Photocaged Pendent Thiol Polymer Brush Surfaces for Postpolymerization Modifications via Thiol-Click Chemistry

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ABSTRACT: In this work, a postpolymerization surface modification approach is reported that provides pendent thiol functionality along the polymer brush backbone using the photolabile protection chemistry of both *o*-nitrobenzyl and *p*-methoxyphenacyl thioethers. Poly(2-hydroxyethyl methacrylate) (pHEMA) brushes were synthesized via surface-initiated atom transfer radical polymerization, after which the pHEMA hydroxyl groups were esterified with 3-(2-nitrobenzylthio)propanoic acid or 3-(2-(4-methoxyphenyl)-2-oxoethylthio)propanoic acid to provide the photolabile protected pendent thiols. Addressing the protecting groups with light not only affords spatial control of reactive thiol functionality but enables a plethora of

INTRODUCTION Engineering polymer surfaces with precise control over polymer architecture, chemical functionality, and spatial orientation of functional groups throughout the interface represents a grand challenge for polymer chemistry-particularly as demand increases for surfaces presenting complex chemistries and morphologies. A rapidly growing strategy to address this challenge involves postpolymerization modification (PPM) of polymer surfaces.¹ PPM of surfaces is a process based on the polymerization of monomers with functional groups that are inert under the polymerization and/or film formation conditions, but can subsequently be quantitatively converted into a broad range of other functional groups. Thus, PPM enables the versatile and modular transformation of physiochemical properties of surfaces, and has been demonstrated using modification chemistries ranging from activated esters^{2,3} and ring opening⁴⁻⁷ to more efficient and robust chemistries based on the "click" family of reactions.^{8,9} Click reactions-with the copper assisted azide-alkyne cycloaddition (CuAAC) reaction being the prominent example¹⁰—exhibit salient features such as high yields, fast reaction kinetics, orthogonal reactivity, and are tolerant to a broad range of reaction conditions. Successful utilization of CuAAC for PPM of surfaces has provided the impetus for continued development of clickthiol-mediated transformations with isocyanates and maleimides providing a modular route to create functional polymer surfaces. This concept was extended to block copolymer brush architectures enabling the modification of the chemical functionality of both the inner and outer blocks of the block copolymer surface. © 2012 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2013**, *51*, 1079–1090

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based PPM strategies;¹¹ however, concern over the presence of residual metal impurities following copper-catalyzed click reactions has driven the development of alternate, metal-free surface modification strategies. Consequently, metal-free click reactions—such as strain-promoted azide-alkyne cycloadditions,¹² Diels–Alder cycloadditions,^{13–17} and thiol-based reactions¹⁸—are rapidly becoming methods of choice for postpolymerization surface modification strategies.

Our group, along with others, has demonstrated thiol-based click reactions—including thiol-ene,¹⁹⁻²² thiol-yne,²²⁻²⁴ and thiol-isocyanate²⁵—as efficient and modular strategies towards engineering multifunctional surfaces.²⁶ Thiol-click reactions are advantageous for PPM of surfaces in that they proceed at room temperature with high efficiency and rapid reaction rates, in the presence of oxygen and water, without expensive and/or toxic catalysts, and exhibit high tolerance toward a broad range of functional groups.^{27,28} In addition, we have recently exploited the orthogonal nature of radicalmediated thiol-yne reactions in sequential combination with base-catalyzed thiol-isocyanate, thiol-epoxy, and thiol-bromo reactions for the design of multifunctional polymer brush surfaces with controlled surface compositions and wetting properties.²⁹ Furthermore, thiol-click reactions also have a significant advantage in that a large number of functional

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thiols are commercially available eliminating the need for multistep synthesis of postmodifiers often encountered in other click-based strategies. In order to exploit the library of commercially available thiols, most examples of thiol-click PPM of surfaces have relied on the immobilization of alkenes, alkynes, or isocyanates as thiol-reactive handles on the surface. However, by using the reverse scenario whereby thiols are immobilized as the reactive handle on the surface, one could easily take advantage of the vast libraries of commercially available maleimides, acrylates, isocyanates, and so forth-all of which are attainable carrying a broad range of pendent functionalities. Such an approach would vastly broaden the thiol-click toolbox for postmodification of surfaces. Aside from serving as a handle for PPM, well-defined polymer surfaces with polyfunctional pendent thiols may also be of interest for immobilization of metallic nanoparticles and for heavy metal capture and remediation applications.

Unfortunately, the desirable characteristics of thiols-i.e., high reactivity and efficiency toward an array of functional groups-also make them intolerable under radical polymerization conditions. The large chain transfer constants of thiols in vinyl polymerizations, self-association via disulfide linkages, and numerous other side reactions eliminate any possibility of incorporating unprotected thiols into macromolecules by direct polymerization. While there are numerous examples of polymer pendent polyfunctional thiols,^{30,31} researchers often resort to protection/deprotection schemes that require harsh reaction conditions to yield the thiol (i.e., conversion of halogens to thioesters followed by extended reflux under basic conditions). For engineering functional surfaces based on tethered thiols, particularly those with delicate underlying substrates, milder synthetic conditions toward the thiol are desirable.

"Caged" compounds, or structures containing photolabile protecting groups (PPGs), are well established in the areas of organic³² and biochemistry as mild alternatives to chemically-induced deprotections.³³ PPGs can be removed by exposure to ultraviolet (UV) light under neutral and reagentfree conditions to yield a variety of reactive functional groups including acids, alcohols, and amines. Light can be used in a direct fashion to immediately trigger a desired modification or indirectly to release a reactive moiety that will then participate in a given activity or modification process, such as PPM. In this way, PPGs have been used for initiator,³⁴ end group³⁵ and side-chain polymer modifications,³⁶⁻³⁸ block copolymers,^{37,39,40} monolayers,⁴¹⁻⁴⁴ twodimensional surface modifications,45-47 and polymer brushes.48 PPG strategies have also been reported for the efficient photolysis of protected thiols based on 2-nitrobenzyl,⁴⁹ phenacyl,^{50,51} benzoinyl,⁵² and coumarinyl⁴⁹ protecting groups; however, these examples are mostly related to biochemistry applications with fewer examples describing photodeprotection of thiols for polymer or surface modifications. Recently, Barner-Kowollik et al. demonstrated o-nitrobenzyl protected thiols as latent pendents on methacrylate-based homopolymers³⁸ and acrylamide-based copolymers³⁸ rendering the thiol functionality inert during controlled radical

