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Postpolymerization Modification of Hydroxyl-Functionalized Polymers with Isocyanates

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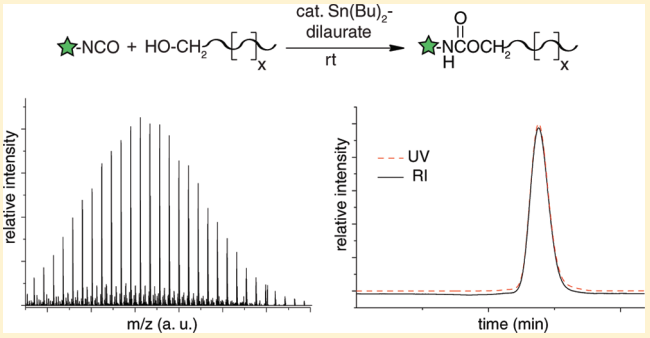
Supporting Information

ABSTRACT: The postpolymerization functionalization of hydroxyl-group terminated polymers (M_n in the range of 1000−6000 g mol^{-1}) such as poly(ethylene glycol) (PEG), poly(*N*-isopropylacrylamide) (PNIPAM), poly(*N*,*N*-dimethylacrylamide) (PDMAM), and poly(*tert*-butyl acrylate) (P*t*BA) with a wide range of functional isocyanate derivatives such as azobenzene, viologen, and anthracene has been investigated. It was shown by ^{1}H and ^{13}C NMR, GPC, Fourier transform infrared spectroscopy (FTIR), and electrospray ionization mass spectrometry (ESI-MS) that a high degree of end-group conversion, typically >98%, with little or no formation of side products can be achieved at ambient temperature. PNIPAM, PDMAM, PtBA, and PHEAM polymers have been obtained by reversible addition−fragmentation chain transfer (RAFT) radical polymerization from a hydroxyl-group containing chain transfer agent (CTA). The formation of the carbamate has been shown to be compatible with the trithiocarbonate end-group of the RAFT polymers. Additionally, this approach allows for the direct functionalization of RAFT polymers without the need of additional steps such as deprotection or aminolysis of the CTA. This route was subsequently used for the preparation of a variety of side-chain functional polymers from poly(*N*-hydroxyethyl acrylamide) (PHEAM). Three different high yielding methods have been employed to prepare the isocyanates (R−NCO). Either amino or carboxylic acid precursors have been converted into the desired R−NCO or hydroxyl group moieties have been reacted with an excess of 1,6-hexamethylene diisocyanate (HDI) to statistically form the monofunctional product.



INTRODUCTION

The development of efficient synthetic protocols to decorate polymers with functional units remains a key interest in macromolecular chemistry.[1−4] The advent of controlled/living polymerization techniques has led to routinely accessible well-defined macromolecular architectures and functional polymers. Most notably, controlled radical polymerization (CRP) methods such as reversible addition−fragmentation chain transfer (RAFT) and atom transfer radical polymerization (ATRP) protocols as well as ring-opening polymerizations (ROP) have been employed under a wide range of conditions to introduce functional end-groups or side-chains in polymers.[5−12] Nevertheless, postpolymerization functionalization methodologies are still needed if the desired functionality is not compatible with the polymerization conditions.

Macromolecule modifications typically rely on efficient synthetic protocols that guarantee a nearly quantitative conversion of the polymer end-/side groups with little or no formation of side products. Furthermore, mild reaction conditions are desirable to avoid degradation of either the polymer or the functionality to be introduced while the rate of conversion should be relatively high. Chemical reactions that fulfill the aforementioned features have been commonly termed "click" reactions in the literature but a more precise definition stresses the importance of equimolarity in polymer synthesis.[13,14] Among those reactions that fulfill all of the 'click'-criteria, one of the most widely utilized transformations is based on the alkyne−azide cycloaddition and is very versatile in postpolymerization modification of ATRP polymers.[15−19] Recently, nitroxides have been employed for postpolymerization functionalization of ATRP polymers.[20,21] On the other hand, Diels−Alder cycloaddition reactions[22−25] and thiol−ene Michael additions[26−28] have received considerable interest for postpolymerization functionalization of RAFT polymers.[29−31] However, shortcomings in the orthogonality of azides and monomers[32] as well as instabilities of the RAFT end-groups[33] and their side reactions after aminolysis[34] have also been discussed in the literature. Hydroxyl-functionalities both in monomer and initiator/CTA

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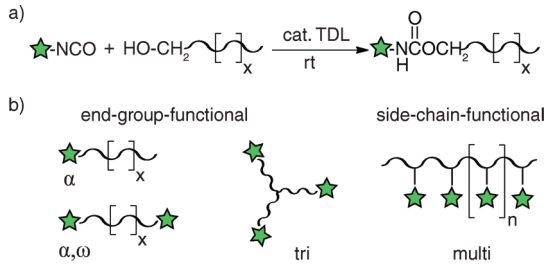
Scheme 1. (a) Postpolymerization Functionalization of Hydroxyl End Groups and Side Chains of Polymers with Isocyanates Achieved by Ambient Temperature Reaction under Dibutyltin Dilaurate (TDL) Catalysis and (b) Polymer Architectures Employed in the Current Study, where the Carbamate Linker Is Omitted for Clarity



