

Urea-bearing copolymers for guest-dependent tunable self-assembly†

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RAFT polymerization was used to synthesize urea-bearing methyl methacrylate copolymers for binding carboxylate isosteres.

Supramolecular polymers are emerging as a promising class of materials for a broad range of applications, including thermo-plastic materials¹ and as frameworks toward device fabrication.² The self-assembly of these materials is driven by noncovalent forces³—including electrostatic, hydrogen bonding, metal coordination, and van der Waals interactions—to afford noncovalent networks tunable in strength and reversibility.⁴ Polymers bearing pendant molecular recognition elements are an important subset of these materials.^{5–10} For example, Schubert and Hofmeier⁵ synthesized methyl methacrylate copolymers bearing terpyridyl functionalities to create reversible supramolecular networks in the presence of Fe²⁺ or Zn²⁺ ions. Other researchers have utilized noncovalent interactions to alter the miscibility of polymer blends which are typically immiscible.⁶

Two approaches are possible in the formation of molecular recognition-bearing polymers: (1) post-modification of a polymer backbone containing reactive side groups, and (2) the polymerization of a molecular recognition-containing monomer. Rotello and co-workers⁷ have derivatized polystyrene-based random and block copolymers with hydrogen bonding units for the formation of micelles and vesicles, using the post-modification approach. Alternatively, there have been significant contributions by Weck and co-workers⁸ who demonstrated the ring-opening metathesis polymerization (ROMP) of monomers bearing hydrogen bonding and metal coordination elements. While many of these polymers have been synthesized using radical polymerization schemes,⁹ there has been less attention to employing controlled metal-free radical polymerization routes,¹⁰ such as reversible addition–fragmentation chain transfer (RAFT) polymerization¹¹ and nitroxide mediated polymerization (NMP).¹²

The choice of molecular recognition functionalities employed is a key component of supramolecular polymers. Urea functionalities are one example that have been utilized to form supramolecular polymers and polymeric networks *via* self-recognition—*i.e.*, urea functionalities interacting with other urea functionalities (A–A system)—particularly by Meijer and co-workers (Fig. 1).¹³ Ureas are known,¹⁴ however, to bind carboxylate derivatives and their isosteres (such as sulfonates, phosphonates, and phosphates), and have been incorporated into host molecules for binding anion guests.¹⁵ These noncovalent interactions employ ion–dipole forces

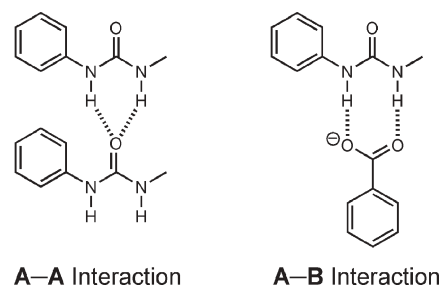
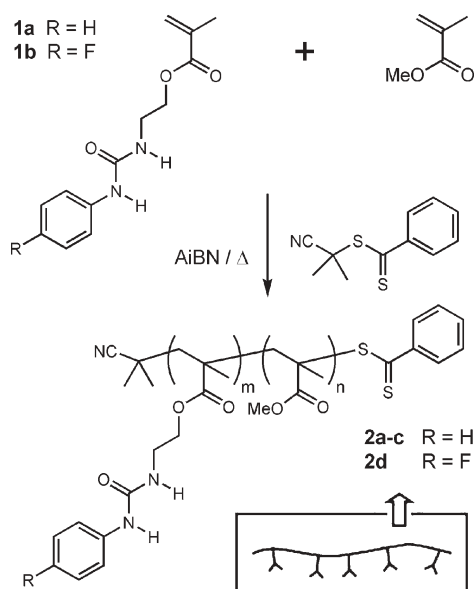


Fig. 1 A–A and A–B interactions with urea functionalities.

in concert with hydrogen bonding—and are effective in a range of hydrogen bonding and non-hydrogen bonding solvents. Herein, we present (Scheme 1) the controlled radical copolymerization of methyl methacrylate and a urea-bearing methacrylate monomer—*via* RAFT polymerization—for binding a range of carboxylate isosteres.

The urea-containing monomers **1a** and **1b** are easily synthesized from the commercially available isocyanatoethyl methacrylate in the presence of aniline or 4-fluoroaniline, respectively. Both monomers are purified by recrystallization, and, thus, do not require any chromatography (ESI†). The fluorine in the *para*-position of **1b** was added both to increase the binding strength of the urea, and also as an ¹⁹F NMR probe to observe the binding of guests.

Copolymerization of methyl methacrylate (MMA) with the urea-containing monomer **1b** was investigated using a 122 : 12 : 1



Scheme 1 Polymerization by RAFT.

