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Selective Synthesis of a [3]Rotaxane Consisting of Size-Complementary Components and Its Stepwise Deslippage

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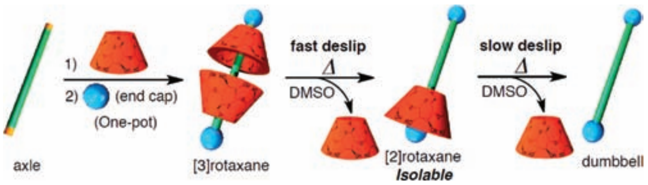
ABSTRACT



An α-cyclodextrin-based size-complementary [3]rotaxane with an alkylene axle was selectively synthesized in one pot via an end-capping reaction with 2-bromophenyl isocyanate in water. Thermal degradation of the [3]rotaxane product yielded not only the original components but also the [2]rotaxane. Thermodynamic studies suggested a stepwise deslippage process.

Size-complementary rotaxanes,[1] which contain a wheel, an axle, and a size-complementary group to end-cap the wheel cavity, are unique rotaxanes.[2] The rotaxane structure is kinetically stabilized enough to be isolated under normal conditions, but it can be dissociated into its components when certain conditions are satisfied. The dynamic properties of rotaxanes have been utilized to develop polymers capable of undergoing reversible polymerization[3] and network polymers that are degradable and recyclable under specific stimuli in order to avoid damage to the trunk polymer due to the lack of covalent bond breaking at the cross-linking points.[4,5] While such achievements have been made with crown ether/ammonium and crown ether/paraquat rotaxane systems,[3−5] no cyclodextrin (CD)-based size-complementary [3]rotaxane has been reported, except the one described by Harada, probably because of the synthetic challenges.[6] We have recently disclosed the one-pot high-yielding synthesis of CD-based

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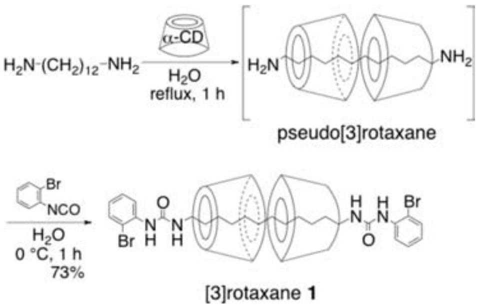
polyrotaxanes in water.[7] We expected that this synthetic protocol would be applicable to simple rotaxanes, and because a simple alkylene axle-containing α-CD-based rotaxane has not been reported to date, we have studied the synthesis and properties of such a rotaxane.[7,8] In this paper, we report the synthesis and unique deslipping behavior of a size-complementary α-CD-based [3]rotaxane.

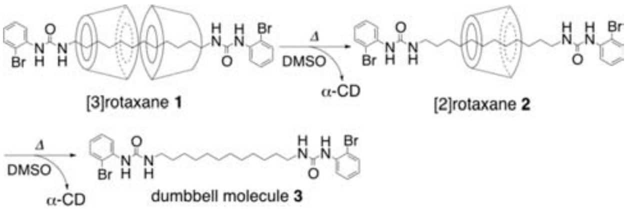
Prior to the synthesis of the size-complementary [3]rotaxane, we examined both the size of the end-cap group and the length of the axle component by Corey, Pauling, and later improved by Kultun (CPK) model studies. It was found that the 2-bromophenyl group serves as an end-cap group that is size-complementary to α-CD and that dodecamethylene has an appropriate axle length. The one-pot synthesis of [3]rotaxane was carried out according to our previously reported method for CD-based polyrotaxanes.[8] The threading complexation of 1,12-diaminododecane and α-CD in refluxing water for 1 h to form pseudo[3]rotaxane gave a heterogeneous mixture to which 2-bromophenyl isocyanate was added at 0 °C. The resulting mixture was allowed to stand for 1 h to end-cap the axle termini (Scheme 1). Standard workup afforded corresponding [3]rotaxane **1** in 73% yield. Two remarkable results were achieved: (i) the yield was exceptionally high in spite of the heterogeneous system and (ii) no [2]rotaxane was formed.[9] Meanwhile, neither phenyl- nor 2-methylphenyl isocyanate could be used as the end-cap group, both yielding only a dumbbell-shaped product. It is interesting that subtle differences in the size and electronic properties of the end-cap group markedly affected the end-cap function.

