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RAFT Polymerization of "Splitters" and "Cryptos": Exploiting Azole-*N*-carboxamides As Blocked Isocyanates for Ambient Temperature Postpolymerization Modification

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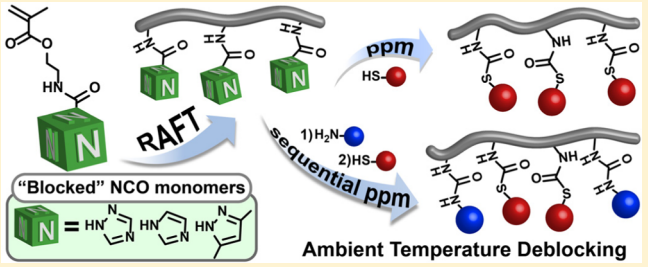
Supporting Information

ABSTRACT: A postpolymerization modification strategy based on ambient temperature nucleophilic chemical deblocking of polymer scaffolds bearing *N*-heterocycle-blocked isocyanate moieties is reported. Room temperature RAFT polymerization of three azole-*N*-carboxamide methacrylates, including 3,5-dimethylpyrazole, imidazole, and 1,2,4-triazole derivatives, afforded reactive polymer scaffolds with well-defined molecular weights and narrow dispersities ($Đ$ < 1.2). Model analogues possessing the same *N*-heterocycle blocking agents with varied leaving group abilities were synthesized to determine optimal deblocking conditions. The reactivity of the azole-*N*-carboxamide moieties toward nucleophiles can be tuned simply by varying the structure of the azole blocking agents (reactivity order: pyrazole < imidazole < triazole). DBU-catalyzed reactions of thiols with imidazole- and 1,2,4-triazole-blocked isocyanate scaffolds were shown to occur rapidly and quantitatively under ambient conditions. Differences in reactivity of 1,2,4-triazole- and 3,5-dimethylpyrazole-blocked isocyanate copolymers with various nucleophiles at room temperature facilitated sequential and postpolymerization modification. This strategy advances the utility of blocked isocyanates and promotes the chemistry as a powerful postmodification tool to access multifunctional polymeric materials.



INTRODUCTION

Engineering modular macromolecules via postpolymerization modification (PPM) of reactive polymer scaffolds—an approach with origins dating back to the late 1800s—has emerged as a powerful, contemporary method to access soft materials with complex architectures and multifunctional compositions.[1−5] PPM strategies provide access to a library of functional polymers from a single scaffold upon chemical transformation of reactive moieties incorporated in the polymer backbone, at the chain ends, or as pendent groups using an array of modifying derivatives.[6,7] Synthetic routes to modular polymer scaffolds have rapidly advanced via a powerful synergism between click chemistry[8] and reversible-deactivation radical polymerization (RDRP) techniques—such as reversible addition−fragmentation chain transfer (RAFT) polymerization and atom-transfer radical polymerization (ATRP).[3] RDRP methods enable the polymerization of monomers with chemoselective pendent groups that are inert during the polymerization but activated under specific postpolymerization conditions to provide a set of modified polymers with well-defined molecular weight characteristics and controlled architectures. Click reactions are most commonly used for PPM because these transformations are rapid, high-yielding, and proceed under mild conditions.[8] Advancements in synthetic protocols have extended PPM strategies to polymer scaffolds containing two or more reactive moieties enabling the synthesis of multifunctional materials using orthogonal,[9] sequential,[10,11] or cascade transformations.[12]

Reactions of isocyanates with various nucleophiles (e.g., alcohols, amines, and thiols) have been widely used to cross-link or chain extend polymers, and have underpinned common technologies such as polyurethane/polythiourethane coatings, foams, and thermoplastic elastomers for more than 70 years.[13,14] However, these isocyanate chemistries have been scarcely employed in PPM strategies despite the fact that the nucleophilic addition of amines and thiols to isocyanates proceeds with hallmark characteristics of a click reaction. Recent efforts by our group,[15−17] and others,[18−20] have demonstrated the synthesis of isocyanate functionalized polymer scaffolds and subsequent PPM of these scaffolds using various X−NCO (X = OH, NH_2, SH) addition reactions as routes to multifunctional polymers and surfaces. While the isocyanate functionality is stable toward radical-mediated chemistries, including RAFT polymerization,[21,22] isocyanates are highly reactive and inherently sensitive to water, making NCO-functional polymers difficult to handle and store prior to modification. An approach that exploits the versatility of X−

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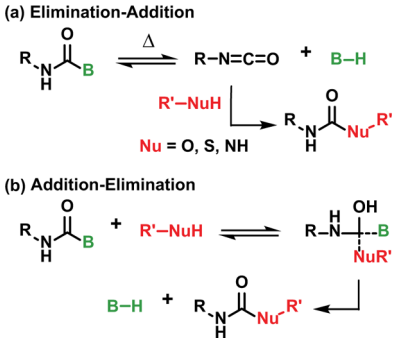
NCO chemistry while mitigating the inherent instability of the isocyanate would be advantageous in PPM strategies.

In this direction, we were inspired by the reversibility of urea and urethane bonds. The dynamic nature of these linkages has recently been exploited for the design of reversible and self-healing polymers (using sterically hindered ureas),[23,24] and historically for the design of latent isocyanates in coating formulations.[25,26] Latent isocyanates, also known as "splitters", "cryptos", and "blocked" isocyanates, are adducts containing a relatively weak bond formed by the reaction of isocyanates and active hydrogen compounds, such as oximes, phenols, and N-based compounds (e.g., amides, imides, and azoles).[27−29] According to the elimination-addition mechanism shown in Scheme 1a, the blocked isocyanate adduct dissociates at elevated temperature to regenerate the parent isocyanate, which then reacts with nucleophilic substrates to yield more thermally stable urethanes, ureas, and thiourethanes. The elimination-addition process has been used in coatings applications for shelf-stable 1K formulations that can be activated at elevated temperatures; however, relatively high temperatures (100−200 °C) are often necessary to facilitate the deblocking reaction. For this reason, blocked isocyanates have received little attention for contemporary postpolymerization modification processes. Several examples have been reported that employed bisulfite-blocked and oxime-blocked NCOs as monolayers[30] or polymer thin films[31] for DNA microarrays;[30,31] however, these surfaces required deblocking at 180 °C under vacuum prior to postmodification with amines. Postmodification of a caprolactam-blocked hyperbranched polymer surface with polyethylenimine was reported by Asri et al.[32] − a process that required immobilization reactions at 125 °C for up to 52 h. Bode et al.[33] recently reported the synthesis of α,ω-carboxy-terminated telechelics via RAFT polymerization and subsequent conversion of these end groups to 3,5-dimethylpyrazole-blocked isocyanates. The pyrazole-blocked telechelics were then reacted with amines and alcohols at 130 °C to achieve postmodification of the chain ends. Although multiple synthetic steps, high temperatures, and lengthy reactions times were required to effect the PPM process, Bode's work demonstrates the potential synergism of controlled radical polymerization and blocked NCOs to access functional polymer materials.

