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Feature Article

Interaction of cyclodextrins with side chains of water soluble polymers: A simple model for biological molecular recognition and its utilization for stimuli-responsive systems

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Abstract

This article demonstrates that the interaction of cyclodextrins (CDs) with side chains of water soluble polymers is useful not only as simple models for biological molecular recognition but also as building blocks in nanotechnological applications. In the interaction of CDs with polymer side chains, the selectivity of CDs was enhanced by the steric effect of the polymer main chain and by interaction at multi-sites (i.e., collectivity). Utilizing the interaction of CDs with polymer side chains, stimuli-responsive systems were constructed from simple components.

Keywords: Cyclodextrins; Polymer side chains; Interaction

1. Introduction

Biological macromolecules, such as nucleic acids and proteins, are recognized by other chemical species with high selectivity to form precisely and delicately controlled supramolecular structures which express various functions for maintaining living activities [1–3]. Here the high selectivity may be attained by noncovalent bonds through their side chains, i.e., nucleosides in nucleic acids and substituents of amino acid residues in proteins. It is important to understand how their side chains provide the high selectivity in the recognition of biological macromolecules for the purpose of construction of artificial molecular recognition systems with high selectivity. Since we have been aware of the importance of side chains, we have been studying the interaction of cyclodextrins (CDs) with polymer side chains attached to water soluble polymers as a simple model system for biological molecular recognition.

CDs are cyclic oligomers of D-(+)-glucopyranose units bound to each other through α-1,4-glucoside bonding. CDs of 6, 7, and 8 glucopyranose units are called α-, β-, and γ-CDs, respectively. Since CDs interact selectively with hydrophobic compounds of a size and shape matching their cavity to form inclusion complexes in aqueous media, they have attracted much interest as biomimetic compounds, such as enzyme models [4–7].

Before 1990s, there were only a few papers on the interaction of CDs with polymer side chains in aqueous media [8–10], but, since our first paper [11] on the molecular recognition of alkyl side chains attached to poly(acrylamide) backbone by CDs was published in 1997, an increasing number of research groups began to focus on the interaction of CDs with polymer side chains. Most of the research groups have been focusing on manipulation of association properties of hydrophobically modified water soluble polymers.

Recent years have brought considerable interest in studying hydrophobically modified water soluble polymers because of their relevance to biological macromolecular systems and also because of their potential in commercial applications such as water-borne paint and coating fluids, cosmetics, personal care

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goods, drug delivery systems, and water treatment [12–14]. Hydrophobic self-associations in these amphiphilic polymers are induced in water within the same polymer chain or between different chains depending on macromolecular architecture [15]. When hydrophobes in amphiphilic polymers are included by CDs, hydrophobic associations are disrupted, resulting in changes in association properties of the polymers. If interpolymer hydrophobic associations dominate over intrapolymer ones, the formation of inclusion complexes of CDs with hydrophobes leads to dissociation of interpolymer aggregates, resulting in a decrease in the solution viscosity [16–23]. On the other hand, if hydrophobic associations dominantly occur intramolecularly, the formation of inclusion complexes of CDs with hydrophobes causes a transition of the polymer conformation from a compact one to an extended one [24]. It has been also reported that the lower critical solution temperature of thermally responsive polymers is controlled by complexation of CDs [25–28]. To the best of our knowledge, however, there have been no papers from the viewpoint of the selectivity of CDs in the interaction with polymer side chains.

In order to understand how polymer side chains enhance the selectivity in molecular recognition in biological systems and to construct artificial molecular recognition systems with high selectivity, we have been investigating the interaction of CDs with side chains of water soluble polymers. In this article, we describe: (i) examples in which side chains enhance the selectivity of CDs and (ii) stimuli-responsive systems utilizing molecular recognition of polymer side chains by CDs.

2. Experimental

2.1. Materials

α-, β-, and γ-Cyclodextrins (α-, β-, and γ-CDs, respectively) were purified by recrystallization from water. Acrylamide (AAm) was purified by recrystallization of ethyl acetate. Acrylic acid (AA) and alkyl methacrylates were purified by distillation under reduced pressure. 2,2′-Azobis(isobutyronitrile) (AIBN) was recrystallized from methanol. Poly(acrylic acid) (p(AA)) samples of average molecular weights of 25,000 and 250,000 were purchased from Wako Pure Chemical Industries, Ltd. Milli-Q water was used for all the measurements except for NMR. Other reagents were used without further purification.

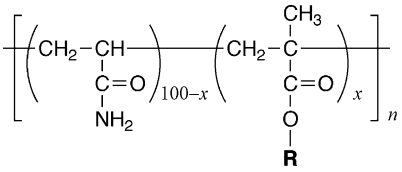
Benzyl, (1-naphthyl)methyl, and (2-naphthyl)methyl acrylates were prepared from acryloyl chloride and the corresponding alcohols, respectively. *N*-Methacryloyltryptophan (MTrp) [29] and *N*-methacryloylphenylalanine (MPhe) [30,31] were prepared from methacryloyl chloride and the corresponding amino acids, respectively. Sodium salts of tryptophan and phenylalanine (Trp and Phe, respectively), used as model compounds, were prepared by neutralization with an equimolar amount of NaOH and then recovered by freeze-drying. Mono-3-deoxy-3-amino-α-CD (3-NH_2-α-CD), mono-6-deoxy-6-amino-α-CD (6-NH_2-α-CD), and mono-deoxy-6-amino-β-CD (6-NH_2-β-CD) were prepared according to the procedure of Toda et al. [32,33]. *N*-Aminododecane-*p*-phenylazobenzamide was prepared from *p*-phenylbenzoic acid and dodecamethylenediamine by amide coupling with *N*,*N*′-dicyclohexylcarbodiimide (DCC).

2.2. Polymer preparation

2.2.1. Preparation of guest polymers

Poly(acrylamide)-based guest polymers (p(AAm/*n*-C_4(11)), p(AAm/*i*-C_4(11)), p(AAm/*t*-C_4(9)), p(AAm/C_6(9)), p(AAm/*i*-C_8(2)), and p(AAm/C_{12}(1)) in Scheme 1 and p(AAm/Bz(*x*)), p(AAm/1Np(*x*)), and p(AAm/2Np(*x*)) in Schemes 2 and 4, where *x* is the mol% content of aromatic group) were prepared by free radical copolymerization of AAm and the corresponding guest monomers, using AIBN as an initiator. The copolymers obtained were purified by reprecipitation. Compositions of the polymers were determined by elemental analysis and ^{1}H NMR.

Polymers of MTrp and MPhe (pMTrp and pMPhe, respectively, in Scheme 3) were prepared by free radical polymerization of the corresponding monomers, using AIBN as an



R = -$CH_2CH_2CH_2CH_3$
x = 11, p(AAm/*n*-C_4(11))

-$CH_2CH(CH_3)_2$
x = 11, p(AAm/*i*-C_4(11))

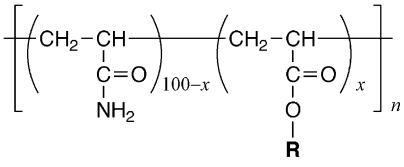
-$C(CH_3)_3$
x = 9, p(AAm/*t*-C_4(9))

-$CH_2CH_2CH_2CH_2CH_2CH_3$
x = 9, p(AAm/C_6(9))

-$CH_2CH(C_2H_5)CH_2CH_2CH_2CH_3$
x = 2, p(AAm/*i*-C_8(2))

-$CH_2(CH_2)_{10}CH_3$
x = 1, p(AAm/C_{12}(1))

Scheme 1. Chemical structure of p(AAm)-based guest polymers carrying alkyl groups.



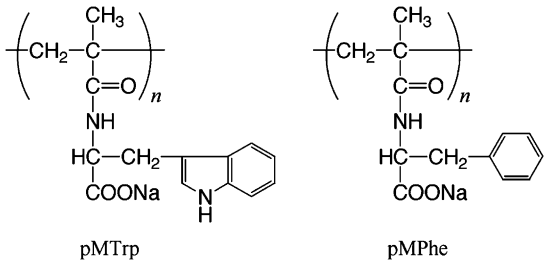
R = -CH_2-

x = 1.5 and 2.3, p(AAm/1Np(*x*))

-CH_2-

x = 1.4 and 1.9, p(AAm/2Np(*x*))

Scheme 2. Chemical structure of p(AAm)-based guest polymers carrying naphthyl groups.



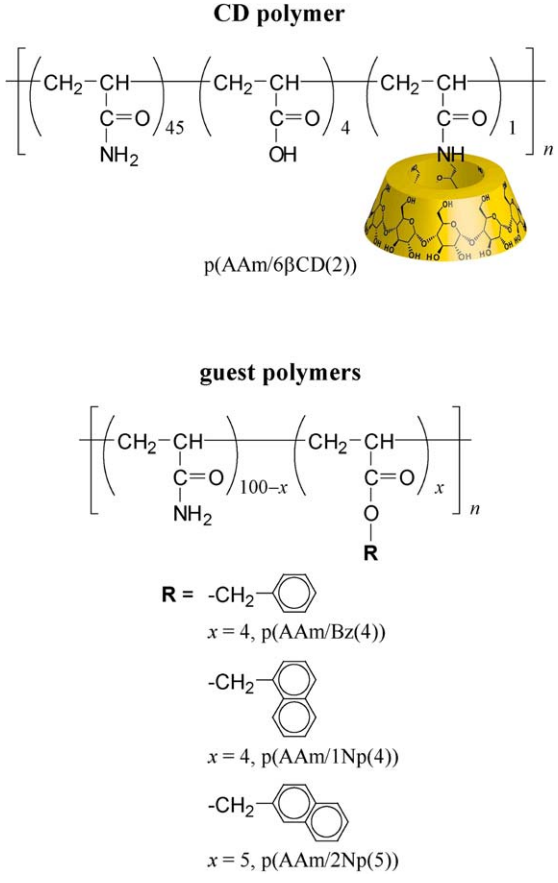
Scheme 3. Chemical structures of pMTrp and pMPhe.

initiator. The polymers obtained were purified by reprecipitation. Both the polymers were neutralized with an equimolar amount of 0.10 M NaOH, and then recovered by freeze-drying.

Poly(acrylic acid)-based guest polymers (p(AA/C_{12}(5)) in Scheme 5 and p(AA/C_{12}Azo(3)) in Scheme 6) were prepared by amide coupling of the corresponding amines, with the higher molecular weight p(AA) using DCC. The polymers obtained were purified by dialysis against pure water for a week and then recovered by freeze-drying. The degrees of modification were determined by elemental analysis and ^{1}H NMR.

2.2.2. Preparation of CD polymers

A poly(acrylamide)-based β-CD polymer (p(AAm/6βCD(2)) in Scheme 4) was prepared by amide coupling of 6-NH_2-β-CD with an AAm/AA copolymer of $M_w = 1.1 \times 10^5$, in which the AA content was 10 mol%, using *N*-ethyl-*N*′-(dimethylaminopropyl)carbodiimide. Poly(acrylic acid)-based α-CD polymers (p(AA/3αCD(2)) and p(AA/6αCD(2)) in Scheme 6) were prepared by amide coupling of the corresponding mono-deoxyamino-α-CD (3-NH_2-α-CD and 6-NH_2-α-CD, respectively) with the lower molecular weight p(AA) using DCC. The polymers obtained were purified by dialysis against pure water for a week. The degrees of modification were determined by ^{1}H NMR.



Scheme 4. Chemical structures of p(AAm/6βCD(2)) and p(AAm)-based guest polymers carrying aromatic groups.

2.3. Measurements

^{1}H NMR spectra were measured on a JEOL JNM EX270 spectrometer at 30 °C using D_2O as a solvent.

Two dimensional nuclear Overhauser effect spectroscopy (2D NOESY) data were obtained on a Varian UNITY INOVA plus 600 spectrometer at 30 °C using D_2O as a solvent. Mixing time before the acquisition of free induction decay was carefully varied and then fixed at 200 ms to obtain a genuine NOE and to avoid the effect of spin diffusion.

