Novel Supramolecular Hydrogels as Artificial Vitreous Substitutes

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Summary: The possibility of employing self-healing gels as potential artificial vitreous substitutes is being explored. Advancement of traditional synthetic hydrogels as vitreous substitutes is hindered by their fragmentation upon injection into the vitreous cavity leading ultimately to inflammation. Preliminary work involved developing first generation self-healing gels, using amphiphilic tri-block copolymers of poly(propylene glycol)-*block*-poly(ethylene glycol)-*block*-poly(propylene glycol) (PPG-PEG-PPG) as the building block. Eight linear self-healing gels are synthesized by tethering an ureidopyrimidinone system to synthetically modified PPG-PEG-PPG via the formation of a bis-urea as a linker. The reversible nature of the hydrogen bonds permits alteration of their physical properties by changing the environment, yet retaining desirable characteristics. Despite low solubility in water, these polymers demonstrated associating behaviour under the investigated conditions, which is encouraging. Future generations of self-healing gels should involve the selection of a more hydrophilic core and/or star-like polymers to facilitate gel formation and strengthen the network.

Keywords: amphiphilic; gels; hydrogen bonding; tri-block copolymers; ureidopyrimidinone

Introduction

Temporary or permanent vitreous replacements play a vital role in the treatment of various ophthalmic diseases. These replacements often take the form of liquid or solutions of polymers injected into the eye cavity. However, the fragmentation of synthetic polymers upon injection causes post-operative complications such as opacification and inflammation.[1,2] To eliminate this problem, eight self-assembling, supramolecular polymers were synthesized for evaluation as potential artificial vitreous substitutes with self-healing capacity (Figure 1). These linear polymers were obtained by modifying the end groups of commercially-available PPG-PEG-PPG having different chain lengths, molecular weights and poly(propylene glycol) (PPG)/poly(ethylene glycol) (PEG) ratios.

The stability of the inter-polymer association is increased with the incorporation of PPG, which is expected to stabilize the hydrogen bonding in water by hydrophobic interactions. The formation of the hydrogel is aided by incorporating hydrophilic PEG oligomers in the molecule.

The quadruple hydrogen bonding motif of 2-ureido-4[1*H*]-pyrimidinone (UPy) (Figure 2) is designed to form strong dimers [dimerization constant (K_{dim}) = 10^7 L mol^{-1} in chloroform at 25 °C], and hence employed as the gelating group.[3] The specific interaction of the UPy units produces a reversible hydrogel network. The reversible behaviour of these gels is

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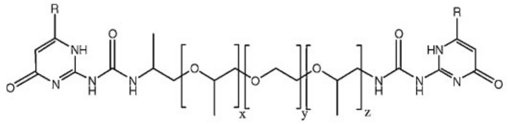

Polymer 1: 2,000 g/mol, 50 % PPG
Polymer 2: 3,300 g/mol, 90 % PPG
R = Methyl (M), Propyl (P),
Isopropyl (I), Adamantyl (A)

Figure 1.
The structure of UPy-modified main-chain polymers as hydrogelators.

expected to permit intraocular injection without causing permanent fragmentation of the network, as the gel fragments can rejoin due to the regeneration of hydrogen bonds.

To prevent disruption of the hydrogen bonds by the water molecules, alkyl substituents with increasing shielding ability [R = methyl (M), propyl (P), isopropyl (I) and adamantyl (A)] were introduced at position 6 of the pyrimidinone ring, while PPG of various chain lengths adjacent to the UPy were employed (Figure 2). For simplicity, the molecules formed by coupling PPG-PEG-PPG of 2,000 g mol^{-1} and 3,300 g mol^{-1} to UPy having R = methyl (M) are denoted as 2M and 3M, respectively. The same coding system will be adopted throughout this article.

Association/Disassociation Behaviour

The association/disassociation behaviour of the UPy groups was studied by ^{1}H NMR spectroscopy under a range of conditions (concentration, temperature and solvent). The lowest concentration for which hydrogen bonding was observed was determined as being 5 mM and this concentration was used for subsequent studies.

The broadening and reduced intensities of the peaks due to NH$_{a\text{-}c}$ ($\sim$13, 12, 10 ppm) upon heating, as shown in Figure 3, reveals reduced hydrogen bonding behaviour at increased temperatures, and is evident in all samples. At 50 °C, the different relative intensities of the peaks of NH$_{a–c}$ for 3M and 3A, respectively, (Figure 3, circled) could suggest the presence of two tautomeric forms, contributed by the different alkyl substituents (Figure 4).

