Atom Transfer Polymerization: Use of Uridine and Adenosine Derivatized Monomers and Initiators

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ABSTRACT: The multifunctional monomers 5′-methacryloyluridine and 5′-methacryloyladenosine have been polymerized under atom transfer polymerization conditions, giving products of narrow polydispersities as consistent with living polymerization. Initiators derived from both uridine and adenosine have also been used to terminally functionalize poly(methyl methacrylate) and poly(styrene). Both hydroxyl-protected and unprotected initiators successfully gave polymers of predictable and narrow PDI. Atom transfer polymerization of methyl methacrylate with the protected 5′-bromoisobutyroyluridine initiator **2** with NMPI ligand in conjunction with copper(I) bromide gives polymer with an M_n of 13 100 with a very narrow PDI of 1.06 (M_n of 11 000 ^{1}H NMR). The initiator efficiency is less than unity (e.g., 0.81 for the above reaction), similar to that observed with nonfunctional initiators. ^{1}H NMR is used to demonstrate the presence of the initiator in the polymer. The results demonstrate that this living polymerization system is inert to a multitude of functionality in the initiator, including secondary hydroxyl, silyl ether, tertiary amine, primary amine, secondary amide, etc. Atom transfer polymerization has been used to synthesize well-defined poly(nucleoside)-based polymers which have tremendous potential for templating and polymers used in applications that require biorecognition.

Introduction

Atom transfer polymerization is emerging as an efficacious, controlled polymerization method leading to a range of structurally diverse polymers.[1−5] This type of polymerization proceeds over a wide temperature range[6] and is unaffected by many impurities and functional groups present in monomers, reagents, solvents, etc., including phenolic radical inhibitors,[7] water,[8] and trace carboxylic acid.[9] A range of systems have been described using different metal catalysts in conjunction with an activated alkyl halide (chloride or bromide) initiator, e.g., Ru(II),[5] Cu(I),[2,10] Ni(II),[11,12] Rh(I),[13] and Fe(II).[14] We have been concentrating on Cu(I)Br in conjunction with a Schiff base ligand which has proved very effective for methacrylates leading to polymers with controlled M_n and narrow PDI, 1.1−1.2.[15,16] This system facilitates the synthesis of a range of novel polymers that contain many different types of functionality without the need for protecting group chemistry. Living radical polymerization has already been exploited for the synthesis of polymers with potential biological activity. Synthetic glycolipids with narrow PDI have been prepared by nitroxide-mediated polymerization of sugar-containing monomers with lipophilic initiators,[17] and well-defined glycopolymers have been reported from atom transfer polymerization.[18] Indeed, synthetic polymers containing sugar units are of increasing interest.[19,20] We have been interested in the application of atom transfer polymerization to polymers of potential biological activity. Recently we reported on the incorporation of simple sugars such as glucose into star polymers and the use of cholesterol as an initiator.[21,22]

This current work was designed to exploit, and further demonstrate, the functional group tolerance of atom transfer polymerization by its application to the polymerization of multifunctional nucleoside-containing monomers and initiators. Nucleotides are known to play an important role in nature due to their ability to recognize their complementary bases by hydrogen-bonding interactions.[23] Such recognition is utilized for template-directed synthesis of biopolymers such as DNA and RNA. The interaction of synthetic analogues of polynucleic acids with DNA or RNA has found medicinal uses as antisense drugs.[24−26] We have previously shown that poly(5′-acryloyluridine) acts as a template for the radical polymerization of the complementary 5′-acryloyladenosine in the presence of 5′-acryloyluridine.[27] The synthesis of poly(methyl methacrylate) and poly(styrene) terminally functionalized with these biologically important nucleosides is also described.

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Experimental Section

General Procedures. All reactions were carried out under an atmosphere of nitrogen. Reagents were purchased from the following sources: acryloyl chloride (Aldrich, 96%), acetone oxime (Lancaster, 98%), adenosine (Lancaster, 99%), uridine (Lancaster, 99%), pyridine (Fisons, 99.5%), TMS−Cl (Lancaster, 98+%), TBDMS−Cl (Lancaster, 97%), silver nitrate (Lancaster, 99+%), dimethylformamide (Aldrich, anhydrous, 99.8%), AIBN (BDH, 97%), 2-pyridinecarboxaldehyde (Avocado, 99%), pentylamine (Aldrich, 99%), activated basic alumina (Aldrich), ethyl bromoisobutyrate (Avocado, 98%), CAL 435 (Novo Nordisk, immobilized on polystyrene). *N*-(*n*-pentyl)-2-pyridylmethanimine (NPMI) was prepared as described previously.[15] TREN was synthesized from the commercially available tris(2-aminoethyl)amine by methylation.[28] Toluene was deaerated by bubbling nitrogen through it prior to use. Copper(I) bromide (Avocado, 98%) was purified according to literature procedure.[29] All solvents were purchased from BDH and were used as supplied. Column chromatography refers to flash chromatography on Merck silica gel (Art. No. 109385). TLC was carried out on precoated plates (silica gel 60 F254, Merck 5715), and the products were visualized using UV light or potassium permanganate dip.

Analysis. Molecular weight distributions were measured using size exclusion chromatography (SEC) on a system equipped with a guard column, two 30 cm mixed D columns (Polymer Laboratories), and a differential refractive index detector, using tetrahydrofuran at 1 mL min^{-1} as eluent. The

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SEC was calibrated with 12 poly(MMA) standards in the range 6.85×10^5−200 g mol^{-1}. NMR spectra were recorded on Bruker AC250 and AC400 spectrometers. FTIR spectra were recorded on a Bruker Vector 22 spectrometer fitted with an attenuated total reflection (ATR) cell. Conversions were measured gravimetrically and the samples dried under vacuum at 80 °C until no further reduction of weight was detected (∼34 h). Methanol (2.0 mL) was added twice to the samples to aid the removal of toluene. DSC was carried out on a Perkin-Elmer Pyris 1 differential scanning calorimeter, and the T_g's quoted refer to inflection midpoints.