Absorption spectra were recorded on a Shimadzu UV-2500PC spectrophotometer at 25 °C using a 1 cm path length quartz cuvette.

Steady state fluorescence spectra were measured on a Hitachi F-2500 fluorescence spectrophotometer using a 1 cm path length quartz cuvette with excitation at 281 and 275 nm for (1-naphthyl)methyl (1Np) and (2-naphthyl)methyl (2Np) groups, respectively. The slit widths for both excitation and emission sides were kept at 10 nm during measurement.

Circular dichroism (cd) spectra were recorded on a Jasco J-820 spectropolarimeter using a 1 mm path length quartz cuvette.

Rheological measurements were performed with a REOLOGICA DynAlyser 100 stress-controlled rheometer equipped with a cone and plate at 25 °C by using a circulating water bath. The radius of the cone was 25 mm, and the angle between the cone and plate was 4°. For creep recovery measurements, the obtained creep compliance-time data were analyzed by using a conventional four-element mechanical model where Maxwell and Kelvin-Voigt bodies are connected in series [34]. When a constant shear stress is applied instantaneously to a viscoelastic solution at time (t) zero, the creep compliance at any given time t is represented as

$$J(t) = J_0 + J_d(1 - \exp(-t/\lambda)) + t/\eta \quad (1)$$

where $J(t)$ is the creep compliance at time t, J_0 is the instantaneous compliance for the elastic deformation of the Maxwell body, J_d is the compliance for the Voigt body, λ is the retardation time for the creep, and η is the steady shear viscosity. For creep recovery measurements under photoirradiation, a homemade glass plate equipped with UV (NSHU550B, Nichia Co.) or blue (NSPB500S, Nichia Co.) light emitting diodes was employed.

Sample solutions containing p(AA)-based CD and guest polymers were measured under basic conditions (pH ≈ 10). Other sample solutions were measured under neutral conditions (pH ≈ 7) without added salt.

2.4. Photoisomerization of azobenzene derivatives

4,4′-Azodibenzoic acid (ADA) and p(AA/C_{12}Azo(3)) were isomerized by photoirradiation using a 500 W Xe lamp (Ushio Inc.) equipped with a cut-off filter (Hoya UV34) and a band-pass filter (Hoya U340) for UV light, or with a cut-off filter (Hoya Y45) for visible light. The distance between the sample cell and the lamp was fixed at 40 cm.

3. Molecular recognition of polymer side chains by cyclodextrins

As described in Section 1, it is considered that side chains in biological macromolecules are considerably responsible for the high selectivity of biological molecular recognition. The selectivity may be enhanced by some factors including (i) the steric effect of the main chain and (ii) interaction at multi-sites (i.e., collectivity). In this section, we describe examples in which these factors enhance the selectivity of CDs in macromolecular recognition of polymer side chains.

3.1. Enhancement of the selectivity of cyclodextrins by the steric effect of polymer main chain

3.1.1. Interaction of CDs with polyacrylamides modified with alkyl groups [11]

We started the investigation on the interaction of CDs with polymer side chains using poly(acrylamide)s (p(AAm)s) modified with alkyl groups (Scheme 1) because CDs do not interact with p(AAm) itself. As alkyl groups, *n*-butyl (*n*-C_4), isobutyl (*i*-C_4), *t*-butyl (*t*-C_4), hexyl (C_6), isooctyl (*i*-C_8), and dodecyl (C_{12}) groups have been chosen. The interaction of CDs with alkyl side chains attached to p(AAm) backbone was investigated by ^{1}H NMR spectroscopy. Fig. 1 demonstrates an example of ^{1}H NMR spectra of p(AAm/*n*-C_4(11)) in the absence and presence of 50 mM α-CD. The spectrum in the absence of α-CD (Fig. 1a) shows broad resonance bands due to protons in the polymer main chain in the regions 1.3–1.9 and 2.0–2.4 ppm. This spectrum also exhibits resonance bands due to methyl and methylene protons in the *n*-C_4 side chain at ca. 0.9 and 1.1 ppm, respectively. Although, in the spectrum in the presence of 50 mM α-CD (Fig. 1b), the resonance bands due to the polymer main chain do not show a significant shift, the resonance bands due to methyl and methylene protons in the *n*-C_4 side chain exhibit downfield shifts, indicative of the formation of inclusion complexes of α-CD with *n*-C_4 side chains. On the other hand, ^{1}H NMR spectra of p(AAm/*t*-C_4(11)) in the absence and presence of 50 mM α-CD (data not shown) were practically the same, indicating that α-CD does not interact with *t*-C_4 side chains in the guest polymer.

To determine the association constant (*K*) for the formation of inclusion complexes of α-CD with *n*-C_4 side chains, ^{1}H NMR spectra were measured in the presence of varying concentrations of α-CD and peak shifts ($\Delta\delta$) were calculated. Using these data, reciprocals of $\Delta\delta$ ($\Delta\delta^{-1}$) were plotted in Fig. 2 against the reciprocal of α-CD concentration ($[\alpha\text{-CD}]^{-1}$). These plots exhibit a good linear relationship, indicating the formation of

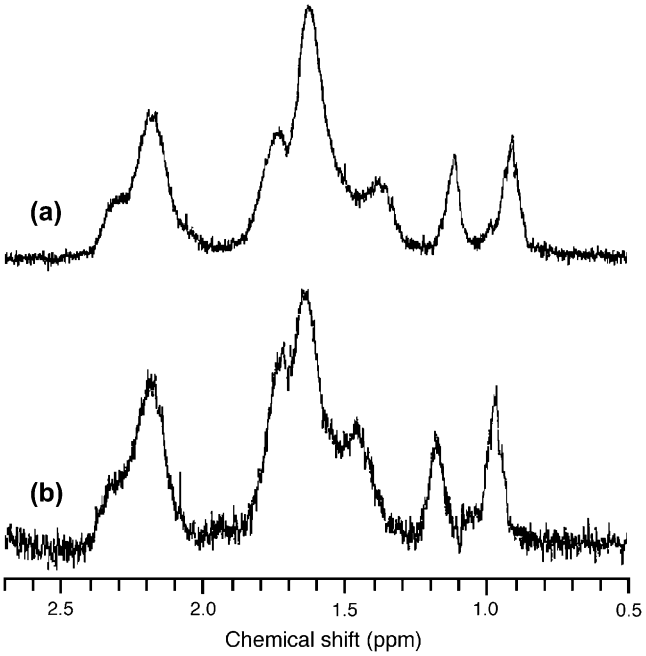


Fig. 1. ^{1}H NMR spectra for p(AAm/*n*-C_4(11)) (*n*-C_4 unit concentration = 1 mM) in the absence (a) and presence (b) of 50 mM α-CD in D_2O.

1:1 complexes of α-CD and *n*-C_4 side chains [35]. From slopes and intercepts of the straight lines in Fig. 2, the *K* value was determined to be 5.5×10^1 M^{-1} for the formation of inclusion complexes of α-CD with *n*-C_4 side chains [36].

Values of *K* for all the systems examined were determined by ^{1}H NMR spectroscopy as listed in Table 1. These *K* values demonstrate that α-, β-, and γ-CDs interact most strongly with p(AAm/C_{12}(1)) among all the polymers examined because of the hydrophobicity of C_{12} side chain. These *K* values also indicate that α-CD interacts favorably with linear alkyl side chains, β-CD interacts preferably with branched alkyl side chains, and γ-CD interacts only weakly with all the alkyl side chains examined presumably because of their cavity sizes. It should be noted here that α-CD interacts with p(AAm/*n*-C_4(11)) (5.5×10^1 M^{-1}) and does not with p(AAm/*t*-C_4(9))

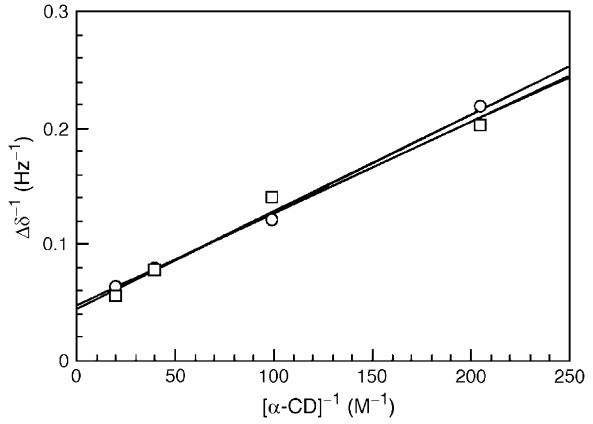


Fig. 2. $\Delta\delta^{-1}$ as a function of $[\alpha\text{-CD}]^{-1}$ for methyl (circle) and methylene (square) protons in the α-CD–p(AAm/*n*-C_4(11)) system.

Table 1
Association constants (K) of complex formation of CDs with alkyl side chains attached to polyacrylamide backbone

Polymer code	K (M^{-1})[a]		
	α-CD	β-CD	γ-CD
p(AAm/*n*-C_4(11))	5.5×10^1	–[b]	–[b]
p(AAm/*i*-C_4(11))	3.6×10^1	–[b]	–[b]
p(AAm/*t*-C_4(9))	–[b]	3.4×10^2	5.7×10^1
p(AAm/C_6(9))	2.9×10^2	1.1×10^2	–[b]
p(AAm/*i*-C_8(2))	2.0×10^2	2.9×10^2	5.1×10^1
p(AAm/C_{12}(1))	9.9×10^2	6.6×10^2	2.5×10^2

[a] K values include errors less than ±10%.
[b] The K value was not determined because of no significant peak shift.

whereas β-CD interacts with p(AAm/*t*-C_4(9)) (3.4×10^2 M^{-1}) and does not with p(AAm/*n*-C_4(11)). On the other hand, α-CD interacts with both the corresponding model compounds, i.e., *n*-butyl and *t*-butyl alcohols, with K values of 2.0×10^1 and 6 M^{-1}, respectively. These observations indicate that CDs interact more selectively with alkyl side chains attached to p(AAm) backbone than with low molecular weight model compounds, alcohols. This may be because the polymer main chain restricts the direction of inclusion of CDs. Therefore, it is concluded that the steric effect of the polymer main chain can enhance the selectivity of CDs.

3.1.2. Interaction of CDs with polyacrylamides modified with aromatic groups [37]

We also investigated the interaction of CDs with aromatic side chains attached to p(AAm) backbone (Scheme 2) by steady state fluorescence and circular dichroism (cd) spectroscopies to explore whether or not the steric effect of the polymer main chain enhances the selectivity of CDs toward aromatic groups. Steady state fluorescence data indicated that β-CD interacted more strongly with 1Np and 2Np groups in the guest polymers than did α- and γ-CDs. Using steady state fluorescence data, K values were determined to be 1.1×10^2 and 2.0×10^2 M^{-1} for the complex formation of β-CD with the 1Np and 2Np moieties in the guest polymers, respectively. Comparison of these K values with those for the guest model compounds (1-naphthyl)methanol (1NpMeOH) and (2-naphthyl)methanol (2NpMeOH) (2.4×10^2 and 7.4×10^2 M^{-1}, respectively), indicated that the polymer main chain did not enhance the selectivity of β-CD toward these aromatic guest moieties. Cd spectroscopy for the polymers and the model compounds in the presence of β-CD indicated that β-CD included polymer-carrying 1Np groups shallowly whereas it included polymer-carrying 2Np groups deeply, in which the longer axis of the Np group is rather parallel to the rotation axis of β-CD (Fig. 3).

