, entry 6)

Preparation of 1·F: TBAF in THF (0.30 mL, 0.30 mmol, 1.0 M) was added to a solution of *sec*-ammonium PF_6-type rotaxane **1·PF$_6$** (98 mg, 0.10 mmol) in THF (1.0 mL). The solution was stirred at room temperature for 30 min under air. Diethyl ether (5 mL) was added to the solution and the reaction mixture was stirred vigorously in an ice bath. The precipitate was removed by filtration and washed with diethyl ether. The combined filtrate was concentrated on a rotary evaporator and dried in vacuo to obtain **1·F** as the residual colorless solid (83 mg, 97% yield), which was used without further purification in the neutralization reaction. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.88 (s, 2H), 7.56 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 7.13 (s, 1H), 6.97 (s, 2H), 6.88–6.80 (m, 8H), 6.77 (s, 1H), 5.58 (s, 2H), 4.07 (t, J = 4.5 Hz, 8H), 3.92 (d, J = 5.5 Hz, 2H), 3.84 (d, J = 5.5 Hz, 2H), 3.78–3.69 (m, 8H), 3.35–3.29 (m, 4H), 3.23–3.17 (m, 4H), 2.34 (s, 6H), 2.28 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 167.0, 148.4, 141.4, 140.4, 137.8, 137.2, 134.6, 134.3, 130.5, 128.1, 128.0, 127.8, 127.7, 126.3, 1205., 111.7, 69.6, 69.4, 67.8, 66.9, 53.1, 53.0, 21.2, 21.0 ppm; IR (KBr): $\tilde{\nu}$ = 3323, 2918, 2876, 1713, 1505, 1454, 1312, 1251, 1217, 1125, 1054, 742 cm^{-1}; FAB-HRMS calcd for $C_{50}H_{62}FNO_{10}$: 836.4374 $[M-F]^+$; found: 836.4394.

Preparation of *sec*-amine-type [2]rotaxane 2: Compound **1·F** (50 mg, 58 μmol) was dissolved in THF (0.5 mL) and stirred vigorously with 10% Na_2CO_3 (5.0 mL) for 5 min at room temperature. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over anhydrous $MgSO_4$, followed by solvent removal on a rotary evaporator and drying in vacuo to obtain **2** as the residual colorless solid (50 mg, 100% yield). M.p. 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.88 (s, 2H), 7.56 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 7.14 (s, 1H), 6.98 (s, 2H), 6.89–6.81 (m, 8H), 6.77 (s, 1H), 5.57 (s, 2H), 4.08 (t, J = 4.4 Hz, 8H), 3.95 (s, 2H), 3.87 (s, 2H), 3.78–3.69 (m, 8H), 3.36–3.30 (m, 4H), 3.25–3.19 (m, 4H), 2.29 (s, 6H), 2.18 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 167.0, 148.4, 141.5, 140.6, 137.8, 137.2, 134.6, 134.3, 130.5, 128.2, 128.0, 127.8, 126.4, 125.5, 120.6, 111.8, 69.7, 69.4, 67.8, 66.9, 52.9, 30.3, 21.2, 21.0 ppm; IR (KBr): $\tilde{\nu}$ = 3163, 2919, 2879, 1713, 1505, 1454, 1311, 1251, 1215, 1124, 1053, 742 cm^{-1}; FAB-HRMS calcd for $C_{50}H_{61}NO_{10}$ 836.4374 $[M+H]^+$; found: 836.4343.

