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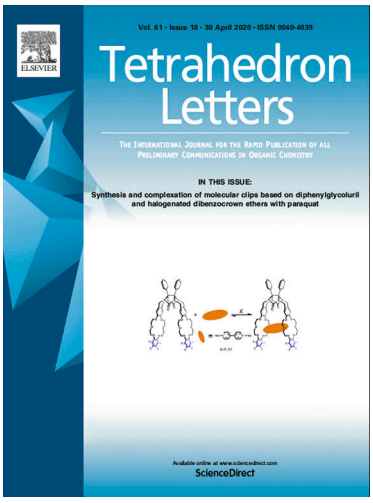

Change in the rate of pseudo[1]rotaxane formation by elongating the alkyl-chain-substituted diphenylethynylene linked to permethyl α-cyclodextrin

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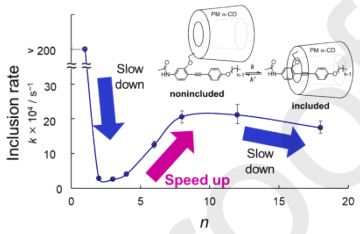

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Change in the rate of pseudo[1]rotaxane formation by elongating the alkyl-chain-substituted diphenylethynylene linked to permethyl α-cyclodextrin

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ABSTRACT

Herein, we report the kinetics of pseudo[1]rotaxane formation from permethyl α-cyclodextrin attached to a flexible-chain-substituted diphenylethynylene. When the chain is an alkyl group, the rate of formation shows different trends over three regions of chain length: deceleration (chain length = 1–3), acceleration (4–8), and re-deceleration (> 12). This behavior is driven by a relative decrease in the $\Delta H^{\ddagger}$ of the transition.

Introduction

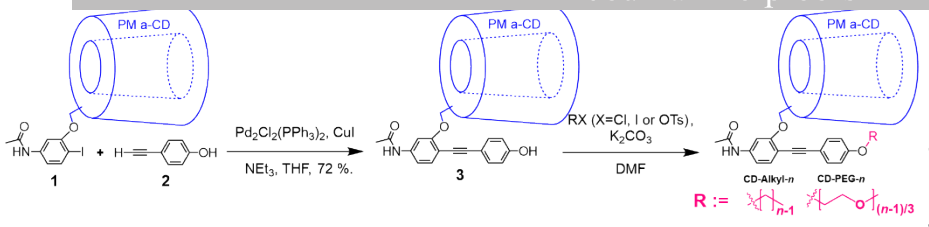
Host-guest chemistry has been applied in various areas of scientific research, such as molecular recognition,[1–4] molecular machines,[5,6] biological-system analogues,[7] and catalysts.[8] Investigations into the structure formation and selectivity of host-guest complexes focus primarily on the thermodynamic stability, or Gibbs free energy of reaction (ΔG°), of the complexes.[9] Furthermore, when considering the chemical reactions in host-guest chemistry, the inclusion of kinetic studies, or Gibbs free energy of activation ($\Delta G^{\ddagger}$), has revealed that characteristics of these host-guest systems are based on the dynamics of their complexing.[10] In particular, guest exchange dynamics have recently attracted attention, and an artificial model system has been developed that mimics the transport and trapping phenomena observed in biological systems.[11,12] Several groups have reported on the relationship between the structures and kinetics of host-guest complexes, mainly pseudo[2]rotaxane formation, by using steric hindrance,[13–16] guest solvation,[17] and the introduction of long-chain substituents[18] were studied. Furthermore, these studies demonstrated the successful control of the transition free energy ($\Delta G^{\ddagger}$) of host-guest complex formation. In many cases, introducing larger substituents onto the host or guest slows down the host-guest formation reaction due to the steric hindrance. However, an intriguing system was reported in which the elongation of the substituent accelerated the formation reaction.[18] Overall, the complexing of host and guest is a rapid process; hence, kinetic analyses are not as sufficiently carried out as thermodynamic analyses.

