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A divergent synthetic route to functional copolymer libraries *via* modular polymers

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High-throughput polymer synthesis enables rapid exploration of chemical space but remains limited by batch-to-batch inconsistencies that can obscure structure–property relationship trends. To address this challenge, we developed a synthetic approach to produce multifunctional copolymers using post-polymerization modification of activated ester modular polymers with commercially available amines. Easily derivitized parent polymers—poly(tetrafluorophenyl acrylate) and poly(tetrafluorophenyl styrene sulfonate)—were synthesized by RAFT polymerization to yield single polymer batches containing highly reactive tetrafluorophenyl esters or sulfonate esters on each repeat unit. Tuning post-polymerization modification reaction conditions enabled the addition of sub-stoichiometric amounts of amines (relative to the repeat unit) to yield partially functionalized intermediates that could then be further derivatized. Reaction monitoring by ^{19}F NMR spectroscopy confirmed good control over these sequential post-polymerization modifications. This synthetic route produced a variety of copolymers with defined comonomer ratios while preserving the underlying polymer structure (degree of polymerization, dispersity, tacticity) for both the acrylate and styrene sulfonate backbones. We further applied this approach in a divergent manner to create a small library of structurally distinct copolymers from a single parent batch in three synthetic steps. This modular, divergent synthesis demonstrates a general route to structurally consistent copolymer libraries that enable systematic studies of structure–property relationships and can accelerate functional materials discovery.

Introduction

As high-throughput screening methods have advanced, high-throughput synthetic approaches have developed in parallel. High-throughput methods have been used in the pharmaceutical industry for decades,[1–4] and have more recently begun being employed in polymer chemistry.[5–9] In the context of polymer synthesis, these approaches have enabled the rapid production of large libraries of polymers with varying compositions to quickly discover new structures, establish structure–property relationships, and optimize polymerization conditions.

Ideally, the creation of these polymer libraries accelerates the discovery of new materials by enabling researchers to rapidly explore a wide range of chemical space and identify materials with optimal properties for a specific application. For example, copolymer libraries have been synthesized and screened for antibacterial activity, ultimately revealing structure–activity relationships that can guide the future development of antibacterial materials.[10–13] Additionally, high-throughput synthetic techniques have been applied to stimuli-responsive polymers to optimize synthetic methods and generate libraries of polymers with tuneable properties.[14–19] Despite these successes, many polymer structures remain inaccessible by direct (co)polymerization due to incompatibility in polymerization conditions, synthetically challenging monomers, or differences in comonomer reactivity ratios.[20,21] Furthermore, even the most well-controlled syntheses produce mixtures of polymer chains with slight (or not so slight) differences in degree of polymerization (DP), tacticity, and dispersity. While robotic platforms can often keep these variations to a minimum, structural variables are not perfectly controlled among different samples.[22–26] In applications where these minor structural changes can produce large effects, a synthetic approach capable of holding these variables constant—while still enabling rapid synthesis of many structurally related materials—is desirable.

Modular polymers, that is, polymers that can be easily modified post-polymerization,[27,28] offer several key advantages that streamline and enhance materials discovery. With a modular approach, a single parent material may be

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synthesized and subsequently derivatized to produce a library of materials that share key structural features, *e.g.*, DP, dispersity, and tacticity. While many modular polymer strategies exist,[29–31] modular polymers featuring activated esters, specifically perfluorophenyl esters, are particularly effective because of their facile functionalization by nucleophilic acyl substitution. This approach has been well-developed to produce homopolymer libraries,[32–34] and to a more limited extent, copolymers.[35,36] For example, Hawker, Bates, and coworkers recently demonstrated a high-throughput combined chromatographic and robotic method to generate a block copolymer library with varied block length and composition, based on a modular polymer block. Though limited to a series of homo-di-block copolymers, this work highlights the opportunity to extend modular polymer strategies to more compositionally complex copolymers.[37] As high-throughput synthesis evolves, the full potential of copolymer synthesis by a modular approach invites further exploration.

Here, we demonstrate a divergent synthetic strategy to copolymer libraries by sub-stoichiometric functionalization in a modular polymer-based approach. This strategy enables synthesis of copolymer libraries with high degrees of uniformity in composition, DP, and dispersity. This approach also enables synthesis of diverse copolymers while eliminating the variability inherent in other synthetic approaches and enabling access to copolymer structures inaccessible by direct polymerization.

