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Title	Slow Intermolecular Complexation-Decomplexation Exchanges of Cyclodextrins in Fullerene and Its Derivative Complexes
Author(s)	Ikeda, Atsushi; Mae, Tomoya; Sugikawa, Kouta; Komaguchi, Kenji; Konishi, Toshifumi; Hirao, Takehiro; Haino, Takeharu
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Relation	



Slow Intermolecular Complexation–Decomplexation Exchanges of Cyclodextrins in Fullerene and Its Derivative Complexes

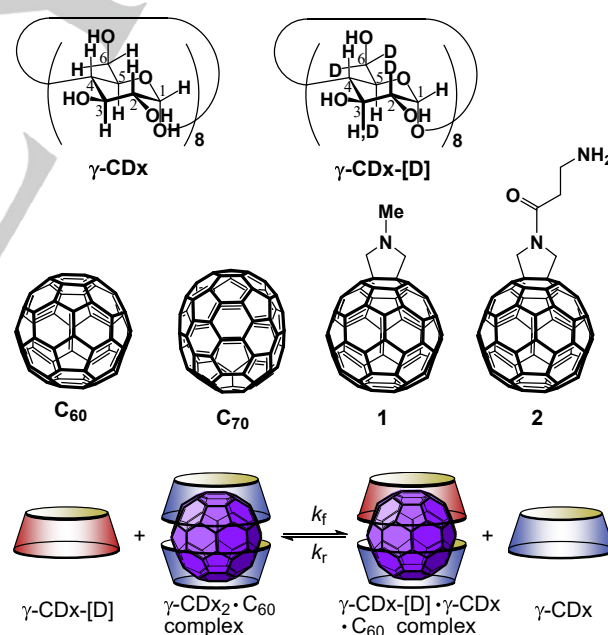
Atsushi Ikeda,^{*[a]} Tomoya Mae,^[a] Kouta Sugikawa,^[a] Kenji Komaguchi,^[a] Toshifumi Konishi,^[b] Takehiro Hirao,^[c] and Takeharu Haino^[c]

Abstract: Fullerenes (C_{60} and C_{70}) and several functionalized C_{60} derivatives can be encapsulated in two γ -cyclodextrins (γ -CDs). Although intermolecular complexation–decomplexation exchange of γ -CDx is known to be very slow, the exchange rates have yet to be quantitatively measured. Herein, we determined that the pseudo-first-order association and dissociation rate constants for the γ -CDx $_2$ • C_{70} complex were 4.3 and 0.6 s⁻¹ at 23 °C, respectively. In contrast, the intermolecular exchange rates for the γ -CDx $_2$ • C_{60} and C_{60} derivative complexes were slower than the time scale of exchange spectroscopy NMR experiments and the exchange rate constants were in the order of 10⁻⁴ s⁻¹. Furthermore, a γ -CDx $_2$ • C_{60} derivative complex was shown to have different intermolecular exchange rates for the two γ -CDs depending on steric hindrance from the substituent on the C_{60} derivative.

Unfortunately, γ -CDx $_2$ • C_{60} , C_{70} , and C_{60} derivative complexes are thermally labile and often precipitate out when heated.^[7] Therefore, an investigation into the intermolecular complexation–decomplexation exchange with γ -CDs is important to understand the stabilities of these complexes. Although we have reported the existence of an equilibrium between free and complexed γ -CDs in the γ -CDx $_2$ • C_{60} complex, even at ambient temperature,^[8] the rate has yet to be determined. Furthermore, for γ -CDx $_2$ • C_{60} derivative complexes, it would be interesting to investigate whether a substituent on the C_{60} derivatives influences intermolecular complexation–decomplexation exchange between the two γ -CDs. Herein, we have studied the equilibrium rates between free and complexed γ -CDx in γ -CDx $_2$ • C_{60} , C_{70} , and C_{60} derivative complexes, and the influence of the substituent on the C_{60} derivative.

Introduction

A variety of different lipophilic photoactive compounds, such as fullerenes and porphyrins, can be encapsulated in the lipophilic central cavities of two cyclodextrins (CDs).^[1,2] Therefore, CDs can be used as water-solubilizing and stabilizing agents of these photoactive compounds.^[1,2] Formation of these complexes prevents self-aggregates of the photoactive compounds forming through hydrophobic and π - π stacking interactions in water. The photoactive compounds isolated by CDs can lead to inhibition of self-quenching of photoexcited states and improved quantum yields for energy or electron transfer.^[3,4] Complexes of fullerenes (C_{60} and C_{70}) and several functionalized C_{60} derivatives with γ -CDs can be easily prepared in high concentration using mechanochemical high-speed vibration milling (HSVM) apparatus.^[5] Furthermore, these complexes show high photodynamic activity for human cervical cancer HeLa cells.^[6]



Scheme 1. Intermolecular complexation–decomplexation exchange of γ -CDx in the γ -CDx $_2$ • C_{60} complex.

