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Derek L. Patton *et al.*

Thiol–isocyanate “click” reactions: rapid development of functional polymeric surfaces

Thiol–isocyanate “click” reactions: rapid development of functional polymeric surfaces†

Ryan M. Hensarling,^a Santosh B. Rahane,^a Arthur P. LeBlanc,^a Bradley J. Sparks,^a Evan M. White,^b Jason Locklin^b and Derek L. Patton^{*a}

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Functional, micropatterned and multicomponent polymer brush surfaces can be rapidly fabricated via base-catalyzed thiol–isocyanate “click” reactions.

Applications for advanced functional polymeric surfaces that possess precisely engineered properties are expanding rapidly. Such demands necessitate the development of fabrication methods for soft material surfaces with precise control over functionality, architecture, reactivity and domain size for an array of applications ranging from biosensors to microelectronics.¹ Among several surface functionalization strategies recently developed, those involving robust and efficient click reactions are particularly attractive for orthogonal and site-selective immobilization of functional moieties.² Several outstanding examples involving conventional Cu-catalyzed azide–alkyne^{3–5} and photoactivated Cu-free azide–alkyne cycloadditions⁶ illustrate the power of click strategies for tailor-made surfaces. Additionally, we and others have demonstrated thiol–click reactions, including thiol–ene^{7–10} and thiol–yne,¹¹ as rapid, robust, and efficient immobilization strategies toward patterned, multicomponent surfaces. Our current efforts focus on expanding the “toolbox” of modular reactions that allow immobilization of functionally complex molecules onto solid substrates by exploiting efficient linking strategies. Herein, we report thiol–isocyanate (thiol–NCO) chemistry as a modular approach toward surface engineering by demonstrating the rapid generation of a library of functional, patterned, and multicomponent polymer brush surfaces using a single substrate precursor.

The base-catalyzed reaction of thiols with isocyanates yielding thiourethanes has been known for over 50 years,^{12,13} but has only recently been recognized for its potential as a click reaction.^{14,15} Despite impressive potential, these reactions have been scarcely exploited for polymer synthesis^{16,17} and postmodification.^{18,19} For functional surfaces, isocyanate chemistry has only been explored in

a few instances that focused on reactions with amines (urethane linkages) for immobilizing functional moieties on self-assembled monolayers for biosurfaces,^{20,21} photoswitchable wettability,²² organometallic surfaces,²³ and self-cleaning/anti-fog surfaces.²⁴ To our knowledge, thiol–isocyanate chemistry has yet to be explored as a modular approach to surface engineering. Considering rapid kinetics, quantitative conversions, and vast libraries of commercially available and/or naturally occurring thiols, we envisioned the fabrication of highly functional surfaces using base-catalyzed thiol–NCO reactions to modify densely tethered NCO-containing polymer brush surfaces. As we will show, this approach works equally well with thiols or amines. This platform is analogous, but *orthogonal* to our recently reported radical-mediated thiol–yne click approach.¹¹ Additionally, the NCO group is inert to radical polymerization conditions eliminating any need and synthetic effort to protect the “clickable” moiety during surface-initiated photopolymerization (SIP).

As shown in Fig. 1a, silicon substrates were first functionalized with a chlorosilane derivative of commercially available 2-hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone (Irgacure 2959) photoinitiator.^{11,25} These substrates were subsequently inserted into



Fig. 1 (a) Schematic procedure for surface-initiated photopolymerization of 2-isocyanatoethyl methacrylate and subsequent X-isocyanate functionalization (X = thiol or amine). (b) Schematic procedure for patterning NCO-containing polymer brush surfaces with sequential X-isocyanate reactions.

