Self-Threading and Dethreading Dynamics of Poly(ethylene glycol)-Substituted Cyclodextrins with Different Chain Lengths

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Received January 12, 2007; Revised Manuscript Received February 24, 2007

ABSTRACT: Poly(ethylene glycol) (PEG)-substituted cyclodextrins (CDs) with different chain lengths have been synthesized. PEG-substituted CDs formed self-threading complexes in aqueous solutions. The conformation of PEG-substituted CDs changed from a self-threading form to a dethreading form in the presence of an equal molar amount of 1-adamantanecarboxylic acid (AdCA) as a competitive guest and exchanged between a self-threading form and a dethreading form in the presence of a half molar amount of AdCA. The conformational exchange dynamics of PEG-substituted CDs were studied by means of variable-temperature NMR and 2D EXSY NMR experiments, and it was revealed that the conformational exchange rates decreased exponentially with the PEG chain length of the substituent.

Introduction

The concept of molecular machine has received much attention in various fields of science, especially chemical and biological field in recent years.[1] A molecular machine is defined as an assembly of a discrete number of molecular components designed to perform mechanical-like movements as a consequence of appropriate external stimuli.[1g] In biological system, there are many excellent molecular machines such as myosins,[2] ATP synthases,[3] or chaperonins.[4] Recent developments of observation and measurement techniques have allowed us to understand the mechanism of such biological molecular machines. In chemical field, design and construction of molecular or supramolecular systems which perform machine-like movement in response to an appropriate external stimulus are actively worked on for artificial molecular machines.[5] However, most of the artificial molecular machines reported so far consist of relatively small molecules. Considering that the biological molecular machines consist of polypeptides, it is a desirable attempt to introduce a polymer to the existing molecular machines.

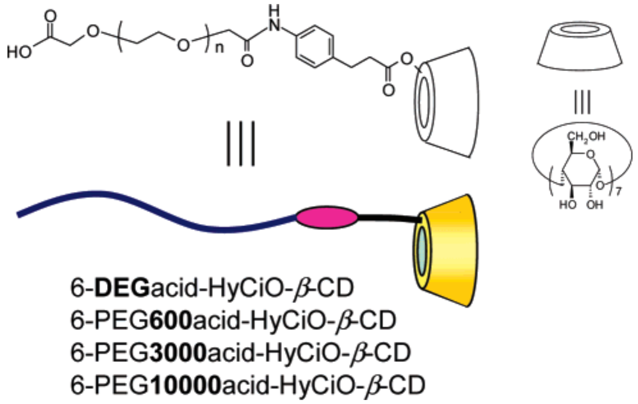

Figure 1. Structure of PEG-substituted CDs.

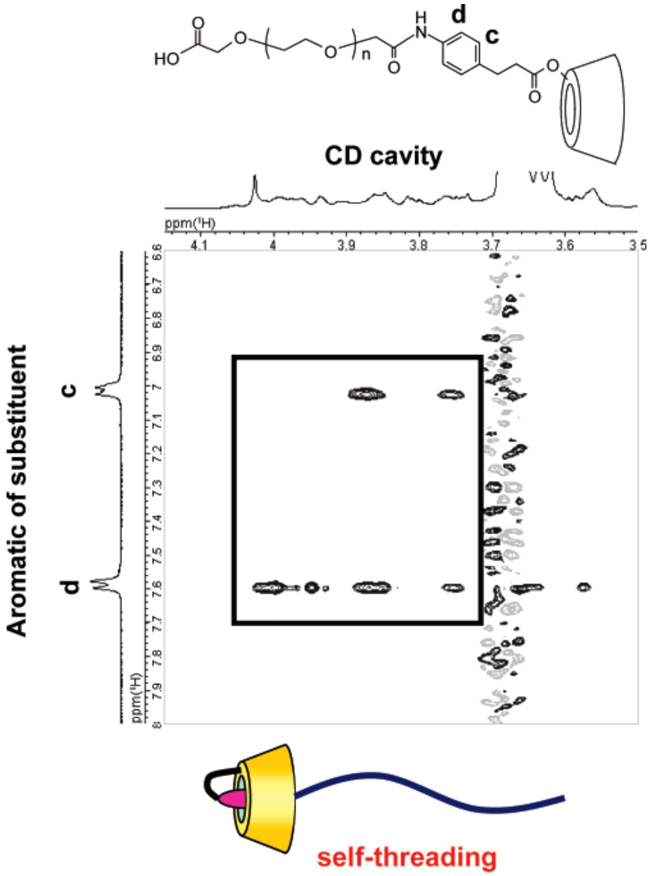

Figure 2. Partial 2D ROESY ^{1}H NMR spectrum of 6-PEG600acid-HyCiO-β-CD in D_2O at 30 °C and the proposed conformation.

