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# Rational Design for Rotaxane Synthesis through Intramolecular Slippage: Control of Activation Energy by Rigid Axle Length

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**Abstract:** We describe a new concept for rotaxane synthesis through intramolecular slippage using π-conjugated molecules as rigid axles linked with organic soluble and flexible permethylated α-cyclodextrins (PM α-CDs) as macrocycles. Through hydrophilic–hydrophobic interactions and flipping of PM α-CDs, successful quantitative conversion into rotaxanes was achieved without covalent bond formation. The rotaxanes had high activation barrier for their de-threading, so that they were kinetically isolated and derivatized even under conditions unfavorable for maintaining the rotaxane structures. $^1$H NMR spectroscopy experiments clearly revealed that the restricted motion of the linked macrocycle with the rigid axle made it possible to control the kinetic stability by adjusting the length of the rigid axle in the precursor structure rather than the steric bulkiness of the stopper unit.

## Introduction

Rotaxanes have gained great importance as functionalized materials since the macrocycles enhance the threading axle properties,[1,2] and the development of their new synthetic methodologies would be a significant advancement. Rotaxanes are typically synthesized through the construction of "dynamic" entwining structures of axles and macrocycles using noncovalent interactions (Figure 1a, step 1), for example, coordination, π–π interactions, hydrophilic–hydrophobic interactions, and hydrogen bonds. Subsequently, these threading structures are fixed to form stable rotaxanes via covalent-bond formation in the axle or macrocycle (step 2).[2,3] The step 2 process, however, must be carried out under reaction conditions that allow for the formation of the noncovalent interactions required for entwining in step 1, which restricts the scope of reactions for rotaxane synthesis.

As an exceptional methodology to evade such problems, kinetically stable rotaxanes were successfully synthesized only by heating solutions of macrocycles and dumbbell-shaped axles in appropriate solvents (Figure 1b).[4] Macrocycles with sizes similar to those of the stoppers of the dumbbell unit ($R \approx r$) could mechanically pass over the stoppers at high temperature, thus exceeding the activation energy derived from the steric barrier between the macrocycles and stoppers. In this methodology, which is classified as "slippage",[5] all covalent bonds in the components are fully constructed in the previous steps. The kinetically stable rotaxane structures, therefore, can be formed only under conditions that are appropriate for the entwining process (step 1′) without a covalent bond formation process (step 2). Moreover, after isolation, these structures can be kinetically utilized, even under conditions that are unfavorable for the entwining processes (step 1′). In spite of these advantages, expanded π-conjugated axles, which could be applied to various functional materials, have rarely been reported by using slippage synthesis. Such synthetic difficulty is derived from the low solubility of the individual π-conjugated axles and from the low efficiency for their encapsulation, resulting in synthetic problems such as harsh reaction conditions and low yields.[6] Accordingly, insulated conjugated systems have been classically synthesized by simultaneous entwining and covalent bonding reactions (Figure 1a)[1] or by construction of cyclic side chains orthogonal to the conjugated axles.[7]

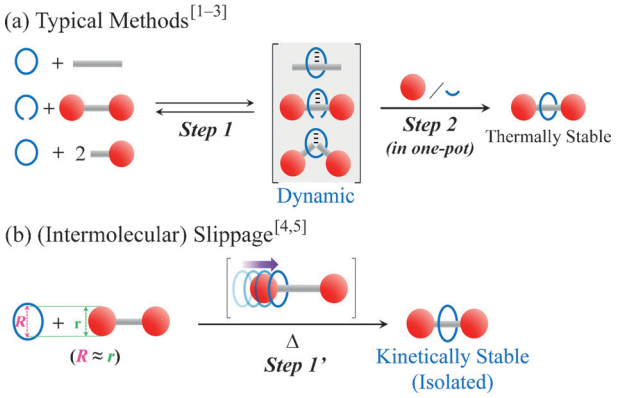


**Figure 1.** Illustration of synthetic methodologies for rotaxanes.

In our studies on the synthesis of highly insulated π-conjugated molecules,[8] we focused on a transition state in the entwining process of [1]rotaxanes, where the cyclic molecules are linked with the axle (Figure 2). Conventional [1]rotaxane precursors,[9] including our previous work,[8] had low activation

