

Synthesis and Shuttling Behavior of Rotaxanes Consisting of Crown Ether Wheel and Disulfide Dumbbell with Two Ammonium Centers[†]

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Several [2]- and [3]rotaxanes bearing some functional groups on their wheel components and spacers with different lengths between two ammonium centers on their dumbbell components were prepared in good yields from dibenzo-24-crown-8-ether derivatives and dumbbell-shaped bis(sec-ammonium salt)s having a centrally located disulfide linkage, by utilizing the reversible thiol-disulfide interchange reaction. The shuttling behaviors of the [2]rotaxanes were investigated by ¹H NMR by use of the spin polarization transfer-selective inversion recovery technique. It was found that the change in spacer length in the axle resulted in a drastic change in shuttling rate of the [2]rotaxanes, although the introduction of the functional groups to the wheels did not affect the shuttling behavior at all.

Key Words : [2]Rotaxane, Crown ether, Ammonium salt, Disulfide, Shuttling

Introduction

One of the most striking features of interlocked molecules such as catenanes and rotaxanes is that their components can undergo relative movement without breaking covalent bonds.¹ This kind of dynamic processes such as shuttling have attracted much attention, because it is possible to control the relative positioning of their components through some external stimuli and they are hence expected to be molecular modules for future nano-scaled devices such as nano-computers (Scheme 1).²

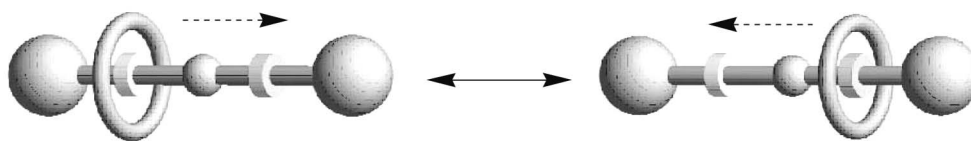
Recently, Stoddart *et al.* reported a catenane-based nano-calculator.³ In order to understand the relative movement such as shuttling processes and to explore catenane- and rotaxane-based nano-devices, it is necessary to investigate the effects of wheel and axle structures *etc.* Meanwhile, we have recently developed a new synthetic method "entering"

for [2]- and [3]rotaxanes by utilizing the thiol-disulfide interchange reaction (Scheme 2).⁴

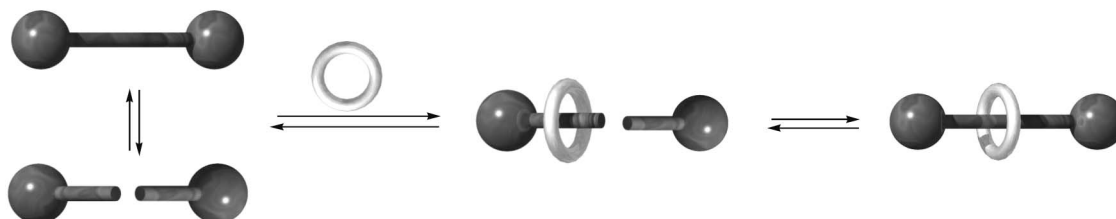
The yields of the rotaxanes can be well-controlled by the solvent, concentration, and temperature, since the whole process is reversible. Important features of this method involve the efficient thiol-disulfide interchange reaction under mild conditions and the tolerance of disulfide for many functional groups so that it is possible to introduce some functionalities to rotaxanes to control their shuttling behaviors. In this paper, we describe synthesis and shuttling behavior of rotaxanes having different functional group on the wheel and different spacer length in the axle.

