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ARTICLE

One-pot polymer brush synthesis *via* simultaneous isocyanate coupling chemistry and “grafting from” RAFT polymerization

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ABSTRACT: One-pot ‘grafting from’ of polystyrene on polydopamine coated SiO₂ particles was investigated using a newly developed carbonyl-azide reversible addition-fragmentation chain transfer (RAFT) agent. Simultaneously during the RAFT polymerization of styrene, the carbonyl-azide group of the CTA rearranges into an isocyanate moiety permitting the one-pot coupling to functional surfaces. The one-pot coupling to the polydopamine surfaces was investigated, separately, using both the non-catalyzed amine-isocyanate coupling and the metal catalyzed alcohol-isocyanate coupling. Thermogravimetric analysis showed that the catalyzed one-pot ‘grafting from’ process produced nearly double the weight increase, and thus higher grafting density, when compared to the uncatalyzed system. These results are consistent with more available hydroxyl groups on the polydopamine surface. Finally, both one-pot ‘grafting from’ approaches exhibited higher grafting density when compared to their analogous ‘grafting to’ strategies using α -isocyanate terminated polystyrene and thus superseding previous ‘grafting from’ processes where two-steps were normally required.

1 Introduction

The ability to modify and control the surface properties of materials has advanced several areas with particular interest in biomedicine and biomedical engineering where past efforts have significantly improved our understanding of biology and thus our ability to create novel treatments and devices for a plethora of medical treatments.^{1,2} In the past decade polymer brushes have come to the fore of surface modification chemistry given their tremendous versatility. The properties of polymer brush coatings can be varied by modifying the chain length and molecular weight, monomer structure and stereochemistry, branch composition^{3,4} and end-group functionality.^{5,6} Polymer brush materials are defined as chains that are tethered to the desired surface or interface at one end through either physisorption or covalent attachment methods.⁷ A polymer brush regime exists when the radius of gyration of the chains exceeds the distance between attachment points, thereby forcing the polymer chains to stretch away from the surface, maximizing their conformational entropy, and thus forming a brush configuration.⁸ In addition to enhanced polymer properties when compared to the bulk polymer properties,⁸⁻¹⁰ polymer brushes exhibit a higher density of chains in a given surface area compared to bulk polymers.¹¹ This leads to an increase in the amount of chain interactions with the environment, a key feature for biological applications such as protein binding and cell uptake.

The covalent attachment of polymers on a surface can be obtained through either a ‘grafting to’ or ‘grafting from’ technique.¹² In the ‘grafting to’ approach, a premade end-functional polymer is attached to the surface through a simple and sometimes ‘click’ chemistry reaction. This process leads to a rather limited grafting density as the long polymer chains bound to the surface hinder the attachment of further chains in a localized area on the surface due to steric crowding. For this reason, producing a dense polymer layer *via* the ‘grafting to’ method becomes progressively more difficult for polymers with increasing chain lengths or as the concentration of polymer chains on the surface increases. While this is a reliable, one-step process it is not preferred when higher grafting densities are demanded. Truly high grafting density polymer brushes can be created *via* the two-step ‘grafting from’ process. In the case of controlled radical polymerization, such as atom transfer radical polymerization (ATRP)^{8,9} and reversible addition-fragmentation chain transfer (RAFT) polymerization,¹³ the initiator (for ATRP) or the chain transfer agent (for RAFT, bound through the R-group) must be attached to the surface prior to the polymerization being conducted, thus growing polymers directly from the surface. Steric hindrance issues are minimized due to the diffusion of small monomeric units to the growing brush surface rather than the bulky pre-made polymer chains in the ‘grafting to’ approach.

Although uniform polymer brush layers of a high grafting density can be obtained, one of the main disadvantages of the ‘grafting from’ approach is the two-step procedure – the need to

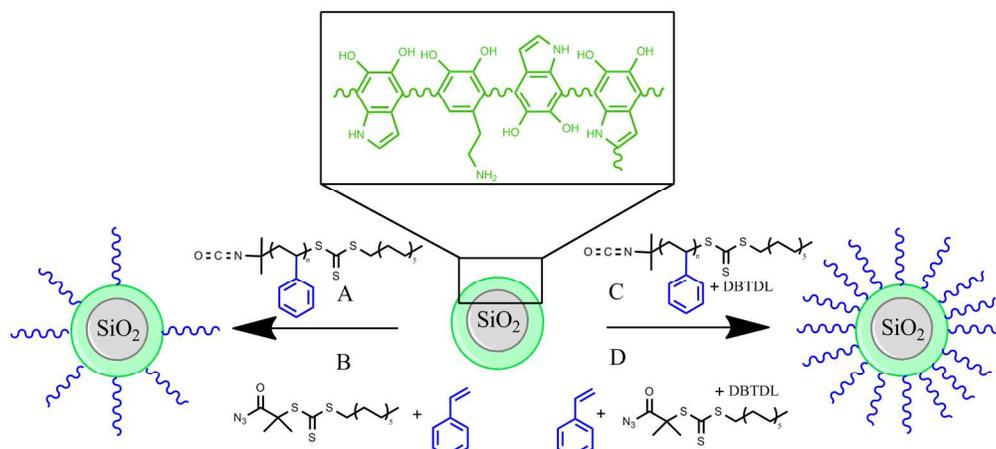
pre-functionalize the surface before polymerization can commence. The creation of a one-step ‘grafting from’ process, whilst maintaining the superior grafting density over the ‘grafting to’ technique, would represent a more streamlined and labor efficient approach. Thus far to date in the literature, only one attempt has been made at a one-pot polymer brush synthesis through the simultaneous polymerization and surface grafting process on silica nanoparticles by Rajan and Brittain.¹⁴ This work utilized an alkyne functionalized RAFT agent and azide surface modified silica nanoparticles to perform *in situ* copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) and RAFT polymerization. Although this work was highly novel, the approach still requires a two-step surface pre-functionalization reaction, prior to polymerization, to introduce azido groups on the silica surface for coupling¹⁴ rather than working with the highly abundant surface hydroxyl groups on the silica particles. In addition to the multiple surface modification steps prior to simultaneous RAFT polymerization and coupling, there are issues with regard to copper removal and potential metal contamination. Thus, a process which moves away from a metal catalyzed process would be extremely advantageous.