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barriers for self-inclusion processes using noncovalent interactions (Figure 2a, step 1) due to their short or flexible axles ($R > a$ or $b$). Thus, the resultant rotaxanes were dynamic pseudorotaxanes that could be fixed to form [1]rotaxanes through covalent-bond formation with the axle (step 2) under the same condition as those in step 1. We report herein that rigid π-conjugated axles ($b > R \approx a$) were successfully entwined with their linked macrocycles to form kinetically stable rotaxanes (Figure 2b, step 1′), namely, through "intramolecular slippage". Owing to the linkage between the axle and macrocycle, this methodology has the advantages of high solubility of the expanded π-conjugated axles and entropically assisted insulation, which results in efficient transformation under mild conditions when compared with classical (intermolecular) slippage. Moreover, the linkage defines the motion area of the macrocycle around the rigid axle (Figure 2b, pink circle), which controls the threading direction and barrier. The rigid π-conjugated axle with length $R \approx a$ could thread only at high temperatures. In contrast to classical [1]rotaxane systems, this relationship ($R \approx a$) is maintained in π-conjugated rotaxanes because of the axle rigidity. Thus, the entwining structures could be sterically fixed at ambient temperature and kinetically isolated without the introduction of three-dimensional bulky stoppers on the axle unit. Consequently, the rotaxanes formed through intramolecular slippage could be isolated and derivatized to form further functionalized and thermally stable rotaxanes, even under conditions in which maintaining the rotaxane structure is thermodynamically unfavorable. This method completely separates the entwining-structure formation (step 1′) and covalent-bond formation processes (step 2) for π-conjugated rotaxane synthesis. In this study, we describe the design, versatility, expansibility, and mechanism of this new method for rotaxane synthesis using intramolecular slippage.

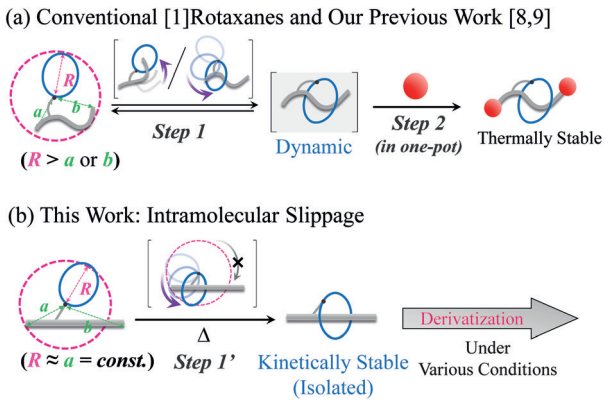



**Figure 2.** Illustration of synthetic methodologies for [1]rotaxanes. The pink circle in (b) is the restricted motion area of a cyclic molecule; the threading direction and barrier are determined by the geometric relation, $b > R \approx a$, between the pink circle and gray rigid axle.

## Results and Discussion

### Molecular design

As a precursor for intramolecular slippage, **1** consisted of a rigid and linear axial oligo(phenylene ethynylene) (OPE) linked with permethylated α-cyclodextrin (PM α-CD), which has high organic solubility and a deep cavity (Figure 3). The PM α-CD in **1** could not thread into the linked OPE axle on the right side because of steric bulk, as is evident from the geometric relation $R < b$.[8c] In PM α-CD, all the hydroxyl groups of native α-CD are methylated, which inhibit intramolecular hydrogen bonds. Therefore, the glucopyranose units in PM α-CD derivatives can fully rotate around the 1,4-glucopyranose bonds with a high activation barrier. Although this process is well known as "flipping",[10] as shown in Figure 3a, the [1]rotaxanes synthesized by flipping have been dynamic with unthreaded precursors, which were categorized by their flexible or short axles ($R > a$ or $b$; Figure 2a). On the other hand, using the flipping process, the linked PM α-CD in **1** could thread on the left side of the rigid OPE axle to form rotaxane **1**′ (Figure 3b). Concomitantly, since the motion of PM α-CD in **1** is restricted owing to its linkage with the axle, the substituent (X) on the OPE can control axial length ($a$; Figure 2b) and can efficiently act as a steric barrier for insulation by flipping (steps D–F in Figure 3b).[11] Consequently, this process involving flipping of linked PM α-CD is expected to have a high activation energy for transformation and to yield kinetically stable π-conjugated rotaxanes, that is, intramolecular slippage.