3.1.3. Interaction of CDs with polymethacrylamides carrying hydrophobic amino acid residues [38]

Recently, we have investigated the association behavior of poly(methacrylamides) carrying hydrophobic amino acid residues, tryptophan and phenylalanine (pMTrp and pMPhe, respectively, in Scheme 3), by steady state fluorescence, NMR, and dynamic light scattering measurements to explore polymer structural factors which cause distinctions in their

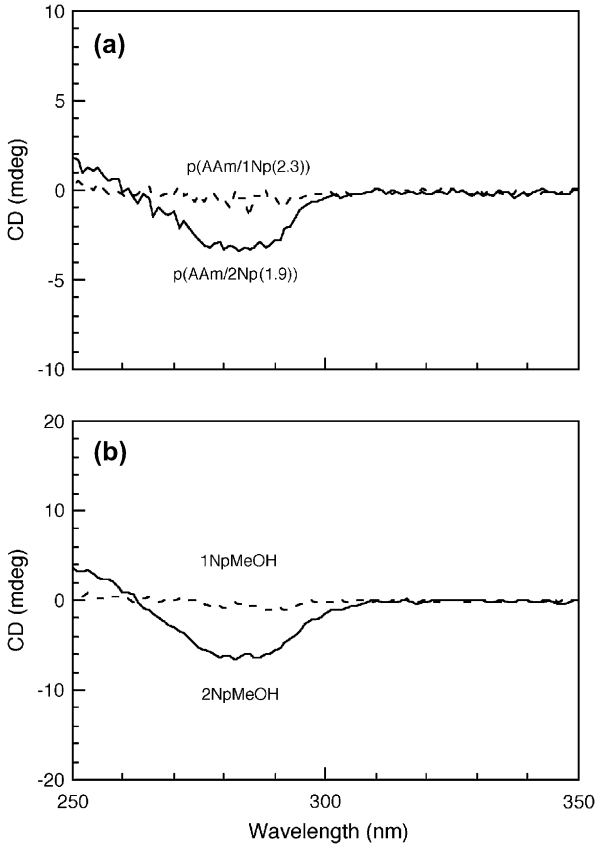


Fig. 3. Cd spectra for the β-CD–p(AAm/1Np(2.3)) and β-CD–p(AAm/2Np(1.9)) systems (a) and the β-CD–1NpMeOH and β-CD–2NpMeOH systems (b). [β-CD] = 8.0 mM.

association properties [39]. Characterization data indicated as follows: at pH ≈ 5 (<apparent pK_a (≈5.8)), both the polymers formed hydrophobic microdomains and pMTrp had a stronger tendency for interpolymer association than did pMPhe; at pH > apparent pK_a, both the polymers adopted a rather extended conformation, in which a significant fraction of aromatic groups were located close to the polymer main chain presumably because of hydrophobic and CH-π interactions. We have also investigated the interaction of CDs with these polymers as a simple model for molecular recognition of proteins.

As reference systems, the interaction of CDs with model compounds, i.e., sodium salts of tryptophan and phenylalanine (Trp and Phe, respectively) was investigated by ^{1}H NMR spectroscopy. Fig. 4 shows ^{1}H NMR spectra for 1 mM α-, β-, and γ-CDs measured in the absence and presence of 30 mM Trp and Phe. These spectra contain the resonance bands due to protons in CDs as shown in this figure. The resonance bands due to C_1, C_3, C_5, and C_6 protons exhibit considerable upfield shifts upon addition of Trp and Phe. These upfield shifts may be caused by the ring current of the aromatic rings in Trp and Phe, indicative of the formation of inclusion complexes. To determine K values for the CDs–Trp and CDs–Phe systems, ^{1}H NMR spectra were measured at varying concentrations of Trp and Phe, respectively. Using these spectra, differences between the chemical shifts of the resonance bands due to the

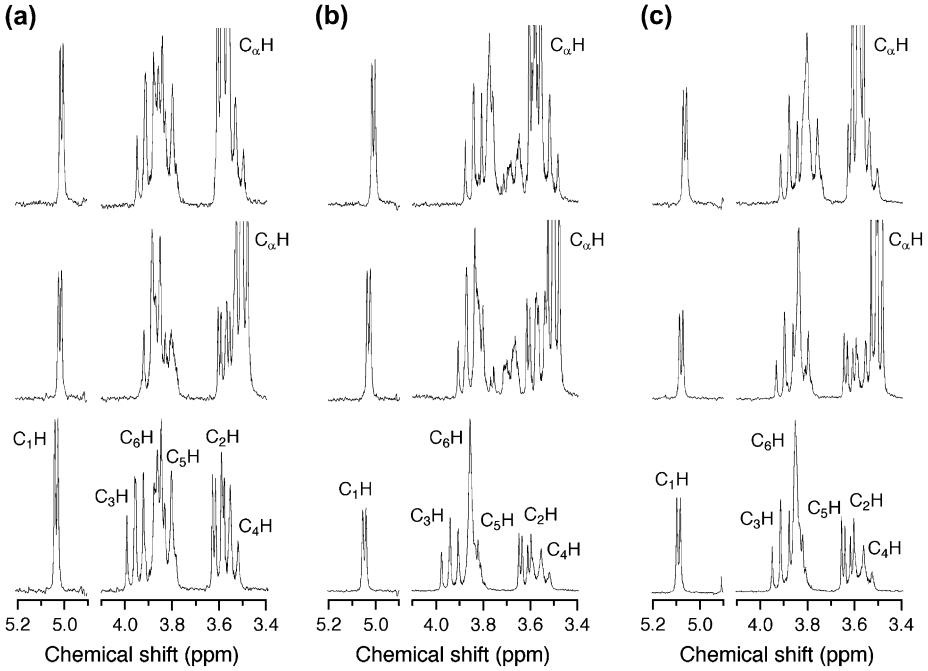


Fig. 4. ^{1}H NMR spectra of 1 mM α-, β-, and γ-CDs (a, b, and c, respectively) in the presence of 30 mM Trp (top) and Phe (middle), and in the absence of the model compounds (bottom).

C_1 and C_3 protons were calculated, and changes in the difference ($\Delta(\delta_{C1H} - \delta_{C3H})$) are plotted in Fig. 5 as a function of the concentration of the model compound ([Xaa]). Given the formation of 1:1 inclusion complexes, K values were determined by fitting data in Fig. 5 using

$$\Delta(\delta_{C1H} - \delta_{C3H}) = a_1 K[\mathrm{Xaa}]/(1 + K[\mathrm{Xaa}]) \quad (2)$$

where a_1 is a constant (Table 2) [36]. These K values of Trp and Phe are in fairly good agreement with those determined by calorimetry [40,41].

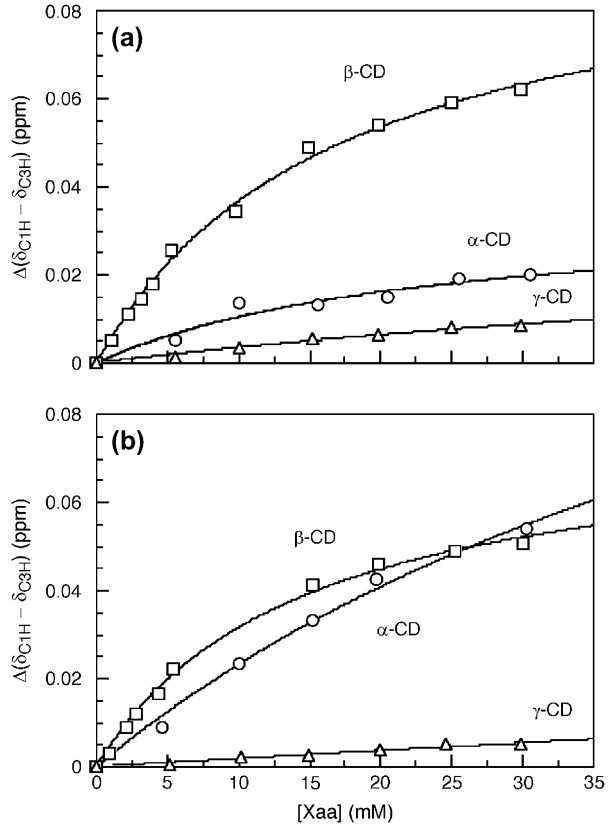


Fig. 5. $\Delta(\delta_{C1H} - \delta_{C3H})$ as a function of the concentration of the model compounds (c_{mc}) for the CDs–Trp and CDs–Phe systems. The best fitted curves using Eq. (2) are also shown.

The interaction of CDs with pMTrp and with pMPhe was also investigated by ^{1}H NMR spectroscopy. ^{1}H NMR spectra of 1 mM α-, β-, and γ-CDs were measured in the absence and presence of pMTrp and pMPhe (20 mM monomer units). As an example, Fig. 6 shows expanded spectra for the resonance band due to C_1 protons in CDs, which does not overlap the resonance bands due to protons in the polymers. In contrast to our expectation, significant peak shifts were not observed upon addition of pMTrp and pMPhe. However, it should be noted that, in the presence of pMTrp, the resonance bands due to C_1 protons are broader than those in its absence. These broad spectra in the presence of pMTrp are ascribable to an increase in the rotational correlation time of CDs, indicating that CDs interact with pMTrp. In the case of pMPhe, on the other hand, the spectrum of the β-CD–pMPhe mixture exhibits only a slight

Table 2
Association constants (K) for complex formation of CDs with Trp and with Phe[a]

	K (M^{-1})		
	α-CD	β-CD	γ-CD
Trp	$(4.3 \pm 0.6) \times 10^1$	$(5.9 \pm 0.5) \times 10^1$	$(1.2 \pm 0.6) \times 10^1$
Phe	$(1.6 \pm 0.5) \times 10^1$	$(6.9 \pm 0.7) \times 10^1$	$(0.3 \pm 0.1) \times 10^1$

[a] Determined using the difference between chemical shifts of the resonance bands due to C_1 and C_3 protons in CD ($\Delta(\delta_{C1H} - \delta_{C3H})$) at 30 °C.

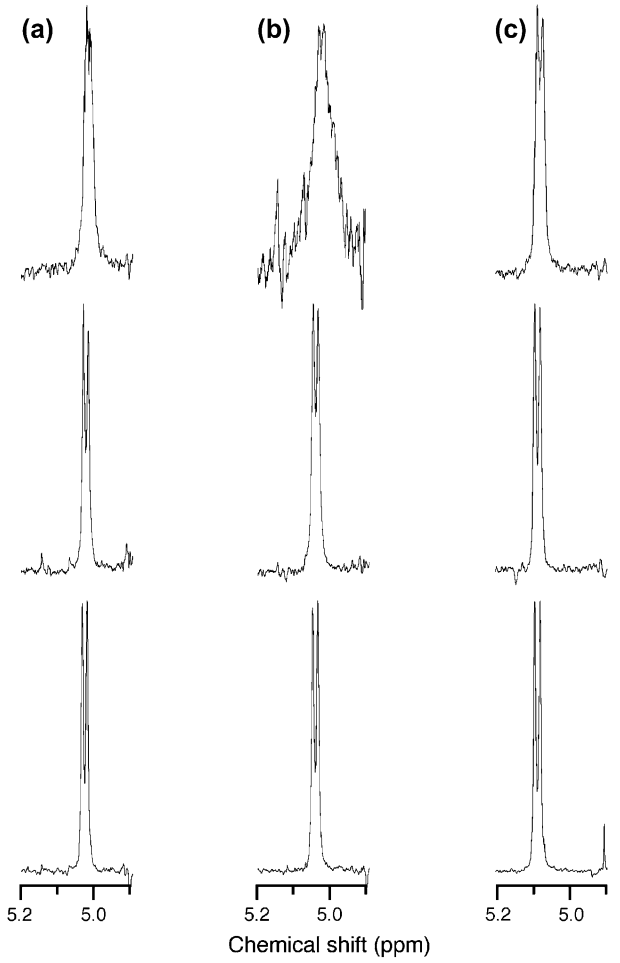


Fig. 6. ^{1}H NMR spectra of 1 mM α-, β-, and γ-CDs (a, b, and c, respectively) in the presence of pMTrp (top) and pMPhe (middle) (20 mM monomer units), and in the absence of the polymers (bottom).

broadening, but the spectra of the α-CD–pMPhe and γ-CD–pMPhe mixtures do not. These observations indicate that CDs interact only weakly or do not interact with pMPhe.

