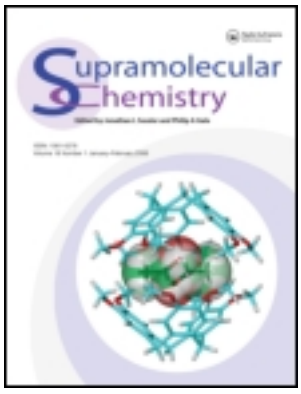

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An efficient synthetic entry to rotaxanes utilising reversible cleavage of aromatic disulphide bonds

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Reversible cleavage of an aromatic disulphide bond of a dumbbell-shaped molecule having two *sec*-ammonium salt moieties enabled the insertion of the disulphide linkage through a crown ether to give the corresponding [2]- and [3]rotaxanes. The formation of the rotaxanes proceeded much more rapidly than the case of an aliphatic disulphide system.

Keywords: rotaxane; dynamic covalent chemistry; disulphide bond

Rotaxanes prepared by reversible cleavage of aromatic disulphide bond

Rotaxanes have occupied an important position in chemistry and related fields since Ogino's first directed synthesis of cyclodextrin-containing rotaxane in 1981 (*1*). In addition to the challenges to create molecular switches and devices (*2*), those to obtain sophisticated and useful polymers containing rotaxane skeletons have also been carried out on the basis of the synthetic protocol of rotaxanes (*1–3*). Therefore, the development of an efficient synthetic route to rotaxanes is always an important issue. The significance of dynamic covalent chemistry in rotaxane synthesis has been recognised (*4–7*), whereas we have reported the efficient synthesis of [2]- and [3]rotaxanes using reversible cleavage of aliphatic disulphide linkages (*8*). As the disulphide bond is tolerant to various functional groups and reaction conditions, this method could be applied to construct more complex materials: poly[3]rotaxane (*9*) from a bifunctional dibenzo-24-crown-8-ether (DB24C8) and polyrotaxane network (*10*) from poly(DB24C8). Furthermore, the polyrotaxane network could be quantitatively decross-linked to the starting main chains with high efficiency (*10*). Although, the reversible cleavage of aliphatic disulphide bond actually provides a powerful method to construct rotaxane skeletons, the low-cleavage efficiency of the disulphide bond required considerable time to reach the equilibrium (*8*). To overcome such an issue, we envisioned that the use of aromatic disulphide bonds would shorten the reaction time because it shows highly efficient cleavage efficiency. Herein, we describe the facile synthesis of crown ether-based [2]- and [3]rotaxanes from a dumbbell-shaped bis(ammonium salt) possessing an aromatic disulphide linkage **1**.

Ditopic *sec*-ammonium salt **1** (0.10 M) and DB24C8 (0.30 M) were mixed in $CDCl_3$–CD_3CN (7/3) (Scheme 1). The addition of a catalyst (benzenethiol, 10 mol%) to the mixture was followed by the monitoring of the ^{1}H NMR spectral change (Figure 1). Several signals assigned to the axle component (signals a–g) were shifted to the signals a′–g′ in the spectrum obtained after 31 h. In particular, signals a (1.33 ppm), d (3.85 ppm) and e (4.30 ppm) clearly shifted to a′ (1.18 ppm), d′ (4.56–4.52 ppm) and e′ (4.73–4.69 ppm), respectively. As these shifts agreed with those of our previously reported results (*8*), the formation of rotaxanes was strongly suggested. The purification of the reaction mixture was carried out by preparative size exclusion chromatography (SEC) to yield [2]rotaxane **2** (2%) and [3]rotaxane **3** (87%). The structures of the rotaxanes were determined by ^{1}H NMR (Figure 2), ^{13}C NMR, IR and HRMS (see Supplementary Material, available online). The rotaxanation ratio was determined from the ^{1}H NMR integral ratio of signal d′ to the total of the signals 1, 2, 1′ and 2′. The time-dependent rotaxanation ratio is shown in Figure 3. When the reaction was carried out at 60°C, the reaction was fast so that the reaction system reached equilibrium within 12 h. When the reaction temperature was lowered, the reaction became slower and required longer time to reach equilibrium. The reaction reached equilibrium within only 31 h at 0°C. On the other hand, it took about 20 days for aliphatic disulphidic axle **1′** under the same conditions (*8*). The big difference in the reaction rate between **1** and **1′** clearly supported the initially proposed superiority of aromatic disulphides.