Results and Discussion

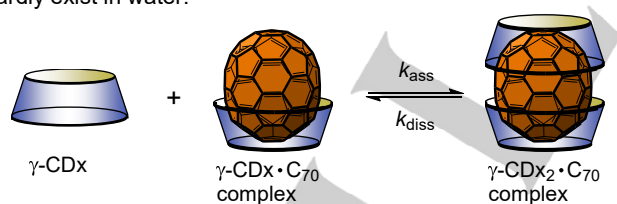
In 1D ¹H NMR spectra (Figures S1 and S2 in the Supporting Information), separation of the γ -CDx peaks between the γ -CDx $_2$ • C_{60} or C_{70} complexes and free γ -CDx implied that (i) the intermolecular complexation–decomplexation exchange rate was

[a] Prof. A. Ikeda, T. Mae, Dr. K. Sugikawa, Dr. K. Komaguchi
Department of Applied Chemistry, Graduate School of Engineering
Hiroshima University
1-4-1 Kagamiyama, Higashi-Hiroshima 739-8527, Japan
E-mail: aikeda@hiroshima-u.ac.jp

[b] Dr. T. Konishi
Department of Chemistry, College of Engineering
Shibaura Institute of Technology
307 Fukasaku, Minuma-ku, Saitama 337-8570, Japan.

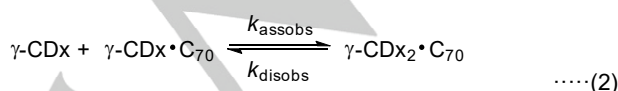
[c] Dr. T. Hirao, Prof. T. Haino
Department of Chemistry, Graduate School of Science
Hiroshima University
1-3-1 Kagamiyama, Higashi-Hiroshima 739-8526, Japan

slower than the NMR time scale or (ii) the anticipated equilibrium between the complexation–decomplexation exchange did not exist. Using multi-deuterium-labeled γ -CDx (γ -CDx-[D]), we previously demonstrated the existence of an equilibrium between free and complexed pristine γ -CDx in the γ -CDx₂•C₆₀ complex, even at ambient temperature and the validity of hypothesis (i) (Scheme 1).^[6] To evaluate the exchange rates, 2D ¹H–¹H exchange spectroscopy [EXSY; also known as nuclear Overhauser effect spectroscopy (NOESY)] NMR experiments were performed on γ -CDx₂•C₆₀ and C₇₀ complexes. For the γ -CDx₂•C₆₀ complex, a cross peak between the H-1 protons of free γ -CDx and H-1' protons of complexed γ -CDx was not observed at a mixing time (t_m) of 1.5 s (Figure 1a). This indicated that the intermolecular exchange rate was slower than the time scale of the EXSY NMR experiment. In contrast, the γ -CDx₂•C₇₀ complex is known to be less stable than the γ -CDx₂•C₆₀ complex when heated to 80 °C or when a small amount of DMSO is added.^[5f,7] Therefore, the intermolecular exchange rate in the γ -CDx₂•C₇₀ complex was anticipated to be much faster than that in the γ -CDx₂•C₆₀ complex. In the γ -CDx₂•C₇₀ complex, cross peaks between the H-1 protons of free and complexed γ -CDx were observed at $t_m = 0.5, 0.75, \text{ and } 1.0 \text{ s}$. A mixing time of 0.5 s was selected as the optimum value to maximize exchange peaks and minimize loss of diagonal peaks (Figure 1b). From the intensities of the cross and diagonal peaks measured at mixing times of 0 and 0.5 s, pseudo-first-order exchange rates between the free and complexed γ -CDx (k_{assobs} and k_{dissobs} in Eq. 2) were obtained using EXSY calculation software (ExsyCalc).^[9] The pseudo-first-order association and dissociation rate constants were determined to be 4.3 s^{-1} and 0.6 s^{-1} , respectively, at 23 °C (Eq. 2). These constants were the exchange rates under equilibrium conditions. Eq. 4 was obtained from the relationship between Eq. 1 (Scheme 2) and Eq. 3. Therefore, the second-order association rate constant, k_{ass} , can be obtained from the plot of [γ -CDx•C₇₀ complex] vs. k_{assobs} .^[10] From Eq. 4, k_{diss} could have almost the same value as k_{dissobs} .^[10] However, determining [γ -CDx•C₇₀ complex] is difficult because the γ -CDx•C₇₀ complex and free C₇₀ hardly exist in water.