polymerization, but amendable via sequential light-triggered deprotection and thiol-ene PPM process. Wosnick and Shoichet⁵³ covalently modified agarose hydrogels with a 6-bromo-7-hydroxycoumarin sulfide derivative, which upon phototriggered deprotection and thiol-Michael reaction with maleimide-functionalized biomolecules, enabled the development of three-dimensional chemical patterns within the hydrogel. Examples using surface-bound photolabile protected thiols as reactive handles for postmodification of surfaces have been limited to self-assembled monolayers.^{41,42,46} For example, Chen et al.⁴⁶ described photopatterning of biomolecules on planar surfaces upon photolysis of an o-nitrobenzyl protected thiol monolayer. Upon exposure of the thiol, biomolecules were immobilized via disulfide and thiol-Michael reactions. Wavelength-selective PPGs have also been used to expose thiols as reactive head groups on monolayers by exploiting wavelength-selective photolysis of various PPG derivatives enabling independently addressable functional moieties.^{41,42} Aside from our own example demonstrating the PPM of pendent thiols via thiol-Michael on cysteine-containing polypeptide brushes,²¹ we are currently unaware of any literature reporting the synthesis of well-defined polymer brush surfaces bearing pendent thiols for modular PPM.

In the present work, we report a postpolymerization surface modification approach that provides pendent thiol functionality along the polymer brush backbone using the photolabile protection chemistry of both o-nitrobenzyl (o-NB) and p-methoxyphenacyl (p-MP) thioethers. Addressing the protecting groups with light enables a plethora of thiol-mediated transformations with isocyanates and maleimides providing a versatile route to create complex, functional polymer surfaces. The experiments described in this article were performed using poly(hydroxyethyl methacrylate) (pHEMA) brushes synthesized via surface-initiated atom transfer radical polymerization (SI-ATRP), which were esterified with 3-(2-nitrobenzylthio)propanoic acid or 3-(2-(4-methoxyphenyl)-2-oxoethylthio)propanoic acid to provide the photolabile protected pendent thiols. SI-ATRP of HEMA was chosen for this work as it serves as a model brush platform allowing excellent control over film thickness, and it enables facile synthesis of block copolymer brushes for investigation of photolysis and thiol-click PPM processes on more advanced brush architectures. A principal advantage of the postmodifiable brush platform is that it provides a larger number of modifiable sites per unit area of substrate as compared to conventional self-assembled monolayers (SAMs), while also decoupling the polymer synthesis step from the immobilization of sensitive functional groups on the surface thereby avoiding expensive monomer synthesis and reducing potential side reactions.

EXPERIMENTAL

Materials

All reagents and solvents were obtained at the highest purity available from Aldrich Chemical Company or Fisher Scientific and used without further purification unless otherwise specified. Single-side polished silicon wafers were purchased from University Wafers. Monomers, 2-hydroxyethyl methacrylate (HEMA, 97% Aldrich), and 2-(dimethylamino)ethyl methacrylate (DMAEMA, 99% Aldrich), were passed through a neutral alumina column to remove the inhibitor. Reagents, 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU), dimethylphenylphosphine (DMPP), and anhydrous triethylamine (TEA) for deprotection and thiol-click reactions were also obtained from Aldrich and used as received. Cyanophenyl maleimide was synthesized according to reported literature procedures.^{54,55}

Characterization

A Varian Mercury Plus 300 MHz NMR spectrometer operating at a frequency of 300 MHz with VNMR 6.1 C software was used for proton and carbon analysis. Wettability of the unmodified and modified polymer brushes was measured using a Ramé-hart 200-00 Std.-Tilting B. goniometer. Static (θ_{sw}) contact angles were measured using 10- μ L water droplets in combination with DROPimage Standard software. Ellipsometric measurements were carried out using a Gaertner Scientific Corporation LSE ellipsometer with a 632.8 nm laser at 70° from the normal. Refractive index values of 3.86, 1.45, 1.43, and 1.5 for silicon, oxide layer, photoinitiator monolayer, and all polymer layers, respectively, were used to build the layer model and calculate layer thicknesses.56,57 The chemical nature of the polymer brush surfaces was characterized by Fourier transform infrared spectroscopy (FTIR) in grazing angle attenuated total reflectance mode (GATR-FTIR) using a ThermoScientific FTIR instrument (Nicolet 8700) equipped with a VariGATR^{TM} accessory (grazing angle 65°, germanium crystal; Harrick Scientific). Spectra were collected with a resolution of 4 cm⁻¹ by accumulating a minimum of 128 scans per sample. All spectra were collected while purging the VariGATR[™] attachment and FTIR instrument with N₂ gas along the infrared beam path to minimize the peaks corresponding to atmospheric moisture and CO₂. Spectra were analyzed and processed using Omnic software. Atomic force microscopy was performed using a Bruker Icon in tapping mode. The samples were scanned with T300R-25 probes (Bruker AFM Probes) with a spring constant of 40 Nm⁻¹. Confocal microscopy was performed on fluorescently patterned surfaces using a Zeiss LSM 710 operating with two lasers (433 and 548 nm) correlating to the absorption of fluorescein and rhodamine. The fluorescent images were processed using ZEN software.

Synthesis of 10-Undecen-1-yl 2-Bromo-2methylpropionate (ATRP Initiator Precursor)

10-Undecen-1-yl 2-bromo-2-methylpropionate was synthesized according to literature procedures.⁵⁸ Pyridine (2.1 g, 26.5 mmol) was added to ω -undecylenyl alcohol (4.27 g, 25.1 mmol) in 25 mL of anhydrous tetrahydrofuran (THF) and subsequently cooled to 0 °C followed by the dropwise addition of 2-bromoisobutyryl bromide (6.1 g, 26.5 mmol). The reaction was stirred overnight at r.t. followed by dilution with hexanes (50 mL) and washing with 2N HCl (2×) and deionized H₂O (2×). The organic phase was dried with MgSO₄, filtered, and concentrated via rotary evaporation. The colorless oily residue was purified using flash chromatography (5:1 hexanes: ethyl acetate, $R_{\rm f}=0.7$) to give 7.25 g (91%) of the ester as a colorless oil.