### Reversible interconversion via intramolecular slippage

Intramolecular slippage by full rotation of one glucopyranose unit in PM α-CD (flipping) was confirmed by $^1$H NMR analysis of **1a** with different polar solvents. Uninsulated **1a** was dissolved in $CD_3OD/D_2O$ (2:1), a high polarity solvent (Figure 4a). The time course of the changes in chemical species at 60 °C was followed in $^1$H NMR spectroscopy, as shown in Figure 4b–d and g. The aromatic proton peaks corresponding to uninsulated **1a** gradually diminished and could no longer be detected after 2 h. Accordingly, those corresponding to insulated **1a**′ gradually appeared and predominated at longer times, indicating quantitative conversion of **1a** to **1a**′ due to hydrophilic–hydrophobic interactions. In DOSY NMR spectrum of **1a**′, a single band at $\log D = -9.33$ was observed, which is a similar value to that of **1a** ($\log D = -9.36$). The DOSY NMR experiments indicated that the transformation from **1a** to **1a**′ was an intramolecular process without any oligomerization of **1a**.

The thus-formed **1a**′ possessed high stability and could be kinetically isolated by extraction, even when using low polarity organic solvents, as confirmed by the $^1$H and ROESY NMR spectra (Figure 4e),[12,13] because the slightly exposed substituent (X) on the rigid OPE axle acted as an efficient stopper for rotaxane **1a**′. Insulated **1a**′ maintained its structure after 24 h at room temperature, even in thermodynamically unfavorable solvents, such as deuterated $CHCl_3$ and THF (Figure S11 in the Supporting Information), which indicated the kinetic stability