Methacryloylacetone Oxime. A solution of methacryloyl chloride (5.0 g, 47.8 mmol) in dichloromethane (50 mL) was cooled in an ice bath, and a mixture of acetone oxime (2.33 g, 31.9 mmol) and triethylamine (3.55 g, 35.1 mmol) in dichloromethane (50 mL) was added dropwise. When the addition was complete, the reaction mixture was stirred at room temperature for 3 h and the precipitate filtered. The solution was washed with saturated sodium hydrogen carbonate (2 × 20 mL), dried ($MgSO_4$), and evaporated in vacuo to give an orange oil. Column chromatography (30% ethyl acetate in 40−60 °C petroleum ether) gave the product as a light orange oil (4.31 g, 96%). It is noted that the use of the crude methacryloylacetone oxime had very little effect on the yield of the subsequent methacrylation reactions. ^{1}H NMR ($CDCl_3$): δ 6.10 (1H, m), 5.57 (1H, m), 2.02 (3H, s), 1.98 (3H, s), 1.95 (3H, s). ^{13}C NMR ($CDCl_3$): δ 165.0, 164.7, 135.7, 126.3, 22.4, 18.8, 17.4.

Bromoisobutyroylacetone Oxime. A solution of bromoisobutyroyl bromide (5.0 g, 21.7 mmol) in ether (100 mL) was cooled in an ice bath, and a solution of acetone oxime (1.59 g, 21.7 mmol) and triethylamine (3.30 g, 32.6 mmol) in ether (50 mL) was added dropwise. When the addition was complete, the reaction mixture was stirred at room temperature for 1 h and the precipitate filtered. The solution was washed with saturated sodium hydrogen carbonate (50 mL) and then water (50 mL) and dried ($MgSO_4$). Evaporation in vacuo gave an orange oil which required no further purification (4.51 g, 93%). ^{1}H NMR ($CDCl_3$): δ 2.06 (3H, s), 2.05 (3H, s), 1.98 (3H, s). ^{13}C NMR ($CDCl_3$): δ 169.1, 166.2, 55.2, 31.3, 22.3, 17.4. IR, ν_{max} (neat): 1759, 1375, 1276, 1146, 868 cm^{-1}. HRMS (FAB) calcd for $C_7H_{12}BrNO_2$ (M^+): 222.0127. Found: 222.0130.

Synthesis of 5′-Methacryloyluridine, 3 (General Procedure). To a suspension of uridine (1.0 g, 4.10 mmol) in dioxane (40 mL) was added a catalytic amount of 2,6-di-*tert*-butyl-4-methylphenol (radical inhibitor), methacryloylacetone oxime (1.73 g, 12.3 mmol), and CAL 435 (5.50 g). The reaction mixture was then stirred at 60 °C for 52.5 h, the enzyme filtered, and silica gel (2.3 g) added to the filtrate. The solvent was evaporated in vacuo (60−70 °C) and the solid residue purified by column chromatography (4% methanol in ethyl acetate) by dry loading to give the product as a white solid (1.06 g, 83%); mp 85−88 °C. ^{1}H NMR (d_6-DMSO): δ 11.37 (1H, s, NH), 7.58 (1H, d, J = 8.1 Hz), 6.04 (1H, s), 5.73 (1H, m), 5.62 (1H, d, J = 8.1 Hz), 5.50 (1H, bs, OH), 5.31 (1H, bs, OH), 4.20−4.45 (2H, m), 4.15−3.90 (3H, m), 1.89 (3H, s). ^{13}C NMR (d_6-DMSO): δ 166.7, 163.4, 150.9, 141.0, 135.9, 126.6, 102.3, 89.2, 81.3, 73.1, 70.0, 64.4, 18.4. IR, ν_{max} (solid): 3380, 3205, 2970, 1667, 1456, 1379, 1266, 1099 cm^{-1}. HRMS (CI) calcd for $C_{13}H_{17}N_2O_7$ (MH^+): 313.1036. Found: 313.1033.

Synthesis of 5′-Bromoisobutyroyluridine, 1. Following the general procedure with uridine (1.0 g, 4.10 mmol), dioxane (40 mL), bromoisobutyroyl bromide (2.73 g, 12.3 mmol), and CAL 435 (5.50 g) with stirring for 16 h at 60 °C. The product was purified by column chromatography (ethyl acetate) to give the product as a white solid (0.85 g, 53%); mp 72−74 °C. ^{1}H NMR (d_6-DMSO): δ 11.14 (1H, s, NH), 7.38 (1H, d, J = 8.1 Hz), 5.52 (1H, d, J = 4.9 Hz), 5.39 (1H, dd, J = 8.1 Hz, J = 6.0 Hz), 5.28 (1H, bs, OH), 5.08 (1H, bs, OH), 4.20−4.00 (2H, m), 3.95−3.65 (3H, m), 1.97 (3H, s), 1.95 (3H, s). ^{13}C NMR (d_6-DMSO): δ 171.1, 163.4, 150.9, 141.0, 102.4, 88.9, 81.2, 73.2, 69.9, 65.7, 57.3, 30.6 (2C). IR, ν_{max} (solid): 3600−2700 (br), 2930, 2855, 1677, 1462, 1389, 1260, 1161, 1100, 1076 cm^{-1}. HRMS (CI) calcd for $C_{13}H_{18}BrN_2O_7$ (MH^+): 393.0297. Found: 393.0298.

Synthesis of 5′-Methacryloyladenosine, 5. Following the general procedure with adenosine (1.0 g, 4.11 mmol), dioxane (40 mL), methacryloylacetone oxime (1.74 g, 12.33 mmol), and CAL 435 (5.50 g) with stirring for 22 h at 60 °C. The product was purified by column chromatography (25% methanol in ethyl acetate) to give the product as a white solid (0.56 g, 44%); mp 205−210 °C (decomposition). ^{1}H NMR (d_6-DMSO): δ 8.28 (1H, s), 8.15 (1H, s), 7.34 (2H, bs, NH_2), 6.03 (1H, s), 5.93 (1H, d, J = 4.7 Hz), 5.70−5.55 (1H + OH, m), 5.43 (1H, bs, OH), 4.69 (1H, t, J = 4.9 Hz), 4.44 (1H, dd, J = 12.1 Hz, J = 6.0 Hz), 4.30−4.22 (2H, m), 4.01 (1H, q, J = 7.2 Hz), 1.86 (3H, s). ^{13}C NMR (d_6-DMSO): δ 166.7, 156.5, 153.1, 149.6, 140.1, 136.0, 126.5, 119.5, 88.3, 81.7, 73.3, 70.5, 64.5, 18.3. IR, ν_{max} (solid): 3326, 3119, 1715, 1636, 1574, 1574, 1476, 1320, 1295, 1162, 1080 cm^{-1}. HRMS (CI) calcd for $C_{14}H_{17}N_5O_5$ (MH^+): 335.1230. Found: 335.1226.

