Synthesis of Hydrophilic Polar Supports Based on Poly(dimethylacrylamide) via Copper-Mediated Radical Polymerization from a Cross-Linked Polystyrene Surface: Potential Resins for Oligopeptide Solid-Phase Synthesis

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ABSTRACT: A series of cross-linked polystyrene-based resins, Wang, Merrifield, and primary amino functional beads, have been transformed into initiators for transition-metal-mediated radical polymerization. Wang and amino functional resins have been condensed with 2-bromoisobutyryl bromide to give approximately quantitative conversion to initiator groups as monitored by FTIR and gel-phase ^{13}C NMR spectrometry. In each case efficient polymerization of *N*,*N*-dimethylacrylamide (DMAc) has been demonstrated. Polymerization occurs with the $RuCl_2(PPh_3)_3$ system in conjunction with $Al(O^iPr)_3$ with the reaction proceeding most efficiently with a toluene/ethanol solvent mixture which gives the best swelling of the composite particle. Surprisingly, copper(I) bromide with the pyridine imine type catalysts also led to efficient polymerization. Polymerization proceeds effectively directly from chloromethyl functional Merrifield resins given a 75% increase in weight at 130 °C after 55 h. Yields are significantly greater for derivatized Wang resins giving over 1000% weight increase under similar conditions. Gel-phase NMR shows the grafted polymer. Statistical copolymerization of DMAc with *N*-acryoyl sarcosine methyl ester (ASME) proceeds under the same conditions to give even higher yields at over 1500% weight increase. Gel-phase NMR shows two different amide carbonyls at 175.1 and 176.1 ppm along with the ester carbonyl from incorporation of ASME at 170.1 ppm. Hydrolytically more stable resins are formed from the amide derivatized initiator used under a range of conditions. Scanning electron microscopy of the resins shows spherical products with little observable breakage. Catalyst is removed from the resin using an organic soluble EDTA salt. These resins have potential in continuous solid-phase oligopeptide synthesis.

Introduction

Solid supports find widespread application in all areas of synthetic chemistry, from supported catalysts in traditional organic synthesis to combinatorial and parallel synthesis.[1] Although polymer-supported reagents had been used for many years in ion-exchange and acidic resins, a defining moment was the pioneering work by Merrifield in 1963 which demonstrated solid-phase oligopeptide synthesis from chloromethylbenzene functionalized cross-linked polystyrene resins.[2] These resins, now known as “Merrifield resins”, and resins subsequently modified with 4-hydroxybenzyl alcohol as “Wang resins” have given a basis to a whole new field of supported reagents and synthetic methods.[3] These types of resins are usually made by suspension polymerization with particle size, uniformity, and swelling of the beads controlled by a mixture of reagent concentrations, stirring speed, and mode of agitation.[4] These gel-type resins and related macroporous resins, where an organic cosolvent is added to the polymerization, led to a range of resin morphologies. However, in general, these classes of resins are hydrophobic and will swell only in nonpolar organic solvents, rendering them inefficient for reactions in more polar organic media and/or water. An excellent way to introduce hydrophilicity into polymer supports is to graft on various preformed polymers. This approach is used successfully in Tentagel resins where poly(ethylene glycol) chains emanate form hydroxyl attachment points on the resin surface.[5] However, this class of resins is usually limited to polyethers grafted onto polystyrene-based resins. Soluble polymer supports are also becoming increasingly popular where soluble linear polymers have functionality along the backbone or at the terminus of the macromolecules.[6] Both poly(ethylene glycol) and polystyrene have proved popular in this respect. These soluble polymers can be designed as new platforms for organic synthesis, and parallel and combinatorial approaches have been utilized using TEMPO-mediated living radical polymerization.[7]

Living radical polymerization techniques have been successfully exploited by Janda to provide libraries of soluble polymer supports for use in catalyst immobilization and synthesis.[7] Nitroxide-mediated living radical polymerization has been successfully employed from a range of surfaces including silicon[8,9] and silica[10] with macrosurfaces down to nanosurfaces. Hodges has reported a range of “designer resins” using Merrifield resins functionalized with a TEMPO-based initiator, “rasta resins”.[11] Transition-metal-mediated radical polymerization has also been used to grow living polymers from different surfaces modified with initiating groups.[12] This has typically been utilized to modify surface properties with thin films covalently anchored to a flat surface.[8] Patten has recently employed transition-metal-mediated radical polymerization from 75 nm silica nanoparticles to prepare well-defined polymer−nanoparticle hybrids.[10] We recently reported the use of

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modified Wang resins as initiators for the copper-mediated radical polymerization of methyl methacrylate and benzyl methacrylate.[13] These experiments were carried out with Wang resins so that the polymer could be subsequently cleaved from the resin and harvested to give soluble homopolymers and block copolymers, free from catalyst residues, with controlled M_n and narrow polydispersity. Resins based on poly(dimethylacrylamide) and poly(dimethylacrylamide/acryloyl sarcosine methyl esters) have been developed for the solid-phase synthesis of peptides and oligonucleotides as well as for protein sequencing. Indeed, conventional radical polymerization via γ-irradiation has been previously utilized to prepare similar functionalized resins.[14−16] The acryloyl sarcosine ester is copolymerized with DMAc and subsequently transformed into a primary amine by reaction with ethylenediamine to give an anchoring point for subsequent oligopeptide growth. These resins are typically prepared by (inverse) suspension polymerization giving quite small particles with poor mechanical performance. Rigid polar composite supports have been prepared via the γ-irradiation of polyethylene and polypropylene in the presence of ASME and DMAc which have also been utilized for oligopeptide synthesis.[17] These resins provide excellent solvent compatibility for peptide synthesis, which are swollen by solvents such as DMF, water, and other hydrophilic solvents used in solid-phase peptide synthesis.