Since the seminal work of Messersmith and coworkers¹⁵ into the mussel-inspired self-polymerization of dopamine, research into this area of biomimetic polymeric coatings has intensified considerably. Messersmith and coworkers were able to show that pH-buffered aqueous solutions of dopamine spontaneously crosslink to form a thin and robust polymer coating on an array of flat materials dipped into the solution.¹⁵ Furthermore, the surfaces were capable of cell adhesion, multi-layer reactions through the amine and hydroxyl groups on the polydopamine coating, as well as microlithography imprinting. This discovery has led to increased research efforts into this area, where polydopamine coatings have been investigated for hollow nanocapsule generation,¹⁶ biomimetic surfaces,¹⁷ and even living-cell encapsulation.¹⁸ The biocompatibility of this material has made it of particular interest for biomedical devices, especially in the arena of economical scaffolds for metallization and polymer growth.¹⁹⁻²¹

In addition to the biomedical potential for these surfaces, they represent useful substrates for modification through the abundance of hydroxyl and, both primary and secondary, amine groups. For this purpose, isocyanate chemistry is of great interest due to its capability to react efficiently with a wide

range of (naturally occurring) functional groups such as amines and alcohols, found in particularly high abundance on the surface of polydopamine substrates. Recently, an interesting approach has been reported by Gody *et al.*²² where the RAFT polymerization of vinyl monomers with a carbonyl-azide chain transfer agent precursor allows for the synthesis of well-defined α -isocyanate terminated polymers *via* an *in situ* Curtius rearrangement. A carbonyl-azide RAFT agent (dodecyl isobutryl azide trithiocarbonate, DIAzTC) was created which, when used for polymerization of a number of different monomers, would rearrange into an α -isocyanate-terminated RAFT-grown polymer early on in the polymerization process. The traditional RAFT polymer characteristics of highly controlled molecular weight and narrow M_w/M_n were preserved. Furthermore Gody *et al.*²² showed that the newly formed isocyanate group could couple with an alcohol bearing molecule while simultaneously growing the polymer. This breakthrough distinctly describes the first record of such a system, and also creates the possibility of extending this process to surface modifications, as well as coupling to primary amines. If the hydroxyl or amine bearing group resides on the surface of a material, then a one-pot simultaneous RAFT polymerization and ‘grafting from’ process can be attained without the need for tedious surface pre-modification steps.

To test the capabilities of this one-pot ‘grafting from’ polymerization reaction to various surface functional groups present on the same substrate material, we utilized polydopamine nanoparticles, obtained from the coating of SiO₂ particles with polydopamine, as our substrate of interest. The polydopamine surface provides a robust and uniform polymeric substrate on which to test the coupling of DIAzTC grown polystyrene to both amine and hydroxyl moieties. RAFT polymerizations of styrene, in the presence of the polydopamine particles (PDA), were conducted both with and without the use of a tin catalyst (Scheme 1). Without the tin catalyst, coupling occurs solely through the surface amine groups, while using the catalyst permits coupling to both the surface amine and hydroxyl groups. The grafting density of the polystyrene modified surfaces was performed using a combination of thermogravimetric analysis (TGA) of the surfaces and gel permeation chromatography (GPC) analysis of the free polystyrene.



Scheme 1. Various reaction pathways for performing the ‘grafting to’ (A and C) and ‘grafting from’ (B and D) techniques of RAFT synthesized polystyrene chains on polydopamine particles.

2 Experimental

2.1 Materials

Unless otherwise stated, all materials were obtained from Sigma-Aldrich and used without any further purification. Silica nanoparticles (SiO_2 , 99.8%), dopamine hydrochloride (Sigma), tris(hydroxymethyl)aminomethane (TRIS, $\geq 99.8\%$), dibutyltin dilaurate (DBTDL, 95%), benzyl amine (97%), hexyl isocyanate (97%), and toluene (99.5%) were all used as received. Dodecyl isobutryl azide trithiocarbonate (DIAzTC) and isocyanate-terminated RAFT grown polystyrene were prepared according to conditions previously described in the literature.²² Styrene ($\geq 99\%$) was de-inhibited by passing through basic alumina prior to use. Azobisisobutyronitrile (AIBN) was recrystallized from methanol.

