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Slipping synthesis of cucurbit[7]uril-based [2]rotaxane in organic environment

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ABSTRACT

A dumbbell molecule with one naphthalimide and one isophthalic acid stoppers was synthesized and could fold into the cavity of cucurbit[7]uril (CB[7]) in formic acid to form a 1:1 complex. Once the solution of the complex was heated, the CB[7] ring would slip over the isophthalic acid unit, producing a stable [2]rotaxane. The energy barrier ($\triangle H^{\ddagger}$) of this slippage was estimated as 109 kJ mol^{-1}.

Rotaxanes are interlocked molecular systems where one or more macrocycles are trapped by a dumbbell-shaped molecule. Resulting from the possibility of the macrocycles to conduct linear movements along the dumbbell-shaped molecule, rotaxanes have found applications in areas of molecular switches,[1] logic gates,[2] memories,[3] machines,[4] and catalytic systems,[5] and thus have attracted the attention of an ever-increasing group of researchers. Cucurbiturils (CBs) are a series of barrel-shaped macrocycles that are obtained from the acid-catalyzed cyclization between glycoluril and formaldehyde. Owing to their easy synthesis, high stability, and strong binding affinities with cationic guests, CBs are one of the superior macrocyclic candidates in constructing rotaxanes.[6] CB-based rotaxanes are usually obtained using the capping strategy which involves a threading process between the CB ring and a linear guest and the consequent stopping by bulky ends. Because these threading processes occur only in aqueous environments, water-soluble organic intermediates and aqueous organic reactions are demanded, and as a result, there are only a few methods reported in the construction of CB-based rotaxanes, namely Click cycloaddition,[7] dinitrophenyl stopping,[8] amide-bond formation,[9] and coordinating stopping.[10] Herein we demonstrate a slipping strategy to synthesize a CB-based [2]rotaxane in an organic acid, which is simple with good-yield, and suitable for non-water soluble guest. This methodology might open a new way toward the supramolecule fabrication of CBs.

The slippage strategy for rotaxane is usually carried out by mixing the macrocycle and the dumbbell together in a certain solvent and then heating at a high temperature that the macrocycle could overcome the activation energy to slip over the dumbbell's stopper. When the solution is cooled down, the rotaxane was formed because the re-dissociation into the components becomes impossible as a result of the energy barrier. In this work, cucurbit[7]uril (CB[7]) was chosen as the ring component for its appropriate cavity for adopting a wide range of guests, as well as for the relative large choice of the stoppers for the slippage. The dumbbell molecule **2** consists of one linear alkyl viologen unit linked by two stoppers—one 1,8-naphthalimide group and one isophthalic acid (Scheme 1). The alkyl viologen unit can bind firmly with CB[7],[11] and its location between the two stoppers would greatly stabilize the formed [2]rotaxane by increasing the dissociation energy barrier. The distance between the two carbonyls on the isophthalic acid is about 7.0 Å (optimized by MM2, Fig. S4, Supplementary data), which is greater than the annular diameter (5.4 Å) but smaller than the equatorial width (7.3 Å) of CB[7],[12] and would be suitable for the CB[7] slippage.

The dumbbell molecule **2** was synthesized from the bromohexylation of 4-amino-1,8-naphthalimide **2c** (Scheme S1, Supplementary data), followed by the mono-quaternization with 4,4-bipyridine, and finally linked with the isophthalic stopper. Although there is cationic viologen on the axle, **2** could hardly dissolve in water, whereas it has a good solubility in organic solvents of strong polarity, such as CH_3OH, DMSO, and HCOOH. The solution of **2** in formic acid presents a yellowish-green color but turns pale with the addition of CB[7], indicating the existence of binding behavior between them. Job's plot curve (Fig. S5, Supplementary data) reveals that **2** forms a 1:1 complex with CB[7] (**2@CB**) and the binding constant K was determined as 500 M^{-1} (Fig. S6, Supplementary data).

The ^{1}H NMR spectroscopy is a useful technique for the binding mode identification of CB-based inclusion complexes. It has been

