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Synthesis of Novel Polymer/Urea Peptoid Conjugates Using RAFT Polymerization

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ABSTRACT: The synthesis of novel urea peptoids and their conjugation to polymers prepared using reversible addition−fragmentation chain transfer (RAFT) polymerization is reported. Statistical copolymers of poly(styrene-*co*-3-azidopropyl methacrylate) (poly(styrene-*co*-AzPMA)) and poly(3-*O*-methacryloyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose-*co*-AzPMA) (poly(MAIpGlc-*co*-AzPMA)) were synthesized with high molecular weight and narrow molecular weight distributions. The polymer conjugates were formed using copper-catalyzed azide/alkyne cycloaddition chemistry and confirmed by FTIR and ^{1}H NMR spectroscopy. Following conjugate formation with poly(MAIpGlc-*co*-AzPMA) and the urea peptoid the isopropylidene groups were removed using dilute trifluoroacetic acid. This yielded a sugar functionalized water-soluble, polymer/urea peptoid conjugate. Reactions with fluorescent compounds demonstrated that the peptoids can be further modified after conjugation to the polymer.

Introduction

While the synthesis of new macromolecules and materials has advanced dramatically in recent years, the challenge of preparing "tailor-made materials" continues. In meeting this goal, it has been recommended that chemistries with increased synthetic precision and control of multiple functionality using simple, robust protocols need to be developed.[1] As part of our approach in synthesizing polymers using these principles, we have become interested in a class of peptidomimetics known as urea peptoids.[2] Many classes of peptidomimetics have been developed including N-substituted glycines (peptoids), oligocarbamates, hydrazinopeptides, oligosulfones, and (α−β unsaturated) peptidosulfonamides.[3] For comparison, the peptide, peptoid, and urea peptoid structures are shown in Figure 1. The resistance of peptoids to enzymatic degradation compared to peptides and the hydrogen-bonding properties of the urea peptoid backbone open areas of research including folded and helical structures.[4] Fischer and co-workers[5] suggested that four urea units may initiate folding, while Violette and co-workers[6] reported seven residues can form a stable helix. Our interest primarily stems from the fact that urea peptoids are attractive compounds due to their ease of synthesis and ability to incorporate a large number of diverse and functional side groups.

Coupled with the goal of "tailor-made materials" is the increasing interest in complex polymers containing biological groups, i.e., peptide- and protein-conjugates to make new "chimera" materials.[7−9] While not the only polymerization technique used for the synthesis of polymer conjugates, reversible addition−fragmentation chain transfer (RAFT) polymerization has proven adept for this purpose.[10] RAFT polymerization has the benefits of being highly controlled, tolerant of a large number of functional groups, and the ability to be conducted in a variety of media.[11−13] Börner[14] prepared a RAFT chain transfer agent (CTA) coupled to the N-terminus of a GGRGDS peptide sequence. Polymerization of *n*-butyl acrylate (*n*BA) afforded a polymer with one peptide sequence as an end-group. Wiss and co-workers[15] conjugated an activated ester functional RAFT CTA to a collagen-like peptide. The subsequent polymer−peptide conjugate exhibited triple-helical structure showing that the self-assembly properties of the peptide remained intact. In an alternative strategy RAFT polymers with a pyridyl disulfide end-group have been used to conjugate a hexapeptide.[16] Peptides can also be conjugated to the polymer backbone using reactive pendant groups; for example, Hwang and co-workers[17] have prepared RAFT polymers with nitrophenyl and protected aldehyde functional monomers for coupling with the tripeptide sequence RGD. *N*-Acryloylsuccinimide polymers have been synthesized by RAFT and used for the conjugation of peptides for anthrax toxin inhibition.[18] Recently, Boyes' group[19] reported conjugation of peptides to RAFT polymers for the preparation of novel targeting/treatment anticancer agents. Fewer examples exist of peptoid−polymer conjugates. Recently, an engineered cationic protein polymer was used as a scaffold for the conjugation of a peptoid as well as other groups.[20] The peptoid was coupled to the lysine residues of the protein polymer using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC) with *N*-hydroxysulfosuccinimide.

Herein we report our first examples of the synthesis of a urea peptoid trimer and its conjugation to polymers prepared using RAFT polymerization and show that the urea peptoids can be further functionalized postconjugation. We have used polystyrene for proof-of-principle purposes and 3-*O*-methacryloyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (MAIpGlc) to demonstrate that this chemistry can easily be coupled with more complex polymers. This is the first report, to our knowledge, of urea peptoid−polymer conjugates and offers a route to diverse polymers combining synthetic precision and control of multiple functional groups with simple, robust modular chemistry.

Experimental Section

All starting reagents were purchased from Aldrich at the highest purity available and used as received unless otherwise stated. *N*-(2-Nitrobenzenesulfonyl)-2-imidazolidone was prepared according to the method of Wilson and Nowick.[2] The RAFT agents *S*,*S*′-bis(α,α′-dimethyl-α″-acetic acid)trithiocarbonate and

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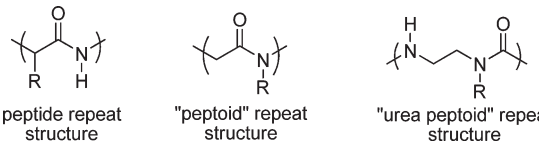


Figure 1. Comparison of a generic peptide, peptoid, and urea peptoid repeat structures.

S-1-dodecyl-*S*′-(α,α′-dimethyl-α′′-acetic acid)trithiocarbonate were prepared in accordance to literature procedures.[21] The sugar functionalized monomer 3-*O*-methacryloyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (MAIpGlc) was prepared following the reports of Fukuda's group.[22,23] The azide-containing monomer 3-azidopropyl methacrylate (AzPMA) was synthesized following literature procedures.[24] Styrene was passed through basic alumina immediately before use.

Compound 1. *N*-(2-Nitrobenzenesulfonyl)-2-imidazolidone (4.00 g, 14.7 mmol) and (dimethylamino)pyridine (DMAP) (0.75 g, 6.1 mmol) were added to a solution of diethylamine (2.90 mL, 29.4 mmol) in 37 mL of pyridine. The reaction flask was sealed with a rubber septum, purged with N_2 for 30 min, and then immersed in preheated oil bath at 50 °C for 6 h. After this time the solvent was removed using a rotary evaporator, the residue dissolved in CH_2Cl_2, and the resulting solution washed with 0.5 M aqueous HCl and dried over Na_2SO_4. The solvent was removed to afford the crude sulfonamide, which was purified by column chromatography using silica gel (silica gel 60 Å, 70−230 mesh) with ethyl acetate:hexane (3:1 v/v) as the mobile phase. The product was dried in a vacuum oven to afford 5.00 g of white solid. Yield: 99%. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.13 (t, J = 7.2 Hz, 6 H, 2 CH_3CH$_2$N), 3.24−3.28 (m, 6 H, 2 CH$_3$CH_2N and CH$_2$CH_2NH-Ns), 3.40−3.42 (m, 2H, CH_2CH$_2$-NHCH$_2$), 4.91 (bs, 1 H, *NH*), 6.14 (bs, 1 H, *NH*CO), 7.73−7.85 (m, 3 H, aromatic H), 8.11−8.14 (m, 1 H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.77 (2 *C*H$_3$CH$_2$N), 40.54 (*C*H$_2$CH$_2$NH-Ns), 41.27 (2 CH$_3$*C*H$_2$N), 44.43 (CH$_2$*C*H$_2$NH-Ns), 125.25, 131.07, 132.75, 133.51, 133.58, 148.12 (aromatic *C*H), 157.54 (*C*ONH). FT-IR (cm^{-1}): $\nu_{(NH)}$ = 3274, $\nu_{(CH)}$ = 2930, $\nu_{(CO)}$ = 1630, $\nu_{(phenyl)}$ = 1544. MS (TOF MS ES+): 345.1473 M + 1.

