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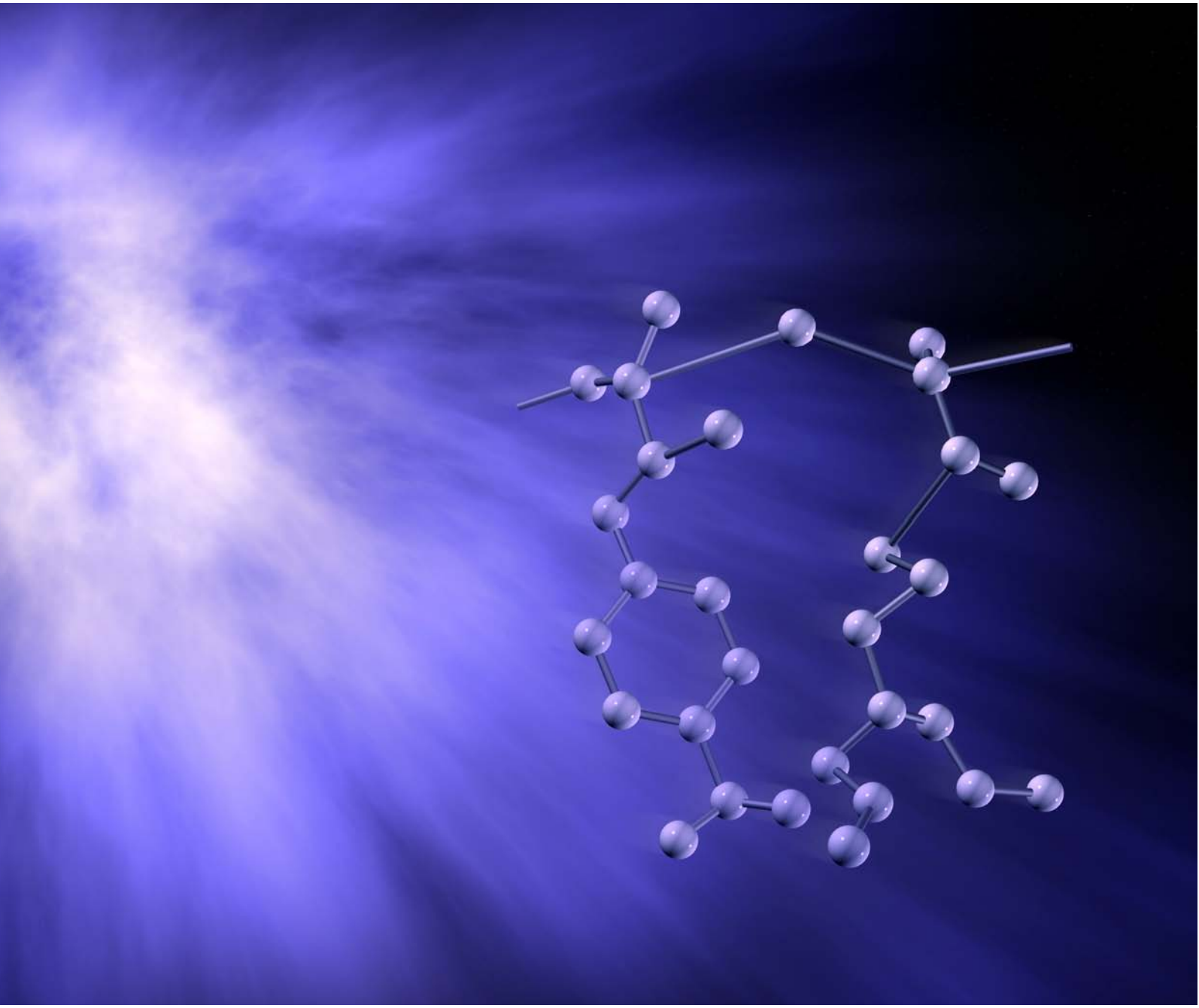

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Reactive block copolymer scaffolds†

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Block copolymers with sequences of differential reactivity were synthesized, and the step-wise and selective derivatization to form a new block copolymer was demonstrated.

