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A molecular switch based on acid and base promoted, cation governed binding in a crown ether threaded rotaxane

Yuji Tokunaga,* Tatsuya Nakamura, Megumi Yoshioka and Youji Shimomura

Department of Materials Science and Engineering, Faculty of Engineering, University of Fukui, Fukui 910-8507, Japan

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Abstract—A rotaxane, containing both oligo ethylene glycol and secondary ammonium cation binding sites for a threaded crown ether, has been prepared. ^{1}H NMR spectroscopy has been used to show that the crown ether moiety in the rotaxane undergoes acid–base and alkali metal cation dependent switch from binding at the ammonium cation position to cooperative binding to the metal cation at the oligo ethylene glycol site.

The change in the relative positioning of rotaxane components is an interesting strategy for the design of nanometer switches.[1] Recently, a novel rotaxane was described, in which its threaded macrocycle could be relocated with high positional integrity between two well-separated binding sites in response to various stimuli, including light,[2] electrochemical reduction and oxidation,[3] temperature,[2h,k,4] pH,[3a,5] solvent polarity,[6] and chemical additives.[2g,7] The results of these studies stimulated exploratory investigations aimed at developing other rotaxane based molecular switches. In one effort in this area, we observed that rotaxanes, composed of crown ethers enveloping oligo ethylene glycol axles, display simultaneous coordination of the macrocycle and linear polyether to metal cations, in a fashion analogous to that of lariat-type crown ethers.[8] However, studies of a rotaxane, having both an oligo ethylene glycol and an ammonium cation binding site in the axle and a [24]crown as the macrocycle, did not reveal any alkali metal cation promoted movement of the crown between the two binding sites. This result is likely due to the fact that hydrogen-bonding between the ammonium cation group and the [24]crown is too strong, thus preventing joint participation of the crown and oligo ethylene glycol group in binding to alkali metal cations.

It is known that, in contrast to those of [24]crowns, association constants for complex formation between [27]crowns and ammonium ions are only moderate.[9] Thus, in order to better regulate regioselective binding at two different sites, we have designed a rotaxane with a [27]crown as the threaded macrocycle. Below, we describe the synthesis of a new rotaxane, comprising of both an ammonium cation and an oligo ethylene glycol unit as molecular recognition sites in the axle component and a mobile threaded [27]crown ether. In addition, we present observations which demonstrate that movement of a [27]crown moiety between the two binding sites can be promoted by acid and base in the presence of metal cations (Fig. 1).

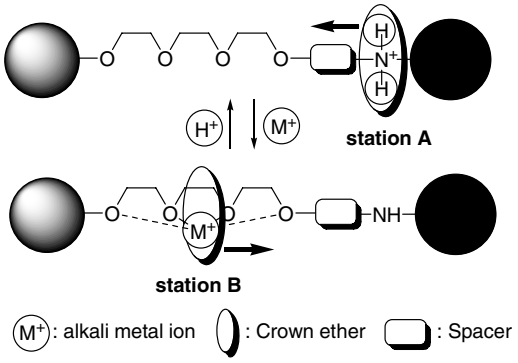

Figure 1. A model for the control of reversible shuttling of a crown ether group between amine (A) and oligo ethylene glycol (B) stations by protons and alkali metal cations (M^+).

Keywords: Rotaxane; Molecular switch; pH-responsive; Hydrogen bonding; Alkali metal ion.
* Corresponding author. Tel./fax: +81 776 27 8611; e-mail: tokunaga@matse.fukui-u.ac.jp