Compound 2. Compound **1** (2.80 g, 8.1 mmol) was dissolved in 12 mL of *N*,*N*-dimethylformamide (DMF), and K_2CO_3 (2.80 g, 20.3 mmol) and benzyl chloride (5.10 g, 40.5 mmol) were added. The reaction was allowed to proceed at room temperature overnight. The DMF was removed by vacuum distillation, and the residue dissolved in CH_2Cl_2 and passed through Celite. The solution was concentrated and the product isolated by column chromatography using silica gel (silica gel 60 Å, 70−230 mesh) with ethyl acetate:hexane (3:1 v/v) as the mobile phase. The product was dried in vacuum to afford 3.30 g of white solid. Yield: 94% ^{1}H NMR ($CDCl_3$): δ (ppm) 1.13 (t, J = 7.2 Hz, 6 H, 2 CH_3CH$_2$N), 3.22 (q, J = 7.2 Hz, 4 H, 2 CH$_3$CH_2N), 3.31 (dd, J = 5.6, 11.6 Hz, 2 H, CH_2CH$_2$N-Ns), 3.49 (t, J = 5.6 Hz, 2 H, CH$_2$CH_2N-Ns), 4.60 (s, 2 H, N CH_2Ph), 4.67 (s, *NH*), 7.24−7.28 (m, 3 H, aromatic H), 7.36−7.41 (m, 2 H, aromatic H), 7.64−7,71 (m, 3 H, aromatic H), 7.96 (d, J = 7.6 Hz, 1 H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.80 (2 *C*H$_3$CH$_2$N), 38.33 (*C*H$_2$CH$_2$NH-Ns), 41.15 (2 CH$_3$*C*H$_2$N), 47.80 (CH$_2$*C*H$_2$NH-Ns), 51.71 (N*C*H$_2$C$_6$H$_5$), 124.18, 128.08, 128.19 (2 C), 128.59, 128.81 (2 C), 130.97, 131.81, 133.57, 135.56, 147.91 (aromatic *C*H), 157.10 (*C*ONH). FT-IR (cm^{-1}): $\nu_{(NH)}$ = 3349, $\nu_{(CH)}$ = 2973, 2931, $\nu_{(CO)}$ = 1628, $\nu_{(phenyls)}$ = 1538. MS (TOF MS ES+): 435.0002 M + 1.

Compound 3. Compound **2** (3.30 g, 7.6 mmol) was dissolved in 38 mL of DM,F and K_2CO_3 (3.10 g, 22.8 mmol) and benzenethiol (1.70 g, 15.2 mmol) were added. The reaction was allowed to proceed at room temperature overnight. The DMF was removed by vacuum distillation, and the residue dissolved in CH_2Cl_2 and passed through Celite. The solvent was removed to afford the crude secondary amine which was purified using column chromatography on silica gel (silica gel 60 Å, 70−230 mesh) with CH_2Cl_2:MeOH (10:1 v/v) as the mobile phase. The solvent was removed and the product dried in vacuum to yield 1.50 g. Yield: 81%. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.15 (t, J = 7.2 Hz, 6 H, 2 CH_3CH$_2$N), 2.87−2.89 (m, 3 H, CH_2CH$_2$NHCO and *NH*Ar), 3.28 (q, J = 7.2 Hz, 4 H, 2 CH$_3$CH_2N), 3.41 (t, J = 5.4 Hz, 2 H, CH$_2$CH_2NHCO), 3.88 (s, 2 H, CH_2NHBn), 5.28 (s, 1 H, *NH*CO), 7.30−7.39 (m, 5 H, aromatic H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.85 (2 *C*H$_3$CH$_2$N), 39.59 (*C*H$_2$-CH$_2$NHBn), 41.22 (2 CH$_3$*C*H$_2$N), 48.59 (CH$_2$*C*H$_2$NHBn), 52.90 (N*C*H$_2$C$_6$H$_5$), 127.71, 128.64 (4 C), 137.63 (aromatic *C*H), 157.73 (*C*ONH). FT-IR (cm^{-1}): $\nu_{(NH)}$ = 3330 (b), $\nu_{(CH)}$ = 2971, 2930, $\nu_{(CO)}$ = 1618, $\nu_{(phenyl)}$ = 1532, $\nu_{(C=C\ bend)}$ = 742, 698. MS (TOF MS ES+): 250.0874 M + 1.

Compound 4. The procedure is similar to that described for **1**. *N*-(2-Nitrobenzenesulfonyl)-2-imidazolidone (1.95 g, 7.2 mmol) and DMAP (0.37 g, 3 mmol) were added to a solution of compound **3** (1.50 g, 6.0 mmol) in 15 mL of dry pyridine. The reaction was heated at 60 °C overnight. The product was isolated using the method described for compound **1** to generate 2.70 g of **4**. Yield: 87%. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.15 (t, J = 7.2 Hz, 6 H, 2 CH_3CH$_2$N), 3.08 (appear dd, J = 5.6, 8.4 Hz, 2 H, CH_2NC$_5$H$_6$), 3.23−3.29 (m, 6 H, 2 CH$_3$CH_2N and CH_2-CH$_2$NCH$_2$C$_6$H$_5$), 3.34−3.38 (m, 2 H, CH_2CH$_2$N-Ns), 3.45 (appear dd, J = 4.8, 9.6 Hz, 2 H, CH_2N-Ns), 4.51 (s, 2 H, N*C*H$_2$C$_5$H$_6$), 4.70 (s, 1 H, *NH*CO), 7.04 (s, 1 H, *NH*CO), 7.16 (s, 1 H, *NH*-Ns), 7.23−7.27 (m, 3 H, aromatic H from C$_6$H$_5$), 7.30−7.34 (t, J = 7.0 Hz, 2 H, aromatic H from C$_6$H$_5$), 7.71−7.81 (m, 3 H, aromatic H from Ns), 8.15−8.17 (m, 1 H, aromatic H from Ns). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.63 (2 *C*H$_3$CH$_2$N), 39.99 (*C*H$_2$CH$_2$NHBn), 40.78 (*C*H$_2$CH$_2$N-Ns), 41.27 (2 CH$_3$*C*H$_2$N), 44.37 (CH$_2$*C*H$_2$NHBn), 46.57 (CH$_2$-*C*H$_2$NH-Ns), 51.02 (N*C*H$_2$C$_6$H$_5$), 124.89, 127.31, 127.78, 128.58, 130.98, 132.48, 133.24, 134.35, 138.81, 148.05 (aromatic *C*H), 158.16 (*C*ONEt$_2$), 158.59 (*C*ONH). FT-IR (cm^{-1}): $\nu_{(NH)}$ = 3307 (s), $\nu_{(CH)}$ = 2974, 2932, $\nu_{(CO)}$ = 1617, $\nu_{(phenyl)}$ = 1535, $\nu_{(C=C\ bend)}$ = 729. MS (TOF MS ES+): 521.0078 M + 1.