Although substituted and nonsubstituted acrylamides can be polymerized with both RAFT[18] (radical addition fragmentation chain transfer) and nitroxide-mediated controlled radical polymerization[19] processes they have proven difficult by transition-metal-mediated chemistry. Matyjaszewski reported that *N*,*N*-dimethylacrylamide (DMAc), *N*-*tert*-butylacrylamide, and *N*-(2-hydroxypropyl)methacrylamide give low conversions in bulk and solution in attempts to polymerize with copper(I)-based catalysts with linear amine and unsubstituted bipyridine ligands.[20] However, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane gave high yields in short times but with little molecular mass control. Brittain also reported that attempts to use copper-based living radical chemistry lead to poor control, giving polymers with broad polydispersity.[21] This was explained as being due to complexation of the amide group at the copper. In addition, we have also found that initiators that contain an amide link, as opposed to an ester link α to the initiating halide, lead to much high molecular mass than predicted due to poor initiator efficiency.[22] This may also be due to complexation of the amide group to copper(I) and copper(II). Indeed, an elegant method to obtain narrow polydispersity polymers and block copolymers based on poly(acrylamides) has been reported by Brocchini via an indirect approach.[23] However, contrary to these poor results with copper(I)-based catalysts, Sawamoto has reported the $RuCl_2(PPh_3)_3$-mediated living radical polymerization of DMAc to give polymers with controlled molecular weights and relatively narrow molecular weight distributions.[24] For these reasons our initial attempts to grow acrylamide-based polymers from the surface of polystyrene beads employed Ru-based catalysts. However, at an early stage of our investigation, Wirth reported that acrylamide itself could be successfully polymerized from the surface of silica functionalized with a benzyl chloride-based initiator using unsubstituted bipyridine in conjunction with copper(I) chloride as catalyst.[25] The authors claimed polydispersities of <1.5 (via MALDI TOF MS) from solution polymerization in DMF solvent to polymers with controlled M_n and narrow polydispersity.

Thus, following this report we turned our own attention to copper(I) pyridine imine catalysts for the surface initiated polymerization of substituted acrylamides such as DMAc. Although we have previously reported on the use of surface initiation from modified Wang resins, this approach would be primarily for the synthesis and recovery of targeted polymers by living polymerization. The present approach is to utilize surface initiation to make hydrophilic and functional resins for use as new resins in there own right. These materials might find use in the synthesis of oligopeptides by these interested in this field or as new scavenger resins which are finding increasing applications in synthesis. This paper reports our findings from this work.

Experimental Section

Analysis, Reagents, and General Methodology. All manipulations were performed using standard Schlenk or syringe techniques under an atmosphere of nitrogen. NMR spectra were recorded on Bruker AC250, DPX 300, and AC400 spectrometers. FTIR spectra were recorded on a Bruker Vector 22 spectrometer fitted with an attenuated total reflection (ATR) cell. Residual copper analysis was determined using a Leeman Labs inductively coupled plasma atomic emission spectrophotometer (ICP-AES) calibrated with Leeman Labs ICP standards.

Toluene (Romil, 99.9%), THF (BDH, 99%), ethanol (A.R.), potassium phthalimide (Aldrich, 98%), hydrazine monohydrate (Acros, 99%), tris(triphenylphosphine)ruthenium(II) chloride (Alfa, 99.95%), aluminum isopropoxide (Aldrich, 98+%), *N*,*N*-dimethylformamide (BDH, 98%), triethylamine (BDH, 99%), ethylenediaminetetraacetic acid, EDTA (Lancaster 99%), tetrabutylammonium hydroxide, 1.0 M solution in methanol (Aldrich), acetonitrile (BDH), *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine, PMDTA (Aldrich 99%), and 2-bromoisobutyryl bromide (Aldrich, 98%) were used as received. *N*,*N*′-Dimethylacrylamide (Aldrich, 99%) and *N*-acryloylsarcosine methyl ester (received from Avecia Ltd.) were passed through an alumina column immediately before use in order to remove inhibitors and impurities. Merrifield (chloromethylpolystyrene), Wang, and hydroxymethylpolystyrene (HMPS) resins were used as received from Avecia Ltd. All beads are 150−300 μm and are 1% cross-linked. Resin loadings are as per sample determined by elemental analysis. The source of vinylbenzyl chloride is from copolymerization of chloromethylstyrene with styrene. Copper(I) bromide (Aldrich, 98%) was purified according to the method of Keller and Wycoff.[26] The preparation of *N*-(*n*-octyl)-2-pyridylmethanimine has been described in previous publications.[27,28]

Conversion of Wang Resin into a Copper-Mediated Radical Polymerization Initiator. Wang resin (5.00 g, 4 mmol g^{-1}) was placed into a round-bottom flask, and THF was added (100 mL). Triethylamine (3 mL, 0.02 mol) was subsequently added followed by 2-bromoisobutyryl bromide (2.5 mL, 0.02 mol). The reaction was left stirring overnight using an overhead stirrer with slow stirring to minimize resin fracture. The solid was then filtered and washed with DCM (dichloromethane), acetone, and copious water. The solid was then immersed in water and stirred for 2 h. The product was filtered and dried overnight.

Yield = 6.5 g. IR (solid, ATR cell) ν_{CO}: 1731 cm^{-1}; elemental analysis: C = 66.93%, H = 5.84%.