Neutralization through a protection/deprotection protocol

Preparation of *N*-Troc [2]rotaxane 3Troc: Triethylamine (0.35 mL, 2.5 mmol) and 2,2,2-trichloroethyl chloroformate (0.27 mL, 2.0 mmol) were added to a solution of [2]rotaxane **1·PF$_6$** (0.49 g, 0.5 mmol) in THF (5 mL) at room temperature. The solution was stirred for 19 h at room temperature and the reaction mixture was diluted with dichloromethane (10 mL) and water (5 mL). The organic layer was washed with 3 M HCl, water, 5% Na_2CO_3, and brine. After the mixture had been dried over anhydrous $MgSO_4$ and filtered, the solvent was removed under reduced pressure. The crude product was purified by preparative gel permeation chromatography (GPC) with $CHCl_3$ as the eluent to obtain **3Troc** as a colorless solid (0.45 g, 89% yield). M.p. 100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (m, 2H), 8.12 (m, 2H), 7.09 (s, 1H), 7.03 (d, J = 8.0 Hz, 2H), 6.90–6.81 (m, 12H), 6.00 (m, 2H), 4.81 (s, 1H), 4.72 (s, 1H), 4.33 (m, 2H), 4.25 (s, 2H), 4.12–4.03 (m, 8H), 3.76–3.72 (m, 4H), 3.66–3.62 (m, 4H), 3.30–3.27 (m, 4H), 2.96–2.90 (m, 4H), 2.27 (s, 6H), 2.20 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 154.8, 154.7, 148.5, 138.1, 137.6, 137.5, 137.3, 136.8, 134.1, 133.9, 130.8, 129.2, 129.1, 128.2, 127.0, 126.8, 125.8, 125.7, 120.5, 120.4, 111.5, 95.8, 75.2, 69.5, 69.3, 67.9, 66.8, 49.3, 48.9, 48.8, 48.2, 21.2, 20.8 ppm; IR (KBr): $\tilde{\nu}$ = 2920, 1716, 1505, 1454, 1310, 1251, 1218, 1125, 1052, 738 cm^{-1}; elemental analysis calcd for $C_{53}H_{62}Cl_3NO_{12}$: C 62.94, H 6.18, N 1.38; found: C 62.85, H 6.12, N 1.57; FAB-HRMS calcd for $C_{53}H_{62}Cl_3NO_{12}$: 1032.3215 $[M+Na]^+$; found: 1032.3235.

Preparation of 1·OAc: Activated zinc powder (0.2 g, 3.0 mmol) was added to **3**Troc (0.3 g, 0.3 mmol) dissolved in acetic acid (3 mL). The suspension was stirred vigorously for 3 h at room temperature. The suspension was diluted with $CHCl_3$ (10 mL) and zinc powder was removed by filtration. The combined filtrate was washed with water and brine. After drying over anhydrous $MgSO_4$, the solvent was removed under reduced pressure. The residue was used without further purification (0.26 g, 97% yield). M.p. 123 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.60 (s, 2H), 7.35 (br, 4H), 7.29 (s, 1H), 6.92–6.89 (m, 4H), 6.86–6.83 (m, 4H), 6.79 (s, 3H), 5.26 (br, 2H), 4.55 (br, 2H), 4.44 (br, 2H), 4.04 (br, 8H), 3.69 (br, 8H), 3.43 (br, 8H), 2.31 (s, 6H), 2.04 (s, 6H), 1.78 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 172.6, 165.7, 147.2, 138.1, 137.4, 134.8, 129.6, 129.5, 127.8, 126.9, 126.5, 121.0, 112.4, 70.0, 69.7, 67.6, 65.6, 51.8, 51.6, 22.2, 20.8, 20.7 ppm; IR (KBr): $\tilde{\nu}$ = 3422, 2921, 5873, 1717, 1506, 1458, 1308, 1253, 1214, 1122, 1055, 953, 746 cm^{-1}; FAB-HRMS calcd for $C_{52}H_{65}NO_{12}$: 836.4374 $[M-OAc]^+$; found: 836.4386.

Neutralization of 1·OAc (preparation of 2): A solution of **1**·OAc (0.26 g, 0.29 mmol) in THF (5 mL) was neutralized by washing with saturated aqueous Na_2CO_3. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvent was removed, **2** was obtained as a colorless solid (240 mg, 99% yield).