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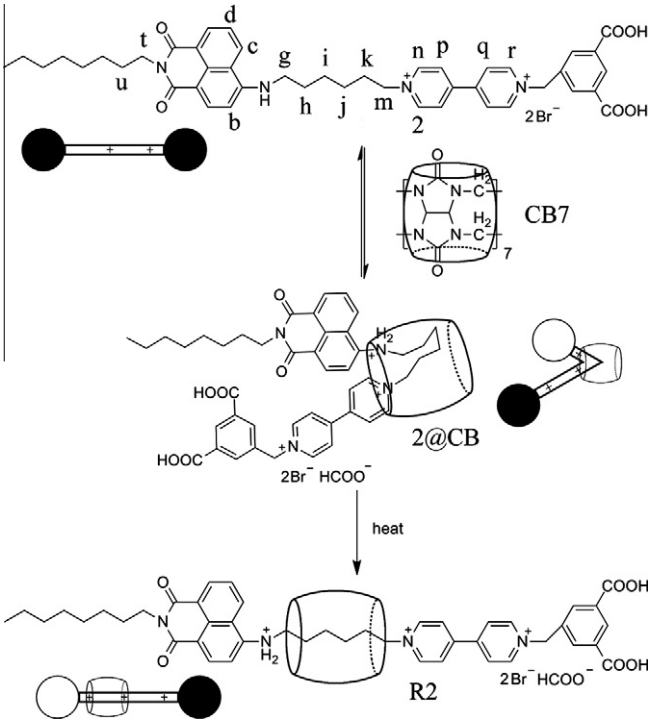

Scheme 1. The formation of **2@CB** and **R2** in 95% HCOOH.

found that the guest protons inside the hydrophobic cavity of cucurbituril lie in a magnetic shielding region and their NMR signals undergo an upfield shift; on the contrary, the outside ones undergo deshielding effects and have downfield-shifted signals, whereas those near the carbonyl rim are scarcely affected.[13]

Figure 1 shows the ^{1}H NMR signals of **2** (20 mM) and its mixing with 2.0 equiv. of CB[7] (the ratio of **2@CB** was estimated as 91.6% by the binding constant K of **2** and CB[7] in 95% HCOOH, Fig. S6, Supplementary data) in 95% deuterated HCOOH at 298 K. Compared with the dumbbell molecule, the viologen proton H_n and all the hexyl protons on **2@CB** undergo shielding effects ($\Delta\delta H_n = -0.17$, $\Delta\delta H_g = -0.12$, $\Delta\delta H_h = -0.65$, $\Delta\delta H_i = -0.61$, $\Delta\delta H_j = -0.73$, $\Delta\delta H_k = -0.74$, $\Delta\delta H_m = -0.35$); the protons on the naphthalimide and other protons on the viologen unit show downfield-shifted signals ($\Delta\delta H_b = 0.51$, $\Delta\delta H_c = 0.26$, $\Delta\delta H_d = 0.22$, $\Delta\delta H_p = 0.12$, $\Delta\delta H_q = 0.25$, $\Delta\delta H_r = 0.01$). These facts reveal that the CB[7] ring encircles the hexyl group with the naphthalimide and viologen units sticking out from the openings of CB[7]. Further 2D ^{1}H NOESY NMR measurement (Fig. S7, Supplementary data) shows the proximity of H_g to H_i/H_k, indicating that **2@CB** adopts a conformation where the middle hexyl chain of **2** folds into the cavity of CB[7] (Scheme 1).

The slipping experiment was then conducted by mixing **2** with 1.1 equiv of CB[7] in formic acid and the mixture was heated under reflux for 48 h. TLC analysis (ethanol:water:40% HBr solution = 25:10:1) displayed a new product ($R_f = 0.1$). This is different from **2@CB**, which dissociates into two parts and only **2** can be found when analyzed by TLC. The solution was then cooled and concentrated by evaporation, the resulting solid was purified by chromatography and the new product (**R2**) was found as a yellow solid. The solid was proved to be a [2]rotaxane through the followed identification, and the obtained yield was 57%.

The ^{1}H NMR spectroscopy of **R2** in 95% deuterated HCOOH is shown in Figure 1d. Similar to **2@CB**, the hexyl protons on **R2** undergo shielding effects, and the protons on the naphthalimide and the viologen ones (H_p, H_q, H_r) conducts de-shielding effects. However, there are no distinct NOEs that could be found between the two ends of the hexyl unit in **R2** under the same situation as **2@CB** (Fig. S8, Supplementary data). These phenomena indicate that **R2** is a [2]rotaxane where the CB[7] ring resides over the hexyl group and one of the positive charge of the viologen unit (Scheme 1).