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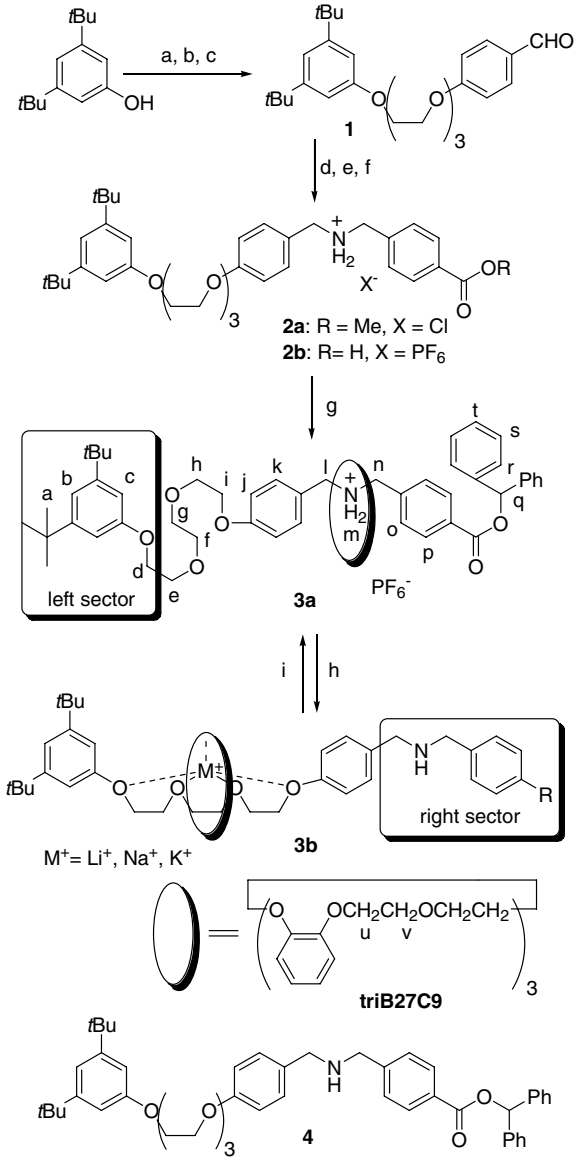
The rotaxane **3a** investigated in this effort was prepared by the sequence shown in Scheme 1. Introduction of the triethylene glycol unit and aryl spacer group of the target takes place in the conversion of 3,5-di-*tert*-butylphenol into aldehyde **1**. Treatment of **1** with aminomethyl benzoate ester followed by reduction gives the corresponding secondary amine **2a**, which is saponified and acidified to form ammonium salts **2b**. Esterification of **2b** with diphenyldiazomethane in the presence of 3 equiv of tribenzo[27]crown9 (triB27C9) then affords the ammonium salt form (**3a**) of the rotaxane.[10] The successful preparation of **3a** shows that interaction between the triB27C9 moiety and secondary ammonium groups is strong, and that the diphenylmethyl end group is sufficiently bulky to prevent unthreading.



Scheme 1. Reagents and conditions: (a) $Cl(CH_2CH_2O)_3H$, KI, K_2CO_3, 98%; (b) MsCl, Et_3N; (c) 4-hydroxybenzaldehyde, K_2CO_3, 90% (two steps); (d) 4-methoxycarbonylbenzylamine, $MgSO_4$; (e) $NaBH_4$; HCl, 53% (two steps); (f) NaOH; HCl; NH_4PF_6, 89%; (g) Ph_2CN_2, triB27C9, 74%; (h) $MOCH_2CF_3$ or MPF_6, Et_3N, (i) CH_3CO_2H.

In a manner similar to that seen in dibenzo[24]crown8–ammonium system,[8] strong hydrogen-bonding interaction between the triB27C9 and ammonium cation groups fixes the position of the macrocycle along the axis of **3a**. This conclusion is supported by analysis of the ^1H NMR spectrum of the **3a** (Fig. 2a) which contains a concentration independent NH resonance at 7.70 ppm and resonances for the pairs of benzylic protons (H_l and H_n) at 4.48 and 4.59 ppm that are characteristic of those in the spectra of crown–ammonium salt type rotaxane.[8] No significant changes in the chemical shifts of the protons in rotaxane **3a** are observed following the addition of an excess of $LiPF_6$. Thus, it appears that hydrogen-bonding interaction between the crown and ammonium cation in **3a** is stronger than cooperative coordination of the crown with the Li^+ complexed oligo ethylene glycol.