If appropriately designed, blocked NCOs may also undergo direct displacement reactions with good nucleophiles at ambient temperatures−a process known as chemical deblocking that typically proceeds via an addition−elimination mechanism (Scheme 1b). In one of the few examples of ambient temperature chemical deblocking of isocyanates for polymer postmodification, Penelle et al.[34] demonstrated the synthesis of a water-soluble ionic poly(methacrylate) containing pendent isocyanates blocked with sodium 4-hydroxybenzenesulfonate. The electron-withdrawing sulfonate group on the phenol served to activate the blocked adduct toward displacement by an amine; however the modification reaction was slow (requiring 72 h) and the polymer product exhibited poor solubility. With interest in fully exploiting ambient temperature deblocking for PPM processes, we turned out attention to azole-*N*-carboxamide-blocked isocyanate analogues that have been used extensively as acyl transfer reagents.[35−37] Azole-*N*-carboxamides offer a wide spectrum of reactivity in nucleophilic reactions, where reactivity depends on the number and location of nitrogen atom in the azole ring.[38] Imidazole-*N*-carboxamides, and the more reactive 1,2,4-triazole-*N*-carboxamides, are particularly activated toward nucleophilic reactions with amines and thiols to give ureas and thiocarbamates, respectively, in high yield at ambient temperatures.[37,39−41] These characteristics make azole-*N*-carboxamides ideal candidates as blocked isocyanates for the development of a modular PPM platform under mild conditions.

In this work, we aim to significantly broaden the utility of blocked isocyanate chemistry for postmodification processes by employing azole-*N*-carboxamides as polymer pendent groups. This strategy will reduce the temperature range required to facilitate the isocyanate deblocking process in the presence of nucleophilic modifiers. Herein, we report the synthesis of well-defined *N*-heterocycle-blocked isocyanate polymer scaffolds via room temperature RAFT polymerization and successfully demonstrate postpolymerization modification of these scaffolds with thiols and amines at *ambient* temperatures. *N*-Heterocyclic blocking agents—including 3,5-dimethylpyrazole, imidazole, and 1,2,4-triazole, incorporated as pendent moieties along the polymer backbone—were chemically deblocked with thiols using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst. We further exploit differences in reactivity of pyrazole- and triazole-blocked adducts in a copolymer as a facile route to multifunctional polymers via sequential postpolymerization modification reactions. Notably, the current work brings blocked isocyanate chemistry into an enabling temperature range for efficient polymer modification strategies.

Scheme 1. (a) Elimination−Addition and (b) Addition−Elimination Mechanisms for Deblocking Blocked Isocyanates



RESULTS AND DISCUSSION

Monomer and Model-Blocked NCOs: Synthesis and Stability. In order to investigate polymer pendent-blocked isocyanates as scaffolds for ambient temperature postpolymerization modification with thiols, three isocyanatoethyl methacrylate monomers blocked with a series of *N*-heterocycles were synthesized (Scheme 2a) including NCOP (pyrazole-blocked), NCOI (imidazole-blocked), and NCOT (triazole-blocked). NCOP was commercially available. The one-step monomer reactions were carried out in diethyl ether or a 2:1 (v:v) mixture of diethyl ether−THF at room temperature for 1−3 h. Both imidazole and 1,2,4-triazole monomers precipitated readily as stable crystalline solids, and were easily isolated in high yields (76−96%) by isolation via vacuum filtration. A primary advantage of employing blocked NCO monomers for synthesis of functional polymer scaffolds as compared to free isocyanate analogues lies in the significant enhancement in hydrolytic stability of blocked NCOs. Figure 1 shows the hydrolytic degradation kinetics for NCOP, NCOI, NCOT, and the unprotected isocyanatoethyl methacrylate (IEM) in

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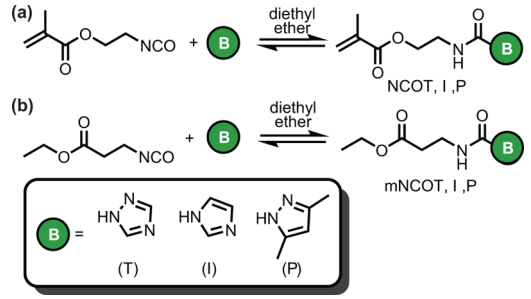
Scheme 2. Synthetic Routes to (a) Blocked NCO Monomers and (b) Model-Blocked NCO Analogues



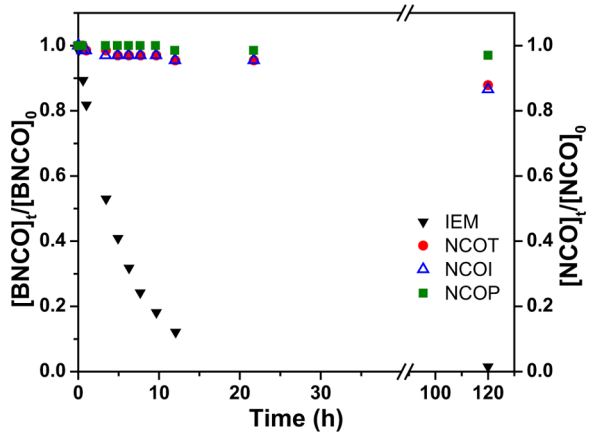


Figure 1. Hydrolytic stability plots for NCOP, NCOI, NCOT, and IEM in DMSO-d_6 containing 1% D_2O at 20 °C. The reactions were followed using ^1H NMR.

DMSO-d_6 containing 1% D_2O at 20 °C. NCOP showed the highest hydrolytic stability with less than 3% hydrolysis observed after 120 h. NCOI and NCOT were also quite stable and showed <5% and ~13% hydrolysis at 12 and 120 h, respectively. In stark contrast, the unblocked IEM underwent ~20% hydrolysis after 1 h, and approached 90% hydrolysis at 12 h.

Because thiols undergo Michael addition reactions with methacrylates,[42] model blocked NCO analogues without the methacrylate group were used to investigate the relative rates of chemical deblocking with thiols under various conditions. Model blocked NCO analogues were synthesized from ethyl-3-isocyanatopropionate, as shown in Scheme 2b. The model compounds are denoted mNCOP, mNCOI, and mNCOT for 3,5-dimethylpyrazole-, imidazole-, and 1,2,4-triazole-blocked 2-isocyanatoethyl propionates, respectively. The *N*-heterocycle blocking agents investigated in this work were chosen based on previous reports of a good balance between latency and reactivity of the respective blocked isocyanates at relatively lower temperatures as compared to more common blocking agents such as phenols and amides.[43,44] More importantly, 3,5-dimethylpyrazole, imidazole, and 1,2,4-triazole provide a range of leaving group pK_a (DMSO) values (pyrazole, 19.8 > imidazole, 14.4 > 1,2,4-triazole, 10.3) allowing study of room temperature deblocking with nucleophiles. As the pK_a of the *N*-heterocycle decreases (i.e., becomes a better leaving group), the extent of room temperature deblocking via the addition–elimination pathway is expected to increase.

Chemical Deblocking *N*-Heterocycle-Blocked Isocyanates with Thiols: Model Reactions. To our knowledge, there are no previous reports detailing the reaction of thiols with blocked isocyanates for polymer postmodification. In the first stage of this study, real-time ^1H NMR analysis was utilized to study the influence of blocking group, catalyst concentration, and reaction temperature on the kinetics and selectivity of reacting 1-hexanethiol with model blocked isocyanates (mNCOP, mNCOI, and mNCOT). From these experiments, optimal conditions for polymer modification were determined.

In a typical model reaction, a blocked isocyanate analogue was reacted with 1.1 equiv of 1-hexanethiol in the presence of DBU at room temperature. Traditionally, DBU was considered a non-nucleophilic base, but has recently been shown to function as a strong nucleophilic catalyst in numerous reactions.[45,46] In the case of chemical deblocking of isocyanates with thiols, DBU likely functions as both a base catalyst by generating the nucleophilic thiolate species while also acting as a nucleophilic catalyst via transient displacement of the *N*-heterocycle blocking agent to afford the more reactive zwitterionic amidine–isocyanate adduct.[47,48] Although detailed kinetic analysis (i.e., determination of reaction order and rate constants) for these reactions will require additional focus beyond the scope of this paper, the data shown here establish conditions applicable for rapid and efficient postpolymerization modifications.