Trimethylsilyl Protection of 5′-Methacryloyluridine, 4 (General Procedure). To a solution of 5′-methacryloyluridine (4.0 g, 12.8 mmol) in dioxane (100 mL) was added pyridine (3.59 g, 44.8 mmol) followed by dropwise addition of trimethylsilyl chloride (4.17 g, 38.4 mmol). The reaction mixture was heated at 60 °C for 1 h and then treated dropwise with more trimethylsilyl chloride (2.78 g, 25.6 mmol) while heating at 60 °C. When the addition was complete, the reaction mixture was heated at 60 °C for a further 1.5 h to give a white precipitate. The dioxane was evaporated in vacuo (∼40 °C) and the residue treated with ether (60 mL) and water (130 mL). The layers were separated, the aqueous phase was extracted with more ether (2 × 40 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The resulting orange oil was purified by column chromatography (40% ethyl acetate in 40−60 °C petroleum ether) to give the product as a colorless oil which solidified under high vacuum to give a white solid (**1**, 4.27 g, 73%); mp 46−48 °C. ^{1}H NMR ($CDCl_3$): δ 9.93 (1H, s, NH), 7.60 (1H, d, J = 8.1 Hz), 6.05 (1H, s), 5.70−5.60 (2H, m), 4.50 (1H, m), 4.35−5.20 (2H, m), 4.20 (1H, m), 4.00 (1H, dd, J = 6.8 Hz, J = 4.5 Hz), 1.95 (3H, s), 0.14 (9H, s), 0.09 (9H, s). ^{13}C NMR ($CDCl_3$): δ 166.5, 163.6, 150.0, 139.5, 135.8, 125.9, 101.8, 90.9, 80.6, 75.5, 69.8, 62.3, 18.3, 0.00 (3C), −0.15 (3C). IR, ν_{max} (solid): 2957, 1674, 1455, 1250, 1153, 1048, 837 cm^{-1}.

Trimethylsilyl Protection of 5′-Bromoisobutyroyluridine, 2. Following the general procedure with 5′-bromoisobutyroyluridine (0.60 g, 1.53 mmol), dioxane (10 mL), pyridine (0.43 g, 5.34 mmol), trimethylsilyl chloride (0.50 g, 4.58 mmol, added in one go), and stirring at 60 °C for 2 h. The crude product was purified by column chromatography (30% ethyl acetate in 40−60 °C petroleum ether) to give the product as a clear oil which solidified under high vacuum to give a white foamy solid (**2**, 0.70 g, 93%); mp 133−135 °C. ^{1}H NMR ($CDCl_3$): δ 9.76 (1H, s, NH), 7.75 (1H, d, J = 8.1 Hz), 5.78 (1H, dd, J = 8.1 Hz), 5.74 (1H, d, J = 2.5 Hz), 4.60−3.90 (5H, m), 1.94 (3H, s), 1.93 (3H, s), 0.14 (9H, s), 0.11 (9H, s). ^{13}C NMR ($CDCl_3$): δ 171.1, 163.5, 150.0, 139.8, 102.2, 90.5, 80.4, 75.5, 69.6, 63.5, 55.1, 30.8, 30.7, 0.00 (3C), −0.08 (3C). IR, ν_{max} (solid): 3700−3000 (br), 2953, 2855, 1681, 1457, 1250, 1158, 1097, 835, 760 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{33}BrN_2O_7Si_2$ (M^+): 536.1010. Found: 536.0995.

TBDMS Protection of 5′-Methacryloyladenosine, 6. To a solution of 5′-methacryloyladenosine (0.40 g, 1.19 mmol) in DMF (1.5 mL) was added silver nitrate (0.61 g, 3.58 mmol) and the solution stirred until it dissolved (∼5 min). To this clear solution was added TBDMS−Cl (0.43 g, 2.50 mmol), and the reaction mixture was stirred for 50 min to give a gray/blue precipitate. To this was added pyridine (0.38 g, 4.77 mmol), and the stirring continued for 5 min. Water (20 mL) and dichloromethane (50 mL) were then added, and the two-phase mixture was filtered. The organic phase was washed with water (4 × 20 mL), then dried ($MgSO_4$), and evaporated in vacuo to give an orange oil. This was purified by column chromatography (40% ethyl acetate in 40−60 °C petroleum ether) to give the product as a white solid (0.41 g, 61%); mp 165−166 °C. ^{1}H NMR ($CDCl_3$): δ 8.30 (1H, s), 7.93 (1H, s); 6.19 (2H, s, NH_2), 6.07 (1H, s), 5.72 (1H, d, J = 7.4 Hz), 5.58 (1H, s), 4.91 (1H, t, J = 4.3 Hz), 4.59 (1H, m), 4.45−4.20 (3H,

m), 1.92 (3H, s), 0.90 (9H, s), 0.80 (9H, s), 0.07 (3H, s), 0.05 (3H, s), −0.02 (3H, s), −0.18 (3H, s). IR, ν_{max} (solid): 3117, 2928, 2854, 1716, 1680, 1608, 1330, 1252, 1661, 1075 cm^{-1}. ^{13}C NMR ($CDCl_3$): δ 167.4, 156.1, 153.3, 149.9, 140.2, 136.3, 126.5, 120.9, 90.1, 82.4, 74.9, 72.3, 63.5, 26.2 (3C), 26.1 (3C), 18.8, 18.4, 18.3, −4.02 (3C), −4.33 (3C), −4.54 (6C). Anal. Calcd for $C_{26}H_{45}N_5O_7Si_2$: C, 55.39; H, 8.05; N, 12.43. Found: C, 55.23; H, 8.03; N, 12.42.

