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2-(Pyridin-2-yl)ethanol as Protecting Group for Carboxylic Acids: Chemical and Thermal Cleavage, and Conversion of Poly[2-(Pyridin-2-yl)ethyl Methacrylate] to Poly(methacrylic Acid)

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Experimental Section

Materials
2-(Pyridin-2-yl)ethanol (98%), methacryloyl chloride (97%), methyl methacrylate (MMA, 99%), styrene (Sty, > 99%), 1-methoxy-1-trimethylsiloxy-2-methyl propene (MTS, 95%), 2-cyanoprop-2-yl dithiobenzoate (97%), tetrabutylammonium hydroxide (40% w/w in water), benzoic acid (99.5%), 1,4-dioxane (99.8%), 2,2-diphenyl-1-picrylhydrazyl hydrate (DPPH, 95%), basic alumina (≥ 97%), calcium hydride (CaH₂, 90-95%) and potassium metal (99%) were purchased from Aldrich, Germany. Synthesis grade triethylamine (Et₃N), n-hexane (96%) and tetrahydrofuran (THF, 99.8%) were obtained from Scharlau, Spain. THF was used as the mobile phase in chromatography (HPLC grade), and as solvent (reagent grade) for the polymerizations. 2,2’-Azobis(isobutyronitrile) (AIBN, 95%), methanol (99.9%), ethanol (99.9%), dimethyl sulfoxide (DMSO, 99%), deuterated dimethyl sulfoxide (d₆-DMSO, 99.9%), and deuterated chloroform (CDCl₃, 99.8%) were purchased from Merck, Germany. Finally, sodium metal (98%) was from Fluka.

Methods

Purification of Solvents, Monomers, Initiators and Catalysts. THF was dried by being refluxed in a specially-constructed still over a potassium-sodium alloy for three days and was freshly distilled prior to use. 1,4-Dioxane was distilled from CaH₂. Tetrabutylammonium dibenzoate (TBABB, GTP catalyst) was synthesized by the reaction of tetrabutylammonium hydroxide and benzoic acid in water, following the procedure of Dicker et al. [1], and was kept under vacuum until use. MMA and Sty were passed through basic alumina columns to remove the polymerization inhibitors and any other acidic impurities, and they were subsequently stirred over CaH₂ (to remove the last traces of moisture and protic impurities) in the presence of added DPPH free-radical inhibitor, and stored in the refrigerator at about 5 ºC. Finally, they were freshly distilled under vacuum just before their use and kept under a dry argon atmosphere. The GTP initiator MTS was distilled once prior to the polymerization, without any contact with calcium hydride or basic alumina to avoid the risk of hydrolysis. AIBN was recrystallized twice from ethanol. All glassware was dried overnight at 145 ºC and assembled hot under dynamic vacuum prior to use.

Synthesis of 2-(Pyridin-2-yl)ethyl methacrylate (PyEMA). 2-(Pyridine-2-yl)ethanol (10 mL, 10.93 g, 0.0888 mol), Et₃N (99 mL, 72 g, 0.71 mol) and absolute THF (62.5 mL) were transferred to a 500-mL round-bottomed flask containing a magnetic stirring bar. The solution was stirred and cooled down to 0 ºC. After stabilization of the temperature, methacryloyl chloride (10.74 mL, 11.60 g, 0.111 mol) was added dropwise using a glass syringe and the reaction was stirred for 2 h at 0 ºC. Subsequently, the mixture was filtered to remove triethylamine hydrochloride and passed twice through a basic alumina column to remove methacrylic acid (hydrolysis product of excess methacryloyl chloride) and any other acidic impurities. Then, the solvent was evaporated off to give pure monomer in 90% yield.
Finally, PyEMA was stirred over CaH₂ in the presence of DPPH to remove all the moisture and the last traces of protic impurities. PyEMA was characterized using \(^1\)H and \(^{13}\)C NMR spectroscopy. \(^1\)H NMR (CDCl₃, δ): 1.80 ppm (a, s, CH₂=CHCH₃, 3 H), 3.09 ppm (e, t, -OCH₂CH₂-, 2 H), 4.45 ppm (d, t, -OCH₂CH₂-, 2 H), 5.44 ppm (c, s, olefinic H trans to CO₂, 1 H), 5.95 ppm (b, s, olefinic H cis to CO₂, 1 H), 7.09 ppm (f, 1 H), 7.24 ppm (h, 1 H), 7.51 ppm (g, 1 H), and 8.48 ppm (i, 1 H). \(^{13}\)C NMR (CDCl₃, δ): 18.24 ppm (a, s, CH₂=CHCH₃, 1 C), 37.43 ppm (f, s, -OCH₂CH₂-, 1 C), 63.84 ppm (e, s, -OCH₂CH₂-, 1 C), 121.60 ppm (j, s, aromatic, 1 C), 123.43 ppm (h, s, aromatic, 1 C), 125.46 ppm (c, s, CH₂=CHCH₃, 1 C), 136.24 ppm (b, s, CH₂=CHCH₃, 1 C), 136.32 ppm (i, s, aromatic, 1 C), 149.46 ppm (k, s, aromatic, 1 C), 158.12 ppm (g, s, aromatic, 1 C) and 167.25 ppm (d, s, CO₂, 1 C).

