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Articles

Highly Efficient “Click” Functionalization of Poly(3-azidopropyl methacrylate) Prepared by ATRP

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ABSTRACT: To prepare polymers with pendant functionality capable of participating in highly efficient Cu^I-catalyzed 1,3-dipolar cycloaddition of azide and alkynes, monomers with acetylene or azido groups were polymerized via controlled radical polymerization. Atom transfer radical polymerization (ATRP) of propargyl methacrylate (PgMA) resulted in high polydispersities ($M_w/M_n > 3$), multimodal molecular weight distributions, and cross-linked networks at moderate to high conversion. The poor results obtained with this monomer were presumably due to addition of the propagating radicals to the acetylene group, transfer reactions, and/or interference with the catalyst. A novel monomer, 3-azidopropyl methacrylate (AzPMA), was polymerized via ATRP with good control of the polymer molecular weight distribution and retention of chain functionality. Poly(3-azidopropyl methacrylate) was coupled with propargyl alcohol, propargyl triphenylphosphonium bromide, propargyl 2-bromoisobutyrate, and 4-pentynoic acid via a highly efficient “click” reaction in the presence of a Cu^I catalyst. The azido-functionalized polymer demonstrated enhanced reactivity as compared to small molecules with comparable structures. The ability of the coupling reactions to be conducted at room temperature without significant excess of reagents makes this an attractive alternative to preparing (co)polymers with high degrees of functionalization.

Introduction

Controlled/living radical polymerization (CRP) techniques facilitate the preparation of a broad variety of polymeric materials with predetermined molecular weights, narrow molecular weight distributions, and high degrees of chain end functionalization.[1] When compared to their ionic counterparts, CRP methods provide comparable control while having the advantage of enhanced functional group tolerance and the ability to be conducted under less stringent conditions. The most widely investigated CRP methods are atom transfer radical polymerization (ATRP),[2−6] reversible addition−fragmentation chain transfer (RAFT) polymerization,[7] and nitroxide-mediated polymerization (NMP).[8,9] ATRP has emerged as one of the most widely used CRP methods due to the facile experimental setup and the use of readily accessible and inexpensive initiators and catalysts.

Despite the progress made in the field of CRP toward the direct polymerization of functional monomers, postpolymerization modification remains a viable means of incorporating functionality that is potentially incompatible with synthetic, characterization, or processing conditions.[10,11] A drawback of such a method of functionalization is the possibility of relatively low yields and side reactions with other groups within the polymer. Efficient and specific reactions are desirable in order for postpolymerization modification to be highly successful. Recently, one such group of reactions, generally called “click” reactions, has gained a great deal of attention due to its high specificity, quantitative yields, and near-perfect fidelity in the presence of most functional groups.[12−15]

Initially, NMP was employed to prepare block copolymers that were then modified to contain azido or acetylene groups to be further coupled in subsequent click reactions that led to fluorescently labeled copolymers or shell-cross-linked micelles.[16,17] Recently, there have been reports of using click chemistry reactions in combination with ATRP to prepare block copolymers[18] as well as functional telechelic[19] and chain-extended polystyrene.[20] Polymers prepared by ATRP are particularly well-suited to subsequent end-group modification via Cu^I-catalyzed azide−alkyne coupling because the halogen terminal groups that result from the polymerization can be easily converted to azido groups.[21,22] Additionally, pendant moieties were modified by click functionalization of acrylonitrile (co)polymers with sodium azide, which resulted in well-defined polymeric tetrazoles.[23]

Herein, we further extend the application of click chemistry toward the modification of side-chain functional groups for polymers prepared by ATRP. A novel azido-containing monomer was directly polymerized and subsequently modified with model alkynes to efficiently prepare functional (co)polymers.

Experimental Section

Materials. Propargyl methacrylate was purchased from Polysciences Inc. and purified by passing through basic

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alumina. *N,N*-dimethyaminoethyl methacrylate (DMAEMA; Aldrich) was purified in the same fashion. All other reagents and solvents were purchased from Aldrich or Acros and used as received unless otherwise noted. Deoxygenation of the solvents and liquid reagents was accomplished by bubbling with nitrogen.