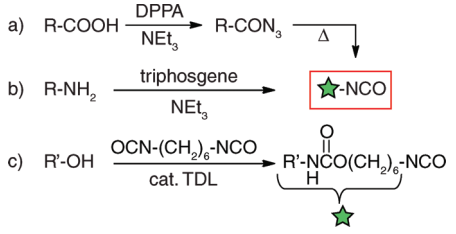
are compatible with CRP protocols with no need of (de)-protection steps. Additionally, anionic ROP typically leads to a hydroxyl end-group after quenching. Several approaches for the transformation of hydroxyl-groups after polymerization have been demonstrated. One example is the one-step conversion of the HO-group into esters utilizing activated carboxylic acids that can, in principle, lead to high end-group fidelity.[35] Conversion of the hydroxyl- to an amino end-group in a two step procedure (typically a Mitsunobu reaction and subsequent hydrazinolysis) has also been demonstrated[36] which allows for the formation of hydrolytically stable amide-bonds in a subsequent step. In addition, hydroxyl end-groups can also be converted into leaving groups[37] and subsequently displaced in a S_N2 reaction by a nucleophile. However, multistep postpolymerization reactions are not only more time-consuming but also have a higher chance of accumulation of nonreacted end-groups than a one-step procedure.

Isocyanates are well-known to react efficiently with thiols, amines and alcohols; however, unprotected amino and thiol groups cannot withstand certain CRP polymerization conditions. Recently, the "thiol−isocyanate conjugation" has been utilized to modify RAFT polymers after aminolysis to form thiocarbamates.[38,39] The rapid reaction of alcohols and isocyanates under tin(II) or tertiary amine catalysis to form carbamates is well documented.[40] It has been largely employed for polyurethane synthesis;[41−44] however, it has been utilized very infrequently for postpolymerization modification.[45] Herein, the postpolymerization functionalization of hydroxyl-group terminated polymers such as poly(ethylene glycol) (PEG), poly(*N*-isopropylacrylamide) (PNIPAM), poly(dimethylacrylamide) (PDMAM), and poly(*tert*-butyl acrylate) (PtBA) with a wide variety of functional aromatic and aliphatic isocyanates is reported (Scheme 1). The procedure was also applied for the preparation of side-chain functional polymers from poly(*N*-hydroxyethyl acrylamide) (PHEAM)).

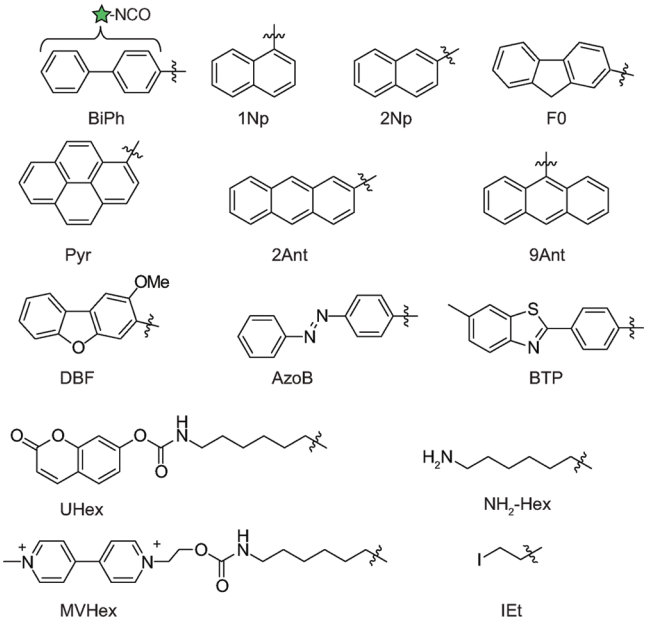
RESULTS AND DISCUSSION

Isocyanate Preparation. First, the preparation of required functional aliphatic and aromatic isocyante derivatives from either carboxylic acids, amines or alcohols as depicted in Scheme 2 is described. In the past, the laboratory synthesis of isocyanates from carboxylic acids and amines required the use of the potentially explosive sodium azide or highly toxic phosgene. Since the (re)discovery of diphenylphosphoryl azide (DPPA)[46] isocyanates can be safely prepared from carboxylic acids via thermal

Scheme 2. Isocyanates Prepared from (a) Carboxylic Acids *via* Acyl Azides through Thermal Curtius Rearrangements, (b) from Amines Using Ambient Temperature Reaction with Triphosgene and NEt_3, and (c) from Statistical Mono-Functionalization of HDI with Alcohols



Scheme 3. Wide Range of Functional End Groups Employed To Show the Versatility of the Isocyanate-Based Post-Polymerization Modification of Polymers