¹H NMR (CDCl₃, δ ppm): 1.28–1.72 (br m, 14H), 1.93 (s, 6H), 2.05 (q, 2H), 4.16 (t, 2H), 4.9–5.02 (m, 2H), 5.74–5.87 (m, 1H) ¹³C NMR (CDCl₃, δ ppm): 25.93, 28.50, 29.07, 29.23, 29.30, 29.52, 29.56, 30.95, 33.95, 56.16, 66.36, 114.25, 139.34, 171.89.

Synthesis of (11-(2-Bromo-2-methyl)propionyloxy) undecyltrichlorosilane (ATRP Initiator-Tricholorsilane)

In a glovebox under a N_2 atmosphere, 10-undecen-1-yl 2-bromo-2-methylpropionate (0.27 g, 0.84 mmol, 1 equiv), trichlorosilane (0.57 g, 4.2 mmol, 5 equiv), about 3 mL of anhydrous toluene, and five to six drops of Pt-divinyl tetramethyl disiloxane complex in vinyl silicone were allowed to react overnight. Toluene and excess trichlorosilane were removed under vacuum to yield (11-(2-bromo-2-methyl) propionyloxy)undecyltrichlorosilane (0.37 g, 96.9%). Dry toluene (3.1 mL) was added creating a stock 271 mM solution. The catalyst and any solids were removed by a syringe filter before use.

¹H NMR (CDCl₃, δ ppm): 1.23–1.45 (br m, 16H), 1.54–1.75 (m, 4H), 1.93 (s, 6H), 4.16 (t, 2H) ¹³C NMR (CDCl₃, δ ppm): 22.16, 24.22, 25.69, 28.26, 29.07, 29.22, 29.38, 30.71, 55.88, 66.02.

Immobilization of ATRP Initiator-Trichlorosilane on SiO₂ Surfaces

Silicon wafers were cut into appropriate sized pieces and ultrasonically cleaned in DP2300 ultrahigh performance general purpose cleaner and degreaser (Branson Ultrasonics) for 5 min. The wafers were then wiped gently with lens paper or a cotton-tipped applicator to remove silicon dust from the wafer dicing process. After wiping, the wafers were ultrasonicated for an additional 10 min, rinsed multiple times with DI water, and ultrasonicated in deionized water for 15 min. The wafers were then placed into a RCA-1 solution (five parts deionized H₂O, one part 27% ammonium hydroxide, and one part 30% hydrogen peroxide) for 15 min at 70 °C to remove any organic residues before initiator immobilization. The wafers were rinsed thoroughly with DI water, dried under a stream of N₂, and transferred into an acrylic glove box where they were placed into a toluene solution of (11-(2-bromo-2-methyl)propionyloxy)undecyltrichlorosilane (4 mM) at room temperature for 16 h without stirring. The wafers were removed from the solution, rinsed extensively with toluene, dichloromethane, and dimethylformamide before drying under a stream of N₂. The initiatorfunctionalized silicon wafers were stored in toluene at -20°C until use.

Synthesis of 3-(2-Nitrobenzylthio) Propanoic Acid (o-NB) 3-Mercaptopropionic acid (2.95 g, 23.1 mmol) and anhydrous TEA (1.83 g, 18.1 mmol) were added to 2-nitrobenzyl bromide (2.5 g, 11.6 mmol) in anhydrous acetone (150 mL) under a N₂ atmosphere and allowed to react overnight. The salt by-product was filtered and the crude product was isolated via rotary evaporation. The crude product was



redissolved in ethyl acetate (100 mL), washed with 0.5 M HCl ($4\times$, 75 mL wash) and brine ($1\times$, 75 mL), dried using MgSO₄. After filtration, the product was concentrated via rotary evaporation. The product crystallized upon removing excess solvent. The crystalline product was finally washed with hexanes and dried under vacuum (1.9 g, 68.1%).

¹H NMR (CDCl₃, δ ppm): 2.59–2.64 (t, 2H), 2.70–2.74 (t, 2H), 4.10 (s, 2H), 7.26–7.59 (m, 3H), 7.96–7.99 (d, 1H), 11.12 (b s, 1H) ¹³C NMR (CDCl₃, δ ppm): 26.64, 33.86, 34.47, 125.76, 128.76, 132.1, 133.37, 134.0, 149.01, 177.94.

Synthesis of 3-(2-(4-Methoxyphenyl)-2-oxoethylthio) Propanoic Acid (*p*-MP)

3-Mercaptopropionic acid (2.32 g, 21.8 mmol) and anhydrous TEA (1.44 g, 14.2 mmol) were added to 2-bromo-4'methoxyacetophenone (2.5 g, 10.9 mmol) in anhydrous acetone (150 mL) under an N₂ atmosphere and allowed to react overnight. The salt by-product was filtered and crude product was isolated via rotary evaporation. The crude product was redissolved in ethyl acetate (100 mL), washed with 0.5 M HCl (4×, 75 mL wash) and brine (1×, 75 mL), dried using MgSO₄ followed by concentration of the product via rotary evaporation. The product crystallized upon placing into freezer at -20 °C. The crystalline product was washed with hexanes to remove any residue impurities and dried under vacuum (2.6 g, 88.7%).

¹H NMR (CDCl₃, δ ppm): 2.70–2.73 (d, 2H), 2.81–2.87 (d, 2H), 3.79 (s, 2H), 3.88 (s, 2H), 6.92–6.97 (d, 2H), 7.93–7.97 (d, 2H), 11.12 (b s, 1H) ¹³C NMR (CDCl₃, δ ppm): 26.81, 34.15, 36.93, 55.65, 114.14, 128.18, 131.39, 164.14, 177.27, 193.43.