Preparation of [3]rotaxane 6·F: TBAF (1.8 mmol) in THF (1.0 M, 1.8 mL) was added to a solution of **6·PF$_6$** (0.60 g, 0.30 mmol) in THF (3.0 mL) at room temperature, and the solution was stirred for 30 min. After the solvent was removed under reduced pressure, the residue was extracted with diethyl ether. The insoluble part was removed by filtration through celite. The combined filtrate was concentrated under reduced pressure. The residue was purified by reprecipitation from diethyl ether/hexane. The combined colorless powder **6·F** (0.43 g) was used without further purification.

Preparation of amine-type [3]rotaxane 7:[3] Aqueous Na_2CO_3 (1.0 g in 10 mL H_2O) was added to **6·F** (0.43 g) dissolved in diethyl ether (10 mL), and the reaction mixture was stirred vigorously for 10 min. After separa-

tion of the organic layer, the aqueous layer was extracted with $CHCl_3$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to obtain **7** as a colorless solid (0.42 g, 0.25 mmol, 82% yield over 2 steps). Mp 116–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.02 (d, J = 1.8 Hz, 4H), 7.59 (t, J = 1.8 Hz, 2H), 7.56 (d, J = 8.0 Hz, 4H), 7.30 (d, J = 8.0 Hz, 4H), 6.84–6,76 (m, 16H), 5.56 (s, 4H), 4.06 (br s, 16H), 3.78 (s, 4H), 3.76 (br s, 16H), 3.34–3.31 (m, 8H), 3.23–3.22 (m, 8H), 2.56 (t, J = 7.4 Hz, 4H), 1.33 (m, 4H), 1.30 (s, 36H), 1.07 ppm (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 167.4, 150.9, 148.4, 141.0, 134.1, 130.1, 128.4, 128.3, 128.0, 127.9, 126.8, 124.0, 123.9, 120.5, 111.8, 69.9, 69.7, 69.5, 67.8, 67.0, 53.1, 49.7, 34.9, 31.3, 30.3, 27.8 ppm; IR (KBr): $\tilde{\nu}$ = 3435, 2959, 2924, 2871, 1715, 1593, 1505, 1454, 1251, 1126, 1055, 741 cm^{-1}; FAB-HRMS calcd for $C_{100}H_{136}N_2O_{20}$: 1685.9765 $[M+H]^+$; found: 1685.9788.