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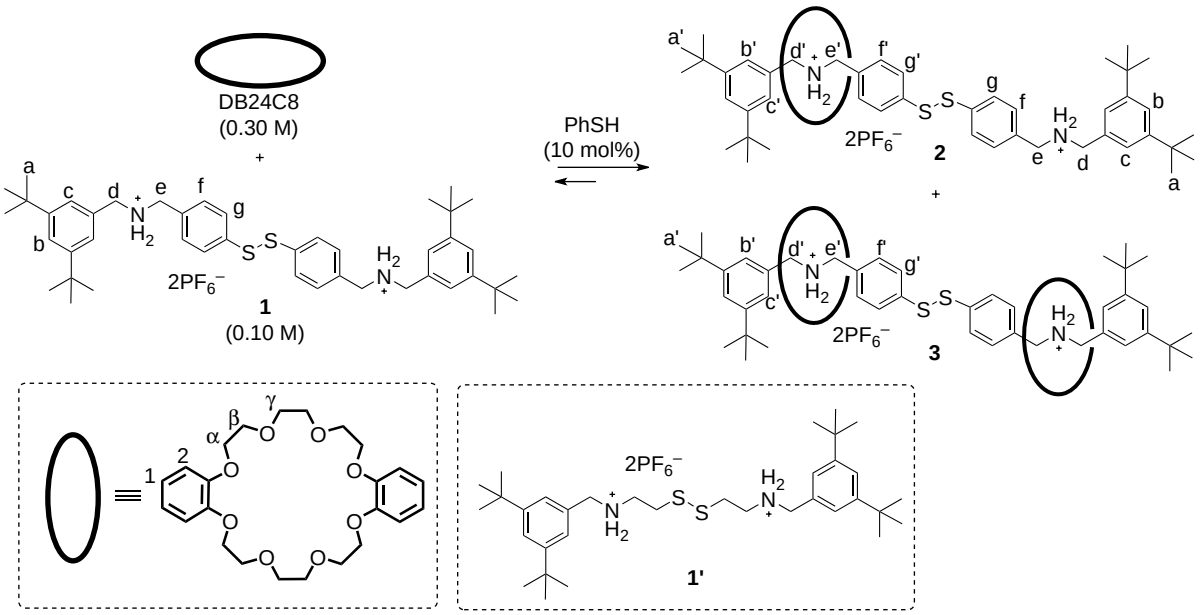


Scheme 1. Synthesis of [2]- and [3]rotaxanes via disulphide exchange.

The much higher reactivity of the aromatic disulphide moiety of **1** than **1′** can be accounted for by assuming the concentration of intermediate unsymmetrical disulphide and thiol derived from **1** or **1′**, formed by the initial reaction with the catalyst thiol. Namely, the formation of rotaxane, more precisely, the insertion of the disulphide linkage through the crown ether wheel occurs only with the unsymmetrical disulphide **III** and the half-dumbbell-type thiol **IV** as intermediates, each of which has a small terminal capable of threading DB24C8 (Scheme 2). Therefore, it is easily conceivable that the rate difference between **1** and **1′** is attributed not only to the small equilibrium constant (k_1/k_{-1}) but also to the small threading rate (k_1) itself. In other words, the advantage of the aromatic disulphide linkage-containing axle component like **1** comes from the fast initial S—S bond cleavage of the axle component by the thiol catalyst (*11*).