Compound 5. The reaction was performed using the procedure described for compound **2**. A 100 mL round-bottomed flask containing **7** (2.60 g, 5.0 mmol), K_2CO_3 (2.10 g, 15.2 mmol), and CH_3I (3.60 g, 25.0 mmol) in 13 mL of DMF was used, and the product was isolated using the procedure described for compound **2** to yield 2.50 g of product. Yield: 94%. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.11 (t, J = 7.2 Hz, 6 H, 2 CH_3CH$_2$N), 2.95 (s, 3 H, CH_3N), 3.20−3.27 (m, 6 H, 2 CH$_3$CH_2N and CH_2 CH$_2$N C$_5$H$_6$), 3.39 (appear dd, J = 5.6, 10.0 Hz, 4 H, CH_2CH_2N C$_5$H$_6$), 3.47 (appear dd, J = 5.4, 11.0 Hz, 2 H, CH_2N-Ns), 4.51 (s, 2 H, N*C*H$_2$ C$_6$H$_5$), 5.13 (bs, 1 H, *NH*CO), 5.99 (bs, 1 H, *NH*CO), 7.25−7.28 (m, 3 H, aromatic H from C$_6$H$_5$), 7.31−7.35 (m, 2 H, aromatic H from C$_5$H$_6$), 7.63−7.70 (m, 3 H, aromatic H from Ns), 7.96−7.99 (m, 1 H, aromatic H from Ns). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.72 (2 *C*H$_3$CH$_2$N), 34.65 (*C*H$_2$CH$_2$NBn), 36.44 (*C*H$_2$CH$_2$N-Ns), 38.39 (CH$_3$*C*H$_2$N), 39.79 (CH$_2$*C*H$_2$NBn), 40.93 (CH$_3$*C*H$_2$N), 46.80 (CH$_2$*C*H$_2$N-Ns), 49.82 (*C*H$_3$N-Ns), 50.84 (N*C*H$_2$C$_6$H$_5$), 124.06, 127.13, 127.26 (2 C), 128.54 (2 C), 130.48, 131.76, 132.15, 133.63, 138.36, 148.08 (aromatic *C*H), 157.86 (*C*ONEt$_2$), 158.64 (*C*ONH). FT-IR (cm^{-1}): $\nu_{(NH)}$ = 3325, $\nu_{(CH)}$ = 2931, $\nu_{(CO)}$ = 1624, $\nu_{(C=C\ bend)}$ = 728. MS (TOF MS ES+): 535.2339 M + 1.

Compound 6. The reaction was performed using the procedure described for compound **3** using compound **5** (2.40 g, 4.5 mmol), K_2CO_3 (1.90 g, 13.8 mmol), and benzenethiol (0.74 g, 6.8 mmol) in 9 mL of DMF. The product was isolated using the procedure described for compound **3** to yield 1.45 g of **5**. Yield: 92%. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.13 (t, J = 7.2 Hz, 6 H, 2 CH_3CH$_2$N), 2.50 (s, 3 H, CH_3N), 2.88 (t, J = 5.4 Hz, 2 H, CH_2NC$_6$H$_5$), 3.24 (dd, J = 7.0, 14.2 Hz, 6 H, 2 CH$_3$CH_2N and CH_2 CH$_2$NC$_6$H$_5$), 3.38 (t, J = 6.8 Hz, CH_2CH$_2$NHCH$_3$), 3.47 (dd, J = 5.2, 10.8 Hz, CH_2NHCH$_3$), 3.79 (bs, 1 H, *NH*CH$_3$), 4.52 (s, 2 H,

NCH$_2$Bn), 5.19 (bs, 1 H, *NH*CO), 6.46 (bs, 1 H, *NH*CO), 7.24−7.27 (m, 3 H, aromatic H from C_5H_6), 7.34 (t, J = 7.2 Hz, 2 H, aromatic H from C_5H_6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.78 (2 *C*H$_3$CH$_2$N), 34.89 (*C*H$_2$CH$_2$NBn), 39.29 (*C*H$_2$CH$_2$NCH$_3$), 39.80 (CH$_2$*C*H$_2$NBn), 41.16 (2 CH$_3$*C*H$_2$N), 46.88 (CH$_2$*C*H$_2$NCH$_3$), 51.05 (*C*H$_3$NH), 51.16 (N*C*H$_2$C$_6$H$_5$), 127.30 (2 C), 127.34, 128.67 (2 C), 138.25 (aromatic *C*H), 157.86 (*C*ONEt$_2$), 159, 15 (*C*ONH). FT-IR (cm^{-1}): $\nu_{(NH)}$ = 3310, $\nu_{(CH)}$ = 2971, 2931, $\nu_{(CO)}$ = 1616, $\nu_{(C=C\ bend)}$ = 700. MS (TOF MS ES+): 350.1647 M + 1.

Compound 7. The reaction was performed using the procedure described for compound **1** with **6** (1.45 g, 4.3 mmol), *N*-(2-nitrobenzenesulfonyl)-2-imidazolidone (1.4 g, 5.1 mmol), and DMAP (0.26 g, 2.2 mmol) in 10 mL of dry pyridine. The product was isolated using the procedure described for compound **1** to yield 2.1 g of white solid. Yield: 81%. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.11 (t, J = 7.2 Hz, 6 H, 2 C*H*$_3$CH$_2$N), 2.89 (s, NC*H*$_3$), 3.20−3.38 (m, 16 H, 2 CH$_3$*C*H$_2$N and all *C*H$_2$ groups in main chain), 4.55 (s, 2 H, N*C*H$_2$C$_6$H$_5$), 5.00 (bs, 1 H, *NH*CH$_3$), 6.86 (bs, 1 H, *NH*CO), 7.14 (bs, 1 H, *NH*CO), 7.25−7.28 (m, 3 H, aromatic H from C_6H_5) 7.33 (t, J = 6.8 Hz, 2 H, aromatic H from C_6H_5), 7.67−7.77 (m, 3H, aromatic H from Ns), 8.08 (d, J = 9.6 Hz, 1 H, aromatic H from Ns). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.75 (2 *C*H$_3$CH$_2$N), 35.22 (*C*H$_3$N), 39.36 (*C*H$_2$CH$_2$NCH$_3$), 39.63 (*C*H$_2$CH$_2$NBn), 40.68 (*C*H$_2$CH$_2$NH-Ns), 41.11 (*C*H$_2$NCH$_3$), 44.41 (2 CH$_3$*C*H$_2$N), 46.75 (CH$_2$*C*H$_2$NBn), 48.55 (CH$_2$*C*H$_2$-NHNs), 50.79 (N*C*H$_2$C$_6$H$_5$), 124.82, 127.37, 127.42 (2 C), 128.73 (3 C), 130.96, 132.47, 133.28, 134.05, 148.05 (aromatic *C*H), 158.00 (*C*ONEt$_2$), 158.60 (*C*ONBn), 159.70 (*C*ONCH$_3$). FT-IR (cm^{-1}): $\nu_{(NH)}$ = 3326, $\nu_{(CH)}$ = 2930, $\nu_{(CO)}$ = 1616, $\nu_{(C=C\ bend)}$ = 728. MS (TOF MS ES+): 621.1813 M + 1.

Compound 8. The reaction was performed using the procedure described for compound **2** with **7** (1.80 g, 2.9 mmol), K_2CO_3 (0.8 g, 5.8 mmol), and 3-bromopropyne (80 wt % in toluene solution) (2.17 g, 14.5 mmol) in 15 mL of DMF. The product was isolated using the procedure described for compound **2** to yield 1.75 g of yellow oil. Yield: 92%. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.12 (t, J = 7.2 Hz, 6 H, 2 C*H*$_3$CH$_2$N), 2.20 (t, J = 2.0 Hz, 1 H, C≡*CH*), 2.88 (s, 3 H, N C*H*$_3$), 3.21−3.27 (m, 6 H, 2 CH$_3$*C*H$_2$N and C*H*$_2$ CH$_2$N C_5H_6), 3.34−3.45 (m, 8 H, 4 C*H*$_2$ on urea−peptoid main chain), 3.56 (t, J = 5.6 Hz, 2 H, *CH*$_2$N-Ns), 4.28 (d, J = 2.4 Hz, 2 H, *CH*$_2$C≡CH), 4.50 (s, 2 H, N *CH*$_2$ C_5H_6), 5.21 (bs, 1 H, *NH*CO), 5.79 (bs, 1 H, *NH*CO), 6.26 (bs, 1H, *NH*CO), 7.23−7.26 (m, 3 H, aromatic H from C_6H_5), 7.31 (t, J = 7.4 Hz, 2 H, aromatic H from C_6H_5), 7.65−7.69 (m, 3 H, aromatic H from Ns), 8.01 (dd, J = 1.4, 7.4 Hz, aromatic H from Ns). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.76 (2 *C*H$_3$CH$_2$N), 35.02 (*C*H$_3$N), 36.61 (*C*H$_2$CH$_2$-NCH$_3$), 37.97 (*C*H$_2$CH$_2$NBn), 39.72 (*C*H$_2$CH$_2$NNs), 39.88 (CH$_2$*C*H$_2$NCH$_3$), 41.01 (2 CH$_3$*C*H$_2$N), 46.49 (CH$_2$*C*H$_2$NBn), 46.88 (CH$_2$*C*H$_2$NHNs), 48.61 (N*C*H$_2$C≡CH), 50.60 (N*C*H$_2$-C$_6$H$_5$), 74.16 (C≡*C*H), 76.95 (*C*≡CH), 124.13, 127.23, 128.60, 130.77, 131.84, 132.62, 133.73, 138.21, 148.11 (aromatic *C*H), 157.93 (*C*ONEt$_2$), 158.60 (*C*ONBn), 159.32 (*C*ONCH$_3$). FT-IR (cm^{-1}): $\nu_{(NH)}$ = 3303, $\nu_{(CH)}$ = 2932, $\nu_{(C\equiv CH)}$ = 2234, $\nu_{(CO)}$ = 1623, $\nu_{(phenyl)}$ = 1539, $\nu_{(C=C\ bend)}$ = 714. MS (TOF MS ES+): 659.1726 M + 1.