A pseudo[1]rotaxane composes of a ring and an axle covalently bonded. This structure not only plays an important role in protein transport, such as for Sec proteins,[19] but also forms an interesting lasso-peptide analogue that exhibits various physiological activities.[20] The design of pseudo[1]rotaxanes allows for control over their dynamics timescales, because the connection between the ring and the axle limits both of their mobilities. This control makes it possible to study the kinetics of these complexes, which provides a simplified, convenient model for the quantitative understanding of host-guest dynamics. Nevertheless, only a couple of papers have been reported on the kinetics of pseudo[1]rotaxane formation.[21,22]

Our group have reported the syntheses and applications of [1]rotaxane structures from permethyl α-cyclodextrin (PM α-CD) linked to diphenylethynylene derivatives.[23,24] In this study, to clarify the relationship between the dynamics and structures during the pseudo[1]rotaxane formation (i.e., the inclusion reaction), we systematically investigated how flexible chain substituents introduced onto the diphenylethynylene group would affect the formation kinetics. The diphenylethynylene moiety was expected to not only form a stable host-guest complex with PM α-CD, but also regulate the rate of the inclusion reaction due to its rigidity.[22] In addition, the flexible chain was expected to function as a damper that would alter the inclusion kinetics.[25] It was revealed that the rate of the pseudo[1]rotaxane formation only decreased over chain length regions of 1–3 or >12, but increased over a region of 4–8.

Results and Discussion

As shown in Scheme 1, compound **3** was synthesized by the Sonogashira-Hagihara coupling of a substituted iodobenzene containing a PM α-CD derivative **1** with *p*-ethynyl phenol (**2**). Subsequent reaction of **3** with linear alkyl iodides of varying chain lengths afforded the corresponding PM α-CD derivatives **CD-**



		n	1	2	3	4
CD-alkyl-*n*	R = $-(CH_2)_{n-1}CH_3$	Yield / %	30	67	67	72
		n	6	8	12	18
		Yield / %	58	54	49	34
CD-PEG-*n*	R = $-(CH_2CH_2O)_{(n-1)/3}CH_3$	*n*	4	7	13	≈25
		Yield / %	80	69	67	65

Scheme 2. Synthesis of **CD-alkyl-*n*** and **CD-PEG-*n***

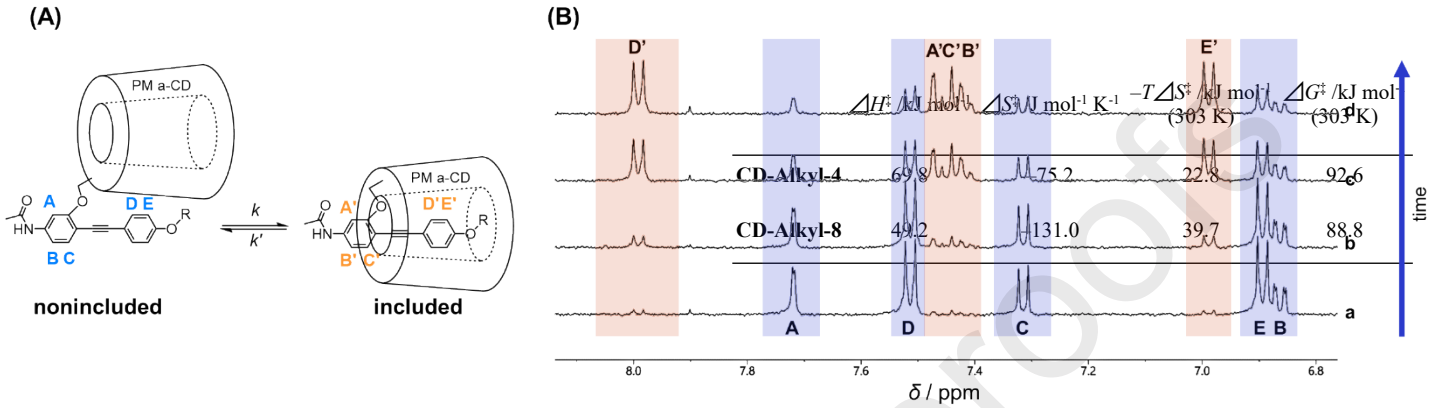


Fig. 1 (A) Equilibrium of the inclusion reaction to form **CD-alkyl-*n***, (B) Changes over time in the ^{1}H NMR spectra of **CD-alkyl-2** in CD_3OD at 298 K (aromatic region; a: 10 min; b: 53 min; c: 107 min; d: 272 min.).