^aSchool of Polymers and High Performance Materials, University of Southern Mississippi, 118 College Drive #5050, Hattiesburg, MS, USA. E-mail: derek.patton@usm.edu; Fax: +1 601-266-5880; Tel: +1 601-266-4792

^bDept. of Chemistry, Faculty of Engineering, and the Center for Nanoscale Science and Engineering, University of Georgia, Athens, GA, 30602, USA

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Fig. 2 Commercially available thiols/amines used for X-isocyanate click reactions: mercaptopropionic acid (1), 1-dodecanethiol (2), thioglycerol (3), *N*-acetyl-L-cysteine (4), benzyl mercaptan (5), 1-adamantanethiol (6), thiocholesterol (7), 3-mercaptopropyl polyhedral oligomeric silsesquioxane (POSS) (8), furfuryl mercaptan (9), benzyl amine (10), and hexyl amine (11).

a microchannel reactor containing 2-isocyanatoethyl methacrylate (1 : 6 v/v in dry THF) and irradiated with $UV_{\lambda_{\max}=365\text{nm}}$ light ($\sim 140 \text{ mW cm}^{-2}$, 20 min, $\sim 28 \text{ nm}$ brush thickness). For the fabrication of a $15 \text{ mm} \times 65 \text{ mm}$ substrate only 1 mL of monomer solution was required to fill the microchannel reactor, drastically reducing the cost of this approach. After extensive washing in THF and toluene, the brush surfaces were analyzed by grazing-angle attenuated total reflection FTIR (GATR-FTIR), ellipsometry and water contact angle measurements. Polymer brush formation was confirmed by the presence of the asymmetric stretching vibration of the isocyanate group (2275 cm^{-1}) and carbonyl stretching vibration for esters (1729 cm^{-1}) (Fig. 3).²⁶ The resulting NCO-containing polymer brushes served as a “universal” reactive precursor for subsequent thiol–NCO click reactions eliminating the synthetic effort associated with the use of multiple functional monomers. Despite the known sensitivity of NCO functional groups, no special handling of the substrates was required prior to thiol modification. NCO-modified surfaces could be stored up to two weeks in nitrogen-flushed, septum-sealed test tubes with no observable loss in functionality or degradation in reactivity.

The nucleophilic addition of primary thiols or amines to isocyanates generates a thiourethane or urea linkage, respectively (Fig. 1a). Amine–NCO reactions are self-catalyzed while thiol–NCO reactions require the addition of a base catalyst—the identity of which is known to have a pronounced effect on the reaction kinetics.¹⁷ Tertiary amine catalysts facilitate rapid reactions *via* generation of (1) a more electron deficient carbonyl carbon within the isocyanate moiety and (2) a strongly nucleophilic thiolate ion.^{15,17} For thiol–NCO reactions herein, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.2 mol% with respect to thiol) was used as catalyst. To explore the efficacy of the isocyanate click reactions on surfaces, we selected a library of commercially available thiols and amines for functionalization (Fig. 2): 3-mercaptopropionic acid (MPA) (pH responsive), 1-dodecanethiol (DDT) (hydrophobic), 1-thioglycerol (hydrophilic), *N*-acetyl-L-cysteine (model peptide attachment), benzyl mercaptan, 1-adamantanethiol, thiocholesterol (biomembrane attachment), 3-mercaptopropyl polyhedral oligomeric silsesquioxane (POSS), furfuryl mercaptan, hexyl amine, and benzyl amine. These reactions were carried out under ambient air, temperature, and humidity conditions to afford functional polymeric brushes. Subsequently, the substrates were washed extensively with multiple solvents to eliminate



Fig. 3 GATR-FTIR spectra of brushes on SiO_x substrates (key peaks are identified): (a) poly(2-isocyanatoethyl methacrylate) brush (2275 cm^{-1} , NCO) (red) reacted with (b) 3-mercaptopropionic acid ($3320\text{--}3000 \text{ cm}^{-1}$, COO–H), (c) 1-dodecanethiol ($2954, 2924, 2852 \text{ cm}^{-1}$, C–H), (d) 1-thioglycerol ($3573\text{--}3125 \text{ cm}^{-1}$, OH), (e) *N*-acetyl-L-cysteine ($3450\text{--}3162 \text{ cm}^{-1}$, CO–NH), (f) benzyl mercaptan ($3084, 3058, 3025 \text{ cm}^{-1}$, =C–H; $1517, 1493, 1451 \text{ cm}^{-1}$, C=C), (g) 1-adamantanethiol ($2906, 2850 \text{ cm}^{-1}$, C–H), (h) thiocholesterol ($2936, 2903, 2865, 2850 \text{ cm}^{-1}$, C–H), (i) 3-mercaptopropyl polyhedral oligomeric silsesquioxane (1109 cm^{-1} , Si–O), (j) furfuryl mercaptan ($1204, 1156 \text{ cm}^{-1}$, C–O (cyclic), 1068 cm^{-1} , C–O–C (5-membered rings)), (k) hexyl amine ($2954, 2930, 2856 \text{ cm}^{-1}$, C–H), and (l) benzyl amine ($3085, 3061, 3025 \text{ cm}^{-1}$, =C–H; $1565, 1493, 1451 \text{ cm}^{-1}$, C=C).

