Tunable Polymeric Hydrogels Assembled by Competitive Complexation between Cyclodextrin Dimers and Adamantyl Substituted Poly(acrylate)s

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Introduction

As ideal candidates for biocompatible materials, polymeric hydrogels are of considerable interest because of their potential applications in drug delivery, bioadhesives and tissue engineering.[1–3] The supramolecular assembly through host-guest complexation between cyclodextrin (CD) hosts and hydrophobic guests is a powerful method of constructing tunable and switchable polymeric networks.[4–5] These networks are prepared by mixing the CD substituted polymer and the guest substituted polymer.[6–9] Recently, another interesting way to form polymeric networks by using CD-dimers to crosslink guest substituted polymers was reported,[10–13] whereas our understanding on this system is still limited due to the lack of a systematic study.

In this note, we demonstrate that linked βCD dimers and adamantyl (AD) groups substituted onto poly(acrylates)s (PAA) (Scheme 1) through different flexible polyalkane tethers form polymeric hydrogels with tunable rheological properties controlled by the linked βCD dimer linker length and adamantyl substituted poly(acrylate) tether length. Rheological and 2-D NOESY ^{1}H NMR studies of four binary mixtures of each of *N*,*N*-bis(6^A-deoxy-6^A-β-cyclodextrin)urea (66βCD$_2$ur), and of *N*,*N*-bis(6^A-deoxy-6^A-β-cyclodextrin)succinamide (66βCD$_2$su), with 3% substituted amidoadamantyl (PAAAD), 1-(2-aminoethyl)aminoadamantane (PAAADen), 1-(6-aminohexyl)aminoadamantane (PA AADhn), and 1-(6-aminododecyl)aminoadamantane) (PAAA Dddn) are reported.

Experimental

The βCD dimers (66βCD$_2$ur and 66βCD$_2$su), and the 3.0% AD substituted poly(acrylic acid)s (PAAAD, PAAADen, PAAADhn and PAAADddn) were prepared as previously described.[9,14] 2-D ^{1}H NOESY NMR spectra were recorded at 298.2 K with a mixing time of 0.300 s for solutions of the adamantyl sustituted and either 66βCD$_2$ur or 66βCD$_2$ur with an equimolar ratio of βCD groups to AD substituents in D_2O at pD 7. Rheological measurements were performed on a Physica MCR 101 (Anton Paar GmbH) stress-controlled rheometer with a 25 mm cone and plate geometry. The temperature was 298.2°C controlled to within $\pm$ 0.1°C by a Peltier plate. Samples for the rheological measurements were prepared by dissolving the substituted poly(acrylate) in 0.10 mol dm^{-3} aqueous NaCl in order to screen the electrostatic interactions

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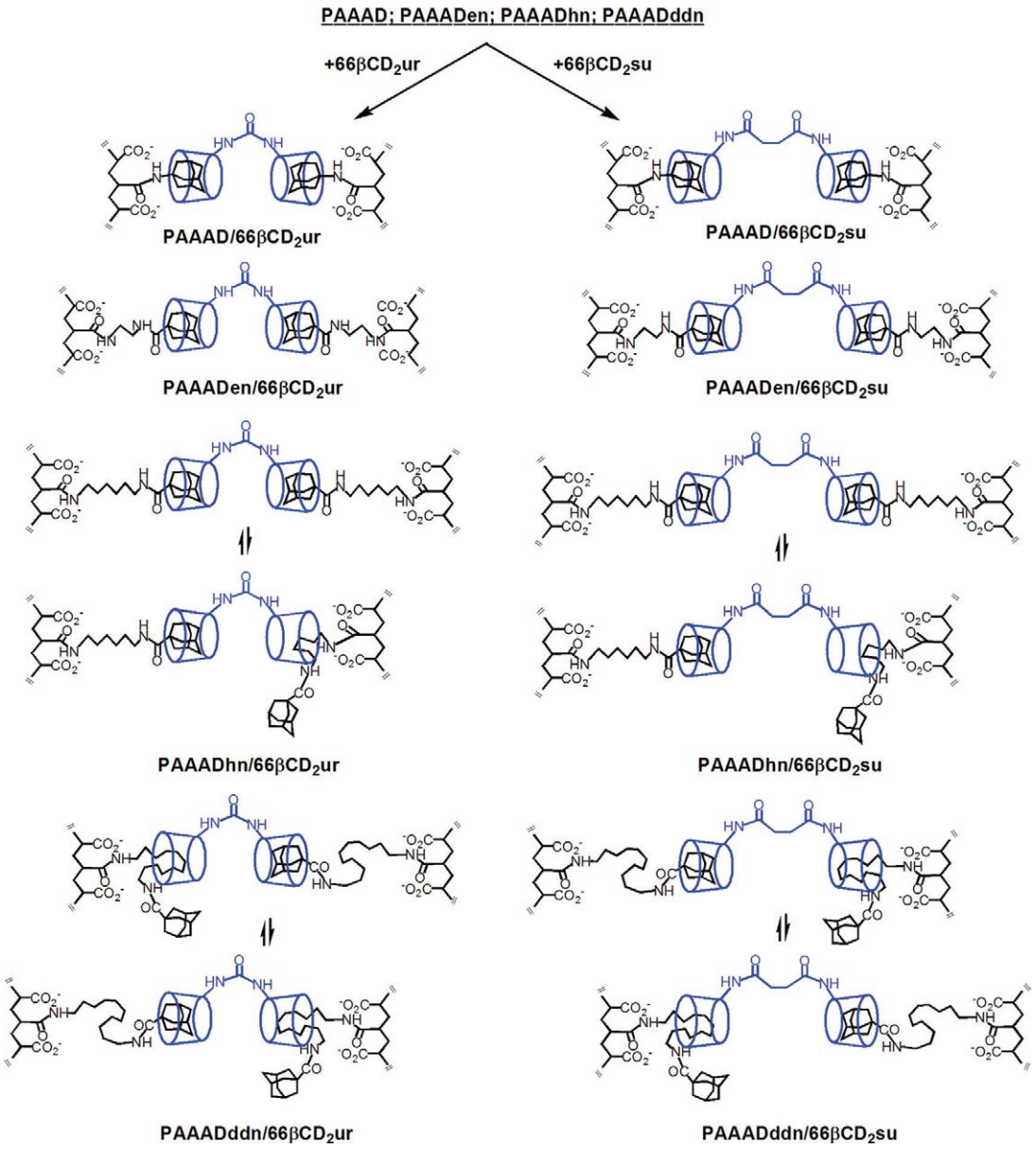