Finally, the yield of rotaxanes grew very high as well as that for **1′** (~90%). It should be noted that the yield was slightly affected by the reaction temperature. According to our previous study on rotaxanation of **1′**, the yield of

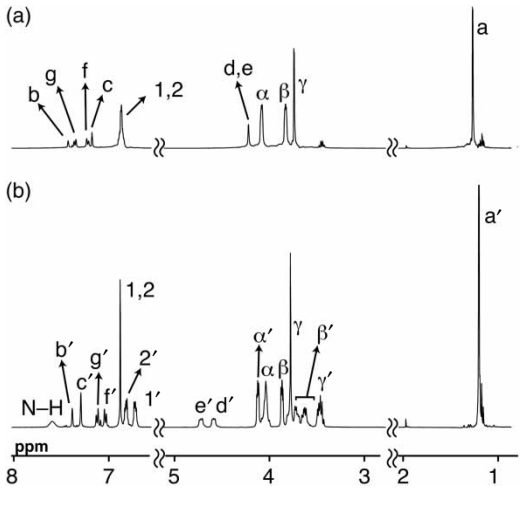


Figure 1. ^{1}H NMR spectra (400 MHz, 298 K) of mixture of DB24C8 (0.30 M) and **1** (0.10 M) in $CDCl_3$–CH_3CN (7/3) after (a) 15 min and (b) 31 h from the addition of 10 mol% benzene thiol.

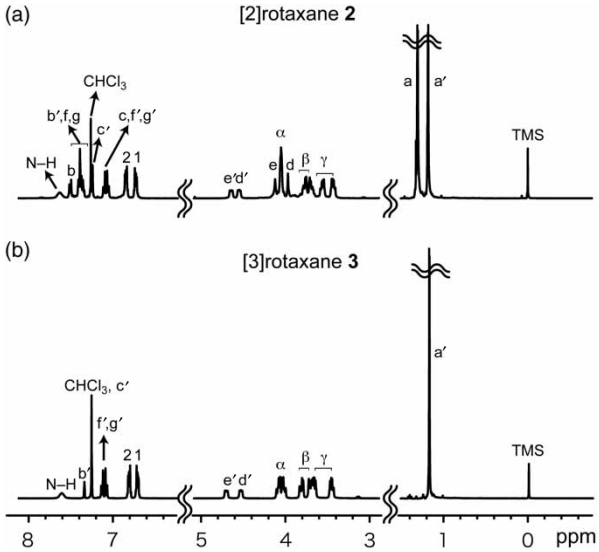


Figure 2. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) **2** and (b) **3**. For symbols of signals, see Scheme 1.

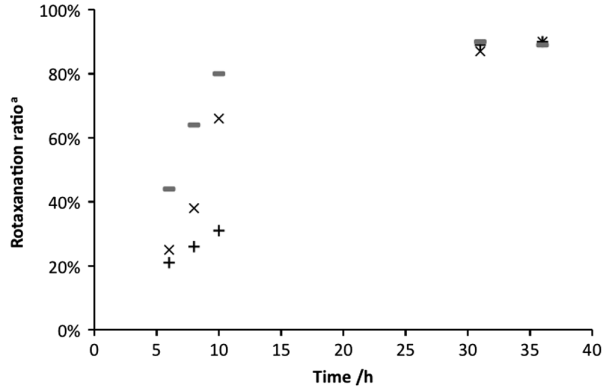


Figure 3. Time-dependent rotaxanation ratio from the mixture of DB24C8 (0.30 M) and **1** (0.10 M) at 0°C (+), 20°C (×) and 50°C (−) in $CDCl_3$–CH_3CN. (a) Rotaxanation ratio was determined from the ^{1}H NMR integral ratio of signal d′ to total of the signals 1, 2, 1′ and 2′ in Figure 1.

rotaxane increased at the lower temperature due to the negative reaction entropy (*8*). However, the yields of rotaxanes for **1** scarcely depended on the temperature. It is well known that the hydrogen bonding between benzylic protons of **1** and DB24C8 results in high-enthalpy gain for rotaxanation (*12*). Thus, we found that the entropic effect on total free energy for rotaxanation became so small that the final yields of rotaxanes were scarcely dependent on the reaction temperature. In other words, the introduction of aromatic moieties into the axle components leads to an increase in the equilibrium constant (k_2/k_{-2}) for rotaxanation. The use of **1** undoubtedly enhances the complexation efficiency or the stability of the complex and thereby contributes to both the formation rate and the yield of rotaxanes. Therefore, the structure of the aromatic disulphide clearly improved not only the yield but also the reaction time in comparison with the case of the aliphatic disulphide axle.