Synthesis of 3-Azidopropanol (AzPOH). 3-Chloropropanol (30 mL, 33.93 g, 0.358 mol) was added to a mixture of water (40 mL), sodium azide (47 g, 2 equiv), and tetrabutylammonium hydrogen sulfate (1 g). The mixture was stirred at 80 °C for 24 h and then at room temperature for 13−14 h. The product was extracted with ether (3 × 80 mL), the resulting solution was dried over sodium sulfate, the solvent was removed on a rotary evaporator, and after vacuum distillation, 3-azidopropanol was obtained (yield: 30.8 g, 85%). ^{1}H NMR in $CDCl_3$ (δ, ppm): 3.76 (t, 2H, CH_2O), 3.46 (t, 2H, CH_2N_3), and 1.84 (tt, 2H, CCH_2C). No unreacted 3-chloropropanol was detected by NMR (in $CDCl_3$: $\delta = 3.80$ (t, 2H, CH_2O), 3.68 (t, 2H, CH_2Cl), and 2.01 ppm (tt, 2H, CCH_2C)). IR spectrum (neat liquid, NaCl plates): 3368 cm^{-1} (broad, ν_{O-H}) and 2103 cm^{-1} (ν_{N_3}). The density of the alcohol was determined as 1.09 g/mL.

Synthesis of 3-Azidopropyl Methacrylate (AzPMA). A solution of 3-azidopropanol (23.5 mL, 0.253 mol), triethylamine (45 mL, 0.323 mol, dried over sodium sulfate), hydroquinone (0.1 g), and methylene chloride (100 mL, dried over sodium sulfate) was cooled in an ice−water bath. Methacryloyl chloride (29 mL, 0.3 mol) was added dropwise over a period of 20 min, and the mixture was stirred in the cooling bath for 1 h and then at room temperature for 14 h. Methylene chloride (100 mL) was added, and the mixture was extracted with an aqueous solution of hydrochloric acid (1/10 v/v, 2 × 100 mL), water (2 × 100 mL), 10 wt % aqueous NaOH (2 × 100 mL), and again with water (2 × 100 mL). The methylene chloride solution was mixed with hydroquinone (0.1 g) and dried over sodium sulfate. The organic solvent was removed under vacuum, and the resulting liquid was distilled under reduced pressure (yield: 49%). (*Caution*: special care should be taken not to heat the azide compound above 75−80 °C because it becomes shock-sensitive at elevated temperatures.) ^{1}H NMR in $CDCl_3$ (δ, ppm): 6.11 (m, 1H, $=CH$), 5.58 (m, 1H, $=CH$), 4.24 (t, 2H, CH_2O), 3.52 (t, 2H, CH_2N_3), and 1.91−2.02 (m, 5H, overlapping $CH_3C=$ and CCH_2C). IR spectrum (neat liquid, NaCl plates): 2100 cm^{-1} (ν_{N_3}) and 1721 cm^{-1} ($\nu_{C=O}$). The density of the monomer was determined as 1.07 g/mL.

ATRP of PgMA. A mixture of acetone (3 mL) and diphenyl ether (0.2 mL) was deoxygenated in a Schlenk flask by five freeze−pump−thaw cycles. The contents were again frozen, and the flask was filled with nitrogen. CuBr (16.6 mg, 0.115 mmol) and 2,2′-bipyridyl (bpy) (36.1 mg, 0.230 mmol) were added to the frozen mixture, and the flask was evacuated and backfilled with nitrogen several times. The deoxygenated monomer, PgMA (3.0 mL, 23 mmol), was added via a nitrogen-purged syringe, and the resulting solution was heated in an oil bath to 50 °C. Deoxygenated ethyl 2-bromoisobutyrate (EtBriBu) (17 μL, 1/200 equiv vs monomer) was injected, and samples were withdrawn periodically for analysis.