Acknowledgements

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[1] N. Kihara, Y. Tachibana, T. Takata, *Chem. Lett.* **2000**, 506–507.
[2] For reviews on rotaxanes, see: a) J.-P. Sauvage, C. Dietrich-Buchecker, *Molecular Catenanes, Rotaxanes and Knots*, Wiley-VCH, Weinheim, **1999**; b) V. Balzani, A. Credi, F. M. Raymo, J. F. Stoddart, *Angew. Chem.* **2000**, *112*, 3484–3530; *Angew. Chem. Int. Ed.* **2000**, *39*, 3348–3391; c) R. Ballardini, V. Balzani, A. Credi, M. T. Gandolfi, M. Venturi, *Acc. Chem. Res.* **2001**, *34*, 445–455; d) A. Harada, *Acc. Chem. Res.* **2001**, *34*, 456–464; e) C. A. Schalley, K. Beizai, F. Vögtle, *Acc. Chem. Res.* **2001**, *34*, 465–476; f) N. Yui, T. Ooya, *Chem. Eur. J.* **2006**, *12*, 6730–6737; g) E. R. Kay, D. A. Leigh, F. Zerbetto, *Angew. Chem.* **2007**, *119*, 72–196; *Angew. Chem. Int. Ed.* **2007**, *46*, 72–191.
[3] M. J. Frampton, H. L. Anderson, *Angew. Chem.* **2007**, *119*, 1046–1083; *Angew. Chem. Int. Ed.* **2007**, *46*, 1028–1064.
[4] For examples of the stabilization of rotaxanes, see: a) E. Cordova, R. A. Bissell, A. E. Kaifer, *J. Org. Chem.* **1995**, *60*, 1033–1038; b) A. H. Parham, B. Windisch, F. Vögtle, *Eur. J. Org. Chem.* **1999**, 1233–1238; c) K. Yoshida, T. Shimomura, K. Ito, R. Hayakawa, *Langmuir* **1999**, *15*, 910–913; d) M. R. Craig, M. G. Hutchings, T. D. W. Claridge, H. L. Anderson, *Angew. Chem.* **2001**, *113*, 1105–1108; *Angew. Chem. Int. Ed.* **2001**, *40*, 1071–1074; e) J. E. H. Buston, F. Marken, H. L. Anderson, *Chem. Commun.* **2001**, 1046–1047; f) A. Credi, S. Dumas, S. Silvi, M. Venturi, A. Arduini, A. Pochini, A. Secchi, *J. Org. Chem.* **2004**, *69*, 5881–5887; g) H. Murakami, A. Kawabuchi, R. Matsumoto, T. Ido, N. Nakashima, *J. Am. Chem. Soc.* **2005**, *127*, 15891–15899; h) P. Franchi, M. Fani, E. Mezzina, M. Lucarini, *Org. Lett.* **2008**, *10*, 1901–1904; i) K. Hirose, Y. Nakamura, H. Takano, K. Nishihara, Y. Tobe, *Tetrahedron Lett.* **2009**, *50*, 3443–3445.
[5] a) R. Chitta, F. D′Souza, *J. Mater. Chem.* **2008**, *18*, 1440–1471; b) T. Takata, *Polym. J.* **2006**, *38*, 1–20; c) T. Takata, N. Kihara, Y. Furusho, *Adv. Polym. Sci.* **2004**, *171*, 1–75; d) M. E. El-Khouly, O. Ito, P. M. Smith, F. D′Souza, *J. Photochem. Photobiol. C* **2004**, *5*, 79–104; e) M. Gunter, *Eur. J. Org. Chem.* **2004**, 1655–1673.
[6] a) P. R. Ashton, R. Ballardini, V. Balzani, I. Baxter, A. Credi, M. C. T. Fyfe, M. T. Gandlfi, M. G. López, M. V. M. Díaz, A. Piersanti, N. Spencer, J. F. Stoddart, M. Venturi, A. J. P. White, D. J. Williams, *J. Am. Chem. Soc.* **1998**, *120*, 11932–11942; b) A. M. Elizarov, S.-H. Chiu, J. F. Stoddart, *J. Org. Chem.* **2002**, *67*, 9175–9181.
[7] a) J. Cao, M. C. T. Fyfe, J. F. Stoddart, *J. Org. Chem.* **2000**, *65*, 1937–1946; b) D. A. Leigh, A. R. Thomson, *Tetrahedron* **2008**, *64*, 8411–8416.
[8] Y. Tokunaga, T. Nakamura, M. Yoshioka, Y. Shimomura, *Tetrahedron Lett.* **2006**, *47*, 5901–5904.
[9] Rotaxanes that possess a crown ether with nitrogen atoms instead of oxygen atoms, such as the 2,6-bis(aminomethyl)pyridine group-containing macrocycle, could be neutralized with aqueous NaOH as shown by Stoddart and co-workers; a smaller association constant of the macrocycle than that of DB24C8 is suggested: a) P. T. Glink, A. I. Oliva, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **2001**, *113*, 1922–1927; *Angew. Chem. Int. Ed.* **2001**, *40*, 1870–1875; b) J. Wu, K. C.-F. Leung, J. F. Stoddart, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 17266–17271.