Synthesis of 5′-Bromoisobutyroyladenosine, 7. Following the general procedure with adenosine (1.0 g, 3.74 mmol), dioxane (40 mL), bromoisobutyroyl bromide (2.49 g, 11.2 mmol), and CAL 435 (5.0 g) with stirring for 23.5 h at 60 °C. The product was purified by column chromatography (5% methanol in ethyl acetate) to give the product as a white solid (415 mg, 28%); mp 82−85 °C. ^{1}H NMR (d_6-DMSO): δ 8.06 (1H, s), 7.90 (1H, s), 7.09 (2H, NH_2, s), 5.68 (1H, d, J = 4.9 Hz), 5.38 (1H, OH, bs), 5.18 (1H, OH, bs), 4.42 (1H, bs), 4.30−4.00 (3H, m), 3.90 (1H, m), 1.62 (6H, s). ^{13}C NMR (d_6-DMSO): δ 171.0, 156.4, 153.0, 149.6, 140.0, 119.5, 88.1, 81.5, 73.3, 70.4, 65.7, 57.4, 30.5. IR, ν_{max} (solid): 3600−2600 (br), 1732, 1636, 1599, 1575, 1473, 1271, 1161, 1101, 1042 cm^{-1}. HRMS (CI) calcd for $C_{14}H_{19}BrN_5O_5$ (MH^+): 416.0570. Found: 416.0577.

TBDMS Protection of 5′-Bromoisobutyroyladenosine, 7. To a solution of 5′-bromobutyroyladenosine (2.0 g, 5.96 mmol) in DMF (7.5 mL) was added silver nitrate (3.04 g, 17.9 mmol), and the solution was stirred until it dissolved (∼5 min). To this clear solution was added TBDMS−Cl (2.55 g, 2.55 mmol), and the reaction mixture was stirred for 50 min to give a gray/blue precipitate. To this was added pyridine (1.91 g, 23.9 mmol), and the stirring continued for 1 h. Water (250 mL) and dichloromethane (200 mL) were then added, and the two-phase mixture was filtered. The organic phase was washed with water (4 × 50 mL), then dried ($MgSO_4$), and evaporated in vacuo to give an orange oil. This was purified by column chromatography (45% ethyl acetate in 40−60 °C petroleum ether) to give the product as a white solid (2.75 g, 82%); mp 160−163 °C. ^{1}H NMR ($CDCl_3$): δ 8.32 (1H, s), 8.02 (1H, s), 6.10 (2H, NH_2, bs), 5.90 (1H, d, J = 4.7 Hz), 4.95 (1H, t, J = 4.3 Hz), 4.70−4.15 (4H, m), 1.90 (6H, s), 0.92 (9H, s), 0.80 (9H, s), 0.10 (9H, s), −0.03 (3H, s), −0.21 (3H, s). ^{13}C NMR ($CDCl_3$): δ 179.1, 163.2, 160.4, 157.3, 147.7, 128.1, 97.0, 89.7, 82.1, 79.6, 72.2, 63.1, 38.5 (2C), 33.5 (3C), 33.3 (3C), 25.7, 25.5, 3.24, 2.99, 2.92, 2.69. IR, ν_{max} (solid): 3150, 2928, 2856, 1734, 1675, 1602, 1471, 1252, 1149, 1095, 991, 832, 776. HRMS (CI) calcd for $C_{26}H_{47}BrN_5O_5Si_2$ (MH^+): 644.2299. Found: 644.2290.

Polymerization of 4 Using *N*-(*n*-Pentyl)-2-pyridylmethanimine as Ligand (General Procedure). Copper(I) bromide (3.1 mg, 0.0219 mmol) and **4** (100 mg, 0.219 mmol) were placed in a Schlenk tube and deaerated by pumping and then purging with nitrogen three times. To this solid mixture was added solutions of pentyl ligand (7.7 mg, 0.0438 mmol) in deaerated toluene (0.5 mL) and ethyl bromoisobutyrate (4.4 mg, 0.0219 mmol) in deaerated toluene (0.5 mL). The mixture was deaerated by four freeze−pump−thaw cycles and then heated at 90 °C for 16 h. The solution was then transferred to a round-bottom flask using ethyl acetate to wash out the Schlenk tube. The solvent was evaporated in vacuo, and the resulting solid was washed with a mixture of dichloromethane and petroleum ether 40−60 °C (1:1) to remove any unreacted monomer. The resulting solid was dissolved in methanol and filtered through a pad of basic activated alumina to remove the copper. This gave the polymer as a light green solid (60 mg, 42%); T_g = 137.1 °C. ^{1}H NMR (d_6-DMSO): δ 11.4 (1H, bs), 7.62 (1H, bs), 5.76 (1H, bs), 5.68 (1H, m), 4.60−3.50 (5H, m), 1.50−0.50 (5H, m), 0.50-(−0.60) (18H, m). IR, ν_{max} (solid): 2955, 1683, 1454, 1376, 1250, 1149, 1071, 941, 879, 837, 750 cm^{-1}. M_n = 6500, M_w = 7300, P_D = 1.12.

Polymerization of MMA Using the Unprotected Uridine Initiator, 1. Following the general procedure with copper(I) bromide (10.9 mg, 0.0763 mmol), initiator (30 mg, 0.0763 mmol), MMA (0.76 g, 7.63 mmol), pentyl ligand (26.9 mg, 0.153 mmol), and deaerated toluene (3 mL). The reaction mixture was heated at 90 °C for 19 h and poured into petroleum ether, 40−60 °C (100 mL). The precipitate was filtered and passed through a pad of activated basic alumina and then silica gel using dichloromethane as eluent to give the poly(methyl methacrylate) as a white solid (645 mg); T_g = 123.7 °C. ^{1}H NMR ($CDCl_3$): δ 3.85−3.35 (3H, bs), 2.20−0.60 (5H, m). IR, ν_{max} (solid): 3149, 2950, 2857, 1732, 1677, 1603, 1463, 1250, 1147, 1096, 991, 834, 776 cm^{-1}. M_n = 22 500 (30 400 by ^{1}H NMR), M_w = 26 800, P_D = 1.19.