A representative sequence of real-time ^1H NMR spectra for the DBU-catalyzed room temperature reaction of 1-hexanethiol with mNCOI is shown in Figure 2. Conversion was measured via integration of the protons β to the urea (peak c), relative to the unchanging methylene protons α to the ester at 4.04 ppm (peak b). Figure 3 shows the blocked isocyanate conversion plots for the DBU-catalyzed reaction of 1-hexanethiol with the series of model *N*-heterocycle-blocked isocyanates. The reaction of 1-hexanethiol with mNCOP with 10 mol % DBU at 20 °C yielded only 18% conversion after 19 h—a result that points to the relative stability of the 3,5-dimethylpyrazole-blocked isocyanate which typically requires temperatures around 130 °C for quantitative reaction with amines and alcohols.[33] Conducting the same mNCOP chemical deblocking reaction with thiol at 50 °C provided a significant increase in the rate of the reaction, with 88% conversion achieved after 19 h. By contrast, the reactions of 1-hexanethiol with mNCOI and mNCOT proceeded rapidly at 20 °C using lower DBU concentrations (5 mol %). The chemical deblocking of mNCOI with 1-hexanethiol in the presence of 5 mol % DBU at room temperature was nearly quantitative after 30 min. The significant increase in reactivity of mNCOI is not unexpected; imidazole is more activating than 3,5-dimethylpyrazole.[38] Staab also showed that imidazole-*N*-carboxamides readily dissociate into isocyanate and imidazole in a rapid equilibrium at room temperature (e.g., 16% dissociation at 20 °C in chloroform).[37,49] The reaction of 1-hexanethiol with mNCOT under the same conditions was quite rapid, reaching 95% conversion within 30 s, and then almost quantitative conversion within 5 min (Figure 3). The higher reactivity of mNCOT (due to activating effect of an additional nitrogen atom in the azole ring[38]) also allowed for reducing the DBU concentration to 1 mol % while still providing quantitative thiourethane conversion within 30 min at 20 °C (Figure S1, Supporting Information). It is worth noting that triethylamine was also explored as a catalyst; however, high catalyst loading (>30 mol % TEA) was required to achieve kinetic profiles comparable to those with low DBU concentrations (Figure S2, Supporting Information). The *N*-heterocycle blocking agents follow the

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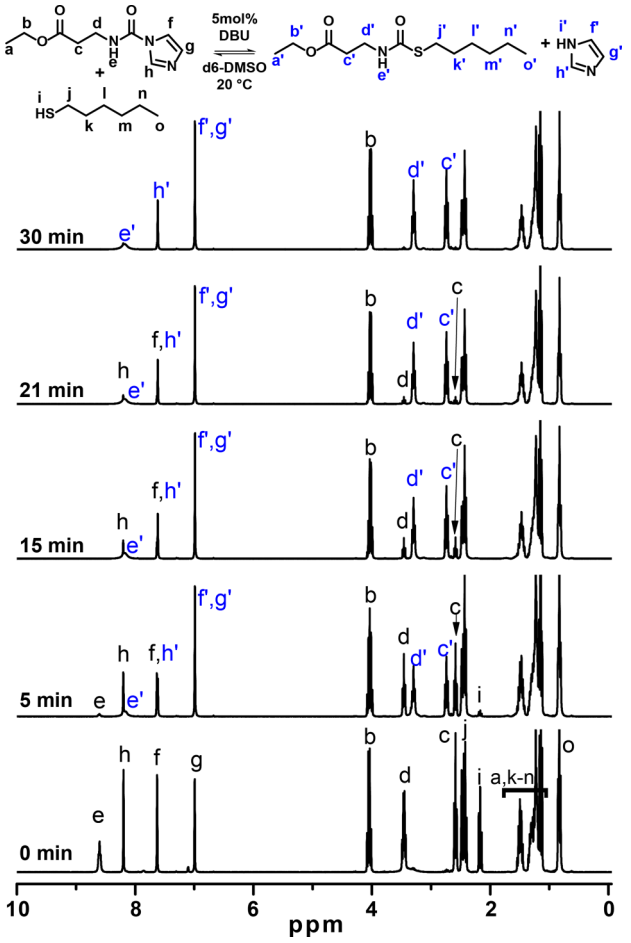


Figure 2. ^{1}H NMR spectra for the reaction of mNCOI with 1-hexanethiol in the presence of 5 mol % DBU (scheme pictured above spectra) at room temperature as the reaction proceeds. Peaks are label corresponding with the structure above.

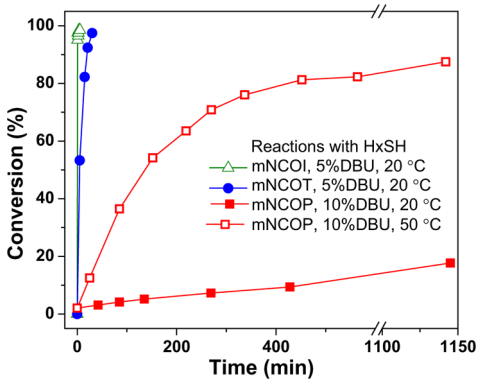
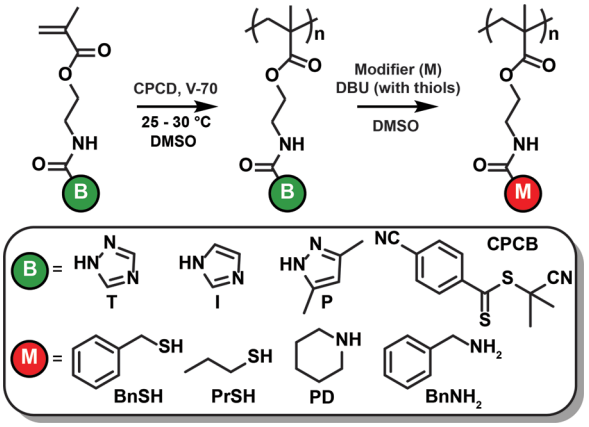


Figure 3. Conversion versus time plots for the following reactions (red ■) mNCOP + 1-hexanethiol +10 mol % DBU at 20 °C, (red □) mNCOP + 1-hexanethiol +10 mol % DBU at 50 °C, (blue ●) mNCOI + 1-hexanethiol + 5 mol % DBU at 20 °C, and (green △) mNCOT + 1-hexanethiol + 5 mol % DBU at 20 °C.

expected trend of 1,2,4-triazole > imidazole >3,5-dimethylpyrazole in terms of leaving group ability based on their pK_a values. The kinetic profiles for the reaction of thiols with mNCOI and mNCOT indicate that imidazole and 1,2,4-triazole may be the ideal blocking agents as polymer pendent scaffolds for postpolymerization modification. Importantly, the full series of *N*-heterocycle blocking agents provides a range of reactivity that may be exploited for sequential modification via appropriate choice of reaction conditions.