Scheme 1. One-Pot Synthesis of [3]Rotaxane **1** from 1,12-Diaminododecane and α-CD via the Urea End-Capping Method



[3]Rotaxane **1** was sufficiently stable to carry out ^1H NMR measurements in DMSO-d_6 at rt. The spectrum was consistent with the structure of **1** (Figure 1A). To examine the size-complementarity of the components of **1**, a solution of **1** in DMSO-d_6 was heated at 100 °C for 2.5 h. A clear spectral change occurred just after heating at 100 °C and progressed based on the heating time, indicating the prompt thermal degradation of **1**. Analysis of the product supported the formation of not only [2]rotaxane **2** but also dumbbell-shaped molecule **3**, both of which were easily

Scheme 2. Thermal Degradation of [3]Rotaxane **1** to [2]Rotaxane **2** and a Dumbbell Molecule **3** via the Deslippage of α-CD



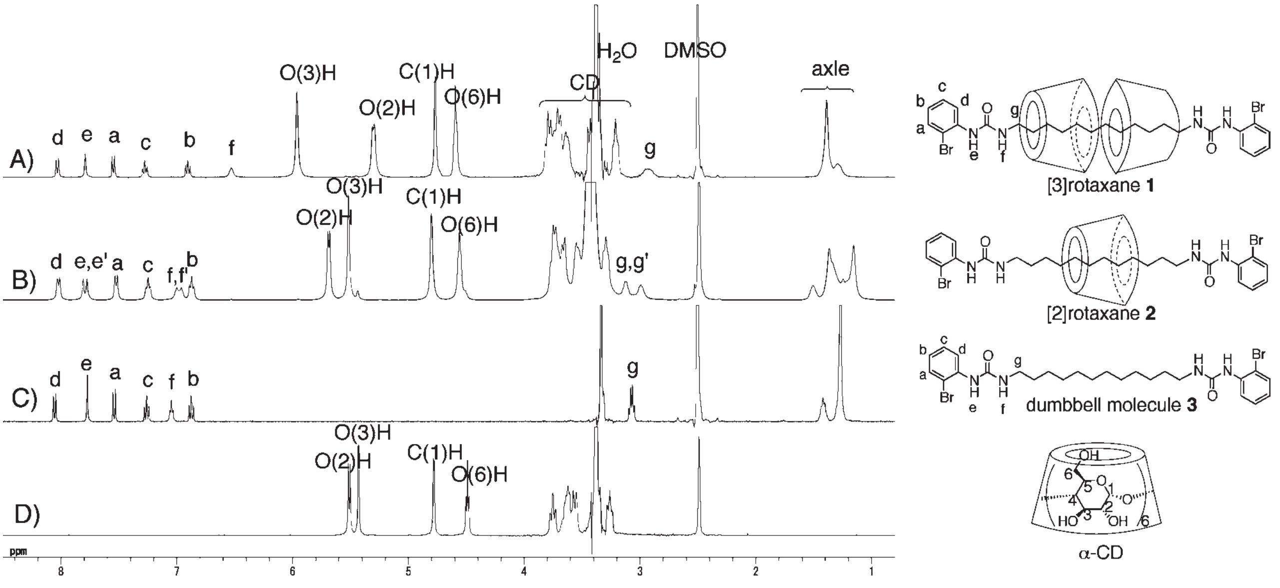


Figure 1. ^1H NMR spectra of (A) **1**, (B) **2**, (C) **3**, and (D) α-CD (400 MHz, DMSO-d_6, 298 K).

purified by reversed phase column chromatography (Scheme 2). This result indicated the occurrence of thermal deslipping of α-CD from **1** as well as **2**, which is consistent with the initial prediction that **1** consists of size-complementary components. The isolation of [2]rotaxane **2** (54% yield) indicated that (i) deslipping from **2** to **3** is slower than that from **1** to **2**, and (ii) [2]rotaxane, which is difficult to synthesize by the typical synthetic procedure, is readily obtained,[9,10] although it was not predicted on the basis of the structural characteristics of **1** and **2**.

Figure 1 shows the ^{1}H NMR spectra of **1**, **2**, and **3**, which coincide well with their structures. In spectrum A, the simple signal pattern that was observed around the urea N–H signals (e and f: δ = 6.50 ppm) and the α-proton signals (g: δ = 3.00–2.86 ppm) suggested structural symmetry. Therefore, **1** is expected to have a symmetrical head-to-head CD arrangement, judging from previous reports that the secondary hydroxyl groups of the CD face each other.[7,11] On the other hand, in spectrum B, the split signals around both the axle termini and alkylene chain were consistent with the unsymmetrical structure of **2**, whose lack of symmetry originates from the unsymmetrical nature of the α-CD moiety (Figure 1B). In this spectrum, the pairs of N–H protons (e, e′: δ = 7.81 and 7.78 ppm, f, f′: δ = 7.00 and 6.96 ppm) and the protons at the α-position (g, g′: δ = 3.06 and 2.99 ppm) of the urea groups appeared separately. The chemical shifts of the OH protons at the 2-, 3-, and 6-positions and the C–H proton at the 1-position of the CDs were diagnostic for **1**, **2**, and **3** because of the large differences in chemical shift. In addition the high resolution mass spectral data of **1** and **2** strongly supported their structures.[12]

