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Remarkable Effects of Chirality on Deslipping Reactions of Diastereomeric Rotaxanes and Relevant Mechanism Involving Pre-Equilibrium

Keiji Hirose,* Yamato Nakamura, and Yoshito Tobe

Division of Frontier Materials Science, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 563-8531, Japan

hirose@chem.es.osaka-u.ac.jp

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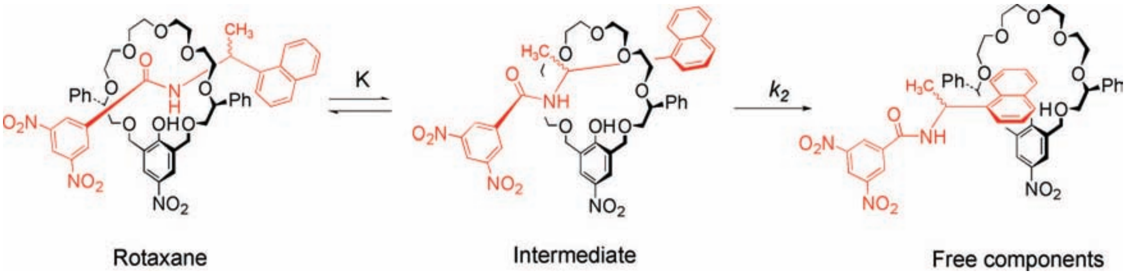
ABSTRACT



The first clear differentiation on deslipping rates affected by the difference in the diastereomeric stereocenters of rotaxanes up to 8.4 times and unexpectedly large steric kinetic isotope effect on the deslipping reaction (ca. 20%) were observed. On the basis of the kinetic parameters, steric kinetic isotope effect, and ^{1}H NMR spectra of the nondeuteriated and deuteriated rotaxanes, we propose a deslipping mechanism involving pre-equilibrium.

The deslipping reaction is a characteristic reaction of rotaxanes by which the ring and axle components are disconnected without breaking a covalent bond.[1] Ease of deslipping is affected not only by the relative size of the ring and the stopper units but also by subtle structural changes such as the length of the axle and the flexibility of the components.[1e,f] However, there are no reports that focus on the difference between deslipping rates of diastereomeric rotaxanes, even though a large difference is expected because of steric restriction between the ring and dumbbell components connected by mechanical bonding. Herein we report a large difference between the deslipping rates of diastereomeric rotaxanes **1**·(*S*)-**2** and **1**·(*R*)-**2** (Scheme 1) up to 8.4 times and a relevant mechanism involving pre-equilibrium between the conformers with respect to the position of the axle component relative to the ring, which was elucidated on the basis of the activation parameters and the steric kinetic isotope effect.

As diastereomeric rotaxanes, we designed **1**·(*S*)-**2** and **1**·(*R*)-**2** composed of homochiral ring component **1** with *S,S* configuration and enantiomeric axle component (*S*)-**2** or (*R*)-**2** (Scheme 1). Ring component **1** was chosen because of the excellent chiral recognition property of this ring system toward secondary amines.[2] Component **2** was used, because the 3,5-dinitrobenzyl stopper is large enough to trap it kinetically within the rotaxane structure,[3] whereas the

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[1] (a) Raymo, F. M.; Houk, K. N.; Stoddart, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 9318–9322. (b) Ashton, P. R.; Baxter, J.; Fyfe, M. C. T.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 2297–2307. (c) Chiu, S.-H.; Rowan, S. J.; Cantrill, S. J.; Clink, P. T.; Garrell, R. L.; Stoddart, J. F. *Org. Lett.* **2000**, *2*, 3631–3634. (d) Hübner, F. M.; Nachtsheim, G.; Li, Q. Y.; Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 1269–1272. (e) Afffeld, A.; Hübner, F. M.; Seel, C.; Schalley, C. A. *Eur. J. Org. Chem.* **2001**, 2877–2890. (f) Linnartz, P.; Bitter, S.; Schalley, C. A. *Eur. J. Org. Chem.* **2003**, 4819–4829. (g) Felder, T.; Schalley, C. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2258–2260. (h) Nygaard, S.; Laursen, B. W.; Flood, A. H.; Hansen, C. N.; Jeppesen, J. O.; Stoddart, J. F. *Chem. Commun.* **2006**, 144–146.

