Polymer Networks Assembled by Host−Guest Inclusion between Adamantyl and β-Cyclodextrin Substituents on Poly(acrylic acid) in Aqueous Solution

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ABSTRACT: Polymer networks have been constructed through host−guest inclusion between β-cyclodextrin (β-CD) and 1-(2-aminoethyl)amidoadmantyl (ADen) substituents on poly(acrylic acid) (PAA). The structure of the networks and the host−guest interactions between the β-CD and ADen groups were studied by rheology and 2D ^{1}H NOESY NMR spectroscopy. The maximum viscosity of the mixture of β-CD substituted PAA (β-CDPAA) and ADen substituted PAA (ADenPAA) occurred at a 1:1 β-CD:ADen substituent ratio which confirmed their binary inclusion. The viscosity of the mixture of the two polymers decreased upon addition of native β-CD due to its ability to compete favorably with the β-CD substituents of β-CDPAA in the inclusion of the ADen substituents of ADenPAA and the consequent disintegration of the polymer network. The rheological properties of the polymer networks were temperature sensitive. In the temperature range 10−35 °C, the storage modulus and the loss modulus obeyed a time−temperature superposition. The horizontal and vertical temperature shift factors, a_T and b_T, obeyed a simple Arrhenius relationship for which the activation energies were found to be 70.3 ± 0.4 and −2.2 ± 0.1 kJ mol^{-1}, respectively. 2D ^{1}H NOESY NMR studies showed the ADen substituent to be included within the native β-CD and β-CD substituent cavities.

Introduction

β-cyclodextrin (β-CD) is a cyclic oligomer composed of seven glucopyranose units, which form a truncated cone-shaped and partly hydrophobic cavity with internal diameters of 6.0 Å and 6.4 Å for the rings formed by the H5 and H3 hydrogens (Figure 1), respectively, and a depth of 7.9 Å.[1,2] In aqueous solution, the β-CD cavity is occupied by water molecules which are readily displaced by a hydrophobic guest of appropriate size[2−6] including those substituted onto polymer chains.[7−10] The adamantyl moiety is one such guest which forms a strong host−guest inclusion complex with β-CD due to its good size-match to the β-CD cavity as shown by Eftink.[3] Subsequently, the inclusion by β-CD and adamantyl as a substituent in either a molecule or a polymer chain has been used in a range of supramolecular assembly studies.[6,11−19] From studies of the inclusion of the adamantyl moieties of adamantane-1-ammonium cation and adamantane-1-carboxylate anion by native β-CD and β-CD substituted polymers, Wenz concluded that almost all β-CD polymer substituents were accessible to adamantyl guests, but the binding constant for the β-CD polymer substituent was lower than that for native β-CD.[11]

Both CD and adamantyl substituted polymers have been prepared by substitution onto a polymer chain and by polymerization of either CD or adamantyl containing monomers.[7,15,17,20−22] In this study we have chosen to control the molecular weight and molecular weight distribution of such polymers through the substitution of either β-CD or adamantyl onto poly(acrylic acid) (PAA) of established molecular weight and molecular weight distribution. The new polymer networks studied were those formed by β-CD (β-CDPAA) and 1-(2-aminoethyl)amidoadmantyl, or ADen, substituted poly(acrylic