Synthesis of Poly(AzPMA). The typical procedure for the ATRP of AzPMA is as follows. A mixture of AzPMA (2.0 mL, 13 mmol), acetone (2 mL), and diphenyl ether (0.15 mL) in a 10 mL Schlenk tube was degassed by five freeze−pump−thaw cycles, and CuBr (9.3 mg, 0.065 mmol) and 2,2′-bipyridine (bpy, 20.2 mg, 0.129 mmol) were added to the frozen mixture under a nitrogen flow. The tube was closed, evacuated, and backfilled with nitrogen several times, and the reaction mixture was heated to 50 °C. After dissolving the complex, deoxygenated EtBriBu (9.5 μL, 0.065 mmol) was injected. Samples were withdrawn periodically to monitor molecular weight evolution and conversion. After 8 h, the flask was removed from heat and opened to expose the catalyst to air. The resulting solution was diluted with chloroform, passed through a neutral alumina column to remove the catalyst, and precipitated into methanol to give polyAzPMA ($M_n = 12\,300$; $M_w/M_n = 1.44$). In another experiment, in which the targeted degree of polymerization at complete conversion was lower (100), the amounts of catalyst and initiator were decreased 2-fold.

Synthesis of PolyAzPMA-*b*-poly(*N,N*-dimethylaminoethyl methacrylate). A mixture of polyAzPMA ($M_n = 18\,400$, $M_w/M_n = 1.33$) (1.0 g, 0.054 mmol), DMAEMA (0.85 g, 5.0 mmol), $CuCl_2$ (3 mg, 0.02 mmol), and acetone (2.7 mL) in a 10 mL Schlenk tube was degassed by three freeze−pump−thaw cycles, and CuCl (11 mg, 11 mmol) was added under nitrogen flow. The tube was closed, evacuated, and backfilled with nitrogen several times, and the flask was placed in a 40 °C oil bath. 1,1,4,7,10,10-Hexamethyltriethylenetetraamine (HMTETA) (35 μL, 0.022 mmol) was added via syringe to begin the polymerization, and after 3 h, the flask was removed from heat and opened to expose the catalyst to air. The resulting solution was diluted with chloroform, passed through a neutral alumina column to remove the catalyst, and precipitated into methanol to give polyAzPMA-*b*-polyDMAEMA (conversion = 71%, $M_n = 30\,200$ g/mol; $M_w/M_n = 1.37$).

Click Functionalization of PolyAzPMA. Homopolymers and block copolymers of AzPMA were reacted with various functional alkynes (propargyl alcohol (PgOH); propargyl triphenylphosphonium bromide ($PgPPh_3Br$); 4-pentynoic acid (PA); propargyl 2-bromoisobutyrate[20] (PgBriBu), Scheme 1) in the presence of a Cu^I catalyst. The general reaction conditions involved polyAzPMA (1 equiv of $-N_3$, 0.05 M), alkyne (1.1 equiv), and CuBr (0.5 equiv) being dissolved in deoxygenated DMF-d_7 (PgOH, PA, PgBriBu) or DMSO-d_6 ($PgPPh_3Br$). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.1 equiv) was included in the reactions of $PgPPh_3Br$. The reactions were allowed to proceed at room temperature under a nitrogen atmosphere, and conversion was monitored by ^{1}H NMR spectroscopy.

Analyses. Monomer conversion was determined with a Shimadzu GC 14A gas chromatograph with a flame ionization detector and a J & W Scientific 30 m DB608 column (injector temperature = 250 °C; detector temperature = 270 °C; column initial temperature = 50 °C; initial time = 2 min; heat ramp = 40 °C/min; column final temperature = 170 °C; final time = 3 min). Apparent molecular weights were determined by size exclusion chromatography (SEC) (Waters microstyragel columns (guard, 10^5, 10^3, and 10^2 Å) calibrated with poly(methyl methacrylate) standards) at a flow rate of 1 mL/min in THF eluent at 35 °C for the AzPMA homopolymerization samples and in DMF, containing 50 mM LiBr at 50 °C for the polyAzPMA macroinitiator and polyAzPMA-*b*-polyDMAEMA copolymer. ^{1}H NMR spectroscopy was conducted in $CDCl_3$, DMF-d_7, or DMSO-d_6 using a Bruker Avance 300 MHz spectrometer.