Scheme 2. Association and dissociation of γ -CDx in the γ -CDx•C₇₀ complex.

$$d[\gamma\text{-CDx}_2\cdot\text{C}_{70}]/dt = k_{\text{ass}}[\gamma\text{-CDx}][\gamma\text{-CDx}\cdot\text{C}_{70}] + k_{\text{diss}}[\gamma\text{-CDx}_2\cdot\text{C}_{70}] \quad \dots(1)$$



$$d[\gamma\text{-CDx}_2\cdot\text{C}_{70}]/dt = k_{\text{assobs}}[\gamma\text{-CDx}\cdot\text{C}_{70}] + k_{\text{dissobs}}[\gamma\text{-CDx}_2\cdot\text{C}_{70}] \quad \dots(3)$$

$$k_{\text{ass}}[\gamma\text{-CDx}] \approx k_{\text{assobs}}, \quad k_{\text{diss}} \approx k_{\text{dissobs}} \quad \dots(4)$$

As mentioned above, the intermolecular exchange rate in the γ -CDx₂•C₆₀ complex was slower than the time scale of the EXSY NMR experiments. If intermolecular exchange occurs more slowly than the human time scale, it is possible to observe changes in the ¹H NMR spectra. ¹H NMR spectra were measured immediately after mixing the aqueous solutions of the pristine γ -CDx₂•C₆₀ complex and γ -CDx-[D] (Figures 2a–c and S3). The solution of pristine γ -CDx₂•C₆₀ complex in Figure 2a–c was added to a solution containing a 2-fold excess of γ -CDx-[D]. The ¹H NMR spectrum of this mixture is shown in Figure 2b. The doublet peak at 5.02 ppm corresponding to the H-1 proton in pristine γ -CDx₂•C₆₀ complex was gradually replaced by a singlet peak in the γ -CDx-[D]₂•C₆₀ complex. In contrast, when the γ -CDx-[D]₂•C₆₀ complex and pristine γ -CDx solutions were mixed, the singlet peak was replaced by a doublet peak (Figure S4). After adding γ -CDx-[D] to pristine- γ -CDx₂•C₆₀ complex solution, pristine γ -CDx₂•C₆₀ complex was gradually replaced by γ -CDx-[D]₂•C₆₀ complex because the values of [γ -CDx-[D]]/([γ -CDx] + [γ -CDx-[D]]) increased with incubation time (Figure 3a). A similar phenomenon was observed after the addition of pristine γ -CDx to the γ -CDx-[D]₂•C₆₀ complex solution (Figure 3b). Constants k_f and k_r were the forward reaction second-order rate constant for the

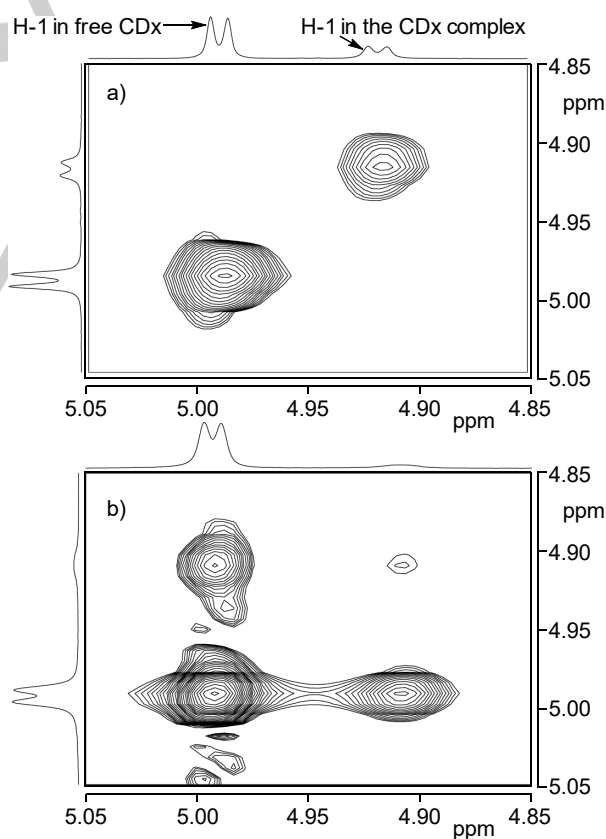


Figure 1. Partial 2D ¹H–¹H EXSY spectra of a) γ -CDx₂•C₆₀ and b) γ -CDx₂•C₇₀ complexes in D₂O at 23 °C.