Curtius rearrangement (see Scheme 2a). Following this procedure, 2-naphthoic acid, biphenyl-4-carboxyl acid, and 9-anthranoic acid were transformed into the corresponding isocyanates derivatives (see Scheme 3). The amino group of 2-fluorene amine, 2-anthracene amine, 1-pyrene amine, 4-phenylazophenyl amine, 2-amino-3-methoxydibenzo[*b*,*d*]furan, and 6-methyl-2-(4-aminophenyl)benzothiazole was converted into an isocyanate functionality with the use of triphosgene[47] (a solid phosgene analogue) in an ambient temperature reaction with high yields (see Scheme 2b). Furthermore, functional units containing a hydroxyl group can be reacted with an excess of 1,6-hexamethylene diisocyanate (HDI) to form the monofunctional addition product carrying one remaining isocyanate group for subsequent reaction as demonstrated for 1-(2-hydroxyethyl)- 1′-methyl-[4,4′-bipyridine]-1,1′-diium di(hexafluorophosphate) and umbelliferone (Scheme 2c). In addition, some isocyanates such as 1-naphthyl isocyanate and 2-chloro-ethyl isocyanate are also commercially available. The latter was transformed into 2-iodo-ethyl

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isocyanate by a Finkelstein reaction prior to reaction with PEG (see Supporting Information for details of all aforementioned compounds).

The chemical structures for the functional units containing an isocyanate group are shown in Scheme 3. The investigated functional moieties include fluorophores (Pyr, BTP), photoactive chromophores (AzoB), redox-active species/radical traps (such as MVHex, 2Ant), base/oxidation sensitive species (F0) and chemically modifiable units (such as IEt). Numerous reports have described the use of azobenzenes and viologens (paraquat) for light- and redox-switching[48−50] applications, respectively as well as their participation in host−guest type interactions in supramolecular systems.[51−54] Despite their usefulness, viologens are difficult to conjugate with high efficiency to macromolecules. The reaction of alkyl halides with 1-methyl-[4,4′-bipyridin]-1-ium in a S_N2 fashion have been reported; however, they show slow kinetics. Moreover, the decomposition of viologen in the presence of most (in)organic bases impedes standard amide or ester coupling schemes (see ref 55 and references therein).

Table 1. Fluorene (F0) End Group Functionalized Poly(ethylene glycol) (PEG) Polymers Prepared from Hydroxyl-Terminated PEGs by Reaction with F0-NCO

polymer architecture	M_n (g mol^{-1})	% functionalization (^{1}H NMR)[a]	% functionalization (ESI-MS)[b]
α	2200	>99	97.7
α	5200	98	[c]
α,ω	2400	>99	96.3
tri	1800	>99	97.6

[a] Measured by the integration of the methoxy-end group vs the methylene group adjacent to the carbamate linkage for α functional PEG; integration vs backbone for α,ω and trifunctional PEG ($CDCl_3$). [b] Measured by the relative integration of peak for $[F0\text{-}PEG\text{-}OMe+Na]^+$ vs $[HO\text{-}PEG\text{-}OMe+Na]+$ at same DP for α functional PEG; integration of $[product + Na]^+$ vs all [not fully reacted PEG species$+Na]^+$ for α,ω and trifunctional PEG. [c] not determined.

Functionalization of Hydroxyl-Terminated Polymers. With the isocyanate derivatives in hand, the postpolymerization modification of hydroxyl-terminated polymers was pursued to obtain end-terminated functional polymers. Typically, 3−5 equiv of the isocyanate component were employed to drive the conversion of the hydroxyl end-group to completion. Dibutyltin-dilaurate (TDL) was employed as a catalyst at ambient temperature (Scheme 1) in anhydrous dichloromethane (DCM) as a solvent. Anhydrous acetonitrile was used for MVHex on account of its poor solubility in DCM. The excess of isocyanate can be readily removed by precipitation, washing steps or dialysis depending on both the type of isocyanate and polymer used (see Supporting Information).

Initially, commercially available monohydroxyl functional poly(ethylene glycol) monomethyl ether (HO-PEG-OMe) of different molecular weight (1100, 2000, and 5000 g mol^{-1}) was reacted with variable isocyanate derivatives. Moreover, α,ω- and trifunctional carbamate linked PEG derivatives were also prepared (see Table 1 and Supporting Information, Tables S1, S2, and S3). The incorporation of isocyanate derivatives into the polymer was confirmed by ^{1}H and ^{13}C NMR spectroscopy. Figure 1a and b depict the ^{1}H and ^{13}C NMR spectra of fluorene terminated PEG−OMe (2,000 g mol^{-1}) as an example. The degree of functionalization was determined from the ^{1}H NMR spectrum by relative integration of the well-separated methoxy-end-group (proton ω in Figure 1a) to the methylene group (proton *c* in Figure 1a) the ^{1}H NMR integrationadjacent to the carbamate linkage (signals at 3.39 and 4.47 ppm respectively, in $CDCl_3$). For α,ω and trifunctionalized PEGs, integration versus the backbone was performed. Table 1 collates the degree of functionalization for the fluorene PEGs prepared in the current study (the degree of functionalization for the rest of the materials is presented in Supporting Information, Tables S1, S2, and S3). Near quantitative conversion is obtained in all cases with no detectable side products (such as fluorenone).