**Alternative method for the synthesis of the PyEMA monomer.** A preliminary investigation has also been performed to exploit the reversibility of the thermolysis reaction to synthesize the PyEMA monomer. To this end, methacrylic acid (2 mL, 0.203 g, 0.0185 mol), were allowed to react in the bulk at 60 °C for 24 h, leading to PyEMA formation at 35% yield (in the crude).

**Polymerizations**

**GTP.** GTP was performed in spherical glass flasks using TBABB as polymerization catalyst, MTS as initiator and THF as solvent, and introducing the monomer(s), PyEMA and MMA. PyEMA was both homo- and block co-polymerized with MMA at room temperature (starting temperature 27 °C) without thermostating, and monitoring the polymerization exotherm using a digital thermometer to follow the progress of the polymerization reaction. We illustrate below the block copolymerization procedure of PyEMA by describing in detail the GTP preparation of the PyEMA₁₀⁻b-MMA₅₀ copolymer.

A 50-mL round-bottomed flask containing a stirring bar was loaded with a catalytic amount of TBABB (~20 mg, ~40 μmol, ~3% mol relative to the initiator), immediately sealed with a rubber septum, and purged with dry argon. Subsequently, 25.7 mL freshly distilled THF was transferred into the flask via a glass syringe, followed by the addition of 0.3 mL of the MTS initiator (0.258 g, 1.48 mmol). Then, 2.8 mL of PyEMA (2.8 g, 14.8 mmol) was slowly added using a glass syringe producing an exotherm (26 – 38 °C). The exotherm abated within 5 min, and samples (2 × 0.1 mL) were extracted for analyses by gel permeation chromatography (GPC) (GPC number-average molecular weight = \(M_n = 1500\) g mol⁻¹ compared to the theoretical value expected on the basis of the monomer-initiator feed ratio of 2012 g mol⁻¹; polydispersity index = PDI = \(M_w/M_n = 1.17\); \(M_n\) is the weight-average molecular weight) and \(^1\)H NMR spectroscopy (complete monomer conversion; degree of polymerization, DP, determined to be 12 by end-group analysis, compared to the theoretically expected value of 10). Afterwards, 7.88 mL of MMA (7.41 g, 74 mmol) was slowly added using a glass syringe producing an exotherm (29 – 58 °C). The exotherm abated within 10 min, 0.5 mL methanol was added to terminate the polymerization, and samples (2 × 0.1 mL) were again obtained for GPC (GPC \(M_n = 4200\) g mol⁻¹ compared to the theoretically expected value of 7022 g mol⁻¹; PDI = 1.10) and \(^1\)H NMR spectroscopy (complete monomer conversion: PyEMA content in copolymer = 13.7% mol compared to 16.7% mol expected from the comonomer feed ratio and given complete comonomer conversion).

**RAFT Polymerization of PyEMA.** A solution of PyEMA (1.5 mL, 1.5 g, 7.8 mmol), 2-(cyanoprop-2-yl) dithiobenzoate RAFT CTA (0.0173 g, 0.0784 mmol), and AIBN (0.0085 g, 0.049 mmol) in 1,4-dioxane (1.1 mL) were transferred to a 50-mL round-bottomed flask containing a magnetic stirring bar. This resulted in a monomer solution at a concentration of 3 M. The system was degassed by three freeze-pump-thaw cycles and was subsequently placed in an oil bath at 65 °C for 24 h. Monomer conversion, measured by \(^1\)H NMR spectroscopy, was 100%, whereas polyPyEMA molecular weight characteristics, as measured
by GPC, were: $M_n = 12,000 \text{ g mol}^{-1}$ (theoretically expected molecular weight = 19,344 g mol$^{-1}$) and PDI = 2.37. The polymer was purified by precipitation in $n$-hexane and dried in vacuo.