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ratio (methyl methacrylate : **1b** : cyanoisopropyl dithiobenzoate chain transfer agent) in DMF-*d*₇ at 65 °C. The relationship between the molecular weight (M_n) and the percent conversion is linear, which suggests that the polymerization is a controlled living process (ESI†). Moreover, the linearity of the semilogarithmic kinetic plot suggests a constant concentration of active radical species during the polymerization. The polydispersity index (PDI) was low, with the highest value being 1.14 at near full conversion. Several polymers, varying in composition and molecular weight, were synthesized (Table 1) by altering the monomer-to-initiator ratio and/or the methyl methacrylate to urea-bearing methacrylate ratio. The incorporation of the urea-bearing monomer **1a** or **1b** into the polymer backbone was verified by ¹H NMR spectroscopy. The percent incorporation of **1a** into **2a** and **2b**, and **1b** into **2d**, was consistent with the initial composition of **1a/b** and methyl methacrylate in the reaction mixture. However, in cases where the composition of **1a/b** in the reaction was greater than 10%, the polymerization rate was greatly diminished, resulting in a bimodal distribution of polymers and a lower yield of polymer **2c** (ESI†). These data suggest that, while both **1a** and **1b** have similar reactivities to methyl methacrylate, the intermolecular hydrogen bonding interactions of the urea moieties can hinder the polymerization.

The polymers were soluble in a range of polar and nonpolar solvents. In non-hydrogen bonding solvents such as CDCl₃, the urea N–H resonances in the ¹H NMR spectrum (10 mM of the urea side chain, 298 K) were significantly broad and flattened, suggesting their involvement in inter- and intramolecular hydrogen bonding interactions with other urea functionalities or methyl ester groups of the polymer backbone. While the polymer is initially soluble in CDCl₃, a precipitate—likely arising from the aggregation of polymer chains *via* intermolecular interactions—was observed in the solution after a period of two days. The formation of aggregates was reversible, and the solution became homogeneous with heating. However, in DMSO-*d*₆, the polymers are readily soluble and the N–H resonances were present as distinct broad singlets due to the solvation of the urea functionalities by solvent molecules.

The binding properties¹⁶ of the copolymers were determined in DMSO-*d*₆ by ¹H NMR spectroscopy (and ¹⁹F NMR spectroscopy in the case of polymer **2d**). This solvent was chosen for our investigations for two reasons: (1) the urea–urea interactions are negligible in this solvent,¹⁷ and (2) the guest molecules **3a–c** (as their tetrabutylammonium salts) are readily soluble in DMSO-*d*₆ but not CDCl₃. As representative examples for the binding studies, polymers **2a** and **2d** (M_n = 22.1k and 17.0k, respectively) were investigated. Titration of a solution of guest **3a**, **3b**, or **3c** (Fig. 2) into the host copolymer **2a** resulted in a downfield shift of the

Table 1 Characterization of polymers

Polymer	$M_n \times 10^{-3}/$ g mol ⁻¹ ^a	PDI ^a	MMA monomer : urea-MMA monomer	Urea composition in polymer (%) ^b
2a	22.1	1.09	20:1	4.5
2b	10.3	1.10	10:1	10.1
2c	4.6	1.16 ^c	8:1	23.5
2d	17.0	1.06	20:1	4.7

^a Determined by GPC in THF. ^b Determined by ¹H NMR spectroscopy. ^c Bimodal distribution (see ESI).

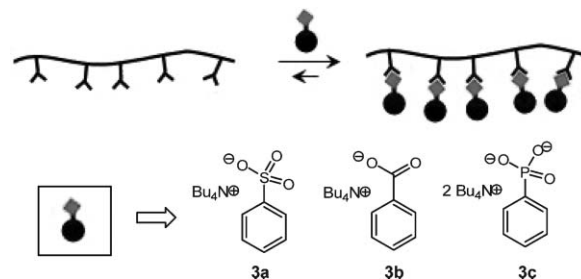


Fig. 2 Sulfonate **3a**, carboxylate **3b**, and phosphonate **3c** guests for binding urea-bearing polymers.

Table 2 Association constants (K_a) for monomer **1a** and polymers **2a** and **2d** (10 mM solutions in DMSO-*d*₆ with respect to urea functionalities) for binding to guest molecules **3a–c**

Guest	K_a for 1a /M ⁻¹ ^a	K_a for 2a /M ⁻¹ ^a	K_a for 2d /M ⁻¹ ^a	K_a for 2d /M ⁻¹ ^b
3a	>10	>10	>10	>10
3b	149	117	145	146
3c	3010	2970	— ^c	— ^c

^a The K_a values were determined by ¹H NMR spectroscopy (400 MHz, 298 K) titration experiments and the data were analyzed using the NMR-Tit¹⁸ curve-fitting program. ^b The K_a values were determined by ¹⁹F NMR spectroscopy (376 MHz, 298 K) titration experiments and the data were analyzed using the NMR-Tit¹⁸ curve-fitting program. ^c Decomposition of the urea functionalities was observed.