Conversion of Merrifield (Chloromethylstyrene) Resin into an Amide Containing LRP Initiator. Chloromethylated beads (3.00 g, 12 mmol) were placed into a round-bottom flask, and DMF (100 mL) was added. Potassium phthalimide (11.19 g, 0.06 mol) was then added, and the reaction was heated for 7 h at 110 °C by a thermostated oil bath with overhead stirring. After cooling, toluene (100 mL) was added; the mixture was filtered and subsequently washed with water (100 mL), methanol (100 mL), and diethyl ether (100 mL). The solid was dried under vacuum at room temperature overnight and then at 60 °C for 24 h.

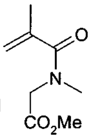
Phthalimidomethylated cross-linked polystyrene beads were immersed in ethanol (150 mL) and hydrazine monohydrate (3.5 mL, 0.07 mol) added. The reaction was then heated, with stirring to 80 °C for 3 h. After cooling, water (100 mL) was added, the reaction mixture filtered, and the solid washed with methanol (50 mL) and diethyl ether (50 mL). The resulting solid was dried in a vacuum oven overnight at room temperature and then for a day at 50 °C. Aminomethylated polystyrene (2.00 g) was placed into a round-bottom flask with anhydrous THF solvent. Triethylamine (1.1 mL) and 2-bromoisobutyryl bromide (1 mL) were added. The mixture was stirred overnight at room temperature. The resulting cream solid was filtered and washed with DCM, acetone, and copious water before being dried in a vacuum oven overnight. Yield = 2.65 g. IR (solid, ATR cell) ν_{CO}: 1715 cm^{-1}; elemental analysis: C = 86.62%, H = 7.42%, N = 1.63%

Polymerization of *N,N*-Dimethylacrylamide onto Wang Resin Using $RuCl_2(PPh_3)_3$ as a Catalyst. Wang resin (0.2 g, 4 mmol g^{-1} loading) that had been reacted with the acid bromide to give an initiator was placed into a round-bottom flask and an overhead stirrer fitted. This was then deoxygenated with three vacuum/nitrogen fill cycles. A Schlenk tube was charged with DMAc (8.3 mL, 0.08 mol), $RuCl_2(PPh_3)_3$ (0.38 g, 4×10^{-4} mol in 16.5 mL of toluene), and $Al(O^iPr)_3$ (0.32 g, 1.5×10^{-3} mol in 13 mL of toluene), respectively. The solution was degassed using three freeze/pump/thaw cycles and injected via degassed syringes into the round-bottom flask in the order $RuCl_2(PPh_3)_3$, monomer, $Al(O^iPr)_3$. The reaction was heated to 80 °C and left overnight. After this time the reaction was filtered and washed with (1) THF/toluene, (2) DCM, (3) THF/methanol, (4) THF/water, and (5) methanol. The product was recovered as a brown solid (0.72 g). Elemental analysis: C = 48.38%, H = 6.83%, N = 7.24%. IR (solid, ATR cell) ν_{CO}: 1611 cm^{-1}.

Polymerization of *N,N*-Dimethylacrylamide onto Wang Resin Using $RuCl_2(PPh_3)_3$ with Ethanol as a Cosolvent. The initiator derivatized Wang resin (0.4 g, 2 mmol g^{-1} loading) was placed into a round-bottom flask. A Schlenk tube was charged with ethanol (10 mL) and degassed using the freeze/pump/thaw method. The round-bottom flask was then deoxygenated with three vacuum/nitrogen fill cycles. The ethanol was added to the round-bottom flask. Three Schlenk tubes were filled with DMAc (8 mL, 0.08 mol), $RuCl_2(PPh_3)_3$ (0.38 g, 4×10^{-4} mol in 16.5 mL of toluene), and $Al(O^iPr)_3$ (0.32 g, 1.5×10^{-3} mol in 13 mL of toluene). These were degassed using the freeze/pump/thaw method and added to the round-bottom flask in the order $RuCl_2(PPh_3)_3$, monomer, $Al(O^iPr)_3$. The flask was heated at 65 °C and the reaction left for 18 h. After this time the beads were filtered and washed in the same manner as above. The beads were allowed to dry in the fume hood overnight before being placed in a vacuum oven to dry. The product was isolated as a white solid (1.32 g). Elemental analysis: C = 64.14%, H = 8.32%, N = 9.67%. IR (solid, ATR cell) ν_{CO}: 1627 cm^{-1}.

Typical Homopolymerization of *N,N′*-Dimethylacrylamide (DMAc) from the Surface of Aminomethyl-PS-DVB Resin. For the homopolymerization of DMAc, a monomer-to-initiator ratio of 30:1 was chosen. *N,N*-Dimethylacrylamide was filtered through basic alumina and degassed by bubbling N_2 for 30 min before use. Dimethylformamide (DMF) was degassed by bubbling N_2 for 30 min. Into a dry Schlenk tube was placed copper(I) bromide (0.114 g, 8×10^{-4} mol), aminomethyl-PS-DVB resin (0.8 g, 8×10^{-4} mol), and a stirrer bar. The Schlenk tube was then deoxygenated with three vacuum/nitrogen fill cycles. DMF (10 mL) and monomer (2.5 mL, 24×10^{-3} mol) were added and the Schlenk heated to 80 °C. When the vessel had attained this temperature, *N*-(*n*-octyl)-2-pyridylmethanimine (0.36 mL, 1.6×10^{-3} mol) was added, and the reaction mixture turned a dark brown color. The reaction was allowed to proceed for 5 h with vertical agitation (using an Argonaut FirstMate parallel synthesizer apparatus) before the Schlenk was removed from heat, exposed to air, and briefly immersed into liquid N_2 to quench the reaction. A number of experiments were carried out with no agitation during the reaction. After cooling the resin was filtered and washed with DMF, toluene, THF, DCM, THF, toluene, DMF, and methanol. The resin was then transferred to a sample bottle and dried in a vacuum oven. Yield = 1.41 g. $^{13}C\ \{^1H\}$ NMR ($CDCl_3$, 298K 100.6 MHz) δ: $-C(O)N(CH_3)_2$ 175.2; $-N(CH_3)_2$ 37.6 and 35.2 ppm. IR (solid, ATR cell) ν_{CO}: 1623 cm^{-1}. Elemental analysis: C = 62.97%, H = 8.75%, N = 11.51%.