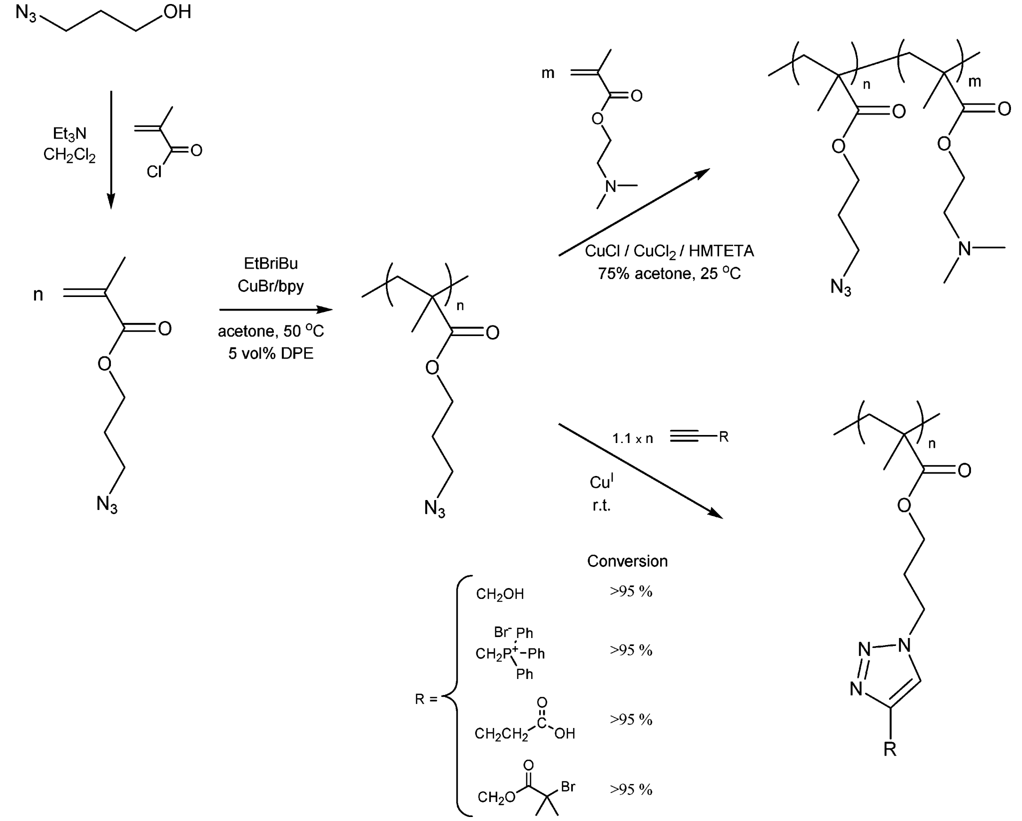
Results and Discussion

The Cu^I-catalyzed Huisgen[24] 1,3-dipolar cycloadditions are excellent candidates to functionalize polymeric materials due to their high yields and specificity. To facilitate direct functionalization via azide−alkyne coupling, an acetylene- or azido-containing monomer can be polymerized, and the resulting polymer can be reacted with a compound containing the appropriate complementary functionality. Both routes were considered for the current study.

ATRP of PgMA. Initially, ATRP of the commercially available propargyl methacrylate was attempted at 50 °C in acetone with [PgMA]:[EtBriBu]:[CuBr]:[bpy] = 200:1:1:2. While first-order kinetics and relatively good agreement between theoretical and experimental molecular weights were observed (Figure 1), the molecular weight distributions of the resulting polymers were bimodal and broad ($M_w/M_n > 3.3$ at 50% monomer conversion) (Figure 2).

The poor control observed for the ATRP of PgMA may be due, in part, to radical addition to the acetylene groups, which can lead to branching and cross-linking at high conversion. Indeed, insoluble gels were observed for polymerizations that reached >80% conversion.