Polymer Synthesis. After determination of optimal deblocking conditions with thiols, the *N*-heterocycle-blocked NCO methacrylate monomers were polymerized by RAFT using 2-cyano-2-propyl 4-cyanobenzodithioate (CPCB) as the chain transfer agent (Scheme 3). Dithiobenzoates with electron

Scheme 3. RAFT Polymerization and Postmodification of Blocked NCO Polymers with Thiols or Amines



withdrawing Z-group substituents, such as CPCB, have been shown to provide good control and low dispersities for methacrylates.[50] DMSO was chosen as the polymerization solvent since NCOP, NCOI, and NCOT are readily soluble in this solvent at room temperature. The temperature sensitivity of the pendent *N*-heterocycle-blocked isocyanate moieties present a challenge for controlled polymerizations under standard conditions. Initial RAFT polymerizations conducted at 60−70 °C led to broad dispersities, particularly for mNCOI and mNCOT. Despite reported deblocking temperatures greater than 100 °C for pyrazole-, imidazole-, and triazole-blocked isocyanate derivatives, thermal deblocking and subsequent side reactions occur over a range of temperatures. Side reactions ensue when amines generated by the hydrolysis of deblocked isocyanates react to form cross-links. To avoid complications associated with thermal deblocking during polymer synthesis, polymerizations were conducted at either 25 or 30 °C using V-70—an azo initiator with a 10 h half-life decomposition temperature of 30 °C. Conversion, molecular weight, and dispersity data obtained from exploratory polymerizations of each monomer at 25 or 30 °C and $[M]_o$:$[CTA]_o$:$[I]_o$ = 300:1:0.2 are shown in Table S1; these data were used to select experimental conditions for polymerization kinetics discussed below. Temperature sensitivity and solubility of the blocked NCOI and NCOT polymers also present a challenge for characterization since size exclusion chromatography (SEC) analysis was conducted in DMF (0.2 M LiBr) at 65 °C. pNCOI and pNCOT samples were postmodified with 1-propanethiol, using DBU as a catalyst, prior to SEC analysis to avoid issues with thermal deblocking during analysis. Thus, all polymer molecular weight and dispersity data for NCOI and NCOT reflect the characteristics of the modified polymers. pNCOP was sufficiently stable to enable SEC analysis in the heterocycle-blocked state.

Figure 4a shows the kinetic plot for the polymerization of NCOP at 30 °C. Following a 60 min induction period, linear

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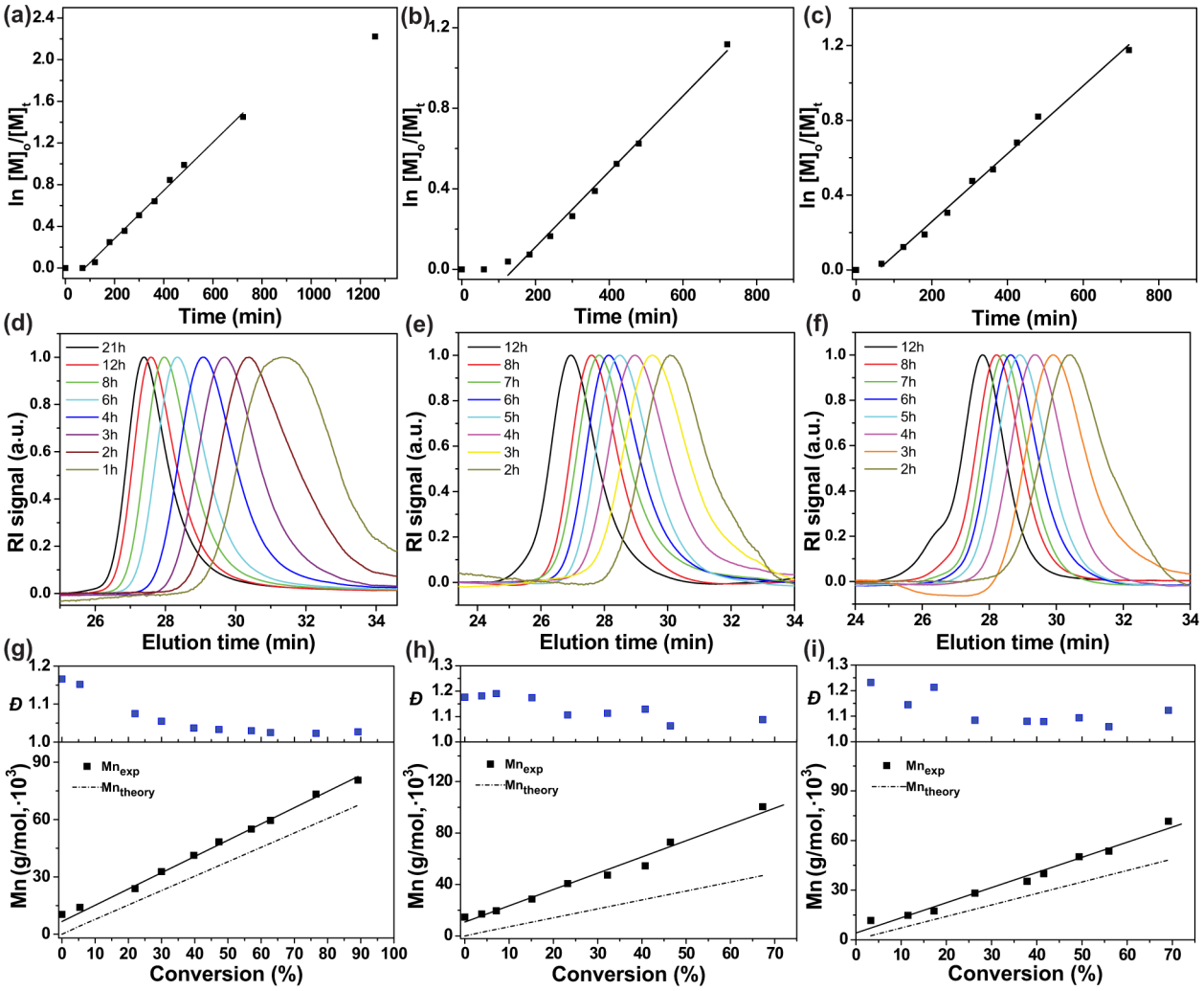

Figure 4. Kinetic plots for CPCD-mediated RAFT polymerization of (a) NCOP at 30 °C, (b) NCOI at 30 °C, and (c) NCOT at 25 °C in DMSO. SEC traces for RAFT polymerization of (d) NCOP, (e) NCOI, and (f) NCOT. Molecular weight and dispersity versus conversion plots for (g) NCOP, (h) NCOI, and (i) NCOT. SEC for NCOP was performed in the blocked form, whereas NCOI and NCOP were modified with propanethiol prior to analysis.

pseudo-first-order kinetic behavior was observed up to 720 min. The induction period may be attributed to an initialization time required for consumption of the CTA, as described by Klumperman et al.,[51,52] or slow fragmentation of the intermediate radical—effects often observed in ambient temperature RAFT polymerizations.[53,54] At longer reaction times (1260 min), deviation from linearity is observed, likely due to a decrease in radical flux associated with half-life of the V-70 initiator ($t_{1/2}$ = 600 min at 30 °C). The SEC chromatograms shown in Figure 4d are symmetrical and shift to lower elution volumes with increasing polymerization time. Additional evidence of a well-controlled polymerization for NCOP is indicated by the linear progression of M_n vs monomer conversion and the narrow molecular weight distributions ($Đ \leq$ 1.10 above 20% conversion), as shown in Figure 4g. The experimentally determined molecular weights ($M_{n,exp}$) values are higher than values predicted based upon conversion ($M_{n,theory}$) for a 300:1 $[M]_0$:$[CTA]_0$ ratio. The discrepancy in $M_{n,exp}$ determined by MALLS and $M_{n,theory}$ may be attributed to irreversible coupling of CTA intermediate radicals or incomplete CTA consumption during the initialization stage.[51] Nonetheless, control for NCOP could be maintained up to high conversions (>90%) to yield relatively high molecular weight polymer (M_n > 80K g/mol).

