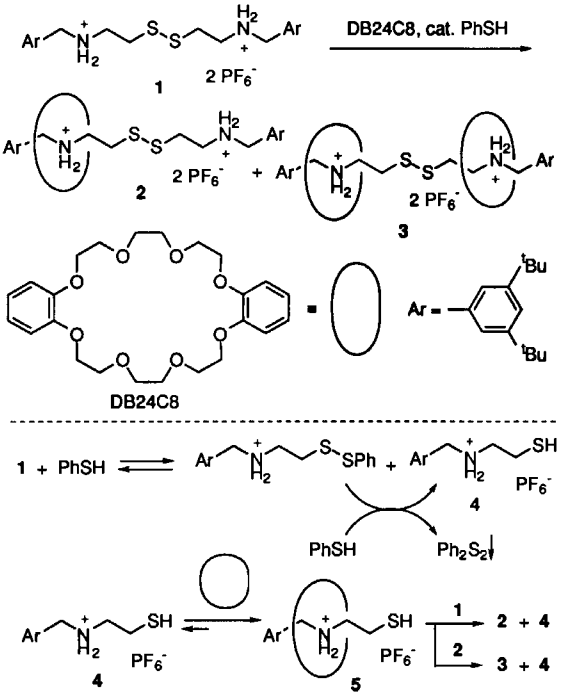
"Unlock-Lock" Approach to [2] and [3]Rotaxanes: Entering of a Ring through Disulfide Linkage That is Unlocked by Thiol "Key"

Yoshio Furusho, Toshihide Hasegawa, Akiyoshi Tsuboi, Nobuhiro Kihara, and Toshikazu Takata*
Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Sakai, Osaka 599-8531

(Received September 2, 1999; CL-990762)

Bifunctional secondary ammonium salt bearing disulfide linkage at the center and bulky group at the both termini was mixed with dibenzo-24-crown-8. During reversible cleavage of the disulfide linkage catalyzed by benzenethiol, crown ether entered the disulfide linkage to afford corresponding [2] and [3]rotaxanes.

Recently, interlocked compounds such as catenanes and rotaxanes have occupied much attention.[1] Among many synthetic strategies toward such compounds, one of the most attractive methods is self-aggregation based on "unlock-lock" principle,[2] where a certain chemical bond in the component molecules was "unlocked" to be labile or free by a certain "key" stimulation, and after self-aggregation to form the precursor, the chemical bond is "locked" by the removal of the key to give the desired interlocked compounds. As the latent labile chemical bonds, coordination of nitrogen ligand to the transition metal ion[2a] and carbon-carbon double bond in the presence of metathesis catalyst[2b] have been reported. We were prompted to use disulfide linkage as the latent labile chemical bond because the disulfide linkage can be unlocked by various key stimulation,[3] *i.e.*, nucleophile, photo-irradiation, and heating. In this paper, we wish to report a novel "lock" in combination with "key" for the preparation of [2] and [3]rotaxanes, *i.e.*, thiol-catalyzed reversible open-close of disulfide linkage.



Scheme 1.

Bifunctional secondary ammonium salt **1** possessing disulfide linkage at the center and 3,5-di-*tert*-butylphenyl groups at the both termini was prepared. ^{1}H-NMR spectrum of a mixture of **1** and dibenzo-24-crown-8 (DB24C8) was simple superimposition of each spectrum, and was not changed by heating at 100 °C at all.

Among the candidate keys to unlock the disulfide, we selected benzenethiol as a thiophilic nucleophile.[3] Thus, catalytic amount of benzenethiol (0.01 mol/L) was added to a mixture of **1** (0.1 mol/L) and DB24C8 (0.2 mol/L) in CD_3CN at room temperature. After 1 h, a new set of ^{1}H-NMR signals appeared, and a small amount of white precipitates formed. After 24 h, a further new set of peaks appeared in the ^{1}H-NMR spectra. These observations indicated some chemical changes by the presence of thiol. The system reached a stationary state after 30 days. From the reaction mixture, desired [2]rotaxane **2** (8%) and [3]rotaxane **3** (58%) were isolated by preparative GPC.[4,5] Comparing their ^{1}H-NMR spectra with those of the reaction mixture, we could assign the new sets of signals in the reaction mixture to each rotaxane, *i.e.*, **2** appeared first and **3** second. Figure 1 shows ^{1}H-NMR spectra of these rotaxanes.