Polymerization of MMA Using the Unprotected Adenosine Initiator, 7. Following the general procedure with copper(I) bromide (34.5 mg, 0.24 mmol), initiator (100 mg, 0.24 mmol), MMA (2.41 g, 24.0 mmol), pentyl ligand (84.7 mg, 0.480 mmol), and deaerated toluene (5 mL). The reaction mixture was heated at 90 °C for 16 h and poured into petroleum ether, 40−60 °C (100 mL). The precipitate was filtered and passed through a pad of activated basic alumina and then silica gel using dichloromethane as eluent to give PMMA as a light green solid (2.50 g); T_g = 124.1 °C. ^{1}H NMR ($CDCl_3$): δ 3.85−3.35 (3H, bs), 2.20−0.60 (5H, m). M_n = 17 100, M_w = 21 200, P_D = 1.24.

Reaction of Unprotected Uridine Initiator, 1, under Polymerization Conditions in the Absence of Monomer. Following the general procedure with copper(I) bromide (200 mg, 1.40 mmol), **1** (500 mg, 1.27 mmol), pentyl ligand (490 mg, 2.80 mmol), and deaerated toluene (10 mL). The reaction mixture was heated at 90 °C for 17 h and then transferred to a round-bottom flask, and the solvent was evaporated. The residue was purified by column chromatography (10% methanol in ethyl acetate) to give uridine as a white solid (15.3 mg, 5.0%). ^{1}H NMR (d_6-DMSO): δ 11.30 (1H, bs, NH), 7.88 (1H, d, J = 8.2 Hz), 5.77 (1H, d, J = 5.2 Hz), 5.64 (1H, d, J = 8.2 Hz), 5.33 (OH, d, J = 5.1 Hz), 5.12 (OH, d, J = 4.8 Hz), 4.10−3.75 (3H, m), 3.70−3.40 (2H, m).

Results and Discussion

The unprotected and silyl-protected 5′-bromoisobutyroyluridine and 5′-bromoisobutyroyladenosine atom transfer polymerization initiators and monomers (**1**−**8**, Figure 1) were synthesized using a modified procedure of Moris and Gotor,[30] using the enzyme *Candida antarctica lipase* 435 (CAL 435) with an activated acetoneoxime ester (Figure 2). This is an attractive method for the synthesis of monomers as the reaction is regiospecific, circumventing the need for protecting group chemistry at this stage. The methacryloylacetone oxime was synthesized using methacryloyl chloride and acetone oxime with triethylamine base in dichloromethane (96% yield). The bromoisobutyroylacetone oxime was synthesized in a similar fashion using bromoisobutyroyl bromide with ether as solvent (93% yield).

Polymerization of MMA and Styrene Using Uridine and Adenosine Derived Initiators. Atom transfer polymerization of methyl methacrylate with the protected 5′-bromoisobutyroyluridine initiator **2** with NMPI ligand in conjunction with copper(I) bromide as catalyst proceeds effectively at 90 °C in toluene solution to give a polymer with structure shown in Figure 3. SEC of the product showed an M_n of 13 100 with a very narrow PDI of 1.06 (Table 1). This compares very favorably to an M_n of 11 000 determined by integration of the appropriate regions in the ^{1}H NMR spectrum. These reaction conditions would be expected to give virtually quantitative conversion after 19 h with a theoretical M_n of 10 000 g mol^{-1} assuming a living polymerization. The initiator efficiency from these data is 0.81, which is similar to that observed with nonfunctional initiators. The ^{1}H NMR spectrum (Figure 4) clearly shows the presence of the initiator in the polymer; the singlet at 8.25 ppm is from the N−H, doublets at 7.38 and 5.79 ppm are from the alkene group, the singlet at 5.68 ppm is from the 1′-proton, and

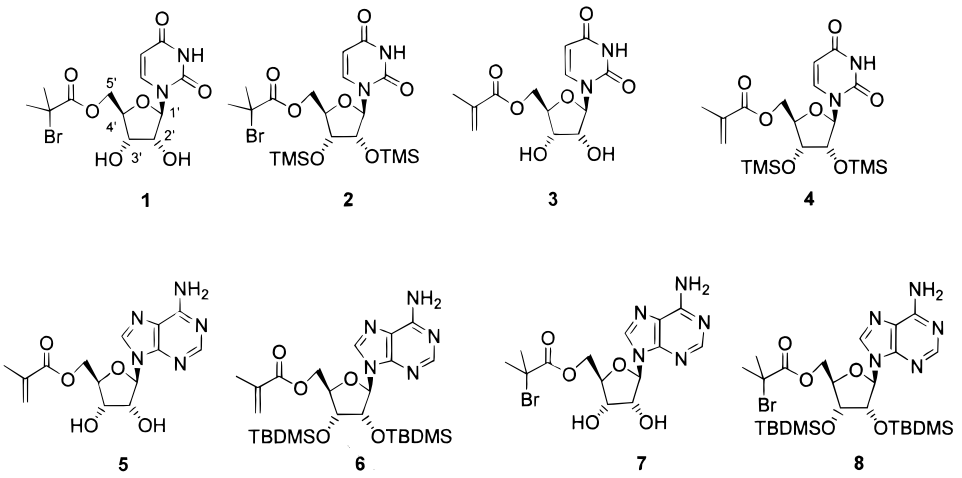

Figure 1. Initiators and monomers used in this work.