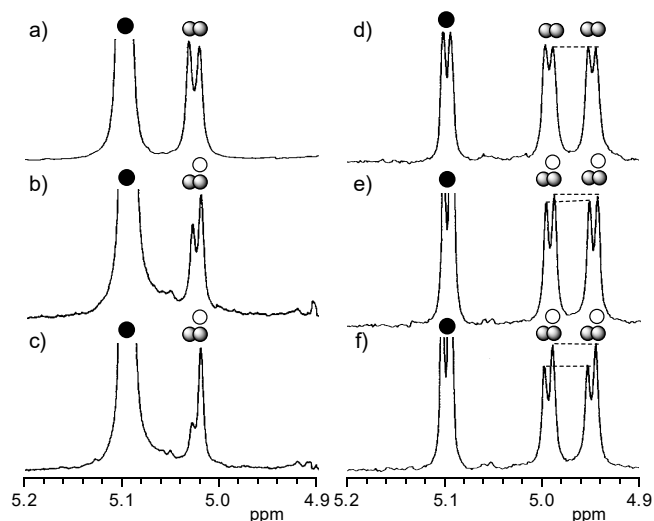


Figure 2. Partial ^1H NMR spectra of $\gamma\text{-CDx}_2\cdot\text{C}_{60}$ complex a) before and after adding $\gamma\text{-CDx-[D]}$, b) immediately after mixing, and c) 24 h after mixing, and of the $\gamma\text{-CDx}_2\cdot\mathbf{1}$ complex d) before and after adding $\gamma\text{-CDx-[D]}$, e) immediately after mixing, and f) 24 h after mixing in D_2O at 23°C (●: free $\gamma\text{-CDx}$ and $\gamma\text{-CDx-[D]}$, ○: $\gamma\text{-CDx}$ complexed with $\mathbf{1}$, ◐: $\gamma\text{-CDx-[D]}$ complexed with $\mathbf{1}$).

exchange between $\gamma\text{-CDx-[D]}$ and pristine $\gamma\text{-CDx}$ in the $\gamma\text{-CDx}_2\cdot\text{C}_{60}$ complex and reverse second-order rate constant for the exchange between pristine $\gamma\text{-CDx}$ and $\gamma\text{-CDx-[D]}$ in the $\gamma\text{-CDx-[D]}_2\cdot\text{C}_{60}$ complex, respectively (Scheme 1). If the values of k_f and k_r are equal, owing to $\gamma\text{-CDx-[D]}$ having a similar structure to $\gamma\text{-CDx}$,^[8] the pseudo-first-order rate constant ($k = k_f \approx k_r$; Scheme 1) can be expressed using Eq. S5 (see Supporting Information). Constant k was determined to be $2.0 \times 10^{-4} \text{ s}^{-1}$ using Eq. S5, which corresponded to a half-life of approx. 320 s. The constant was the exchange rate before an equilibrium state was reached, and was, therefore, different to the rate constant from the EXSY NMR experiment of the $\gamma\text{-CDx}_2\cdot\text{C}_{70}$ complex. However, the half-life indicated that the intermolecular exchange rate in the $\gamma\text{-CDx}_2\cdot\text{C}_{60}$ complex was much slower than that in the $\gamma\text{-CDx}_2\cdot\text{C}_{70}$ complex. In contrast, when the aqueous solution of $\gamma\text{-CDx}$ was added to the solution of $\gamma\text{-CDx-[D]}_2\cdot\text{C}_{60}$ complex, k was determined to be $1.6 \times 10^{-4} \text{ s}^{-1}$ using the same method, which corresponded to a half-life of approx. 400 s (Figure 3b). These rate constants (k) between $\gamma\text{-CDx}$ and $\gamma\text{-CDx-[D]}$ for the exchange of the C_{60} complex were virtually identical.

In the $\gamma\text{-CDx}_2\cdot\mathbf{1}$ complex, there are two kinds of complexed $\gamma\text{-CDx}$ s due to the presence of the substituent of $\mathbf{1}$,^[11] with the intermolecular exchange rates between the two complexed $\gamma\text{-CDx}$ s expected to be different. First, the $\gamma\text{-CDx}_2\cdot\mathbf{1}$ complex peaks were assigned. Generally, it is difficult to assign all peaks of complexed $\gamma\text{-CDx}$ in $\gamma\text{-CDx}_2\cdot\text{guest}$ complexes because all proton peaks for the free and complexed CDx s, except for H-1, appear as a dense collection of overlapping signals in the same region (3.3–3.8 ppm). In the ^1H - ^1H COSY (correlation spectroscopy) of the $\gamma\text{-CDx}_2\cdot\mathbf{1}$ complex, as shown in Figure 4, three issues complicated the assignment; (i) overlapping of H-2 and H-4 protons in complexed $\gamma\text{-CDx}$; (ii) very weak cross peaks between H-5 and H-6 in complexed $\gamma\text{-CDx}$; and (iii) two types of complexed

$\gamma\text{-CDx}$ existing with the presence (H-1'-H-6') and absence (H-1''-H-6'') of the substituent of $\mathbf{1}$. However, the assignment was supported by the appearance of cross peaks between H-1 and other protons and between methyl protons of $\mathbf{1}$ and one set of complexed $\gamma\text{-CDx}$ in the NOESY spectrum (Figure S5). These assignments, summarized in Table 1, are consistent with the ^1H NMR spectrum of the deuterated $\gamma\text{-CDx}$ ($\gamma\text{-CDx-[D]}$) $\cdot\mathbf{1}$ complex (Figure 5a). Furthermore, these assignments were not contradicted by the ^1H NMR spectrum of the $\gamma\text{-CDx-[D]}_2\cdot\mathbf{1}$ complex (Figure 5b). These results clearly indicated two types of $\gamma\text{-CDx}$ were present in a 1:1 stoichiometry in the $\gamma\text{-CDx}_2\cdot\mathbf{1}$ complex. In other words, the $\gamma\text{-CDx}_2\cdot\mathbf{1}$ complex formed a [2] pseudorotaxane conformation in which the substituent penetrates the upper rim of either of two $\gamma\text{-CDx}$ s, in agreement with the crystal structure of a $\gamma\text{-CDx}_2\cdot\text{fullerene}$ derivative complex.^[5c]