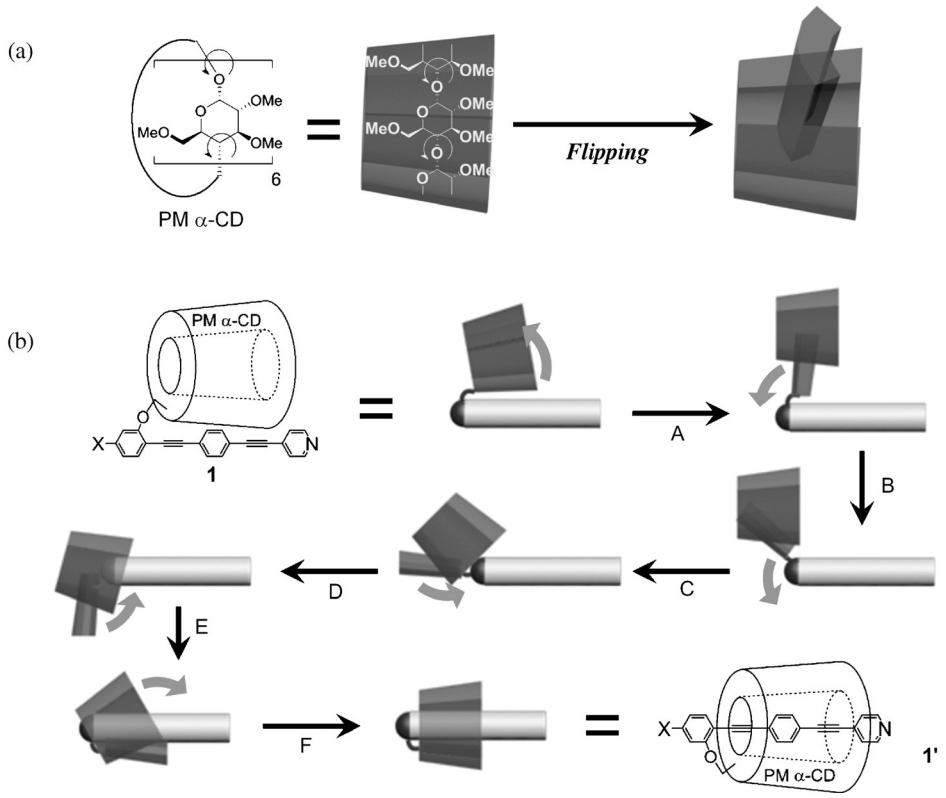



**Figure 3.** a) Structure and flipping of PM α-CD. b) Threading mechanism by PM α-CD flipping of **1** to **1**′.

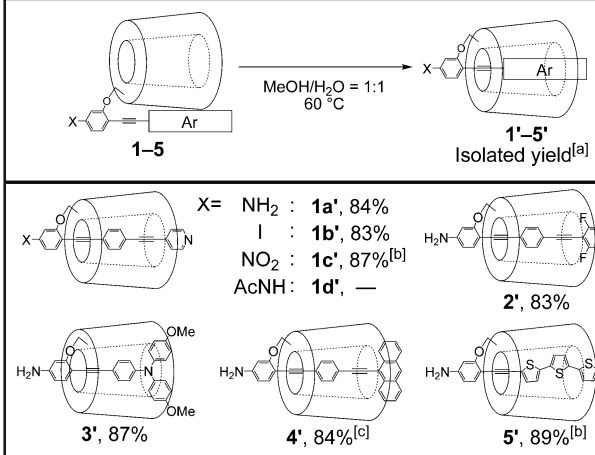
of **1a**′. Similarly, **1a**′ was quantitatively converted into **1a** and isolated by heating in THF, which is a low polarity solvent (Figure 4f and h, and Figure S10 in the Supporting Information). These results demonstrated the reversible slippage interconversion between **1a** and **1a**′ through PM α-CD flipping.

### Scope of substrates for intramolecular slippage

Amine-substituted and iodo-substituted OPEs (**1a** and **1b**, respectively) showed quantitative conversion into their insulated counterparts (**1a**′ and **1b**′, respectively) by heating in MeOH/$H_2O$ = 1:1, and were isolated with high yields (84 and 83%, respectively; Table 1) without requiring any removal process for uninsulated substrates; no evidence of the uninsulated substrates was found by $^1$H NMR analysis of the products (Figures S1–S7 in the Supporting Information). In contrast, substitution of OPE with an electron-withdrawing nitro group (**1c**) prevented quantitative conversion in $CD_3OD/D_2O$ = 1:1 because the efficiency of insulation by CDs was influenced by the electron density on the axle unit.[14] However, **1c** fully converted into its insulated structure **1c**′ in a higher polarity solvent (MeOH/$H_2O$ = 1:2) and was isolated in 87% yield. Namely, quantitative intramolecular slippage transformations of **1a**–**c** could be performed by simple adjustments in solvent polarity regardless of the electronic character of the substituents because of the entropically assisted insulation due to the linkages. On the other hand, acetyl-substituted **1d** did not undergo intramolecular slippage, with no changes observed by heating in $CD_3OD/D_2O$ = 2:1 as a polar solvent (Figure S12 in the Supporting Information). The non-conversion of **1d**, which has a bulkier acetyl moiety ($a > R$ in Figure 2b) in place of the amino group ($a \approx R$) of **1a**, indicates that entwining by flipping at the amino group side in the conversion from **1a** and **1a**′ occurs as shown in Figure 3.

Quantitative slippage conversions into insulated structures were demonstrated for a variety of π-conjugated axles. All the π-conjugated structures in precursors **2**–**5** (Table 1) were con-

**Table 1.** Scope of substrates.




[a] Yields after extraction with organic solvents. [b] MeOH/$H_2O$ (1:2) was used as reaction solvent. [c] MeOH/$H_2O$ (5:4) at 65 °C was used as reaction condition.