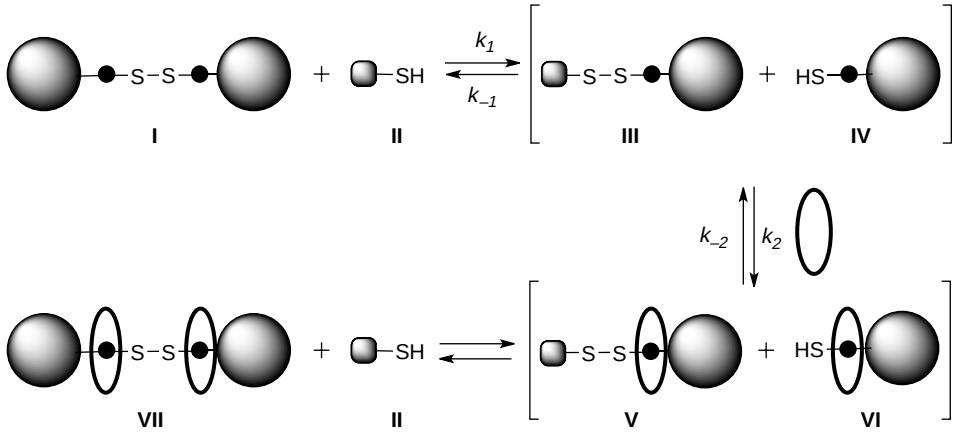
The effect of the catalyst concentration on the yield of rotaxane **3** was investigated. In the reaction at 20°C for 12 h, **3** was obtained in 87% yield in the presence of 10 mol% of benzenethiol. Since benzenethiol and **1** become equilibrium via the thiol–disulphide interchange as shown in Scheme 1, the amount of catalyst should be determined from the viewpoints of both the reaction rate and the equilibrium rate. As shown in Table 1, 1 mol% of benzenethiol afforded **2** (44%) and **3** (26%), suggesting that the reaction system did not reach equilibrium. In fact, when the concentration of benzenethiol was decreased to 0.1 mol%, the yields of the rotaxanes actually decreased to 6% (**2**) and 7% (**3**). These results revealed that the thermodynamic stability of the rotaxanes is important for high-yield synthesis; the equilibrium rate is also a key factor.

In this work, we achieved the efficient synthesis of rotaxanes using the dynamic nature of aromatic disulphide linkages in which a dramatic shortening of the reaction time was observed. Since the complexation between the aromatic disulphide axle and the crown ether wheel was favourable enough to shift the equilibrium to the product side, kinetic considerations became important to obtain them in high yields in this system. Therefore, the high-yield synthesis of the rotaxanes could be accomplished in a wide range of temperature in a short time. The present

Table 1. The effect of concentration of benzenethiol on the rotaxane yield.[a]

	Yield/%[b]	
(PhSH)/mol%	**2**	**3**
10	2	87
5	13	75
1	44	26
0.1	6	7

[a] The reaction was performed using **1** (0.10 mol/l) and DB24C8 (0.30 mol/l) in $CHCl_3$–CH_3CN (7/3) at 20°C for 12 h.
[b] Isolated yield.



Scheme 2. Reaction mechanism of rotaxane formation.

simultaneous achievement of both high yield and high speed via the fast equilibrium of a covalent bond can give some insight into the construction of complicated and sophisticated systems by molecular integration.

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