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Synthesis and Characterization of 5-Aminosalicylic Acid Based Poly(anhydride-esters) by Solution Polymerization

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5-aminosalicylic acid; polyanhydride; polymer drug; solution polymerization; triphosgene

INTRODUCTION

Polyanhydrides are useful biomaterials due to their excellent *in vivo* biocompatibility and their easy degradation within the body in the absence of enzymes.^{1–3} This facile biodegradation, owing to the hydrolytic lability of the anhydride bonds, makes polyanhydrides particularly useful as matrices for drug delivery applications, as controlled drug release can occur concurrently with the predictable biodegradation of the polyanhydride matrix.

Over the last decades, several synthetic methods have been developed for the formation of polyanhydrides: melt-condensation, solution, interfacial, and ring opening.^{3–8} A major advantage of melt condensation is the simplicity of the technique whereby a high yield of polymer is obtained. However, heat-sensitive monomers are not suitable due to the high temperatures typically required for polymerization (=180 °C) as they may form cyclic molecules^{6,9,10} or undergo thermal rearrangement.¹¹ In contrast, solution polymerization requires milder conditions but requires exact stoichiometry and produces relatively lower yields due to monomer-based impurities.

This article describes the use of solution polymerization to successfully incorporate derivatives of 5-aminosalicylic acid (5-ASA) into polyanhydride backbones, thereby creating biodegradable polymers with high molecular weights and good solubilities in low-boiling organic solvents. Because of its lower vapor pressure, the solid phosgene equivalent, triphosgene, was used to perform the solution polymerizations as it is safer than phosgene derivatives. The reported synthetic approach is an improvement over a previous melt-polymerization method¹² and is significant for two reasons. First, the initial incorporation of 5-ASA into poly(anhydrides-esters) and poly(anhydrides-amides) via melt condensation polymerization required six steps, whereas the approach outlined herein requires half as many reactions, thereby being more efficient. Second, polymers obtained via melt condensation exhibited no measurable glass transition temperatures and were found to be largely insoluble in low-boiling organic solvents, leading to difficulties in subsequent polymer processing. In contrast, the solution polymerization method reported herein generates higher molecular weight polymers with measurable glass transition temperatures and enhanced solubilities in organic solvents, thereby producing more processable materials.

5-ASA was chosen because of its success in treating colonic diseases such as inflammatory bowel disease,^{13–15} Crohn's disease,^{16,17} and ulcerative colitis.^{12,13,18} For colitis therapies, 5-ASA is conjugated to sulfapyridine to form sulfasalazine; although the sulfasalazine increases absorption by the small intestine, the sulfapyridine byproduct is responsible for the majority of side effects. In addition to treating colonic diseases, the antioxidant activity of 5-ASA has been associated with a variety of metabolic activities: enhancement of histamine activity,¹⁹ inhibition of T-cell proliferation,²⁰ lipoxygenase synthesis,^{21,22} and a potential scavenger of oxygen-derived free radicals.²³ 5-ASA has also been used for the inhibition of colonic aberrant tumors²⁴ and dermatological treatments.²⁵

Because of its broad medical utility, several research groups have been actively pursuing synthesis of 5-ASA derivatives as well as 5-ASA related polymers. Several groups have appended 5-ASA onto methacrylate polymers,^{26–30} acrylate hydrogels,³¹ polysaccharides,^{32–35} and dendrimers.³⁶ Alternately, 5-ASA has been directly incorporated into the backbones of polyanhydrides,^{12,37} polyamides,^{17,38} and polyurethanes^{39,40} to increase the 5-ASA bioavailability.

In this article, linear alkyl chains of various lengths were introduced onto the amino groups of 5-ASA to generate different derivatives that were subsequently polymerized by solution polymerization. The impact of alkyl chain length of the amine protecting group on the physical and chemical properties of the resulting polymers was investigated using various analytical methods. In addition, this article investigates the effect of linker length on the properties of the resulting 5-ASA-containing polymers.

EXPERIMENTAL

Materials

All reagents and solvents were purchased from Aldrich (Milwaukee, WI). Methylene chloride was purified by using a solvent purification system from Solv-Tek (Berryville, VA), and triethylamine was distilled over CaH_2 . All other reagents or solvents were used without further purification.

Characterization

^1H NMR measurements were performed on a Varian 200- or 300-MHz instrument (Palo Alto, CA). Samples (5–10 mg) were dissolved in deuterated dimethyl sulfoxide ($\text{DMSO}-d_6$), with the solvent used as an internal standard. AVATAR 360 FTIR from Thermo Nicolet (Shelton, CT) was used for recording the IR spectra of samples solvent-cast onto NaCl plates. Elemental analyses were provided by QTI (White-house, NJ). Mass spectra were obtained on a LC/MS Finnigan LCQ DUO from Thermo Quest (San Jose, CA).