Scheme 1. Synthesis of AzPMA and the Subsequent ATRP and Postpolymerization Modification with Various Functional Alkynes



Transfer reactions to the monomer or polymer similar to the case of radical polymerization of allyl monomers[25] may also take place and lead to poor control. Further complications can be caused by coordination of monomer and polymer acetylene groups with the ATRP catalyst. Vinyl monomer coordination to $\mathrm{Cu^I}$ complexes used as ATRP catalysts has already been reported;[26,27] because of the strong coordination of alkynes to copper ions, the complexation of monomers or polymers with acetylene groups to copper-based ATRP catalysts is expected to be especially pronounced.[28−30] Though protection of acetylene monomers and subsequent postpolymerization deprotection is possible, an alternate approach toward the synthesis of a click reactive polymer is direct polymerization of an azido-functional monomer.

ATRP of AzPMA. The novel monomer AzPMA was prepared from 3-azidopropanol and methacryloyl chloride and was polymerized via ATRP as outlined in Scheme 1. Good control was observed, as indicated by the semilogarithmic kinetic plot and the linear increase

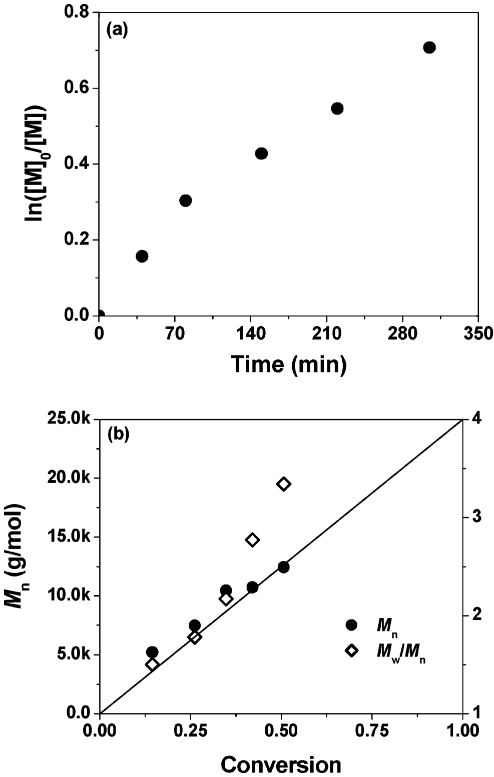


Figure 1. (a) Semilogarithmic kinetic plot and (b) M_n and M_w/M_n vs conversion for the ATRP of PgMA ([PgMA]:[EtBriBu]:[CuBr]:[bpy] = 200:1:1:2, 50 vol % acetone, $T = 50$ °C).

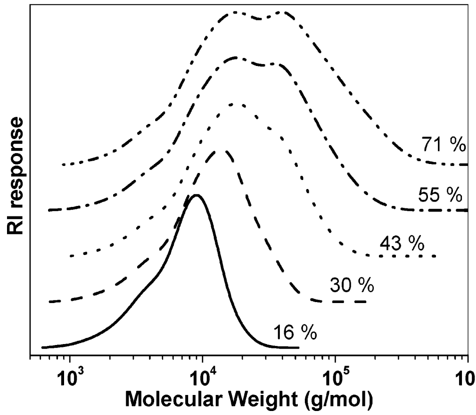


Figure 2. Molecular weight distributions as a function of monomer conversion (labeled on each trace) for the ATRP of PgMA ([PgMA]:[EtBriBu]:[CuBr]:[bpy] = 200:1:1:2, 50 vol % acetone, $T = 50$ °C).