alkyl-*n*, where *n* represents the number of carbon atoms in the alkyl chain (*n* = 1, 2, 3, 4, 6, 8, 12, and 18). Also shown in Scheme 1 are PM α-CD derivatives with a polyethylene glycol (PEG) chain, **CD-PEG-*n*** (*n* = 4, 7, 13, and 25), that were synthesized from compound **3** and PEG methyl ether tosylates with varying chain lengths. [26]

CD-alkyl-*n* quantitatively formed a pseudo[1]rotaxane structure in a highly polar solvent, CD_3OD/D_2O (see SI, Fig. S26, S27), and the equilibrium for this inclusion reaction is shown in Fig. 1A. To thoroughly follow the rotaxane formation, we ran ^{1}H NMR experiments on **CD-alkyl-*n*** in CD_3OD at 298 K and measured the changes in the spectra over time (Fig. 1B and S29). The ratio of included compound to non-included compound was calculated from the integral ratio of their aromatic region protons. The abundance ratio over elapsed time is expressed as Eq. 1, assuming a reversible first-order reaction (see SI),

$$\frac{[\text{included}]}{[\text{nonincluded}]} = \frac{k - ke^{-(k+k')t}}{k' + ke^{-(k+k')t}} \qquad \text{(Eq. 1)}$$

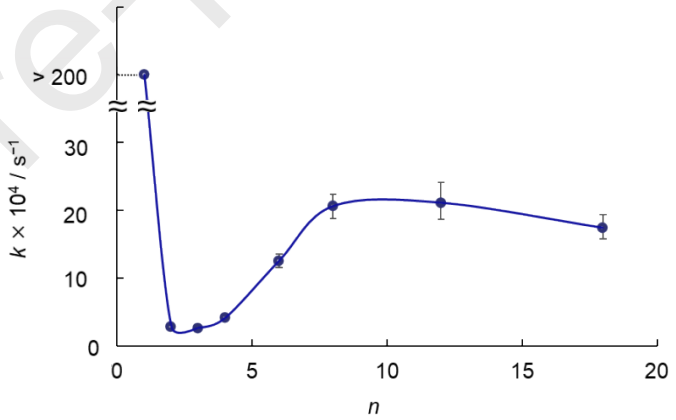


Fig. 2 Dependence of *k* on alkyl chain length *n* for **CD-alkyl-*n*** at 298 K in CD_3OD.

where *k* is the forward for the formation of pseudo[1]rotaxane, *k'* is the reverse reaction rate constant, [included] and [nonincluded] are the concentration of the inclusion are non-inclusion compounds, respectively. The value of *k* for the inclusion reaction of **CD-alkyl-*n*** was calculated by fitting the measured abundance ratio over elapsed time to Eq. 1 (see Fig. S28, S29). The relationship between *k* and the alkyl chain lengths of **CD-alkyl-*n*** is shown in Fig. 2. From the results of the ^{1}H NMR spectra measurements, **CD-alkyl-1** was estimated to have a $k > 2.0 \times 10^{-2}$ s^{-1} (Fig. S31). The values of *k* for **CD-alkyl-2** and **CD-alkyl-3** were 2.8×10^{-4} s^{-1} and 2.6×10^{-4} s^{-1}, respectively; therefore, *k* decreased as the alkyl chain length increased. This suggested that alkyl chain elongation caused steric hindrance, which increased the $\Delta G^{\ddagger}$ during the pseudo[1]rotaxane formation process. Meanwhile, when *n* = 4–8, *k* unexpectedly increased, where the values for **CD-alkyl-4**, **CD-alkyl-6**, and **CD-alkyl-8** were 2.8×10^{-4} s^{-1}, 13×10^{-4} s^{-1}, and 21×10^{-4} s^{-1}, respectively. Specifically, *k* of **CD-alkyl-8** was 8 times larger than that of **CD-alkyl-3**. Furthermore, the *k* values of **CD-alkyl-12** and **CD-alkyl-18** were

decreased again when $n > 12$.[27]

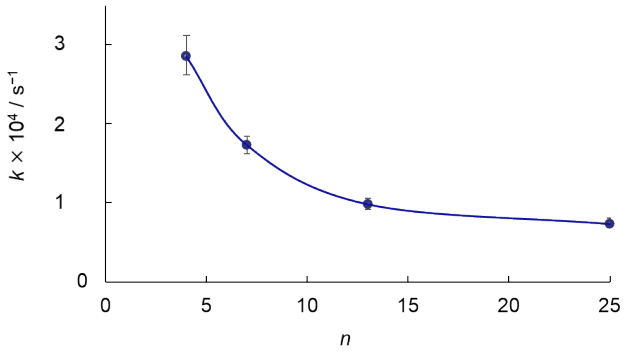


Fig. 3 Dependence of k on alkyl chain length n for **CD-PEG-*n*** at 305 K in CD_3OD.