10.1021/ol802571d CCC: $40.75

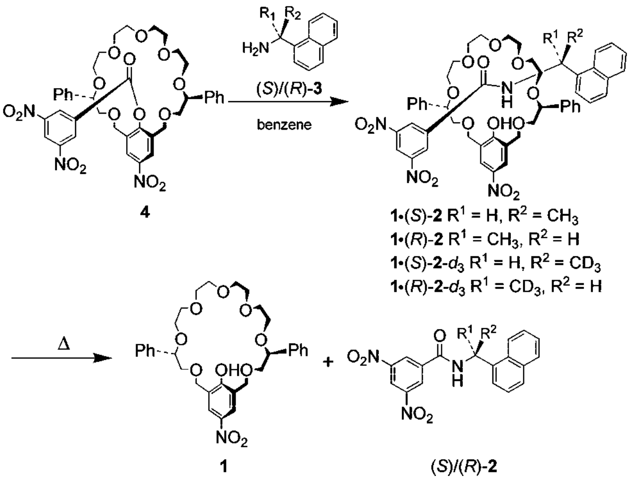
Table 1. Kinetic Parameters for Deslipping Reactions of **1**·(*S*)-**2** and **1**·(*R*)-**2**

solvent	rotaxane	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (eu)	$t_{1/2}{}^{a}$ (h)	$\Delta G^{\ddagger a}$ (kJ mol^{-1})	$k_R/k_S{}^{a}$
toluene-d_8	**1**·(*S*)-**2**	78	−98	223	108	8.4
	1·(*R*)-**2**	75	−91	27	102	
TCE-d_2	**1**·(*S*)-**2**	90	−65	502	110	5.7
	1·(*R*)-**2**	87	−63	87	105	
CD_3CN	**1**·(*S*)-**2**	66	−120	20	102	2.0
	1·(*R*)-**2**	72	−95	10	100	
DMF-d_7	**1**·(*S*)-**2**	61	−117	2.1	96	2.3
	1·(*R*)-**2**	67	−92	0.9	94	
DMSO-d_6	**1**·(*S*)-**2**	63	−111	2.2	96	2.0
	1·(*R*)-**2**	71	−80	1.1	95	

[a] At 298 K calculated from $\Delta H^{\ddagger}$and$\Delta S^{\ddagger}$.

bulkiness of the (*S*)- and (*R*)-1-(1-naphthyl)ethyl stoppers would be ideal for them to slip out from the ring with measurable kinetic barriers.

Scheme 1. Synthesis of Diastereomeric Rotaxanes and Their Deslipping Reactions



The rotaxanes **1**·(*S*)-**2** and **1**·(*R*)-**2** were synthesized via aminolysis of prerotaxane **4** with (*S*)- or (*R*)-**3** in benzene.[3] **1**·(*S*)-**2** and **1**·(*R*)-**2** can be isolated and characterized as kinetically stable compounds; however, especially in the case of the latter compound, deslipping reactions took place slowly even at room temperature in chloroform.

The deslipping rates were measured by ^{1}H NMR spectroscopy in toluene-d_8, tetrachloroethane-d_2 (TCE-d_2), acetonitrile-d_3, DMF-d_7, and DMSO-d_6. All deslipping reactions followed first-order kinetics. From the rate constants at several different temperatures (Table S1 in Supporting Information), the kinetic parameters $t_{1/2}$ (298 K) and k_R/k_S (298 K) were estimated as summarized in Table 1. Apparently, the deslipping reactions of **1**·(*S*)-**2** were slower than those of **1**·(*R*)-**2** ($k_R/k_S > 1$); the largest difference between the reaction rates was observed when toluene-d_8 was used as a solvent ($k_R/k_S = 8.4$). In less polar solvents (toluene-d_8 and TCE-d_2), the lower deslipping rates of **1**·(*S*)-**2** than those of **1**·(*R*)-**2** mainly originate from the larger activation enthalpies of the former. On the other hand, in polar solvents (acetonitrile-d_3, DMF-d_7, and DMSO-d_6), whereas activation enthalpies for the deslipping reactions of **1**·(*S*)-**2** are smaller than those of **1**·(*R*)-**2**, the activation free energies of **1**·(*S*)-**2** are still larger than those of **1**·(*R*)-**2**. Hence, the lower deslipping rates of **1**·(*S*)-**2** than **1**·(*R*)-**2** in polar solvents are attributed to the more negative activation entropies of **1**·(*S*)-**2**. These results suggest that in polar solvents **1**·(*S*)-**2** suffers from greater degree of solvation than **1**·(*R*)-**2** during the deslipping process.