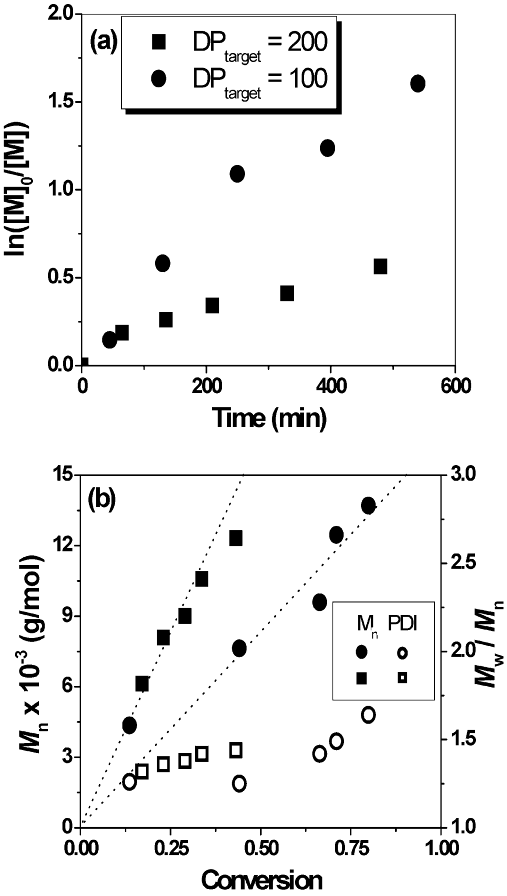


Figure 3. (a) Semilogarithmic kinetic plot and (b) M_n and M_w/M_n vs conversion for the ATRP of AzPMA with [AzPMA]:[EtBriBu]:[CuBr]:[bpy] = 100:1:1:2 (circles) or [AzPMA]:[EtBriBu]:[CuBr]:[bpy] = 200:1:1:2 (squares). 50 vol % acetone, $T = 50$ °C. Theoretical M_n dependence on conversion represented by the dotted lines.

in M_n with conversion for two polymerizations with varying [AzPMA]:[EtBriBu] ratios (Figure 3). SEC analysis indicated the molecular weight distributions were slightly broader than typical for ATRP due to a slight amount of low molecular tailing or small degree of potential side reactions that are known to occur with azide moieties via either thermal or photochemical pathways. Nonetheless, the traces were unimodal, and M_w/M_n remained less than 1.5 below 75% conversion. The controlled nature of the polymerization and retained end-group functionality was further confirmed by an isolated polyAzPMA homopolymer ($M_n = 18\,400$ g/mol, $M_w/M_n = 1.33$) being successfully employed as a macroinitiator to prepare a block copolymer with DMAEMA ($M_n = 30\,200$ g/mol, $M_w/M_n = 1.37$) (Figure 4).

Functionalization of PolyAzPMA. The polyAzPMA homopolymer was isolated, purified, and subsequently reacted with several model alkynes. Previous reports from our group[20] and others[31] have indicated that click reactions are efficient in the absence of an additionally added ligand provided the solvent facilitates sufficient solubility for the Cu^I catalyst. The model alkynes PgBriB, $PgPPh_3Br$, PgOH, and PA were successfully coupled to polyAzPMA in DMF or DMSO with a CuBr catalyst (Scheme 1). Conversions of greater than 95% in less than 2 h were observed at room temperature for the reactions with all of the functional alkynes with the only precaution being the removal of oxygen to prevent oxidation of the catalyst.

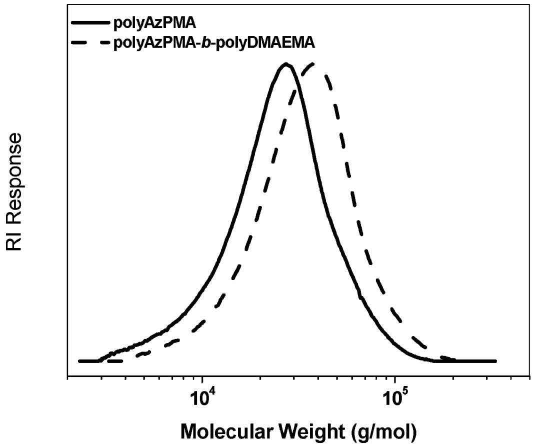


Figure 4. Molecular weight distributions for the polymerization of DMAEMA with a polyAzPMA macroinitiator ($M_n = 18\,400$ g/mol, $M_w/M_n = 1.33$) to yield polyAzPMA-*b*-polyDMAEMA ($M_n = 30\,200$ g/mol, $M_w/M_n = 1.37$). Obtained by SEC in DMF with a PMMA calibration ([DMAEMA]:[polyAzPMA]:[CuCl]:[$CuCl_2$]:[HMTETA] = 92:1:2:0.4:2.4, $T = 40$ °C, 3 h).