The yields of **2** and **3** were monitored by the integral of the ^{1}H-NMR spectra, and were plotted against the reaction time as shown in Figure 2. The yields of **2** and **3** estimated from the

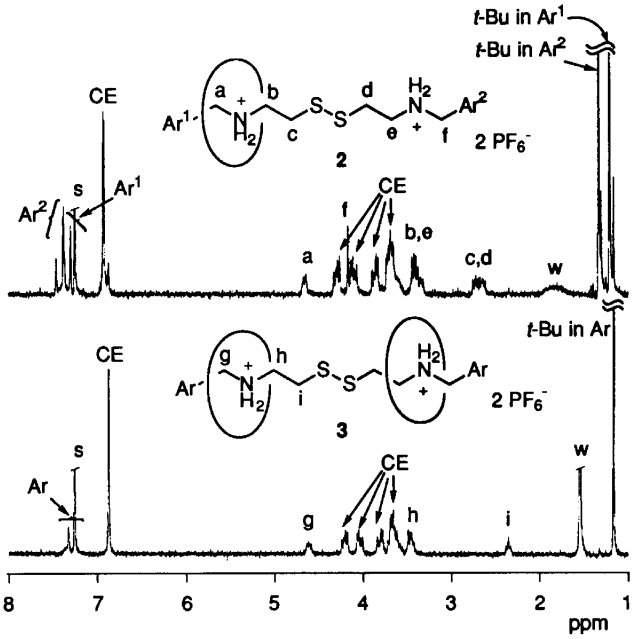


Figure 1. ^{1}H-NMR spectra ($CDCl_3$, 270 MHz, 298 K) of [2]rotaxane **2** and [3]rotaxane **3**. "s", "CE", and "w" denote $CHCl_3$, DB24C8, and water, respectively. Ar is 3,5-di-*tert*-butyl phenyl group. NH signals that appear around 7.3 ppm are very broad.

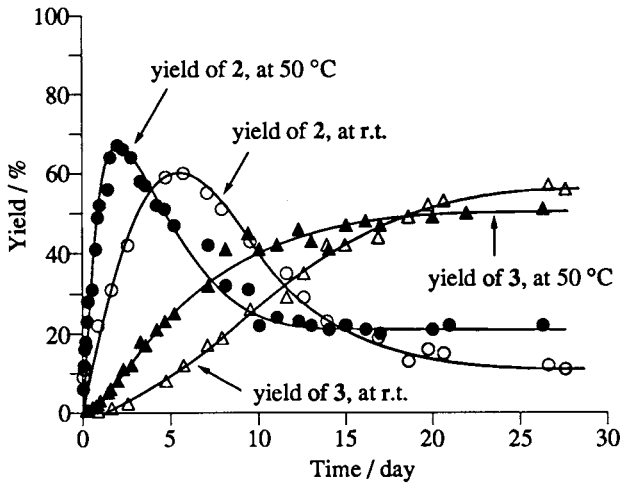


Figure 2. Time-yield curves of **2** and **3** in acetonitrile at r.t. and 50 °C. The yields are monitored by ^{1}H-NMR.

^{1}H-NMR spectra well corresponded to the isolated yields. Further, the precipitates formed at the initial stage of the reaction were identified as diphenyl disulfide.

These results suggest following reaction mechanism (Scheme 1). The reaction is initiated by nucleophilic attack of benzenethiol at disulfide linkage to give diphenyl disulfide and thiol **4** eventually. Since diphenyl disulfide is hardly soluble in acetonitrile, it is precipitated to be eliminated from the reaction system. DB24C8 rapidly enters **4** to afford pseudorotaxane **5**,[7] which undergoes nucleophilic attack at disulfide linkage of **1** to give [2]rotaxane **2**. After **2** is stored up in the system, **5** starts to attack disulfide linkage of **2** to yield [3]rotaxane **3**. Finally, the system reaches an equilibrium where the concentration of **2** and **3** depends on their thermodynamic stability.

The reaction temperature and the amount of thiol used affected the rate of the reaction and the yield as summarized in Table 1 and Figure 1. When the reaction was carried out at 50 °C, the system reached an equilibrium faster, although the equilibrium shifted to the less complexed species because the rotaxane-formation is exothermic. Thus, the yield of **3** decreased at higher temperature while that of **2** increased. As the concentration of thiophenol decreased, the reaction was retarded, so as that it was easy to obtain **2** in a good yield (68%).