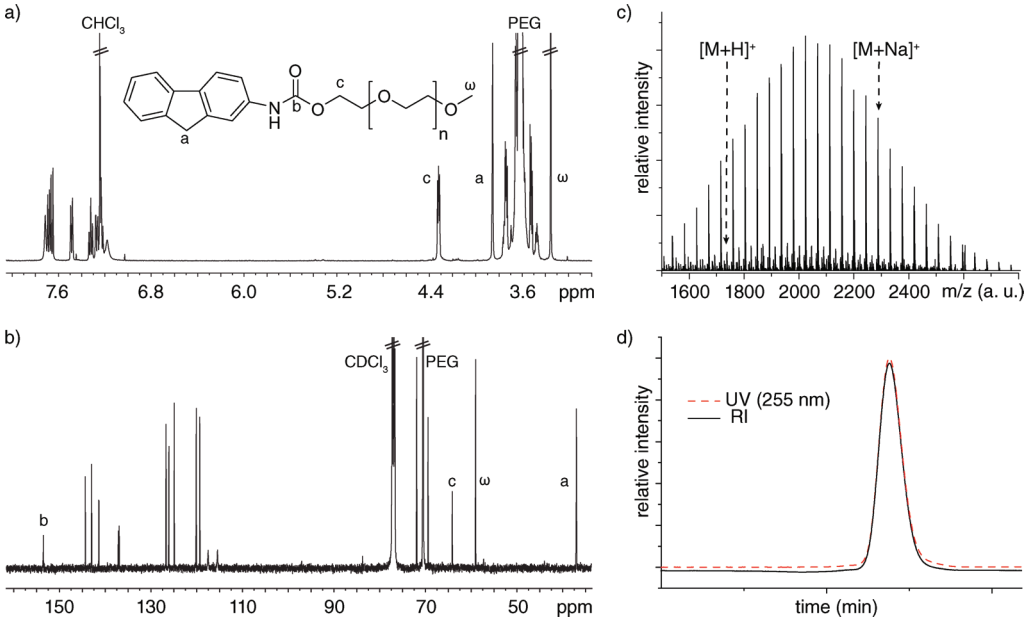

Figure 1. Characterization of **F0-PEG-OMe** (2000 g mol^{-1}) by (a) ^{1}H NMR, (b) ^{13}C NMR, (c) high-resolution ESI-MS, and (d) GPC. These methods confirm the high degree of end-group functionalization (>99%) as well as excellent purity of the material, most notably the absence of the potential oxidation byproduct fluorenone.

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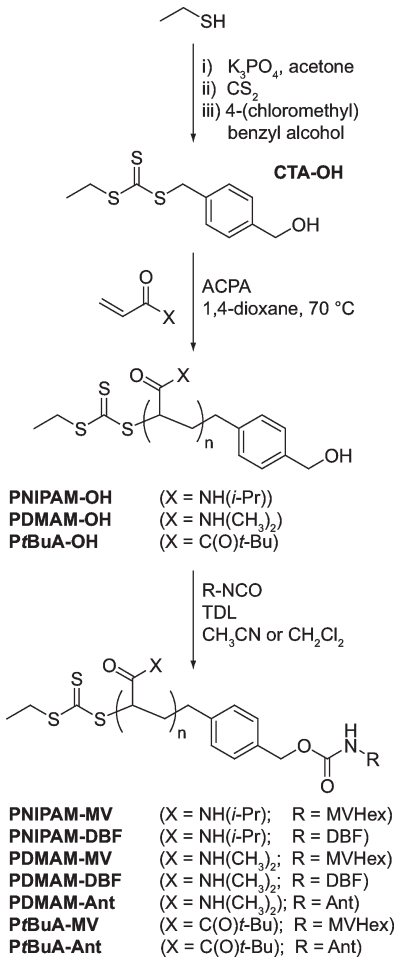
Scheme 4. Synthesis of CTA−OH and RAFT Functional Polymers



A calibration curve by standard addition of known amounts of HO−PEG−OMe (2000 g mol^{-1}) to DBF-PEG−OMe (2000 g mol^{-1}) shows a slope close of 1.08 and supports the accuracy of the ^1H NMR integration (see Figure S1 in the Supporting Information for details). The signals at 154 and 65 ppm in the ^{13}C NMR spectra (Figure 1b) corresponding to the carbamate carbonyl and adjacent methylene group, respectively, gave further evidence for the fluorene incorporation. Additionally, ESI-MS experiments further validated the high degree of end-group conversion and purity of the materials (Table 1 and Supporting Information, Table S1). Finally, the reaction of (HO-PEG-OMe) with an excess of 1,6-hexamethylene diisocyanate (HDI) and subsequent hydrolysis of the isocyanate-end-group allows for a surprisingly simple conversion into an amino-terminated poly(ethylene) glycol. Investigations into the use of the isocyanate-terminated polymers for polymer−polymer ligations are currently underway.