Results and Discussion

Synthesis of Rotaxane. A catalytic amount (0.010 mol·L⁻¹) of benzenethiol was added to a degassed CDCl₃/CD₃CN



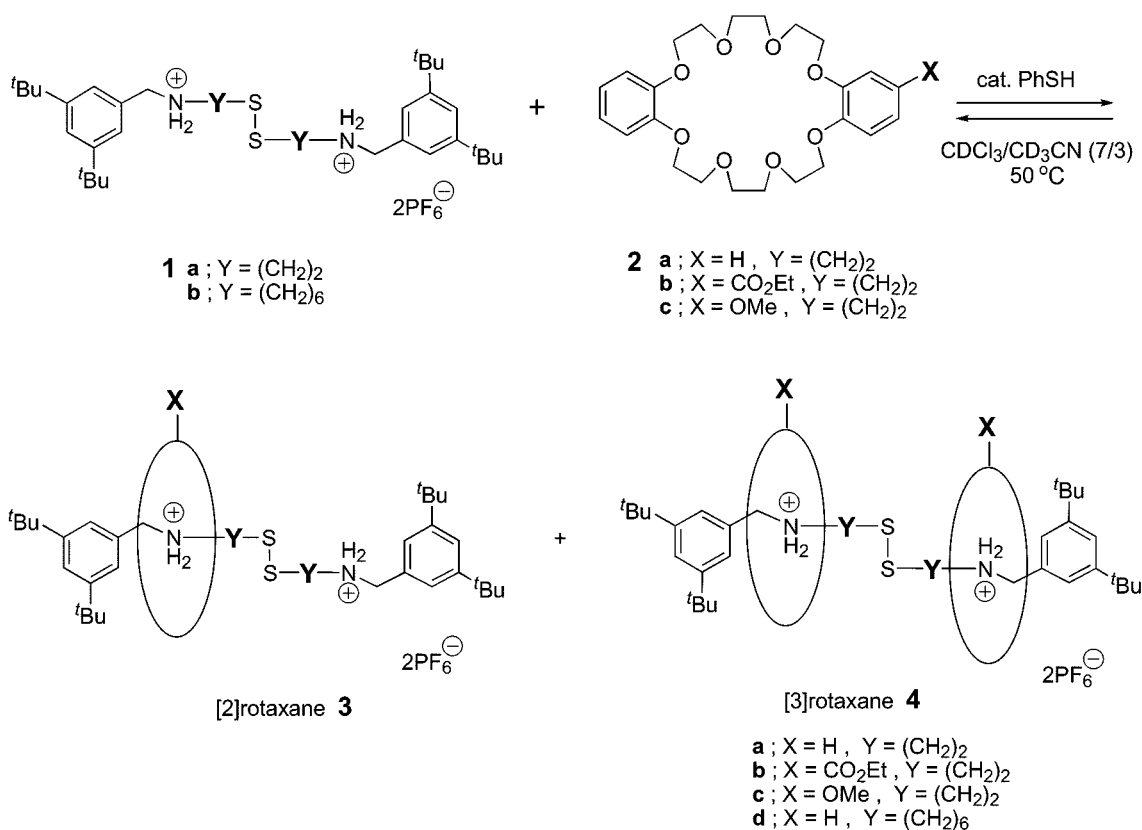
Scheme 1. Shuttling of [2]rotaxane.



Scheme 2. Entering method for preparation of rotaxane.

[†]Dedicated to Professor Yong Hae Kim for his distinguished achievements in organic chemistry.

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Scheme 3. Synthesis of [2]- and [3]rotaxanes by utilization of reversible cleavage of disulfide linkage.

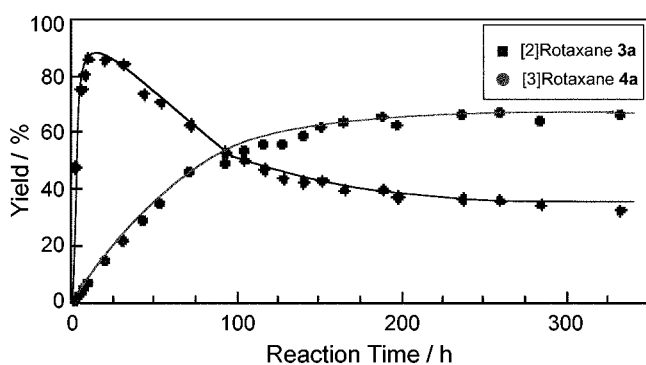


Figure 1. The Time Course of the Yields of [2]Rotaxane (**3a**) and [3]Rotaxane (**4a**). [**1a**] = 0.10 mol·L⁻¹, [**2a**] = 0.20 mol·L⁻¹, [PhSH] = 0.010 mol·L⁻¹ in CDCl₃/CD₃CN (7/3) at 50 °C.