2.2 Synthesis of Polydopamine Particles

TRIS (0.9696 g, 10 mM) was added to de-ionized water (800 mL) to afford a pH ~ 10 solution. SiO_2 particles (2 g) were then added followed by dopamine hydrochloride (1.6 g, 2 $\text{mg}\cdot\text{mL}^{-1}$) and the solution exhibited pH ~ 8.5 . The solution was stirred overnight at 30 °C, then removed from the heat, filtered and rinsed with copious amounts of de-ionized water. The coated particles were then dried fully in a vacuum oven at 40 °C overnight. The coated particles were analyzed using attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR), dynamic light scattering (DLS) and TGA. The main paragraph text follows directly on here.

2.3 'Grafting to' the PDA Particles using Polystyrene and Hexyl Isocyanate

Polystyrene (0.15 g, $M_n = 12,000 \text{ g}\cdot\text{mol}^{-1}$, $D = M_w/M_n = 1.21$) generated previously using the DIAzTC RAFT agent²² was dissolved in toluene (20 mL) and added to a flask containing the polydopamine particles (0.2 g). The solution was sonicated for 10 minutes and then reacted at 65 °C for 21 h. The solution was washed with toluene and filtered with the resulting polystyrene coated particles then dried fully in a vacuum oven at 40 °C overnight. A duplicate reaction was set up with the addition of $3 \times 10^{-3} \text{ g}$ ($4.8 \times 10^{-6} \text{ mol}$) of DBTDL catalyst to the reaction solution to facilitate the coupling of the polystyrene chains to the surface hydroxyls, as well as the amines, on the polydopamine particles. The hydroxyl-driven 'grafting to' reaction was filtered, rinsed, and dried in the same manner as the non-catalyzed system. All polystyrene surface modified particles were analyzed using ATR-FTIR, DLS and TGA.

Duplicate reactions as per the above method were set up with hexyl isocyanate in place of polystyrene to determine the maximum grafting density. 0.250 g ($2.0 \times 10^{-3} \text{ mol}$) of hexyl isocyanate was used for binding to surface amines and 0.250 g ($2.0 \times 10^{-3} \text{ mol}$) of hexyl isocyanate with 0.34 g ($5.4 \times 10^{-4} \text{ mol}$) of DBTDL catalyst was used for binding to surface hydroxyls. As with the polystyrene bound surfaces, the small molecule bound surfaces were analyzed using ATR-FTIR and TGA.

2.4 RAFT Polymerization of Styrene in the Presence of PDA Particles

Polydopamine particles (0.1 g) were placed in one flask and degassed under vacuum for 20 min. The DIAzTC RAFT agent (0.1 g, $2.6 \times 10^{-4} \text{ mol}$) was added to a second flask along with styrene (6.931 g, $6.65 \times 10^{-2} \text{ mol}$) and AIBN ($8.7 \times 10^{-3} \text{ g}$, $5.3 \times 10^{-5} \text{ mol}$). This flask was degassed by bubbling nitrogen through the solution for 20 min prior to cannula transfer to the flask containing the

polydopamine particles. The solution was reacted at 65 °C for 21 h, removed from heat, and the particles washed with THF, filtered, and dried in a vacuum oven at 35 °C for 48 h. The free polymer, collected from the filtered solution after removing the solvent under vacuum, was analyzed using GPC while the polystyrene grafted PDA particles were analyzed using ATR-FTIR, DLS and TGA.

A duplicate reaction was set up with DBTDL catalyst ($4.8 \times 10^{-2} \text{ g}$, $7.6 \times 10^{-5} \text{ mol}$) added to the liquid reactants flask to facilitate the coupling of the generated polystyrene to the surface hydroxyls, as well as the amines, of the polydopamine particles. The reaction was treated, cleaned, and analyzed in the same manner as the uncatalyzed reaction system.

2.5 RAFT Polymerization of Styrene with DIAzTC and *In situ* Coupling to Benzyl Amine

Styrene monomer (1g, $9.6 \times 10^{-3} \text{ mol}$) was added to a flask along with AIBN ($1.26 \times 10^{-3} \text{ g}$, $7.7 \times 10^{-6} \text{ mol}$) and the DIAzTC RAFT agent (0.015 g, $3.8 \times 10^{-5} \text{ mol}$) before degassing with nitrogen bubbling for 20 min. A solution of benzyl amine in toluene at 21.6 $\text{mg}\cdot\text{mL}^{-1}$ (200 μL , 1.05 equiv.) was added to the flask just prior to heating the flask to 65 °C for 21 h to allow for polymerization. After quenching the reaction in an ice bath, the generated polystyrene was purified by precipitation in n-hexane, and dried in a vacuum oven overnight. The purified polymer was analyzed *via* ^1H NMR, THF GPC, and FTIR to determine the extent of polymerization, conversion of the azide to isocyanate, and coupling to the benzyl amine.

2.6 Characterization

Attenuated Total Reflectance-Fourier transform infrared spectroscopy (ATR-FTIR). Spectra were obtained using a Bruker Spectrum BX FT-IR system, using diffuse reflectance sampling accessories and a resolution of 4 cm^{-1} . Each sample was analyzed using 128 scans. SiO_2 was used for the base line spectrum.