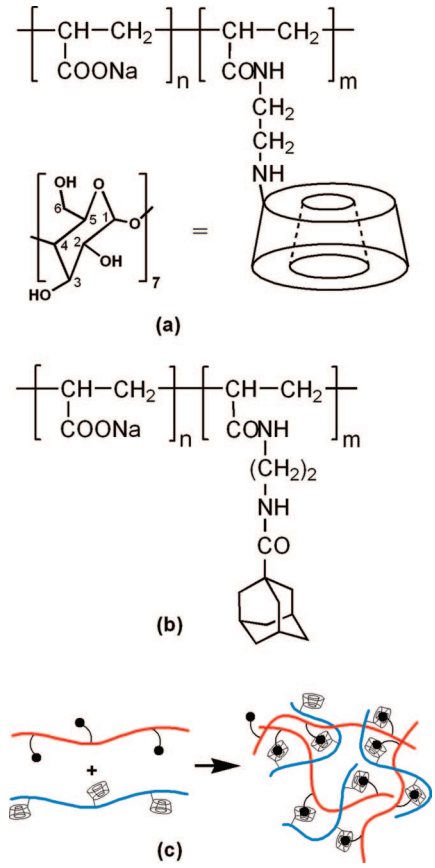

Figure 1. Chemical and schematic structures of (a) β-CDPAA, (b) ADenPAA, and (c) the network formed by (a) and (b).

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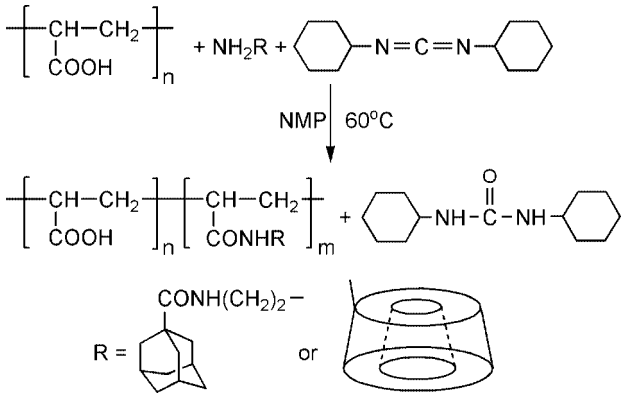

Figure 2. Substitution of ADen and β-CD onto PAA.

acid) (ADenPAA) (Figure 1). The changes in rheological behavior of the network as the mole ratios of β-CD to ADen substituents in β-CDPAA and ADenPAA and native β-CD to ADen substituent in ADenPAA and temperature varied were determined. The host−guest inclusions of the ADen substituents by the β-CD substituents and by native β-CD were studied by 2D ^{1}H NMR NOESY spectroscopy.

Experimental Section

Materials. β-Cyclodextrin from Wacker Biochem. Corp., 1-methyl-2-pyrrolidone (NMP) (99.5%), dicyclohexylcarbodiimide (99%) and methanol (99.5%) from Aldrich, sodium hydroxide (97%) from EM Science, and 1,2-diaminoethane (Ajax), and *N*,*N*-dimethylformamide (DMF) (Ajax) were used as supplied. Poly(acrylic acid) (PAA) (M_w = 250000, $M_w/M_n \approx 2$) was purchased from Aldrich as a 35 wt % solution in water and freeze-dried to a constant weight. Basic alumina (Fluka) was supplied as Brockman Activity I and the appropriate amount of water was added to give Brockman Activities II and III. 6^A-Amino-6^A-deoxy-β-cyclodextrin,[23] 4-nitrophenyl-adamantane-1-carboxylate[4] and 2.9% β-CD substituted poly(acrylic acid)[7] were prepared as previously described (Figure 2).

Preparation of *N*-(2-Aminoethyl)-adamantane-1-carboxamide. A solution of 4-nitrophenyl-adamantane-1-carboxylate (300 mg, 1 mmol) in DMF (5 mL) was added dropwise over 3 h to a vigorously stirred solution of 1,2-diaminoethane (600 mg, 10 mmol) in DMF (5 mL). The reaction mixture was diluted with water (50 mL) and acidified with 10% hydrochloric acid (3 mL) and the solution was washed with dichloromethane (3 × 50 mL). The aqueous solution was made basic with 50% w/w aqueous sodium hydroxide (10 mL) and extracted with dichloromethane (3 × 50 mL). The combined dichloromethane solution was washed successively with water (50 mL) and brine (50 mL) and dried over sodium sulfate. The solution was filtered and the solvent removed under reduced pressure to give the crude product as a waxy solid (100 mg). This was recrystallized from hexane/chloroform to give the pure product as white needles (67 mg, 30%). Mp 137−138 °C (see ref , 139−141 °C for preparation by a different method). δ_H ($CDCl_3$) 6.13 (bs, CONH); 3.32 (m, 2H, $CONHCH_2$); 2.84 (t, J = 6.2 Hz, 2H, CH_2NH_2), 2.05 (bs, 3H, adamantly CH); 1.86 (s, 6H, adamantyl CH_2); 1.72 (s, 6H, adamantyl CH_2). δ_C ($CDCl_3$) 178.15, 41.60, 41.30, 40.54, 39.19, 36.42, 28.05 ppm. IR (nujol): 3311, 1627, 1540 cm^{-1}.