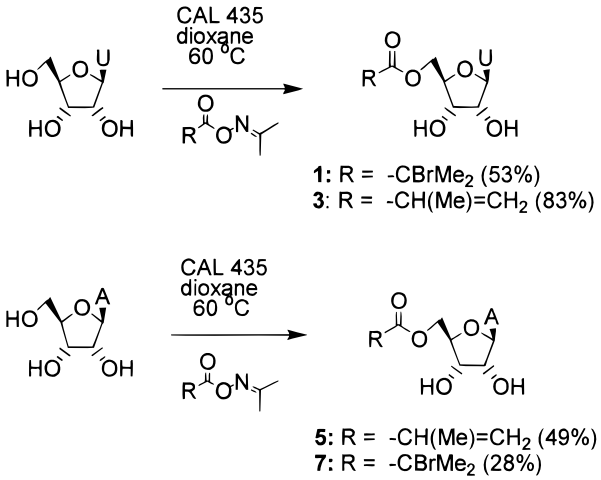

Figure 2. Regiospecific enzymatic synthesis of uridine and adenosine derived initiators and monomers used in this study.

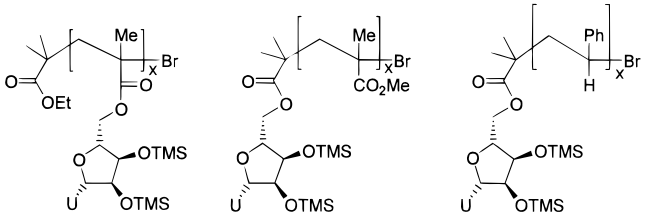

Figure 3. Structure of poly(**4**), PMMA from **2**, and PS from **2** (from left to right).

the remaining protons are in the sugar ring between 4.4 and 3.9 ppm. Analysis by dual detection SEC (UV and DRI detectors) (Figure 5) clearly show the presence

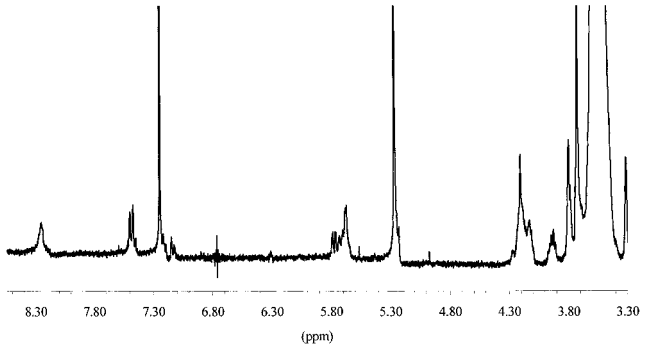

Figure 4. ^{1}H NMR spectrum of PMMA from initiation with **2**.

of the initiator across the entire mass distribution, the UV absorbance at 365 nm being solely from the α-terminal group. Figure 6 shows the evolution of the molecular mass distribution with conversion. For initiator **2**, a single monomodal distribution is observed which shifts to higher mass with conversion, as would be expected. A reduction of the mole equivalents of MMA with respect to **2** to 20/1 results in a decrease in the M_n to 3150 (3760 by NMR) with a PDI of 1.13 as expected for a living polymerization. The reduction in the M_n of the product is reflected in the lower T_g of the polymer (Table 1). Hence, the presence of the amide and sugar groups within the uridine initiator does not seem to adversely effect the controlled polymerization. These promising results prompted us to investigate the use of the unprotected uridine derived initiator **1**. Polymerization of MMA under similar conditions leads to a polymer with narrow PDI. However, we see a reduction in initiator efficiency as observed by the increase in M_n.

Table 1. Polymerization Data for the Polymerization of MMA and Styrene with Functional Initiators[a]

initiator	monomer	[M]/[I]	temp, °C	time, h	M_n, SEC (^{1}H NMR)	PDI	T_g, DSC °C	initiator efficiency
1	MMA	100	90	19	22 500 (30 400)	1.19	123.7	0.46
2	MMA	100	90	17	13 100	1.06	115.4	0.81
2	MMA	20	90	17	3 150 (3 760)	1.13	88.3	0.81
2	STY	100	120	15.5	17 000	1.15	99.8	0.64
7	MMA	100	90	16	17 100	1.24	124.1	0.62
8	MMA	100	90	16	12 600 (16 500)	1.06	116.1	0.83

[a] Reactions carried out as described in the general procedure in toluene (33%) with [*N*-(*n*-pentyl)-2-pyridylmethanimine]/[CuBr] = 2.

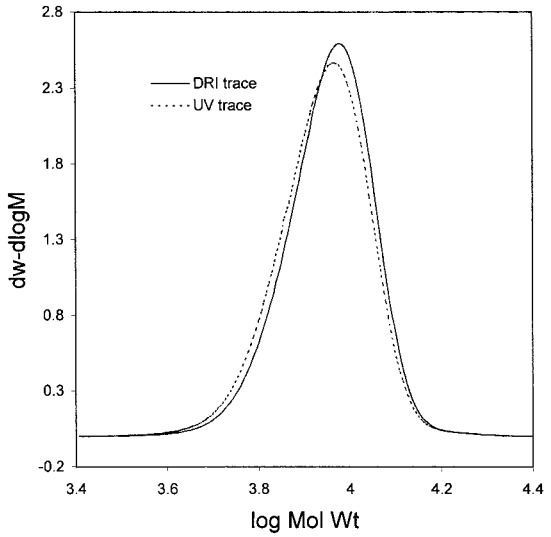

Figure 5. SEC traces for PMMA using **2** as initiator, DRI detection showing a response from the entire molecular structure, and UV absorbance at 365 nm (absorbance for X terminal group) showing incorporation of initiator **2** across the entire mass distribution envelope.

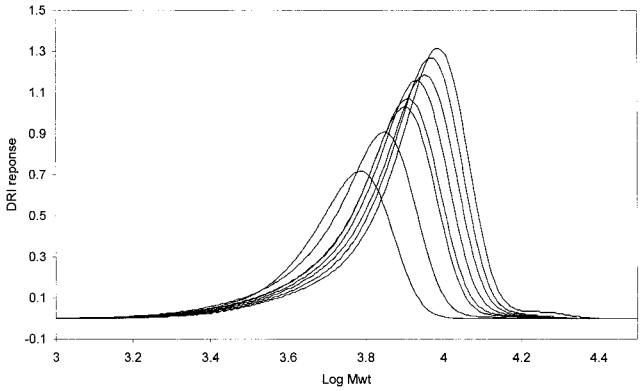

Figure 6. Evolution of molecular mass distribution for the polymerization of MMA with **2**. Area under each chromatogram normalized for conversion so that area is directly proportional to conversion at each time.