Styrene (1.70 mL, 1.55 g, 14.9 mmol) was subsequently polymerized in 1,4-dioxane (0.4 mL) for 24 h at 65 °C using the obtained polyPyEMA (0.4 g) as macroRAFT agent. Styrene monomer conversion, measured by $^1$H NMR spectroscopy, was 84.0%, whereas PyEMA-Sty diblock copolymer molecular weight characteristics, as measured by GPC, were: $M_n = 42,500 \text{ g mol}^{-1}$ (theoretically expected molecular weight = 63,100 g mol$^{-1}$) and PDI = 2.04. The polymer was purified by precipitation in $n$-hexane and dried in vacuo.

**Polymer Characterization**

**Gel Permeation Chromatography.** The molecular weight distributions (MWDs) of all the polymers were recorded using gel permeation chromatography (GPC), from which the values of $M_n$, $M_w$, $M_p$ (peak molecular weight) and the PDI were calculated. A single Polymer Laboratories PL-Mixed “D” column (bead size = 5 $\mu$m; pore sizes = 100, 500, $10^3$ and $10^4$ Å) was used for sample analysis. The mobile phase was THF, delivered using a Waters 515 isocratic pump at a flow rate of 1 mL min$^{-1}$. The refractive index (RI) signal was measured using a Polymer Laboratories ERC-7515A RI detector. The calibration curve was based on eight narrow MW (630, 2680, 4250, 13000, 28900, 50000, 128000 and 260000 g mol$^{-1}$) linear polyMMA standards also supplied by Polymer Laboratories.

**NMR Spectroscopy.** NMR spectroscopy on the starting materials, the monomers and the polymers was performed using 300 and 500 MHz Bruker NMR spectrometers. The NMR solvents used were CDCl$_3$, $d_6$-DMSO, $D_2$O, and $d_5$-methanol.

**DSC.** Differential scanning calorimetry (DSC) was performed using Thermal Instruments (TA) differential scanning calorimeters models Q100 and Q1000. For the measurements on the Q1000 model instrument, sample amounts of 0.5 – 2.0 mg were prepared in hermetically-sealed DSC pans, whereas for the Q100 model instrument sample amounts of 5 – 10 mg were pressed in regular (non-hermetically-sealed) pans. The temperature range covered was from 40 to 275 °C.

**TGA.** Thermal gravimetric analysis (TGA) was performed on a Thermal Instruments (TA) thermogravimetric analyzer model Q500 using ceramic pans. The temperature range from 40 to 600 °C was covered, whereas sample amounts of around 10 mg were loaded.

**Hydrogen Ion Titration.** Aqueous solutions of the PyEMA homopolymers (7 mL of a 1% w/v solution) were titrated in the pH range from 2 to 12 using a 0.5 M NaOH standard solution. The pH of the solution was measured using a Corning PS30 portable pH-meter. The effective pK values of the PyEMA monomer repeating units were calculated as the pH corresponding to 50% ionization. The pH at which polymer precipitation was first observed during the titration was also noted. Effective pK values of the PyEMA units in the homopolymers were determined to be equal to 3.8, whereas precipitation pH values were around 3.5.

**Polymer Deprotection**

**Alkaline Hydrolysis.** The PyEMA$_{55}$ homopolymer and the PyEMA$_{10-b}$-MMA$_{50}$ and the PyEMA$_{100-b}$-Sty$_{500}$ diblock copolymers were subjected to alkaline hydrolysis using sodium hydroxide at room temperature. In a typical experiment, 0.02 g PyEMA$_{55}$ was dissolved in 0.8 mL $d_6$-DMSO; to the resulting polymer solution, 40 µL NaOD 40% in $D_2$O was added, and the mixture was left to react for 12 h. The resulting polymer precipitate was redissolved in $D_2$O and was analyzed using $^1$H NMR spectroscopy. The same procedure was followed for the alkaline hydrolysis of the PyEMA$_{10-b}$-MMA$_{50}$ copolymer, with the only difference being that initial dissolution of the polymer in DMSO necessitated warming up to 50 °C.
**Attempted Acid Hydrolysis.** Acid hydrolysis of the PyEMA$_{55}$ homopolymer was attempted using hydrochloric acid in DMSO. In particular, 0.02 g PyEMA$_{55}$ was dissolved in 0.8 mL $d_6$-DMSO; to the resulting polymer solution, 40 µL DCl 10 M in $D_2$O was added, and the mixture was left for 12 h. Analysis was performed using $^1$H NMR spectroscopy in the initial reaction solvent, $d_6$-DMSO.