Results and discussion

Synthesis and post-polymerization modification of poly (tetrafluorophenyl acrylate) (PTFPA)

We chose poly(tetrafluorophenyl acrylate) (PTFPA) as a model for this study because activated esters are a well-known class of modular polymer, functionalization of the polyacrylate backbone enables access to a variety of polyacrylates and polyacrylamides, and the *para*-proton allows for reaction monitoring by both ^{1}H and ^{19}F NMR spectroscopy.[30,32,38] Monomeric tetrafluorophenyl acrylate (TFPA) was synthesized in one step by the reaction of tetrafluorophenol with acryloyl chloride (Scheme 1 and Fig. S1, S2, SI). TFPA was then polymerized by reversible addition–fragmentation chain-transfer (RAFT) polymerization using 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (DDMAT; Fig. S3 and S4, SI) as a chain-transfer agent to control the molecular weight and dispersity. Size exclusion chromatography (SEC) and NMR confirmed a well-defined polymer structure (Fig. S5–S7, SI).

Activated-ester polymers react quantitatively with nucleophiles (typically primary amines or, in the presence of a catalyst, alcohols[32]) to yield the corresponding functionalized polymer (polyacrylamides or polyacrylates, respectively). In this study, we used unhindered, primary amines due to their facile reactivity. To test our hypothesis that addition of sub-stoichiometric amounts (relative to the repeat unit) of nucleophile would produce isolable polymers with retained modular tetrafluorophenyl functionality, we reacted PTFPA with 0.25 molar equivalents of benzylamine in DMF (Fig. S8, SI). After reacting for 15 hours, we observed ~43% conversion by ^{19}F NMR, higher than what would be expected for only 0.25 equivalents of nucleophile. Similar to previous mechanistic studies,[32] we concluded that the solvent, DMF, may be displacing the activated ester moiety. This solvent displacement would not impact the polymer structure once fully functionalized; however, due to our desire to easily track functionalization by ^{19}F NMR, we screened a series of common organic solvents to determine which would not displace the activated ester (Fig. S9 and Table S1, SI). Gratifyingly, ethyl acetate did not appear to displace the activated ester moiety, even after extensive heating or in the presence of another nucleophile (benzylamine) (Fig. S10, SI). Therefore, we continued to use ethyl acetate for the modification of PTFPA. Addition of 0.5 equivalents of benzylamine in ethyl acetate yielded a functionalization of ~53% after 2 hours. Subsequent addition of 0.5 equivalents of *n*-hexylamine functionalized the remaining tetrafluorophenyl acrylate to form a 50 : 50 poly (benzylacrylamide-*co*-hexylacrylamide) copolymer (Fig. 1).

Scheme 1 Synthesis of PTFPA by RAFT polymerization. Final polymer M_n (SEC) = 24.3 kDa, $Đ$ = 1.58.

Fig. 1 (A) Scheme for functionalization of PTFPA with benzyl- and hexylamine to yield a 50 : 50 random copolymer. (B) Post-polymerization modification was monitored by ^{19}F NMR (375 MHz, DMSO-d_6) with an internal standard and quantified by the ratio of polymeric fluorine (pink circles) to tetrafluorophenoxide (blue triangles) in the reaction solution. Error is calculated by propagating the standard deviation between the two sets of fluorines (*ortho* and *meta* to the oxygen).

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Synthesis and post-polymerization modification of poly (tetrafluorophenyl styrene sulfonate) (PTFPSS)

Activated-ester moieties can be appended to other polymer backbones in addition to polyacrylates. To demonstrate this versatility, we synthesized tetrafluorophenyl styrene sulfonate (TFPSS) to access styrenic backbones. The tetrafluorophenyl styrene sulfonate monomer was synthesized in two steps, first converting sodium styrene sulfonate to the corresponding sulfonyl chloride with thionyl chloride followed by substitution of chloride with tetrafluorophenol (Scheme 2 and Fig. S11–S15, SI). The TFPSS monomer was then polymerized *via* RAFT polymerization resulting in a similar DP to the PTFPA batch (Scheme 2). Molecular weight of the final polymer was confirmed by size-exclusion chromatography (SEC) and matching NMR end-group analysis (Fig. S16–S18, SI). This polymer batch was then used for all subsequent post-polymerization modifications using PTFPSS.