Block copolymers have material properties that enable their use in a wide range of applications including nanolithography, drug delivery, and as templates for complex hybrid materials.[1–8] Function ultimately depends on polymer structure and composition;[9–11] therefore there is general interest in systematically exploring these parameters. For example, modification of side chain functionality, while maintaining a constant overall polymer length and backbone identity would provide critical information on chemical-property relationships. However, typical block copolymer synthesis involves sequential, living polymerization of two different monomers and labor intensive optimization of many reaction parameters, making this goal difficult to achieve.[10–13] We envisioned that a block copolymer containing side chains with differential reactivity could be used as a scaffold to rapidly produce new block copolymers (Scheme 1), eliminating time-consuming monomer synthesis and the need to establish polymerization conditions each time.

Homopolymers and random copolymers with reactive side chains are well known.[8,14] Controlled/"living" radical polymerizations (CRPs) are among those techniques that have emerged to make reactive polymers with low polydispersities.[15–19] One reactive side chain polymer that we have synthesized is poly(*p*-nitrophenyl methacrylate) (pNPMA) by reversible addition–fragmentation chain transfer (RAFT) polymerization.[20] This homopolymer contains an activated ester that can be directly substituted with an amine. We have also synthesized poly(diethoxypropyl methacrylate) (pDEPMA), a polymer containing acetal chains, by free radical polymerization,[21,22] atom transfer radical polymerization (ATRP),[23] and RAFT polymerization.[20] After hydrolysis to aldehydes, this polymer reacts with amines or aminooxy compounds to form imine and oxime linkages, respectively. We envisioned that coupling these two functionalities into a block copolymer would provide a reactive block copolymer scaffold. Although reactive polymers are common, block copolymers with two sequences of different reactivity are rare.[24] In this report, we describe the synthesis of pNPMA-*b*-pDEPMA by RAFT polymerization. The activated ester block was modified directly after synthesis; the acetal sequence reacted only after subjection to mildly acidic conditions. Thus the selective and sequential functionalization to form a new block copolymer was demonstrated (Scheme 2).

Scheme 1 New block copolymer from reactive scaffold.

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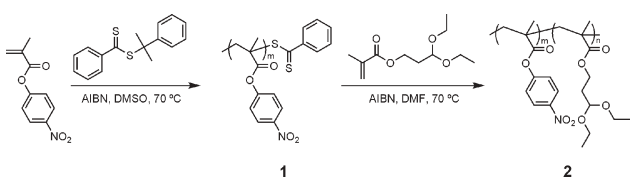
Block copolymer formation by RAFT requires the synthesis of a homopolymer that is subsequently utilized as a chain transfer agent (CTA) in the polymerization of the second monomer. We chose pNPMA (**1**) as the macro-CTA. Therefore, we first carefully investigated the homopolymerization of NPMA. Kinetic studies were conducted to determine the control of polymerization. NPMA was polymerized utilizing initial ratios of [monomer] : [CTA] : [initiator] of 50 : 5 : 1 in DMSO-d_6 (50% w/v) at 70 °C. Cumyl dithiobenzoate (CDB) was used as the CTA and 2,2′-azobisisobutyronitrile (AIBN) as the initiator. The semilogarithmic kinetic plot (Fig. 1a) and evolution of molecular weight plot (Fig. 1b) were linear with respect to time and conversion, respectively, indicating a controlled polymerization. The conversion was high at 90%, and the resulting number-average molecular weight (M_n) was 7800 and polydispersity index (PDI) was 1.20. As we have observed previously for RAFT of NPMA,[20] the M_n value obtained was higher than expected (M_n theory = 1800). The origin of the molecular weight discrepancy is not yet elucidated. The kinetic study of the homopolymerization of DEPMA also indicated a controlled polymerization.†

In order to be utilized as a macro-CTA, **1** must have a dithioester group at the ω-chain end. However, evaluation of this moiety by ^{1}H NMR was complicated by overlapping signals from the nitrophenyl proton peaks of the polymer. Thus, the end group was investigated utilizing UV-Vis spectroscopy and chain extension studies. pNPMA was synthesized with a M_n of 7400 and PDI of 1.21. This polymer was isolated by precipitation into diethyl ether. UV-Vis studies showed that the polymer had a strong absorbance at 504 nm, which corresponded well to the λ_{max} at 520 nm of CDB and indicated the presence of the dithiobenzoate group at the chain end. The subsequent chain extension study was conducted utilizing initial ratios of [NPMA] : [**1**] : [AIBN] of 900 : 5 : 1 in DMSO (50% w/v) at 70 °C. By GPC in DMF, the chain extended polymer had a significantly higher M_n of 29000 (compared to 7400) while maintaining a narrow PDI of 1.19. The



Scheme 2 Block copolymer synthesis.