To gain more insight into the mechanism of the deslipping, steric kinetic isotope effect (SKIE) on the deslipping was examined by using the corresponding trideuterio derivatives **1**·(*S*)-**2**-d_3 and **1**·(*R*)-**2**-d_3, in which the methyl group was replaced by trideuteriomethyl.[4] SKIE was utilized as a good probe to assess steric compression in the transition states of various types of reactions[5] including deslipping reaction of rotaxanes.[1g] The rate constants of **1**·(*S*)-**2**-d_3 and **1**·(*R*)-**2**-d_3 in TCE-d_2 at 70 °C and in DMSO-d_6 at 30 °C were determined, from which k_H/k_D was estimated (Table 2). As a result, while SKIEs of **1**·(*R*)-**2** in TCE-d_2 (0.98 ± 0.02) and **1**·(*S*)-**2** in DMSO-d_6 (0.96 ± 0.02) were small, large isotope effect was observed in the case of **1**·(*S*)-**2** in TCE-d_2 (0.90 ± 0.02) and **1**·(*R*)-**2** in DMSO-d_6 (0.81 ± 0.02). In

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(2) (a) Hirose, K.; Fujiwara, A.; Matsunaga, K.; Aoki, N.; Tobe, Y. *Tetrahedron Lett.* **2002**, *43*, 8539–8542. (b) Hirose, K.; Fujiwara, A.; Matsunaga, K.; Aoki, N.; Tobe, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 555–566.

(3) Hirose, K.; Nishihara, K.; Harada, N.; Nakamura, Y.; Masuda, D.; Araki, M.; Tobe, Y. *Org. Lett.* **2007**, *9*, 2969–2972.

(4) Trideuteriated rotaxanes **1**·(*S*)-**2**-d_3 and **1**·(*R*)-**2**-d_3 were synthesized in the same manner as for **1**·(*S*)-**2** and **1**·(*R*)-**2** using trideuteriated amine **3**-d_3, which was prepared according to the reported procedure: Sawada, M.; Hagita, K.; Imamura, H.; Tabuchi, H.; Yododa, S.; Umeda, M.; Takai, Y.; Yamada, H.; Yamaoka, H.; Hirose, K.; Tobe, Y.; Tanaka, T.; Takahashi, S. *J. Mass Spectrom. Soc. Jpn* **2000**, *48*, 323–332. The degree of isotopic labeling (>98%) was determinined by ^{1}H NMR and mass spectra, and the enantiomeric excess (>99%) was checked by HPLC using a chiral column.

(5) (a) Mislow, K.; Graeve, R.; Gorgon, A. J.; Wahl, G. H. *J. Am. Chem. Soc.* **1963**, *85*, 1199–1200. (b) Hayama, T.; Baldridge, K. K.; Wu, Y.-T.; Linden, A.; Seigel, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 1583–1591. (c) Liu, Y.; Warmuth, R. *Org. Lett.* **2007**, *9*, 2883–2886. (d) Ślebocka-Tilk, H.; Motallebi, S.; Nagorski, R. W.; Turner, P.; Brown, R. S.; McDnald, R. *J. Am. Chem. Soc.* **1995**, *117*, 8769–8776.

Table 2. Steric Kinetic Isotope Effects (= k_H/k_D) on Rate Constants of Deslipping Reactions of **1**·(*S*)-**2** and **1**·(*R*)-**2**

rotaxane	solvent	temp (K)	k_H/k_D
1·(*S*)-**2**	TCE-d_2	343	0.90 ± 0.02
	DMSO-d_6	303	0.96 ± 0.02
1·(*R*)-**2**	TCE-d_2	343	0.98 ± 0.02
	DMSO-d_6	303	0.81 ± 0.02

particular, the observed SKIE of the latter is considerably larger than most of those reported.[6]

With the above data in hand, we propose a plausible mechanism of the deslipping reactions of **1**·(*S*)-**2** and **1**·(*R*)-**2** consisting of two steps as shown in Figure 1a. In the first step, the smaller methyl group of the stopper unit passes through the ring component while the larger naphthyl group is left behind the ring (i.e., TS_1).[1a] Examination of molecular models suggests that the methyl group would pass through the ring with little steric compression, equilibrating the original rotaxane with the Figure 1b. In this mechanism involving the pre-equilibrium, the observed rate constant k_{obs} is expressed by k_1, k_{-1}, and k_2, or K ($=k_1/k_{-1}$) and k_2 as follows:

$$k_{obs} = k_1 \cdot k_2 / k_{-1} = K \cdot k_2$$

The presence of an unusually large SKIE in the deslipping of **1**·(*R*)-**2** in DMSO-d_6 indicates that the equilibrium constant K of the pristine rotaxane is different from that of the deuterated one.