Since [2]rotaxane **2** could be isolated, a kinetic profile of the deslippage of both **1** and **2** was investigated to elucidate the features of the reaction. A solution of **1** in DMSO-d_6 was heated at arbitrary temperatures (333, 353, 373, and 393 K) and subjected to ^{1}H NMR measurements. Figure 2 shows the time-dependent NMR spectral changes of **1** in DMSO-d_6 at 373 K as an example. The spectrum of the reaction mixture distinctly exhibited the intermediary formation of **2** and ultimately converged to a 1:2 molar ratio mixture of **3** and α-CD after 1100 min.

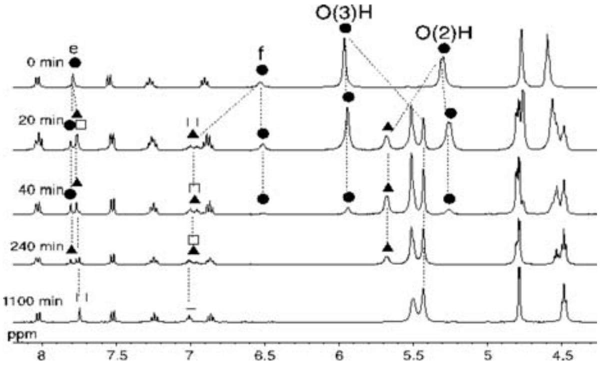


Figure 2. Time-dependent NMR spectral changes around the 8.0–4.5 ppm region (400 MHz, DMSO-d_6, 298 K) during the deslippage reaction of **1**. The reaction was carried out with a solution of **1** (5.1 μmol) in DMSO-d$_6$ (0.6 mL) at 373 K. The diagnostic peaks are marked as **1** (●), **2** (▲), and **3** (□).

The yield–time course curves **1**–**3** are shown in Figure 3. The formation of [2]rotaxane **2** started soon after heating began, while **3** appeared more gradually. The yield of **2** reached its maximum value (ca. 80%) after 1.4 h. With the assumption that these deslippage reactions obeyed first-order kinetics, the rate constants were determined from the time vs ln([rotaxane]/[rotaxane]$_0$) plots using the integral ratios from the ^{1}H NMR spectra (Table 1).[12] Table 1 summarizes the reaction rate constants (k) of the deslippage and the half-lives (τ) of **1** and **2**. The deslippage rate constant of **2** (k_2) was ~10 times smaller than that of **1** (k_1) at all temperature levels, leading to the remarkable difference in

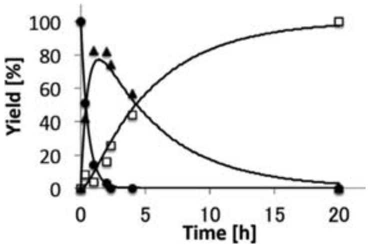


Figure 3. Time course curves of the formation of **1** (●), **2** (▲), and **3** (□). The reaction was carried out with **1** (5.1 μmol) in DMSO-d_6 (0.6 mL) at 373 K. These plots are fitted with the theoretical curves estimated from the kinetic parameters.

Table 1. Rate Constants (k) for The Two-Step Deslippage Reaction of [3]Rotaxane **1** (**1** → **2** → **3**) and Half-Lives (τ) of **1** and **2**[a]

temp/K	k_1/s^{-1}	τ_1/h	k_2/s^{-1}	τ_2/h
333	2.1×10^{-5}	9.2	2.4×10^{-6}	80
353	6.5×10^{-5}	3.0	6.6×10^{-6}	29
373	5.0×10^{-4}	0.39	5.2×10^{-5}	3.7
393	–[b]	–[b]	2.8×10^{-4}	0.68

[a] The reaction was carried out with **1** (5.1 μmol) in DMSO-d_6 (0.6 mL). The terms k_1 and τ_1 are for the reaction **1** → **2**, and k_2 and τ_2, for **2** → **3**. [b] Not determined.

Table 2. Thermodynamic Parameters of Deslippage of **1** and **2**

rotaxane	activation energy (E)[a]/ kJ·mol^{-1}	activation enthalpy ($\Delta H^{\ddagger}$)[b]/ kJ·mol^{-1}	activation entropy ($\Delta S^{\ddagger}$)[b]/ J·mol^{-1}·K^{-1}
[3]rotaxane	81	78	–101
[2]rotaxane	88	85	–99

[a] The activation energy was determined using an Arrhenius plot. [b] The activation enthalpy and entropy were determined using an Eyring plot.