Meanwhile, polyrotaxane is one of supramolecules containing a linear polymer as a component, which is included in cyclic components. There are many reports on the preparation and characterization of polyrotaxanes which consist of cyclodextrins (CDs) and various kinds of linear polymers.[6−8] However, the threading mechanism and dynamics of a linear polymer into CDs have yet to be revealed, and this issue is an essential and important for the dynamics of polymer in solution.[9] Previously, we have reported syntheses of PEG-substituted CDs and their conformational exchange dynamics between a self-threading

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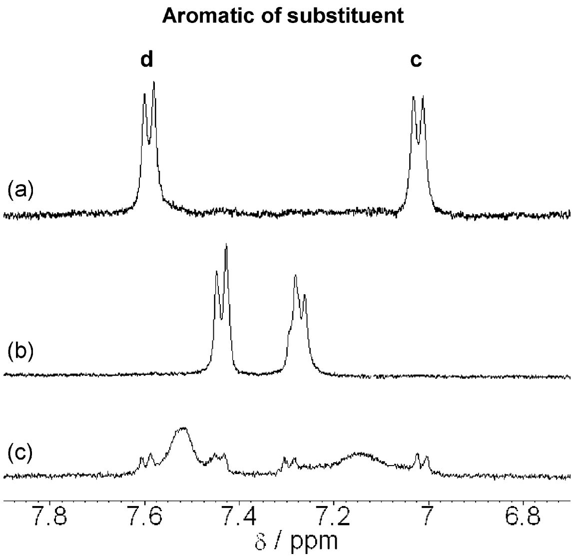

Figure 3. ^{1}H NMR spectra of the aromatic part of 6-PEG600acid-HyCiO-β-CD in D_2O at 30 °C (a) in the absence of AdCA, (b) in the presence of an equal molar amount of AdCA, and (c) in the presence of a half molar amount of AdCA.

form and a dethreading form in aqueous solutions.[10] In this article, we report further research of the self-threading and dethreading dynamics of PEG-substituted CDs with different chain lengths and the dependence of the dynamics on their chain lengths.

Experimental Section

Materials. β-CD, sodium hydroxide (NaOH), *p*-toluenesulfonyl chloride, and 1-adamantanecarboxylic acid (AdCA) were obtained from Nacalai Tesque, Inc. 4-Aminohydrocinnamic acid and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC•HCl) were obtained from Tokyo Chemical Industry Co., Ltd. 3,6,9-Trioxaundecanedioic acid (DEG diacid), PEG 600 diacid (M_n = 600), and PEG 10000 (M_n = 10 000) were obtained from Sigma-Aldrich Corp. PEG 3000 diacid (M_n = 2925) was obtained from NOF Corp.

Measurements. ^{1}H NMR spectra were recorded at 400 MHz on a JEOL-GSX 400 spectrometer. 2D ^{1}H ROESY and EXSY NMR spectra were recorded at 600 MHz on a VARIAN UNITY plus NMR spectrometer. Chemical shifts were referenced to solvent values ($\delta = 4.70$ ppm for HOD, $\delta = 2.50$ ppm for DMSO-d_6) and external standard in solvent ($\delta = 1.96$ ppm for acetonitrile in D_2O). NMR samples of PEG-substituted CDs were prepared as solutions at 3 mM concentration unless stated, and amount of AdCA in the solution was estimated from integrated intensity. Circular dichroism spectra were recorded on a JASCO J820 spectrometer in water with 0.1 cm cell at room temperature. Vapor pressure osmometry (VPO) was carried out by a GONOTEC OSMOMAT 070 vapor osmometer at 40 °C in water. Urea and α-CD were used as instruments standard. Positive-ion matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass measurements were performed on a Shimadzu/KRATOS AXIMA-CFR spectrometer with 2,5-dihydroxybenzoic acid as matrix, α-CD and insulin as standard, and NaCl as cationizing agent. The preparative reversed-phase chromatography was performed with a Waters Delta 600 system (column: SunFire Prep C_{18} 19 × 150 mm).

Synthesis. PEG 10000 diacid was prepared according to the method reported previously.[7f] Mono-6-*O*-(4-aminohydrocinnamoyl)-β-CD (6-AmHyCiO-β-CD), mono-6-*O*-[4-poly(ethylene glycol) 600 acid-hydrocinnamoyl]-β-CD (6-PEG600acid-HyCiO-β-CD), and mono-6-*O*-[4-poly(ethylene glycol) 3000 acid-hydrocinnamoyl]-β-CD (6-PEG3000acid-HyCiO-β-CD) were prepared according to the method reported previously.[10]