RAFT polymerization of NCOI was first attempted at 25 °C; however, an extensive initialization period provided low monomer conversion (~9%) after 300 min (Table S1). At 30 °C, the polymerization of NCOI exhibited an initialization period of approximately 60 min, followed by linear pseudo-first-order behavior up to 700 min indicating good control beyond the initialization period (Figure 4b). The SEC chromatograms shown in Figure 4e are unimodal and shift to lower elution times with increasing reaction time—an observation that translates into a linear relationship between $M_{n,exp}$ vs monomer conversion (Figure 4e). Again, the observed $M_{n,exp}$ values are consistently higher than $M_{n,theo}$ values (Figure 4h). Given the observation of a stable concentration of radicals and the absence of polymer chain coupling (e.g., no observations of high MW shoulders by SEC), the discrepancy is likely, as mentioned previously, attributed to irreversible coupling of CTA intermediate radicals or incomplete CTA consumption during the initialization stage. It is also worth noting that a color change was observed upon addition of the CTA to the NCOI monomer solution (Figure S3). We attribute the color

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change to partial degradation of the CTA via aminolysis with imidazole (approximately 4% CTA degradation in 60 min as indicated by NMR, Figure S3)—a process that would contribute to overshooting the theoretical molecular weight values.[55] The behavior of NCOI in solution, in terms of freely dissociating to give imidazole, is not entirely surprising. As mentioned previously, Staab showed that imidiazole-*N*-carboxamides readily dissociate to imidazole and isocyanates even at room temperature (up to 16% dissociation at 20 °C by FTIR).[35,37]

NCOT was polymerized at 25 °C to evaluate polymerization kinetics. As with the other monomers in this series, RAFT polymerization of NCOT shows linear pseudo-first-order behavior up to 700 min following a 60 min initialization period (Figure 4c). The SEC chromatograms shown in Figure 3h shift to lower elution times and are symmetrical up to the 8h aliquot. At 12h, a high molecular weight shoulder is observed that is approximately double the molecular weight of the main polymer peak and can be attributed to radical−radical coupling. Increasing the polymerization temperature to 30 °C shifted the observation of the high molecular weight shoulder to lower conversions (Figure S4) Analysis of the SEC chromatograms showed dispersities above 1.2 at conversions less than 20% that gradually decreased ($Đ$ < 1.1) with increasing monomer conversion (Figure 4f). Chain coupling above 50% conversion resulted in a small increase in dispersity. A well-controlled polymerization of NCOT was also indicated by a linear increase in $M_{n,exp}$ with conversion (Figure 4i). As with NCOP and NCOI, the $M_{n,exp}$ values were higher than the targeted $M_{n,theo}$; however, due to a shorter initialization period (e.g., minimal CTA side reactions), the expected and actual M_n values for NCOT are in better agreement than those for NCOI. The polymerization kinetics reported in this paper demonstrate that this series of n-heterocyclic-blocked NCO methacrylates can be polymerized to yield controlled molecular weights and dispersities, even when polymers were modified by thiols prior to characterization.

Post-Polymerization Modification. After establishing conditions for controlled polymerization of NCOP, NCOI, and NCOT, the resulting polymers were exploited as scaffolds for postpolymerization modification. For simple proof of concept, two thiols, 1-propanethiol (PrSH) and benzyl mercaptan (BnSH), and two amines, piperidine (PD) and benzyl amine ($BnNH_2$), were chosen to demonstrate post-modification of the blocked NCO polymers. The results obtained from reactions of thiols with small molecule analogues, as described previously, were used to guide the choice of reaction conditions for the polymer modifications described herein. Polymers blocked with 3,5-dimethylpyrazole were isolated via precipitation prior to postmodification, and subsequently modified with PrSH and BnSH at 50 °C with DBU as a catalyst, or PD and $BnNH_2$ at 50 °C without DBU. However, the high reactivity of the pNCOI and pNCOT scaffolds presented a challenge to standard isolation, e.g. precipitation resulted in high molecular weight tailing observed in the isolated SEC traces likely due to instability of the blocked pendent groups. Thus, polymers blocked with imidazole and triazole were efficiently postmodified in crude form at 25 °C to avoid adventitious side reactions. Figure S5 shows the SEC traces for isolated, unmodified pNCOP and pNCOP modified with BnSH. A shift to lower elution time occurs after modification of pNCOP, which is consistent with the increase in molecular weight expected by displacing 3,5-dimethylpyrazole (96.13 g/mol) with BnSH (124.2 g/mol). Table 1 provides a summary of the polymer molecular weights and dispersities following postmodification of pNCOP, pNCOI, and pNCOT with PrSH, BnSH, and PD. As shown, molecular weights greater that 40 kg/mol and low dispersities ($Đ \leq 1.21$) were obtained for all postmodified polymer scaffolds. Typical ^{1}H NMR spectra for the postmodified polymer scaffolds based on pNCOI are shown in Figure 5. The absence of peaks at 6.99, 7.61, and 8.18 ppm in the NMR spectra indicates quantitative chemical deblocking of the imidazole moieties with BnSH (Figure 5a), PrSH (Figure 5b), PD (Figure 5c), and $BnNH_2$ (Figure 5d). The carbamide proton peak of the asymmetrical urea is located at 8.63 ppm prior to modification and shifts to 6.5 or 6.0 ppm upon formation of the new thiocarbamate or urea, respectively. The presence of peak f, representative of each modifier, in each spectrum in Figure 4 also suggests the successful modification of blocked NCO polymers.

Table 1. Molecular Weights and Dispersities for Thiol and Amine Modified Blocked NCO Polymers

entry	polymer	temp[a] (°C)	time[b] (h)	PPM M_{nexp}[c] (kg/mol)	PPM $Đ$[c]
1a	pNCOP−PrSH	50	48	38.3	1.21
1b	pNCOP−BnSH			42.2	1.10
1c	pNCOP−PD			40.1	1.03
1d	pNCOP−$BnNH_2$			29.5[d]	1.04
2a	pNCOT−PrSH	25	12	41.8	1.08
2b	pNCOT−BnSH			51.0	1.07
2c	pNCOT−PD			45.8	1.06
2d	pNCOT−$BnNH_2$			43.3[d]	1.05
3a	pNCOI−PrSH	25	12	74.4	1.08
3b	pNCOI−BnSH			87.4	1.18
3c	pNCOI−PD			73.3	1.11

[a]PPM temperature. [b]PPM time. [c]As determined by SEC−MALLS (DMF with 20 mM LiBr). [d]MW determined on a different column set than all other polymers in the table due to instrumentation issues during the revision process.

Sequential Polymer Modification. Sequential postmodification reactions offer a direct route to multifunctional polymers and find the most utility in scaffolds containing independently addressable reactive moieties. Sequential modifications are typically achieved by either exploiting inherently orthogonal chemical transformations or inducing selective reactivity through judicious choice of reaction conditions. In this section, we describe how the differences in reactivity of 1,2,4-triazole-blocked NCOs and 3,5-dimethylpyrazole-blocked NCOs can be leveraged to achieve sequential polymer modification. Recalling the results from our small molecule model reactions, we observed that reactions of a nucleophile with 3,5-dimethylpyrazole-blocked NCOs were slow or unreactive at room temperature, but could be driven toward higher conversion at elevated temperatures (e.g., 50 °C). Conversely, nucleophiles were found to react rapidly with 1,2,4-triazole-blocked NCOs at 25 °C.