The appearance of peaks due to NH$_{a\text{-}c}$ ($\sim$8.0, 9.5, 11.5 ppm) in deuterated dimethyl sulfoxide (DMSO-d_6), shown in Figure 5, demonstrates hydrogen bonding in the presence of a strong proton acceptor solvent and trace amounts of water. A greater upfield shifting of the peak due to NH$_{a\text{-}c}$, when compared to CDCl$_3$ however, indicates weaker association.[4] The down-

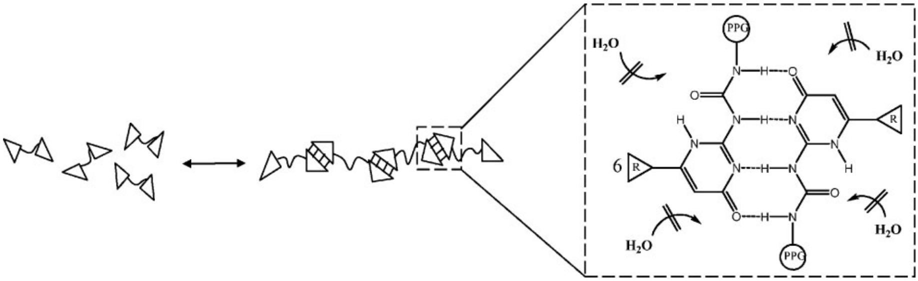

Figure 2.
Schematic diagram of the self-healing hydrogels. By employing different R groups and PPG to shield water molecules, the hydrogen bonds are kept intact.

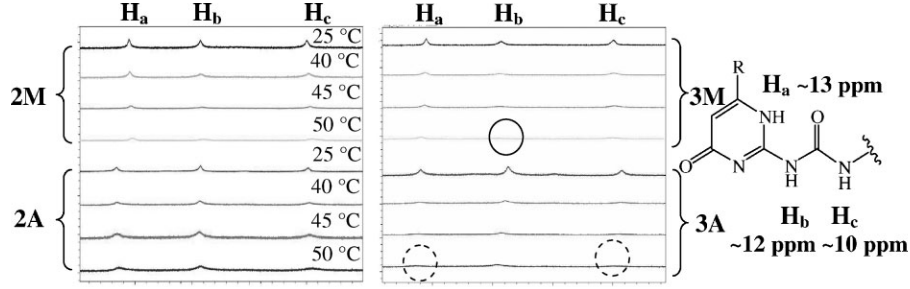

Figure 3.
Partial stack plot of ^{1}H NMR spectra of UPy-modified polymers in deuterated chloroform ($CDCl_3$), 5 mM, 25 °C. The assigned ^{1}H NMR chemicals shifts of H_{a-c} are also shown.

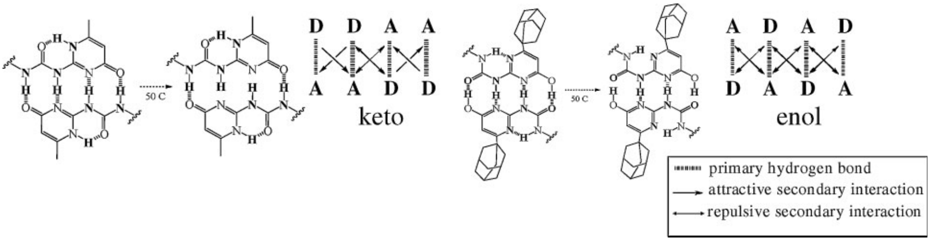

Figure 4.
The stability of the tautomers is dominated by the arrangement of donor (D) and acceptor (A). In the keto confirguration (DDAA array), the presence of less unfavourable repulsive interactions results in a more stable tautomer as compared to the enol form.

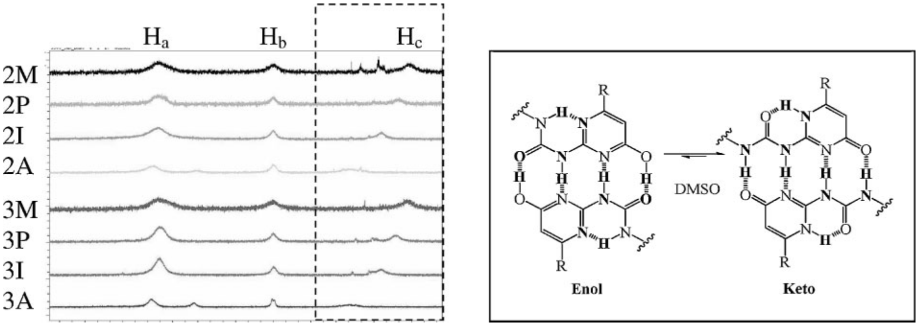

Figure 5.
(Left) Partial stack plot of ^{1}H NMR spectra of UPy-modified polymers in DMSO-d_6, 5 mM, 25 °C. The downfield shifting of peaks due to H_c across different alkyl substituents indicates stronger association hence increasing shielding ability. (Right) Proposed enol and keto tautomeric configurations under solvent influence.

field shift of the peak due to NH_c (Figure 5, boxed) suggests that the shielding capacity increases in the following order:

This trend could also reveal the changing of tautomeric configuration from a less stable enol (more upfield) to a more stable keto form (more downfield), as represented in Figure 5.

Conclusion

The UPy-modified linear tri-block copolymers have demonstrated a range of hydrogen bonding behaviours under the investigated conditions. Gelation behaviour was not observed, perhaps due to the high level of PPG, leading to low hydrophilicity of these polymers in aqueous environment.

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