Compound 9. The reaction was performed using the procedure described for compound **3** with **8** (0.85 g, 1.3 mmol) and benzenethiol (0.21 g, 6.8 mmol) in 9 mL of DMF. The product was isolated using the procedure described for compound **3** to yield 0.51 g of yellow oil. Yield: 82%. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.05 (t, J = 7.2 Hz, 6 H, 2 C*H*$_3$CH$_2$N), 2.16 (t, J = 2.4 Hz, 1 H, C≡*CH*), 2.16 (t, J = 5.8 Hz, 2 H, *CH*$_2$CH$_2$NC$_6$H$_5$), 2.86 (s, 3 H, N C*H*$_3$), 3.12−3.35 (m, 18 H), 4.45 (s, 2 H, N *CH*$_2$Bn), 5.45 (bs, 1 H, *NH*CO), 6.12 (bs, 1 H, *NH*CO), 6.78 (bs, 1H, *NH*CO), 7.16−7.21 (m, 3 H, aromatic H from C_6H_5), 7.21−7.27 (m, 2 H, aromatic H from C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 13.74 (2 *C*H$_3$CH$_2$N), 34.96 (*C*H$_3$N), 37.71 (CH$_2$CH$_2$-NCH$_3$), 39.69 (CH$_2$*C*H$_2$NCH$_3$ and *C*H$_2$CH$_2$NBn), 40.24 (CH$_2$*C*H$_2$NBn), 40.97 (2 CH$_3$*C*H$_2$N), 46.46 (*C*H$_2$CH$_2$NHCH$_2$C≡CH), 48.33 (N*C*H$_2$C$_6$H$_5$), 48.39 (*C*H$_2$NHCH$_2$C≡CH), 50.65 (NH*C*H$_2$C≡CH), 71.86 (C≡*C*H), 81.51 (*C*≡CH), 127.24, 127.32, 128.57 (3 C), 138.33 (from 127.24, 6 aromatic *C*H), 157.97 (*C*ONEt$_2$), 159.03 (*C*ONBn), 159.31 (*C*ONCH$_3$). FT-IR (cm^{-1}): $\nu_{(NH)}$ = 3306, $\nu_{(CH)}$ = 2932, $\nu_{(C\equiv CH)}$ = 2125, $\nu_{(CO)}$ = 1610, $\nu_{(phenyl)}$ = 1530, $\nu_{(C=C\ bend)}$ = 700. MS (TOF MS ES+): 474.4474 M + 1.

Synthesis of poly(Sty-*co*-AzPMA). A 100 mL round-bottom flask was charged with styrene (6.90 mL, 60.0 mmol), AzPMA (540.8 mg, 3.2 mmol), *S*,*S*′-bis(α,α′-dimethylacetic acid)trithiocarbonate (89.1 mg, 0.32 mmol), and azobis(isobutyronitrile) (AIBN) (17.3 mg, 0.11 mmol) in 7 mL of anhydrous anisole. The reaction flask was sealed with a rubber septum, and the contents were purged with N_2 in an ice bath for 30 min and then heated for 18 h at 95 °C before being quenched by exposure to air (O_2) and rapid cooling. The polymer was precipitated from hexane and dried in vacuum to afford 5.3 g of pale yellow powder. Isolated yield: 78%. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.47−3.68 (m, 230 H, *CH*$_2$*CH*$_2$N$_3$, protons from polymer backbone and end groups), 4.24 (bs, 2 H, *CH*$_2$O), 6.51−7.13 (m, 328 H, *CH* of phenyl rings). FT-IR (cm^{-1}): $\nu_{(CH)}$ = 2922, $\nu_{(N3)}$ = 2097, $\nu_{(CO)}$ = 1724, $\nu_{(phenyl)}$ = 1601, $\nu_{(CH\ bend)}$ = 538.

Synthesis of Poly(MAIpGlc-*co*-AzPMA). A 100 mL round-bottom flask was charged with MAIpGlc (4.40 g, 13.5 mmol), AzPMA (120 mg, 0.71 mmol), *S*,*S*′-bis(α,α′-dimethylacetic acid)-trithiocarbonate (51.7 mg, 0.142 mmol), and AIBN (1.1 mg, 0.071 mmol) in 5 mL of anhydrous anisole. The reaction flask was sealed with a rubber septum and purged with N_2 in an ice bath for 30 min; the flask was then heated for 6 h at 70 °C before being quenched by exposure to air (O_2) and rapid cooling. The polymer was precipitated from hexane and dried in vacuum to afford 3.5 g of pale yellow solid. Isolated yield: 77%. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.07−1.94 (m, 334 H, *CH*$_2$CH$_2$N$_3$, all *CH*$_3$, protons from polymer backbone and end group), 3.43 (bs, 2 H, *CH*$_2$N$_3$), 4.02−4.90 (m, 98H, 96 O*CH* + 1 O*CH*$_2$CH$_2$CH$_2$N$_3$), 5.83−5.93 (19 H, O*CH*O). FT-IR (cm^{-1}): $\nu_{(CH)}$ = 2987, $\nu_{(N3)}$ = 2100, $\nu_{(CO)}$ = 1731, $\nu_{(CO\ bend)}$ = 1370, $\nu_{(CH\ bend)}$ = 512.

Synthesis of Urea Peptoid/Polymer Conjugates Using Copper-Catalyzed Azide/Alkyne Cycloaddition Reaction. Poly(MAIp-Glc-*co*-AzPMA) (0.75 g, 0.12 mmol of azide), CuBr (11.3 mg, 0.07 mmol), and **9** (61.4 mg, 0.13 mmol) were mixed in 3 mL of CH_2Cl_2 and purged with dry N_2 gas for 30 min. The ligand *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) (40.8 mg, 0.24 mmol) was added to the solution using a syringe, and the solution immediately turned blue. The reaction was stirred overnight at room temperature. After this time the reaction solution was passed through a short silica column to remove the copper complex using CH_2Cl_2/MeOH = 20:1 (v/v) as the mobile phase. The solvent was removed using a rotary evaporator, and the urea peptide/polymer conjugate dissolved in a minimum amount of CH_2Cl_2, precipitated from heptane, and dried in vacuum for 2 days. 0.70 g of the urea peptoid/polymer conjugate poly-(MAIpGlc-*co*-AzPMA)-**9** was obtained. Isolated yield: 87%. ^{1}H NMR (CD_2Cl_2): δ (ppm) 0.84−2.50 (m, 302 H, *CH*$_2$CH$_2$N$_3$, all *CH*$_3$, protons from polymer backbone and end group), 2.75−4.83 (m, 109H, O*CH*, O*CH*$_2$, N*CH*$_2$CH$_2$*CH*$_2$N$_3$, *CH*$_2$N and N*CH*$_3$ in urea peptoid,) 5.77−5.91 (m, 17 H, 16 O*CH*O + 1 *NH*CO), 6.63 (s, *NH*CO), 6.90 (s, *NH*CO), 7.24−7.51 (5 H from phenyl ring +1 H from triazole ring). FT-IR (cm^{-1}): $\nu_{(CH)}$ = 2987, $\nu_{(CO)}$ = 1732, $\nu_{(CO\ bend)}$ = 1373, $\nu_{(CH\ bend)}$ = 512.