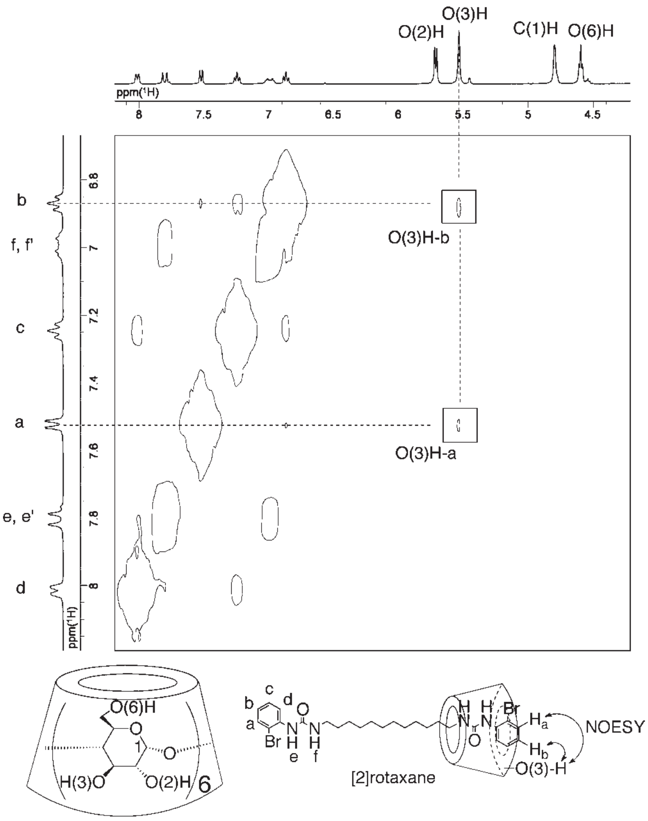


Figure 4. NOESY NMR spectrum of **2** (400 MHz, DMSO-d_6, 298 K).

the half-lives. These results clearly suggest the stepwise deslippage of **1**, including the fast formation of **2** and its slow decomposition to **3**, facilitating the isolation of **2**.

The thermodynamic parameters of the deslippage processes are summarized in Table 2. The activation energy (E) was determined from a plot of $1/T$ vs $\ln k$,[12] whereas the activation enthalpy ($\Delta H^{\ddagger}$) and activation entropy ($\Delta S^{\ddagger}$) were derived from a plot of $1/T$ vs $\ln(k/\mathrm{T})$. As a result, it was found that the deslippage process depends mainly on the enthalpy term ($\Delta H^{\ddagger}$) rather than the entropy term ($T\Delta S^{\ddagger}$). The activation enthalpy of the deslippage of **2** is much larger than that of the deslippage of **1**, implying a thermodynamically stable structure of **2**.

To evaluate the stability of **2**, we acquired a NOESY NMR spectrum (Figure 4). The protons of the axle end group (a and b) have NOE cross peaks with the protons O(3)H of α-CD. This indicates the localization of the α-CD wheel at the one end group by forming an inclusion complex with the α-CD cavity from its head side. This complexation would contribute to the stability of **2** (Scheme 2), being in good accordance with the large $\Delta H^{\ddagger}$ of **2**, as shown in Table 2. On the other hand, the result suggests that the tail face of CD does not effectively form such an inclusion complex. Therefore, the CD moieties in **1** with the head-to-head structure undergo deslippage more rapidly than those in **2**.

In conclusion, the present study has provided several crucial insights and a scientific basis for rotaxane and polyrotaxane studies from the following results: (i) a selective synthesis of new size-complementary [3]rotaxane in 73% yield, (ii) the discovery of the unique deslipping behavior of CD, (iii) an evaluation of the stabilization effect of [2]rotaxane based on the structural features, and (iv) formation of a simple alkylene axle-containing CD-based [2]rotaxane with a covalently capped end for the first time. The results and insights obtained in this study will be utilized in a variety of rotaxane-based systems and materials such as rotaxane switches and degradable and recyclable cross-linked polymers, some of which are currently underway.

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Supporting Information Available. Full experimental details for all new compounds, including ^{1}H NMR, ^{13}C NMR, IR spectra, and details of the kinetic and thermodynamic parameters are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Details on the synthesis of alkylene axle-containing CD-based rotaxanes will be discussed elsewhere (e.g., ref 7).

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(12) See Supporting Information.