Mono-6-*O*-[4-di(ethylene glycol) acid-hydrocinnamoyl]-β-CD (6-DEGacid-HyCiO-β-CD). Synthesis of this compound is essentially the same way as 6-PEG600acid-HyCiO-β-CD, except for using DEG diacid instead of PEG 600 diacid. Yield: 21%. Positive ion MALDI-TOF MS: *m/z* 1508.1 $[M + Na]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.58 (s, 1H, $-$CONH$-$), 7.53 (d, 2H, 3-H of phenyl), 7.16 (d, 2H, 2-H of phenyl), 6.00$-$5.65 (m, 14H, O(2)H and O(3)H of CD), 4.82$-$4.75 (m, 7H, C(1)H of CD), 4.46$-$4.15 (m, 8H, O(6)H and C′(6)H of CD), 4.05 (s, 4H, $-CO-CH_2-O-$ of DEG), 3.85$-$3.17 (m, C(2)H$-$C(6)H of CD and $-CH_2-CH_2-O-$ of DEG overlaps with HOD), 2.80 (t, 2H, phenyl-CH_2-), 2.63 (t, 2H, $-CH_2-CO-$ overlaps with DMSO-d_6). Anal. Calcd for $C_{59}H_{91}O_{42}N{\cdot}7(H_2O)$: C, 43.95; H, 6.56; N, 0.87. Found: C, 44.05; H, 6.44; N, 1.09.

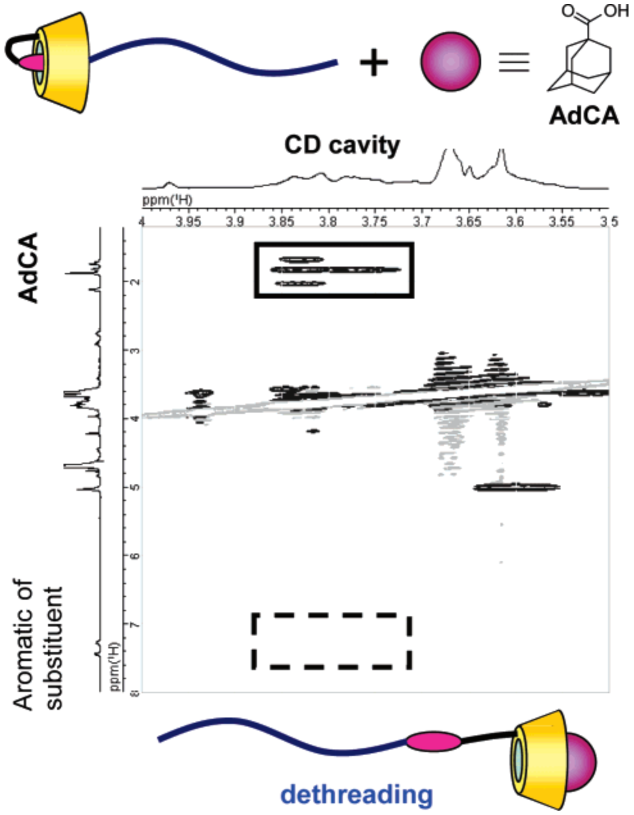

Figure 4. Partial 2D ROESY ^{1}H NMR spectrum of 6-PEG600acid-HyCiO-β-CD in the presence of an equal molar amount of AdCA in D_2O at 30 °C and the proposed conformation.

Mono-6-*O*-[4-poly(ethylene glycol) 10000 acid-hydrocinnamoyl]-β-CD (6-PEG10000acid-HyCiO-β-CD). Synthesis of this compound is essentially the same way as 6-PEG600acid-HyCiO-β-CD, except for using PEG 10000 diacid instead of PEG600 diacid. If the product contains PEG diacid after purification by HPLC, it was further purified by DIAION HP-20 column chromatography to remove PEG diacid (eluted with water/methanol). Yield: 11%. Positive ion MALDI-TOF MS: The mass spectrum exhibited a bell-shaped distribution of ca. 44 *m/z* spaced (mass of ethylene glycol (EG) unit) broad signals centered at 11451.1 *m/z* ($[M (n = 228) + Na]^+$, *n*: the number of EG units). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.49 (s, 1H, $-$CONH$-$), 7.52 (d, 2H, 3-H of phenyl), 7.16 (d, 2H, 2-H of phenyl), 5.90$-$5.65 (m, 14H, O(2)H and O(3)H of CD), 4.83$-$4.75 (m, 7H, C(1)H of CD), 4.43$-$4.12 (m, 8H, O(6)H and C′(6)H of CD), 4.05 (s, 4H, $-CO-CH_2-O-$ of PEG), 3.85$-$3.18 (m, C(2)H$-$C(6)H of CD and $-CH_2-CH_2-O-$ of PEG overlaps with HOD), 2.80 (t, 2H, phenyl-CH_2-), δ 2.62 (t, 2H, $-CH_2-CO-$ overlaps with DMSO-d_6).