Typical (Co)polymerization of *N*-Acryloyl Sarcosine Methyl Ester (ASME) (1) and DMAc. For the (co)polymerization a monomer-to-initiator ratio of 30:1 was chosen with 10% of ASME in the monomer feed. *N,N′*-Dimethylacrylamide was passed through a basic alumina column and placed in a dry Schlenk tube (2.22 mL, 0.0216 mol). This was repeated for ASME (**1**) (0.36 mL, 2.4×10^{-3} mol). Dimethylformamide was added (5 mL), and the contents of the Schlenk were degassed using the freeze/pump/thaw technique. Into a second Schlenk was placed copper(I) bromide (0.114 g, 8×10^{-4} mol), aminomethyl-PS-DVB resin (0.8 g, 8×10^{-4} mol), and a stirrer bar. The Schlenk was then deoxygenated with three vacuum/nitrogen fill cycles. The contents of the first Schlenk were then added to the second using a degassed syringe, and the Schlenk was heated to 80 °C. Once the Schlenk had achieved this temperature *N*-(*n*-octyl)-2-pyridylmethanimine (0.36 mL, 1.6 × 10^{-3}) was added, and the reaction mixture turned a dark brown color. The reaction was allowed to proceed for 5 h with vertical agitation before the Schlenk was removed from heat, exposed to air, and briefly immersed into liquid N_2 to quench the reaction. After cooling, the resin was filtered and washed with DMF, toluene, THF, DCM, THF, toluene, DMF, and methanol. The resin was then transferred to a sample bottle and dried in a vacuum oven. Yield = 2.11 g. Gel-phase ^{13}C NMR: $-C(O)N(CH_3)_2$ at 175.1 ppm; $-C(O)NCH_3$ at 176.1 ppm; $-(C)OOCH_3$ 170.1 ppm; $-C(O)OCH_3$ 52.5 ppm; $-NCH_2C(O)-$ 50.1; $-C(O)N(CH_3)_2$ 37.6 and 36.2 ppm; $-C(O)NCH_3$ 36.9 ppm. IR (solid, ATR cell) ν_{CO}: 1633 and 1742 cm^{-1}. Elemental analysis: C = 62.91%, H = 8.42%, N = 10.6%.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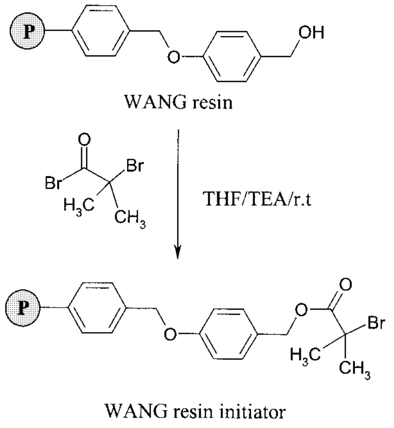
Preparation of $EDTA^{4-}(Bu_4N)^+_4$ Salt. EDTA (1.927 g, 6.25 mmol) was placed into a 250 mL round-bottom flask with a stirrer bar. A 1 M solution of n-$Bu_4N^+\ OH^-$ in methanol (25 mL, 25 mmol) was added, and the mixture was refluxed for ca. 2 h. After this time the solvent was removed in vacuo and subsequently diluted in a large amount of dichloromethane and used immediately in the removal of copper(II) from contaminated beads. ^1H NMR ($CDCl_3$, 298 K, 250.13 MHz) δ: O_2C-CH_2-N 3.3, $CH_3-C_3H_6-N$ 0.9, $CH_3-CH_2-C_2H_4N$ 1.4, $C_2H_5-CH_2-CH_2N$ 1.6 and C_3H_7-CH_2-N 3.2 ppm.

Removal of Copper(II) Bromide from Polymerized Resin. A sample of amphiphilic resin was placed into a column and swollen with DCM and the EDTA solution repeatedly passed through it, turning the salt solution from colorless to a bright blue color. Typical copper content by ICP analysis before washing was 0.2% w/w; after washing with EDTA salt solution was 9.4×10^{-3}% w/w.

Solution-Phase Polymerizations of DMAc. A ratio [M]:[I]:[copper]:[ligand] of 100:1:1:2 was used for these polymerizations. A dry Schlenk tube was charged with DMAc (5.0 mL, 0.048 mol), *N*-(*n*-propyl)-2-pyridylmethanimine (0.15 mL, 9.6×10^{-4} mol), copper(I) bromide (0.0715 g, 4.9×10^{-4} mol), solvent (10 mL), ethyl 2-bromoisobutyrate (0.07 mL, 4.8×10^{-4} mol), and a stirrer bar. The contents were degassed using three freeze/pump/thaw cycles and then heated to 80 °C. When the Schlenk reached reaction temperature, ethyl 2-bromisobu-

Scheme 1



tyrate (0.07 mL, 4.8×10^{-4} mol) was added, and the reactions were allowed to proceed for 5 h. ^{1}H NMR of the reaction mixture showed that no polymerization occurred in toluene, DMF, or acetonitrile. The reaction in DMF was repeated using *N*,*N*,*N′*,*N′*,*N″*-pentamethyldiethylenetriamine (PMDTA) as a ligand (0.2 mL), and ^{1}H NMR of the reaction mixture showed that no polymerization occurred.