Cleavage of Isopropylidenyl Groups from Poly(MAIpGlc-*co*-AzPMA)-9. A solution of 0.10 g of poly(MAIpGlc-*co*-AzPMA)-**9** was stirred for 30 min in 3 mL of trifluoroacetic acid (TFA)/H_2O = 9:1 (v/v). The solution was removed using a stream of dry N_2 gas for 1 h, dried in air for 2 days, and finally dried in vacuum to afford 0.080 g of pale yellow solid. Isolated yield: 99%. FT-IR: (cm^{-1}) $\nu_{(OH)}$ = 3388 (b), $\nu_{(CH)}$ = 2938, $\nu_{(CO)}$ = 1784, 1711, $\nu_{(CO\ bend)}$ = 1144, $\nu_{(CH\ bend)}$ = 510.

Attachment of 5-Carboxyfluorescein to Poly(styrene-*co*-AzPMA)-9. A mixture of 50.0 mg of poly(styrene-*co*-AzPMA)-**9**

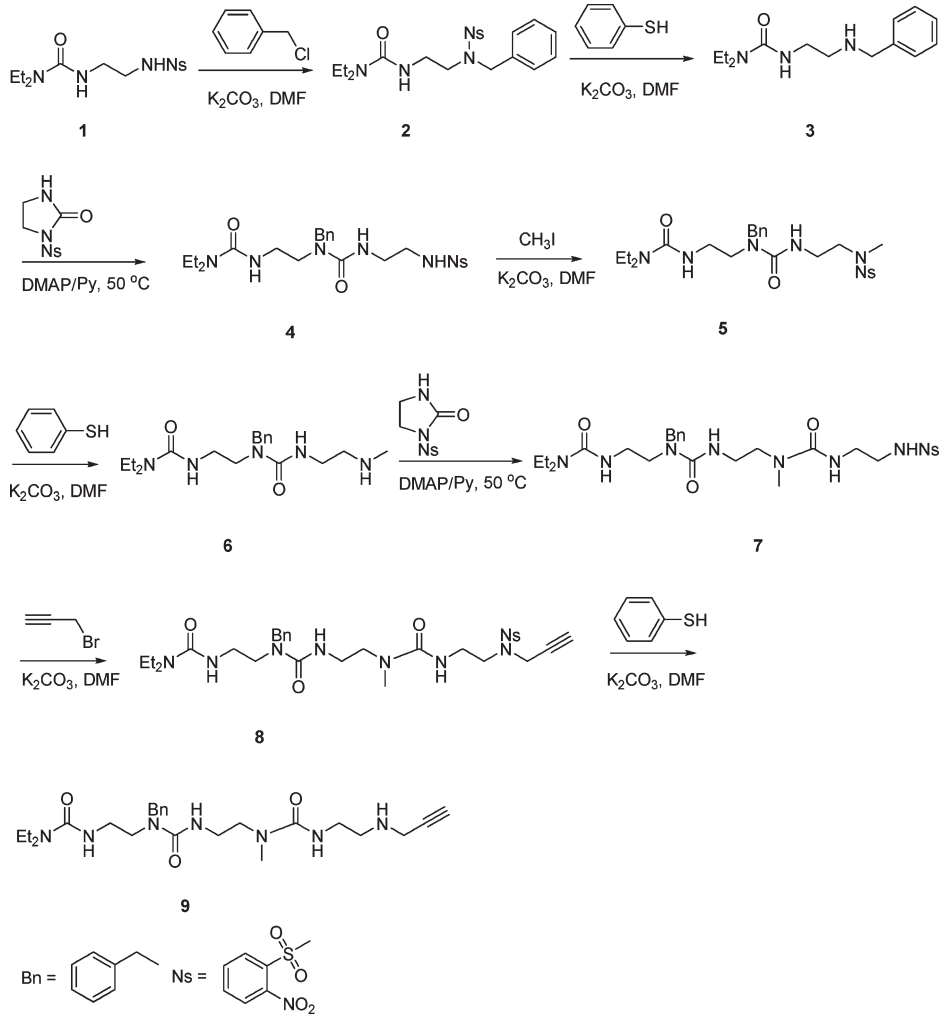


Figure 2. Synthesis of a urea peptoid using an iterative route. Compound **1** is transformed through additions of an alkyl halide (benzyl chloride, methyl iodide, and propargyl bromide), removal of the 2-nitrobenzenesulfonyl (Ns) group with thiophenol, and reactivation with *N*-(2-nitrobenzenesulfonyl)-2-imidazolidone.

(0.014 mmol of NH), 5.8 mg of 5-carboxyfluorescein (0.015 mmol), and 5.8 mg of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (0.028 mmol) in 3 mL of CH_2Cl_2 was stirred under N_2 overnight in a 10 mL round-bottom flask. The reaction was quenched by adding 20 μL of water. The mixture was passed through a short silica gel column to remove unreacted 5-carboxyfluorescein using CH_2Cl_2/MeOH = 20:1 (v/v) as the eluent. The solvent was removed using a rotary evaporator, and the fluorescein attached polymer conjugate dissolved in minimum amount of CH_2Cl_2 and precipitated from heptane to afford 41.7 mg of the final product. Isolated yield: 74%.

Attachment of 3-[4-(Bromomethyl)phenyl]-7-(diethylamino)-coumarin to Poly(styrene-*co*-AzPMA)-9. A mixture of 80.0 mg of poly(styrene-*co*-AzPMA)-**9** (0.022 mmol of NH), 6.7 mg of *N*-(2-nitrobenzenesulfonyl)-2-imidazolidone (0.024 mmol), and 1.4 mg of (dimethylamino)pyridine (DMAP) (0.011 mmol) in 3 mL of pyridine was stirred at 50 °C under N_2 overnight in a 10 mL round-bottom flask. The solvent was removed using a rotary evaporator, and the residue dissolved in CH_2Cl_2, washed with 0.5 M aqueous HCl, and dried over Na_2SO_4. The solvent was removed to afford the crude poly(styrene-*co*-AzPMA)−tetraurea peptoid conjugate, which was purified by column chromatography on silica gel (silica gel 60 Å, 70−230 mesh) using CH_2Cl_2:MeOH (20:1 v/v) as the mobile phase. The polymer solution was dried using a rotary evaporator, dissolved in a minimum amount of CH_2Cl_2, and precipitated from heptane to afford 56.0 mg of intermediate. Next, a mixture of 40.0 mg of the polymer−urea peptoid conjugate activated with the Ns group, 4.6 mg of K_2CO_3 (0.034 mmol), and 4.3 mg of 3-[4-(bromomethyl)phenyl]-7-(diethylamino)coumarin (0.011 mmol) in 3 mL of solvent (DMF/THF = 1:2 (v/v)) was stirred at room temperature overnight. The solvent was removed using a vacuum distillation, and the residue dissolved in minimum amount of CH_2Cl_2 and purified by column chromatography on silica gel (silica gel 60 Å, 70−230 mesh) using CH_2Cl_2:MeOH (20:1 v/v) as the mobile phase. The polymer solution was dried using a rotary evaporator, and the resulting conjugate dissolved in the minimum amount of CH_2Cl_2 and precipitated from heptane to afford 30.8 mg of product. Isolated yield: 34%.