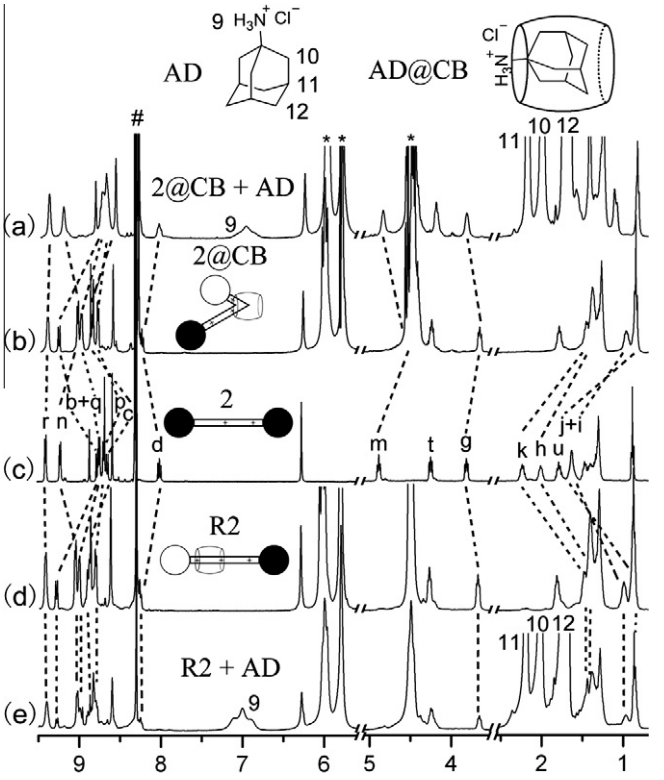

Figure 1. ^{1}H NMR spectra (400 MHz, 95% DCOOD, 298 K) of (a) **2@CB** (20 mM of **2** and 40 mM of CB[7]) with 10 equiv of **AD** after 7 days; (b) **2@CB** (20 mM of **2** and 40 mM of CB[7]); (c) **2** (20 mM); (d) **R2** (20 mM); (e) **R2** (20 mM) with 10 equiv of **AD** after 7 days (∗ peaks of CB[7], # solvent residual signal).

To further confirm the co-conformations of **2@CB** and **R2**, 10 equiv of adamantane ammonium hydrochloride (**AD**), which is of high affinity with CB[7] ($K > 10^{12}$ M^{-1}),[14] were added respectively and the ^{1}H NMR spectra were recorded after 7 days (Fig. 1a and 1e). In the **2@CB + AD** system, the encircled **2** was found to become free, indicating that CB7 was caught by **AD** (**AD@CB**). By contrast, the signals of **R2** remained unaffected after the addition of **AD**. These results prove the fact that **2@CB** is a pseudorotaxane and **R2** is a true [2]rotaxane.

It has been found that the pK_a value of an amine would increase when entering into the cavity of CBs.[15] The measurement of the pK_a values of the 4-amino naphthalimide in **2** and **R2** was then carried out, as shown in Figures S9 and S10 (Supplementary data). The pK_a value of the 4-amino in **2** was 1.16 and that in **R2** was found to be 1.37. Although the pK_a shift is relatively small, the amino group linked to the naphthalimide unit remains intact in **2** but would become protonated in **R2** in 95% HCOOH, which is of a pH value of 1.17. The UV/Vis absorption measurements of **R2** and **2** in 95% HCOOH at 298 K are shown in Figure S11 (Supplementary data). The maximum absorption wavelength of **2** in 95% HCOOH is 454 nm and the color of the solution is yellowish-green, while that of **R2** is about 340 nm and turns colorless. These facts are coincident with the absorption of 4-amino naphthalimide before and after protonization.[16]

The equilibrium constant (K_e) of the slipping process was investigated by monitoring the UV/Vis absorption of **2** and CB[7] mix-

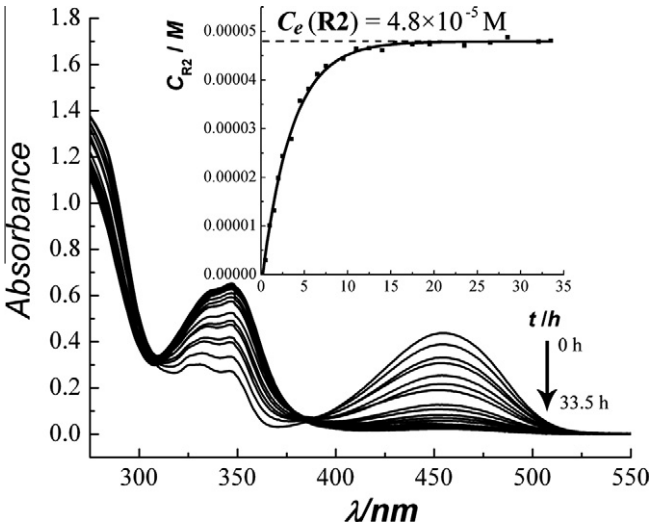

Figure 2. The absorption spectra of **2** and CB[7] mixed in 95% HCOOH (both 5×10^{-5} M) heated at 358 K for different time (from 0 to 33.5 h) and immediately cooled to 298 K. The inset shows the corresponding calculated concentration of **R2** at 454 nm.