Comparison of Merrifield (CMS-DVB Resin) and Wang Resin Initiated Polymerizations of DMAc. The [M]:[I] ratio for these experiments was 500:1, as suggested by Huang and Wirth.[25] Resin (CMS: 0.2 g, 2×10^{-4} mol, Wang resin: 0.1 g, 2×10^{-4} mol) and copper(I) bromide (0.028 g, 2×10^{-4} mol) were placed into a round-bottomed flask, and the flask was deoxygenated with three vacuum/nitrogen fill cycles. A Schlenk tube was then charged with monomer (10.3 mL, 0.1 mol), solvent (DMF, 20 mL) and *N*-(*n*-octyl)-2-pyridylmethanimine (0.09 mL, 4×10^{-4} mol). These were degassed with three vacuum/nitrogen fill cycles. The contents of the Schlenk were added to the round-bottom flask, and the flask was heated to 130 °C. The reaction was allowed to continue for 55 h, prior to the contents of the flask being filtered and washed with THF/toluene, DCM, THF/MeOH, THF/water, and methanol. The beads were then dried in a vacuum oven. CMS resin: yield = 0.355 g (77% increase). gel-phase ^{13}C NMR: $-N(CH_3)_2$ 37.5 and 36.2, $-C(O)$ 175 ppm. IR (solid, ATR cell) ν_{CO} 1622 cm^{-1}. Wang resin: yield = 1.014 g (914% increase). Gel-phase ^{13}C NMR: $-N(CH_3)_2$ 37.5 and 36.2, $-C(O)$ 175 ppm. IR (solid, ATR cell) ν_{CO} 1644 cm^{-1}.

Conversion of Methyl Ester Group to Amine Functionality within the Copolymer on Resins. Resin AM4 was placed into a glass chromatography column, and an EDTA·TBA salt solution was passed through several times prior to drying in vacuo overnight. 1 g of the resin was placed into a 1 L round-bottomed flask with 200 mL (excess) of ethylenediamine; the mixture was agitated using a mechanical shaker overnight. The resin was then collected by filtration and washed with DCM, toluene, and methanol before being the removal of solvent in vacuo overnight. Yield = 0.7617 g, ν_{CO}: = 1632 cm^{-1}.

Swelling Studies on Synthesized Resin. 1.00 g of each resin was placed in a 10 mL measuring cylinder. The solvents were then added up to the 10 mL graduation and left overnight. The volume of the swollen resin was recorded.

Results and Discussion

Initiator functionalized Wang resin was prepared by reaction of Wang resin suspended in THF with 2-bromoisobutyryl bromide (Scheme 1). This resulted in near quantitative conversion of hydroxyl groups to initiator as measured by FTIR and gel-phase ^{13}C NMR. This Wang resin derived supported initiator has the advantage of being relatively easy to prepare but suffers from the hydrolytically cleavable attachment group. A more hydrolytically stable initiator was formed by the transformation of Merrifield resin to primary amine via the phthalimide and subsequent reaction to the amide (Scheme 2). The reaction was monitored by FTIR with the final product showing an intense band at 1715 cm^{-1} from the amide carbonyl group. (See Supporting Information for further IR spectra.) These initiators are referred to as AM0 and W0, respectively, throughout this work.

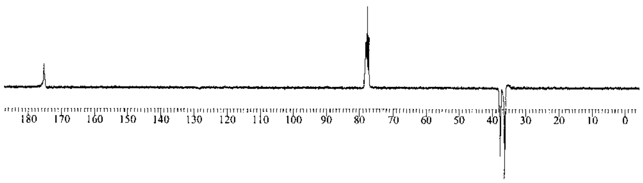


Figure 1. 500 MHz gel-phase PENDANT (CH_0 and CH_2 up, CH_1 and CH_3 down) ^{13}C NMR of DMAc polymerized onto Wang resin, W2, $-C(O)N(CH_3)_2$ 175.2; $CDCl_3$ 77.7; $-N(CH_3)_2$ at 37.6 and 35.2 ppm.

Scheme 2

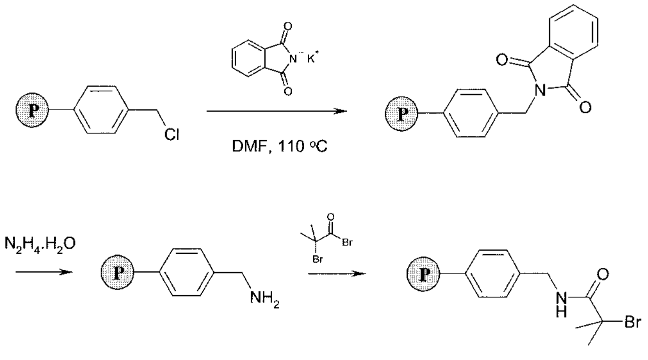


Table 1. Polymerization of DMAc Mediated by $RuCl_2(PPh_3)_3/Al(^iPrO)_3$ from Derivatized Wang Resin in Different Solvents at 80 °C for Reaction in Toluene and 65 °C for Those in Ethanol and Ethanol/Toluene

solvent	weight$_0$ (g)	weight$_{fin}$ (g)	weight increase (g)
toluene	0.2	0.72	0.52
EtOH	0.2	0.62	0.42
EtOH/tol 1:3	0.4	1.32	0.92
EtOH/tol 1:1	0.4	1.22	0.82

Polymerization of DMAc Using $RuCl_2(PPh_3)_3/Al(O^iPr)_3$ as Catalyst. Polymerization of DMAc with Wang resin derived initiator with $RuCl_2(PPh_3)_3/Al(O^iPr)_3$ as catalyst in toluene solvent showed the resins to increase significantly in mass (>100%), with FTIR showing the presence of a carbonyl group at 1627 cm^{-1} in the final product (see Supporting Information). However, toluene was a poor solvent to swell the grafted poly(dimethylacrylamide), and we switched to ethanol as a cosolvent with toluene which gave better swelling of the beads before and during the polymerization reaction. Gel-phase NMR[29] of the resin after polymerization shows a carbonyl peak at 175.2 ppm for the grafted polyamide with peaks at 37.5, and 36.2 ppm from the *N*-methyl groups (Figure 1). The two peaks due to the existence of isomers due to the polymer backbone. The effect of changing the nature of the solvent was investigated with a mixed solvent of ethanol/toluene of 1:3, resulting in the highest conversion of an approximately 200% weight increase (Table 1).