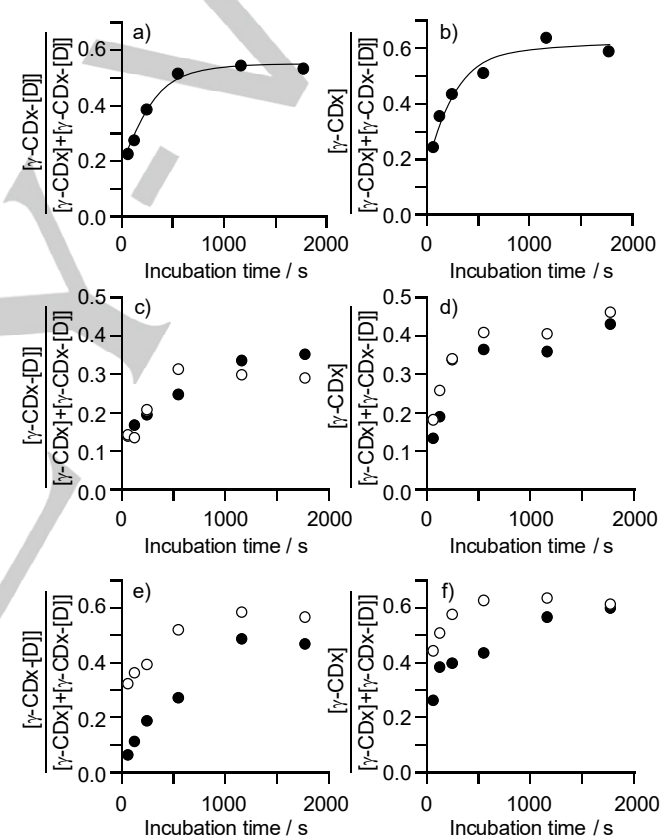


Figure 3. Incubation time-dependence of a), c), and e) $[\gamma\text{-CDx-[D]}]/([\gamma\text{-CDx}] + [\gamma\text{-CDx-[D]}])$ in the complex after adding $\gamma\text{-CDx-[D]}$, and b), d), and f) $[\gamma\text{-CDx}]/([\gamma\text{-CDx}] + [\gamma\text{-CDx-[D]}])$ in the complex after adding $\gamma\text{-CDx}$ in D_2O at 23°C . a) $\gamma\text{-CDx}_2\cdot\text{C}_{60}$ complex, b) $\gamma\text{-CDx-[D]}_2\cdot\text{C}_{60}$ complex, c) $\gamma\text{-CDx}_2\cdot\mathbf{1}$ complex, d) $\gamma\text{-CDx-[D]}_2\cdot\mathbf{1}$ complex e) $\gamma\text{-CDx}_2\cdot\mathbf{2}$ complex, f) $\gamma\text{-CDx-[D]}_2\cdot\mathbf{2}$ complex. Values of $[\gamma\text{-CDx-[D]}]/([\gamma\text{-CDx}] + [\gamma\text{-CDx-[D]}])$ and $[\gamma\text{-CDx}]/([\gamma\text{-CDx}] + [\gamma\text{-CDx-[D]}])$ were evaluated using integrated intensities of their ^1H NMR spectra. [(B–E) ●: values evaluated using H-1' of $\gamma\text{-CDx}$ and $\gamma\text{-CDx-[D]}$ with penetration of the substituent of $\mathbf{1}$ or $\mathbf{2}$, ○: values evaluated using H-1'' of $\gamma\text{-CDx}$ and $\gamma\text{-CDx-[D]}$ without penetration of the substituent of $\mathbf{1}$ or $\mathbf{2}$].

The EXSY NMR spectrum was measured to determine the two intermolecular exchange rates. However, no cross peak was

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present between the H-1 protons of free γ -CDx and H-1' or H-1'' protons of complexed γ -CDx at $t_m = 1.2$ and 1.5 s (Figure S5), indicating that the intermolecular exchange rate was slower than the time scale in the EXSY NMR experiment, in addition to the γ -CDx \cdot C₆₀ complex. Furthermore, Figure S5 shows no cross peaks between H-1' and H-1'' of γ -CDx with and without penetration of the substituent of **1**, respectively. The EXSY NMR spectrum of the γ -CDx \cdot **2**^[5f] complex was measured and gave a similar result to that of the γ -CDx \cdot **1** complex (Figure S6). These results indicated that an intramolecular rotation (flip-flop motion) of **1** or **2** (Scheme 3a and b) was also slower than time scale of the EXSY NMR experiment or did not exist.