Synthesis of pHEMA Brush Surfaces by Surface-Initiated Atom Transfer Radical Polymerization

SI-ATRP was carried out in vacuum purged test tubes equipped with rubber septa. In one tube, HEMA and a water/methanol mixture (1:4 v/v) were degassed by bubbling through with N_2 for 45 min. In a second tube, 2,2'bipyridyl, and copper(I)bromide (40:1:0.5 mol % monomer/ ligand/Cu(I)Br) were degassed by three vacuum/N₂ purge cycles. The monomer solution was transferred by cannula to the tube containing the ligand/Cu(I)Br, and the mixture was stirred for 45 min or until a deep-red, homogeneous solution was obtained. The monomer/catalyst complex was then transferred by cannula into a degassed tube containing the initiator-modified silicon substrate. The reaction proceeded at room temperature. Reaction times were varied to obtain the desired thickness of pHEMA brushes. pHEMA modified substrates were rinsed extensively with water and methanol following polymerization.

Carbodiimide-Mediated Esterification of pHEMA Brush Surface with *o*-NB- and *p*-MP-Protected Thiols

The pendent hydroxyl groups of the pHEMA brushes were modified in anhydrous DMF (6 mL) with *o*-nitrobenzyl (3-(2nitrobenzylthio)propanoic acid) or phenacyl (3-(2-(4-methoxyphenyl)-2-oxoethylthio)propanoic acid) derivatives (0.3 mmol) using 4-dimethylaminopyridine (7.3 mg, 0.06 mmol) and *N*,*N*'-diisopropyl carbodiimide (DIPC) (57 mg, 0.45 mmol). DIPC in anhydrous DMF (1 mL) was added dropwise over 5 min before placing the reaction on a shaker for 16 h. The substrates were rinsed extensively with DMF, THF, and toluene and dried under a stream of N_2 .

Photodeprotection of Brush Pendent *o*-NB- and *p*-MP-Protected Thiols

Deprotection of the protected thiols was facilitated by irradiating the substrates with UV light (365 nm, 70 mW cm⁻², 2 h) in N₂ purged anhydrous dichloromethane with catalytic amounts of DMPP (3.5×10^{-5} M). GATR-FTIR was used to monitor the disappearance of the *o*-nitrobenzyl and *p*-methoxyphenacyl groups.

One-Pot Photodeprotection and Thiol-Click Modification

Protected substrates were irradiated with UV light under the above conditions to facilitate photolysis of the *o*-NB or *p*-MP moieties. The light source was turned off followed by the addition of reagents to facilitate Michael-type thiol-ene and base-catalyzed thiol-isocyanate surface modifications. Modification of the thiol with various functionalities was monitored by ellipsometry, GATR-FTIR and static water contact angle. Details for each set of thiol-click reactions are given below.

Thiol-Isocyanate Modification

A N₂ purged solution consisting of 2-nitrophenyl isocyanate (98.5 mg, 0.6 mmol, 0.1 M), 4-methoxybenzyl isocyanate (85.7 μ L, 0.6 mmol, 0.1 M), dodecyl isocyanate (144.6 μ L, 0.6 mmol, 0.1 M), furfuryl isocyanate (64.3 μ L, 0.6 mmol, 0.1 M), or 1-adamantyl isocyanate (0.11 mg, 0.6 mmol, 0.1 M) in anhydrous DCM (6 mL) was added to the reaction vessel containing the reactive pendent thiol polymer brushes. For rapid reaction kinetics, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.3 mol % with respect to isocyanate) was used as catalyst. The reaction was allowed to react overnight to ensure completion; however, our group has previously reported quantitative base-catalyzed thiol-isocyanate reactions within minutes.²⁵

Thiol-Michael Modification

The reactive pendent thiol polymer brushes were submerged into a N_2 purged anhydrous dichloromethane (6 mL) solution containing cyanophenyl maleimide (0.1 M, 118.9 mg, 0.6 mmol) with 5 equiv. TEA (0.5 M, 418 μ L, 3 mmol) with respect to maleimide. The reaction was allowed to react overnight to ensure completion, however, reactions times are known to be much faster.^{27}

Surface Patterning via Photodeprotection and Orthogonal Thiol-Click Chemistries

Photomasks (copper grids, 200 mesh, hole width: 90 μ m, bar width: 37 μ m) were placed directly on top of *o*-NB-protected thiol polymer brushes and secured in place with a microscope cover glass slide. The glass slide ensured the photomasks were in intimate contact with the surface as well as limited the mobility of the photomasks upon the addition of solvent. For photodeprotection, the substrates were irradiated with UV light (365 nm, 70 mW cm⁻²) for



SCHEME 1 (a) General approach for the synthesis of polymer brush surfaces with pendent photolabile protected thiols and (b) subsequent photodeprotection and thiol-click modification.

1 h in anhydrous dimethylformamide (DMF) to facilitate the photolysis of the o-NB moieties. The photomask was removed and the sample was extensively washed in DMF, THF and toluene followed by reaction of the newly generated reactive pendent thiols with fluorescein isothiocyanate. Only areas exposed to UV light generate free thiols that are available for reaction. A solution of fluorescein isothiocyanate (9.9 mg, 12.7 mM) and DBU (0.127 mM, 100:1 mol/mol % isothiocyanate:DBU) in anhydrous DMF (2 mL) was placed into the reaction vessel containing the polymer brushes and allowed to react for 1 h. After washing the substrate with DMF, THF and toluene the areas within the polymer brush still in a protected state were deprotected to form additional free thiols available for reaction by irradiating the sample with UV light (365 nm, 70 mW cm^{-2}) for 1 h in anhydrous DMF followed by reaction with Texas Red[®] C₂ maleimide. A solution of Texas Red^{\circledast} C_2 maleimide (0.1 mM) and TEA (0.5 mM, 5 equiv in respect to maleimide) in anhydrous DMF (2 mL) was purged with N_2 and subsequently added to the reaction vessel containing the polymer brushes and allowed to react for 1 h. The substrates were extensively washed with DMF, THF, and toluene before confocal microscopy was performed.