any physisorbed material prior to characterization. GATR-FTIR was used to follow the functionalization of the brushes with the various thiols and amines. For the entire series of functional brushes,



Fig. 4 (a) Condensation image of sequential thiol–NCO micropatterned brushes (sulfonate/DDT) showing water droplets selectively nucleating on the hydrophilic sulfonated areas. (b) AFM image of sequential thiol–NCO micropatterned brushes (sulfonate/DDT), $100 \times 100 \mu\text{m}$, Z-scale = 50.0 nm .

quantitative conversion of the tethered isocyanates was observed within *minutes* as indicated by the disappearance of the peak associated with the isocyanate group (2275 cm^{-1}) (Fig. 3) and appearance of peaks indicative of the incorporated thiols and amines (see Table S1† for additional peak assignments). Triethylamine also carried the thiol–NCO reaction to quantitative conversion, albeit in several hours rather than minutes as observed with DBU. Static water contact angles revealed expected changes in wettability related to the functional moieties incorporated into the polymer brushes (Fig. S1†). An increase in thickness of the polymer brushes was observed after functionalization with the various thiols and amines due to an increase in the molar mass of the monomer repeat unit, resulting in an increase in the molecular weight of the brush. Additionally, to broaden the utility of this approach, fluorescent brushes were easily obtained by absorbing acridine orange (fluorescent dye) onto deprotonated MPA functionalized polymer brushes (Fig. S3†). The fluorescent dye adheres to the functionalized polymer brush through an ionic interaction and demonstrates the potential use of orthogonal covalent/non-covalent interactions for fabrication of functional polymer surfaces.

With the development of thiol–NCO click reactions as a platform for surface engineering in mind, the modularity and versatility of our approach was demonstrated by conducting sequential/area-selective thiol–NCO brush modifications using an elastomeric microcapillary patterning process.²⁷ The process is schematically shown in Fig. 1b. A line-patterned PDMS stamp (linewidth: $15.0\text{ }\mu\text{m}$) was used to create defined, micropatterned polymeric surfaces. The stamp was placed in direct contact with the brush surface and a solution of 3-mercapto-1-propanesulfonic acid (300 : 1 mol/mol thiol : DBU) in methanol was wicked in subsequently reacting for 12 min yielding a micropatterned sulfonate/NCO surface. After removing the stamp and washing with methanol and toluene, the unexposed and unreacted isocyanate groups were then subjected to a second thiol–NCO click reaction with DDT (500 : 1 mol/mol thiol : DBU, 12 min) in THF followed by washing with THF and toluene affording the micropatterned, multicomponent surface. Similar patterns could be obtained using sequential combinations of functional thiols and amines. Fig. 4a shows the optical condensation image for the sulfonate/DDT patterned surface. As shown, the hydrophilic sulfonated domains preferentially nucleate condensation of water allowing visualization of the patterned surface.^{11,28} To complement these results, atomic force microscopy (AFM) imaging was used (Fig. 4b) showing height differences created by the incorporation of the two different functional molecules.

Conclusions

In summary, we have demonstrated thiol–NCO click chemistry as a modular platform for rapid and robust fabrication of highly functional, multicomponent surfaces. Although demonstrated here on polymer brush modified planar substrates, this approach is certainly extendable to a broad range of surfaces, including three-dimensional particle substrates. As a functional handle for post-polymerization modification, we anticipate thiol–NCO click reactions to have a significant impact in many areas of polymer/materials chemistry.

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