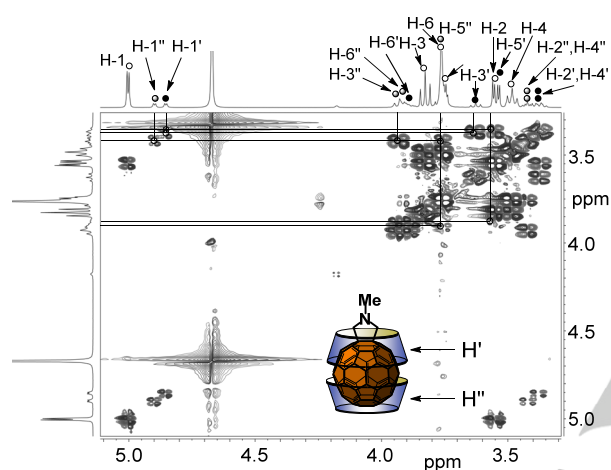


Figure 4. 2D ^1H - ^1H COSY of γ -CDx \cdot **1** complex in D_2O at 23°C (○: free γ -CDx, ●: γ -CDx with penetration of substituent of **1** into the complex, ○: γ -CDx without penetration of substituent of **1** into the complex).

Table 1. Chemical shifts (ppm) of γ -CDx \cdot **1** and γ -CDx-[D] \cdot **1** complexes

Compd.		Chemical shift / ppm					
		H-1	H-2	H-3	H-4	H-5	H-6
γ -CDx \cdot 1	H ^[a]	4.90	3.42	3.93	3.42	3.74-3.76	3.91
complex	H ^[b]	4.85	3.37	3.63	3.37	3.53-3.56	3.88
γ -CDx-[D] \cdot 1	H ^[a]	4.89	— ^[c]	3.92	3.42	3.74	— ^[c]
complex	H ^[b]	4.85	— ^[c]	3.62	3.36	3.54	— ^[c]

[a] Protons assigned to γ -CDx with penetration of the substituent of **1**. [b] Protons assigned to γ -CDx without penetration of the substituent of **1**. [c] Peaks disappeared with deuteration of γ -CDx.

If dissociation of one of the γ -CDx took place through a sailboat-like complex structure (Scheme 3a and b), as observed in γ -CDx \cdot C₆₀ derivative complexes,^[12] the dissociation process should be slowed by steric hindrance of the substituent group in the C₆₀ derivatives. In other words, the dissociation rate of one γ -CDx penetrating the substituent group was slower than that of another γ -CDx. To determine the different rates of two γ -CDx, the solution of pristine γ -CDx \cdot **1** complex was added to a solution containing a 2-fold excess of γ -CDx-[D] and the γ -CDx \cdot C₆₀ complex (Figures 2d-f and S7). In Figure 2d and e, both doublet peaks in the range of 4.9–5.0 ppm were assigned to H-1' and H-1'' protons of γ -CDx with and without penetration of the substituent of **1**, respectively, in the γ -CDx \cdot **1** complex. These peaks were

changed to singlet peaks by replacing pristine γ -CDx with γ -CDx-[D]. Finally, after achieving an equilibrium with the replacement, singlet peaks were observed to overlap the right-hand peak in each doublet (Figure 2f). As shown in Figure 2e, the spectral change of H-1'' at around 5.0 ppm was similar to that of H-1' at around 4.9 ppm, indicating that the intermolecular exchange rate (k_1) was scarcely different from that (k_2) in Scheme 3. Figure 3c also shows that k_1 and k_2 have similar values because the values of $[\gamma\text{-CDx-[D]}]/([\gamma\text{-CDx}] + [\gamma\text{-CDx-[D]}])$ similarly increased for both H-1' and H-1''. A similar result was obtained by replacing from γ -CDx-[D] with pristine γ -CDx (Figures 3c, d, and S8). This result suggested that the substituent of **1** hardly effected steric hindrance of intermolecular complexation–decomplexation exchanges of γ -CDx.