Nevertheless, the initiator is effective to produce functionalized polymers with the end group observed in both the ^{1}H NMR (Supporting Information) and UV detection GPC chromatogram. Polymerization of MMA with **1** as initiator was followed with conversion; see Supporting Information. Figure 7a shows the first-order kinetic plot with a linear dependence with time, k_p[Pol*] = 1.79 × 10^{-3} s^{-1}. The M_n increases with conversion following the theoretical M_n (Figure 7b). Initiator **2** is also effective for the atom transfer polymerization of styrene, with an increase in temperature to 120 °C under otherwise identical reaction conditions. Poly(styrene) was synthesized with an M_n of 17 000 g mol^{-1} (targeted M_n of 10 400, initiator efficiency = 0.64) after 15.5 h.

Having demonstrated the ability to synthesize vinyl polymers with α-uridine functionality derived from the initiator, we turned to the complementary, and more functionally complex, adenosine derived initiators **7** and **8**. Indeed, polymerization of MMA, with the protected initiator **8**, proceeds in a controlled manner with polymer of M_n = 12 600 (16 500 by NMR), PDI = 1.06 (targeted M_n = 10 000) after 16 h at 90 °C. The unprotected initiator **7** also leads to controlled atom transfer polymerization with a small broadening of the

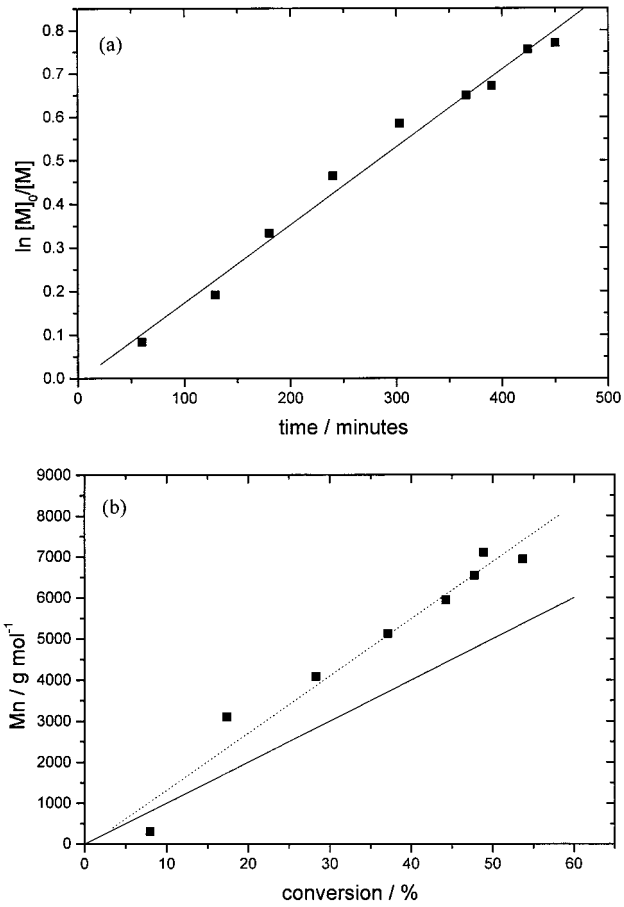

Figure 7. Polymerization of MMA with **1**. (a) First-order kinetic plot for the [initiator]$_0$ = 0.017 mol dm^{-3}, [CuBr]$_0$ = 0.017 mol dm^{-3}, [NMPI]$_0$ = 0.034 mol dm^{-3}, [MMA]$_0$ = 1.70 mol dm^{-3} line represents regression analysis on data. (b) Evolution of molecular mass with conversion. Full line represents expected M_n.

PDI observed, M_n = 17 100, PDI = 1.24. Interestingly, PMMA initiated by **7** shows an increase in T_g to 124.1 °C, approximately 10 °C higher than expected, presumably due to intermolecular interactions associated with the functional α-terminus. Polymerization of MMA initiated by **7** was followed as a function of time; see Supporting Information. Figure 8a shows the first-order kinetic plot with an excellent linear correlation with time, k_p[Pol*] = 1.29 × 10^{-3} s^{-1}. A linear increase in M_n with conversion is observed but with a low initiator efficiency, resulting in a higher than expected M_n (Figure 8b).

These results demonstrate that this system is inert to a multitude of functionality in the initiator, including secondary hydroxyl, silyl ether, tertiary amine, primary amine, secondary amide, etc. This is somewhat surprising as we might have expected the initiator to compete with the Schiff base and TREN ligands for coordination at the active metal center; the initiator is present in similar concentration to both the copper(I) and the ligands employed. Indeed, maybe there is competing coordination, but the copper-containing species formed is still active toward controlled polymerization by activation of the C−Br functional propagating polymer chain. The extent to which this occurs will be determined by the complexation constant of the various groups and is currently under investigation. In a recent paper looking at atom transfer radical polymerization of methacrylamides, it is suggested that polymerization