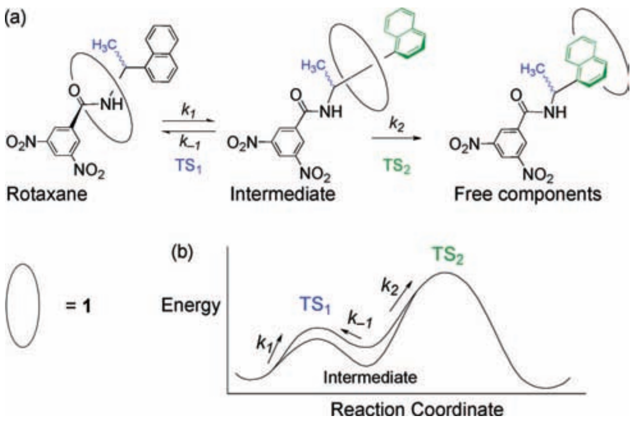

Figure 1. Two-step mechanism of the deslipping reaction (a) and its energy diagram (b).

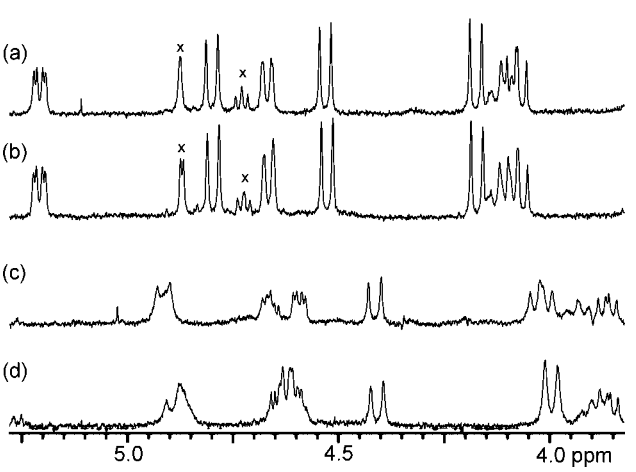

Figure 2. Partial ^{1}H NMR spectra of **1**·(*R*)-**2** and **1**·(*R*)-**2**-d_3. (a) **1**·(*R*)-**2**-d_3 in TCE-d_2 at 343 K and (b) **1**·(*R*)-**2** in TCE-d_2 at 343 K. (c) **1**·(*R*)-**2**-d_3 in DMSO-d_6 at 303 K and (d) **1**·(*R*)-**2** in DMSO-d_6 at 303 K. The mark × represents the signals due to the free ring component **1** generated during the sample preparation and measurement.

To prove this assumption, ^{1}H NMR spectra of nondeuteriated and deuteriated rotaxanes were compared.[7] In the case of the **1**·(*R*)-**2** in TCE-d_2 under which conditions the deslipping reaction exhibited small SKIE, nearly identical signals of nondeuteriated and deuteriated rotaxanes are observed (Figure 2a and b), indicating the equilibrium constants are identical. Similarly, the ^{1}H NMR spectra of **1**·(*S*)-**2** and **1**·(*S*)-**2**-d_3 in TCE-d_2 and DMSO-d_6 are identical (Figures S2 and S3 in Supporting Information, respectively). In contrast, the ^{1}H NMR signals of **1**·(*R*)-**2** in DMSO-d_6 at 4.0, 4.6, 4.9 ppm apparently differ from those of **1**·(*R*)-**2**-d_3 (Figure 2c and d). These results indicate that the deslipping takes place via a mechanism including pre-equilibrium between the ground-state and the intermediate, and the pre-equilibrium constants of **1**·(*R*)-**2** and **1**·(*R*)-**2**-d_3 are different in DMSO-d_6, leading to the large SKIE that was observed. The less negative activation entropy of **1**·(*R*)-**2** in DMSO-d_6 than that of **1**·(*S*)-**2** suggests that the population of the intermediate, which is more susceptible to solvation, relative to the ground-state rotaxane of the former diastereomer is larger than that of the latter. The diastereoselectivity, therefore, depends on both the magnitude and the balance between the pre-equilibrium constant (K) and the rate of the second step (k_2).

In conclusion, we have demonstrated the large difference of the deslipping reaction rates between diastereomeric rotaxanes **1**·(*S*)-**2** and **1**·(*R*)-**2**. On the basis of the kinetic parameters and the steric kinetic isotope effects, a two-step deslipping mechanism including a pre-equilibrium was elucidated.

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Supporting Information Available: Details of experimental and data analysis procedures. This materials is available free of charge via the Internet at http://pubs.acs.org.

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(6) For example, following SKIEs were reported: single bond rotation of a biphenyl derivative (0.84),[5a] bowl-bowl inversion of a corranulene derivative (0.82),[5b] bromination of bis(7-norbornylidene) (0.65).[5d]

(7) Rechavi, D.; Scarso, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 7738–773.