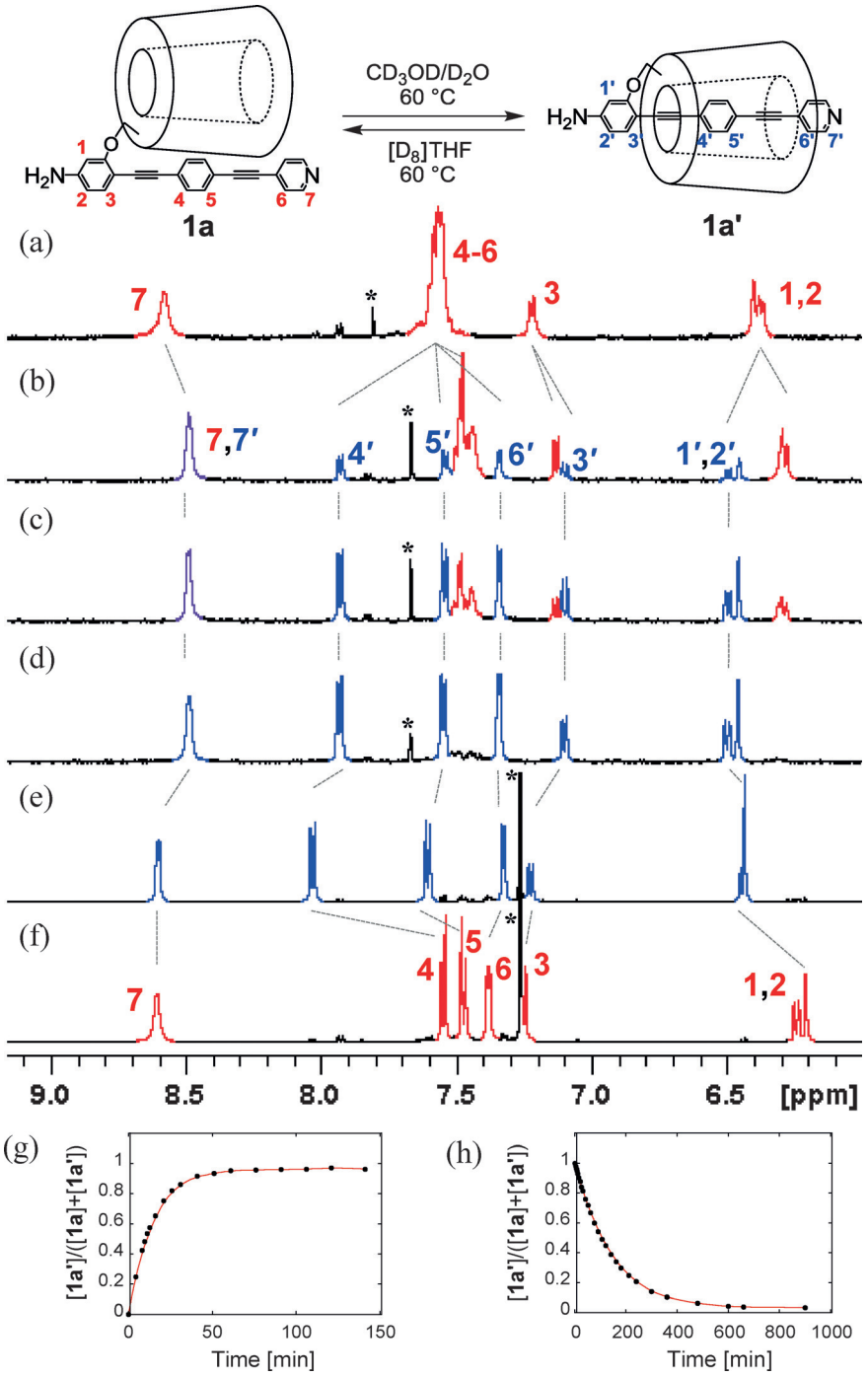



**Figure 4.** Partial $^1$H NMR (500 MHz) spectra of: a) **1a** ($CD_3OD/D_2O$ = 2:1, RT). Time course of **1a** ($CD_3OD/D_2O$ = 2:1, 60 °C): b) 5 min, c) 15 min, and d) 2 h. e) Isolated product (**1a**′) after heating **1a** in $CH_3OH/H_2O$ = 2:1 ($CDCl_3$, RT), and f) isolated product (**1a**) after heating **1a**′ in THF ($CDCl_3$, RT); * indicated the residual $CHCl_3$ peak. Kinetic trace from $^1$H NMR spectra for the transformation of: g) **1a** into **1a**′ in $CD_3OD/D_2O$ = 2:1 at 60 °C, and h) **1a**′ into **1a** in [$D_8$]THF at 60 °C.

structed using general synthetic procedures for covalent bond formations before the intramolecular slippage process. Various π-conjugated units could be applied to this highly efficient insulation procedure. Electron-withdrawing (**2**′), electron-donating (**3**′), and largely extended (**4**′) π-conjugated systems all underwent intramolecular slippage, although their steric and electronic states strongly influenced the insulation efficiency and axial solubility. Moreover, perfect intramolecular slippage was obtained with an oligothiophene backbone (**5**′). This quantitative intramolecular slippage conversion completely removes the need for covalent-bond formation during the rotaxane-formation process and will be a powerful strategy for the construction of various functionalized material with insulated π-conjugated units.