When the formation of complexes considerably inhibits the rotational motion of the components, the K value can be determined utilizing the increase in halfwidth of resonance bands in NMR spectra (i.e., excess halfwidth) [42–44]. Using ^{1}H NMR spectra of CDs–pMTrp mixtures measured at varying polymer concentrations, excess halfwidths for the resonance band due to C_1 protons were determined by curve fitting and plotted in Fig. 7 as a function of the monomer unit concentration ([MXaa]). As shown in this figure, plots are in fairly good agreement with the curves best fitted using Eq. (3) in the [MXaa] regions 0–25, 0–5, and 0–30 mM for α-, β-, and γ-CDs, respectively.

$$\{\text{Excess halfwidth}\} = a_2 K[\text{MXaa}]/(1 + K[\text{MXaa}]) \quad (3)$$

where the formation of 1:1 complexes of CDs with the monomer units is assumed and a_2 is a constant. At [MXaa] higher than these regions, plots deviate from the best fitted curve presumably because of a significant increase in the solution viscosity. From the best fitted curves, the apparent K values were roughly estimated to be 3.0×10^1, 8.3×10^1, and 1.1×10^1 M^{-1} for α-, β-, and γ-CDs, respectively, as listed in Table 3. In the case of pMPhe, on the other hand, the apparent K values were unable to be estimated because the excess halfwidths were smaller than 1 Hz, implying that the apparent K values for pMPhe are significantly smaller than the smallest one for pMTrp (i.e., 1.1×10^1 M^{-1} for the γ-CD–pMTrp system).

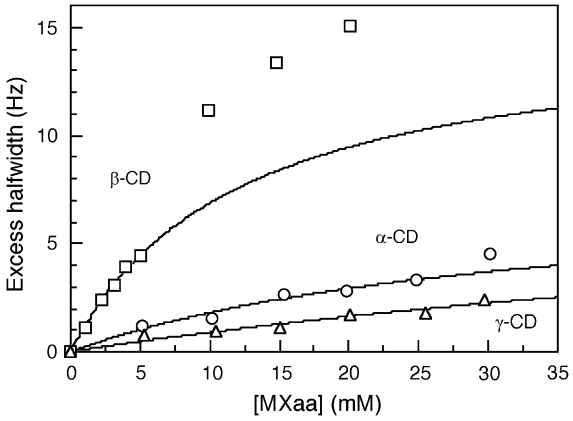


Fig. 7. Excess halfwidth as a function of the monomer unit concentration (c_{mu}) for the CDs–pMTrp systems. The best fitted curves using Eq. (3) in the c_{mu} regions 0–25, 0–5, and 0–30 mM for α-, β-, and γ-CDs, respectively, are also shown.

Here we compare the K values for the polymers with those for the model compounds, although it should be noted that the K values for the polymers are apparent ones because monomer units are extremely localized on the polymer chains. As listed in Table 2, the K values for Trp and Phe are not so different, but there are significant differences in the apparent K values roughly estimated by ^{1}H NMR for pMTrp and pMPhe: the K values for pMPhe are considerably smaller than those for pMTrp. In our previous study [39], the ^{1}H NMR and 2D NOESY spectra indicated that a significant fraction of aromatic rings in pMTrp and pMPhe were located in the close proximity of the polymer main chain presumably because of hydrophobic and CH-π interactions. Furthermore, since the benzyl group in pMPhe is smaller and more hydrophobic than the (3-indolyl)-methyl group in pMTrp, it is likely that benzyl groups in pMPhe interact more strongly with the polymer main chain than do (3-indolyl)methyl groups in pMTrp. Therefore, whereas the Trp residues in pMTrp are readily recognized by CDs, the Phe residues in pMPhe are not because the relatively stronger interaction of the Phe residues with the polymer main chain hinders the interaction of CDs. These observations also indicate that the

Table 3
Apparent association constants (K) for complex formation of CDs with pMTrp and with pMPhe[a]

	K (M^{-1})		
	α-CD	β-CD	γ-CD
pMTrp	$(3.0 \pm 0.2) \times 10^1$	$(8.3 \pm 0.3) \times 10^1$	$(1.1 \pm 0.2) \times 10^1$
pMPhe	—[b]	—[b]	—[b]

[a] Determined using change in the halfwidth of the resonance band due to C_1 protons at 30 °C.
[b] The K value was not determined because of small excess halfwidths.

steric effect of the polymer main chain can enhance the selectivity of CDs.

3.2. Enhancement of the selectivity of cyclodextrins by multi-site interaction [45]

To clarify whether or not the interaction at multi-sites (i.e., collectivity) enhances the selectivity of CDs, we have investigated the interaction of a p(AAm) carrying β-CD moieties (p(AAm/6βCD(2)) in Scheme 4) with p(AAm)s carrying aromatic side chains (p(AAm/Bz(4)), p(AAm/1Np(4)), and p(AAm/2Np(5)) in Scheme 4) because the steric effect of the polymer main chain did not enhance the selectivity of β-CD toward these aromatic guest moieties, as described above [37].

The interaction of β-CD with p(AAm/Bz(4)) was investigated by ^{1}H NMR spectroscopy. The shift of resonance bands due to phenyl protons in p(AAm/Bz(4)) was so small (<0.006 ppm) in the region of β-CD concentration ([β-CD], 0–8.0 mM) that the K value was not determined for the complex formation of β-CD with the benzyl (Bz) moieties in p(AAm/Bz(4)). This observation indicated that β-CD interacted only weakly with the Bz moieties in p(AAm/Bz(4)). The K value for the β-CD–p(AAm/Bz(4)) system might be smaller than that for the α-CD–p(AAm/Bz(4)) system (9.5 M^{-1}) because a downfield shift of ca. 0.012 ppm was observed in mixtures of α-CD and p(AAm/Bz(4)) (data not shown). The interaction of β-CD with p(AAm/1Np(4)) and with p(AAm/2Np(5)) was investigated by steady state fluorescence spectroscopy because 1Np and 2Np groups emit fluorescence. The intensity of fluorescence due to polymer-carrying Np groups increased with increasing [β-CD], indicative of the formation of inclusion complexes [37]. Using these fluorescence data, K values were determined to be 7.7×10^1 and 1.9×10^2 M^{-1} for the complex formation of the β-CD–p(AAm/1Np(4)) and β-CD–p(AAm/2Np(5)) systems, respectively [36].

The interaction of p(AAm/6βCD(2)) with guest polymers was investigated by steady shear viscosity measurements. When CD moieties in CD polymers interact with polymer side chains in guest polymers to form inclusion complexes, interpolymer aggregates are formed, resulting in an increase in the solution viscosity [23,46–51]. Steady shear viscosities were measured for 100 g/L p(AAm/6βCD(2)) in the presence of varying concentrations of guest polymers. Fig. 8 shows a typical example of steady shear viscosity data for mixtures of 100 g/L p(AAm/6βCD(2)) and 50 g/L guest polymers. All the mixtures exhibit a typical behavior of Newtonian liquids. From these data, zero shear viscosities (η_0) were determined and plotted as a function of the concentration of guest polymer (c_{gp}), as shown in Fig. 9. In all the cases, η_0 increases with increasing c_{gp}. Noteworthy is that the increase in η_0 is remarkable for the mixtures containing p(AAm/2Np(5)) relative to those for the mixtures containing p(AAm/Bz(4)) and p(AAm/1Np(4)) although M_w values for the guest polymers were similar ($M_w = (6.7–10) \times 10^3$). In the latter two cases, the increase in η_0 is only slightly larger than that in the case of an AAm homopolymer (p(AAm)) of a similar molecular weight ($M_w = 1.0 \times 10^4$). These data indicate that p(AAm/6βCD(2)) forms

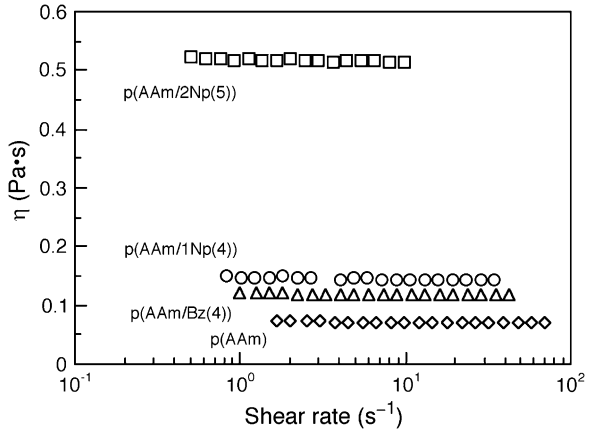


Fig. 8. Steady shear viscosity (η) as a function of shear rate for the mixtures of 100 g/L p(AAm/6βCD(2)) with p(AAm/Bz(4)), with p(AAm/1Np(4)), with p(AAm/2Np(5)), and with p(AAm) (the concentration of guest polymer = 50 g/L).

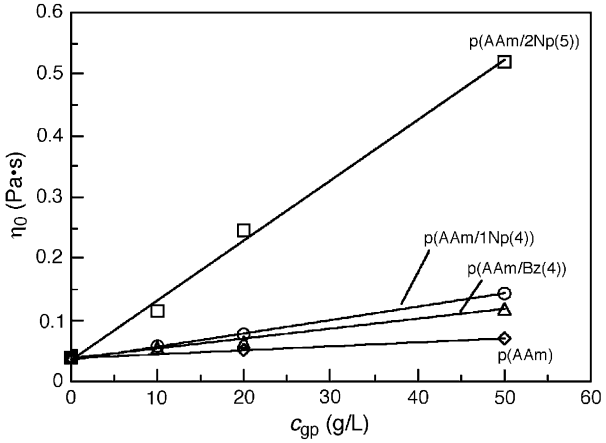


Fig. 9. Zero shear viscosity (η_0) as a function of c_{gp} for mixtures of 100 g/L p(AAm/6βCD(2)) and guest polymers or p(AAm): p(AAm/Bz(4)), p(AAm/1Np(4)), p(AAm/2Np(5)) (circle), and p(AAm).

interpolymer aggregates of a more extended network structure with p(AAm/2Np(5)) than with p(AAm/Bz(4)) or p(AAm/1Np(4)).

To clarify whether the increase in η_0 is caused by complexation of β-CD moieties in p(AAm/6βCD(2)) with guest moieties in the guest polymers, steady shear viscosities were also measured at varying mole fractions ($x_{\beta CD}$) of polymer-carrying β-CD moieties, fixing the total polymer concentration at 100 g/L ($x_{\beta CD}$ = [β-CD unit]/([β-CD unit] + [polymer side chain]), where [β-CD unit] and [polymer side chain] were molar concentrations of β-CD unit and polymer side chain, respectively). From these data, η_0 values were determined and plotted as a function of $x_{\beta CD}$ in Fig. 10. In the case of p(AAm/2Np(5)), plots exhibit a maximum at $x_{\beta CD} \approx 0.5$, suggesting that the increase in η_0 is caused by the formation of 1:1 inclusion complexes of β-CD moieties with polymer side chains. Values of η_0 were also determined for mixtures of p(AAm/6βCD(2)) and p(AAm/2Np(5)) in the presence of 1-adamantanecarboxylic acid (AdCA), with which β-CD interacts much more favorably than with the 2Np moiety [52]. In the

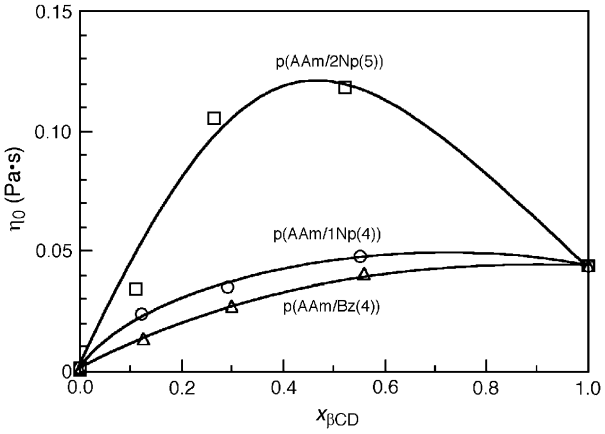


Fig. 10. Zero shear viscosity (η_0) as a function of $x_{\beta CD}$ for mixtures of p(AAm/6βCD(2)) and guest polymers: p(AAm/Bz(4)), p(AAm/1Np(4)), and p(AAm/2Np(5)). The total polymer concentration was fixed at 100 g/L.

presence of AdCA, η_0 does not exhibit the remarkable increase with increasing c_{gp}, as shown in Fig. 11. These observations confirm that the increase in η_0 in mixtures of p(AAm/6βCD(2)) and p(AAm/2Np(5)) is due to the formation of inclusion complexes of β-CD moieties in the CD polymer with 2Np groups in the guest polymer.