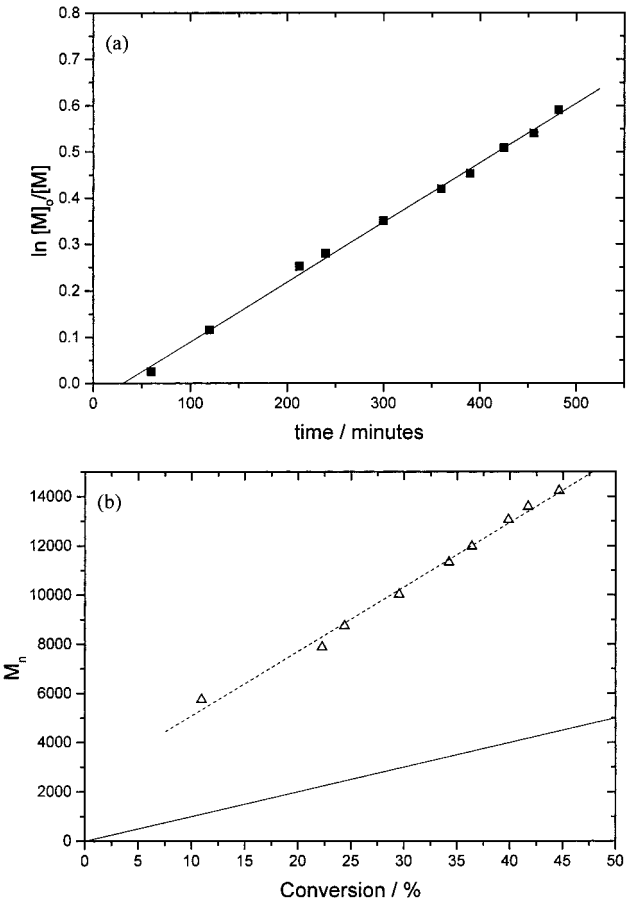

Figure 8. Polymerization of MMA with **7**. (a) First-order kinetic plot for the $[initiator]_0 = 0.018$ mol dm^{-3}, $[CuBr]_0 = 0.018$ mol dm^{-3}, $[NMPI]_0 = 0.037$ mol dm^{-3}, $[MMA]_0 = 1.84$ mol dm^{-3} line represents regression analysis on data. (b) Evolution of molecular mass with conversion. Full line represents expected M_n.

is hindered by nucleophilic displacement of the terminal halogen by an amide group.[31] Clearly this is not a dominant reaction in this present case. We also observe no significant chain transfer to the initiator in any system studied.

Initiator Decomposition Studies. To establish the decomposition mode of the uridine initiator **1**, it was subjected to atom transfer polymerization conditions in the absence of monomer. It was discovered that a small amount of decomposition occurred, leading to a number of products, as judged by TLC. The only isolable product was found to be that resulting from the loss of the bromoisobutyroyl initiator group to give uridine in 5% yield. The adenosine initiator **8** was also found to lose the bromoisobutyroyl group to give adenosine with TBDMS-protecting groups at the 2′- and 3′-positions in 16% yield. There is a marked difference between the initiator efficiency of the protected (**2** and **8**) and unprotected initiators (**1** and **7**) for the polymerization of methyl methacrylate (Table 1). In the case of the unprotected initiators the low initiator efficiency is ascribed to the observation that they are not fully soluble at the start of the reaction; this will lead to an increase in combination of small radicals due to increased local concentration resulting from inhomogeneity in the reaction medium.

Polymerization of Silyl-Protected Monomers. As the uridine monomer **3** and adenosine-derived monomer **5** were only soluble in polar solvents, silyl protection was employed to impart solubility in nonpolar polymerization solvents. The parent uridine hydroxyl functional derivative **3** was protected using trimethylsilyl chloride to give **4**. The adenosine derivatives **5**, being more polar, were protected with the larger *tert*-butyldimethylsilyl (TBDMS) group using TBDMS−Cl with silver nitrate[32,33] and pyridine in DMF to give the disilylated product, **6**. The silyl protection also results in polymers that are soluble in conventional organic solvents facilitating analysis.

Table 2. Polymerization of Silyl-Protected Monomers with Ethyl 2-Isobutyrate Initiator and CuBr in Toluene Solution (33%) at 90 °C with [4]/[Ethyl Isobutyrate] = 10

monomer	ligand	time, h	M_n (SEC)	PDI	T_g, °C (DSC)
4	NPMI	16	6530	1.12	137.1
4	TREN	12.5	8530	1.17	140.1
6	NPMI	44	4000	1.44	142.4
6	TREN	45	3400	1.35	120.4

Polymerization of TMS-protected 5′-methacryloyluridine (**4**) was carried out using both *N*-(*n*-pentyl)-2-pyridylmethanimine (NPMI) and TREN ligands in conjunction with copper(I) bromide and ethyl bromoisobutyrate initiator (Table 2). This gave the TMS-protected poly(5′-methacryloyluridine) in 60% yield with narrow molecular weight distribution, 1.12, as indicated by SEC with NPMI as the ligand (Figure 3). Atom transfer polymerization of **4** using the TREN ligand was carried out with 1 mol equiv of the ligand with respect to copper(I). The resulting polymer showed an M_n of 8530 with PDI = 1.17 after 12 h. Polymerization of the TBDMS-protected 5′-methacryloyladenosine, **6**, with both TREN and NPMI ligands was successful; however, an increase in PDI of 1.35 and 1.44, respectively, is observed at low molecular mass. This might be due to broadening due to an interaction with the SEC columns from the hydrogen-bonding sites all along the polymer chain. Polymerization of **6** proceeds slowly, reaching M_n of approximately 4000 after 45 h at 90 °C.

Conclusions

In summary, it has been shown that atom transfer polymerization of styrene and methyl methacrylate can be carried out to give polymers with predictable M_n and very narrow PDI using both adenosine and uridine derived initiators. Initiators are effective in both the free hydroxyl and silyl-protected forms. Initiator efficiency is considerably reduced, which is probably due to loss of initiator radicals via small molecule radical reactions early in the reaction. The presence of small amounts of hydrogen-bonding moieties at the α-terminus of the polymers can have significant effects on the physical properties of the polymers produced. The hydrogen-bonding interactions of the complementary end groups attached to PMMA are being investigated. The kinetic data for these polymerizations show a linear relationship, indicating the living nature of the polymerization. Silyl-protected adenosine and uridine derived monomers undergo effective atom transfer polymerization to give polymers with narrow PDI. Thus, (1) atom transfer polymerization under these conditions has been shown to be inert to secondary hydroxyl, primary, secondary and tertiary amino, secondary amido, silyl ether, and ester linkages within either the monomer and initiator, and (2) atom transfer polymerization can be used to synthesize well-defined polynucleoside-based polymers which have tremendous potential for templating and polymers used in applications that require biorecognition.

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Supporting Information Available: Additional experimental information, NMR spectra of polymers, and tabulated polymerization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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