To investigate this behavior, variable-temperature NMR experiments were conducted on **CD-alkyl-4** and **CD-alkyl-8** over a range of 298-308 K (Fig. S32-S34). Table 1 shows the $\Delta G^{\ddagger}$, the enthalpy of activation ($\Delta H^{\ddagger}$), and the entropy of activation ($\Delta S^{\ddagger}$) of the inclusion reactions at 303 K, which were obtained from the Eyring plot. As the alkyl chain length increased, $\Delta H^{\ddagger}$ decreased (**CD-alkyl-4**: 69.8 kJ mol^{-1}, **CD-alkyl-8**: 49.2 kJ mol^{-1}), whereas $-T\Delta S^{\ddagger}$ increased (**CD-alkyl-4** : 22.8 kJ mol^{-1}, **CD-alkyl-8** : 39.7 kJ mol^{-1}). Therefore, the decrease in $\Delta G^{\ddagger}$ is due to the decrease in $\Delta H^{\ddagger}$, not $-T\Delta S^{\ddagger}$.

For further investigation, experiments were also conducted on **CD-PEG-*n***, which possess PEG chains that are more hydrophilic than alkyl chains. The abundance ratio of the included compound to the non-included compound was determined using ^{1}H NMR spectroscopy. The sample was run in CD_3OD at 305 K, and the integrations of the aromatic protons were compared. The k for the inclusion reaction was determined using Eq. 1, similar to the k of **CD-alkyl-*n*** (Fig. S30, Table S1). Fig. 3 indicates the relationship between the number of atoms in the PEG chain and k. The dependence of k on the chain length in **CD-PEG-*n*** is significantly different than that in **CD-alkyl-*n***; that is, k decreases monotonically as the PEG chain is elongated. Hence, the remarkable dependence of k on the chain length for the **CD-alkyl-*n*** was related to it specifically being an alkyl chain.

Based on these results, our proposed mechanism of the inclusion process is displayed in Fig. 4. The formation of pseudo[1]rotaxane from the non-included compound involves threading only via the alkyl chain side, since the inclusion reaction k showed a chain length dependence. Additionally, it is known that

on energy barrier.[28] The k values decreased over the regions of n = 1–3 and >12 for both **CD-alkyl-*n*** and **CD-PEG-*n***, but increased in the region of n = 4–8 only for **CD-alkyl-*n***. This remarkable acceleration originates from the contribution of the dominant $\Delta H^{\ddagger}$.

Hence, the rate-determining step would be Fig. 4-C, which is the most strained state, and involves the strong interaction of the chain substituent with the PM α-CD (SI Chapter 5). We focused on the enthalpy change between the alkyl chains and both the PM α-CD and the methanol solvent. Hydrophobic chains, like these

Table 1 Measurements of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ at 303 K during the inclusion reactions for **CD-alkyl-4** and **CD-alkyl-8**

alkyl chains, have a low affinity for polar solvents, such as methanol, but have a high affinity for PM α-CD. In other words, the longer the alkyl chain length is, the greater the chain can stabilize (decrease in $\Delta H^{\ddagger}$) in the PM α-CD, which is what occurs in the transition state. This is observed for the **CD-alkyl-*n*** with chain lengths in the region of n = 4–8. On the other hand, for chains with $n > 12$, the alkyl chain cannot gain further enthalpy stabilization by inclusion. Furthermore, and because $-T\Delta S^{\ddagger}$ increases with the increase in the chain length, the $\Delta G^{\ddagger}$ increases for these **CD-alkyl-*n*** with $n > 12$. Meanwhile, PEG chains are more hydrophilic than alkyl chains and tend to be strongly solvated in polar solvents like methanol; although, they have a lower affinity for the PM α-CD than the alkyl chains.[29,30] Therefore, the PEG substituents of **CD-PEG-*n*** complexes do not stabilize as much as the alkyl substituents of **CD-alkyl-*n***. This is what causes the observed decrease in k as the PEG chain length increased. By comparing the enthalpies of the different substituents in the initial and transition states, the dependence of the rotaxane formation rate on the chain length is clearly demonstrated.