Weight-average molecular weights (M_w 's) and polydispersity indices were determined by gel permeation chromatography on a Waters (Milford, MA) liquid chromatography system, equipped with a 410 differential refractometer, a 510 HPLC pump, and an ISS 200 auto-sampler (Perkin Elmer). Polystyrene standards ($M_w = 184,000, 43,000, 5,000$ Da) from Polymer Standard Service-USA (Warwick, RI) and Polymer Laboratories (Shropshire, UK) were used for calibration. Millenium (version 3.20) software from Waters was used for data collection and processing. The solvent mixture of dimethyl formamide (DMF; 99.9%) and trifluoroacetic acid (0.1%) was used as eluent for analysis at a flow rate of 0.8 mL/min. Polymers (5 mg/1 mL) were dissolved in this solvent system and filtered through 0.45 μm poly(tetrafluoroethylene) from Whatman (Clifton, NJ) syringe filters.

Thermal gravimetric analysis (TGA) was performed using a Perkin Elmer system (Norwalk, CT) with TGA 7 analyzer and TAC 7/DX instrument controllers. Dynamic mechanical

analysis (DMA) was performed using Perkin Elmer system (Norwalk, CT) with TGA 7 analyzer and DMA 7e instrument controllers. Perkin Elmer software for TGA and DMA was used for data collection and processing on Dell OptiPlex GX110 computer. For TGA, samples (~5 mg) were heated at a heating rate of 10 °C/min under dry nitrogen gas. Decomposition temperatures were determined as the onset of decomposition. For DMA, either prepared pellets (~30 mg) or film was heated at a heating rate of 10 °C/min under helium gas. Glass transition temperatures (T_g 's) were determined as the onset of storage modulus transition using DMA. Melting points were measured on Melt Temp from laboratory Devices (Cambridge, MA) with heating rate of 10 °C/min. Qualitative solubilities in CH_2Cl_2 were determined visually by dissolving polymers (100 mg) in a test tube at room temperature for 5 min and classified as turbid or clear. Sessile contact angle measurements were repeatedly made on polymers (~30 mg) solution-cast from methylene chloride on glass cover slips on a model 100 goniometer, Ramé-Hart (Mountain Lakes, NJ).

Synthesis of Amidosalicylate Derivatives (2)

For all amidosalicylate derivatives, similar synthetic procedures were used for each acyl chloride (i.e., butyryl chloride, nonanoyl chloride, and lauryl chloride). For example, compound (**1**) (40 mmol) was dissolved in pyridine (400 mmol) at room temperature. Then, butyryl chloride (44 mmol) was added slowly in the neat state and the solution heated to reflux temperatures for 3 h. After cooling to room temperature, the reaction mixture was poured into 3 N HCl solution (200 mL). The formed precipitates were filtered, washed with 3 N HCl solution (3×300 mL), and dried under vacuum to yield solid.

5-Butanamidosalicylic Acid (2a)—Yield: 69% (beige powder). ^1H NMR ($\text{DMSO}-d_6$): δ (ppm) 9.85 (s, 1H, ArNH), 8.10 (s, 1H, ArH), 7.65 (d, 1H, ArH, $J = 8.0$ Hz), 6.90 (d, 1H, ArH, $J = 8.0$ Hz), 2.25 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 0.90 (b, 3H, CH_3). IR (NaCl, cm^{-1}): 3280–2660 (NH, OH, COOH), 1680 (C=O, acid, amide I), 1530 (amide II). E_{LEM} . A_{NAL} . Cald.: C, 59.19; H, 5.87; N, 6.27. Found: C, 58.64; H, 5.85; N, 6.04. mp: 214–215 °C.

5-Nonanamidosalicylic Acid (2b)—Yield: quantitative (beige powder). ^1H NMR ($\text{DMSO}-d_6$): δ (ppm) 9.90 (s, 1H, ArNH), 8.15 (s, 1H, ArH), 7.70 (dd, 1H, ArH, $J = 6.0, 2.0$ Hz), 6.92 (d, 1H, ArH, $J = 10.0$ Hz), 2.25 (t, 2H, CH_2 , $J = 4.0$ Hz), 1.60 (m, 2H, CH_2), 1.30 (b, 10H, CH_2), 0.85 (b, 3H, CH_3). IR (NaCl, cm^{-1}): 3280–2650 (NH, OH, COOH), 1740 (C=O, acid, amide I), 1640 (amide II). E_{LEM} . A_{NAL} . Cald.: C, 65.51; H, 7.90; N, 4.77. Found: C, 64.71; H, 7.96; N, 4.57. mp: 190–192 °C.