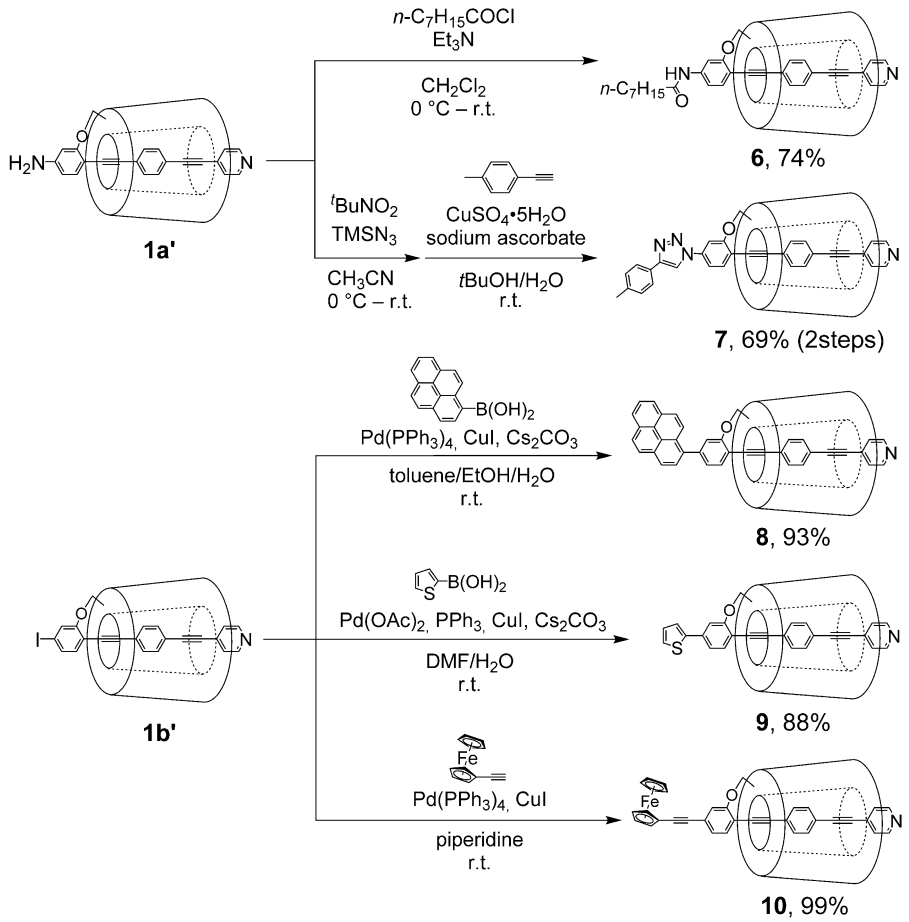
### Derivatization of products

The kinetic stability and synthetic utility of the intramolecular slippage method were clarified by further derivatization of π-conjugated rotaxanes (Scheme 1). Compounds **1a′** and **1b′** were successfully applied to subsequent molecular transformations, even in low polarity solvent systems. Amino-substituted **1a′** could be modified by amidation (**6**) or azidation followed by a Huisgen cycloaddition (**7**) to yield functionalized π-conjugated rotaxanes. Iodo-substituted **1b′** was derivatized by Suzuki–Miyaura coupling (**8** and **9**) or Sonogashira coupling (**10**) to form further expanded π-conjugated rotaxanes. It is notable that no corresponding uninsulated structures were observed in the $^1$H NMR spectra for any of the asymmetrically functionalized π-conjugated rotaxanes without a purification process to remove the uninsulated products, demonstrating sufficient kinetic stability of **1a′** and **1b′** on the reaction timescale for derivatization (Figures S8 and S9 in the Supporting Information). In addition, derivatization accompanied by elongation of the axle enhanced the thermal stability of the rotaxane structure, as the insulation structures were retained even in $CDCl_3$ at 60 °C (Figures S13–17 in the Supporting Information).

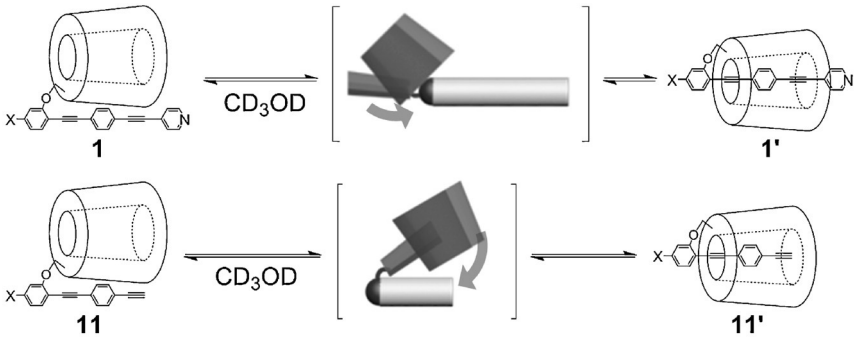
### Kinetic experiment of intramolecular slippage