Expanding this postpolymerization modification procedure, a range of hydroxyl-terminated RAFT polymers was functionalized with representative isocyanate derivatives (Scheme 4). Specifically, hydroxyl-terminated poly(*N*,*N*-dimethylacrylamide) (PDMAM), poly(*N*-iso-propyl-acrylamide) (PNIPAM) and poly(*tert*-butyl acrylate (P*t*BA) were obtained via RAFT polymerization of *N*,*N*-dimethylacrylamide, *N*-isopropylacrylamide and *tert*-butyl acrylate respectively in 1,4-dioxane at 70 °C with compound CTA−OH as the RAFT agent and 4,4′-azobis(4-cyanopentanoic acid) (ACPA) as the radical initiator. The hydroxyl group containing CTA−OH was synthesized in analogy to previously reported one-pot procedures in high yield.[56]

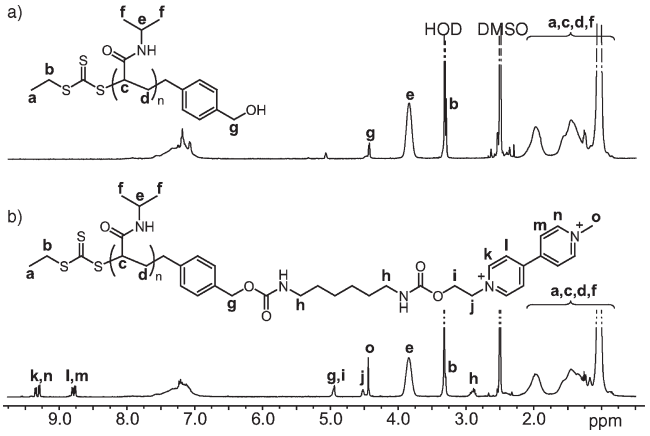


Figure 2. ^1H NMR (DMSO-d_6, 500 MHz) spectra for (a) PNIPAM−OH and (b) PNIPAM−MV.

After isolation, all the polymers were analyzed via a combination of ^1H NMR and size exclusion chromatography (GPC). The GPC traces indicated monomodal and narrow molecular weight distributions for all the hydroxyl group-terminated polymers (see Supporting Information) and gave evidence that free hydroxyl groups did not affect radical polymerizations. The ^1H NMR of PNIPAM−OH is shown in Figure 2a as a representative example. The signals at 4.43 ppm (protons *g*) clearly revealed the presence of the benzyl alcohol moiety attached to the polymer chain. Moreover, the spectrum also displayed signals around 3.30 ppm corresponding to the resonance protons *b* of the ethylsulfanylthiocarbonyl sulfanyl moiety and this verified that compound CTA−OH allowed for RAFT polymerizations. Having prepared the hydroxyl group terminated RAFT polymers, the attachment of an isocyanate-containing moiety was conducted in a similar manner to that described above for the PEG polymers. The ^1H NMR spectrum of PNIPAM−MV is shown in Figure 2b as a representative example. The incorporation of the MV moiety in the polymer was evidenced by the appearance of signals at approximately 9.3 and 8.8 ppm (signals *k*−*n*) corresponding to the aromatic protons of the viologen end-group. Moreover, the signal corresponding to the methylene unit in α position with respect to the hydroxyl group in PNIPAM−OH (signal *g* in Figure 2) shifted from 4.50 to 5.00 ppm upon formation of the carbamate linkage.

Different isocyanate derivatives including MVHex, DBF, and 2Ant have been reacted with PNIPAM, PDMAM and (P*t*BA) as depicted in Scheme 4 with high yields and end-group fidelity (Table 2). Details for synthesis of these materials are shown in the Supporting Information. As such, this approach enables the direct functionalization of RAFT polymers using highly efficient isocyanate conjugation chemistry without the need of additional steps such as deprotection or aminolysis of the CTA. Therefore, the strategy described above avoided the formation of byproducts such as disulfides from the aminolysis. Furthermore, as the CTA was designed to carry the hydroxyl unit at the R-group, it can be expected that *every* polymer chain carries the HO-terminus after RAFT polymerization and is available for functionalization with the isocyanate moiety in the subsequent step.[57]

Finally, it should be also feasible to use the modified polymer as a macroinitiator for subsequent polymerization as the CTA remained intact.

Table 2. End Group Functionalized Polymers Prepared from Hydroxyl-Terminated RAFT Polymers by Reaction with R−NCO

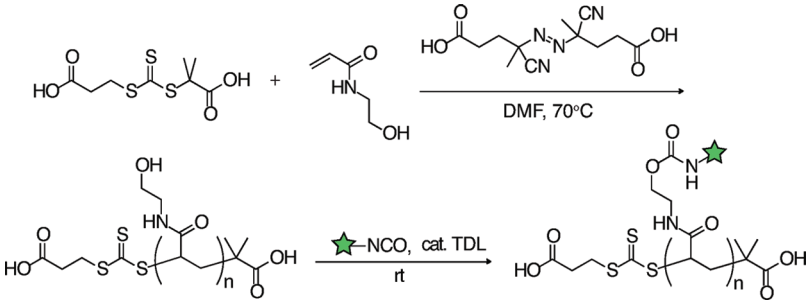
polymer	M_n (g mol^{-1})	% functionalization (^{1}H NMR)[a]	PDI[b]
PNIPAM−DBF	3300	>95	1.45
PDMAM−DBF	2900	>95	1.52
PNIPAM−MV	3600	>95	1.40
PDMAM−MV	3400	>95	1.51
P*t*BuA−MV	4800	>95	1.32
PDMAM−2Ant	3400	85	1.42
P*t*BuA−2Ant	4700	92	1.37

[a] Measured by relative integration of methylene group adjacent to the carbamate linkage vs backbone. [b] From GPC. See Supporting Information for details.