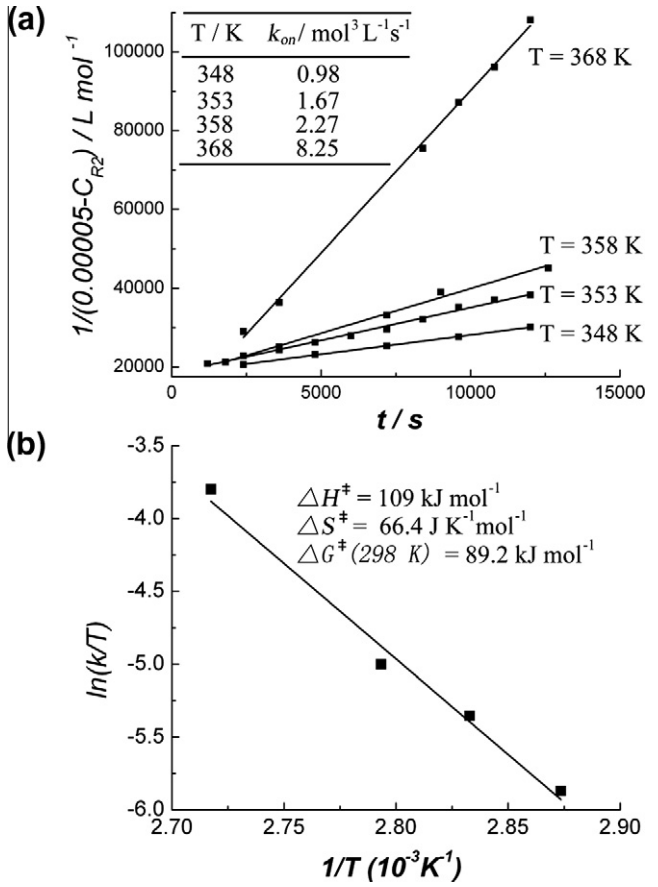

Figure 3. Determination of (a) the rate constants for **2** and CB[7] in 95% HCOOH at four different temperatures (R-square is 0.999 (348 K), 0.992 (353 K), 0.991 (358 K), 0.998 (368 K)); (b) $\triangle H^{\ddagger}$, $\triangle S^{\ddagger}$, and $\triangle G^{\ddagger}$ by eyring equation (R-square is 0.974).

ture in 95% HCOOH (both 5×10^{-5} M) at 358 K, as can be seen in Figure 2. The peak at 454 nm becomes smaller and approaches to zero after 33.5 h. C_e(**R2**) (the equilibrium concentration of **R2** in the mixture solution) was estimated as 4.8×10^{-5} M and K_e was then calculated as 1.2×10^{7} M^{-1}, which is much large than 1×10^{5} M^{-1}. It can thus be deemed that once CB[7] jumps over the isophthalic acid stopper, it will be firmly fixed on the linear axle and the slipping of CB[7] into **2** is not irreversible in 95% HCOOH.

Among the slipping process, CB[7] and **2** must obtain appropriate energy ($\triangle H^{\ddagger}$) to form the activated complex [**2**+CB[7]]‡, and generate the final product **R2**. It is clear that the rate constants k_{on} are not only dependent on the activation enthalpy $\triangle H^{\ddagger}$, but related to the activation entropy $\triangle S^{\ddagger}$ from Eyring equation (Supplementary data). The slipping process was then carried out at four different temperatures (348 K, 353 K, 358 K, 368 K) to obtain the thermodynamic parameters. The rate constants k_{on} can be easily determined by the second order kinetic plot (k_{on} = 0.98 mol^3 L^{-1} s^{-1}, 1.67 mol^3 L^{-1} s^{-1}, 2.27 mol^3 L^{-1} s^{-1}, 8.25 mol^3 L^{-1} s^{-1}, Fig. 3a). The value of the activation enthalpy $\triangle H^{\ddagger}$, the activation entropy $\triangle S^{\ddagger}$, and the free activation enthalpy $\triangle G^{\ddagger}$ (298 K, $\triangle G^{\ddagger} = \triangle H^{\ddagger} - T\triangle S^{\ddagger}$) are evaluated as 109 kJ mol^{-1}, 66.4 J K^{-1}mol^{-1}, and 89.2 kJ mol^{-1}, respectively (Fig. 3b). Compared with the ground state (CB[7] and **2**), a positive value of $\triangle S^{\ddagger}$ means that the activated complex [**2**+CB[7]]‡ is highly disordered and is favorable to the slipping process.

In summary, [2]rotaxane **R2** was synthesized by heating the mixture of a dumbbell compound and the CB[7] ring. The ring slipped over the isophthalic stopper of the dumbbell molecule and was trapped by the hexyl-viologen axle. It should be noted that the construction of this simple CB-based rotaxane was conducted in formic acid using non-water soluble guests, thus may arouse expanding interests on the supramolecular chemistry of CBs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.073.

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