Synthesis, Photodeprotection, and Thiol-Click Modification of Block Copolymer Brush Surfaces

pHEMA-b-pDMAEMA and pDMAEMA-b-pHEMA brush surfaces were prepared in an analogous manner as previously described for the homopolymer pHEMA brush surfaces using 2,2'-bipyridyl and copper(I)bromide (40:1:0.5 mol % mono-mer/ligand/Cu(I)Br). pHEMA or pDMAEMA brushes served as macroinitiator substrates for the chain extension reactions. Reaction times were varied to obtain the desired thickness of outer pDMAEMA or pHEMA blocks. The pendent hydroxyl groups of the pHEMA block within the block

copolymer brushes were modified with *o*-nitrobenzyl thioether units as previously described. For AFM studies, the modified block copolymers were submerged into a 0.01 M HCl aqueous solution for 30 min to protonate the pDMAEMA domains within the block copolymer.

RESULTS AND DISCUSSION

Synthesis of Pendent Thiol Polymer Brushes

Scheme 1(a) shows the general approach for the synthesis of photolabile protected pendent thiol polymer brushes. Silicon substrates were first functionalized with a chlorosilane ATRP initiator derivative, 11-(2-bromo-2-methyl) propionyloxyundecenvltrichlorosilane.58 p(HEMA) brushes were then prepared using SI-ATRP of HEMA in a water/methanol mixture, followed by carbodiimide-mediated esterification with 3-(2-nitrobenzylthio)propanoic acid (1) (o-NB) or 3-(2-(4-methoxyphenyl)-2-oxoethylthio)propanoic acid (2) (p-MP) to provide the polymer brushes with pendent photolabile protected thiols. Conversion to the desired ester derivatives was confirmed by GATR-FTIR (vide infra). Attempts to incorporate the o-NB functional group in the brush by direct SI-ATRP of an o-NB functional methacrylate monomer were successful; however, this approach yielded miniscule film thickness (<10 nm) presumably due to the inhibitory effects of the -NO₂ group.⁵⁹

The inhibition effect is likely amplified given the low concentration of propagating chains relative to monomer concentration in surface-initiated polymerizations. In contrast, SI-ATRP of a *p*-MP methacrylate monomer enabled a direct polymerization approach providing an evident advantage over the *o*-NB derivative, but for comparative purposes, the carbodiimide esterification route was adopted for both systems.

As shown in Scheme 1(b), the o-NB and p-MP moieties are cleaved by irradiation with UV light at 365-nm yielding





SCHEME 2 Photodeprotection of o-nitrobenzyl (*o*-NB) protected thioether.

pendent thiol brush precursors. The resulting pendent thiol moieties along the polymer brush backbone then serve as reactive handles for subsequent thiol-click reactions. In the following sections, we describe the results of photodeprotection of both *o*-NB and *p*-MP PPGs and postmodification via base-catalyzed thiol-isocyanate reactions and thiol-Michael additions with maleimides. The reactions were carried out in a one-pot reaction, meaning that the UV light was turned off following deprotection, and base-catalyzed thiol-isocyanate reactions were facilitated in the same pot by syringing in solutions of either an isocyanate or a maleimide along with the respective catalysts.

Photodeprotection of *o*-NB- and *p*-MP-Protected Thiol Brushes and One-Pot Thiol-Click Modification

Schemes 2 and 3 show the commonly accepted mechanisms for photodeprotecton reactions of o-NB and p-MP derivatives (shown as thiol derivatives for relevance to the current work). A brief discussion of these schemes provides insight for the ensuing photodeprotection studies to yield pendent thiols on the brush platforms. Photodeprotection of o-nitrobenzyl derivatives (9) is known to be initiated by the abstraction of benzylic hydrogen from an excited nitro group producing aci-nitro intermediates (10) and (11).^{33,60,61} Irreversible cyclization to the benzisoxazoline intermediate (12) through the neutral nitronic acid (10) followed by ring-opening yields (13) and ultimately the products 2-nitrosobenzaldehyde (14) and R-SH (15).^{33,61} Å strong solvent and pH dependence has also been shown for the photodeprotection of o-nitrobenzyl derivatives.⁶² The reaction of the deprotected thiol (15) with the nitroso moiety of 2-nitrosobenzaldehyde (14) should be noted as a potential side reaction⁶³ which would reduce the available thiol concentration within the brush. Much less is known about the detailed photode-



SCHEME 3 Photodeprotection of *p*-methoxyphenacyl (*p*-MP) protected thioether.

protection mechanism of *p*-methoxyphenacyl derivatives (**16**). Givens et al.⁶⁴ indicated the photodeprotection proceeded via a triplet-excited state and a spiroketone intermediate (not shown), which may account for byproduct (**20**) in the case of *p*-MP-protected thiols, as (**20**) would result from a nucleophilic ring opening of the spiroketone by a thiol.⁵¹ A more recent study by An et al.⁶⁵ suggested a concerted triplet deprotection and solvolytic rearrangement with little observation of a spiroketone intermediate to provide the deprotected thiol moiety (**17**) and a series of byproducts (**18**, **19**).

Photoinduced deprotection of the caged thiols was investigated under various conditions to facilitate complete removal of the photolabile protecting groups while maximizing thiol yield. Pauloehrl et al.³⁸ previously showed that DMPP, when added in catalytic amounts, prevented the formation of disulfides during photodeprotection of o-NB thioethers eliminating the need for a separate reduction step, thus we adopted similar conditions. The photodeprotection reaction was monitored with GATR-FTIR by observing the disappearance of the asymmetric and symmetric NO₂ stretching vibrations inherent to the aromatic nitro derivative at 1527 and 1350 cm⁻¹ for the *o*-nitrobenzyl PPG, and the aromatic C=C stretching vibrations of the phenacyl derivative at 1600, 1576, and 1515 cm⁻¹ for the *p*-methoxyphenacyl PPG.⁶⁶ The formation of thiol upon deprotection could not be monitored by GATR-FTIR due to the band for S-H stretching vibration being very weak in the region of $2540-2600 \text{ cm}^{-1.66}$ Figure 1 shows the GATR-FTIR spectra for the photolabile caged o-NB- and p-MP-protected pendent thiol polymer brushes upon just photodeprotection and also one-pot photodeprotection and sequential thiol-isocyanate click reactions. The o-NB-protected thiol polymer brushes [Fig. 1(a)] were subsequently deprotected by exposing the surface to UV_{365nm} light irradiation (70 mW cm⁻²) for 2 h in N₂ purged anhydrous DCM in the presence of a catalytic amount of DMPP. Successful deprotection to the thiol was indicated by the complete disappearance of the NO₂ stretching vibrations in the GATR-FTIR [Fig. 1(b)] and a decrease in polymer brush thickness (ca. 9 \pm 1 nm). Similar results were obtained for the photodeprotection of the *p*-MP modified brush surfaces. As shown in Figure 1(d), the aromatic C=C stretching vibrations of the phenacyl derivative at 1600, 1576, and 1515 cm^{-1} present in the protected form were no longer observed following photodeprotection [Fig. 1(e)]. In both cases, the surface becomes more hydrophilic on deprotection and conversion from the aromatic PPG to the pendent thiol (i.e., water contact angle decreases from 73° to 52° for o-NB surface and from 74° to 49° for *p*-MP surface) (Supporting Information Fig. S1).