The strong hydrogen bonding interaction in **3a** can be disrupted by deprotonation of the ammonium cation. To probe the effects of bases, a suspension of $LiOCH_2CF_3$ (0.5 equiv) and **3a** in $CDCl_3$–CD_3CN (2:1) was sonicated for 1 h. New peaks along with those of **3a** arose in the ^1H NMR spectrum of this mixture (Fig. 2b) and the intensities of these peaks directly correlate with the amount of $LiOCH_2CF_3$ that is added (Fig. 2c). The chemical shift changes that take place upon addition of the lithium alkoxide are consistent with the formation of a new substance (**3b**) in which a neutral amine is present and the relative positions of the rotaxane components are changed. This conclusion arises from inspection of the ^1H NMR spectrum of **3b**, which contains new resonances for all of the protons (except NH) in the rotaxane. The resonances for the benzylic protons H_l and H_n in the **3b** are shifted to significantly higher fields, attributable to the loss of deshielding effects associated with the ammonium cation and the aromatic rings of the triB27C8. In addition, resonances for H_o and H_p move to lower fields, a likely result of the disappearance of shielding by the aromatic rings in the macrocycle. Shielding effects of the aromatic moieties are also responsible for upfield shifts in the resonances of the aromatic (H_b and H_c) and *tert*-butyl (H_a) protons in **3b**. The downfield shifts of signals for protons (H_{d-i} and $H_{u,v}$) in the ethylene glycol units are consistent with those documented for crown–oligo ethylene glycol–Li^+ complexation.[8] Finally, ^1H NMR spectral regions associated with the left sector of ammonium salt **3a** and right sector of **3b** are similar to those of **4** (Fig. 2f), a substance lacking the crown and the ammonium group. It is noteworthy that separate signals associated with **3a** and **3b** are present in the spectra prior to complete deprotonation by bases, since observations made in studies of other lariat-type rotaxanes show that complexation with alkali metal ions is kinetically fast on the NMR time scale.[8] Also, ^1H NMR monitored titration showed that **3b** contains one lithium cation per each rotaxane molecule (i.e., 1:0.5 and a 1:1 mixtures **3a** and $LiOCH_2CF_3$ in $CDCl_3$–CD_3CN gave respective 59:41 and 7:93 mixtures of **3a** and **3b**).

The effects of acids and bases in the presence of lithium salts on the relocation of the crown ether group in rotax-

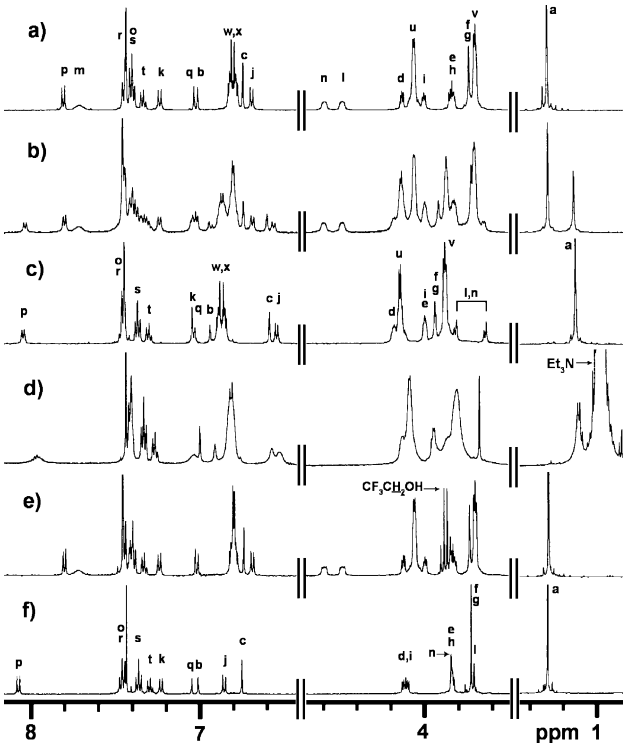


Figure 2. Partial ^{1}H NMR spectra ($CDCl_3$–CD_3CN (2:1)) of (a) **3a**, (b) **3a** (10 mM)+$LiOCH_2CF_3$ (0.5 equiv), (c) **3a** (10 mM)+$LiOCH_2CF_3$ (5 equiv), (d) **3a** (5 mM)+$LiPF_6$ (5 equiv)+Et_3N (0.1%, v/v), (e) **3a** (10 mM)+$LiOCH_2CF_3$ (3 equiv)+AcOH (excess), (f) **4**.