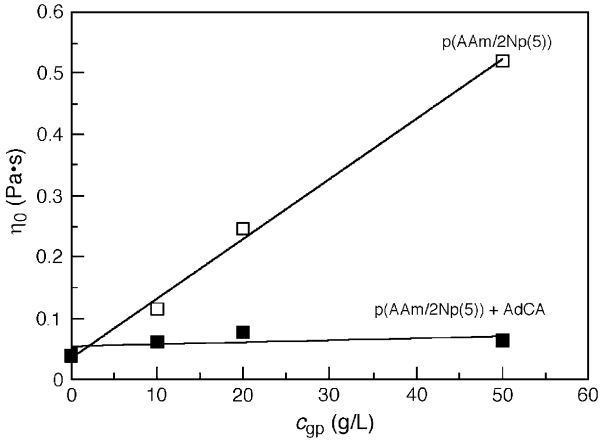


Fig. 11. Zero shear viscosity (η_0) as a function of c_{gp} for mixtures of 100 g/L p(AAm/6βCD(2)) and p(AAm/2Np(5)) in the absence and presence of AdCA. The ratio of [AdCA]/[β-CD unit] was fixed at 1.0, where [AdCA] denotes the molar concentration of AdCA.

Fig. 12 shows a conceptual illustration of interpolymer aggregates of p(AAm/6βCD(2)) and guest polymers, p(AAm/1Np(4)) and p(AAm/2Np(5)). The K value for 1:1 complex formation of native β-CD with the 2Np moieties in p(AAm/2Np(5)) is ca. 2.5 times as large as that for 1:1 complex formation of native β-CD with the 1Np moieties in p(AAm/1Np(4)). Since the formation of inclusion complexes occurs at multi-sites, much larger interpolymer aggregates are formed for the p(AAm/6βCD(2))–p(AAm/2Np(5)) system than for the p(AAm/6βCD(2))–p(AAm/1Np(4)) system, resulting in a considerable difference in η_0. It should be noted that η_0 values for the p(AAm/6βCD(2))–p(AAm/1Np(4)) system are comparable to those for the p(AAm/6βCD(2))–p(AAm/Bz(4)) system although the K value for 1:1 complex formation of native β-CD with the 1Np moieties in p(AAm/1Np(4)) is much larger than that for 1:1 complex formation of native β-CD with the Bz moieties in p(AAm/Bz(4)). These observations indicate that the interaction at multi-sites (i.e., collectivity) enhances the selectivity of p(AAm/6βCD(2)) toward p(AAm/2Np(5)).

4. Utilization of the interaction of CDs with polymer side chains for stimuli-responsive systems

Past decade, stimuli-responsive self-assembling systems have attracted much interest from researchers because of their potentials in a broad range of fields, such as drug delivery systems, sensor systems, and functional nanodevices [53–55]. Utilizing the interaction of CDs with polymer side chains, we have successfully constructed two stimuli-responsive aqueous systems consisting of simple components: (i) stimuli-responsive gel-to-sol transition systems which consist of α- or β-CD, a p(AA) carrying dodecyl groups (p(AA/C_{12}(5)) in Scheme 5), and a stimuli-responsive competing guest, and (ii) photoresponsive systems exhibiting contrast viscosity changes which consist of a p(AA) carrying α-CD moieties (p(AA/3αCD(2)) or p(AA/6αCD(2)) in Scheme 6) and a

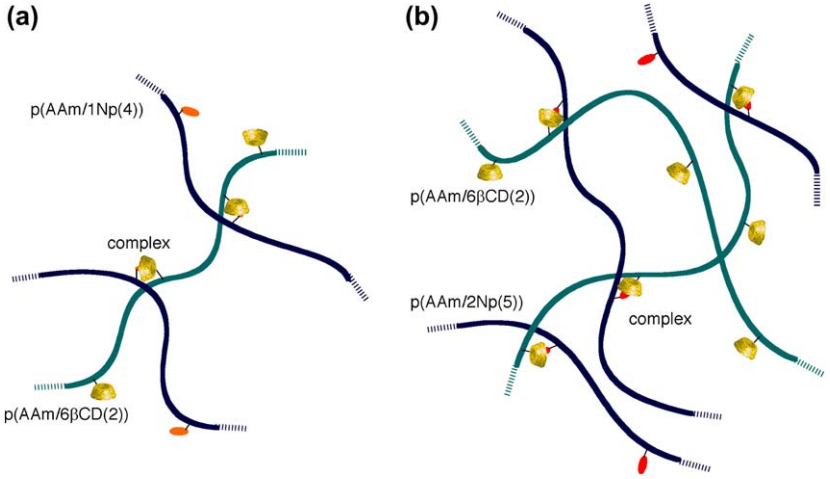
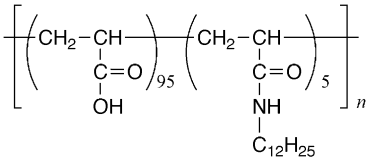


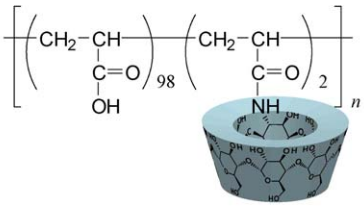
Fig. 12. Conceptual illustration for interpolymer aggregates of p(AAm/6βCD(2)) and guest polymers: p(AAm/1Np(4)) (a) and p(AAm/2Np(5)) (b).



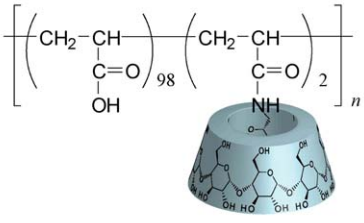
p(AA/C_{12}(5))

Scheme 5. Chemical structure of p(AA/C_{12}(5)).

CD polymers

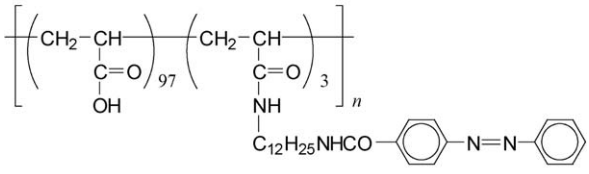


p(AAm/3αCD(2))



p(AAm/6αCD(2))

guest polymer



p(AA/C_{12}Azo(3))

Scheme 6. Chemical structures of p(AAm/3αCD(2)), p(AAm/6αCD(2)), and p(AA/AzoC_{12}(3)).

p(AA) carrying azobenzene moieties (p(AA/C_{12}Azo(2)) in Scheme 6).

4.1. Stimuli-responsive gel-to-sol transition systems

4.1.1. Photoresponsive gel-to-sol transition system [56]

It is known that C_{12} side chains in p(AA/C_{12}(x)), where x denotes the content of C_{12} side chain, associate intra- and intermolecularly in aqueous media, and that solution properties of p(AA/C_{12}(x)) are strongly dependent on the molecular weight (M), the polymer concentration (c_p), and x [57–59]. When M and c_p are high and x is moderate, intermolecular associations usually dominate over intramolecular ones, leading to the formation of interpolymer aggregates with network structures which exhibit viscoelastic properties [60,61]. Creep recovery measurements indicate that 5.0 g/L p(AA) exhibits a typical behavior of Newtonian liquids and 5.0 g/L p(AA/C_{12}(5)) (Scheme 5) shows a viscoelastic behavior (Fig. 13). Using

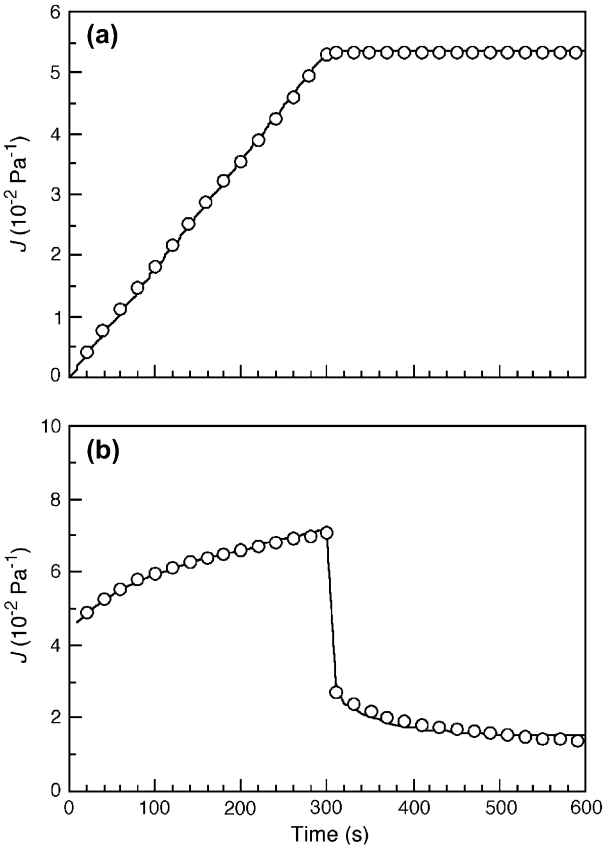


Fig. 13. Creep compliance–time plots for p(AA) (a) and p(AA/C_{12}(5)) (b) measured at 5.0 g/L. Solid lines represent best fit curves obtained by Eq. (1).

Eq. (1), η values for p(AA) and p(AA/C_{12}(5)) were determined to be 5.8×10^{-3} and 2.0×10^{4} Pa s, respectively, under an applied stress of 1.0 Pa.

As we reported previously [51], since α-CD interacts with the C_{12} side chains in p(AA/C_{12}(5)) to form inclusion complexes, hydrophobic associations of C_{12} side chains are inhibited by added α-CD, resulting in a decrease in η for the viscoelastic aqueous solutions of p(AA/C_{12}(5)). Fig. 14 shows η as a function of [α-CD] for mixtures of p(AA) and α-CD and for mixtures of

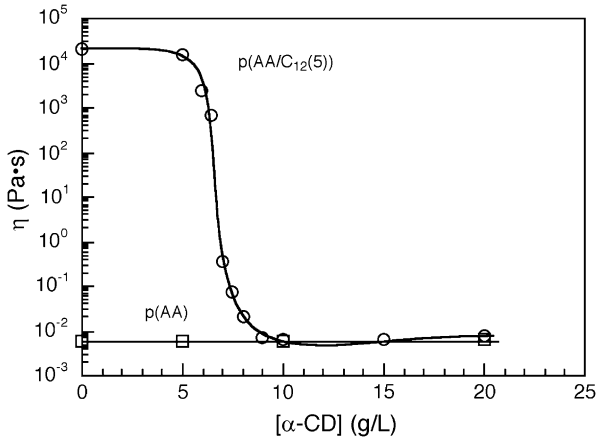


Fig. 14. Steady shear viscosity (η) as a function of [α-CD] for mixtures of p(AA) and α-CD and for mixtures of p(AA/C_{12}(5)) and α-CD under an applied stress of 1.0 Pa. Polymer concentration = 5.0 g/L.

p(AA/C_{12}(5)) and α-CD under an applied stress of 1.0 Pa. In the case of the mixtures of p(AA) and α-CD, η is constant at ca. 6×10^{-3} Pa s independent of [α-CD]. On the other hand, in the case of the mixtures of p(AA/C_{12}(5)) and α-CD, η is practically constant at ca. 2×10^4 Pa s in the [α-CD] region (0–5.0 g/L), but η exhibits a drastic decrease of more than 6 orders of magnitude in a relatively narrow [α-CD] region (5.0–10.0 g/L). This observation indicates that, in this [α-CD] region, the formation of inclusion complexes of α-CD with C_{12} side chains causes a considerable disruption of interpolymer aggregates under an applied stress of 1.0 Pa. At [α-CD] > 10.0 g/L, η values for the mixtures of p(AA/C_{12}(5)) and α-CD are on the same level as those for the mixtures of p(AA) and α-CD, indicating that hydrophobic associations of C_{12} side chains are suppressed by the formation of inclusion complexes at higher [α-CD]. On the basis of these data, [α-CD] was fixed at 10.0 g/L for a sol-to-gel transition by adding a competitive guest to a binary mixture of α-CD and p(AA/C_{12}(5)) as described below.