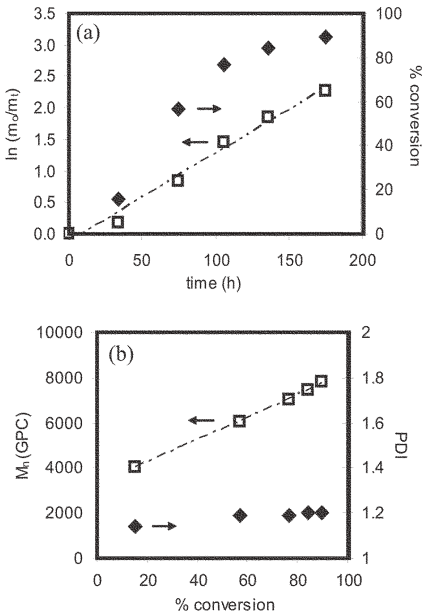


Fig. 1 RAFT of NPMA. Synthesis conditions: [NPMA] : [CDB] : [AIBN] = 50 : 5 : 1. (a) Semi-logarithmic kinetic plot and (b) M_n and PDI (determined by GPC in 0.1 M LiBr in DMF) with respect to percent conversion.

GPC trace (Fig. 2) also indicated minimal dead chains, as no detectable residual homopolymer was observed. These results taken together suggested that a dithiobenzoate group was at the ω-end of pNPMA.

Synthesis of pNPMA-*b*-pDEPMA was undertaken next. The homopolymer **1** used for block polymerization had a M_n (GPC, DMF) of 7000 and a PDI of 1.22. Block copolymer **2** was synthesized with this macro-CTA using initial ratios of [DEPMA] : [**1**] : [AIBN] of 200 : 5 : 1 in DMF at 70 °C. The polymer was prepared in 86% yield after isolation by precipitation into hexanes and extensive dialysis in methanol to remove any homopolymer impurity generated from the RAFT process. By GPC in THF,[25] the M_n was 12 000 with a PDI of 1.24. From ^{1}H NMR, this block copolymer was composed of a 40 to 60 ratio of NPMA to DEPMA units.

The reactivity of the block copolymer was demonstrated through step-wise modification of the side chains. The block copolymer **2** was first mixed with 14-fold excess allylamine and triethylamine at 50 °C in DMSO for 3 h to give **3** (Scheme 3). This

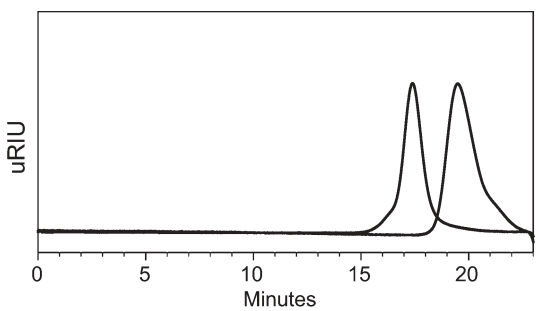
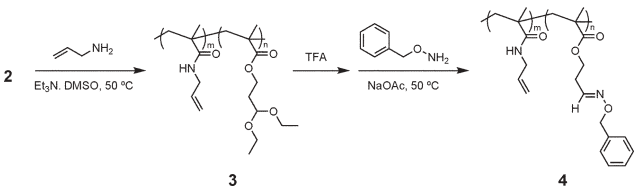


Fig. 2 Chain extension of pNPMA. The chain extended pNPMA (left trace) from the pNPMA macro-CTA (right trace). GPC in 0.1 M LiBr in DMF.



Scheme 3 pNPMA-*b*-pDEPMA functionalization.

functionalized polymer was purified by dialysis in methanol and isolated in 95% yield. Allylamine was chosen to provide a distinct signal by NMR. Comparison of the ^{1}H NMR spectra of the substituted polymer (Fig. 3b) to the unsubstituted polymer (Fig. 3a) clearly showed reaction of the activated block. Peaks for aromatic hydrogens **c** and **d** were absent and the hydrogen peaks from the alkene group **d** and **e** were visible. Furthermore, the acetal side chain proton peaks were visible, indicating that the second block remained unsubstituted. From the NMR spectrum it was calculated that approximately 75% of the nitrophenyl groups were substituted with the allylamine. Side reactions are known to occur with polymeric activated esters,[26,27] and it is likely that glutarimide