ane **3** were investigated. ^{1}H NMR spectral analysis of a mixture of **3a** (10 mM), $LiOCH_2CF_3$ (3 equiv), and excess acetic acid in $CDCl_3$–CD_3CN (Fig. 2e) shows that the interconversion of **3a** and **3b** is reversible. Thus, protonation of **3b** with acetic acid smoothly regenerates **3a** having the macrocycle located at the original ammonium cation position. The switching can be repeatedly cycled by alternating addition of $LiOCH_2CF_3$ and acetic acid, as illustrated in Figure 3. Location of the macrocycle in **3b** can also be promoted by the addition of $LiPF_6$ and Et_3N (Fig. 2d). However, the broad ^{1}H NMR signals seen in this case suggest that the rates of competitive Li^+ and H^+ association–dissociation are fast on the NMR time scale. The Li^+-induced positional change cannot be induced by the week base pyridine, an expected result based on a consideration of the relative

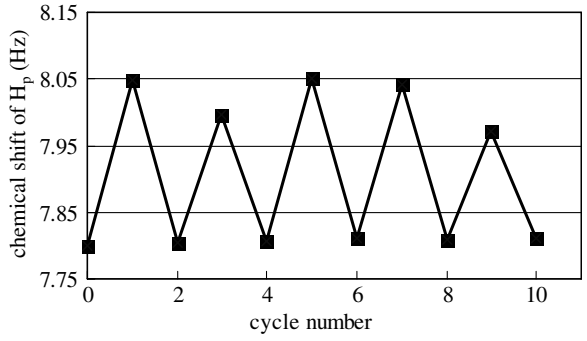


Figure 3. Plot of chemical shift by alternating addition of 3 equiv of $LiOCH_2CF_3$ (low field) and 3 equiv of AcOH in $CDCl_3$ (high field).

pK_a values of the amine site in rotaxane **3** and bases used for deprotonation (CF_3CH_2OH 12.4, Et_3N^+H 11.0, $C_5H_5N^+H$ 5.3). Consequently, shuttling of the crown ether between the binding sites in **3** is controlled by acidity and basicity of the additives and the presence of lithium cations, favoring the ammonium cation station under acidic to weakly basic conditions and the oligo ethylene glycol station under strongly basic conditions.

The discrimination of the macrocycle for the different regions of the axle is expressed in the presence of $NaOCH_2CF_3$, also. Namely, the signals associated with both complexes **3a** and **3b** are independently presented in the ^{1}H NMR spectra, and the shifting of signals was quite similar to the case of $LiOCH_2CF_3$. Moreover, the addition of $NaPF_6$ and Et_3N or KPF_6 and Et_3N promotes the positional change similar to the case of $LiPF_6$-Et_3N.[11]

In conclusion, this effort has led to the construction of a novel rotaxane that contains two different binding locations, an ammonium cation and lithium cation complexed oligo ethylene glycol group, for its threaded [27]crown ether component. Acid–base switching experiments, ^{1}H NMR spectroscopic analysis of changes that take place in the rotaxane upon addition of various combinations of bases and lithium cations show that the crown group undergoes a reversible switch from the ammonium cation station where it is strongly hydrogen bonded to the oligo ethylene glycol station where it cooperatively binds with the alkali metal ion.