As a photoresponsive competitive guest, 4,4′-diazobenzoic acid (ADA) has been chosen because it is soluble in water under basic conditions. The complex formation behavior of α-CD with ADA was investigated by absorption spectroscopy using ADA as received, in which most of ADA molecules take the *trans*-form. The absorption band due to the $\pi \rightarrow \pi^*$ transition of *trans*-ADA around 331 nm shifted to a longer wavelength region with increasing [α-CD], indicating the formation of inclusion complexes of α-CD with ADA [62,63]. Using the spectra in the presence of varying concentrations of α-CD (data not shown), reciprocals of the peak shift ($\Delta\lambda_{max}^{-1}$) were calculated and plotted against $[\alpha\text{-CD}]^{-1}$. From the slope and the intercept of the straight line in the plot, the K value for the complex formation of α-CD with *trans*-ADA was determined to be 1.0×10^4 M^{-1} [36]. Since the K value for the complex formation of α-CD with ADA (1.0×10^4 M^{-1}) is larger than that for the complex formation of α-CD with the C_{12} side chains in p(AA/C_{12}(5)) (2.3×10^3 M^{-1}), α-CD interacts more favorably with ADA than with the C_{12} side chains in ternary mixtures of p(AA/C_{12}(5)), α-CD, and ADA. Fig. 15 shows η as a function of the concentration of ADA ([ADA]) for ternary mixtures of p(AA), α-CD, and ADA and for ternary mixtures of p(AA/C_{12}(5)), α-CD, and ADA. In the case of the ternary mixtures of p(AA), α-CD, and ADA, η is constant at ca. 6×10^{-3} Pa s independent of [ADA]. On the other hand, in the case of the ternary mixtures of p(AA/C_{12}(5)), α-CD, and ADA, as [ADA] is increased, η increases remarkably in the [ADA] region (0–1.0 g/L) and then levels off at ca. 2×10^4 Pa s when [ADA] > 2.0 g/L. At [ADA] > 2.0 g/L, η values for the ternary mixtures of p(AA/C_{12}(5)), α-CD, and ADA are as large as that for α-CD-free p(AA/C_{12}(5)), indicating that α-CD interacts predominantly with ADA and hydrophobic associations of C_{12} side chains are fully restored.

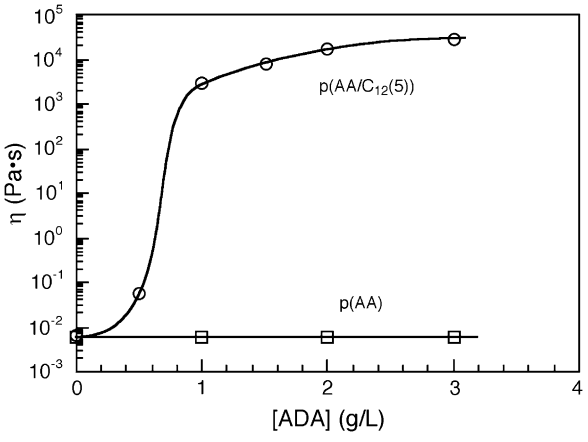


Fig. 15. Steady shear viscosity (η) as a function of [ADA] for mixtures of p(AA), α-CD, and ADA and for mixtures of p(AA/C_{12}(5)), α-CD, and ADA under the applied stresses of 1.0 Pa. Polymer concentration = 5.0 g/L, [α-CD] = 10.0 g/L.

Absorption spectroscopy confirmed that ADA underwent *trans*-to-*cis* and *cis*-to-*trans* photoisomerization upon irradiation with UV (ca. 355 nm) and visible light (>440 nm), respectively, and that α-CD did not interact with *cis*-ADA. Therefore, association and dissociation of C_{12} side chains may be controlled by photoisomerization of ADA, leading to photoresponsive gel-to-sol and sol-to-gel transitions. Fig. 16 shows photographs for a ternary mixture of 5.0 g/L p(AA/C_{12}(5)), 10.0 g/L α-CD, and 2.0 g/L ADA under irradiation with UV and visible light. Before irradiation with light, the ternary mixture exhibits gel-like behavior (Fig. 16a). When the gel-like ternary mixture is irradiated with UV light (ca. 355 nm), the mixture is gradually converted to a sol as shown in Fig. 16b. When the sol ternary mixture is irradiated with visible light (>440 nm), the mixture is gradually converted back to the gel-like mixture as shown in Fig. 16a. Fig. 17 shows changes in η determined by creep recovery for a ternary mixture of 5.0 g/L p(AA/C_{12}(5)), 10.0 g/L α-CD, and 1.0 g/L ADA upon repetitive irradiations of UV and visible light. This figure demonstrates that the ternary mixture exhibits reversible photoresponsive gel-to-sol and sol-to-gel transitions upon repetitive photoirradiations.

On the basis of these data, Fig. 18 shows a conceptual illustration for the photoresponsive gel-to-sol and sol-to-gel transitions. Before irradiation and under irradiation with visible light, ADA takes its *trans* form. Since α-CD interacts more favorably with *trans*-ADA than with the C_{12} side chains, C_{12} side chains associate with each other predominantly through interpolymer hydrophobic interaction, resulting in the formation of physical gel. On the other hand, under irradiation with UV light, ADA takes its *cis* form. Since α-CD interacts

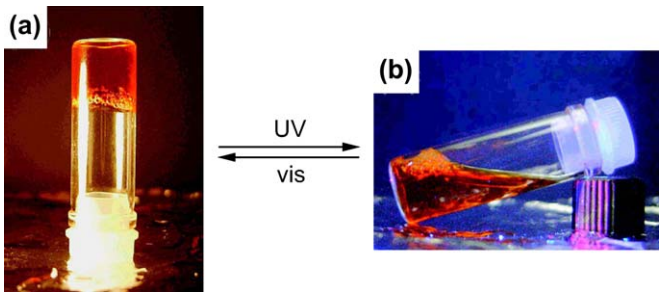


Fig. 16. Photographs for the ternary mixture of 5.0 g/L p(AA/C_{12}(5)), 10.0 g/L α-CD, and 2.0 g/L ADA under photoirradiation with visible (a) and UV light (b).

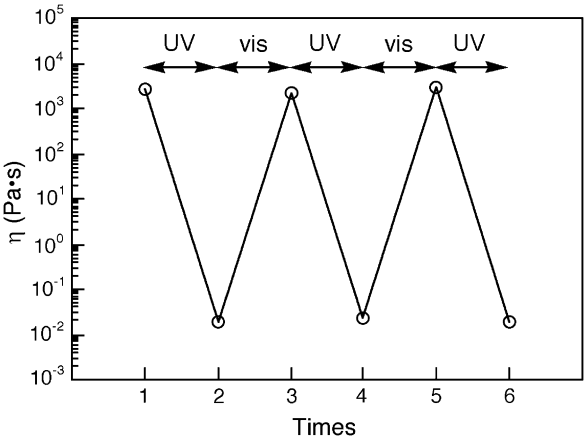


Fig. 17. Changes in η for the ternary mixture of 5.0 g/L p(AA/C_{12}(5)), 10.0 g/L α-CD, and 1.0 g/L ADA by repetitive irradiations with UV and visible light.

much more favorably with C_{12} side chains than with *cis*-ADA, interpolymer hydrophobic associations of C_{12} side chains are suppressed, resulting in the deformation of physical gel.

4.1.2. Redox-responsive gel-to-sol transition system [64]

Since there are only a few examples of redox-responsive hydrogel systems [65,66] relative to pH and temperature responsive hydrogel systems [67–69], we were motivated to construct a redox-responsive system which exhibits a gel-to-sol transition. We have chosen ferrocenecarboxylic acid (FCA) as a redox-responsive competitive guest because of its solubility in water. It is known that β-CD interacts rather strongly with FCA to form 1:1 complexes ($K = 2.2 \times 10^3\ M^{-1}$) whereas β-CD interacts only weakly with oxidized FCA ($K = 3.7 \times 10^1\ M^{-1}$) [70]. After optimization of conditions, we have obtained a redox-responsive system which exhibits a gel-to-sol transition as shown in Fig. 19. In the reduced state of FCA, the ternary mixture of 5.0 g/L p(AA/C_{12}(5)), 12.0 g/L β-CD, and 2.0 g/L FCA exhibits a gel-like behavior (Fig. 19a). On the other hand, after oxidation of FCA with an aqueous solution of sodium hypochlorite, the mixture shows a sol behavior (Fig. 19b). Fig. 20 shows a conceptual illustration for the

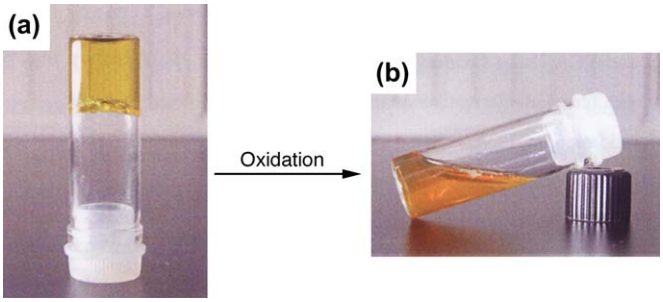


Fig. 19. Photographs for the ternary mixture of 5.0 g/L p(AA/C_{12}(5)), 12.0 g/L β-CD, and 2.0 g/L FCA before (a) and after (b) oxidation.

redox-responsive gel-to-sol transition. Before oxidation of FCA, since β-CD interacts favorably with FCA than with the C_{12} side chains, interpolymer hydrophobic associations of the C_{12} side chains provide the gel mixture. After oxidation of FCA using an oxidizing agent, on the other hand, β-CD interacts dominantly with the C_{12} side chains than with cationic FCA^+, the interpolymer hydrophobic associations of C_{12} side chains are dissociated, resulting in a gel-to-sol transition. We are investigating to construct a redox-responsive system which exhibits repetitive gel-to-sol and sol-to-gel transitions by applied electric potentials.

4.2. Photoresponsive contrasting viscosity changes [71]

As an extension of the photoresponsive system described above in a polymer–polymer interaction system, we have designed poly(acrylic acid)s (p(AA)) carrying α-CD moieties (p(AA/3αCD(2)) and p(AA/6αCD(2))) and a p(AA) carrying azobenzene moieties (p(AA/C_{12}Azo(3))) as shown in Scheme 6. We investigated the interaction of these polymers by absorption spectroscopy, viscometry, and NMR, and observed contrasting viscosity changes upon photoirradiation for the p(AA/3αCD(2))–p(AA/C_{12}Azo(3)) and p(AA/6αCD(2))–p(AA/C_{12}Azo(3)) mixtures.