Multivalent Side-Chain Functionalization. Further extending the postpolymerization functionalization protocol developed above, side-chain functional polymers were synthesized using RAFT polymerization (Scheme 5). Hydroxyl-functional acrylamide monomer, *N*-hydroxyethylacrylamide was used to prepare poly(*N*-hydroxyethylacrylamide) (PHEAm) polymers bearing hydroxyl groups pendant to the main chain. Using this simple, commercially available monomer, polymers were obtained with a high degree of functionality which was subsequently used for isocyanate conjugation.

Initially a polymer of approximately 5700 g mol^{-1} (DP ∼50) PHEAm was synthesized according to established procedures (see Supporting Information). To demonstrate the efficacy of this method for side-chain functionalization of the polymers, three of the above-mentioned isocyanates were chosen: 1Np, 2Ant, and MVHex (see Scheme 3). The characterization of the viologen pendant PHEAm−MV polymer is displayed in Figure 3. Conversion was easily characterized to be a moderate 70% using ^{1}H NMR integration of the appearing aromatic viologen peaks in the region of 9.3−8.3 ppm (signals *c*,*c*′ and *d*,*d*′ in Figure 3b, bottom). There were also corresponding decreases in the peaks

Scheme 5. Reaction Scheme for the Preparation of Side-Chain Functional Polymers by Isocyanate Conjugation to a Hydroxy-Pendant Polymer, Poly(*N*-hydroxyethylacrylamide) (PHEAm), Prepared by Reversible Addition−Fragmentation Chain Transfer (RAFT) Polymerization



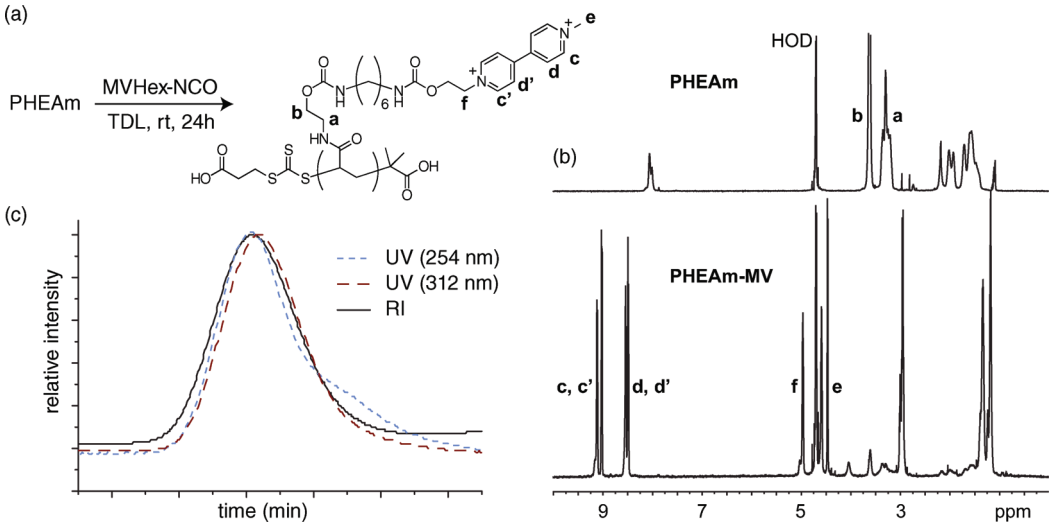


Figure 3. Characterization of **P(HEAm−MV)**, shown in (a) by ^{1}H NMR (b) and GPC (c). Comparison of the ^{1}H NMR spectra of the starting polymer PHEAm (top) and the MVHex conjugated polymer PHEAm−MV (bottom) confirms the degree of functionalization (70%). This is supported by the overlay of GPC traces from the refractive index (RI), UV at 254 nm resulting from the MVHex functionality, and the UV at 312 nm resulting from the trithiocarbonate end group on the polymer.

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from the methylene protons α and β to the hydroxyl-group pendant from the chain of the starting material (apparent at 3.6 and 3.3 ppm, signals a and b in Figure 3b, top, respectively). The aqueous GPC traces in Figure 3c also clearly demonstrated the conjugation of the MVHex units as there is an overlay of the refractive index trace with the UV−visible absorbance traces corresponding to the remaining trithiocarbonate unit on the polymer (312 nm) and the newly conjugated MVHex unit (254 nm). It is interesting to note that in this case, although the retention time of the material in the GPC did not change significantly, the use of light scattering methods for molecular weight determination clearly displayed an increase in molecular weight from 5700 to 52 400 g mol^{-1}, which is the expected increase for a conversion of 70% as determined by ^{1}H NMR data. An increase in the polymer polydispersity index (PDI) from 1.17 to 1.55 was also observed, further supporting the moderate conversion of the side-chain units. The large increase in the molecular weight of a monomeric unit bearing the MV functionality and the random and incomplete distribution of these monomeric units along the polymer chain leads to the observed increase in polydispersity. The moderate conversion of the hydroxy-pendant functionality by conjugation of the MVHex moiety was presumably on account of the di-ionic nature of MVHex, which prevented high conversion due to charge−charge repulsion.