By employing postpolymerization modification, functionality that is potentially incompatible with the polymerization conditions can be incorporated. As an example of the advantageous nature of such a modification route, the 2-bromoisobutyrate moiety could lead to hyperbranched polymers if incorporated pendantly into the monomer structure prior to polymerization.[32-34] The conversion of greater than 95% for the reaction of PgBriB with polyAzPMA indicates that this method successfully introduced functionality that is potentially capable of initiating ATRP to yield graft or macromolecular brush copolymers.[35,36] Potentially, the free or clicked PgBriB could have been activated by the Cu^I catalyst to yield radicals capable of termination by coupling or disproportionation; however, the reaction solution remained soluble, and no vinyl peaks were observed by ^1H NMR spectroscopy, indicating that CuBr complexed or solvated by DMF was insufficiently active alkyl bromide activator.

Coupling of $PgPPh_3Br$ with polyAzPMA resulted in efficient transformation to yield cationic polyelectrolytes. Because of poor solubility of this alkyne species in DMF, the reaction was conducted in DMSO. While the reactions of most of the alkynes considered here demonstrated an appreciable rate in the absence of DBU, the base was essential for the reaction with $PgPPh_3Br$ in order to increase the relative rate of azide−alkyne coupling with respect to the propargyl−allenyl isomerization.[37] Coupling with PA was nearly quantitative as well, which resulted in the preparation of a water-soluble polyanion in basic aqueous media. The success observed for this system establishes coupling of PA, or other acid-containing alkynes, to polymeric azides as an alternative for introducing carboxylic acid groups that are incompatible with the conditions typically employed for ATRP. So far, the major way to prepare poly(carboxylic acid)s by ATRP is to directly polymerize protected polymers that can be converted to the corresponding acids after the polymerization. Protecting groups include *tert*-butyl,[38] benzyl,[39,40] tetrahydropyranyl,[39,40] 4-nitrophenyl,[41] and 1-ethoxyethyl.[42] A postpolymerization modification, namely the reaction of hydroxy group-containing polymers with succinic anhydride, has also been employed to introduce the carboxylic acid groups in polymers prepared by ATRP.[43] The click chemistry route proposed herein is a highly

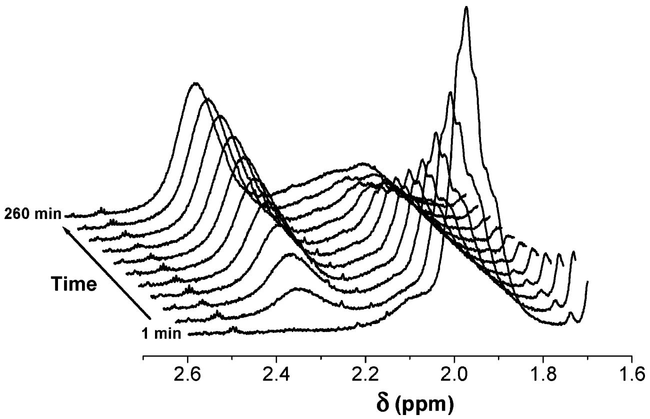


Figure 5. ^{1}H NMR spectra as a function of time for the coupling of PAzPMA and PgOH ([$-N_3$] = 0.05 M, [PgOH] = 0.05 M, [CuCl] = 0.0025 M, DMF-d_7, rt). δ = 1.98 ppm: $-COOCH_2C\mathbf{H}_2CH_2-N_3$; δ = 2.35 ppm: $-COOCH_2C\mathbf{H}_2CH_2-$triazole.