The interaction of α-CD moieties in the CD polymers with Azo moieties in p(AA/C_{12}Azo(3)) was investigated by

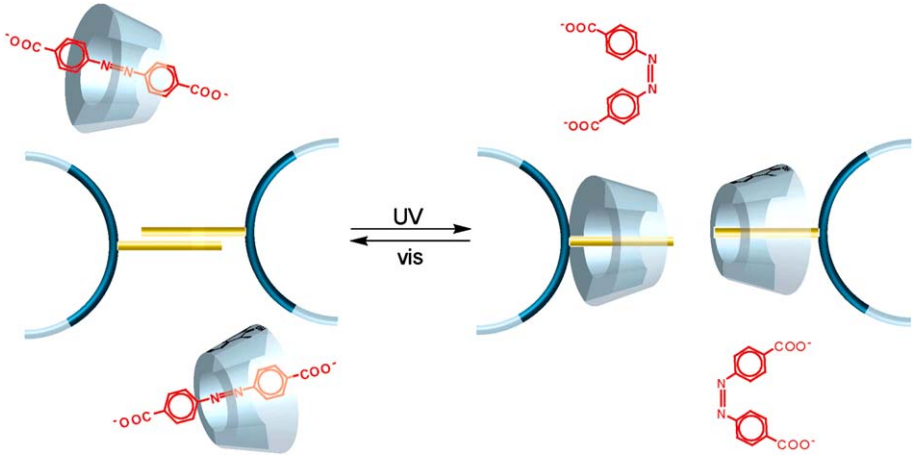


Fig. 18. Conceptual illustration for the photoresponsive hydrogel system.

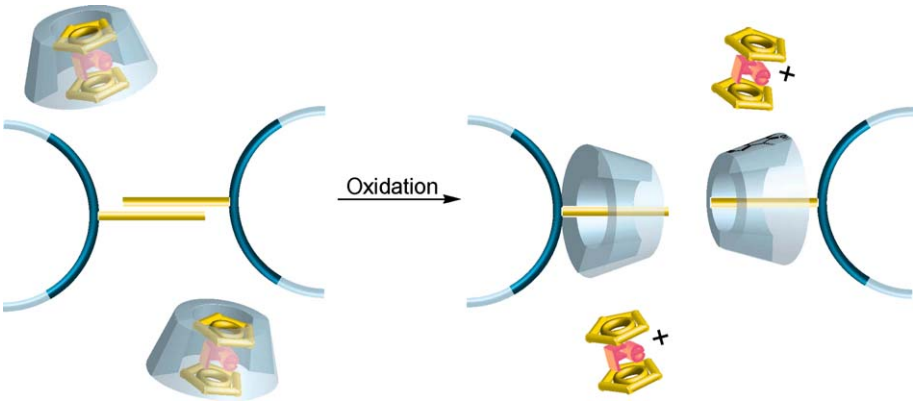


Fig. 20. Conceptual illustration for the redox-responsive hydrogel system.

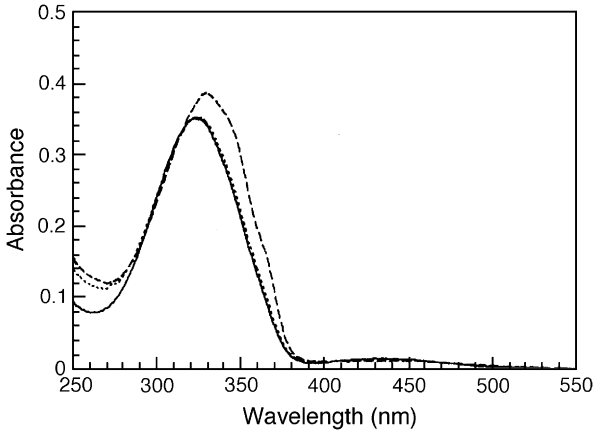


Fig. 21. UV–vis absorption spectra of p(AA/C_{12}Azo(3)) in the absence (solid line) and presence of 5 g/L p(AA/3αCD(2)) (dotted line) and p(AA/6αCD(2)) (broken line).

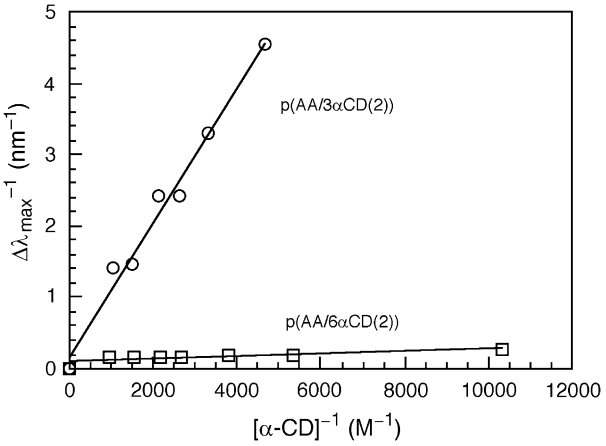


Fig. 22. $\Delta\lambda_{max}^{-1}$ as a function of $[\alpha\text{-CD}]^{-1}$ for the p(AA/3αCD(2))–p(AA/C_{12}Azo(3)) and p(AA/6αCD(2))–p(AA/C_{12}Azo(3)) systems.

absorption spectroscopy. As shown in Fig. 21, when p(AA/3αCD(2)) was added to 0.05 g/L p(AA/AzoC_{12}(3)), the absorption band due to the $\pi \rightarrow \pi^*$ transition of the *trans*-Azo moiety shows only a slight red shift (0.7 nm), indicative of a relatively weak interaction of the α-CD moieties in p(AA/3αCD(2)) with the Azo moieties in p(AA/AzoC_{12}(3)). On the other hand, when p(AA/6αCD(2)) was added to 0.05 g/L p(AA/AzoC_{12}(3)), the absorption band exhibits a larger red shift (6 nm), indicating a significant interaction of the α-CD moieties in p(AA/6αCD(2)) with the Azo moieties. Using these absorption spectra, reciprocals of peak shifts ($\Delta\lambda_{max}^{-1}$) were calculated and plotted in Fig. 22 as a function of $[\alpha\text{-CD}]^{-1}$ for both the p(AA/3αCD(2))–p(AA/AzoC_{12}(3)) and p(AA/6αCD(2))–p(AA/AzoC_{12}(3)) systems. This figure demonstrates linear relationships for both the systems, indicating that α-CD moieties form 1:1 inclusion complexes with Azo moieties [35]. From slopes and intercepts of the straight lines, K values were determined to be 1.4×10^2 and $1.2 \times 10^4\ M^{-1}$ for the p(AA/3αCD(2))–p(AA/AzoC_{12}(3)) and p(AA/6αCD(2))–p(AA/AzoC_{12}(3)) systems, respectively [36]. It should be noted here that these K values are apparent ones because α-CD and Azo moieties are localized on the polymer main chains. However, these K values indicate that p(AA/6αCD(2)) interacts much more favorably with p(AA/C_{12}Azo(3)) than does p(AA/3αCD(2)).

Since the formation of inclusion complexes of α-CD moieties in the CD polymers (p(AA/3αCD(2)) and p(AA/6αCD(2))) with guest moieties in p(AA/C_{12}Azo(3)) should lead to an increase in the solution viscosity [23,46–51], the interaction of the CD polymers (p(AA/3αCD(2)) and p(AA/6αCD(2))) with p(AA/AzoC_{12}(3)) was investigated by steady shear viscosity measurements, as shown in Fig. 23. This figure also includes η values for the p(AA)–p(AA/C_{12}Azo(3)) mixture for comparison. The η values for the p(AA/3αCD(2))–p(AA/C_{12}Azo(3)) and p(AA/6αCD(2))–p(AA/C_{12}Azo(3)) mixtures are larger than those for the p(AA)–p(AA/C_{12}Azo(3)) mixture, indicative of the formation of interpolymer aggregates through the complexation of the CD moieties in the CD polymers with the guest moieties in the guest polymer. The η values for the p(AA/6αCD(2))–p(AA/C_{12}Azo(3)) mixture are 2 orders of magnitude larger than those for the p(AA/3αCD(2))–p(AA/C_{12}Azo(3)) mixture, although both the mixtures employ the same host–guest pair. The difference in η values corresponds to the difference in the apparent K values for the p(AA/3αCD(2))–p(AA/C_{12}Azo(3)) and p(AA/6αCD(2))–p(AA/C_{12}Azo(3)) systems.

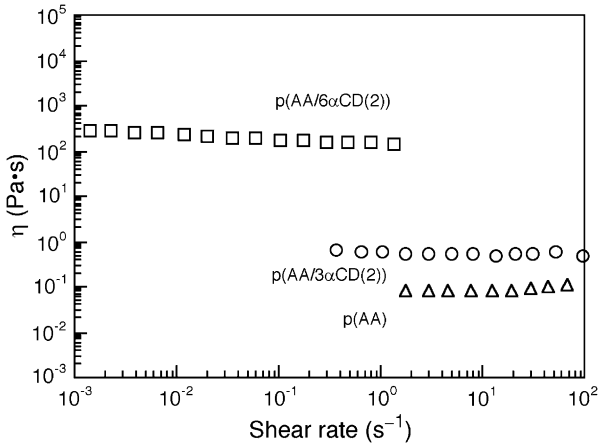


Fig. 23. Steady shear viscosity (η) as a function of shear rate for the mixtures of 10 g/L p(AA/C_{12}Azo(3)) with 15 g/L p(AA/6αCD(2)), p(AA/3αCD(2)), and p(AA) before photoirradiation.

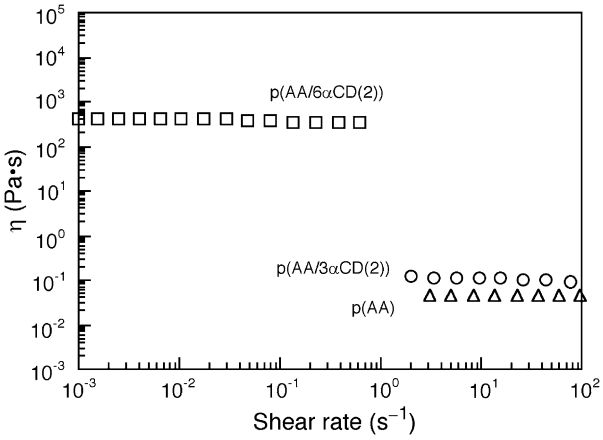


Fig. 24. Steady shear viscosity (η) as a function of shear rate for the mixtures of 10 g/L p(AA/C_{12}Azo(3)) with 15 g/L p(AA/6αCD(2)), p(AA/3αCD(2)), and p(AA) after UV irradiation.

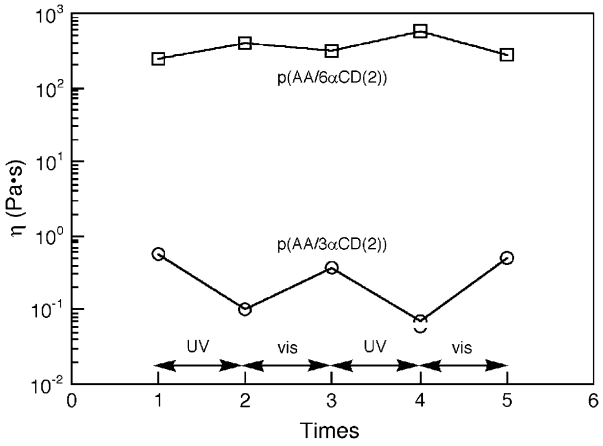


Fig. 25. Changes in η for the mixtures of 10 g/L p(AA/C_{12}Azo(3)) with 15 g/L p(AA/6αCD(2)) and p(AA/3αCD(2)) by repetitive irradiations with UV and visible light.