Gel Permeation Chromatography (GPC). Molecular weight analysis was performed using a Shimadzu modular system containing a DDU-12A degasser, an LC-10AT pump, a SIL-10AD automatic injector, a CTO-10A column oven and a RID-10A refractive index detector. Four Phenomenex columns (100, 10^3 , 10^4 , 10^6 Å pore size, 5 μm particle size) were used for the analyses. Tetrahydrofuran (THF) (HPLC grade, 250 ppm BHT), at 40 °C, with a flow-rate of 1 $\text{mL}\cdot\text{min}^{-1}$ was used as the mobile phase. The injection volume was 50 μL . The samples were prepared at standard concentrations and filtered through 0.45 μm filters. The unit was calibrated using commercially available linear polystyrene standards (0.5-1000 kDa, Polymer Laboratories). Chromatograms were processed using Cirrus 2.0 software (Polymer Laboratories).

Thermogravimetric Analysis (TGA). TGA was carried out using a Perkin Elmer STA6000 instrument. All samples were analyzed under a nitrogen environment with the following heating profile: heat from 30 °C to 100 °C at 40 $^\circ\text{C}\cdot\text{min}^{-1}$, hold at 100 °C for 8 min and then heat from 100 °C to 900 °C at 10 $^\circ\text{C}\cdot\text{min}^{-1}$.

Dynamic Light Scattering (DLS). Light scattering studies of the particles at 0.2 $\text{mg}\cdot\text{mL}^{-1}$ in de-ionized water were conducted using a Malvern Zetasizer Nano Series running DTS software and operating a 4 mW He-Ne laser at 633 nm. The size measurements were carried out in quartz cuvettes at 25 °C, and the temperature was allowed to equilibrate for 5 min. The number-average hydrodynamic particle size and polydispersity index were determined based on an average of five measurements.

3 Results and discussion

We have recently begun research into substrate coatings using polydopamine and its derivatives as useful scaffolds for surface modifications and novel materials and membranes.²³ These robust, biologically inspired coatings have garnered much interest recently due to their facile pH-buffered coating process, cell adhesion capability, as well as usefulness in the microlithographic imprinting arena.¹⁵ Of particular interest is that the lightly cross-linked polydopamine will coat virtually any substrate while permitting a plethora of further reactions to be carried out due to the high concentration of hydroxyl and amine moieties present in the system. For these reasons, several labs in addition to our own have begun investigating the ‘grafting from’ and ‘grafting to’ polymer brush synthesis on polydopamine substrates as a means of surface chemistry modification; however, all of this work has involved multiple steps. Either the pre-polymerization of polymer chains followed by coupling reactions to attach the polymer chains (‘grafting to’ strategy) or through the coupling of agents (ATRP initiators or RAFT agents) to the surface followed by surface polymerizations (‘grafting from’ strategy) have been investigated.²⁴⁻²⁶ While these methods are highly useful, when employed on polydopamine surfaces there is the possibility of aminolysis of the attached RAFT agent during the surface polymerization, competitive binding of the metal halide used during surface ATRP reactions, or low surface grafting densities when employing ‘grafting to’ techniques. Therefore, we were interested in developing a method for performing a one-pot ‘grafting from’ RAFT polymerization process on our polydopamine coated substrates as a means of bypassing these shortcomings. Due to the abundance of hydroxyl and amine groups on the polydopamine surface, isocyanate chemistry as a means for attaching polymers represents a highly efficient and facile means to the surface modification of our scaffolds. Furthermore, the use of SiO₂ nanoparticles coated with polydopamine exhibits high surface areas allowing for ease in surface analysis as well as large concentrations of polymer chains generated in solution available for verification of the living nature of the RAFT polymerization process. As can be seen in Figure 1 (Curve A), the presence of polydopamine was confirmed using ATR-FTIR by the existence of the broad hydroxyl peak observed at 3300 cm⁻¹. Thermogravimetric analysis of the polydopamine nanoparticles showed that the surface coating accounted for 14.46% by weight of the particle samples. These polydopamine particles (PDA) were used in all of the ‘grafting to’ and ‘grafting from’ reactions performed throughout this work.

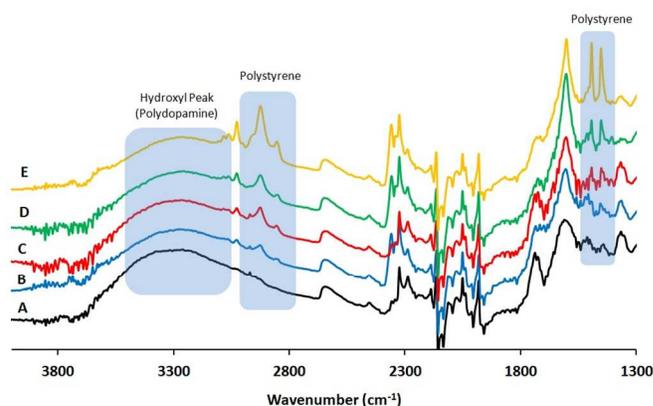


Figure 1. ATR-FTIR analysis of the grafting of polystyrene to PDA particles (PS-g-PDA): (A) PDA, (B) PS ‘grafting to’ the surface, (C) PS ‘grafting to’ the surface in the presence of tin catalyst, (D) PS ‘grafting from’ the surface, and (E) PS ‘grafting from’ the surface in the presence of tin catalyst.