Polymerization of DMAc Using CuBr/Pyridine-imine as Catalyst. Following reports from Wirth that

Table 2. Polymerization of Acrylamides without Agitation[a]

	linker	loading (mmol g^{-1})	monomer	[M]:[I]	temp (°C)	time (h)	start weight (g)	final weight (g)
CMS1	Merrifield	1	DMAc	500	130	55	0.2	0.35
W2	Wang	2	DMAc	500	130	65	0.1	1.01
W3	Wang	2	DMAc:ASME 90:10	500	130	62	0.1	1.74
W4	Wang	2	DMAc:ASME 80:20	500	130	62	0.1	1.81
W5	Wang	1	DMAc:ASME 50:50	30	80	5	4	17.5
AM5	amide	1	DMAc	125	110	4	2	7.7
AM6	amide	1	DMAc	125	90	4	2	9.2
AM6B	amide	1	DMAc	125	90	4	2	7.7
AM7	amide	1	DMAc	125	70	4	2	2.6
AM8	amide	1	DMAc	30	80	5	4	17.5

[a] Polymerization from resin, total monomer volume = 2.5 mL. Copper(I) bromide was used as the catalyst with *n*-octyl-2-pyridinylmethanimine used as the ligand. All reactions were carried out in DMF.

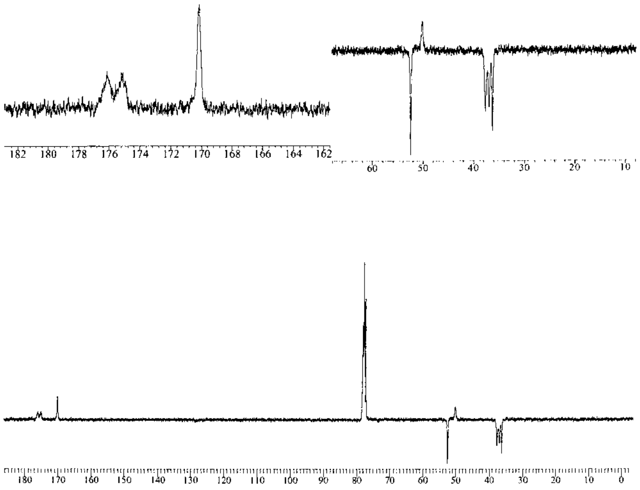


Figure 2. 500 MHz gel-phase PENDANT ^{13}C NMR spectrum of ASME-DMAc (1:1 monomer ratio) statistical copolymer polymerized on Wang resin, $-C(O)N(CH_3)_2$, 175.1 ppm; $-C(O)$-NCH_3, 176.1; $-C(O)OCH_3$, 170.1; $CDCl_3$, 77.6; $-C(O)OCH_3$, 52.5; $-NCH_2C(O)$, 50.1 ppm; $-C(O)N(CH_3)_2$, 37.6 and 36.2 ppm; $-C(O)NCH_3-$, 36.9 ppm.

DMAc could be polymerized from a surface-supported benzyl chloride type initiator,[25] similar experiments were attempted with polystyryl-derived initiators. No agitation was employed in these experiments in an attempt to avoid any mechanical degradation of the resins. Polymerization proceeds effectively directly from chloromethyl functional Merrifield resins given a 75% increase in weight under similar conditions to those reported at 130 °C for 55 h. Yields are significantly greater for derivatized Wang resins giving over 1000% weight increase under similar conditions, W2 (Table 2). Gel-phase NMR, where the resin is swollen in $CDCl_3$ and normal ^{13}C solution NMR spectrum recorded, shows the carbonyl from the amide at 175.2 ppm and two resonances at between 35 and 40 ppm for the *N*-methyl groups. Gel-phase NMR shows the grafted polymer but does not detect the cross-linked core due to restricted mobility.[30] Statistical copolymerization of DMAc with **1** proceeds under the same conditions to give even higher yields at over 1500% weight increase (Table 2). Gel-phase NMR shows the incorporation of the two monomers into the grafted polymer is approximately the same as the monomer feed, indicating similar reactivity ratios as would be expected for this monomer pair (Figure 2). Two different amide carbonyls appear at 175.1 and 176.1 ppm, along with the ester carbonyl from incorporation of **1** at 170.1 ppm. Three bands are observed between 36 and 38 ppm corresponding to two *N*-methyl groups from the dimethylacrylamide and one from the *N*-methyl group of the sarcosine and the methylene group at 52.5 ppm. Incorporation of **1** is also seen in the FTIR spectrum (Figure 3), with an increase in the ester υ_{CO} band as the amount of **1** is increased while the amido carbonyl stays approximately the same intensity.