Conclusion

To determine the effect of structure on the dynamics of pseudo[1]rotaxane formation, our group systematically investigated the effects of flexible chain substituents of a PM α-CD-linked diphenylethynylene group on the kinetics. The results revealed that the k of rotaxane formation from **CD-alkyl-*n*** showed different trends over three regions of chain length: deceleration (n = 1–3), acceleration (n = 4–8), and re-deceleration ($n > 12$). That is, the alkyl chains behaved as dampers or accelerators depending on their length. This behavior contrasts with that seen in **CD-PEG-*n***, where a continuous decrease in k was observed as n increased. This was due to the lack of interaction between the PEG chains and inside of PM α-CD in the transition state. This study demonstrated that the kinetics of pseudo[1]rotaxane formation are dictated by structure and that the guest molecule has different

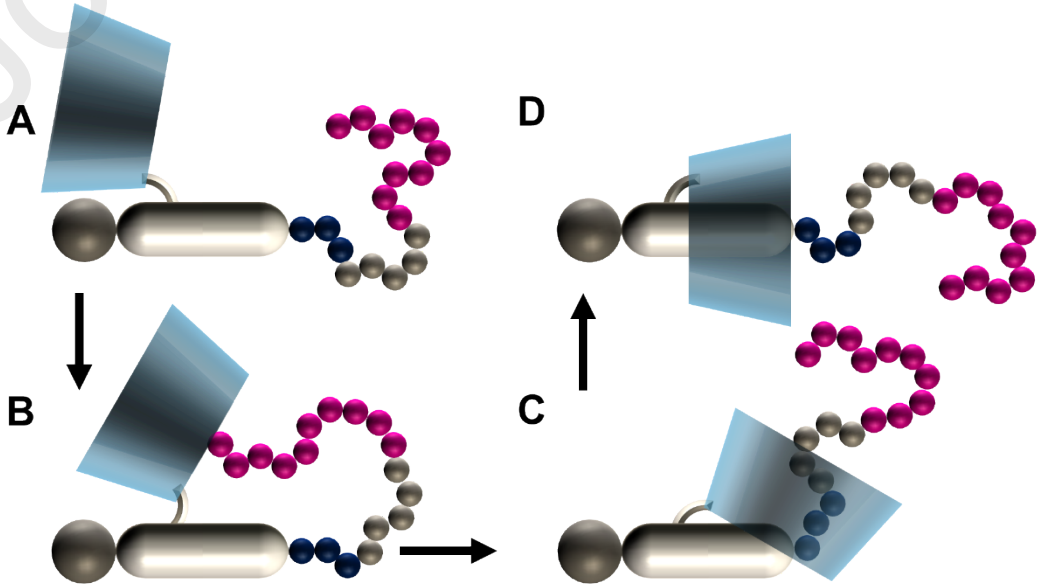


Fig. 4 A proposed mechanism. The first 3 atoms of the chain substituent are represented in black, the next 5 atoms in ash, and the next 10 atoms in red.

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the process of forming new host-guest complexes, but also help to elucidate the mechanisms of these complex biological phenomena relating to non-equilibrium states.

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(26) $n = 25$ is an estimated, average value, as it was synthesized from PEG monomethyl ether with molecular weight distribution.
(27) In this region of chain length, hydrophobic effect between the long alkyl chain and phenylene ethynylene can stabilize system on the nonincluded state (Table S1).
(28) Activation energy measurements performed on a similar molecule substituted with an amino group that has less steric hindrance than the acetamide group,[22] We estimated that the $\Delta H^{\ddagger}$ of threading from the acetamide group side of CD-alkyl-n is to be at least 80 kJ mol^{-1}, which is sufficiently higher than the measured $\Delta H^{\ddagger}$.
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Supplementary Material

Supplementary data to this article can be found online at

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- The k of pseudo[1]rotaxane formation showed different trends over three regions of flexible chain length
- The alkyl chains behaved as dampers or accelerators depending on their length
- The kinetics of pseudo[1]rotaxane formation are dictated by structure
- The findings guide the process of forming new host-guest complexes