(7/3) solution of a mixture of a dumbbell shaped ammonium salt with a centrally located disulfide linkage^{4a-b} (**1a**) (0.10 mol·L⁻¹) and dibenzo-24-crown-8-ether (**2a**) (0.20 mol·L⁻¹). The mixture was allowed to stand at 50 °C (Scheme 3). The reaction progress was monitored by ¹H NMR and the yields of [2]rotaxane^{4a-b} (**3a**) and [3]rotaxane^{4a-b} (**4a**) were determined by ¹H NMR. The time courses of the yields of **3a** and **4a** are shown in Figure 1.

The rotaxane **3a** was formed soon after the initiation, while **4a** gradually appeared. The yield of **3a** reached its maximum value (89%) after 10 h, and rapidly decreased to that at a certain equilibrium state. The signals of **4a** appeared

after ca. 4 h and the yield of **4a** increased with a decrease of that of **3a**. The system reached the equilibrium state after ca. 240 h (*i.e.* 10 days), where the yields of **3a** and **4a** were 35% and 65%, respectively (Table 1). Although the yield of **4a** can be easily enhanced up to ca. 90% by using excess amount of **2a**,^{4b} 1 : 2 mixture of **1a** and **2a** was used in this case for comparison with other systems. Both **3a** and **4a** were isolated with preparative HPLC in similar yields to those of ¹H NMR. The structures of them were characterized by ¹H NMR, FAB-MS, and elemental analysis.

By the same procedures, rotaxanes bearing ethoxy-carbonyl groups ([2]rotaxane (**3b**) and [3]rotaxane (**4b**)) and methoxy groups ([2]rotaxane (**3c**) and [3]rotaxane (**4c**)) were synthesized starting from 1 : 2 mixture of **1a** and **2b**,⁵ and from **1a** and **2c**, respectively (Scheme 3). The rotaxanes **3b**, **4b**, **3c**, and **4c** were purified with preparative HPLC. The structures of them were characterized by the ¹H NMR, FAB-MS, and elemental analysis. The yields of these rotaxanes at

Table 1. Yields of [2]rotaxane **3** and [3]rotaxane **4** at equilibrium in CDCl₃/CD₃CN (7/3) at 50 °C after 14 days

Entry	X	Y	[2]Rotaxane/Yield ^a	[3]Rotaxane/Yield ^a
1	H	(CH ₂) ₂	3a /35%	4a /65%
2	CO ₂ C ₂ H ₅	(CH ₂) ₂	3b /34%	4b /64%
3	OCH ₃	(CH ₂) ₂	3c /37%	4c /61%
4	H	(CH ₂) ₆	3d /54%	4d /46%

^aDetermined by ¹H NMR.

the equilibrium states determined by ^1H NMR were nearly equal to those of **3a** and **4a**. Thus, neither electron-withdrawing nature of the ethoxycarbonyl group **2b** nor the electron-donating nature of the methoxy group of **2c** affected the equilibria, i.e. the yields of the rotaxanes. These results suggest that a wide range of molecular designs can be performed in this synthetic protocol for rotaxane,^{4a-b} undoubtedly being advantageous from viewpoint of the applications of rotaxanes.

Rotaxanes bearing a longer spacer (hexamethylene spacer) between the two ammonium centers ([2]rotaxane (**3d**) and [3]rotaxane (**4d**)) were similarly synthesized by employing 1 : 2 mixture of a dumbbell-shaped bisammonium salt having a centrally-located disulfide linkage⁶ (**1b**) and dibenzo-24-crown-8 ether (**2a**). The reaction forming the rotaxanes was slightly slower than those of the rotaxanes having ethylene spacers (**3a-c** and **4a-c**), and the system reached the equilibrium within 14 days. The yields of **3d** and **4d** were 54% and 46%, respectively, by ^1H NMR at the equilibrium state. The total ratio of the complexation between the wheel and the dumbbell ammonium sites (146/200) in this case was lower than those of other cases (e.g. **3a** & **4a** : 165/200).