To exploit the "staggered" reactivity of pyrazole and triazole derivatives for sequential polymer modifications, copolymers

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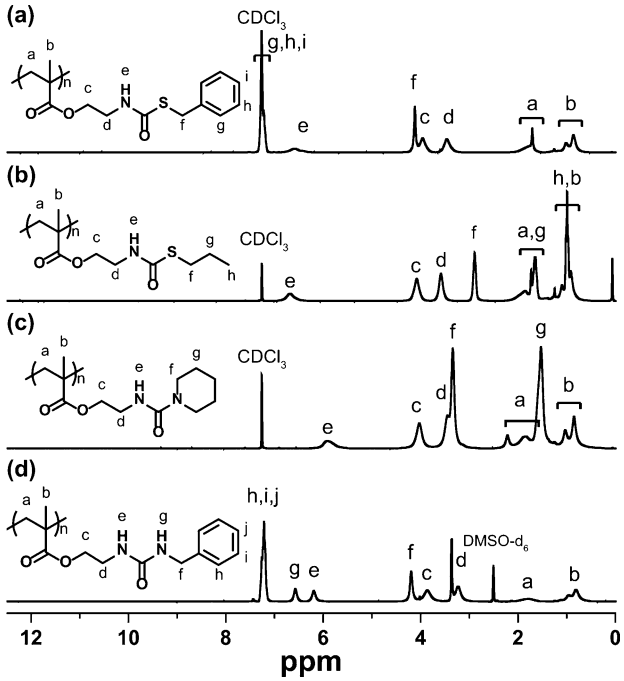

Figure 5. ^{1}H NMR spectra of imidazole-blocked NCO polymers modified at room temperature with (a) benzyl mercaptan, (b) 1-propanethiol, (c) piperidine, or (d) benzyl amine after purification.

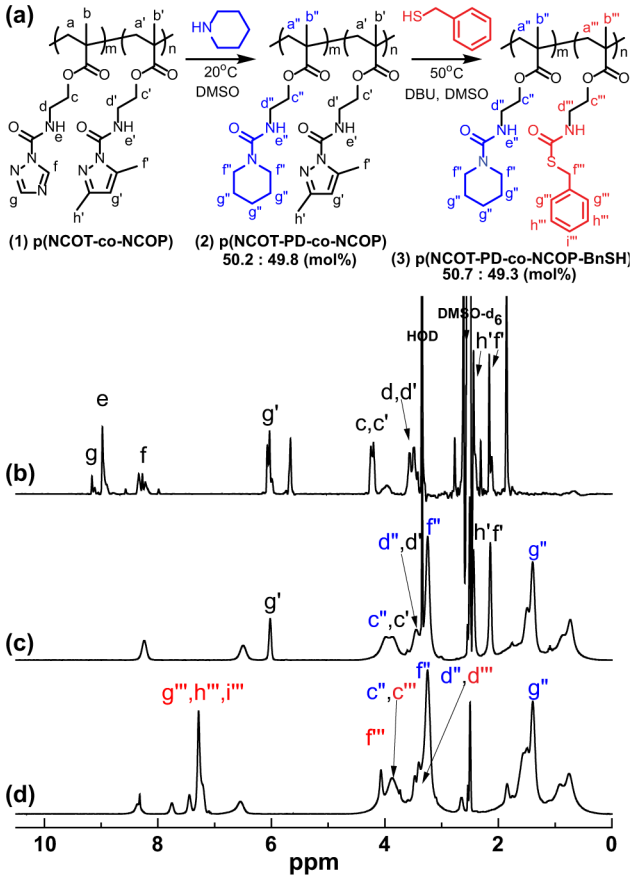

Figure 6. (a) Synthetic route to sequentially modified blocked NCO copolymers. ^{1}H NMR spectra of (b) crude pNCOT-*co*-NCOP (c) after the first modification with piperidine and (d) after the second modification with benzyl mercaptan. All NMR spectra were collected in DMSO-d_6.

were synthesized by RAFT polymerization at 25 °C using a 50:50 molar ratio of NCOT and NCOP monomers. Figure 6a shows the synthetic route used to sequentially modify p(NCOT-*co*-NCOP) copolymers. Figure 6b shows the ^{1}H NMR spectrum of the crude copolymer prior to post-modification. The copolymerization of NCOT and NCOP was stopped after 5 h and the crude polymerization mixture was added to a solution of piperidine at 20 °C to displace the triazole blocking agent. Figure 6c shows the ^{1}H NMR spectrum of the copolymer after piperidine modification and purification by precipitation. The formation of a new carbamide with the amine modifier was confirmed by the presence of PD peaks, labeled f″ (3.27 ppm) and g″ (1.46 ppm) in Figure 6c, and the absence of 1,2,4-triazole peaks located at 8.27 and 9.16 ppm. Notably, the 3,5-dimethylpyrazole blocking agents in the copolymer were still present following the initial modification, as indicated by the presence of protons assigned f′, h′, and g′ in Figure 6c. To gauge the selectivity of the initial modification, a pNCOP homopolymer was modified with PD under identical conditions (12 h, 20 °C) and integration showed less than 3% of the pyrazole blocking agents were displaced by PD (Figure S6). Returning to the copolymer, integration of ^{1}H NMR spectrum (Figure S7a) after piperidine modification indicated the composition of the pendent groups was approximately 50:50 (mol %) piperidine to 3,5-dimethylpyrazole. The piperidine modified copolymer was then sequentially modified with benzyl mercaptan in anhydrous DMSO with DBU at 50 °C to displace the 3,5-dimethylpyrazole blocking agents. The ^{1}H NMR spectrum of the copolymer sequentially modified with PD and BnSH is shown in Figure 6d. The disappearance of the pyrazole peaks at 2.12 ppm (f′), 2.46 ppm (h′), and 5.85 ppm (g′), and the appearance of BnSH peaks at 4.07 ppm (f‴) and 7.22 ppm (g‴, h‴, and i‴), shown in Figure 6d, indicate that the modification with benzyl mercaptan proceeded to high conversion. Furthermore, the peaks attributed to the PD functionalized units (f″ and g″) from the initial modification remain unchanged, where integration (Figure S7b) indicated the composition of the pendent groups was approximately 50:50 (mol %) piperidine to triazole. These results demonstrate the sequential nature of the postmodifications, and while not perfectly selective, point to the utility of using the large difference in reactivity of various blocking agents to design multifunctional polymers in a modular fashion. SEC−RI traces, shown in Figure S8, also support the sequential nature of the postmodification reactions. After modification with piperidine, the molecular weight of p(NCOT−PD-*co*-NCOP) was 43.4 kg/mol with a dispersity of 1.05 and, after the second modification with BnSH, the molecular weight increased to 52.7 kg/mol with a dispersity of 1.24 for p(NCOT−PD-*co*-NCOP−BnSH). The shift to higher molecular weight from the first modification to the second was expected to be relatively small based on the small increase in molecular weight going from 3,5-dimethylpyrazole to BnSH. The increase in dispersity during modification with BnSH may be attributed to various intermolecular side chain reactions that may occur at temperatures as low as 50 °C (e.g., allophanate formation) or in the presence of trace amounts of water (e.g., urea and biuret formation).[56] We are currently exploring other blocking agents that eliminate these unwanted side reactions. The results from ^{1}H NMR and SEC show that with judicious choice of blocking agents and PPM conditions, it is possible to design and synthesize dually modifiable copolymer scaffolds with low

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dispersities and controlled molecular weights. Furthermore, this strategy has the potential for additional versatility by selecting from a variety of thiols, amines, and alcohols available to react with the blocked NCOs.

CONCLUSIONS

In summary, we report the synthesis of well-defined polymethacrylate scaffolds containing pendent *N*-heterocycle-blocked isocyanates via low temperature RAFT polymerization. Judicious choice of *N*-heterocycle blocking agents enabled rapid and efficient postpolymerization modification with thiols and amines at ambient temperature via chemical deblocking. Sequential modification reactions on copolymer scaffolds were demonstrated by exploiting differences in the latent reactivity of pendent triazole- and pyrazole-blocked isocyanates. Triazole-blocked NCO moieties were initially deblocked with an amine at ambient temperature; subsequently, the NCOP units were deblocked with a thiol at 50 °C enabling the synthesis of multifunctional polymer scaffolds. We expect the azole-*N*-carboxamide derivatives employed here as blocked isocyanates for postpolymerization modification will find broad use in other polymer synthetic strategies where balanced latency and reactivity under mild conditions are necessary to engineer functional macromolecular materials.