Preparation of 3.0% Substituted Sodium 1-(2-Aminoethyl)-adamantane-1-carboxamide Poly(acrylate). Polyacrylic acid (0.9 g, 12.5 mmol) was dissolved in 1-methylpyrrolidin-2-one (30 mL) at 60 °C for 24 h. 1-(2-Aminoethyl)-adamantane-1-carboxamide (0.80 g, 0.38 mmol) was added into 1-methylpyrrolidin-2-one (2 mL) followed by dicyclohexyldiimide (1.0 g. 0.48 mmol) and the mixture was stirred at 60 °C for at least 48 h (Figure 2). The reaction mixture was cooled to room temperature and 40% w/w sodium hydroxide solution (35 mL) was added. The resulting white precipitate was washed with NMP (2 × 15 mL) at 60 °C twice and then by methanol (2 × 20 mL) at room temperature. After vacuum filtration, the crude product was twice dissolved in water (12.5 mL) and precipitated in methanol (100 mL). The product was dissolved in water (20 mL) and dialyzed (Spectr/Por 3, molecular weight cutoff: 3500 g/mol) against deionized water for 4 days until the conductivity of water outside the dialysis tube remained constant. The dry product was isolated as the sodium salt by freeze-drying after concentrating the solution. Yield: 70−80%.

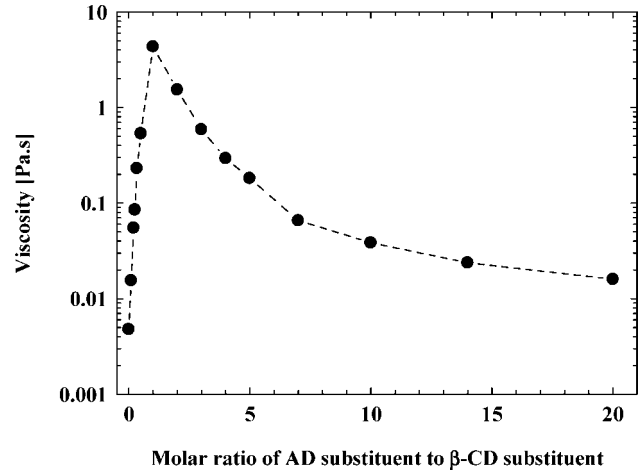

Figure 3. Effect of variation of the ADen:β-CD substituent mole ratio on the zero-shear viscosity of a 2 wt % mixture of β-CDPAA and ADenPAA.

Characterization. ^{1}H NMR spectra were recorded on a Varian Inova 600 spectrometer for samples dissolved in D_2O at 1 wt %. The degrees of substitution of the carboxyl groups in PAA by either β-CD or ADen substituents were determined by comparing areas of the distinctive β-CD and ADen ^{1}H resonances with the PAA CH_2 ^{1}H resonance. The degrees of substitution of β-CD and ADen substituents in β-CDPAA and ADenPAA were determined to be 2.9 mol % and 3.0 mol %, respectively. This is consistent with the molecular weights of β-CDPAA and ADenPAA being 436000 and 268000, respectively. 2D ^{1}H NOESY NMR spectra were recorded at room temperature with a mixing time of 300 ms for a mixture of β-CDPAA and ADenPAA in D_2O with a 1:1 molar ratio of β-CD:ADen substituents.