The conversion for both the 1Np and 2Ant moieties were determined in an analogous way as similar shifts were observed in the ^{1}H NMR spectra. The conversion measured for the relatively unhindered 1Np is very high at 98%, however, as 2Ant is significantly more hindered, conversion decreases to a fairly moderate 65%. This would be expected for side-chain functionalization with such a short linker to the polymer backbone. MVHex yielded a higher conversion than 2Ant, despite being di-ionic, presumably because the isocyanate functionality in MVHex is not as sterically hindered as in the case of 2Ant. GPC analysis could not be directly correlated before and after conjugation for both of these cases as the starting PHEAm was characterized with water as the eluent, while the PHEAm−1Np and PHEAm−2Ant polymers were no longer water-soluble and were therefore characterized using THF as the eluent. Although the molecular weights for these polymers are likely inaccurate as they were determined using polystyrene standards, the PDI data is informative as the PDI for the 2Ant is significantly broadened to 1.57 on account of the moderate conversion, while the PDI for the 1Np was only slightly broadened to 1.22 as the conversion was near quantitative. Similar to MVHex, both cases displayed an overlay of the refractive index and UV−visible absorbance traces, verifying conjugation of the functionality to the polymer backbone.

CONCLUSIONS

The postpolymerization functionalization of hydroxyl-functional polymers (both end group and side chain) by hydrolysis-stable carbamate formation with a wide range of functional isocyanate derivatives yielding a high degree of conversion was demonstrated. Three high yielding methods have been employed to prepare the isocyanates, demonstrating that this method is amenable for use with a wide variety of commercially available starting materials. This approach enables the direct functionalization of RAFT polymers without the need of additional steps such as deprotection or aminolysis of the CTA, producing little to no side products, which are easily removed using standard polymer purification techniques. Additionally, the formation of the carbamate is fast and mild and has been shown to be compatible with the trithiocarbonate group of the RAFT polymers, demonstrating compatibility with relatively labile functionality. In conclusion, we have found that this synthetic route of conjugation can add value to the available repertoire of important post-polymerization functionalization techniques.

EXPERIMENTAL SECTION

Materials. Representative Procedure for Route a. *Synthesis of 2-Naphthoyl Azide.* 2-Naphthoyl azide was prepared in analogy to literature procedures. To a stirred suspension of 2-naphthoic acid (3.4 g, 20 mmol) in 150 mL of dry toluene was added triethylamine (3.1 mL, 22 mmol) and DPPA (4.7 mL, 22 mmol). The solution was stirred at room temperature for 48 h. The solvent was evaporated in vacuum and the purple residue was purified by chromatography on silica with DCM to yield the title compound (2.8 g, 16 mmol, 81%) as a white, waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1H), 7.92 (dd, 1H), 7.85 (d, 1H), 7.80−7.78 (m, 2H), 7.54−7.45 (m, 2H) ppm.

Synthesis of ***2 Np-PEG-OMe*** *(5000 g mol^{-1}).* A solution of 2-naphthoyl azide (1.2 g, 6.0 mmol) in 30 mL anhydrous *o*-dichlorobenzene was heated to 145 °C for 2 h under nitrogen atmosphere in a 100 mL two-neck RBF, equipped with a reflux condenser. After the mixture was cooled down to room temperature, poly(ethylene glycol) 5000 monomethyl ether (3.0 g, 0.6 mmol) dissolved in 10 mL of anhydrous DCM and a drop of TDL was added at once and the mixture was stirred for 48 h at room temperature. The product was obtained by precipitation from cold diethyl ether. The yellowish solid was redissolved in ca. 30 mL DCM, filtered and reprecipitated in cold diethyl ether (2×). Suction filtration yielded **2 Np-PEG-OMe** (5000 g mol^{-}1) (2.6 g, 0.5 mmol, 85%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$: δ = 8.03 (s, 1H), 7.79−7.77 (m, 3H), 7.45−7.38 (m, 4H), 4.39 (t, 2H, 4.7 Hz), (m, PEG backbone), 3.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ δ = 153.4, 135.6, 133.9, 130.1, 128.7, 127.5, 127.4, 126.4, 124.5, 119.2, 114.7, 64.2, 59.0 ppm and PEG backbone signals. The purity was confirmed by THF−GPC.

Representative Procedure for Route b. *Synthesis of 2-fluorene-isocyanate.* To a stirred solution of 2-fluorene amine (3.0 g, 17 mmol) and triethylamine (3.2 mL, 25 mmol) in 150 mL of anhydrous DCM, kept in an ice-bath, was slowly added triphosgene (5.5 g, 19 mmol) in several portions. The ice-bath was removed after 1 h and the mixture was left for stirring at room temperature for 24 h. Purification was achieved by flash chromatography on silica with DCM to yield the title compound (3.0 g, 15 mmol, 85%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, 1H, 7.6 Hz), 7.60 (d, 1H, 8.1 Hz), 7.44 (d, 1H, 7.5 Hz), 7.31−7.27 (m, 1H), 7.24−7.20 (m, 1H), 7.17−7.16 (m, 1H), 7.01 (dd, 1H, 8.1 Hz, 2 Hz), 3.78 (s, 2H) ppm. ^{13}C NMR (80 MHz, $CDCl_3$): δ = 145.1, 143.5, 141.2, 139.9, 132.1, 127.4, 127.3, 125.5, 125.0 123.9, 121.9, 121.0, 120.2, 37.2 ppm. FTIR: $\tilde{\nu}$ = 2250 cm^{-1} (−NCO).