EXPERIMENTAL SECTION

Materials. Karenz MOI-BP (3,5-dimethylpyrazole-blocked isocyanate methacrylate) was obtained from Showa Denko and passed through a neutral alumina plug to remove inhibitor prior to use. Ethyl 3-isocyantopropionate (Aldrich, 98%), 2,2′-Azobis(4-methoxy-2−4-dimethyl valeronitrile) (V-70) (Wako, 96%), 2-isocyanatoethyl methacrylate (TCI, > 98%), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Acros, 98%), 2-cyano-2-propyl 4-cyanobenzodithioate (CPCB) (Aldrich, 98%,), imidazole (Aldrich, ≥ 99%), 1,2,4-triazole (Acros, 99.5%), 3,5-dimethylpyrazole (Aldrich, 99%), 1-propanethiol (Aldrich, 99%), benzyl mercaptan (Fluka, ≥ 99%), piperidine (Aldrich, redistilled, 99.5+%), tetrahydrofuran (THF) (Aldrich, anhydrous, inhibitor free, ≥ 99.9%) and dimethyl sulfoxide (DMSO) (Aldrich, anhydrous, 99.9%) were used as received.

Characterization. NMR studies were conducted using a Varian INOVA 300 MHz NMR spectrometer in DMSO-d_6 or $CDCl_3$ at 25 °C. Model reactions requiring reaction temperatures at 50 °C were acquired on a Bruker Ascend 600 MHz spectrometer using DMSO-d_6, whereas reactions requiring ambient temperatures were acquired on the Varian INOVA 300 MHz NMR. Number-average molecular weight (M_n) and dispersities ($Đ$) were determined using a size exclusion chromatography system consisting of a Waters Alliance 2695 separation module, online multiangle laser light scattering (MALLS) detector fitted with a gallium arsenide laser (20 mW power) operating at 690 nm (MiniDAWN Wyatt Technology Inc.), an interferometric refractometer (Optilab DSP, Wyatt Technology Inc.), and two Polymer Laboratories mixed C columns (5 μm beadsize) connected in series. The eluent used was HPLC grade dimethylformamide (DMF) (0.02 M LiBr) at a flow rate of 0.5 mL/min at 65 °C. The refractive index increment (d*n*/d*c*) of each polymer was determined in DMF (0.02 M LiBr).

2-(1*H*-1,2,4-Triazole-1-carboxamido)ethyl Methacrylate (NCOT). 2-Isocyanatoethyl methacrylate (13.84 g, 89.2 mmol) was added dropwise over 15 min at room temperature to a stirred solution of 1,2,4-triazole (6.16 g, 89.2 mmol) in a 4:5 (v:v) mixture of THF (80 mL) and diethyl ether (100 mL). The reaction was stirred for an additional 3 h after which the product precipitated as a white solid. The solid precipitate was isolated by vacuum filtration, rinsed with THF (20 mL), and dried *in-vacuo* to give the desired product as a white solid (15.16 g, 76%). Mp: 100−103 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.16 (s, 1H), 8.90 (t, J = 5.6 Hz, 1H), 8.27 (s, 1H), 6.02 (s, 1H), 5.65 (s, 1H), 4.23 (t, J = 5.4 Hz, 2H), 3.55 (q, J = 5.5 Hz, 2H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.51, 152.60, 148.02, 144.39, 135.89, 126.05, 62.72, 39.04, 17.99. Anal. Calcd for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99; O, 21.41. Found: C, 48.22; H, 5.38; N, 24.76; O, 21.69.

2-(1*H*-Imidazole-1-carboxamido)ethyl Methacrylate (NCOI). 2-Isocyanatoethyl methacrylate (7.59 g, 48.9 mmol) was added dropwise over 15 min at room temperature to a stirred solution of imidazole (3.33 g, 48.9 mmol) in diethyl ether (100 mL). The reaction was stirred for 1 h, after which the product precipitated as a white solid. The solid precipitate was isolated by vacuum filtration, rinsed with diethyl ether (20 mL), and dried *in vacuo* to give the desired product as a white solid (10.47 g, 96%). Mp: 75−80 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.64 (t, J = 5.2 Hz, 1H), 8.20 (s, 1H), 7.63 (s, 1H), 7.01 (s, 1H), 6.03 (s, 1H), 5.69−5.59 (m, 1H), 4.23 (t, J = 5.5 Hz, 2H), 3.53 (q, J = 5.5 Hz, 2H), 1.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.93, 149.31, 135.98, 129.76, 126.70, 116.70, 63.03, 40.47, 18.30. Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82; O, 21.50. Found: C, 53.89; H, 6.00; N, 18.78; O, 21.70.

3-(1*H*-1,2,4-Triazole-1-carboxamido)propanoate (mNCOT). Ethyl-3-isocyantopropionate (1.89, 13.2 mmol) was added dropwise over 5 min to a stirred solution of 1,2,4-triazole (0.91 g, 13.2 mmol) in a 1:2 (v:v) mixture of THF (15 mL) and diethyl ether (30 mL). The reaction was stirred for 2 h, while the product precipitated as a white solid. The solid precipitate was isolated by vacuum filtration, rinsed with THF (20 mL), and dried *in vacuo* to give 1.62 g (58% yield) of product as a white solid. Mp: 81−85 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.95 (s, 2H), 8.89 (t, J = 5.0 Hz, 1H), 4.12−3.96 (m, 2H), 3.46 (dd, J = 12.2, 6.7 Hz, 2H), 2.59 (t, J = 6.8 Hz, 2H), 1.20−1.05 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.40, 147.12, 140.88, 60.65, 36.81, 33.63, 14.44. Anal. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40; O, 22.62. Found: C, 45.27; H, 5.63; N, 19.97; O, 22.82.

Ethyl 3-(1*H*-imidazole-1-carboxamido)propanoate (mNCOI). Ethyl-3-isocyanatopropionate (1.93 g, 13.5 mmol) was added dropwise over 5 min to a stirred solution of imidazole (0.917 g, 13.5 mmol) in diethyl ether (50 mL) over 10 min. The reaction was stirred for 1 h at room temperature, while a white precipitate formed. The solid precipitate was isolated by vacuum filtration, rinsed with diethyl ether, and dried *in vacuo* to give 2.58 g (91% yield) of product as a white solid. Mp: 80−84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.37 (s, 1H), 7.09 (s, 1H), 7.08−7.02 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.69 (dd, J = 11.8, 5.9 Hz, 2H), 2.67 (t, J = 5.9 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.20, 149.07, 136.11, 129.74, 116.38, 60.92, 36.49, 33.63, 14.09. Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89; O, 22.72. Found: C, 51.21; H, 6.32; N, 19.87; O, 22.80.

Ethyl 3-(3,5-dimethyl-1*H*-pyrazole-1-carboxamido)-propanoate (mNCOP). Ethyl-3-isocyanatopropionate (1.49 g, 10.4 mmol) was added dropwise over 15 min to a stirred solution of pyrazole (1.00 g, 10.4 mmol) diethyl ether (50 mL). The reaction was stirred for 1 h before the product was isolated from diethyl ether by rotary evaporation and dissolved in CH_2Cl_2. The product was then transferred to a separatory funnel and washed with water (1×, 150 mL) and with brine solution (1×, 150 mL). The organic layer was dried over $MgSO_4$ and the filtrate collected. Solvent was then removed by rotary evaporation and dried *in vacuo* to give a colorless oil (2.05 g, 82.4% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68−7.50 (m, 1H), 5.81 (s, 1H), 4.09 (qd, J = 7.1, 1.1 Hz, 2H), 3.63−3.46 (m, 2H), 2.56 (t, J = 6.3 Hz, 2H), 2.46 (s, 3H), 2.10 (s, J = 1.0 Hz, 3H), 1.19 (td, J = 7.1, 1.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.03, 151.42, 150.18, 143.46, 109.72, 60.80, 35.56, 34.38, 14.20, 13.98, 13.62. Anal. Calcd for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56; O, 20.06. Found: C, 55.24; H, 7.37; N, 17.52; O, 18.31.