The steady and dynamic rheological measurements were performed on a Physica MCR 501 (Anton Paar GmbH) stress-controlled rheometer with 25 mm cone and plate geometry. The temperature was controlled to within ±0.1 °C by a Peltier plate. Samples for the rheological measurements were prepared by dissolving the substituted PAA in 0.10 M NaCl aqueous solution in order to screen the electrostatic interactions between the poly(acrylic acid) deprotonated carboxylic acid groups, and the solution pH was adjusted to 7 using 0.10 M aqueous NaOH.

Results and Discussion

Stoichiometry of β-CD/ADen Complexation. The stoichiometry of the host−guest inclusion interactions of the substituents of β-CDPAA and ADenPAA were studied by rheology. The zero-shear viscosities of the mixtures of β-CDPAA and ADenPAA solutions (2 wt %) at different mole ratios of β-CD to ADen substituents were compared with that of either β-CDPAA or ADenPAA alone (2 wt %) which have similar zero-shear viscosities. However, the β-CDPAA/ADenPAA mixtures showed much higher zero-shear viscosities (Figure 3). At a 1:1 β-CD:ADen substituent mole ratio a maximum zero-shear viscosity was reached which was 100-fold greater that of either β-CDPAA or ADenPAA alone. This is consistent with the formation of a cross-linked polymer network due to the β-CD and ADen substituent binary host−guest inclusions which form interpolymer chain linkages. Such binary host−guest

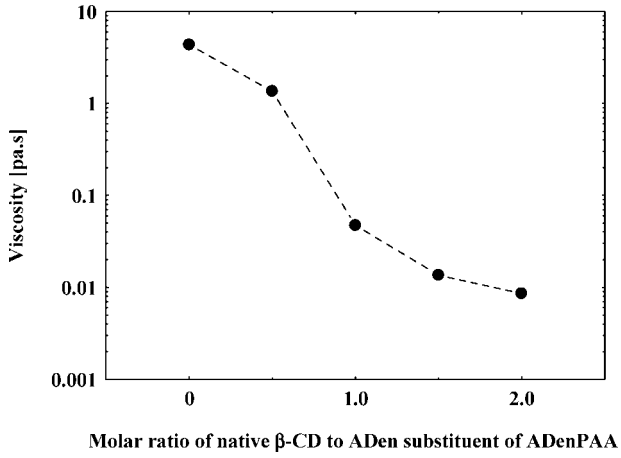

Figure 4. Effect of native β-CD on the zero-shear viscosity of a 2 wt % β-CDPAA/ADenPAA mixture with a β-CD:ADen substituent ratio of 1:1.

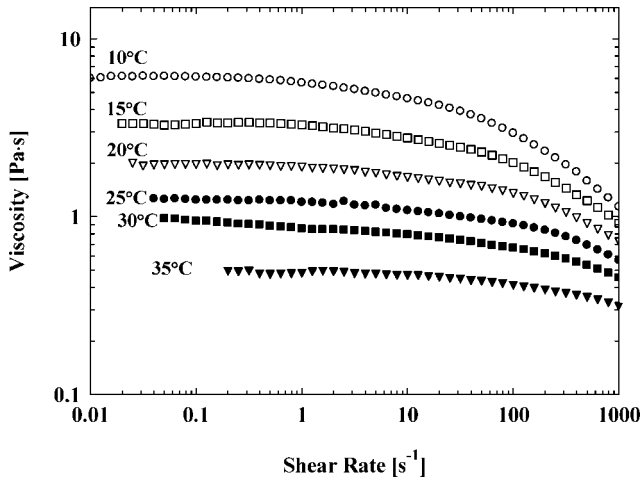

Figure 5. Variation of the viscosity of a 2 wt % β-CDPAA and ADenPAA mixture with a β-CD:ADen substituent mole ratio of 1:1 as a function of shear rate and temperature.

inclusion was also found for the adamantane-1-bromide/native β-CD system in ^{1}H NMR and computational studies.[25−27]