**Iodomethylation and Base Hydrolysis.** The PyEMA$_{55}$ homopolymer was first methylated in DMSO using methyl iodide, and the obtained quarternized polymer was hydrolyzed using potassium carbonate in water. In particular, 0.5 g PyEMA$_{55}$ (2.615 meq of PyEMA units) was dissolved in 10 mL DMSO, and to the resulting polymer solution was added 485 µL methyl iodide (1.115 g, 7.845 mmol). The reaction mixture was left to react overnight (reaction was complete within 1 h). The resulting quarternized polymer was purified by repeated precipitation in acetone and was vacuum dried. Subsequently, 0.2 g methylated polymer (0.600 meq of PyEMA-MeI units) was dissolved in water (3 mL), and to the resulting solution 0.664 g K$_2$CO$_3$ (4.802 mmol) was added, and the reaction mixture was left to react for 1h. The reaction product was purified from K$_2$CO$_3$ and the quarternized 2-vinyl pyridine by dialysis against water for one week, using a dialysis tube with a 3000 Da molecular weight cut-off. The external water was changed once a day. The thus-purified polymer (polyMAA) was isolated by freeze-drying from water.

**Thermolysis in the Bulk at 110, 120 and 130 °C.** A number (~10) of samples (20-30 mg) from the PyEMA$_{55}$ homopolymer were each transferred in to small (capacity of 2 mL) glass vials which were placed in a vacuum oven. Vacuum was applied and the temperature was adjusted to 110 °C. At predetermined time intervals (more frequently in the beginning, every ~1 h, less so at the later stages, ~15 h), a vial was withdrawn and kept for analysis using $^1$H NMR spectroscopy in $d_6$-DMSO. The $^1$H NMR spectra indicated the release of (monomeric) 2-vinyl pyridine which was not completely removed to the vacuum trap, probably due to its rather limited volatility. Thus, the calculation of the extent of thermolysis was not based on the relative amount of 2-vinyl pyridine present, but rather on the percentage reduction of the signals from methylenes in the side-groups of the polymer.

The experiment was repeated in a similar way at the higher temperatures, 120 and 130 °C.

**Thermolysis in Solution at 130 °C.** A sample of PyEMA$_{55}$ (0.5 g) was dissolved in 10 mL DMSO. The solution was transferred in to a 100 mL round-bottomed flask, fitted with a reflux condenser, under a flow of dry argon. The system was placed in an oil bath, thermostated at 130 °C, and left for 24 h. Samples were extracted at predetermined time intervals, which were vacuum-dried at room temperature and analyzed using $^1$H NMR spectroscopy in $d_6$-DMSO.

**Attempted Hydrogenolysis.** A sample of PyEMA$_{55}$ (0.2 g) was dissolved in ethanol where both the starting polymer and possible hydrogenolysis products are soluble. The polymer solution was transferred in to a single-neck round-bottomed flask, fitted with a glass valve. Subsequently, 0.2 g of 10 wt. % Pd on carbon was also introduced in the flask and dispersed by stirring. A balloon was fitted to the neck of the flask, and hydrogen was introduced through the glass valve to inflate the balloon.

**HAZARD WARNING:** Hydrogen is an explosive gas and should be handled with extreme caution!

The balloon was replaced every day and the system was refilled with hydrogen, for 7 days. No reaction was observed in the case of PyEMA$_{55}$. In contrast, in a similar control experiment, using poly(benzyl methacrylate) (BzMA$_{100}$, prepared by RAFT polymerization) instead of PyEMA$_{55}$, hydrogenolysis took place, resulting in poly(methacrylic acid). Due to the insolubility of polyBzMA in ethanol [2], a 9/1 ethyl acetate / methanol solvent mixture was used instead; the present mixture dissolved both the starting polymer and the hydrogenolysis products.
Figure S1. $^1$H and $^{13}$C NMR spectra of the PyEMA monomer recorded in CDCl$_3$. 
Figure S2. $^1$H NMR spectra of PyEMA$_{10}$-b-MMA$_{50}$ before (in CDCl$_3$) and after (in $d_6$-DMSO) alkaline hydrolysis using NaOD in $d_6$-DMSO.

Figure S3. $^1$H NMR spectra of PyEMA$_{55}$ before (in CDCl$_3$) and after (in $d_6$-DMSO) DSC.
**Figure S4.** DSC thermograms of (original) PyEMA$_{55}$ and iodomethylated (and purified) PyEMA$_{55}$ (“PyEMA$_{55}$-MeI”).

**Figure S5.** TGA thermograms of (original) PyEMA$_{55}$ and iodomethylated (and purified) PyEMA$_{55}$ (“PyEMA$_{55}$-MeI”).
Figure S6. Thermolysis kinetics of PyEMA55 in vacuo at different temperatures.

Figure S7. Thermolysis kinetics of PyEMA55 at 130 °C in different solvents.
Figure S8. $^1$H NMR spectrum of the crude from the reaction between methacrylic acid and 2-vinyl pyridine in the bulk. Spectrum was recorded in CDCl$_3$.

References