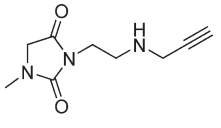
Characterization. ^{1}H and ^{13}C NMR measurements were recorded in $CDCl_3$ and DMSO-d_6 with $Si(CH_3)_4$ as internal standard using a Bruker Ultrashield 400 MHz (100 MHz for ^{13}C). ^{1}H NMR spectra were processed by UXNMR version 2.5 and MestRe-C. Fourier transform infrared (FT-IR) spectra were collected on a Nicolet 6700 spectrometer and analyzed with OMNIC 32 software. Fluorescence and absorbance spectra were performed on Cary Eclipse fluorescence and Cary 50 UV−vis absorbance spectrophotometers. Molecular weights of the statistical copolymers were determined by gel permeation chromatography (GPC) with an Agilent 1100 Series HPLC equipped with a Varian PL gel (5 μm) guard column and two Varian PL gel (5 μm) mixed-C columns (linear rane of MW = 200−2 × 10^6 g/mol) with a filtered tetrahydrofuran (THF) mobile phase at a flow rate of 1.0 mL/min at ambient temperature and miniDAWN TREOS

light scattering (60 mW GaAs linearly polarized laser, 658 nm) calibrated against a 30 000 g/mol polystyrene standard (Wyatt Technology Corp.), Optilab rEX differential refractometer (light source = 658 nm), and Viscostar II viscometer (Wyatt Technology Corp.) detectors. The polymers (~5.0 mg/mL) were dissolved in THF and filtered through 0.2 μm membrane filters. ASTRA software v. 5.4.14 was used to determine molecular weight and polydispersity values. The dn/dc values were determined using the Optilab rEX differential refractometer in offline mode and calculated using Astra software (Wyatt Technology Corp.). Mass spectrometry was performed using a Micromass Q-TOF-2 spectrometer.

Results and Discussion

We prepared urea peptoids in the manner described by Wilson and Nowick.[2] Urea peptoids were chosen as they offer a solution phase synthesis (as opposed to resin bead based[25,26]) where the products can be easily separated and purified using conventional column chromatography. The synthesis of the urea peptoids is simple to perform, iterative in nature, and can be conducted with standard laboratory techniques. The protocol involves three steps: (1) main chain extension, (2) side group attachment, and (3) deprotection. The main chain extension uses a ring-opening reaction of *N*-(2-nitrobenzenesulfonyl)-2-imidazolidone. The structure of this group is shown in Figure 2. Fukuyama's[27] procedure was used for the side group attachment, and the 2-nitrobenzenesulfonyl (Ns) protecting group is removed with thiophenol yielding a secondary amine used in the next iterative cycle. The process is shown in Figure 2. The advantages of Wilson and Nowick's method are that it uses only the imidazolidone and commercially available alkyl halides. Considering the number of alkyl halides available, this gives rise to many potential permutations. This is the basis for our belief that urea peptoids will lead to the facile synthesis of heterogeneous polymers containing multiple functionalities. Additional benefits are that the imidazolidone can be prepared in multigram quantities and stored at room temperature. We selected the side groups used in this study because they are readily identified using NMR spectroscopy allowing for accurate characterization and demonstration of successful coupling to the polymer. We have chosen to couple our urea peptoids and polymers using the facile copper-catalyzed azide/alkyne cycloaddition (CuAAC) reaction and hence have used terminal alkyne moieties in our urea peptoid design.

The synthesis of the urea peptoid trimer **9** is shown in Figure 2. The precursor urea peptoid **1** was chain extended using benzyl chloride, methyl iodide, and 3-bromopropyne to yield **9**. The structure of the final compound was confirmed with ^{1}H NMR spectroscopy which showed the aromatic protons at 7.16−7.21 ppm, the *N*-methyl peak at 2.86 ppm, and the alkyne proton at 2.16 ppm, in conjunction with mass spectrometry that showed a molecular ion peak at m/z 474.45 (calculated m/z = 474.31 M + 1). Urea peptoid **9** serves as a model compound and "proof-of-principle" to demonstrate the versatility in the synthesis of urea peptoids. We have also synthesized a urea peptoid dimer, compound **10** (Figure 3). The synthesis of **10** is described in the Supporting Information.



10

Figure 3. Structure of urea peptoid dimer **10**. The synthesis of **10** is reported in the Supporting Information.

Our initial strategy was to incorporate the sarcosine group into a urea peptoid. However, after extension with 3-bromopropyne we found the product underwent a cyclization reaction. It is known that these types of compounds will undergo cyclization reactions under basic conditions.[28] We removed the Ns group to give the final urea peptoid dimer **10**. The structure of the final compound was confirmed with ^{1}H NMR spectroscopy which showed the *N*-methyl peak at 3.01 ppm and the alkyne proton at 2.23 ppm, in conjunction with mass spectrometry which showed a molecular ion peak at m/z 196.14 (calculated m/z = 196.10 M + 1).

We prepared two statistical copolymers to form the urea peptoid/polymer conjugates: poly(styrene-*co*-AzPMA) and poly(MAIpGlc-*co*-AzPMA). We chose polystyrene for proof-of-principle purposes and poly(3-*O*-methacryloyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose) (poly(MAIpGlc)) to demonstrate that this chemistry can easily be coupled with more complex polymers. Furthermore, following deprotection of the isopropylidine protecting groups the polymer is rendered water-soluble. MAIpGlc is an interesting monomer that has found uses in a range of areas including modifying poly(vinylidene fluoride)[29] and polysulfone membranes,[30] for increased hydrophilicity and nonfouling properties, blood-compatible surfaces,[31] synthesis of core−shell nanoparticles,[32] functionalization of carbon nanotubes,[33] and synthesis of liquid CO_2 amphiphiles.[34] We employed an azide-containing monomer as a comonomer for both polymers to take advantage of copper-catalyzed azide/alkyne cycloaddition reaction in our coupling chemistry. Copper-catalyzed azide/alkyne cycloaddition chemistry has had an enormous impact on polymer chemistry, reflected in the large numbers of original reports and review articles published on this topic in a short space of time.[35,36] Because of the high tolerance for functional groups and conditions, CuAAC chemistry has been readily adapted to include biological molecules.[37] Specific examples include synthesis of glycopolymer conjugates[38,39] and BSA−polymer conjugates.[40] Fewer examples exist of the click reaction being used with peptoid chemistry. Holub and coworkers[41] have used CuAAC chemistry to conjugate peptoid oligomers with 17 α-ethynylestradiol, and CuAAC chemistry has been coupled with N-substituted glycines in the preparation of protein microarrays.[42] The polymerizations were performed under controlled/"living" radical conditions using RAFT conditions. This resulted in the formation of polymers with narrow molecular weight distributions and the potential for formation of block copolymers. For the styrene copolymerization we used the difunctional trithiocarbonate while for the copolymerization of MAIpGlc we used a monofunctional trithiocarbonate. We chose the two different RAFT agents to further show the versatility of our approach. The properties of the two statistical polymers are given in Table 1. We determined the ratio of styrene to AzPMA to be 65:1 and the ratio of MAIpGlc to AzPMA to be 19:1 by ^{1}H NMR spectroscopy. As can be seen from Table 1, the molecular

Table 1. Size Exclusion Chromatography Data for Statistical Copolymers

polymer	dn/dc[a]	M_n[b] (g/mol)	M_w[c] (g/mol)	M_w/M_n	$M_{n,theo}$[d] (g/mol)
poly(Sty-*co*-AzPMA)	0.226	20 000	24 200	1.21	21 800
poly(MAIpGlc-*co*-AzPMA)	0.0963	101 100	107 900	1.07	32 200

[a] dn/dc values were calculated using a Wyatt Optilab rEX detector in offline mode with Astra software. [b] M_n = number-average molecular weight. [c] M_w = weight-average molecular weight. [d] $M_{n,theo}$ = theoretical molecular weight. Theoretical molecular weight = $(([M]_0/[CTA]_0) \times M_r \times p) + M_{CTA}$ where $[M]_0$ = initial monomer concentration, $[CTA]_0$ = initial RAFT agent concentration, M_r = molecular weight of the monomer, p = conversion, and M_{CTA} = molecular weight of the RAFT agent.