Competition between Native β-CD and β-CD Substituents. Native β-CD competed with the β-CD substituent of β-CDPAA in host−guest inclusion of ADen and thereby destroyed the polymer network. As shown in Figure 4, the zero-shear viscosity of the β-CDPAA/ADenPAA mixture decreased on addition of native β-CD. When the mole ratio of native β-CD:ADen substituent reached 2:1 the zero-shear viscosity of the mixture reached a minimum similar to that of either β-CDPAA or ADenPAA alone. This illustrates the ready reversibility of the β-CD/ADen host−guest inclusion and indicates that the network formed between β-CDPAA and ADenPAA is dynamic in nature such that it is perturbed by competing inclusion agents such as native β-CD. According to Wenz,[11] the binding constant for the inclusion of AD substituents by native β-CD can be an order of magnitude higher than that for β-CD polymer substituents.

Temperature Effect on Host−Guest Inclusion. The temperature variations of steady shear viscosities as a function of shear rate for a 1:1 mol ratio mixture of 2 wt % β-CDPAA and 2 wt % ADenPAA aqueous solutions are shown in Figure 5. The viscosities decreased monotonically upon increasing temperature until a significant drop of viscosity occurred at 40 °C probably as a result of a phase transition.

Since the relaxation modes of the β-CDPAA/ADenPAA system varied similarly with temperature in the range region 10−35 °C, a "master curve" was obtained through a time−temperature superimposition of the storage modulus, G′, data at various temperatures on those at the reference temperature of 25 °C (Figure 6a). Thus, the storage modulus, G′, at different temperatures is given by eq 1 where a_T and b_T are the horizontal and vertical shift factors, respectively, T and T_{ref} are the experimental and reference temperatures and ω is the frequency in rad s^{-1}. The same shift factors correctly shifted the loss modulus, G″, data which showed the validity of the superimposition (Figure 6b).

$$b_T G'(\omega, T) = \frac{T}{T_{ref}} G'(a_T \omega, T_{ref}) \quad (1)$$

Assuming that the temperature effect on the host−guest inclusion obeyed the Arrhenius equation, the activation energies were calculated by fitting of the shift factors through equations 2 and 3:

$$a_T = \exp\left(\frac{E_a}{R}\left(\frac{1}{T} - \frac{1}{T_{ref}}\right)\right) \quad (2)$$

$$b_T = \exp\left(\frac{E_b}{R}\left(\frac{1}{T} - \frac{1}{T_{ref}}\right)\right) \quad (3)$$

where E_a and E_b are the activation energies. For the βCDPAA and ADenPAA mixture, the derived E_a and E_b data calculated from the storage and loss moduli, G' and G'', time−temperature superposition were very close. The average values of E_a and E_b are 70.3 ± 0.4 kJ mol^{-1} and −2.2 ± 0.1 kJ mol^{-1}, respectively (Figure 6).

Host−Guest Inclusion Identification by 2D ^{1}H NOESY NMR Spectroscopy. Cross-peaks observed in 2D ^{1}H NOESY NMR spectra identify protons undergoing "through space" dipolar interactions.[28] As such interactions are insignificant at interaction distances of ≥4 Å, the relative intensities of cross-peaks provide structural information. The α, β, and γ protons of the adamantyl moieties of the ADen substituents of ADenPAA show strong cross-peaks arising from dipolar interactions with the H3, H5, and H6 protons (Figure 7a) lining the cavity of native β-CD consistent with host−guest inclusion as shown in Figure 8. Weaker cross-peaks are seen for interactions between the α and γ protons of the ADen substituents and the H2 and H4 protons which are more distant on the exterior of the β-CD cavity.

Because direct substitution of the A glucopyranose units onto the poly(acrylic acid) chain in β-CDPAA rendered them unique each of the other six glucopyranoses (B-G) also became unique due to the homochirality of β-CD. This resulted in each glucopyranose unit having slightly different ^{1}H chemical shifts and their overlap caused the β-CDPAA resonances to be less resolved (Figure 7b) than those of native β-CD. Nevertheless, the β-CDPAA/ADenPAA mixture showed strong cross-peaks arising from dipolar interactions between the H3, H5 and H6 protons of the β-CD substituents and the α, β, and γ protons of the ADen substituents (Figure 7b) consistent with their inclusion by the β-CD substituents (Figure 8).