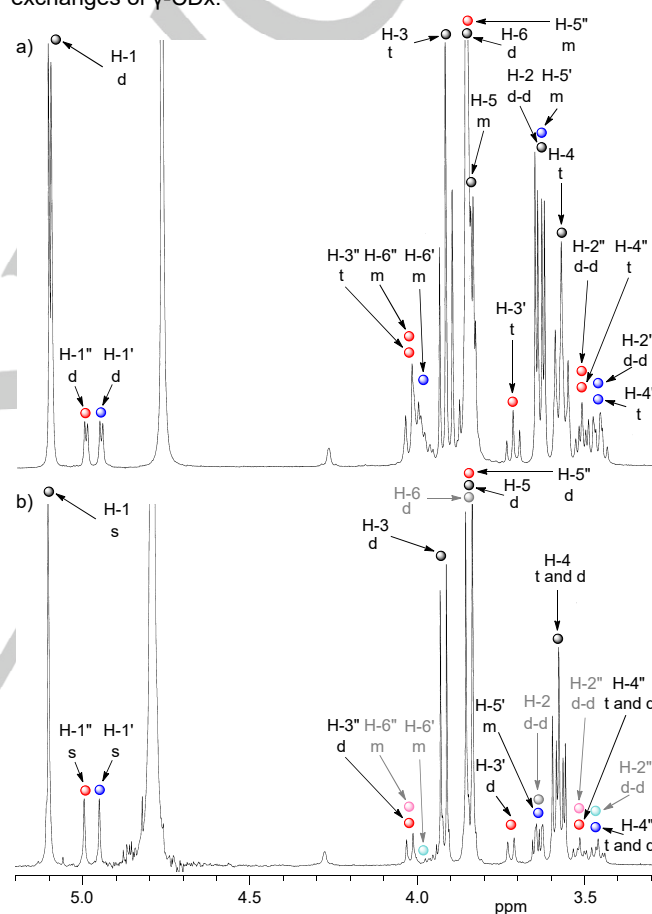


Figure 5. ^1H NMR spectra of a) γ -CDx \cdot **1** and b) γ -CDx-[D] \cdot **1** complexes in D_2O at 23°C (○: free γ -CDx or γ -CDx-[D], ●: γ -CDx or γ -CDx-[D] with penetration of the substituent of **1** in the complex, ○: γ -CDx or γ -CDx-[D] without penetration of the substituent of **1** in the complex, and ●, ○, and ○: peaks that disappeared using γ -CDx-[D]).

We carried out a similar experiment using **2**, which has a larger substituent, complexed with γ -CDx (Figures 6a–c and S9). As shown in Figure 6b, the difference between two peaks in the γ -CDx \cdot **2** complex was larger than that in the γ -CDx \cdot **1** complex, indicating that the γ -CDx \cdot **2** complex had a larger difference between intermolecular exchange rates k_1 and k_2 for γ -CDx with

and without penetration of the substituent of **2**, respectively (Scheme 2). Similarly, when the γ -CDx-[D] \cdot **2** complex and γ -CDx solutions were mixed (Figures 6d–f and S10), the H-1'' signal at 5.00 ppm also changed faster than the H-1' signal at 4.96 ppm (Figure 6e). The final spectra gave similar-shaped peaks for H-1' and H-1'' (Figure 6c and f). These results clearly indicated that C₆₀ derivatives with bigger substituents were more sterically hindered toward intermolecular exchange processes. Figure 3e and f also showed that k_2 was larger than k_1 . If the intramolecular rotation rate (k_3) was faster than the intermolecular exchange rate (k_2), two intermolecular exchange rates k_1 and k_2 , should be averaged to become the same value. However, that the intermolecular exchange processes were

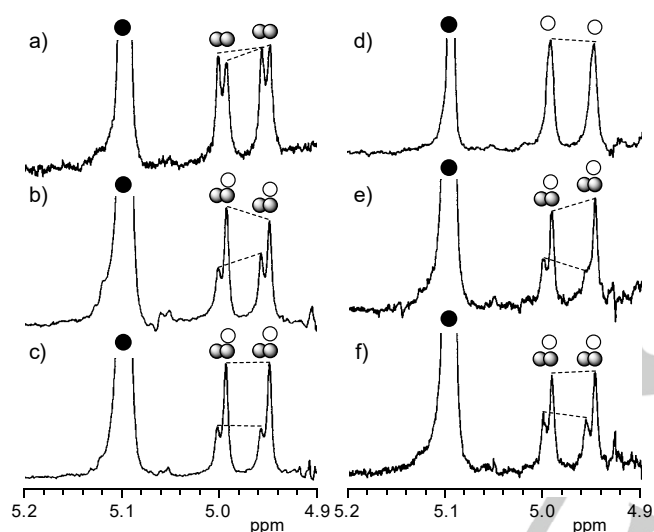
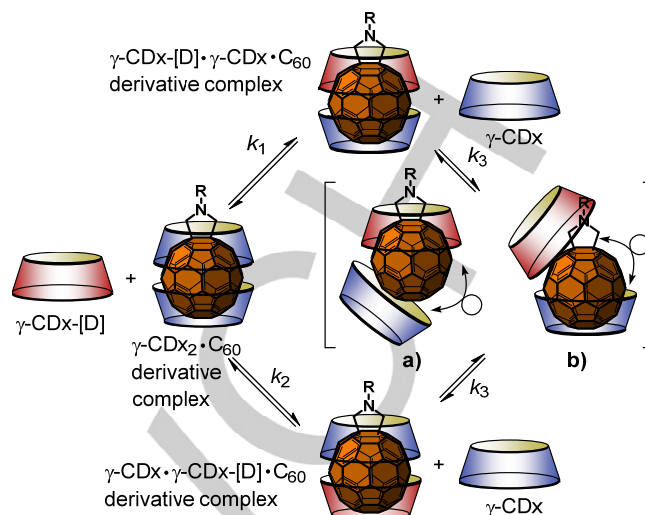