Acknowledgments

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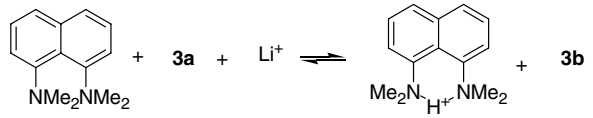
References and notes

1. For selected reviews, see: Sauvage, J.-P.; Dietrich-Buchecker, C. *Molecular Catenanes, Rotaxanes and Knots*; Wiley-VCH: Weinheim, 1999; Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348–3391.
2. (a) Murakami, H.; Kawabuchi, A.; Kotoo, K.; Kunitake, M.; Nakashima, N. *J. Am. Chem. Soc.* **1997**, *119*, 7605–7606; (b) Blanco, M.-J.; Jiménez, M. C.; Chambron, J.-C.; Heitz, V.; Linke, M.; Sauvage, J.-P. *Chem. Soc. Rev.* **1999**, *28*, 293–305; (c) Ashton, P. R.; Ballardini, R.; Balzani, V.; Credi, A.; Dress, K. R.; Ishow, E.; Kleverlaan, C. J.; Kocian, O.; Preece, J. A.; Spencer, N.; Stoddart, J. F.; Venturi, M.; Wenger, S. *Chem. Eur. J.* **2000**, *6*, 3558–3574; (d) Wurpel, G. W. H.; Brouwer, A. M.; van Stokkum, I. H. M.; Farran, A.; Leigh, D. A. *J. Am. Chem. Soc.* **2001**, *123*, 11327–11328; (e) Brouwer, A. M.; Frochot, C.; Gatti, F. G.; Leigh, D. A.; Mottier, L.; Paolucci, F.; Roffia, S.; Wurpel, G. W. H. *Science* **2001**, *291*, 2124–2128; (f) Stanier, C. A.; Alderman, S. J.; Claridge, T. D. W.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 1769–1772; (g) Bottari, G.; Leigh, D. A.; Pěrez, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 13360–13361; (h) Altieri, A.; Bottari, G.; Dehez, F.; Leigh, D. A.; Wong, J. K. Y.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 2296–2300; (i) Wang, Q.-C.; Qu, D.-H.; Ren, J.; Chen, K.; Tian, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2661–2665; (j) Qu, D.-H.; Wang, Q.-C.; Ren, J.; Tian, H. *Org. Lett.* **2004**, *6*, 2085–2088; (k) Murakami, H.; Kawabuchi, A.; Matsumoto, R.; Ido, T.; Nakashima, N. *J. Am. Chem. Soc.* **2005**, *127*, 15891–15899.
3. (a) Bissell, R. A.; Córdova, E.; Kaifer, A. E.; Stoddard, J. F. *Nature* **1994**, *369*, 133–137; (b) Armaroli, N.; Alzani, V. B.; Collin, J.-P.; Gaviña, P.; Sauvage, J.-P.; Ventura, B. *J. Am. Chem. Soc.* **1999**, *121*, 4397–4408; (c) Ballardini, R.; Balzani, V.; Dehaen, W.; Dell'Erba, A. E.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *Eur. J. Org. Chem.* **2000**, 591–602; (d) Altieri, A.; Gatti, F. G.; Kay, E. R.; Leigh, D. A.; Martel, D.; Paolucci, F.; Slawin, A. M. Z.; Wong, J. K. Y. *J. Am. Chem. Soc.* **2003**, *125*, 8644–8654; (e) Tseng, H.-R.; Vignon, S. A.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1491–1495; (f) Jeppesen, J. O.; Nielsen, K. A.; Perkins, J.; Vignon, S. A.; Fabio, A. D.; Ballardini, R.; Gandolfi, M. T.; Venturi, M.; Balzani, V.; Becher, J.; Stoddart, J. F. *Chem. Eur. J.* **2003**, *9*, 2982–3007; (g) Kihara, N.; Hashimoto, M.; Takata, T. *Org. Lett.* **2004**, *6*, 1693–1696; (h) Horie, M.; Suzaki, Y.; Osakada, K. *J. Am. Chem. Soc.* **2004**, *126*, 3684–3685.