Cross-peaks arising from dipolar interactions between the -NDCH$_2$- protons of the 1-(2-aminoethyl)amino linker between the adamantyl moiety and the poly(acrylic acid) chain and the β-CD substituent protons of β-CDPAA were also observed for the β-CDPAA/ADenPAA system. This suggested that the 1-(2-aminoethyl)amino linkers of the ADen substituent in the β-CDPAA/ADenPAA system were closer to the H2 and H4 protons of the β-CD substituent than was the case for native β-CD in the β-CDPAA/native β-CD system for which analogous cross-peaks were not observed. (Neither were similar cross-

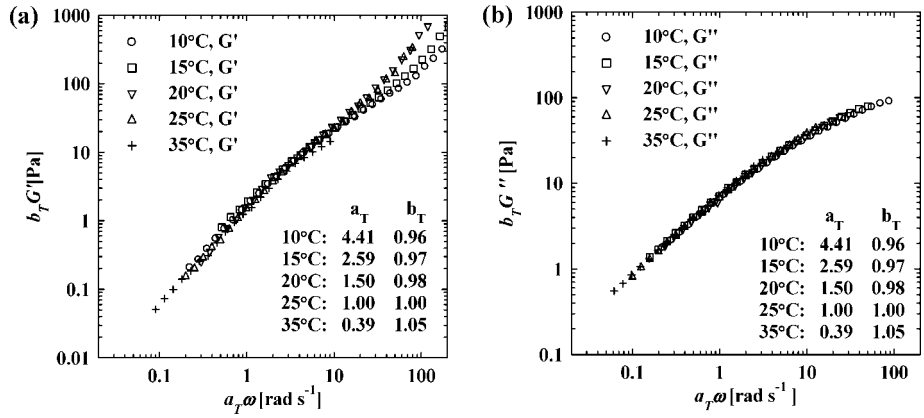

Figure 6. Master curves for the storage modulus G' (*a*) and the loss modulus G'' (*b*) of a 2 wt % β-CDPAA and ADenPAA with a β-CD:ADen substituent mole ratio of 1:1 as a function of frequency after time−temperature superposition.