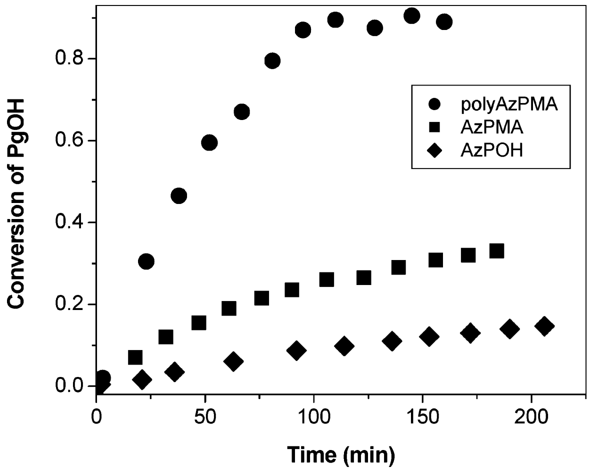


Figure 6. Conversion vs time for the reaction of PgOH with PAzPMA (M_n = 18 400, M_w/M_n = 1.33), AzPMA, and AzPOH as determined by ^{1}H NMR spectroscopy. ([$-N_3$] = 0.05 M, [PgOH] = 0.05 M, [CuCl] = 0.0025 M, DMF-d_7, rt).

efficient alternative approach to the mentioned methods of preparation of well-defined polyacids.

To gain an increased understanding regarding the kinetics of click reactions of polyAzPMA, the coupling reaction with PgOH was monitored by ^{1}H NMR spectroscopy. To facilitate more reliable kinetic characterization, the concentration of Cu^I was reduced to 0.05 equiv with respect to PgOH in order to slow the rate of reaction. By monitoring the methylene protons of unreacted ($-COOCH_2C\mathbf{H}_2CH_2-N_3$, δ = 1.98 ppm) and reacted ($-COOCH_2C\mathbf{H}_2CH_2-$triazole, δ = 2.35 ppm) polyAzPMA, conversion was determined as a function of time (Figure 5). With an equimolar amount of PgOH and azido groups, 90% functionalization was observed in less than 2 h at room temperature. Because of steric constraints and inaccessibility of functional groups along polymer chains, postpolymerization modification reactions are often slower and less efficient than the analogous reaction between two low molecular weight species. However, the rate of azide−alkyne coupling of polyAzPMA was observed to be significantly higher than that for AzPMA monomer (Figure 6). Although vinyl monomers are known to coordinate to Cu^I,[26,27] which could potentially affect the activity of the catalyst, taking into account that methacrylate coordination is relatively weak, it is unlikely that this is the sole explanation for the discrepancy in rates. Moreover, the reaction of PgOH with 3-azidopropanol resulted in similar kinetic profiles as those observed for the monomer.

The accelerated rate of reaction with the polymer was somewhat unexpected but can potentially be explained by anchimeric assistance.[44] Previous reports have shown that polytriazoles can sufficiently solubilize Cu^I.[45] In the absence of additional ligand, triazoles formed along the polyAzPMA backbone can complex Cu^I, leading to an effective higher local catalyst concentration in the immediate vicinity of neighboring unreacted azido groups. Similar autocatalytic results were observed by Rodionov et al.[31] during the coupling of alkynes to diazido compounds.

Conclusions

ATRP of PgMA resulted in high polydispersities, multimodal molecular weight distributions, and cross-linked networks at moderate to high conversion. The poor results obtained with this monomer were presumably due to interference of the acetylene group with the catalyst or propagating radicals.

AzPMA was polymerized via ATRP with good control of the polymer molecular weight and molecular weight distribution. Retention of chain functionality was confirmed by chain extension with DMAEMA to yield a diblock copolymer. PolyAzPMA was coupled with functional alkynes via Cu^I-catalyzed 1,3-dipolar cycloaddition and demonstrated enhanced reactivity as compared to small molecules with comparable structures. The ability of the coupling reactions to be conducted at room temperature without significant excess of reagents makes this an attractive alternative to preparing (co)-polymers with high degrees of functionalization.

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