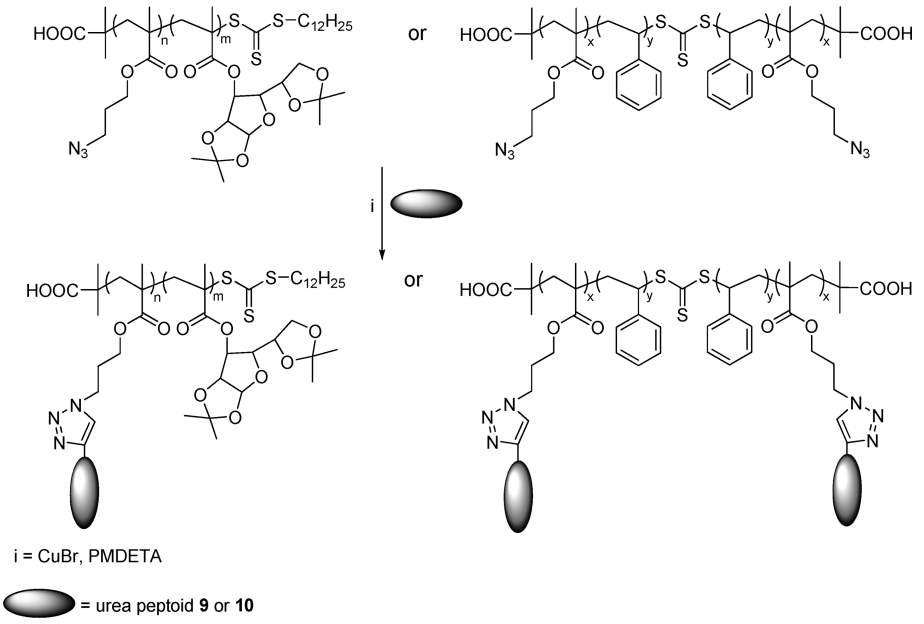


Figure 4. Conjugation of urea peptoids to RAFT polymers using copper-catalyzed azide/alkyne cycloaddition reaction.

weight of poly(MAIpGlc-*co*-AzPMA) was higher than the theoretical molecular weight. We ascribe this difference to loss of the RAFT agent controlling the reaction in the early stages of the polymerization.

We prepared conjugates of urea peptoids **9** and **10** with both azide-functionalized statistical polymers, creating four polymer−urea peptoid conjugates (Figure 4).

The ^{1}H NMR spectrum of poly(MAIpGlc-*co*-AzPMA)-**9** is shown in Figure 5a. We have included the NMR spectra for the conjugation of **10** in the Supporting Information. We further confirmed the formation of the polymer−peptoid conjugates by observing the disappearance of the azide peak at 2100 cm^{-1} in the FTIR spectra of the polymer before and after CuAAC functionalization. To determine the degree of functionalization, we recorded the ^{1}H NMR spectrum of poly(MAIpGlc-*co*-AzPMA)-**9** in CD_2Cl_2 (the spectrum is shown in the Supporting Information). This allowed the integration of peaks originating from the benzene group in the urea peptoid and one proton from the triazole ring between 7.2 and 7.5 ppm from the urea peptoid against the peak due to the proton between the two O atoms on the fused rings from the repeat units of MAIpGlc at 5.79 ppm from the polymer without interference from the NMR solvent. Comparison of the integrals gives a degree of coupling of 16 urea peptoids per polymer chain, which matches the MAIpGlc:AzPMA monomer ratio in the polymer. Therefore, from the NMR data coupled with the FTIR spectra, we believe that the CuAAC reaction is quantitative.

Following the conjugate formation with poly(MAIpGlc-*co*-AzPMA) and **9**, we performed a deprotection reaction to remove the isopropylidene groups using dilute TFA. This yields the water-soluble, sugar-functionalized, polymer−urea peptoid conjugate poly(MAGlc-*co*-AzPMA)-**9**. The deprotection reaction was confirmed using ^{1}H NMR spectroscopy in D_2O. The NMR spectra of the polymer conjugate before and after deprotection are shown in Figure 5a with the corresponding FTIR spectra shown in Figure 6b. The loss of the peaks resulting from the furan ring structure around 6.2 and 4−5 ppm can be seen along with the appearance of a complex multiplet between 3 and 4 ppm from the pyran sugar structure in the ^{1}H NMR spectra. The FTIR spectra show the loss of the peak at 2100 cm^{-1} due to the azide moieties after the conjugation reaction and a large peak at ∼3400 cm^{-1} due to the sugar hydroxyls appearing in the FTIR spectra after removal of the isopropylidene protecting groups.

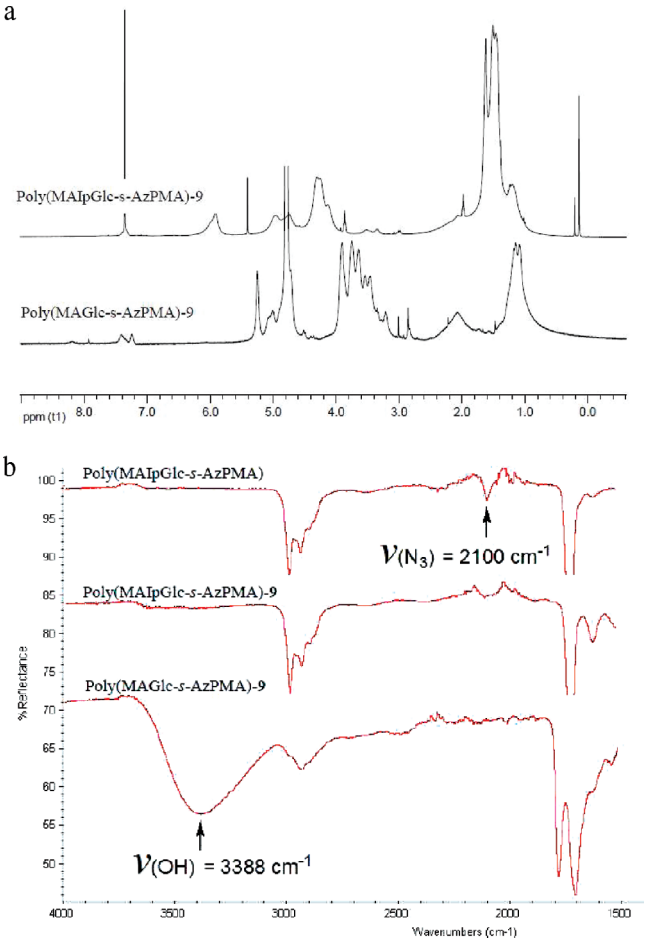


Figure 5. (a) ^{1}H NMR (400 MHz) spectra of poly(MAIpGlc-*co*-AzPMA)-**9** before (in $CDCl_3$) and after (in D_2O) deprotection of isopropylidene groups. (b) FTIR spectra of poly(MAIpGlc-*co*-AzPMA) before and after conjugation to **9** and following deprotection of the isopropylidene groups.