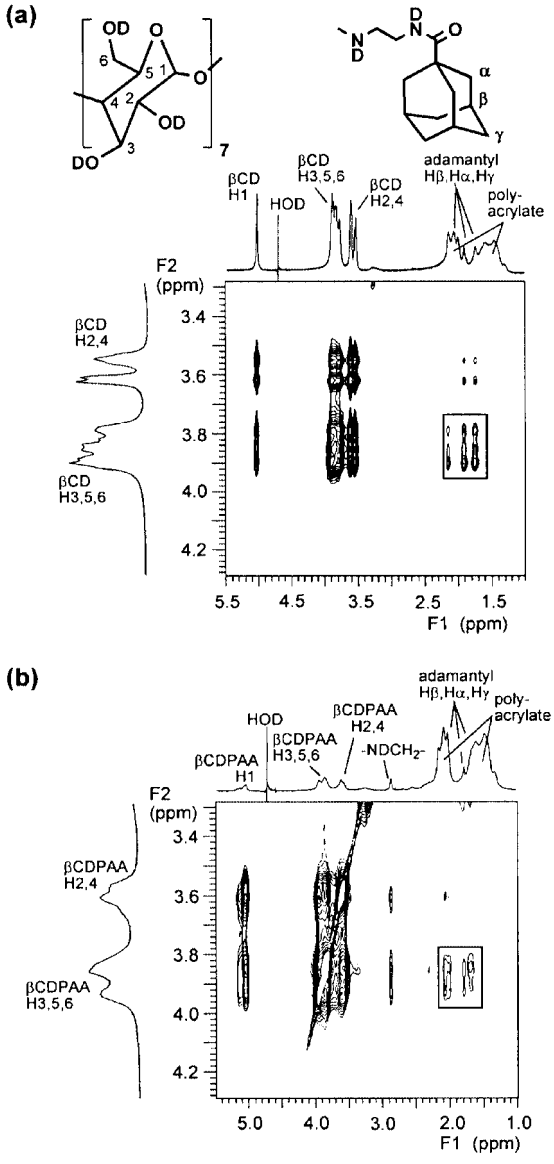

Figure 7. ^{1}H 600 MHz NOESY NMR spectrum showing the NOESY cross-peak enclosed in rectangles s arising from host−guest inclusion in (a) a 1 wt % ADenPAA solution in which the ADen substituent/native β-CD ratio was 1:1 and in (b) a 1 wt % β-CDPAA/ADenPAA mixture in which the ADen/β-CD substituent ratio was 1:1. (The protons of the β-CD hydroxyl groups and the ADen amide groups are replaced by D in D_2O).

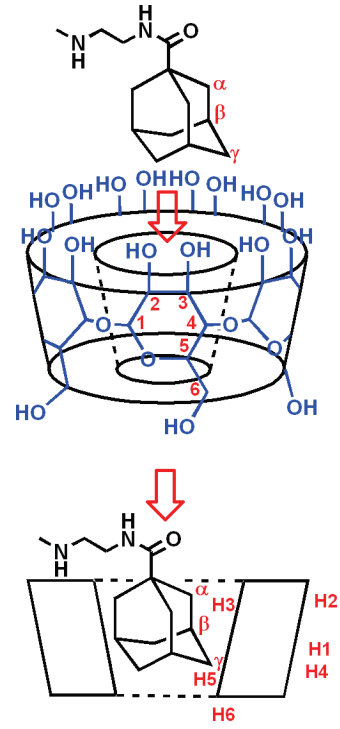

Figure 8. Host−guest inclusion of the adamantly moiety by native β-CD and the β-CD substituents of β-CDPAA.

peaks observed in the β-CDPAA/adamantane-1-carboxylate system.) It may be that the ADen substituent entered more deeply into the β-CD substituent cavity than was the case for native β-CD and thereby brought the $-NDCH_2-$ protons into closer proximity to the β-CDPAA H2−H6 protons or otherwise constrained the -$NDCH_2-$ protons in a closer proximity. The consequence was that both pairs of $-NDCH_2-$ protons experienced similar magnetic environments such that their resonances superimposed to give a greater amplitude by comparison with those of the less constrained native β-CD/ADenPAA system where a lesser magnetic equivalence of the $-NDCH_2-$ protons and superimposition of their resonances occurred.

As the ADen substituents were constrained by their attachment to the poly(acrylic acid) chain and the inclusion of neighboring ADen substituents they may have been less able to attain the optimal inclusion position in the β-CD substituent by comparison with that attained in native β-CD. This is in accord with native β-CD competing favorably with β-CDPAA for inclusion of the ADen substituents.

Conclusion

The host−guest inclusion of the ADen substituents of ADenPAA by native β-CD and the β-CD substituents of β-CDPAA in aqueous solution were studied by rheology and 2D ^{1}H NOESY NMR spectroscopy. The maximum viscosity appeared when the mole ratio of the β-CD and ADen substituents was unity consistent with their host−guest inclusion being binary in nature. Native β-CD competes favorably with the β-CD substituents in inclusion of the ADen substituents to the extent that the β-CDPAA/ADenPAA network disintegrates. By virtue of the stereochemistry of the attachment sites of the ADen and β-CD substituents to the PAA chain it is expected that the adamantyl moiety will enter the β-CD cavity through its wide end and the 2D ^{1}H NOESY NMR data are consistent with this. Similar data confirm the host−guest inclusion of the ADen substituent by native β-CD. The viscosity and the storage and the loss moduli, G' and G'', of the β-CDPAA/ADenPAA system decreased with increasing temperature in the range 10−35 °C and a phase transition occurred between 35 and 40 °C. In the range 10−35 °C, G' and G'' obeyed a time−temperature superposition and a master curve was obtained. The temperature dependence of the horizontal and vertical shift factors, a_T and b_T, displayed simple Arrhenius behavior.

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