To gain better insight and provide a route to quantify the yield of thiol functionality on the surface following photodeprotection, the pendent thiols were "tagged" with isocyanates bearing a structural resemblance to the cleaved PPG via the base-catalyzed thiol-isocyanate reaction. Namely, thiols produced from the photodeprotection of *o*-NB and *p*-MP groups were subsequently tagged with 2-nitrophenyl isocyanate (**3**)



FIGURE 1 GATR-FTIR spectra of photolabile-caged *o*-NB and *p*-MP-protected pendent thiol polymer brushes, subsequent deprotection, and thiol-isocyanate click reactions: (a) photolabile *o*-NB-protected pendent thiol polymer brush, (b) deprotected pendent thiol polymer brush (3.5×10^{-5} M DMPP in DCM), (c) one-pot photodeprotection and thiol-isocyanate reaction with 2-nitrophenyl isocyanate (3) (0.3 mol % DBU in respect to isocyanate), (d) *p*-MP-protected pendent thiol polymer brush (3.5×10^{-5} M DMPP in DCM), (e) deprotected pendent thiol polymer brush (3.5 $\times 10^{-5}$ M DMPP in DCM), and (f) one-pot photodeprotection and thiol-isocyanate reaction with 4-methoxybenzyl isocyanate (4) (0.3 mol % DBU in respect to isocyanate).

and 4-methoxybenzyl isocyanate (4), respectively, in a onepot fashion. Thus, using GATR-FTIR, the ratio of the -NO₂ peak (or the -OCH₃ peak) before photodeprotection and after thiol-isocyanate click will provide insight into the quantity of thiols available for modification. Importantly, we have previously shown that thiol-isocyanate postmodification of brush surfaces proceeds rapidly to full conversion, so we are confident this approach will tag any available thiols for analysis.²⁵ Figure 1 shows the GATR-FTIR spectra of o-NB [Fig. 1(a)] and *p*-MP [Fig. 1(d)] protected pendent thiol polymer brushes and subsequent one-pot photodeprotection and thiol-isocyanate click reactions with 2-nitrophenyl isocyanate [Fig. 1(c)] or 4-methoxybenzyl isocyanate [Fig. 1(f)]. Photochemical conversion to free thiol was estimated by taking the ratio of the integrated peak area of the NO₂ symmetric stretching vibration (1350 cm⁻¹) for the *o*-NB brushes before photodeprotection and after thiol-isocyanate click, and the integrated peak area of the aromatic phenacyl C=C stretching vibration (1515 cm⁻¹) before photodeprotection and after thiol-isocyanate click for the p-MP brushes. The carbonyl band (C=0, 1730 cm^{-1}) was used as a reference peak as the area of this peak remained constant during the surface modifications, (i.e., the C=O peak associated with formation of a thiourethane linkage (-S-CO-NH-) on the thiol-isocyanate click reaction appears at 1650 cm⁻¹).⁶⁶ Accordingly, the photolabile o-NB- and p-MP-protected pendent thiol polymer brushes yield 77 \pm 2% and 88 \pm 3%

reactive free thiols, respectively, on photodeprotection when performed in the presence of a catalytic amount of DMPP as a reducing agent. Additionally, an increase in brush thickness was observed upon one-pot photodeprotection and thiolisocvanate click in both o-NB- and p-MP-protected samples, where an increase from 21.4 ± 0.2 nm (o-NB protected) to 24.2 \pm 0.1 nm (clicked with 3) and from 19.1 \pm 0.8 nm (*p*-MP protected) to 24.1 \pm 0.2 nm (clicked with 4) was measured, respectively (Supporting Information Table S1). The slight increase in brush thickness despite less than quantitative availability of thiol can be attributed to the replacement of the thioether-linked o-NB and p-MP pendent groups with the larger molecular weight thiourethane-linked pendent groups derived from 3 and 4. Despite the use of DMPP, the formation of disulfides or other adventitious side products resulting from the photodeprotection precludes the possibility of achieving quantitative yields of reactive free thiol on the brush surface. For comparison, the formation of free thiols for both o-NB- and p-MP-protected polymer brushes decreased to 63 \pm 1% and 75 \pm 2%, respectively, when reducing agent was not used during photodeprotection. GATR-FTIR spectra of samples with and without DMPP during the photodeprotection are available in the Supporting Information (Fig. S1).