Results and Discussion

Conformation of PEG-Substituted CD in Aqueous Solution. Figure 1 shows the structure of PEG-substituted CD. First,

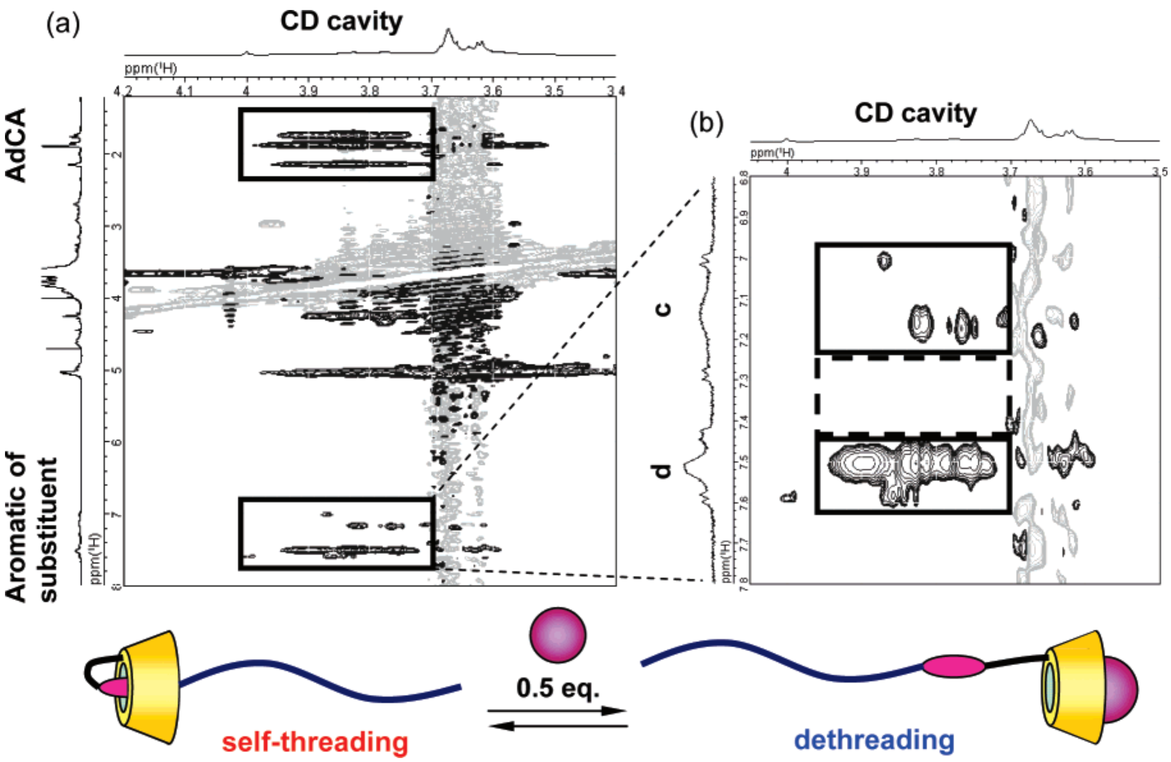

Figure 5. Partial 2D ROESY ^{1}H NMR spectrum of 6-PEG600acid-HyCiO-β-CD in the presence of a half molar amount of AdCA in D_2O at 30 °C and the proposed conformational exchange.

we investigated the conformation of PEG-substituted CD in aqueous solution. Figure 2 shows the 2D ROESY ^{1}H NMR spectrum of 6-PEG600acid-HyCiO-β-CD in D_2O. The correlation signals from the rotational nuclear Overhauser effects (ROEs) between the aromatic protons of the substituent (c and d) and the protons of the CD cavity (C(3)H and C(5)H) were observed (framed region), indicating that the aromatic part of the substituent was included in the CD cavity. The molecular weight measured by VPO in aqueous solution showed about 1900 g/mol. Moreover, the NMR spectrum of 6-PEG600 acid-HyCiO-β-CD showed no concentration dependency, indicating that the correlation signals were not due to the formation of intermolecular complex in the measurement range (see Supporting Information). From these results, it was found that 6-PEG600acid-HyCiO-β-CD formed a self-threading complex in aqueous solution. The other PEG-substituted CDs with different chain lengths showed similar results to 6-PEG600acid-HyCiO-β-CD.

Conformational Change of PEG-Substituted CD. The conformational change of PEG-substituted CD by external stimulus was investigated. AdCA was used as a competitive guest because it was strongly included in a β-CD. Figure 3 shows changes of the spectrum of the aromatic part of 6-PEG600acid-HyCiO-β-CD in D_2O in the absence and presence of AdCA. In the presence of an equal molar amount of AdCA, the signals of the aromatic protons largely shifted (Figure 3b). The 2D ROESY ^{1}H NMR spectrum (Figure 4) showed no correlation signals between the aromatic protons and the protons of the CD cavity (dashed framed region). Alternatively, strong correlation signals between the protons of AdCA and those of the CD cavity were observed, indicating that the substituent completely went out to water by the inclusion of AdCA into the CD cavity (solid framed region). This conformational change has been studied by circular dichroism spectroscopy.[10] From these results, it was found that the conformation of 6-PEG600acid-HyCiO-β-CD changed from a self-threading form to a deth-