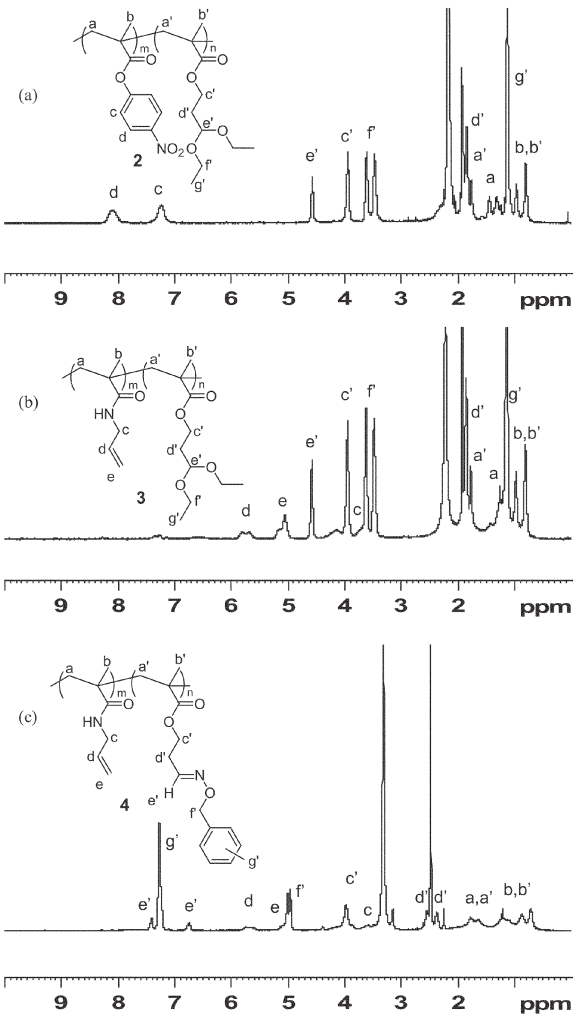


Fig. 3 ^{1}H NMR spectra of (a) pNPMA-*b*-pDEPMA in CD_3CN (**2**), (b) allylamine-functionalized block in CD_3CN (**3**), and (c) bisfunctionalized block in DMSO-d_6 (**4**).

formation lowered the over-all percent of substitution.[28] The IR spectra confirmed that conjugation had occurred. The carbonyl stretch of the nitrophenyl ester at 1753 cm^{-1} was no longer visible after substitution, while the strong amide C=O stretch at 1667 cm^{-1} was observed.

Polymer **3** was redissolved in DMSO and TFA (50% v/v) to deprotect the acetal side chains, forming aldehydes *in situ*. After stirring at room temperature for 20 min, an excess of *O*-benzylhydroxylamine hydrochloride was added. This substrate was chosen because conjugation would be easy to identify by NMR. The reaction was stirred for 3 h at 50 °C and the product purified *via* dialysis in methanol to give **4** in 98% yield. The ^{1}H NMR spectrum (Fig. 3c) indicated that oxime bond formation had occurred. The oxime proton peaks **e′** and the aromatic hydrogens **g′** of the benzyl group were now present along with the alkene peaks from the previous substitution. The acetal peaks **f′** and **g′** of **3** were no longer visible. From the ^{1}H NMR spectrum it was determined that *O*-benzylhydroxylamine was conjugated in 89% yield. Inspection of the IR spectrum confirmed that substitution had occurred. Although the expected weak C=N stretch of the oxime was obscured by the strong amide carbonyl stretch, the characteristic CH wag and ring bend frequencies at 749 and 699 cm^{-1}, respectively, of the benzyl group were visible. Taken together, these results demonstrated bisfunctionalizaiton of the polymer.

We have introduced here a block copolymer scaffold that reacts step-wise and selectively with small molecules to form a new block copolymer. Specifically, we demonstrated the synthesis of a block copolymer with activated ester and protected aldehyde side chains. Step-wise and selective functionalization with amine and aminooxy compounds was shown. Although one new block copolymer was demonstrated, we predict that many different block copolymers may be synthesized from this single precursor. Therefore, it is anticipated that the strategy reported herein will be useful for systematic variation of structural and compositional parameters necessary to access desirable material properties of block copolymers. This should provide a convenient way to generate multifunctional block copolymers for applications in drug delivery, gene therapy, combinatorial materials chemistry, and nanotechnology.

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