Fig. 24 demonstrates the shear rate dependency of η for the p(AA)–p(AA/C_{12}Azo(3)), p(AA/3αCD(2))–p(AA/C_{12}Azo(3)), and p(AA/6αCD(2))–p(AA/C_{12}Azo(3)) mixtures

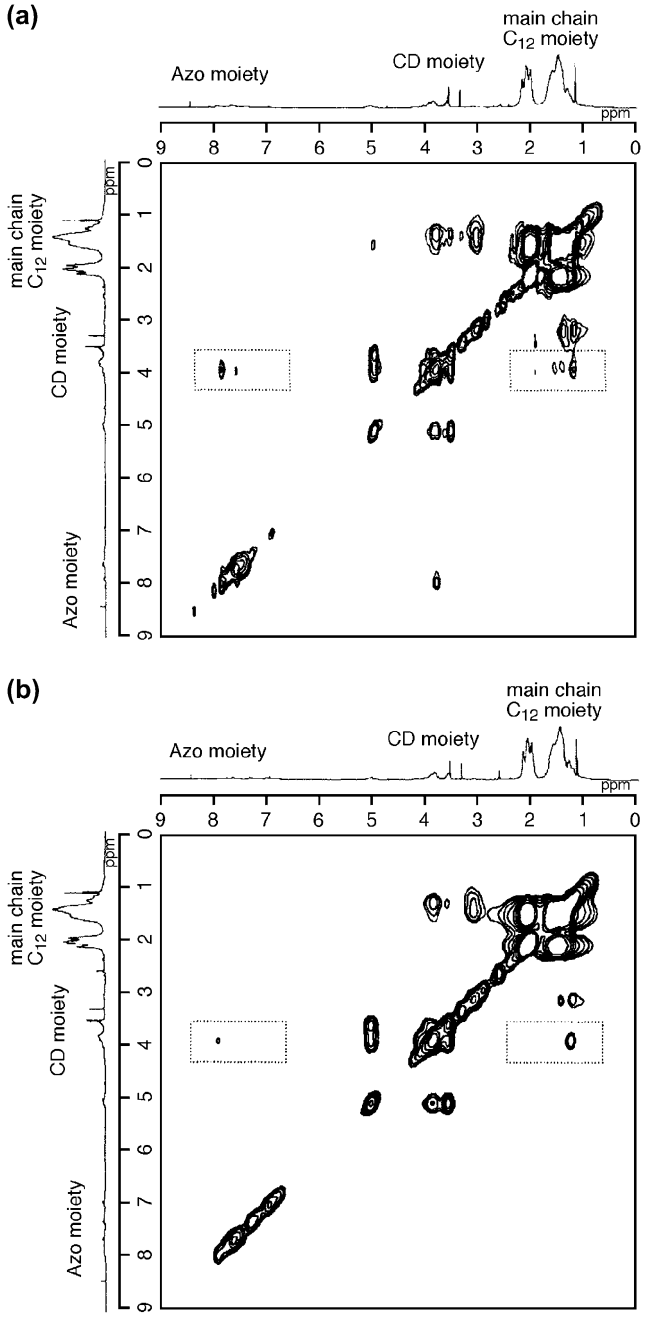


Fig. 26. 2D NOESY spectra for the p(AA/3αCD(2))–p(AA/C_{12}Azo(3)) mixture before (a) and after (b) UV irradiation.

after irradiation with UV light for 24 h, when the contents of *cis*-Azo moieties were estimated to be ca. 0.8 by ^{1}H NMR for all the mixtures. In the case of the p(AA/3αCD(2))–p(AA/C_{12}Azo(3)) mixture, η values after UV irradiation (Fig. 24) are nearly an order of magnitude smaller than those before irradiation (Fig. 23). Since α-CD does not interact with *cis*-azobenzene derivatives [62,63], the decrease in η for the p(AA/3αCD(2))–p(AA/C_{12}Azo(3)) mixture suggests that the UV irradiation provides dissociation of the inclusion complexes of α-CD moieties in p(AA/3αCD(2)) with guest moieties in p(AA/C_{12}Azo(3)). On the other hand, in the case of the

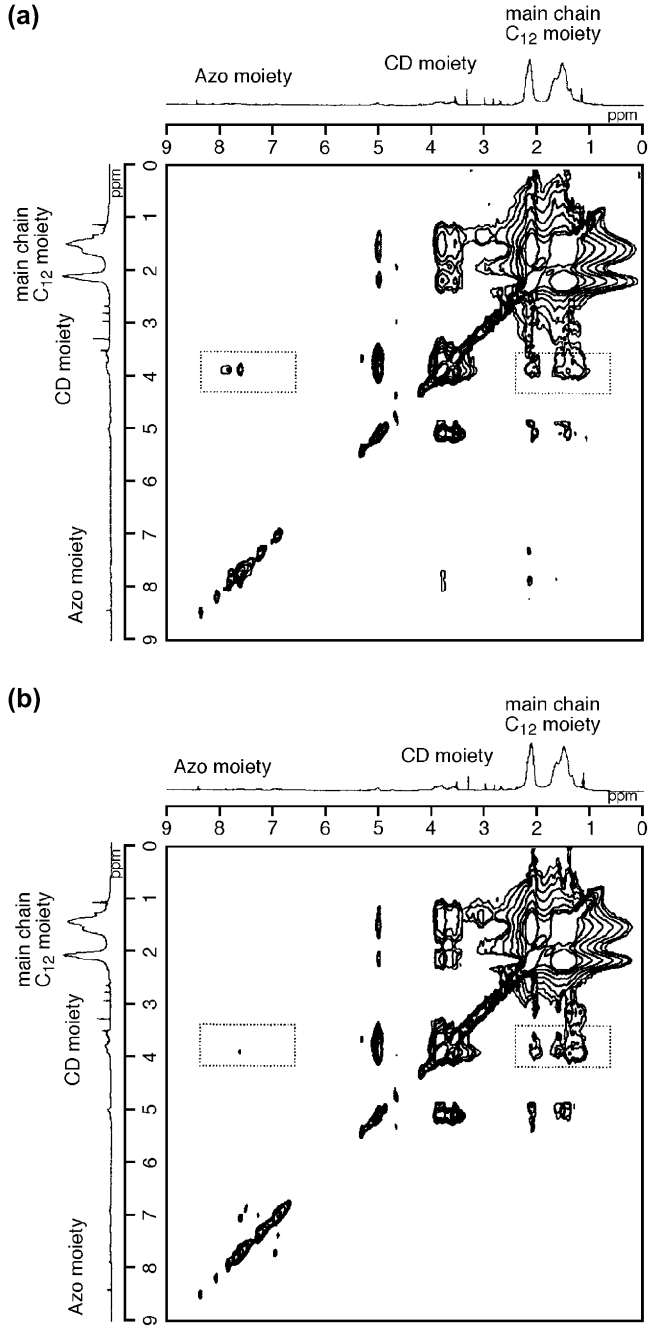


Fig. 27. 2D NOESY spectra for the p(AA/6αCD(2))−p(AA/C_{12}Azo(3)) mixture before (a) and after (b) UV irradiation.

p(AA/6αCD(2))−p(AA/C_{12}Azo(3)) mixture, η values after UV irradiation are slightly larger than those before irradiation. The slight increase in η suggests that the UV irradiation provides interlocked inclusion complexes, in which the α-CD moiety in p(AA/6αCD(2)) stays on the C_{12} linker in p(AA/C_{12}Azo(3)). As shown in Fig. 25, these contrasting photoresponsive η changes occur repetitively upon successive irradiation of UV and visible light.

To explore how the α-CD moiety in the CD polymers interacts with p(AA/C_{12}Azo(3)) before and after UV irradiation, 2D NOESY spectra were measured. The NOESY spectrum for the p(AA/3αCD(2))−p(AA/C_{12}Azo(3)) mixture before UV irradiation (Fig. 26a) shows correlation peaks between the α-CD moiety and both the Azo and C_{12} moieties, indicating that the α-CD moiety in p(AA/3αCD(2)) interacts not only with the Azo moiety but also with the C_{12} linker. The spectrum for the p(AA/3αCD(2))−p(AA/C_{12}Azo(3)) mixture after UV irradiation (Fig. 26b) exhibits only weak correlation peaks between the α-CD moiety and the Azo and C_{12} moieties. Since these weak correlation peaks are due to the residual *trans*-Azo moieties, this spectrum is indicative of dissociation of inclusion complexes after photoisomerization. On the other hand, the NOESY spectrum for the p(AA/6αCD(2))−p(AA/C_{12}Azo(3)) mixture before UV irradiation (Fig. 27a) shows correlation peaks between the α-CD and the Azo and C_{12} moieties. The correlation peaks between the α-CD moiety and the C_{12} linker are more intense than those between the α-CD moiety and the Azo moiety, indicating that the α-CD moiety in p(AA/6αCD(2)) interacts with the C_{12} linker more favorably than with the Azo moiety. The spectrum of the p(AA/6αCD(2))−p(AA/C_{12}Azo(3)) mixture after UV irradiation (Fig. 27b) exhibits significant correlation peaks between the α-CD and the C_{12} linker although it does not show significant correlation peaks between the α-CD moiety and the Azo moiety, indicative of the formation of interlocked complexes.

On the basis of these data described above, it is concluded that the contrasting η changes upon photoirradiation are ascribable to the difference in how the α-CD moiety in the CD polymers interacts with p(AA/C_{12}Azo(3)) after photoisomerization (Fig. 28). For both the mixtures in the *trans*-Azo state (i.e., before irradiation with UV light or after irradiation with visible light), α-CD moieties interact with C_{12}Azo moieties to form inclusion complexes. For the p(AA/3αCD(2))−p(AA/C_{12}Azo(3)) system in the *cis*-Azo state (i.e., after UV irradiation), the inclusion complexes are predominantly dissociated, resulting in the considerable η decrease. Whereas, for the p(AA/6αCD(2))−p(AA/C_{12}Azo(3)) system, interlocked complexes are formed in the *cis*-Azo state, resulting in the slight η increase.

5. Conclusion

The interaction of CDs with side chains of water soluble polymers was investigated as a simple model for biological molecular recognition. The selectivity of CDs was enhanced by the steric effect of the polymer main chain and by interaction at multi-sites (i.e., collectivity). Utilizing the interaction of CDs with polymer side chains, two types of stimuli-responsive systems were constructed from simple components. One is stimuli-responsive gel-to-sol transition systems which consist of α- or β-CD, a dodecyl-modified p(AA), and a stimuli-responsive competitive guest. The other is photoresponsive systems exhibiting contrast viscosity changes which consist of an α-CD-modified p(AA) and an azobenzene-modified p(AA). On the basis of these data, it is demonstrated that the interaction of CDs with polymer side chains is useful not only as simple models for biological molecular recognition but also as building blocks in nanotechnological applications.

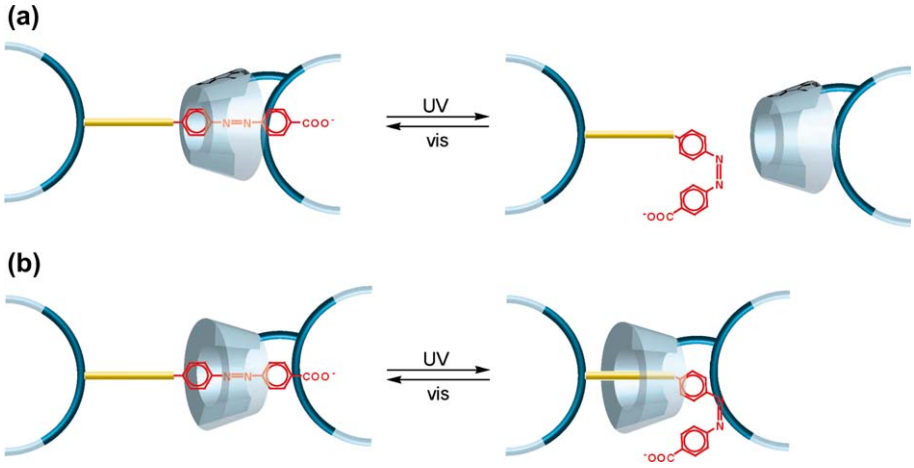


Fig. 28. Conceptual illustration for the contrasting viscosity changes for the p(AA/3αCD(2))–p(AA/C_{12}Azo(3)) (a) and p(AA/6αCD(2))–p(AA/C_{12}Azo(3)) systems (b).

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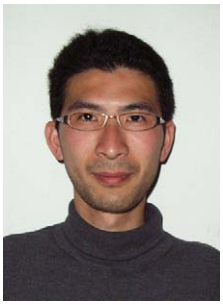

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