Unlike PTFPA, PTFPSS was significantly less susceptible to unwanted displacement by solvent and these post-polymerization reactions could be conducted in DMF (Fig. 2A). To form a 50 : 50 poly((benzylsulfonamido)styrene-*co*-(hexylsulfonamido)styrene) copolymer analogous to the polyacrylate shown in Fig. 1A, 0.52 equivalents of benzylamine were added to the PTFPSS. This addition resulted in an apparent 60% conversion of polymeric tetrafluorophenyl groups to tetrafluorophenoxide (Fig. 2B). We attributed this slight discrepancy to hydrolysis by residual water present in DMF. A subsequent addition of 0.54 equivalents of hexylamine displaced the remaining tetrafluorophenyl units, yielding the desired 50 : 50 copolymer.

Polymer library generation by a divergent synthetic approach

To further evaluate the scope of the post-polymerization modification of PTFPA and PTFPSS, we added 0.1 equivalents of benzylamine to the parent polymers in ten sequential portions. We used a sequential addition of amines in this reaction and in subsequent experiments to show that a controlled amount of the polymeric tetrafluorophenyl functionalization was retained after each post-polymerization modification. These reactions were quantified after each addition (0.1 mol equiv. benzylamine, 2 h reaction time) using ^{19}F NMR spectroscopy. Interestingly, the PTFPA modification displayed limited control with all the tetrafluorophenyl groups being cleaved by the sixth addition (Fig. S19, SI). We attributed this excess displacement to a combination of the reaction solvent, ethyl acetate, displacing the activated ester after long exposure

Scheme 2 Synthesis of TFPSS monomer and subsequent RAFT Polymerization. Final polymer M_n (SEC) = 33 kDa, $Đ$ = 1.40.

Fig. 2 (A) Scheme for functionalization of PTFPSS with benzyl- and hexylamine to yield a 50 : 50 random copolymer. (B) Post-polymerization modification was monitored by ^{19}F NMR (375 MHz, DMSO-d6) with an internal standard and quantified by the ratio of polymeric fluorine (pink circles) to tetrafluorophenoxide (blue triangles) in the reaction solution. Error is calculated by propagating the standard deviation between the two sets of fluorines (*ortho* and *meta* to the oxygen).

periods and the NMR solvent, DMSO-d_6, displacing the ester during the NMR analysis. Closer monitoring of the reaction progress by ^{19}F NMR spectroscopy revealed that functionalization was complete after only 45 minutes and at a lower temperature of 45 °C (Fig. S20 and Table S2, SI). Excess displacement was avoided by decreasing the reaction time and temperature for future reactions. Additionally, to prevent displacement during NMR spectroscopic characterization, we carried out NMR experiments in acetone-d_6 rather than DMSO-d_6. Under these conditions, the reaction behaved as expected with each addition of 0.1 equivalents of nucleophile corresponding to an approximately 10% increase in the amount of free leaving group (tetrafluorophenoxide) present in solution (Fig. 3, left, blue). In contrast to the PTFPA, the PTFPSS system immediately behaved as expected by cleaving ~10% of the tetrafluorophenyl groups with each 0.10 mol equiv. of benzylamine after 2 h of reaction (Fig. 3, right, pink).

To access more complex multifunctional copolymers, we used a divergent synthetic approach to generate a small library of four structurally different polymers in three synthetic steps (Fig. 4). First, 0.25 equivalents of benzylamine were added and allowed to react, then the reaction solution was split into two equal portions. To the first portion, 0.5 equivalents of *n*-hexylamine were added while 0.5 equivalents of furfurylamine were added to the second and both were allowed to react. The reaction solutions for this second generation were then split into two equal portions again and the remaining 0.25 equivalents of tetrafluorophenyl ester were functionalized by allylamine or either *n*-hexylamine or furfurylamine depending on what was used in the second generation. Following each reaction period, the reaction solution was characterized by ^{19}F NMR (Tables S3 and S4, SI) to ensure full substitution of each