Shuttling Behavior. The energy barriers of shuttling and spinning processes in interlocked systems have been determined by the standard coalescence method in many cases.⁷ However, this method has disadvantages that the determination of coalescence temperature is inherently subjective and often becomes difficult because of poor shimming *etc.* On the other hand, the dynamic spin polarization transfer by selective inverse recovery (SPT-SIR) technique⁸ has none of these disadvantages mentioned above and has emerged as a new tool for determination of the energy barriers of shuttling processes. The shuttling behavior of the [2]rotaxanes (**3a-d**) was investigated by the SPT-SIR technique. The results are summarized in Table 2.

As indicated in Table 2, the activation free energy ΔG^\ddagger_{295} for the shuttling of **3a** showed 15.9 ± 0.1 kcal·mol⁻¹ that corresponded to the shuttling rate of 8.88 s⁻¹ (entry 1). **3b** and **3c** had the same ΔG^\ddagger_{295} of 15.9 ± 0.1 kcal·mol⁻¹ as that of **3a** (entries 2 and 3). On the other hand, ΔG^\ddagger_{295} of **3d** was estimated to be 17.9 ± 0.5 kcal·mol⁻¹ that corresponded to the shuttling rate of 0.323 s⁻¹, which was much slower than those of **3a-c** (entry 4). Thus, it is concluded that the shuttling is hardly affected by the substituent on the wheel

crown ether. However, the elongation of the spacer between the two ammonium centers (*i.e.* the two stations) resulted in considerable lowering in rate of the shuttling. These results clearly reveal that the distance between the two stations of the ammonium centers is an important factor for the control over the shuttling behavior. The fact that there is no effect by introduction of polar group on the wheel seems to coincide the assumption that the shuttling can be affected by the structural rigidity at the transition state much more than electronic effect, judging from the higher activation free energy in the case with a longer spacer presumably attributable to the higher structural flexibility of the dumbbell.

Summary

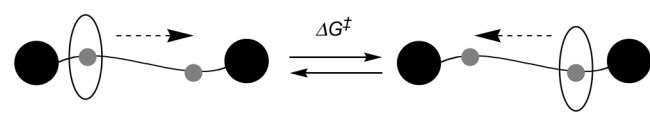
Regardless of the substituent on the crown ether wheel, [2]- and [3]rotaxanes could be synthesized in good yields. Although the introduction of a longer spacer between the two ammonium stations to the axle component causes a decrease in ratio of the complexation to the rotaxane formation, the synthetic method utilized in the construction of interlocked systems via the thiol-disulfide interchange reaction is emphasized again as an excellent protocol.^{4a-b} As for the control over shuttling behavior, distance between the two stations on the axle component was proved to exert the rate of the shuttling much more effectively than electronic effect of the substituent on the wheel in this system. This may be attributed to the flexibility change in the axle component.

Experimental Section

General. The melting points were measured on a Yanagimoto micro melting-point apparatus and were uncorrected. IR spectra were recorded on a JASCO FT-IR model 230 spectrometer. ^1H NMR measurements were performed on a JEOL JNM-GX-270 spectrometer in CDCl_3 with tetramethylsilane as an internal reference. FAB-MS measurements were performed on a Finnigan TSQ-70 instrument. For preparative HPLC, a JAICO LC-908 system with columns JAIGEL 1 (ϕ 20 mm \times 600 mm) and JAIGEL 2 (ϕ 20 mm \times 600 mm) was used.

4-Methoxy-dibenzo-24-crown-8 Ether (2b). To a solution of 4-formyl-dibenzo-24-crown-8-ether (447 mg, 0.938 mmol)⁹ in CH_2Cl_2 (6.0 mL) was added *m*-chloroperbenzoic acid (mCPBA, 69 mg, 0.40 mmol) and the mixture was stirred at ambient temperature for 43 h. The mixture was subjected to suction filtration and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate, and the solution was washed successively with 3% Na_2SO_3 , water, and brine, dried over anhydrous MgSO_4 , and evaporated to dryness. The residue was chromatographed over SiO_2 (CHCl_3 /ethy acetate (1/1)) to afford 4-formyloxy-dibenzo-24-crown-8-ether (DB24C8-OCHO) in 74% yield as a white solid. ^1H NMR (270 MHz, CDCl_3) δ 8.26 (s, 1H, CHO), 6.91-6.66 (m, 7H, ArH), 4.16-4.12 (m,