3.1 Grafting Polystyrene to PDA Particles

Previously²² we have shown the successful one-pot ‘clicking’ nature of the DIAZTC RAFT agent to an alcohol while simultaneously synthesizing various polymers. Due to the large quantity of hydroxyl groups on the surface of the PDA particles, we were interested in extending this isocyanate coupling chemistry to our materials. This would represent a novel, one-pot simultaneous RAFT polymerization and ‘grafting from’ surface modification technique unique from any of the previous work utilizing RAFT and CuAAC ‘click’ chemistry.¹⁴ Furthermore, as polydopamine particles also possess primary amine groups,¹⁵⁻²¹ the DIAZTC RAFT agent can also react with these groups, after undergoing Curtius rearrangement to form the isocyanate. We expect this to be another possible pathway to one-pot polymerization/‘grafting from’ surface modification due to the decreased rate of aminolysis of the trithiocarbonate, compared to their dithioester counterparts, and the high reactivity of isocyanates towards alkyl amines. Thus, this would represent the first instance of performing simultaneous, one-pot RAFT polymerization and ‘grafting from’ polymer brush synthesis through either hydroxyl or hydroxyl/amine surface functional groups without the need for surface pre-functionalization.

To investigate the full potential of this one-pot process, both the ‘grafting to’ of α -isocyanate terminated polystyrene and one-pot polymerization/‘grafting from’ approaches were investigated using the PDA particles. Although successful results have been previously reported for the one-pot RAFT polymerization of styrene and alcohol-isocyanate coupling with a very fast re-arrangement of the carbonyl-azide into the isocyanate at the polymerization onset, the authors have not studied the kinetics of the alcohol-isocyanate coupling.²² In our approach, this element is crucial so as to avoid low grafting densities due to steric hindrance effects. If the Curtius rearrangement and subsequent surface coupling occurs late during the polymerization, then large polymer chains will be coupling to the surface and potentially giving rise to low grafting density brushes more akin to a mushroom regime than a polymer brush regime. However, if the rearrangement and surface coupling occurs soon after the onset of polymerization, then small oligomeric chains will be coupling to the surface with very limited steric hindrance effects and a high grafting

density well within the polymer brush regime should be obtained.

It is therefore critical that our one-pot RAFT polymerization/‘grafting from’ technique be analyzed with a comparable ‘grafting to’ technique. Provided all the polymer chains generated, whether utilizing a ‘grafting from’ or ‘grafting to’ approach, have similar molecular weights, then the ‘grafting to’ technique should represent the lowest possible grafting density. Fortunately, the α -isocyanate ends of the polymer chains, generated during the Curtius rearrangement, are rather stable in the absence of amines or hydroxyl groups in the reaction system. Thus, RAFT polymerization of styrene using DIAzTC was performed, in the absence of PDA particles, to yield α -isocyanate terminated polystyrene chains. These polystyrene chains were used for ‘grafting to’ experiments both with and without tin catalyst, to test the amine/alcohol and amine only coupling, respectively. As shown in Figure 2, the molecular weight and the M_w/M_n [*N.B.* – recently named dispersity (D) by IUPAC, and formerly known as PDI or polydispersity] generated in the absence of PDA particles (Curve C) was in good agreement with the ‘free polymer’ generated during the one-pot RAFT polymerization/‘grafting from’ experiments (Curve A and B). Prior research²⁷⁻²⁹ has shown that the molecular weight of polymer brushes generated *via* ‘grafting from’ (when cleaved from the surface) is similar to those of the ‘free polymer’ generated *in situ*. Thus, the ‘free polymer’ generated during our one-pot ‘grafting from’ reactions should be the same molecular weight as the polymer brushes on the PDA particles. As with the ‘grafting to’ experiments, these one-pot RAFT polymerization/‘grafting from’ reactions were performed both with and without a tin catalyst to investigate the coupling and polymer brush synthesis from surface amine/alcohol sites and amine sites, respectively. It should be noted that the one-pot RAFT polymerization/‘grafting from’ in the presence of a tin catalyst (Curve A) resulted in a slightly decreased molecular weight with the emergence of high molecular weight shoulder, as well as a broadening of the dispersity to 1.40. However, when compared to the other two traces (α -isocyanate terminated polystyrene and ‘grafting from’ without tin catalyst) the difference in the M_w for all samples are within $1000 \text{ g}\cdot\text{mol}^{-1}$. Furthermore, the polystyrene generated in solution without any PDA particles present (Curve C) showed a slightly asymmetric nature to the curve. We speculate that this could be due to traces of water present during the polymerization. A repeat polymerization was performed and showed a much more narrow dispersity (See Supporting Information). Thus, due to the reactivity of the isocyanate group, it is likely that special care should be taken to ensure low water content, *via* the reactants or air in the system, in order to prevent these side reactions.