Upon optimization of the photodeprotection and thiol-click modifications of the brush surfaces, the scope of the thiolclick reactions was broadened to include other functionalities. Photodeprotection of the o-NB- and p-MP-protected brushes was facilitated as previously described in the presence of catalytic amounts of DMPP (3.5×10^{-5} M). Figure 2 and Supporting Information Figure S2 show the GATR-FTIR of the photolabile o-NB- and p-MP-protected thiol polymer brushes after modification via one-step photodeprotection and thiol-click reactions. For brevity, the thiol-click reactions for the o-NB and p-MP derivatives will be discussed collectively as the results were similar in each case. The polymer brushes before and after one-pot photodeprotection and thiol-click surface modification were characterized by GATR-FTIR, ellipsometry, and water contact angle measurements. Figure 2(a-c) and Supporting Information Figure S2(a-c)show the GATR-FTIR following thiol-isocyanate click of the pendent thiols produced from o-NB and p-MP cleavage, respectively, in the presence of DBU (0.3 mol % in respect to isocyanate) with dodecyl isocyanate (5), furfuryl isocyanate (6) and adamantyl isocyanate (7). In each case, FTIR confirms a successful thiol-click modification due to the appearance of peaks indicative of the functional isocyanates, for instance, aliphatic C-H stretching vibrations (2954, 2924, and 2852 cm^{-1}) was observed for dodecyl isocyanate [Fig. 2(a) and Supporting Information Fig. S2(a)] and for adamantyl isocyanate [Fig. 2(c) and Supporting Information Fig. S2(c)]. For modification with furfuryl isocyanate, C-H and =C-H stretching vibrations occur between 3000 and 2800 cm^{-1} ; however, spectral overlap of the polymer backbone in the ether region (C-O-C asymmetric stretch, 1270-1060 cm⁻¹) makes explicit confirmation of a successful thiol-isocyanate modification with furfuryl isocyanate by GATR-FTIR difficult [Fig. 2(b) and Supporting Information



FIGURE 2 GATR-FTIR spectra after one-pot photodeprotection and thiol-click modifications (base-catalyzed thiol-isocyanate and Michael-type thiol-ene) of *o*-NB-protected pendent thiol polymer brushes with (a) dodecyl isocyanate, (b) furfuryl isocyanate, (c) adamantyl isocyanate, and (d) cyanophenyl maleimide.

Fig. S2(b)]. Lastly, Figure 2(d) and Supporting Information Figure S2(d) show the GATR-FTIR spectra for polymer brushes modified with cyanophenyl maleimide (**8**) via Michael-type thiol-ene reactions in the presence of 5 equiv of TEA. The incorporation of cyanophenyl maleimide in the brush was evident by the appearance of a C \equiv N stretching vibration at 2227 cm⁻¹ and aromatic C=C stretching vibrations at 1610 and 1510 cm⁻¹. All one-pot reactions show expected water contact angles (Supporting Information Fig. S3) and increases in film thickness on modification (Supporting Information Table S1).

Surface Patterning via Photodeprotection and Orthogonal Thiol-Click Chemistries

As a stimulus for deprotection, light has the added benefit of spatial and temporal control useful for surface patterning. To demonstrate this control, we conducted sequential/areaselective orthogonal surface reactions via base-catalyzed thiol-isothiocyanate and thiol-Michael additions with fluorescein isothiocyanate and Texas Red[®] C₂ maleimide, respectively, using a simple photopatterning technique. Photomasks (copper grids, hole width: 90 µm, bar width: 37 µm) were placed in contact with the brush surface, immersed in anhydrous DMF and irradiated with UV light for 1 h (365 nm, 70 mW cm⁻²) to facilitate the photolysis of the *o*-NB moieties only in the light exposed areas. After exposure, substrates were immersed in a solution of fluorescein isothiocyanate/DBU for 1 h. The initial click reaction immobilized fluores-

cein on the brush surface only in the light exposed areas creating a well-defined pattern as shown by fluorescence microscopy (Supporting Information Fig. S4). The remaining *o*-NB protecting moieties were subsequently cleaved by UV flood exposure liberating free thiols available for further functionalization. Texas Red[®] C₂ maleimide was then immobilized onto the surface in the presence of TEA to generate multifunctional micropatterns in a sequentially orthogonal fashion. Figure 3 shows the fluorescence microscopy images of the fluorescein/Texas Red[®] C₂ micropatterns under illumination with two lasers (433 and 548 nm). Well-defined edges [Fig. 3(b)] indicate a sharp interface between the two domains illustrating spatially resolved patterns can be achieved via cleavage of PPGs and PPM thiol-click processes.

Postpolymerization Modification of Block Copolymer Brushes

With the retention of the bromine end group from SI-ATRP, chain extension enables preparation of block copolymer brushes containing photolabile thiol moieties available for postmodification within the upper or lower block (Scheme 4). Relatively few reports have demonstrated the PPM of block copolymer brush surfaces despite the potential of using the block copolymer brush architecture to control access and the microenvironment of pendent functional groups.^{3,67} Block copolymer brushes with o-NB-protected thiols in the inner block were synthesized using pHEMA with a thickness of 14.6 \pm 0.4 nm as a macroinitiator for polymerization of DMAEMA. The thickness of the DMAEMA block was 22.1 \pm 0.3 nm after 40 min of polymerization at room temperature. Block copolymers with o-NB-protected thiols in the outer block were prepared analogously using instead a pDMAEMA macroinitiator for chain extension with HEMA. In both cases, the o-NB-protected thiol was added via esterification of the pHEMA as described for the homopolymer brush samples resulting in a net thickness increase of about 15 nm.

Figure 4 shows the GATR-FTIR spectra of the block copolymer surfaces with o-NB pendent thiol in the inner [Fig. 4(a)] and outer [Fig. 4(c)] blocks. Both surfaces show the characteristic peaks for the -NO2 asymmetric and symmetric stretching vibrations (1527 and 1350 cm^{-1}) of the *o*-NB block and for aliphatic amine N-C-H stretching vibrations, 2820 and 2770 cm^{-1} , and C–N stretching vibration 1270 cm⁻¹ of the DMAEMA block. When the outer block consisted of DMAEMA units, protonation in 0.01 M HCl (pH 2) resulted in a weak NH^+ stretching vibration at 2250 cm⁻¹. Upon one-pot photodeprotection and thiol-isocyanate click with dodecyl isocyanate, both samples show the disappearance of the NO₂ stretching vibrations and appearance of C-H stretching vibrations at 2989, 2930, and 2860 cm^{-1} and $(CH_2)_n$ 1470 cm⁻¹ indicative of dodecyl moieties within inner [Fig. 4(b)] and outer [Fig. 4(d)] blocks. The corresponding GATR-FTIR spectra for the homopolymer brushes can be found in Supporting Information Figure S5.