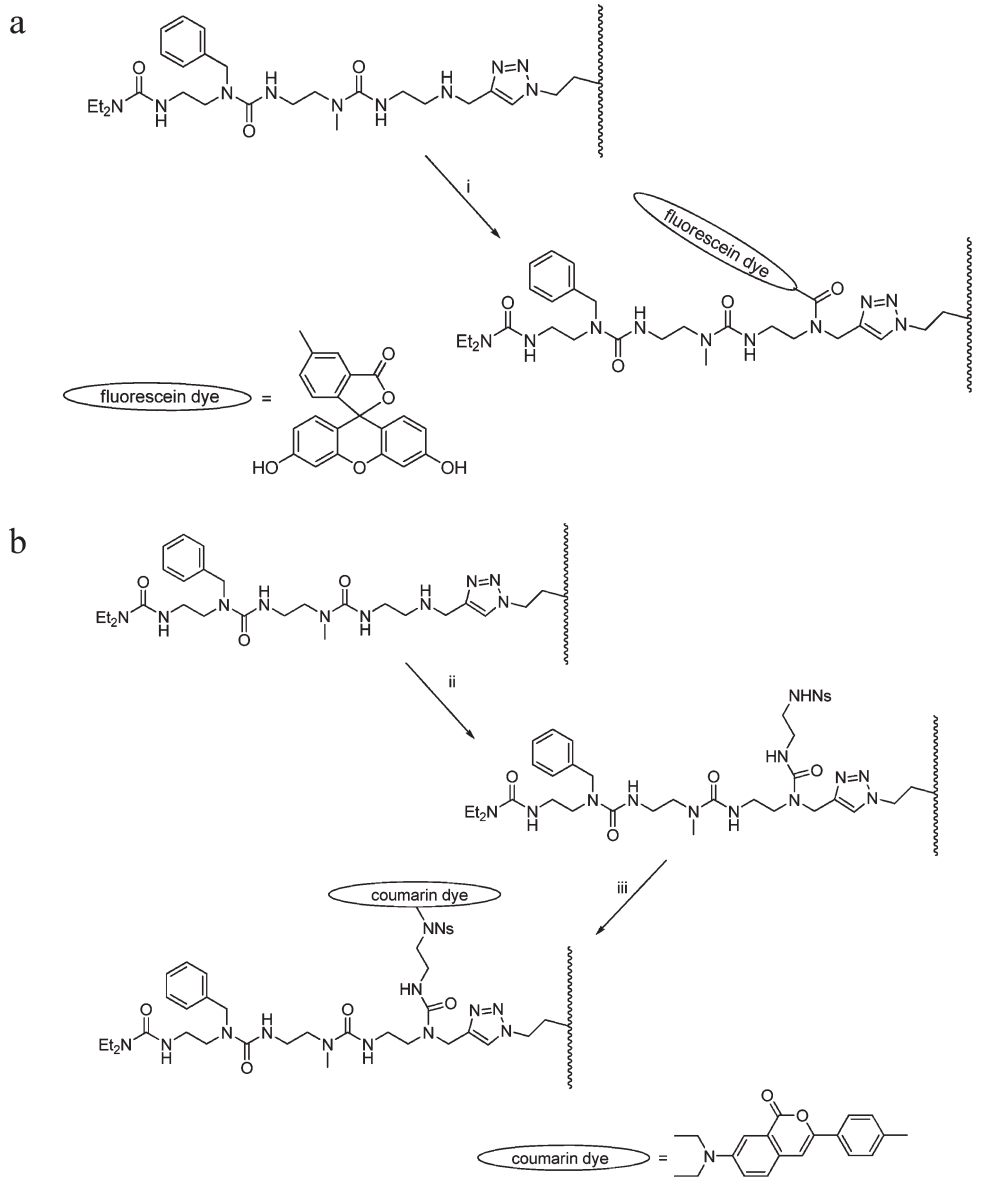


Figure 6. Extension of poly(styrene-*co*-AzPMA)-**9** with (a) 5-carboxyfluorescein and (b) 3-[4-(bromomethyl)phenyl]-7-(diethylamino)coumarin. (i) = DCC, 5-carboxyfluorescein; (ii) DMAP, pyridine, *N*-(2-nitrobenzenesulfonyl)-2-imidazolidone; (iii) 3-[4-(bromomethyl)phenyl]-7-(diethylamino)coumarin, K_2CO_3.

While not ideal for direct comparison, the change in polarity of poly(MAGlc-*s*-AzPMA) after removal of the isopropylidene protecting groups resulted in the use of D_2O as the NMR solvent rather than performing the NMR characterization in $CDCl_3$ for both polymers.

We have shown that the peptoids can be further modified after conjugation to the polymer using reaction with fluorescent compounds. The addition of fluorophores is an effective demonstration that the urea peptoids can be further modified as the polymer/urea peptoid conjugate possesses no innate fluorescence. We have taken two strategies: First, we coupled 5-carboxyfluorescein to poly(styrene-*co*-AzPMA)-**9** directly using DCC coupling chemistry (Figure 6a). Alternatively, we performed an iterative synthesis step of addition and attachment using an alkylbromine-functionalized coumarin derivative (Figure 6b).

Following addition of the fluorescent compounds the polymer/urea peptoid conjugates were strongly fluorescent while the parent polymer conjugates were not. This demonstrates that the urea peptoids are able to be further functionalized postcoupling with the polymer. The fluorescence spectra are shown in Figure 7 with the spectra of the dyes shown as comparison.

We next determined how effective the coupling reaction was to the polymers. This was achieved using UV spectroscopy and preparing a standard concentration curve for each dye. We chose to use UV spectroscopy rather than fluorescence to eliminate concerns about changes in the quantum yield of the fluorophore postcoupling to the urea peptoid/polymer and possible self-quenching effects. Interestingly, both routes appear to give nearly identical coupling efficiencies, with 88% efficiency for the fluorescein carbodiimide coupling and 89% efficiency for the coumarin coupling iteration cycle.

Conclusions

We have demonstrated the combination of a powerful set of reaction strategies (RAFT polymerization, urea peptoid synthesis, and CuAAC coupling reactions) that are both complementary in nature and simple to perform. The reactions are high-yielding, and extension of the urea peptoid sequences can be performed either pre- or postcoupling to the polymer chain. The macromolecular constructs reported here serve as a "first step" toward urea peptoid-containing chimera polymers, and we are

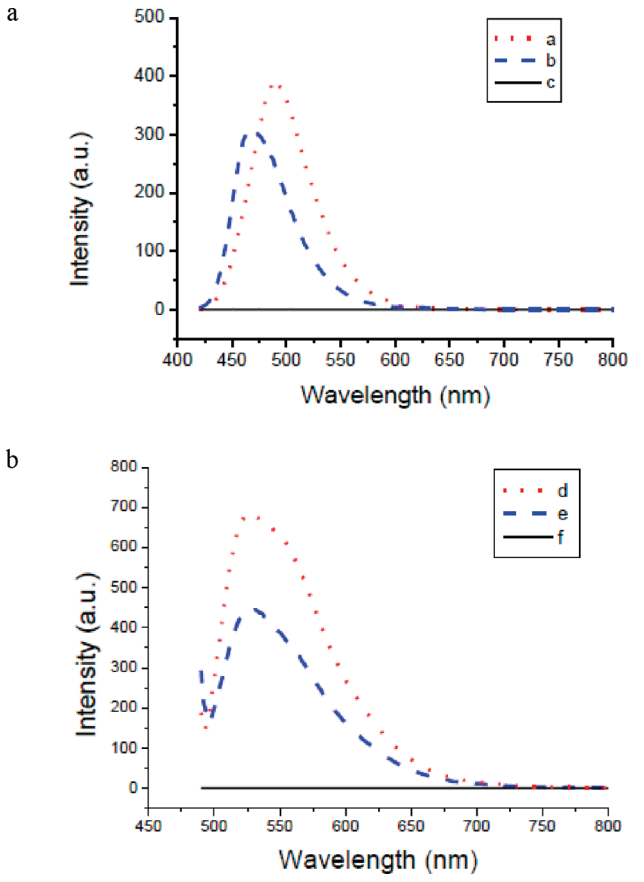


Figure 7. Fluorescence spectra from poly(styrene-*co*-AzPMA)-**9** before and after functionalization with dye molecules. (a, ex: 410 nm): (a) = 3-[4-(bromomethyl)phenyl]-7-(diethylamino)coumarin solution (0.02 mg/mL); (b) = poly(styrene-*co*-AzPMA)-**9**−coumarin conjugate solution (0.2 mg/mL); (c) = poly(styrene-*co*-AzPMA)-**9**. (b, ex: 480 nm): (d) = 5-carboxyfluorescein solution (0.1 mg/mL); (e) = poly(styrene-*co*-AzPMA)-**9**−fluorescein conjugate solution (1 mg/mL); (f) = poly(styrene-*co*-AzPMA)-**9** solution (1 mg/mL).

actively pursuing this modular chemistry for possible applications in nanotechnology, potential therapeutics, and complex fluids.

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Supporting Information Available: Synthesis of urea peptoid **10**; Beer−Lambert plots prepared for fluorescein and coumarin dyes incorporation study; ^{1}H, ^{13}C NMR, and FT-IR spectra of the urea peptoids and GPC traces of the polymers prepared in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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