4. Bottari, G.; Dehez, F.; Leigh, D. A.; Nash, P. J.; Pérez, E. M. P.; Wong, J. K. Y.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5886–5889.
5. (a) Martínez-Díaz, M.-V.; Spencer, N.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **1997**, *36*, 1904–1907; (b) Ashton, P. R.; Ballardini, R.; Balzani, V.; Baxter, I.; Credi, A.; Fyfe, M. C. T.; Gandolfi, M. T.; Gómez-López, M.; Martínez-Díaz, M.-V.; Piersanti, A.; Spencer, N.; Stoddart, J. F.; Venturi, M.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 11932–11942.
6. (a) Lane, A. S.; Leigh, D. A.; Murphy, A. *J. Am. Chem Soc.* **1997**, *119*, 11092–11093; (b) Gong, C.; Gibson, H. W. *Angew. Chem., Int. Ed.* **1997**, *36*, 2331–2333; (c) Ros, T. D.; Guldi, D. M.; Morales, A. F.; Leigh, D. A.; Prato, M.; Turco, R. *Org. Lett.* **2003**, *5*, 689; (d) Hannam, J. S.; Lacy, S. M.; Leigh, D. A.; Saiz, C. G.; Slawin, A. M. Z.; Stitchell, S. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3260–3264; (e) Pérez, E. M.; Dryden, D. T. F.; Leigh, D. A.; Teobaldi, G.; Zerbetto, F. *J. Am. Chem. Soc.* **2004**, *126*, 12210–12211.
7. (a) Jimenez-Molero, M. C.; Dietrich-Buchecker, C.; Sauvage, J.-P. *Chem. Eur. J.* **2002**, *8*, 1456–1466; (b) Keaveney, C. M.; Leigh, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1222–1224; (c) Vignon, S. A.; Jarrosson, T.; Iijima, T.; Tseng, H.-R.; Sanders, J. K. M.; Stoddart, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 9884–9885; (d) Leigh, D. A.; Pěrez, E. M. *Chem. Commun.* **2004**, 2262–2263; (e) Ghosh, P.; Federwisch, G.; Kogej, M.; Schalley, C. A.; Haase, D.; Saak, W.; Lützen, A.; Gschwind, R. M. *Org. Biomol. Chem.* **2005**, *3*, 2691–2700.
8. Nagawa, Y.; Suga, J.; Hiratani, K.; Koyama, E.; Kanesato, M. *Chem. Commun.* **2005**, 749–751; Hiratani, K.; Kaneyama, M.; Nagawa, Y.; Koyama, E.; Kanesato, M. *J. Am. Chem. Soc.* **2004**, *126*, 13568–13569; Tokunaga, Y.; Kakuchi, S.; Shimomura, Y. *Heterocyles* **2004**, *63*, 2713–2718.
9. Tokunaga, Y.; Yoshioka, M.; Nakamura, T.; Goda, T.; Nakata, R.; Kakuchi, S.; Shimomura, Y, unpublished results.
10. Tokunaga, Y.; Kakuchi, S.; Akasaka, K.; Nishikawa, N.; Shimomura, Y.; Isa, K.; Seo, T. *Chem. Lett.* **2002**, 810–811.
11. Since the recognition of rotaxane for a metal ion and for proton are competitive, proton-sponge® is used as a base to get the association constant (K). K values of Li^+ and Na^+ are calculated to be $10 \pm 0.2\ M^{-1}$ and $26 \pm 2.5\ M^{-1}$ from the integration of the corresponding species in the ^1H NMR ($CDCl_3$–CD_3CN (1:1), 27 °C) spectra of mixtures of rotaxane (3 mM), proton-sponge® (6 mM), and $LiPF_6$ or $NaPF_6$ (3 mM), respectively.



$$K = \frac{[\text{proton-sponge-H}^+]\,[\mathbf{3b}]}{[\text{proton-sponge}]\,[\mathbf{3a}]\,[\text{Li}^+]} \quad (M^{-1})$$