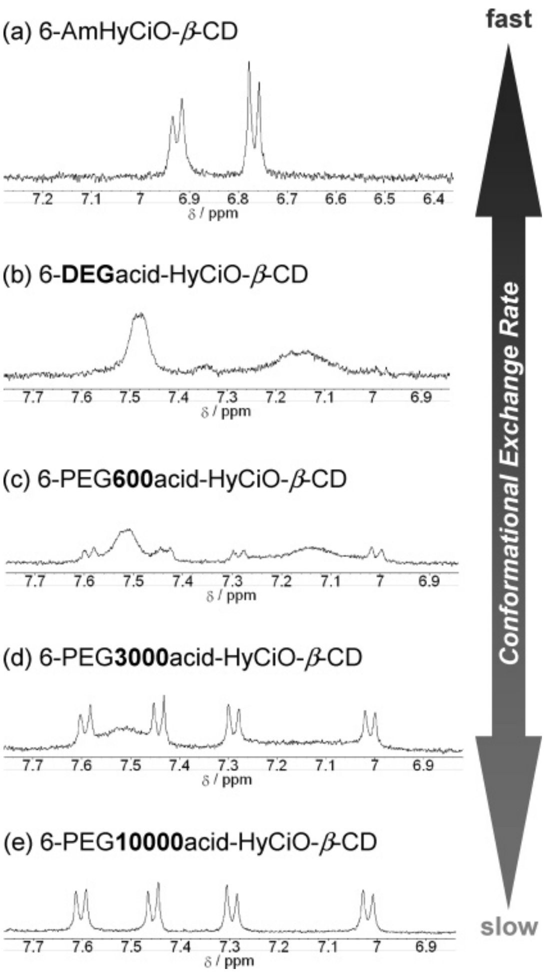

Figure 6. ^{1}H NMR spectra of the aromatic part of 6-AmHyCiO-β-CD and PEG-substituted CDs in D_2O in the presence of a half molar amount of AdCA at 30 °C.

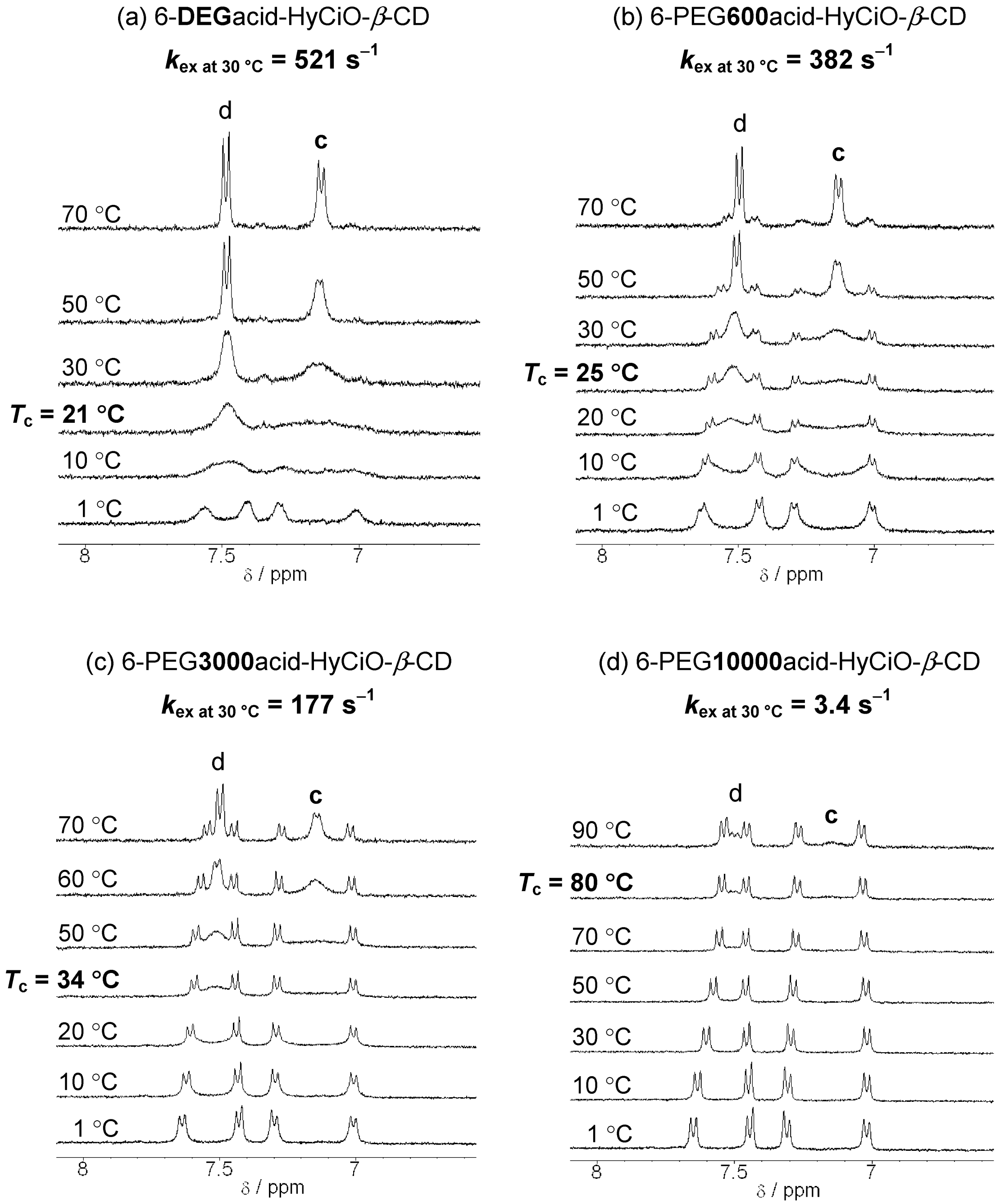

Figure 7. Results of variable-temperature NMR experiments of PEG-substituted CDs in the presence of a half molar amount of AdCA in D_2O.[12]