Synthesis of ***F0-PEG-OMe (2000 g mol^{-1})****.* To a solution of (0.5 g, 2.2 mmol) 2-fluorene isocyanate and poly(ethylene glycol) 2000 monomethyl ether (1.0 g, 0.5 mmol) in 10 mL of anhydrous DCM was added a drop of TDL, and the mixture was stirred for 48 h at room temperature. The product was obtained by precipitation from cold diethyl ether. The solid was redissolved in ca. 30 mL DCM, filtered and reprecipitated in cold diethyl ether. Suction filtration yielded **F0-PEG-OMe** (2000 g mol^{-1}) (0.8 g, 3.6 mmol, 72%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (s, 1H), 7.73−7.69 (m, 2H), 7.52 (d, 2H, 7.5 Hz), 7.30−7.22 (m), 4.38 (t, 2H, 4.6 Hz), 3.90 (s, 2H), 3.80−3.47 (m, PEG backbone), 3.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.6, 144.4, 143.0, 141.4, 137.2, 137.0, 126.7, 126.1, 124.9, 120.1, 119.4, 117.5, 115.5, 64.2, 59.0, 37.0 ppm and PEG backbone signals. FTIR: $\tilde{\nu}$ = 1727 cm^{-1} (−NH(CO)O−). The purity was confirmed by THF−GPC.

Representative Procedure for Route c. *Synthesis of* ***MV-Hex-NCO di(hexafluorophosphate)***. To a solution of 1-(2-hydroxyethyl)-1′-methyl-[4,4′-bipyridine]-1,1′-diium di(hexafluorophosphate) (0.5 g, 1.0 mmol) in 200 mL anhydrous acetonitrile was added excess 1,6-hexamethylene diisocyanate (2 mL) and a drop of TDL. The reaction mixture was stirred for 24 h at room temperature. (The conversion can be followed by infrared spectroscopy.) The solvent was evaporated under reduced pressure to approximately 10 mL, and 200 mL of anhydrous diethyl ether was added. A sticky, yellowish precipitate formed and the mixture was stored in the freezer for 30 min. Then the solvent was decanted and the residue redissolved in a minimum amount of anhydrous acetonitrile. The the above-described steps were repeated (2×), and the yellowish, sticky solid was dried under reduced pressure to yield the title compound (0.6 g, 87%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.31 (d, 2H, 6.7 Hz), 9.26 (d, 2H, 6.7 Hz), 8.77 (d, 2H, 6.7 Hz), 8.73 (d, 2H, 6.7 Hz), 7.22 (s, 1H), 4.93 (t, 2H, 4.7 Hz), 4.49 (t, 2H, 4.8 Hz), 4.41 (s, 3H), 3.28 (t, 2H, 6.2 Hz), 2.87 (q, 2H, 6.3 Hz), 1.46 (quin, 2H, 7.2 Hz), 1.35−1.12 (m, 6H) ppm; ^{13}C NMR (80 MHz, DMSO-d_6) δ = 155.3, 149.0, 148.0, 146.7, 146.4, 126.4, 126.1, 121.5, 62.1, 60.4, 48.1, 42.5, 30.4, 29.1, 25.6, 25.5 ppm. FTIR: $\tilde{\nu}$ = 2267 (-NCO), 1713 (−NH(CO)O−) cm^{-1}. HRMS: m/z calcd for $[M - H]^+$, 383.2072; found, 383.2077; calcd for $[M + PF_6]^+$, 529.1792; found, 529.1797.

Synthesis of ***MV-Hex-PEG-OMe (5000 g mol^{-1})***. To a solution of MV−Hex−NCO di(hexafluorophosphate) (0.5 g, 0.7 mmol) in 20 mL of anhydrous acetonitrile were added poly(ethylene glycol) 5000 monomethyl ether (1.0 g, 0.2 mmol) and a drop of TDL. The reaction mixture was stirred for 24 h at room temperature. The solvent was evaporated under reduced pressure, 100 mL of DCM was added, and the resulting slurry was sonicated for 5 min. The remaining solid was filtered off and washed with 100 mL of DCM. The solvent of the combined organic phases was removed under reduced pressure to yield an off-white solid. Counterion exchance and further purification can be achieved by dialysis against 0.5 wt % aqueous sodium chloride solution (2×, 12 h) followed by dialysis against deionized water (2×, 12 h). Lyophilization yields the title compound as a fluffy, white solid (0.9 g, 0.16 mmol, 80%). ^{1}H NMR (500 MHz, D_2O): δ = 9.11 (d, 2H, 6.0 Hz), 9.03 (d, 2H, 6.0 Hz), 8.54 (d, 2H, 6.0 Hz), 8.85 (d, 2H, 6.0 Hz), 4.66 (s, 3H), 4.14 (mc, 2H), 3.79−3.50 (m, PEG backbone), 3.33 (s, 3H), 2.97 (m, 2H), 2.2−0.8 (m) ppm. FTIR: $\tilde{\nu}$ = 1714 cm^{-1} (−NH(CO)O−).

■ ASSOCIATED CONTENT

Supporting Information. Synthetic procedures and characterization for the remaining materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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