Scheme 1. The structures of the linked βCD dimers (66βCD2ur and 66βCD2su), and AD substituted PAAs (PAAAD, PAAADen, PAAADhn, PAAADddn).

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between the poly(acrylate) carboxylate groups, and the solution pH was adjusted to 7 using 0.10 mol dm^{-3} aqueous NaOH.

Results and Discussion

An insight into the polymer networks (Figure 1) is gained from rheology studies (Figure 2). The zero shear viscosity of 3.3 wt % aqueous solutions of PAAAD (0.0055), PAAADen (0.0050) and PAAADhn (0.0050) are similar while that of PAAADddn (0.010) is higher probably due to hydrophobic association of the dodecyl tethers producing weak crosslinking between adjacent polymer strands (zero-shear viscosities (Pa.s) are shown in parentheses). All the rheological measurements are repeated at least three times, and the zero-shear viscosities are the average data. Binary 3.3 wt % aqueous solutions of the substituted poly(acrylate)s and 66$\beta$$CD_2$ur, with βCD groups and adamantyl substituents equimolar, show a systematic increase in shear viscosity as the tether length increases from PAAAD (0.017), PAAADen (0.18) to PAAADhn (0.69) followed by a decrease for PAADddn (0.09). When 66$\beta$$CD_2$su is used a similar trend is observed: PAAAD (0.036), PAAADen (0.32), PAAADhn (1.4) and PAAADddn (1.1), and the zero-shear viscosity was greater for each system. This indicates that the longer linker between the two βCD in 66$\beta$$CD_2$su favors host-guest complexation to form polymer interstrand crosslinks by comparison with the shorter linker in 66$\beta$$CD_2$ur. Similarly, the increase in adamantyl tether length favors the formation of crosslinks up to the hexyl tether, but further increase in length to the dodecyl tether decreases viscosity either due to a decrease in the effectiveness of crosslinking or due to increased flexibility in the crosslink due to its increased length.

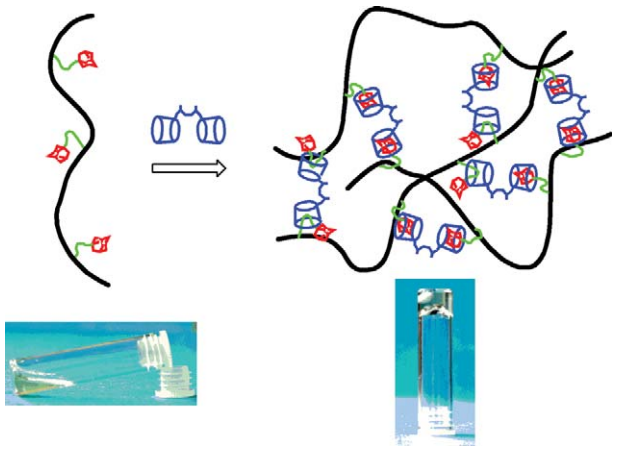

Figure 1. Zero shear viscosities of a) PAAAD, PAAADen, PAAADhn and PAAADddn and their binary mixtures with b) 66βCD_2ur and c) 66βCD_2su.