reading form in the presence of an equal molar amount of AdCA. The other PEG-substituted CDs with different chain lengths showed similar results to 6-PEG600 acid-HyCiO-β-CD.

Conformational Exchange of PEG-Substituted CD in the Presence of a Half Molar Amount of AdCA. In the presence of a half molar amount of AdCA in D_2O solution of 6-PEG600acid-HyCiO-β-CD, the signals of the aromatic protons shifted and broadened with small signals (Figure 3c). The 2D ROESY ^{1}H NMR spectrum (Figure 5) showed the correlation signals between the protons of the CD cavity and both the protons of AdCA and the aromatic protons (framed regions in Figure 5a). These results indicated that the CD cavity included the aromatic part of the substituent and AdCA alternatively, that is, the conformation of PEG-substituted CD exchanged between a self-threading form and a dethreading form, in addition, the conformational exchange was relatively slow in NMR time scale due to its PEG chain of the substituent. In the detailed spectrum between the CD cavity and the aromatic part (Figure 5b), the correlation signals between the broad signals and the small signals at 7.02 and 7.59 ppm of the aromatic protons and the signals of the protons of the CD cavity were observed (solid framed regions), while no correlation signals between the small signals at 7.29 and 7.44 ppm of the aromatic protons could be observed (dashed framed region). The chemical shift values, 7.02 and 7.59 ppm, correspond with that of a self-threading form, and the chemical shift values, 7.29 and 7.44 ppm, correspond with that of a dethreading form. Furthermore, the small signals did not coalesce even at high temperature (see variable-temperature NMR experiments part). Therefore, it is considered that the small signals were due to the species that did not participate in the conformational exchange, whereas the broad signals were due to the species that participate in the conformational exchange.