In order to examine the mechanism of intramolecular slippage transformation between **1a–c** and **1a′–c′**, detailed thermodynamic and kinetic parameters were determined from $^1$H NMR experiments in $CD_3OD$ as a lower polarity solvent, in which mixtures of uninsulated **1a–c** and insulated **1a′–c′** were thermodynamically formed, whereas in higher polarity $CH_3OH/H_2O$ (1:1) quantitative conversion to **1a′–c′** was obtained, as shown in Table 1. The temperature dependence of the kinetic constants (Table S1 in the Supporting Information), which were determined by fitting the time course of the existence ratio of the insulated and uninsulated units at 40, 50, and 60 °C, gave the thermodynamic and kinetic parameters for association and activation (Table S2 in the Supporting Information).[15]

Figure 5 summarizes the association and activation energies at 25 °C. On increasing the electron densities of the π-conjugated guest unit by changing the substituent (X),[16] the association energies increased (**1c** < **1b** < **1a**). This indicates that the driving force for inclusion was C–H···π interactions between the π-conjugated units in the axles and the inner protons of PM α-CDs. On the other hand, the activation energies were




**Scheme 1.** Derivatization of kinetically stable rotaxanes.




| Unit | X | $-\Delta G^{\circ}$ [kJ mol$^{-1}$] | $E^{\ddagger}$ [kJ mol$^{-1}$] |
|---|---|---|---|
| **1a** | $NH_2$ | 3.18 | 103 |
| **1b** | I | 0.53 | 105 |
| **1c** | $NO_2$ | –2.93 | 108 |
| **11a** | $NH_2$ | 3.32 | 91.8 |
| **11b** | I | 1.16 | 91.6 |
| **11c** | $NO_2$ | –1.88 | 91.4 |

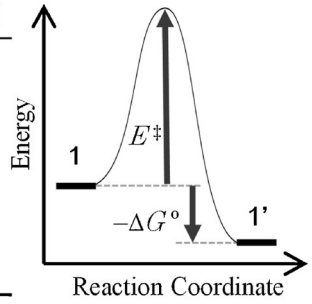



**Figure 5.** Kinetic and thermodynamic data for **1** and **11** at 25 °C.

high enough to allow the product to be kinetically isolated (103–108 kJ mol$^{-1}$, Figure 5) and were influenced by the size of the substituent ($NH_2 < I < NO_2$, see Figure S46 in the Supporting Information), which is also supported by the significant difference in the kinetic constants for different substituents (Table S1 in the Supporting Information). These results clearly demonstrated that the enlarged activation barriers owing to the rigid axles (length *a* in Figure 2b) linked with PM α-CD are responsible for the kinetic stability of rotaxanes formed through intramolecular slippage. The units **11a–c** bearing shorter OPE axles ($b < R$ in Figure 2b), where the linked PM α-CD threads through on the terminal alkyne sides,[8a] had smaller activation energies (91.4–91.8 kJ mol$^{-1}$) that were independent of the substituent, whereas the association energies showed a trend similar to that observed for **1a–c**.[17] These results further support the influence on the activation energies of **1a–c** by steric effects of the substituents, rather than by electronic effects.

## Conclusions

In conclusion, a new synthetic strategy for kinetically stable π-conjugated rotaxanes through intramolecular slippage of linked PM α-CDs was successfully developed. This was achieved by restricting motion between the axle and macrocycle and by adjusting the length of the π-conjugated rigid axle without the introduction of three-dimensional bulky terminal stopper groups. The effective transformation was supported by the linkage between the axle and macrocycle, making it possible to separate formation of the entwining structure (step 1′ in Figure 2) from covalent bond formation processes (step 2) in π-conjugated rotaxane synthesis. These results indicate the versatility and remarkable tolerance of this intramolecular slippage method for the synthesis of various insulated π-conjugated materials.

## Experimental Section

Experimental details are provided in Supporting Information.

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**Keywords:** cyclodextrins · host-guest systems · rotaxanes · supramolecular chemistry

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