N–H resonances (6.01 and 8.56 ppm) of the urea functionalities. The NMR-Tit curve-fitting program¹⁸ was used to determine the association constants (K_a) for the 1 : 1 interactions between guests and receptors (Table 2).¹⁹ The binding affinity was dependent upon the guest molecule, with the order of K_a 's from weakest to strongest being: sulfonate **3a** < carboxylate **3b** < phosphonate **3c**. Kelly and Kim,¹⁴ in the investigation of their urea-based anion receptors, noted the same trend for the binding of carboxylate isosteres, which correlates to the pK_b of the guest ion—as the basicity of the anion increases, the strength of the interaction increases. Interestingly, the association constants observed for the binding of each guest to the polymer-bound urea are of the same order as the individual urea–guest interactions (Table 2). And thus, the strength of the molecular recognition is only slightly mitigated by having the urea component attached to the polymer backbone.

Copolymer **2d**, which contains a fluorophenyl urea, was also investigated for its binding to the guest molecules. The fluorine atom was sensitive to the binding of the guest and could be observed by ¹⁹F NMR spectroscopy. The shift of the fluorine signal with the titration of guest, was used to determine the K_a 's for the binding of guests **3a** and **3b**. The association constants determined by ¹⁹F NMR spectroscopy for guests **3a** and **3b** were consistent with the values obtained by ¹H NMR spectroscopy. In the presence of guest **3c**, the ¹⁹F NMR spectrum became increasingly complex—with the appearance of several new resonances—which is indicative of the decomposition of the urea functionalities. This phenomenon has been observed previously—Gale, and Amendola *et al.* have both noted previously²⁰ that electron withdrawing substituents increase the acidity of the urea protons, thus making them more susceptible to deprotonation by basic anions.

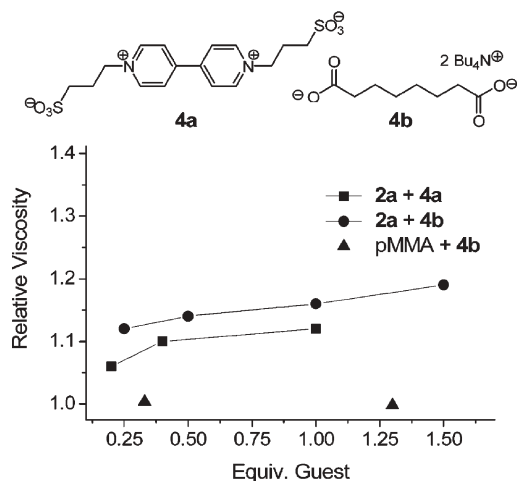


Fig. 3 Solution viscosity measurements at 26 °C of **2a** and pMMA ($M_n = 15.1k$, PDI = 1.10) in DMSO (20 g L^{-1}) with increasing amounts of divalent **4a** or **4b**. The relative viscosity was determined using polymer **2a** as the reference. Equivalents of guest is relative to urea units on the polymer.

Solution viscosity measurements using disulfonate **4a** and dicarboxylate **4b** were measured in order to investigate the supramolecular crosslinking of the polymer chains. As shown in Fig. 3, the viscosity of a solution of polymer **2a** (20 g L^{-1} in DMSO) increases with the addition of divalent guest **4a** or **4b**. The increase in viscosity observed with polymer **2a** is consistent with an increase in molecular weight due to supramolecular crosslinking of the polymer chains. In comparison, when the divalent **4b** is added to a pMMA homopolymer a viscosity response is not observed. Changes in the viscosity are also related to the strength of the noncovalent interaction—smaller changes were observed with disulfonate **4a** than dicarboxylate **4b**. This result parallels the weaker urea–guest interactions observed with sulfonate **3a** than carboxylate **3b** by NMR spectroscopy.²¹

In conclusion, we have investigated the synthesis of methacrylate copolymers bearing pendant urea groups using RAFT polymerization. Copolymers containing up to 10 mol% of the urea functionality were synthesized in a controlled living process to afford polymers with defined molecular weights and low PDI's. The molecular recognition elements employed in this paper can all be synthesized relatively easily. The urea-containing methyl methacrylate monomers were synthesized and isolated with minimal purification required. Since urea functionalities interact with carboxylate anions and its isosteres with varying degrees of strength, a route for tuning the strength of these interactions has been developed.

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