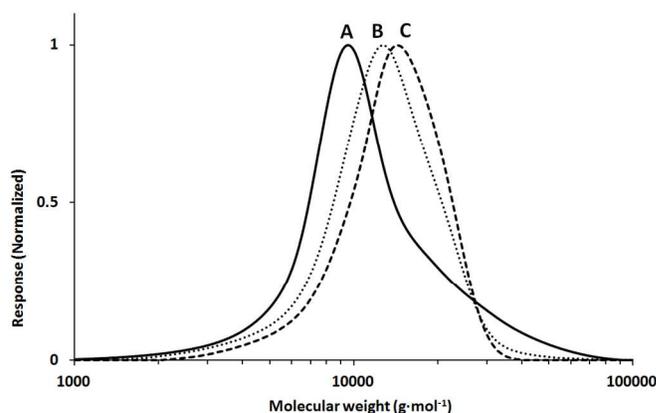


Figure 2. GPC traces of polystyrene chains generated with α -carbonyl azide RAFT agent (A) in the presence of PDA particles with tin catalyst; (B) in the presence of PDA particles and no catalyst; and (C) with no catalyst or PDA particles.

Analyzing the weight increase of polymer chains bound to the surface using thermogravimetric techniques allowed for the estimation of when the coupling reaction to the surface occurs during the polymerization. When the TGA results for coupling the polystyrene chains to the amine moieties (no tin catalyst) on the surface were analyzed, it was seen that the particles generated *in situ* during the one-pot ‘grafting from’ and RAFT polymerization had roughly 4% more organics than for the ‘grafting to’ process. The TGA data for all the samples are given in Table 1, and as can be seen, the ‘grafting from’ process showed a 28.36% weight loss while the ‘grafting to’ process showed a 24.85% weight loss. All of the PDA particle samples used in each grafting experiment were from the same synthesis lot, and thus contained similar weight contents of PDA, and all had a particle diameter of 95 nm *via* DLS analysis. Since the polystyrene chains were shown to be of similar molecular weight, the mass increase for the samples must be due to an increase in the number of chains on the particle surface and thus a measure of the changing grafting density. Normalizing the data by removing the organics due to the PDA particle, the weight loss due to just the polymer chains during the ‘grafting to’ and ‘grafting from’ techniques was 10.4% and 13.90%, respectively.

Table 1. DLS and TGA results for grafted particles

Sample	Particle diameter (nm)	Weight Loss (percent)	Graft Density (chains·nm ⁻²)
PS-PDA (‘grafting to’ w/o Sn)	136	24.85	0.12
PS-PDA (‘grafting from’ w/o Sn)	120	28.36	0.13
PS-PDA (‘grafting to’ w/ Sn)	125	25.45	0.17
PS-PDA (‘grafting from’ w/ Sn)	139	36.33	0.30

Based on the TGA data, a surface grafting density was determined for the polymer chains attached to the PDA particles. The grafting densities for the amine moiety coupling reactions were calculated according to the method described by Bao *et al.* (equation 1).³⁰

$$\sigma = \frac{\delta \times V \times W_{poly} \times N_A}{W_{silica} \times M_n \times SA} \quad (1)$$

In this equation, W_{poly} is the percent weight loss of the polymer attached (total organics minus the weight loss of the PDA shell), W_{silica} is the percent weight loss of the silica remaining, M_n is the molecular weight of the grafted molecule or chain, δ is the density of silica (given as $2.07 \text{ g}\cdot\text{mL}^{-1}$) and N_A is Avogadro's number. The volume (V) and surface area (SA) of the silicon dioxide core were calculated based on a particle diameter of 50 nm resulting in $6.55 \times 10^3 \text{ nm}^3$ and $7.85 \times 10^3 \text{ nm}^2$, respectively. Using this equation, it can be shown that the one-pot RAFT polymerization/'grafting from' reaction to amine moieties yields a slightly higher grafting density than the analogous 'grafting to' methodology (0.13 compared to $0.12 \text{ chains}\cdot\text{nm}^{-2}$). Although both systems reside in the polymer brush regime,³¹ which is typically grafting densities above $0.1 \text{ chains}\cdot\text{nm}^{-2}$, the two systems exhibit virtually the same, relatively low polymer brush grafting density.

The tin catalyzed coupling reactions to the surface hydroxyls and amine functionalities of the polydopamine particles were subjected to the same grafting density analysis. Both the tin catalyzed 'grafting to' and one-pot RAFT polymerization/'grafting from' techniques gave noticeably higher percent weight loss values than their amine coupling analogues (Table 1). Considering that the tin catalyzed system promotes isocyanate coupling to the surface hydroxyls as well as primary amines, it is not surprising that more polymer brush chains were observed when tin was added to the system. A typical example of the TGA data, in this instance comparing the two tin catalyzed systems, is depicted in Figure 3. An even greater increase in the grafting density can be observed for the tin catalyzed one pot RAFT polymerization/'grafting from' ($0.30 \text{ chains}\cdot\text{nm}^{-2}$) than the tin catalyzed 'grafting to' ($0.13 \text{ chains}\cdot\text{nm}^{-2}$), more than twice as many chains attached to the particle surface. This grafting density increase for the 'grafting from' samples shows that the coupling of the DIAzTC RAFT agent was occurring early on in the one-pot reaction, regardless of the surface moiety targeted. The early coupling allowed the growth of the surface-bound polymers to proceed as they would for traditional 'grafting from', that is, free from the steric hindrance that limits the grafting density of the 'grafting to' processes. To verify this, a comparable RAFT agent, butyl dimethyl acetic acid trithiocarbonate (BDMAATC), was bound to the surface and polystyrene brushes generated in a traditional 'grafting from' process from the PDA particles. A grafting density of $0.31 \text{ chains}\cdot\text{nm}^{-2}$ was calculated, which is in line with that calculated using the one-pot 'grafting from' process (See Supporting Information). The organic compounds in both samples are made up of the same weight percentage of polydopamine and differing weight percentages of polystyrene polymer (brushes).