Changes in the topography of the block copolymer surfaces as a result of thiol-click modifications of the inner and outer



FIGURE 3 Fluorescence microscopy images of polymer brushes patterned with fluorescein isothiocyanate (squares) and Texas Red[®] C₂ maleimide (bars) with 433 and 548 nm lasers, respectively, at magnifications of (a) $5 \times$ and (b) $20 \times$.

blocks as well as solvent treatment were characterized by AFM in tapping mode. The height images show the geometric roughness of the surface while the phase images reveal the distribution of different polymer domains present at the brush interface. The DMAEMA block was protonated to create a more hydrophilic domain compared to the more hydrophobic pendent dodecyl-modified block. After protonation with 0.1 M HCl, the surfaces were dried, rinsed with toluene, and finally dried with a stream of N₂. To better understand the morphological changes of the block copolymer surfaces, the height and phase images of each system are shown in Figure 5. For comparison, the AFM images for unmodified and modified homopolymer brushes and the



-NO a) -NR₃H⁺ 1527 2250 1350 Absorbance (a.u.) b) c) d) 3000 2500 2000 1500 1000 Wavenumber (cm⁻¹)

unprotonated block copolymers are given in the supporting information (Supporting Information Figs. S6 and S7). Figure

5(a,c) show the topography and phase images for the block

copolymer surfaces with o-NB-protected pendent thiol in the

inner and outer blocks, respectively. These surfaces do not

SCHEME 4 General approach for block copolymer synthesis, one-pot photodeprotection and thiol-click modification. The analogous inverse block sequence (pendent thiol upper block) was also synthesized, but is not shown.

FIGURE 4 GATR-FTIR of block copolymers (p(inner block)-*b*-p(outer block)) after PPG modification and thiol-click reaction with dodecyl isocyanate: (a) photolabile *o*-NB pendent thiol-modified pHEMA-*b*-pDMAEMA polymer brush (protonated), (b) pHEMA pendent thiol-*b*-pDMAEMA polymer brush clicked with dodecyl isocyanate (protonated), (c) pDMAEMA-*b*-NB pendent thiol-modified pHEMA polymer brush (protonated), and (d) pDMAEMA-*b*-pHEMA pendent thiol polymer brush clicked with dodecyl isocyanate (protonated).



FIGURE 5 Tapping mode AFM images (height/phase) of block copolymers: (a) photolabile *o*-NB pendent thiol-modified pHEMA-*b*-pDMAEMA polymer brush (protonated), (b) pHEMA pendent thiol-*b*-pDMAEMA polymer brush click with dodecyl isocyanate (protonated), (c) pDMAEMA-*b*-photolabile *o*-NB pendent thiol-modified pHEMA polymer brush (protonated), and (d) pDMAEMA-*b*-pHEMA pendent thiol polymer brush clicked with dodecyl isocyanate (protonated).

show a significant change in topography when DMAEMA is in a deprotonated [Supporting Information Fig. S7(a-b,e-f)] versus protonated state [Fig. 5(a,c)] (i.e., the differences in hydrophobicity of the protonated DMAEMA and the o-NB blocks are not significant). However, upon photodeprotection and functionalization with dodecyl isocyanate [Fig. 6(b,d)], the height images reveal an increase in roughness and more pronounced domain-like topography. The phase images also show a greater contrast between domains, particularly when comparing samples containing an *o*-NB inner block and

protonated DMAEMA outer block [Fig. 5(a)] with the equivalent structure containing an inner block modified with dodecyl isocyanate [Fig. 5(b)]. The observed changes in topography and phase are likely derived not only from the greater contrast in hydrophobicity among dodecyl and protonated tertiary amine-containing blocks, but also from the final solvent treatment with toluene before imaging. In comparison, samples containing dodecyl-pendent groups in the outer block [Fig. 5(d)] show little rearrangement due to toluene exposure, as the solvated block already dominates the interface as in the case of the dodecyl-modified HEMA homopolymer [Supporting Information Fig. S6(g-h)]. Water contact angle measurements of the block copolymer surfaces, shown as insets in Figure 5, also indicate the presence of a mixed chemical composition at the brush-air interface. Samples containing protonated DMAEMA as the outer block with o-NB and dodecyl-modified inner blocks showed water contact angles of 50.1° and 61.3° , respectively. These values are much higher than the protonated pDMAEMA homopolymer brush (13.5°) , indicating that both the inner and outer blocks contribute to the observed wettability. Similarly, the reverse scenario, where protonated DMAEMA units formed the inner block with the outer block consisting of o-NB and dodecyl moieties showed water contact angles of 57.2° and 63.6°, respectively—values slightly lower than either the o-NB or dodecyl-modified homopolymers (Supporting Information Fig. S8). Combined, these results show that PPM of pendent thiols via thiol-click reactions can be successfully used to tailor the functionality of complex polymer brush architectures-including the inner and outer blocks of a block copolymer brush surface.

CONCLUSIONS

We have demonstrated a postpolymerization surface modification approach that provides pendent thiol functionality along the polymer brush backbone using the photolabile protection chemistry of both o-nitrobenzyl and p-methoxyphenacyl thioethers. Addressing the protecting groups with light enables a plethora of thiol-mediated transformations with isocyanates and maleimides providing a versatile route to create complex, functional polymer surfaces. GATR-FTIR analysis showed that greater than 70% of the protected pendent thiols are available for postmodification following photodeprotection. Also, the generation of reactive free thiols was controlled spatially during photodeprotection with photomasks affording patterned, multifunctional surfaces via orthogonal thiol-click chemistries. One-pot modification processes combining photodeprotection and sequential thiol-click of the brush surface were explored. This concept was extended to block copolymer architectures enabling the modification of the chemical functionality of both the inner and outer blocks of the block copolymer surface. The combination of phototriggered thiol-click functionalization and controlled radical surface-initiated polymerization provides an attractive and modular approach to tailor the chemical functionality and architecture of polymer surfaces. The approach described also enables spatial immobilization of functional groups in multiple dimensions, that is, laterally via photolithography and vertically via architectural design of block copolymer brushes; efforts in these directions are ongoing.

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