Table 2. Shuttling behavior of [2]rotaxane **3** in CD_3CN



Entry	X	Y	[2]rotaxane/ ΔG^\ddagger_{295} ^a
1	H	(CH_2) ₂	3a / 15.9 ± 0.1 kcal·mol ⁻¹
2	$\text{CO}_2\text{C}_2\text{H}_5$	(CH_2) ₂	3b / 15.9 ± 0.1 kcal·mol ⁻¹
3	OCH_3	(CH_2) ₂	3c / 15.9 ± 0.1 kcal·mol ⁻¹
4	H	(CH_2) ₆	3d / 15.9 ± 0.1 kcal·mol ⁻¹

^aDetermined by ^1H NMR using SPT-SIR technique.

8H, CH₂), 3.93-3.80 (m, 16H, CH₂).

A mixture of DB24C8-OCHO thus prepared (330 mg, 0.670 mmol), K₂CO₃ (2.23 g, 16.1 mmol) in MeOH (16 mL) was stirred under Ar atmosphere at ambient temperature for 9 h. The mixture was subjected to the ordinary suction filtration. To the mixture was added 2 M HCl aq. and the resulting mixture was extracted with CHCl₃. The CHCl₃ layer was washed with brine, dried over anhydrous MgSO₄, and evaporated to dryness to afford 4-hydroxy-dibenzo-24-crown-8 ether (DB24C8-OH) in 98% yield as a white solid. ¹H NMR (270 MHz, CDCl₃) δ 6.89 (s, 5H, ArH), 6.73 (d, *J* = 8.6 Hz, 1H, ArH), 6.46 (s, 1H, OH), 6.33 (d, *J* = 8.7 Hz, 1H, ArH), 4.15-4.06 (m, 8H, CH₂), 3.92-3.76 (m, 16H, CH₂).

To a suspension of NaH (60% oil dispersion, 32.6 mg, 0.814 mmol) in THF (3.0 mL) was added a solution of DB24C8-OH prepared above (291 mg, 0.626 mmol) in THF (9.0 mL) under Ar atmosphere, and the mixture was stirred at ambient temperature for 1 h. After addition of MeI (267 mg, 1.88 mmol), the mixture was refluxed for 3 h and then allowed to cool to 0 °C. To the mixture was added 2 M HCl aq. and the resulting mixture was extracted with CHCl₃. The CHCl₃ layer was washed with brine, dried over anhydrous MgSO₄, and evaporated to dryness. The residue was chromatographed over SiO₂ to afford 4-methoxy-dibenzo-24-crown-8 ether (**2c**) in 86% yield as a white solid. Mp. 68-71 °C. ¹H NMR (270 MHz, CDCl₃) δ 6.88-6.79 (m, 5H, ArH), 6.48 (d, *J* = 3.0 Hz, 1H, ArH), 6.38 (dd, *J*₁ = 8.9 Hz, *J*₂ = 3.0 Hz, 1H, ArH), 4.17-4.08 (m, 8H, CH₂), 3.93-3.83 (m, 16H, CH₂), 3.75 (s, 3H, OMe). FAB-MS (matrix: mNBA) *m/z* 478 [M⁺].

General Procedure for the Synthesis of [2]Rotaxane (3) and [3]Rotaxane (4). To a CD₃CN/CDCl₃ solution (0.3 mL/0.7 mL) of **1** (0.10 mmol) and **2** (0.20 mmol) was added a catalytic amount of benzenethiol (1.0 μL, 0.010 mmol). The solution was sealed in an NMR tube (ϕ 5 mm), which was heated at 50 °C. The reaction progress was monitored by ¹H NMR. The mixture was evaporated to dryness. The residue was subjected to preparative HPLC to afford [2]rotaxane (**3**) and [3]rotaxane (**4**).