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Further insight into the structures of the polymer networks is gained from 2-D NOESY ^{1}H NMR spectroscopy. The spectrum of the most viscous system, a binary solution of PAAADhn and 66βCD_2su with equimolar βCD groups and adamantyl substituents (Figure 3) shows strong cross-peaks arising from interaction between the annular $H^{3,5,6}$ of 66βCD_2su and the adamantyl H^{2-4}, and weaker cross-peaks arising from interaction between the annular $H^{3,5,6}$ of 66βCD_2su, and the methylene protons of the hexyl tether of PAAADhn. This is consistent with a dominant host-guest complexation occuring in which the βCD annuli of PAAADhn act as hosts for the adamantyl guest and a less favored isomeric host-guest complexation occuring in which the βCD annuli of PAAADhn act as hosts for part of the hexyl tether, while the adamantyl substituent remains outside the βCD annuli as shown in Figure 1.

The 2-D NOESY ^{1}H NMR spectra of binary solutions of PAAAD and either 66βCD_2ur or 66βCD_2su with equimolar βCD groups and adamantyl substituents show strong cross-peaks arising from interaction between the annular $H^{3,5,6}$ of either 66βCD_2ur or 66βCD_2su and the adamantyl H^{2-4} only. Similarly, only cross-peaks arising from interaction between the annular $H^{3,5,6}$ of either 66βCD_2ur, or 66βCD_2su and the adamantyl H^{2-4} of PAAADen are observed consistent with the ethyl tether being too short to compete with the adamantyl substituent as a guest in the annuli of the βCD hosts. In contrast, the spectra of binary solutions of PAAADddn and either 66βCD_2ur or 66βCD_2su show strong cross-peaks arising from interaction between the annular $H^{3,5,6}$ of either 66βCD_2ur or 66βCD_2su and the adamantyl H^{2-4} and the protons of the docecyl tether. (The cross-peaks due to the dodecyl protons are stronger relative to those arising from adamantyl H^{2-4} than is the case in the PAAADhn and either 66βCD_2ur or 66βCD_2su discussed earlier partially because of the greater number of dodecyl protons). Thus, host-guest complexation of the adamantyl substituent occurs in all eight binary systems (Scheme 2) and isomeric host-guest complexation of the hexyl and dodecyl tethers also occurs in the four PAAADhn and PAAADddn binary systems.

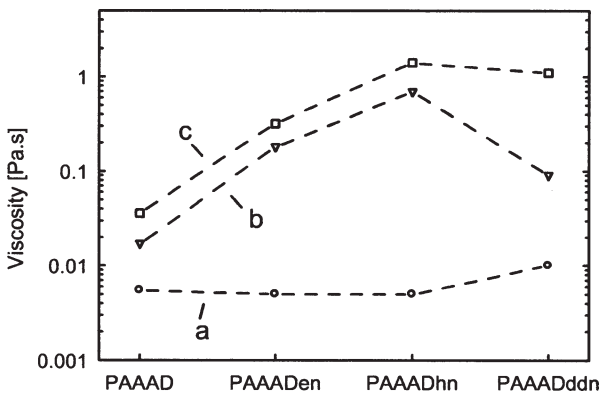


Figure 2. 2D ^{1}H NOESY NMR spectrum of PAAADhn and 66βCD_2su with equimolar βCD groups and adamantyl substituents.

The cross-peaks enclosed in rectangles A and B arise from interactions between the annular $H^{3,5,6}$ of 66βCD_2su and the adamantyl H^{2-4} and the hexyl tether protons, respectively.