Figure 6. Partial ^1H NMR spectra of $\gamma\text{-CDX}_2\cdot\mathbf{2}$ complex a) before and after adding $\gamma\text{-CDX-[D]}$, b) immediately after mixing, and c) 24 h after mixing, and of $\gamma\text{-CDX-[D]}\cdot\mathbf{2}$ complex d) before and after adding $\gamma\text{-CDX}$, e) immediately after mixing, and f) 24 h after mixing in D_2O at 23 °C (●: free $\gamma\text{-CDX}$ and $\gamma\text{-CDX-[D]}$, ○: $\gamma\text{-CDX}$ complexed with **2**, ○: $\gamma\text{-CDX-[D]}$ complexed with **2**).

observed on a human time scale by ^1H NMR showed that explanation (ii) was correct, because cross peaks between H-1' and H-1'' of $\gamma\text{-CDXs}$ were observed in the EXSY NMR spectra of the $\gamma\text{-CDX}_2\cdot\mathbf{2}$ complex using NOE. Therefore, the intramolecular rotation rate was slower than the intermolecular exchange rate in the $\gamma\text{-CDX}_2\cdot\mathbf{2}$ complex. Free energy simulations of the $\gamma\text{-CDX}_2\cdot\text{C}_{60}$ complex have shown that the dissociation of a single $\gamma\text{-CDX}$ most likely takes place via a sailboat-like complex structure.^[12] To rotate **2** intramolecularly, two $\gamma\text{-CDXs}$ need to further spread by adopting a sailboat-like complex structure (Scheme 3a and b). However, a single $\gamma\text{-CDX}$ would dissociate before intramolecular rotation because of the bulkiness of the substituent of **2**.



Scheme 3. Two pathways of intermolecular complexation-decomplexation exchange for $\gamma\text{-CDX}$ in the $\gamma\text{-CDX}_2\cdot\text{C}_{60}$ derivative complex and intramolecular rotation.

Conclusions

In summary, we found that the intermolecular exchange rate of $\gamma\text{-CDX}$ in the $\gamma\text{-CDX}_2\cdot\text{C}_{60}$ complex was much slower than that in the $\gamma\text{-CDX}_2\cdot\text{C}_{70}$ complex and was on the human time scale. This result agreed with the fact that the $\gamma\text{-CDX}_2\cdot\text{C}_{60}$ complex is much more stable than the $\gamma\text{-CDX}_2\cdot\text{C}_{70}$ complex toward heat or polar organic solvents. Furthermore, $\gamma\text{-CDX}_2\cdot\text{C}_{60}$ derivative complexes had $\gamma\text{-CDX}$ intermolecular exchange rates on the human time scale. C_{60} derivative **2** showed that intermolecular exchange rate k_2 , toward $\gamma\text{-CDX}$ without penetration of the substituent, was faster than intermolecular exchange rate k_1 and intramolecular exchange rate k_3 .

Supporting Information Summary

Experimental procedures and complete 1D and 2D ^1H NMR spectra were placed in the Supporting Information.

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Conflict of interest

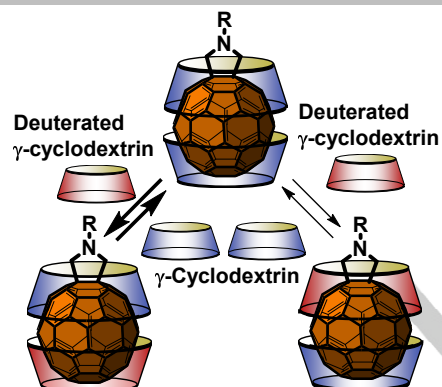
The authors declare no conflict of interest.

Keywords: cyclodextrins • fullerenes • host-guest systems • pseudorotaxanes • NMR spectroscopy

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Atsushi Ikeda,* Tomoya Mae, Kouta Sugikawa, Kenji Komaguchi, Toshifumi Konishi, Takehiro Hirao, and Takeharu Haino

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Slow Intermolecular Complexation–Decomplexation Exchanges of Cyclodextrins in Fullerene and Its Derivative Complexes

Intermolecular exchange rates of the intermolecular exchange rates for γ -cyclodextrin₂•C₆₀ and C₆₀ derivative complexes were slower than the time scale of exchange spectroscopy NMR experiments and the exchange rate constants were in the order of 10⁻⁴ s⁻¹. Furthermore, the γ -cyclodextrin₂•C₆₀ derivative has different intermolecular exchange rates via two pathways because of steric hindrance by a substituent on the C₆₀ derivative.