[10] N. Kihara, Y. Koike, T. Takata, *Chem. Lett.* **2007**, *36*, 208–209.
[11] Y. Tachibana, H. Kawasaki, N. Kihara, T. Takata, *J. Org. Chem.* **2006**, *71*, 5093–5104.
[12] a) A. G. Kolchinski, D. H. Busch, N. W. Alcock, *J. Chem. Soc. Chem. Commun.* **1995**, 1289–1291; b) P. R. Aston, P. T. Glink, J. F. Stoddart, P. A. Tasker, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1996**, *2*, 729–736.
[13] a) M. Montalti, L. Prodi, *Chem. Commun.* **1998**, 1461–1462; b) C.-F. Lin, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Chem. Eur. J.* **2007**, *13*, 4350–4355.
[14] a) K. Nakazono, S. Kuwata, T. Takata, *Tetrahedron Lett.* **2008**, *49*, 2397–2401; b) S. Suzuki, K. Nakazono, T. Takata, *Org. Lett.* **2010**, *12*, 712–715.
[15] a) S. J. Rowan, J. F. Stoddart, *Polym. Adv. Technol.* **2002**, *13*, 777–787; b) S.-H. Chiu, S. J. Rowan, S. J. Cantrill, P. T. Glink, R. L. Garrell, J. F. Stoddart, *Org. Lett.* **2000**, *2*, 3631–3634; c) Y. Furusho, G. A. Rajukumar, T. Oku, T. Takata, *Tetrahedron* **2002**, *58*, 6609–6613; d) Y. Makita, N. Kihara, T. Takata, *J. Org. Chem.* **2008**, *73*, 9245–9250.
[16] a) P. R. Ashton, I. Baxter, M. C. T. Fyfe, F. M. Raymo, N. Spencer, J. F. Stoddart, A. J. P. White, D. J. Williams, *J. Am. Chem. Soc.* **1998**, *120*, 2297–2307; b) Y. Tachibana, N. Kihara, Y. Furusho, T. Takata, *Org. Lett.* **2004**, *6*, 4507–4509; c) Ion pair study on pseudorotaxane stability: J. W. Jones, H. W. Gibson, *J. Am. Chem. Soc.* **2003**, *125*, 7001–7004; d) C. A. Schalley, T. Weilandt, J. Brüggemann, F. Vögtle, *Top. Curr. Chem.* **2004**, *232–242*, 141–200; e) Y. Sohgawa, H. Fujimori, J. Shoji, Y. Furusho, N. Kihara, T. Takata, *Chem. Lett.* **2001**, 774–775.
[17] Steric protection in the rotaxane system: a) J. J. Gassensmith, J. M. Baumes, B. D. Smith, *Chem. Commun.* **2009**, 6329–6338; b) A. Mateo-Alonso, P. Brough, M. Prato, *Chem. Commun.* **2007**, 1412–1414; c) T. Oku, Y. Furusho, T. Takata, *Org. Lett.* **2003**, *5*, 4923–4925; d) A. H. Parham, B. Windish, F. Vögtle, *Eur. J. Org. Chem.* **1999**, 1233–1238.
[18] N. Georges, S. J. Loeb, J. Tiburcio, J. A. Wisner, *Org. Biomol. Chem.* **2004**, *2*, 2751–2756.
[19] a) S. J. Loeb, J. A. Wisner, *Chem. Commun.* **2000**, 845–846; b) S. J. Cantrill, A. R. Pease, J. F. Stoddart, *J. Chem. Soc. Dalton Trans.* **2000**, 3715–3734.
[20] N. Watanabe, T. Yagi, N. Kihara, T. Takata, *Chem. Commun.* **2002**, 2720–2721.
[21] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463; the acidity of HF is weaker than malonic ester (pK_a = 13.3) and the same as succinimide (pK_a = 14.7) in DMSO.
[22] Efficient formation of **2** can be reasonably explained by assuming that HF is liberated from the system in a gaseous state or that the complex with **2** has an association constant that is too small to maintain its salt form due to the low acidity of HF; by judging from the pK_a value of benzylammonium fluoride in DMSO (pK_a = 10.16),[23] the acidity seems similar in THF.
[23] M. R. Crampton, I. A. Robotham, *J. Chem. Res. Synop.* **1997**, 22–23.

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