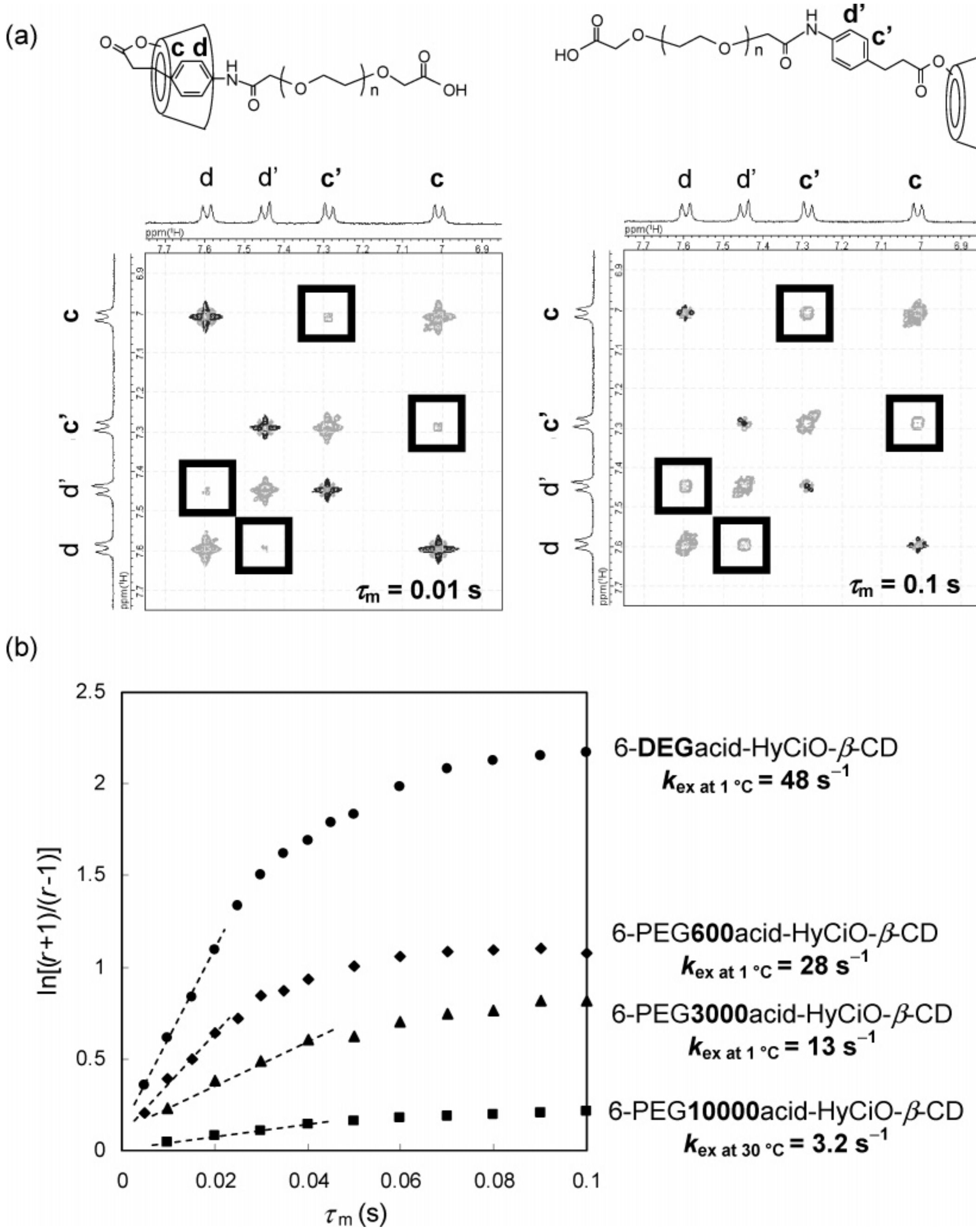

Figure 8. Result of 2D EXSY NMR experiments: (a) Example of 2D EXSY ^{1}H NMR spectrum (6-PEG10000acid-HyCiO-β-CD at 30 °C at $\tau_m = 0.01$ and 0.1 s). (b) Plots of $\ln[(r + 1)/(r - 1)]$ as a function of τ_m and the conformational exchange rates of PEG-substituted CDs with different chain lengths.

It was anticipated that the shapes of signals were different among PEG-substituted CDs with different chain lengths because the broadness was related to the threading dynamics of PEG chain into the CD cavity. Figure 6 shows the ^{1}H NMR spectra of the aromatic part of 6-AmHyCiO-β-CD and PEG-substituted CDs in D_2O in the presence of a half molar amount of AdCA. In the case of 6-AmHyCiO-β-CD without PEG chain, the signals of the aromatic protons were sharp (Figure 6a). The signals of 6-DEGacid-HyCiO-β-CD were broad (Figure 6b); however, the broadness was less than that of 6-PEG600acid-HyCiO-β-CD (Figure 6c). In the case of 6-PEG3000acid-HyCiO-β-CD with a longer PEG chain, one of signals was broad but the other was split (Figure 6d). In the case of 6-PEG10000 acid-HyCiO-β-CD with a long PEG chain, both signals were completely split, indicating that its conformation hardly exchanged (Figure 6e).

In contrast, the chemical shift values and signal shapes of the protons of AdCA were similar among the PEG-substituted CDs with different chain lengths, indicating that the exchange rate of AdCA between PEG-substituted CDs did not contribute to the difference in the conformational exchange rate of PEG-substituted CDs (see Supporting Information). These results led us to the conclusion that the conformational exchange rate of PEG-substituted CD decreased as its PEG became longer.

Conformational Exchange Rates of PEG-Substituted CDs. The conformational exchange rate constants of PEG-substituted CDs in the presence of a half molar amount of AdCA were estimated by variable-temperature NMR experiments. The conformational exchange rate constant at a coalescence temperature was estimated by using the approximate expression[11]

$$k_c = \frac{\pi \Delta \nu}{\sqrt{2}}$$

where k_c is the conformational exchange rate constant at a coalescence temperature and $\Delta\nu$ is the chemical shift difference between the signal of the aromatic protons in the absence of AdCA and those in the presence of an equal molar amount of AdCA. The coalescence temperature T_c was estimated on the coalescence signal in the signal c of the aromatic protons. The free energy of activation for the conformational exchange at T_c and the extrapolated values of the conformational exchange rate constants at 30 °C were obtained from the Eyring equation:

$$k_{ex} = \left(\frac{k_B T}{h}\right) \exp\left(-\frac{\Delta G^{\neq}}{RT}\right)$$

where k_{ex} is the conformational exchange rate constant, k_B is the Boltzmann constant, T is the absolute temperature, h is the Planck constant, $\Delta G^{\neq}$ is the free energy of activation for the conformational exchange, and R is the gas constant. From this experiment, the $k_{ex\ \mathrm{at}\ 30\ °C}$ of PEG-substituted CDs were estimated, as shown in Figure 7.