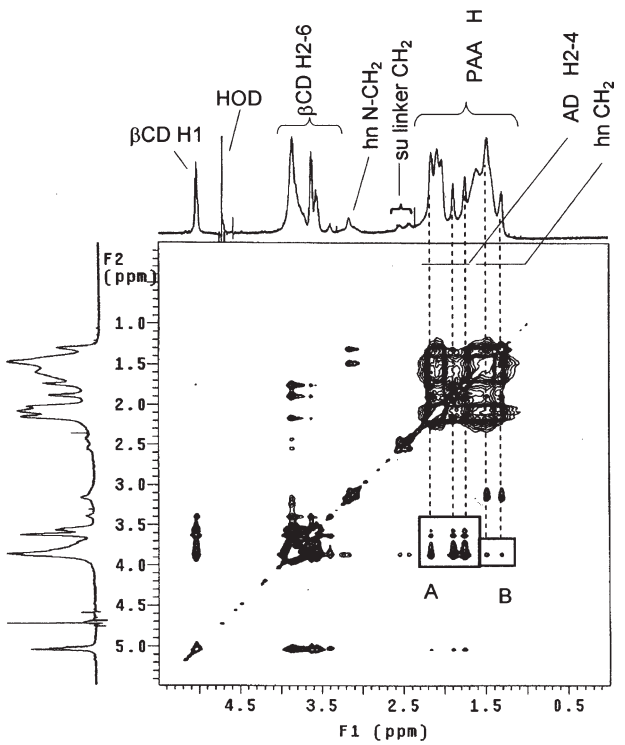
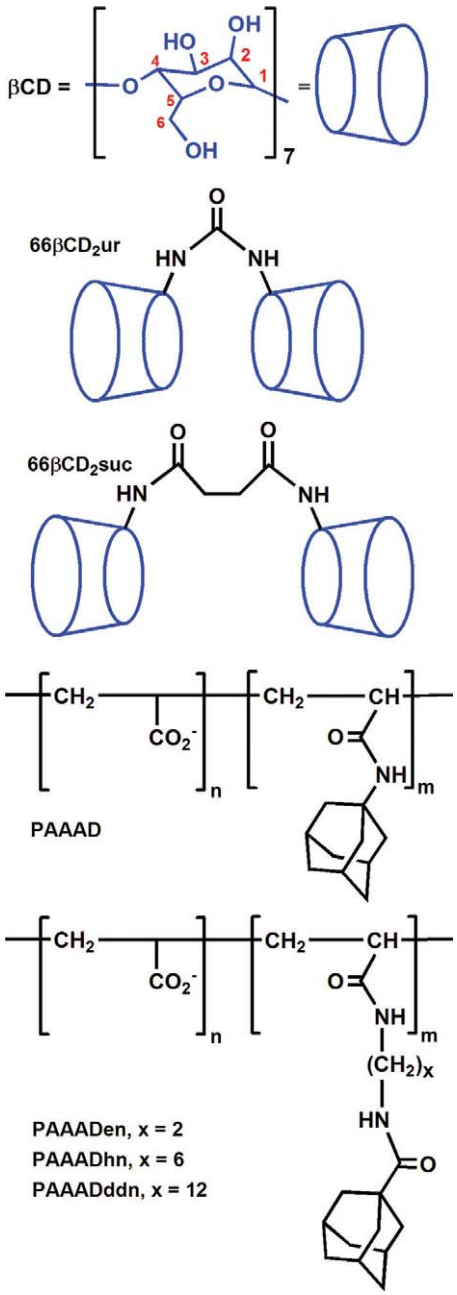


Figure 3. Schematic illustration of the competitive host-guest complexation in which either the adamantyl substituent (in red) or the alkyl tether (in green) guest in the βCD annuli to form a polymer network.

Photos are 20% PAAADhn solution (left) and its binary mixture (right) with a 1.5 molar equivalent concentration of 66βCD_2su.

Conclusions

Three conclusions are drawn from the viscosity and ^{1}H NMR data. First, the greater length of the linker in 66βCD_2su by comparison with that of 66βCD_2ur, results in higher viscosities and stronger polymer networks. This probably arises from a combination of an averaged greater distance between adjacent poly(acrylate) backbones, and a of lessening the steric interactions



Scheme 2. The dominant species in solution in equimolar solutions of either PAAAD, PAAADen, PAAADhn or PAAADddn, and between either 66βCD2ur or 66βCD2su.

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between them and the longer linker allowing greater flexibility to form host-guest complexes. Second, the increasing length of the adamantyl tether from PAAAD to PAAADhn also progressively decreases steric hindrance between the poly(acrylate) backbones as tether length and ease of host-guest complexation increases and polymer network formation strengthens. Third, the decrease in viscosity with increase in tether length in PAAADddn, which is paricularly marked for the PAAADddn/66βCD$_2$ur binary system, may be partly attributable to the increased flexibility allowed in the poly(acrylate) network when adamantyl host-guest complexation occurs. The effect of the isomeric dodecyl tether host-guest complexation on viscosity is less certain. Clearly, the seperation between the poly(acrylate) backbones decreases and steric hindrance between them increases when such complexation involves one or both annulii of either 66βCD$_2$su or 66βCD$_2$ur, as shown in Figure 3. The net effect of this competition between the isomeric host-guest complexations is smaller for the PAAADddn/66βCD$_2$su binary system, possibly because of the greater length of the linker between the two βCD host annulii.

Acknowledgments

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