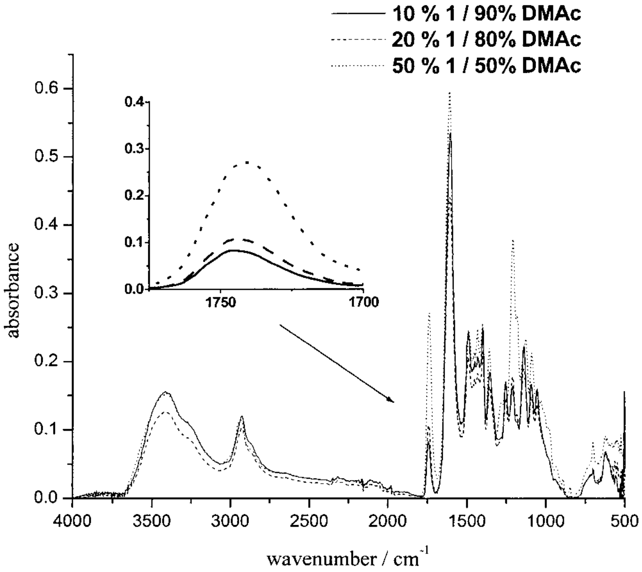


Figure 3. FTIR spectra of random (co)polymerizations of DMAc and ASME from Wang resin.

In an attempt to make more hydrolytically stable resins under optimized reaction conditions the amide derivitized initiator was used under a range of conditions (Table 2). Reducing the monomer concentration by approximately a factor of 4 to 125:1, and lowering the temperature to 110 °C produced beads with an increase in size apparent to the naked eye after just 4 h. Reducing the temperature further to 90 °C increased the rate of polymerization, presumable due to a decrease in the rate of termination. A further reduction in temperature to 70 °C resulted in a drastic reduction in the polymerization after 4 h. Scanning electron microscopy of the resins from AM5 shows that even after the wash procedure beads, which are spherical in nature with little observable breakage, are formed (Figure 4a); however, there is a large distribution of particle size which is attributed to the lack of agitation during the polymerization. When an inappropriate washing procedure or magnetic stirring is used, the beads suffer mechanical damage (Figure 4b).

To circumvent these problems, vertical agitation from an Argonaut FirstMate apparatus was employed. This apparatus stirs vertically using compressed air to drive

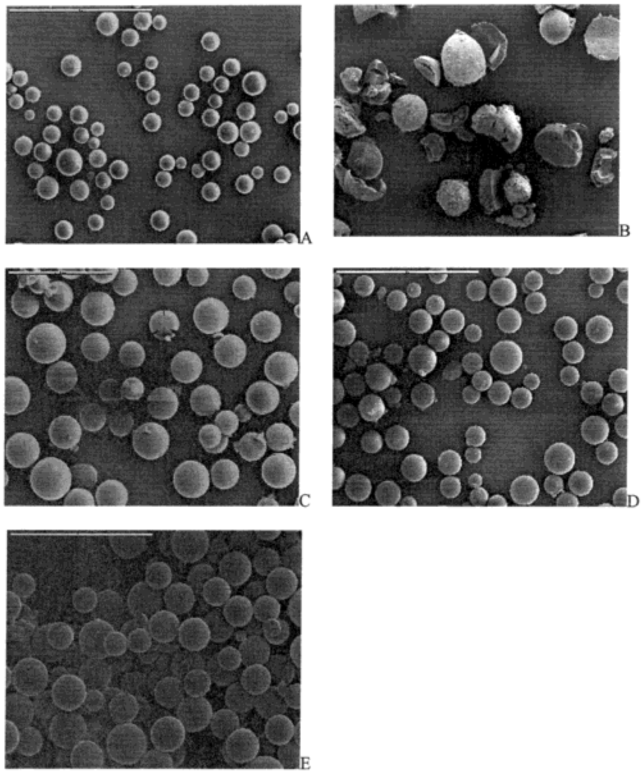


Figure 4. SEM images of the resins. (A) AM5 resin following polymerization and wash procedure. The resin size has a large distribution ascribed to the reaction method. This polymerization was undertaken in a Schlenk tube with no stirring. However, note the lack of stirring does result in the resin showing no breakage. (B) The effect of bad reaction and washing conditions for resin AM5 which causes mechanical breakage of the beads. (C) The reaction ratios used in the production used in the production of this resin (AM2) are identical to those used in resin A. However, only half the solvent was used. This has the benefit of increasing the final yield in the same time period. The polymerization was carried out with vertical agitation, and as can be seen, the resin remains within a relatively narrow size range (with respect to (A)) with a few broken beads. (D) statistical copolymer of *N*,*N*′-dimethylacrylamide and **1** polymerized from a PS-DVB resin, AM4. This resin shows some heterogeneity in size and some breakage. The polymerization was carried out with vertical agitation. (E) Resin from reaction AM4 (A) after clean up with EDTA·TBA salt solution. This process introduces very little or no damage to the resin.

Table 3. Polymerization of Acrylamides with Vertical Stirring[a]

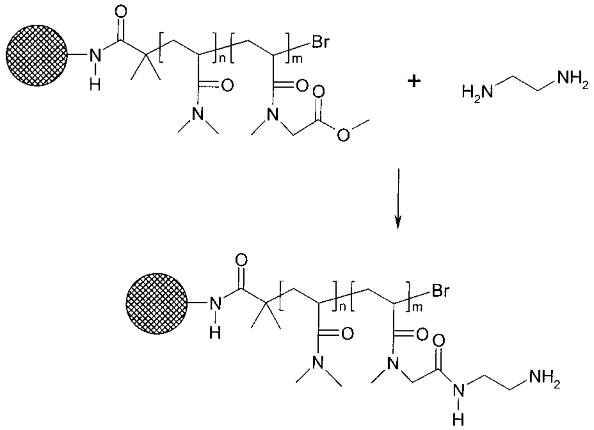
	linker	amount of DMF (mL)	monomer	temp (°C)	final wt (g)
AM1	amide	10	DMAc	80	1.41
AM1B	amide	10	DMAc	80	1.51
AM2	amide	5	DMAc	80	1.82
AM2B	amide	5	DMAc	80	1.96
AM3	amide	10	DMAc	90	1.77
AM4	amide	5	DMAc:ASME 1:1	80	2.11
W1	Wang	10	DMAc	80	0.75

[a] Polymerization from 0.8 g of resin with a loading = 1 mmol g^{-1}, [M]/[initiator] = 30:1, polymerization time of 5 h, total monomer volume = 2.5 mL. All reactions were carried out in DMF and catalyzed by the copper(I) bromide/*n*-octyl-2-pyridinylmethanimine system.