In variable-temperature NMR experiment for 6-PEG10000acid-HyCiO-*β*-CD, the exchange signals coalesced only at high temperature, 80 °C, because of its slow conformational exchange. Consequently, 2D exchange spectroscopy (EXSY) NMR experiment which was more appropriate for such a slow exchange process was also performed (Figure 8).[13] The 2D EXSY spectra (Figure 8a) shows the cross signals between the signals of the aromatic protons from the self-threading form (c and d) and those from dethreading form (c′ and d′), indicating that these species have chemical exchange (framed regions). In 2D EXSY NMR experiment, the conformational exchange rate constants can be estimated by using the following equation[14]

$$\ln\left(\frac{r+1}{r-1}\right) = k_{ex}\tau_m$$

where τ_m is the mixing time and r is defined by the following equation

$$r = \frac{4x_s x_d (I_{cc} + I_{c'c'})}{I_{cc'} + I_{c'c}} - (x_s - x_d)^2$$

where x_s and x_d are the mole fraction of a self-threading form and a dethreading form, respectively. In this case, $x_s = x_d = 0.5$; hence

$$r = \frac{I_{cc} + I_{c'c'}}{I_{cc'} + I_{c'c}}$$

where $I_{cc'}$ and $I_{c'c}$ are the intensities of the cross signals between the signal c and c′, respectively. I_{cc} and $I_{c'c'}$ are the intensities of the diagonal signals. Figure 8b shows the results of 2D EXSY NMR experiments. The $k_{ex\ \mathrm{at}\ 30\ °C}$ extrapolated from the $k_{ex\ \mathrm{at}\ 1\ °C}$ for 6-DEGacid-HyCiO-*β*-CD, 6-PEG600acid-HyCiO-*β*-CD, and 6-PEG3000acid-HyCiO-*β*-CD by the Eyring equation, assuming that $\Delta G^{\neq}$ is constant and the $k_{ex\ \mathrm{at}\ 30\ °C}$ for 6-PEG10000acid-HyCiO-*β*-CD in 2D EXSY NMR experiments were commensurate with those obtained by variable-temperature NMR experiment.

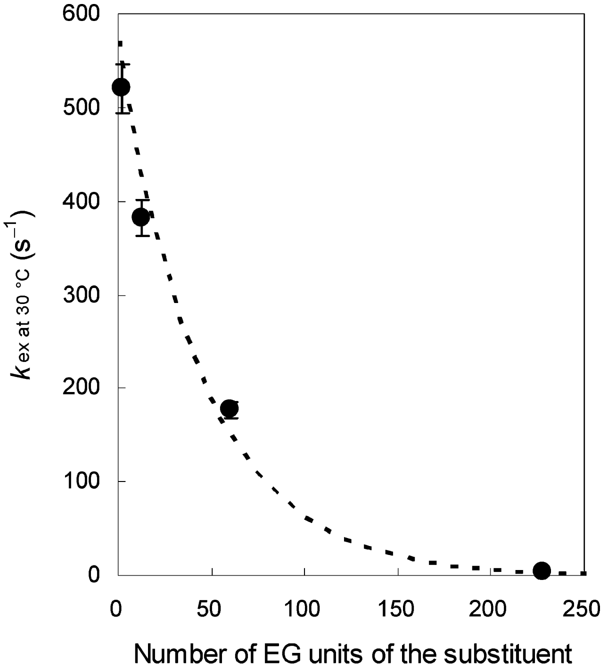

Figure 9. Dependence of the conformational exchange rate constants at 30 °C of PEG-substituted CDs on the number of EG units of the substituent.

Finally, it was revealed that the conformational exchange rate constant of PEG-substituted CD decreased exponentially with the number of ethylene glycol (EG) units of the substituent,[15] that is, the PEG chain length of the substituent as shown in Figure 9.

Conclusions

PEG-substituted CDs with different chain lengths were synthesized, and they formed the self-threading complexes in aqueous solutions. The conformation of PEG-substituted CDs changed from a self-threading form to a dethreading form in the presence of an equal molar amount of AdCA as a competitive guest. In the presence of a half molar amount of AdCA, the conformation exchanged between a self-threading form and a dethreading form. The conformational exchange rate constants of PEG-substituted CDs were estimated by variable-temperature NMR and 2D EXSY NMR experiments, and it was revealed that the conformational exchange rate of PEG-substituted CD decreased exponentially with the PEG chain length of the substituent. We believe that the knowledge of conformational exchange dynamics of PEG-substituted CDs contributes to the understanding of threading mechanism and dynamics of linear polymer into CDs and that the self-threading complex of PEG-substituted CDs and their conformational change has a potential to lead to novel applications of linear polymer.

Acknowledgment. We thank the Center of Excellence (21COE) program “Creation of Integrated EcoChemistry” of Osaka University for support. We also thank S. Adachi for 2D ROESY and EXSY NMR measurements and analyses and Dr. A. Hashidzume and Dr. T. Ogoshi for his helpful suggestions.

Supporting Information Available: Additional NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The values of $k_{\text{ex at 30 °C}}$ should be viewed as having at least 5% error because this estimation includes some approximations and extrapolations.

(13) Since the target signals need to be split in EXSY NMR experiments, the measurements for 6-DEGacid-HyCiO-β-CD, 6-PEG600acid-HyCiO-β-CD, and 6-PEG3000acid-HyCiO-β-CD were performed at low temperature. The $k_{\text{ex at 1 °C}}$ for 6-DEGacid-HyCiO-β-CD allows for a margin of error because the target signals were slightly broad even at 1 °C.

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MA070095Q