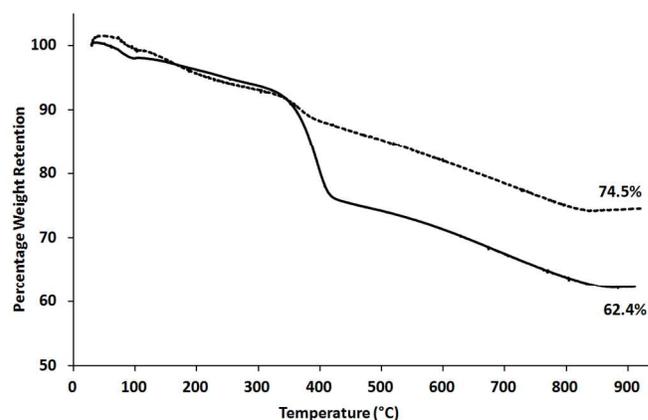


Figure 3. Typical TGA curves for 'grafting to' (74.5% residual weight) and one-pot RAFT polymerization/'grafting from' (62.4%) reactions of polystyrene in the presence of tin catalyst.

3.2 Surface Coverage and RAFT Agent Activity

In order to estimate the grafting density limit, the 'grafting to' reactions were replicated using hexyl isocyanate as a small molecule model that would not be affected by steric hindrance effects which limit the grafting density for longer polymer brushes. To ensure that this method would help calculate the theoretical grafting density limits, an excess of material was used for both the tin catalyzed and uncatalyzed reactions. A molar amount one hundred times larger than the molar amounts used in the polymer brush reactions was used to ensure that all surface amines or amines/hydroxyls were reacted. Assuming all available surface amines and amines/hydroxyls had reacted with the hexyl isocyanate molecules, the increase in weight loss measured during the TGA analysis should give a reasonable approximation of the surface concentration of amines and hydroxyls. It was found that there were $1.37 \times 10^{-3} \text{ mol}$ of surface amines per gram of polydopamine particles and $1.17 \times 10^{-3} \text{ mol}$ of surface hydroxyls per gram of particles. Converting these values using the reported $380 \text{ m}^2\cdot\text{g}^{-1}$ surface area yields values of 2.17 and $1.85 \text{ molecules}\cdot\text{nm}^{-2}$, respectively. While this would imply that the 'grafting to' and one-pot RAFT polymerization/'grafting from' had resulted in merely a 10% surface modification, it is also possible that the hexyl isocyanate used to determine the surface functionality was penetrating into the polydopamine substrate rather than merely reacting on the surface.

All of the polystyrene reactions with the PDA particles were conducted for 21 h, regardless of one-pot RAFT/'grafting from' or 'grafting to' or the use of a tin catalyst. This was the same reaction time for all of the 'grafting from' and 'grafting to' reactions employed during this research. Furthermore, this was a similar time frame employed in the original work with the DIAzTC RAFT agent reactions with alcohol functionalities.²² Gody *et al.* showed that the Curtius rearrangement from the carbonyl azide to the α -isocyanate was complete in approximately 4 h. However, quantitative coupling between the α -isocyanate and the alcohol moieties took 20 h. Coupling experiments between the α -isocyanate polystyrene and benzyl amine, a model amine compound, to test the time duration for quantitative coupling was performed as an analogue to the previous alcohol coupling work. As can be seen in Figure 4,

after 21 h all of the azide was converted to isocyanate as evident from the loss of the peak at 2150 cm^{-1} . However, there still persists a trace amount of α -isocyanate groups after 21 h as evident from the peak at 2243 cm^{-1} . Potential aminolysis of the RAFT agent due to the presence of benzyl amine in the system could account for the trace amount of α -isocyanate being observed in the FTIR spectrograph. Gel permeation chromatography of the polystyrene (Figure 5) showed that the polymer exhibited a low dispersity ($D = 1.12$) with an M_n of $9,300\text{ g}\cdot\text{mol}^{-1}$ ($DP_{\text{GPC}} \approx 86$) in agreement with the theoretical M_n of $9,100\text{ g}\cdot\text{mol}^{-1}$. The analysis of the final polymer by ^1H NMR reveals a high efficiency for the one-pot RAFT/amine-isocyanate coupling with a yield around 96%. This coupling yield was proven *via* ^1H NMR analysis of the chain ends showing the presence of the benzyl urea linkage (see Supporting Information).