General Procedure for RAFT (Co)Polymerization of Blocked Isocyano Methacrylates. Blocked NCO functional monomer (8.0×10^{-3} mol), or a mixture of blocked NCO monomer and comonomer (total 8.0×10^{-3} mol), was added to a vial and dissolved in anhydrous DMSO (6.5 mL). RAFT agent (2-cyano-2-propyl 4-cyanobenzodithioate, CPCB) (2.6×10^{-5} mol), initiator (V-70) (5.2×10^{-6} mol), and *p*-xylene (NCOP and NCOT, 100 μL, ^{1}H NMR internal standard) or 1,3,5-trioxane (NCOI, 70 mg, ^{1}H NMR internal

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standard) were then combined in the vial with monomer and solvent. The final volume was adjusted by adding anhydrous DMSO to achieve a final solution volume of 8 mL ($[M]_0$= 1 M). V-70 was added under the above polymerization conditions as a solution in anhydrous THF (1.6 mg/100 μL) and CPCB was added as a solution in anhydrous DMSO (6.5 mg/100 μL). The polymerization solution was capped with a rubber septum and purged with N_2 for 30 min. Polymerizations were conducted at either 25 or 30 °C. An initial aliquot (200 μL) was taken after purging, but prior to placing the vial in a preheated oil bath. After placing the reaction vessel in the oil bath, aliquots for kinetic measurements were taken at timed intervals. Each aliquot was exposed to oxygen and quenched in liquid N_2. After warming to room temperature, a portion of each aliquot (50 μL) was analyzed by ^{1}H NMR (DMSO-d_6) to determine monomer conversion and the remaining portion (150 μL, 1.5 × 10^{-4} mol blocked NCO) was modified immediately with 1-propanethiol (2 mmol) and 10 mol % DBU (2 × 10^{-4} mol) for analysis by SEC−MALLS. pNCOP was analyzed by SEC−MALLS without prior modification. pNCOP was purified by precipitation in 10-fold excess diethyl ether-ethyl acetate (9:1) (2×) and finally in diethyl ether (1×). Unmodified pNCOT and pNCOI were not isolated. The modification of blocked NCOT and NCOI polymers with thiols and their subsequent purification is described in detail in a later section.

Model Reaction Kinetics of Thiol-Modification of Blocked Isocyanates. For a typical thiol modification model reaction, model blocked NCO (2 mmol) was dissolved in DMSO-d_6 (1 mL, $[mNCO]_0$= 0.2 M) and a thiol (0.2 mmol) was added. The solution was transferred to an NMR tube for ^{1}H NMR analysis. An initial ^{1}H NMR spectrum was obtained of the thiol plus model blocked NCO and then the catalyst (DBU or TEA) (0.01, 0.05, 0.1, or 0.3 equiv) was added. Subsequent ^{1}H NMR experiments were collected at timed intervals to determine conversion of blocked NCO to thiocarbamate by comparing the relative integral areas of the alpha hydrogens of the ethyl ester (4.04 ppm, 2H) to the β hydrogens (2.60 ppm, 2H) of the nitrogen in the NCO functional group. For model reactions at elevated temperatures, the NMR tube was placed in an oil bath at 50 °C in between ^{1}H NMR collection at timed intervals or heated to 50 °C during scan collection in the NMR instrument as described in the characterization section. In the case of model reactions with amines, an initial ^{1}H NMR experiment was collected for the model blocked NCO in DMSO-d_6 and an amine was added to the NMR tube (2.2 mmol). Additional ^{1}H NMR experiments were collected at timed intervals to determine the conversion of blocked NCO to a new carbamide by comparing the same relative integrals areas described above.

General Procedure for Post-Polymerization Modification of Blocked NCO Polymers with Thiols. *Procedure for Room Temperature Modification of 1,2,4-Triazole- and Imidazole-Blocked NCO Polymers.* Synthesis of polymers for postpolymerization modification was conducted according to the general RAFT procedure provided and stopped after 5 h by exposing to oxygen and quenching with liquid N_2. After quenching, polymers were allowed to warm to room temperature and modified as a crude polymerization solution. In a model modification reaction with a thiol, the crude polymerization solution (8 mmol) was added dropwise to a solution of thiol (80 mmol) and DBU (0.8 mmol) and stirred for 12−18 h at room temperature. Thiol-modified polymers were isolated by precipitation first into a 9:1 (v:v) mixture of methanol and water (9:1) from DMSO and then diethyl ether (2×) from THF. In an exemplary modification reaction with an amine, the crude polymerization solution (4 mmol) was added dropwise to a vial containing an amine (40 mmol) and stirred for 12−18 h at room temperature. Amine-modified polymers were precipitated in 10-fold excess diethyl ether-ethyl acetate (9:1) (2×), and diethyl ether (1×). Polymers were redissolved in methanol in between precipitations.

Procedure for Modification of 3,5-Dimethylpyrazole-Blocked NCO Homopolymers at 50 °C. Synthesis of polymers for postpolymerization modification of pNCOP were conducted according to the general RAFT procedure provided in the Experimental Section and stopped after 5 h. NCOP homopolymers were isolated prior to modification as described previously. In a model reaction with a thiol, purified pNCOP (1 mmol of blocked NCO) was dissolved in anhydrous DMSO (2 mL) and added to a solution of thiol (10 mmol) and DBU (1 mmol). In the case of modification with an amine, pNCOP in DMSO was added dropwise to a vial containing the amine (10 mmol). The reaction flask was then placed in a preheated oil bath set at 50 °C and stirred for 48 h. The modified polymer was isolated by precipitation in 10-fold excess diethyl ether−ethyl acetate (9:1) (2×) and finally in diethyl ether (1×). Polymers were redissolved in THF in between precipitations.

Procedure for Sequential Thiol-Modification of Blocked NCO Copolymers. Copolymerizations of NCOT and NCOP were conducted according to the general RAFT procedure provided and stopped after 5 h. In a typical sequential blocked NCO modification, the NCOT units of the copolymer were modified first by adding the crude polymerization solution (8 mmol (NCOP + NCOT)) dropwise to a solution of amine (X) (80 mmol). The reaction was stirred at room temperature for 12 h. The amine modified copolymer with unreacted NCOP units was isolated by precipitation first in diethyl ether-ethyl acetate (9:1) (2×) and then diethyl ether (1×). For modification of the second blocked NCO unit, p(NCOT−X-*co*-NCOP) (0.75 mmol of NCOP) was dissolved in anhydrous DMSO (1.5 mL) and added to a solution of thiol (Y) (7.5 mmol) and DBU (0.75 mmol). The modification reaction was then stirred at 50 °C for 24 h and the resulting polymer, p(NCOT−X-*co*-NCOP−Y), was isolated by precipitation in 10-fold excess diethyl ether−ethyl acetate (9:1) (2×) and finally in diethyl ether (1×).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.5b02377.

Model reaction kinetics with trimethylamine as catalyst, initial RAFT polymerization conditions, CTA stability, and additional NMR and SEC data (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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