Table 1. Preparation of rotaxanes **2** and **3**[a]

[PhSH] / mol·L^{-1}	Temperature / °C	Time / day	Yield[b] / % 2	3
0.01	r.t.	30	8	58
0.01	50	30	29	52
0.001	50	10	68	13

[a] In acetonitrile. [**1**] = 0.1 mol/L. [DB24C8] = 0.2 mol/L.
[b] Isolated yield.

In conclusion, we have demonstrated validity of a novel couple of "lock" and "key," disulfide and thiol, and the first example of rotaxane preparation utilizing "unlock-lock" principle. Unlocking and locking could be controlled easily by the addition and removal of the key catalyst. Because of the potential availability of the disulfide system, synthesis of various interlocked molecules by this principle is under active investigation.

We acknowledge financial support by Grant-in-Aid for Scientific Research on Priority Areas (A) (No. 11133258) from the Ministry of Education, Science, Sports and Culture and grant from The Association for the Progress of New Chemistry.

References and Notes

1 Recent reviews: a) J.-C. Chambron and J.-P. Sauvage, *Chem. Eur. J.*, **4**, 1362 (1998). b) S. A. Nepogodiev and J. F. Stoddart, *Chem. Rev.*, **98**, 1959 (1998). c) A. Harada, *Acta Polymer.*, **49**, 3 (1998). d) V. Balzani, M. Gómez-López, and J. F. Stoddart, *Acc. Chem. Res.*, **31**, 405 (1998).

2 a) M. Fujita, *Acc. Chem. Res.*, **32**, 53 (1999). b) T. J. Kidd, D. A. Leigh, and A. J. Wilson, *J. Am. Chem. Soc.*, **121**, 1599 (1999).

3 "Organic Chemistry of Sulfur," ed by L. Field and S. Oae, Plenum Press, New York (1977), Chap. 7.

4 Rotaxane structure was confirmed by ^{1}H-NMR spectra, FAB-MS, and the fact that **2** and **3** survived several repetition of chromatographic operation. **2**: ^{1}H NMR (270 MHz, CD_3CN): δ 7.6-7.2 (br, 2H), 7.51 (s, 1H), 7.44 (s, 1H), 7.30 (s, 2H), 7.26 (s, 2H), 7.0-6.8 (m, 8H), 4.7-4.6 (m, 2H), 4.3-3.4 (m, 30H), 3.1-3.0 (m, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 1.31 (s, 9H), 1.19 (s, 9H) ppm; FAB-MS (*m*-NBA): *m/z* 1006 [M^+-PF_6]. **3**: ^{1}H NMR (270 MHz, CD_3CN): δ 7.51 (t, *J* = 1.6 Hz, 2H), 7.38 (d, *J* = 1.6 Hz, 4H), 7.3-7.1 (br, 4H), 7.0-6.9 (m, 8H), 6.9-6.8 (m, 8H), 4.5-4.4 (m, 4H), 4.2-3.3 (m, 56H), 1.24 (s, 18H) ppm; FAB-MS (*m*-NBA): *m/z* 1601 [M^+-PF_6].

5 ^{1}H-NMR spectrum of **2** at room temperature shows that two ammonium groups are under the different circumstances, indicating crown ether is localized at one of the ammonium groups. At elevated temperature, however, ^{1}H-NMR spectrum of **2** indicates that two ammonium groups become equivalent. These observations clearly indicates that the crown ether ring "shuttles"[6] between the two ammonium "stations." The activation energy of this shuttling is 68.2 ± 0.5 kJ/mol at 50-60 °C calculated by using Eyring equation.

6 P. R. Ashton, D. Philip, N. Spencer, and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, **1992**, 1124.

7 a) P. R. Ashton, E. J. T. Chrystal, P. T. Glink, S. Menzer, C. Schiavo, N. Spencer, J. F. Stoddart, P. A. Tasker, A. J. P. White, and D. J. Williams, *Chem. Eur. J.*, **2**, 709 (1996). b) P. T. Glink, C. Schiavo, J. F. Stoddart, and D. J. Williams, *Chem. Commun.* **1996**, 1483.