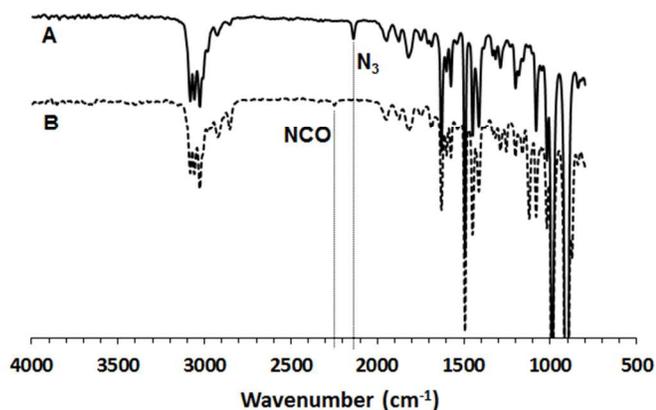


Figure 4. FTIR spectra showing the one-pot RAFT polymerization of styrene and benzyl amine-isocyanate coupling; (A) before starting the polymerization with the signal of the initial carbonyl-azide from the CTA and (B) after RAFT polymerization.

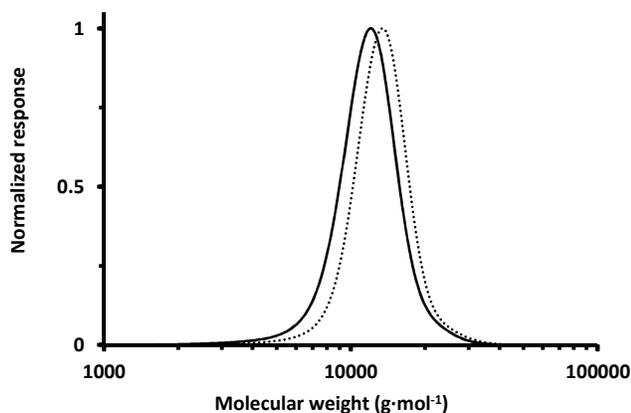


Figure 5. Comparison of the GPC traces obtained for the RAFT homopolymerization of styrene with the DIAzTC CTA without benzyl amine (dash line) and with benzyl amine (solid line; one-pot RAFT / amine-isocyanate coupling).

For these reasons, the α -isocyanate coupling reactions between the small hexyl isocyanate molecule and the PDA particles were all conducted to 21 h, to ensure optimum coupling. Unfortunately, hexyl isocyanate penetration into the PDA substrate leading to reaction with interior primary amine and hydroxyl sites must have occurred. This could explain why

there is a higher concentration of amines than hydroxyls, which should not be the case for the dopamine self-polymerization reaction.¹⁵⁻¹⁸ The majority of the amine groups present in polydopamine coatings are secondary amines due to the cyclization of dopamine to form the indole. These secondary amines have a much lower reactivity³² than their primary amine counterparts. Thus, the amine group concentration measured would have to be primary amine groups, as the reaction between secondary amines and isocyanates is extremely slow, slower than even the reaction with alcohols, when no catalyst is present.³³ In addition, considering that there was very little increase in the grafting density between the ‘grafting to’ and one-pot RAFT polymerization/‘grafting from’ after 21 h of reaction, the maximum coverage should have been attained and the hexyl isocyanate reaction should represent a sizable amount of polydopamine layer penetration.

Since the hexyl isocyanate has most likely penetrated throughout the interior of the polydopamine substrate, and the concentrations of accessible primary amines and hydroxyls were roughly the same, information about the hydroxyl groups can also be gleaned. Given the structure of polydopamine (Figure 1), the concentration of accessible hydroxyls for hexyl isocyanate coupling should be considerably higher. This would suggest that the hydroxyls of the catechol structure do not have similar reactivities, or that the reactivity of the second hydroxyl group to hexyl isocyanate is reduced significantly after the first coupling reaction. If this extends to the hydroxyls on the surface, then the reactivity of both hydroxyls would not be the same as well. This observation has also been seen by other groups, where it was also surprisingly shown that aromatic catechols and substituted aromatic alcohols exhibit a high reactivity towards isocyanates, which is contrary to the typically poor reactivity of aromatic alcohols to isocyanates.^{34, 35} It is this, in conjunction with the potential for steric hindrance of chains in such close proximity, that the surface grafting density is not significantly higher than $0.3\text{ chains}\cdot\text{nm}^{-2}$. Even though we did not obtain a higher grafting density than this amount, the α -isocyanate coupling reaction using the simultaneous RAFT polymerization/‘grafting from’ still generated surface grafted chains in a polymer brush regime.

4 Conclusions

In this work, we have shown that the typical two-step ‘grafting from’ process can be successfully superseded by a one-pot process. By using the carbonyl-azide functionalized DIAzTC RAFT agent, which undergoes Curtius rearrangement to an α -isocyanate during polymerization, coupling to a surface happens early enough that a proper ‘grafting from’ process is facilitated and a polymer brush layer can be created. Furthermore, we have shown for the first time that the isocyanate coupling to primary amines is preferred relative to RAFT agent aminolysis such that the resulting decomposition of RAFT agent and polymer chains is at a minimum. While we have only shown this to work for polystyrene systems, Gody *et al.*²² showed their RAFT agent to work for other monomers of similarly low k_p values as styrene. So it is more than likely that this one-pot ‘grafting from’ method will be useful for many more polymer brush and coated surface systems.

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