The spectral data of [2]rotaxane (**3a**) and [3]rotaxane (**4a**) were reported previously.^{4a-b}

[2]Rotaxane (3b): ¹H NMR (270 MHz, CD₃CN) δ 7.6-7.2 (m, 13H, ArH), 4.65 (m, 2H, ArCH₂N), 4.3-3.0 (m, 32H, CH₂), 2.8-2.5 (m, 4H, CH₂), 1.32 (s, 18H, *t*-Bu), 1.31 (m, 3H, CH₃), 1.17 (s, 18H, *t*-Bu). FAB-MS (matrix: mNBA) *m/z* 1079 [M-2PF₆]⁺. Elemental analysis calcd (%) for C₆₁H₉₄F₁₂N₂O₁₀P₂S₂·(H₂O)_{0.5}: C53.15, H6.95, N2.03; found: C53.11, H7.15, N2.06.

[3]Rotaxane (4b): ¹H NMR (500 MHz, CDCl₃) δ 7.60 (d, *J* = 8.5 Hz, 2H, ArH), 7.46 (s, 2H, ArH), 7.25-7.17 (m, 10H, ArH, NH), 4.52-4.45 (m, 4H, CH₂), 4.26 (q, *J* = 7.0 Hz, 4H, CH₂), 4.20-3.32 (m, 52H, CH₂), 2.20-2.17 (m, 4H, CH₂), 1.30 (t, *J* = 7.0 Hz, 6H, CH₃), 1.29 (s, 36H, *t*-Bu). FAB-MS (matrix: mNBA) *m/z* 1600 [M-2PF₆]⁺. Elemental analysis calcd (%) for C₈₈H₁₃₀F₁₂N₂O₂₀P₂S₂·(H₂O)₁: C55.39, H6.97,

N1.47; found: C55.44, H7.11, N1.48.

[2]Rotaxane (3c): ¹H NMR (270 MHz, CD₃CN) δ 7.6-6.4 (m, 13H, ArH), 4.65 (m, 2H, ArCH₂N), 4.3-3.4 (m, 31H, CH₂ and OCH₃), 3.14 (m, 2H, CH₂), 2.8-2.5 (m, 4H, CH₂), 1.32 (s, 18H, *t*-Bu), 1.19 (s, 18H, *t*-Bu). FAB-MS (matrix: mNBA) *m/z* 1036 [M-2PF₆]⁺. Elemental analysis calcd (%) for C₅₉H₉₂F₁₂N₂O₉P₂S₂·(H₂O)₁: C52.67, H7.04, N2.08; found: C52.91, H7.13, N2.12.

[3]Rotaxane (4c): ¹H NMR (500 MHz, CDCl₃) δ 7.28-7.19 (m, 10H, ArH, NH), 6.81-6.75 (m, 10H, ArH), 6.36 (s, 2H, ArH), 6.35 (d, *J* = 8.5 Hz, 2H, ArH), 4.53-4.46 (m, 2H, CH₂), 4.15-3.99 (m, 8H, CH₂), 3.89-3.73 (m, 8H, CH₂), 3.6-3.48 (m, 34H, CH₂, CH₃), 2.18-2.14 (m, 4H, CH₂), 1.11 (s, 36H, *t*-Bu). FAB-MS (matrix: mNBA) *m/z* 1514 [M-2PF₆]⁺. Elemental analysis calcd (%) for C₈₄H₁₂₆F₁₂N₂O₁₈P₂S₂·(H₂O)₁: C55.31, H7.07, N1.54; found: C55.16, H7.17, N1.57.

[2]Rotaxane (3d): ¹H NMR (270 MHz, CD₃CN) δ 7.6-6.8 (m, 14H, ArH), 4.62 (m, 2H, ArCH₂N), 4.2-2.4 (m, 34H, CH₂), 1.7-1.0 (m, 16H, CH₂), 1.31 (s, 18H, *t*-Bu), 1.19 (s, 18H, *t*-Bu).

[3]Rotaxane (4d): ¹H NMR (270 MHz, CD₃CN) δ 7.6-6.8 (m, 24H, ArH), 4.62 (m, 4H, ArCH₂N), 4.3-3.2 (m, 56H, CH₂), 2.47 (t, *J* = 7.2 Hz, 4H, CH₂), 1.5-1.0 (m, 16H, CH₂), 1.19 (s, 36H, *t*-Bu). FAB-MS (matrix: mNBA) *m/z* 1569 [M+2H-2PF₆]⁺.

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