Table 4. Swelling of Resins in Different Solvents

mL g^{-1}	methanol	water	ether	DCM	DMF	THF
Wang resin	0.1	0	2	6	5	6.2
W2	10	10	0	10	8.4	0.8
W5	1.1	0.5	0.1	1.6	1.3	0.5

Scheme 3



a magnetic bar within the reactor, resulting in little damage during the polymerization. Table 3 reports results from this experimental arrangement showing that efficient polymerization occurs at between 80 and 90 °C from both Wang and amide functionalized resins over 5 h. Scanning electron microscopy shows a better size distribution with some evidence of mechanical damage. When the amount of solvent is reduced, 33 vol % monomer, an increase in yield is attained with no increase in the amount of damage (Figure 4c); the same is true when the temperature is increased to 90 °C. Figure 4d shows the 50/50 DMAc/**1** copolymer with vertical agitation that does show increased heterogenity in particle size and more mechanical breakage than for the DMAc homopolymer.

Immediately following the polymerization and solvent wash procedure, the resin has an emerald green color from copper(II) complexed to the amide groups along the chain. The color can be removed by washing in a column with TBA$^+$EDTA$^-$ solution, which forms a deep blue solution on contact with the resin. The resin is washed in a column until no more blue color is observed, leaving the resin as an off-white material. This final catalyst removal wash does not lead to mechanical rupture (Figure 4e).

The amount the resins swelled in various solvents was measured by soaking the beads in a range of solvents overnight (Table 4; also see Supporting Information). Poly(DMAc) beads were found to swell considerably in hydrophilic solvents (over 1000%) such as methanol, water, and DMF. Incorporation of ASME reduced the swelling in hydrophilic solvents. The shape of the resin remained visibly intact throughout the swelling procedures.

These resins have potential application for use in continuous solid-phase synthesis of oligopeptides as reported earlier by Sherrington.[17] In order for this the acryloylsarcosine methyl ester is first converted to the free primary amine (Scheme 3). Reaction of the acryloylsarcosine methyl ester functional resin AM4 was carried out with ethylenediamine at ambient temperature overnight. Reaction was observed by gel-phase ^{13}C NMR by the appearance of a peak at 45.4 ppm from the linker $-CH_2N-$ group (Figure 5). Further reaction of the primary amine group in oligopeptide synthesis has not been carried out and is outside the scope of expertise of our laboratory.

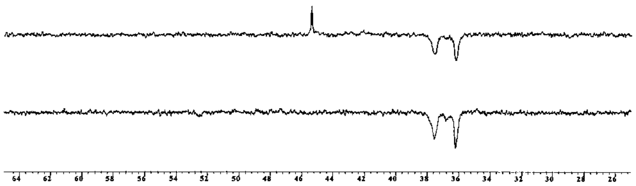


Figure 5. Partial overlay of the gel-phase PENDANT ^{13}C NMR spectra of ASME-DMAc (9:1) monomer ratio statistical copolymer from amide initiator (AM4) (lower spectrum), $-C(O)N(CH_3)_2$, 175.0 ppm; $-C(O)N(CH_3)_2$, 37.6 and 36.2 ppm; $-C(O)NCH_3-$, 36.8 ppm, and aminated amphiphilic resin (upper spectrum), $C(O)N(CH_3)_2$, 174.7 ppm; $-N(CH_2)_2N-$, 45.4 ppm; $-C(O)N(CH_3)_2$, 37.5 and 36.1 ppm; $-C(O)NCH_3-$, 36.9 ppm.

Summary and Conclusions

Derivatized Wang and amino functional poly(styrene) resins can be used for the efficient copper(I)-mediated radical polymerization of acrylamide derivatives. As the grafted polymer has not been removed from the cross-linked initiators, it is not possible to comment on the mechanism of polymerization. However, the only initiators present are those derived via the copper-mediated homolysis of a C−Br bond that might lead to either controlled or normal free radical polymerization. This is in contrast to polymerization in solution, which are unsuccessful as in accordance with previously reported work. Polymerization ensues with or without agitation to give resins with a mass increase of up to 1000%. Appropriate agitation and washing enables the resin to be recovered as essentially monodisperse particles with excellent spherical appearance suitable for further reaction. Copolymerization of a protected amine group via **1** proceeds via statistical copolymerization as verified by both gel-phase NMR and FTIR. The composition of the final grafted beads may be changed trivially. Removal of catalyst from the amide derivatized resin is complicated by the coordination of the resin to the copper. This is alleviated by washing the resin with an organic soluble EDTA salt which removes the catalyst as a copper(II) solution to give colorless product. The resin's swelling behavior in hydrophilic solvents is similar to other DMAc resins and indicates that this type of resin has potential in application in hydrophilic environments. The resins are suitable for further reaction as either reactive or scavenger resins. The difference between our observations in solution and from the surface of the resin cannot be fully explained at present and will be the focus of further study.

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Supporting Information Available: IR spectra of the Wang resin, Merrifield resin, phthalimido methylated beads, primary amine substituted beads, amide initiator, and beads after polymerization; gel-phase ^{13}C NMR spectrum of beads; and plot of swelling of resins. This material is available free of charge via the Internet at http://pubs.acs.org.

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