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Entry	Functionalization (%)									
Target	10	20	30	40	50	60	70	80	90	100
TFPA	11 ± 2	21 ± 5	29 ± 2	37 ± 6	50 ± 2	57 ± 3	68 ± 5	78 ± 3	89 ± 5	98 ± 3
TFPSS	11.1 ± 0.1	19.5 ± 0.5	29.5 ± 0.6	42.9 ± 0.4	53 ± 1	64 ± 1	74.1 ± 1.5	84.3 ± 0.2	92.3 ± 0.5	97 ± 1

Fig. 3 Synthesis of benzylamine homopolymers with PTFPA (left, blue) or PTFPSS (right, pink) parent polymer through 10, sequential 0.1 mol equivalent additions of benzylamine with near quantitative functionalization tracked through ^{19}F NMR.

Fig. 4 Divergent route to a polymer library with varying benzyl-, hexyl-, furfuryl-, and allylamine functionalization.

individual functionality, as these amines exhibit different intrinsic reactivities toward the tetrafluorophenyl ester and a single-portion addition would obscure control over the extent of functionalization. While the PTFPA behaved as expected, it should be noted that for the divergent modification of the PTFPSS targeting a (1) 25% benzylamine, (2) 50% hexylamine, (3) 25% furfurylamine composition, the expected ^{1}H NMR integration ratio would be 1 : 2 : 1; however, the observed ratio was benzylamine : hexylamine : furfurylamine = 1 : 2 : 0.5. When the order of addition was changed to (1) 25% benzylamine, (2) 25% furfurylamine, (3) 50% hexylamine, the observed ratio improved to 1 : 1.7 : 1. We attribute the incomplete incorporation of amines in this series to steric hindrance arising from the combined use of three relatively bulky amines. This dependence on the order of addition indicates nearby repeat units interact during substitution, which in turn could affect the distribution of different substituents along the polymer chain. Although full analysis of the substituent distribution is beyond the scope of this study, we observed no anomalous behaviors indicative of block- or gradient-like distributions. However, consideration of these interactions in reaction design is critical to maintain uniform functionalization.

While we did not isolate the first- or second-generation materials in this work, this divergent synthetic approach could yield a total of seven distinct polymers in three synthetic steps. The number of distinct, final polymers could be increased by increasing the number of divisions per generation, thereby enabling rapid production of large polymer libraries. The final four polymers synthesized in this work varied in comonomer identity and amount (Fig. S21–S28, SI). The two final benzyl acrylamide-*co*-hexyl acrylamide-*co*-furfuryl acrylamide copolymers had the same comonomer identities but different ratios of functionalization. Although four polymers were produced using this divergent approach, we

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demonstrated control over ten sequential additions, in theory potentially generating over a thousand different materials even with only two divisions per generation. Additionally, while we used relatively simple, commercially available amines for this study to avoid complex characterization, this method could be expanded to incorporate a wide range of functionality, including orthogonal functionality that could be further derivatized by subsequent post-polymerization modification (*e.g.*, thiol–ene click chemistry at the allylacrylamides). Thus, this divergent method enables the synthesis of copolymers with controlled structural variations in few synthetic steps while holding parent polymer parameters (DP and dispersity) consistent.

Conclusions

In conclusion, we demonstrated a divergent synthetic strategy to generate a library of multi-functional copolymers using a modular polymer approach. This strategy was effective for polystyrene (PTFPSS) and polyacrylate (PTFPA) backbones, though conditions differed due to displacement by solvent in the reaction and NMR experiments, or steric effects. We showed access to a variety of polymer compositions using commonly available amines, but we believe this approach could be more generalizable to other nucleophiles, allowing for diverse functionalities to be incorporated. This strategy will enable synthesis of copolymer libraries with high degrees of uniformity in composition, DP, and dispersity, offering a route to improving existing high-throughput polymer synthesis methods.

Author contributions

RHB: conceptualization, investigation, methodology, visualization, writing-original draft. CMBG: conceptualization, investigation, methodology, visualization, writing-original draft. ZS: investigation, methodology, visualization, writing-review & editing. RBJ: investigation. TDE: investigation. MDS: conceptualization, funding acquisition, project administration, supervision, writing-review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: detailed experimental procedures and full NMR spectra. See DOI: https://doi.org/10.1039/d5py01156f.

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