5-Dodecanamidosalicylic Acid (2c)—Yield: quantitative (beige powder). ^1H NMR ($\text{DMSO}-d_6$): δ (ppm) 9.85 (s, 1H, ArNH), 8.15 (s, 1H, ArH), 7.70 (dd, 1H, ArH, $J = 12.0, 4.0$ Hz), 6.95 (d, 1H, ArH, $J = 10.0$ Hz), 2.28 (t, 2H, CH_2 , $J = 8.0$ Hz), 1.60 (m, 2H, CH_2), 1.30 (b, 16H, CH_2), 0.80 (b, 3H, CH_3). IR (NaCl, cm^{-1}): 3500–2690 (NH, OH, COOH), 1690 (C=O, acid, amide I), 1640 (amide II). E_{LEM} . A_{NAL} . Cald.: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.43; H, 8.72; N, 3.82. mp: 190–192 °C.

Diacid Synthesis (3, 4)

For all diacids (**3**, **4**), similar synthetic procedures for each diacyl chloride (i.e., sebacoyl chloride or dodecanedioyl chloride) were used. For example, a slight molar excess of compound (**2a**) (8.1 mmol) was dissolved in 70 mL DMF and 25 mL pyridine at 0 °C. Then, sebacoyl chloride (3.7 mmol) was added slowly in the neat state and continuously stirred at 0 °C for 4 h (except (**3c**), which was heated to 80 °C for 4 h). The reaction mixture was poured into 3 N HCl solution (200 mL) and the remaining solid removed by filtration. Solid

was washed with 3 N HCl solution (3 × 300 mL) and recrystallized with hexane/ethyl acetate (7:3) to purify the solid.

1,10-Bis-5-butanamidosalicyl-sebacate (3a)—Yield: 66% (white crystals). ¹H NMR (DMSO-*d*₆): δ (ppm) 10.10 (s, 2H, ArNH), 8.20 (s, 2H, ArH), 7.85 (d, 2H, ArH, *J* = 10.0 Hz), 7.10 (d, 2H, ArH, *J* = 10.0 Hz), 2.55 (t, 4H, CH₂), 2.30 (t, 4H, CH₂, *J* = 6.0 Hz), 1.70 (b, 8H, CH₂), 1.40 (b, 8H, CH₂), 0.90 (t, 6H, CH₃, *J* = 6.0 Hz). IR (NaCl, cm⁻¹): 3380–2690 (COOH), 3320 (NH), 1770 (C=O, ester), 1690 (C=O, amide I), 1650 (amide II). MS (M + Na⁺) *m/z* Calcd. for C₃₂H₄₀O₁₀N₂Na 635.7, Found 635.3; *T*_d = 214 °C, mp: 154–156 °C.

1,10-Bis-5-nonanlamidosalicyl-sebacate (3b)—Yield: 84% (white powder). ¹H NMR (DMSO-*d*₆): δ (ppm) 10.12 (s, 2H, ArNH), 8.15 (s, 2H, ArH), 7.85 (d, 2H, ArH, *J* = 10.0 Hz), 7.15 (d, 2H, ArH, *J* = 8.0 Hz), 2.55 (t, 4H, CH₂), 2.25 (m, 4H, CH₂), 1.60 (m, 8H, CH₂), 1.30 (m, 28H, CH₂), 0.85 (b, 6H, CH₃). IR (NaCl, cm⁻¹): 3310–2670 (COOH), 3310 (NH), 1760 (C=O, ester), 1720 (C=O, amide I), 1650 (amide II). MS (M + Na⁺) *m/z* Calcd. for C₄₂H₆₀O₁₀N₂Na 775.9, Found 775.6; *T*_d = 215 °C, mp: 154–156 °C.

1,10-Bis-5-dodecanamidosalicyl-sebacate (3c)—Yield: 45% (pink solid). ¹H NMR (DMSO-*d*₆): δ (ppm) 9.80 (s, 2H, ArNH), 8.10 (s, 2H, ArH), 7.65 (d, 2H, ArH, *J* = 12.0 Hz), 6.90 (d, 2H, ArH, *J* = 10.0 Hz), 2.55 (t, 4H, CH₂), 2.25 (t, 4H, CH₂), 1.60 (m, 8H, CH₂), 1.30 (m, 40H, CH₂), 0.90 (t, 6H, CH₃, *J* = 10.0 Hz). IR (NaCl, cm⁻¹): 3200–3000 (COOH), 3270 (NH), 1750 (C=O, ester), 1690 (C=O, amide I), 1670 (amide II). MS (M + Na⁺) *m/z* Calcd. for C₄₈H₇₂O₁₀N₂Na 860.1, Found 859.6; *T*_d = 230 °C, mp: 168–170 °C.

1,12-Bis-5-butanamidosalicyl-dodecanoate (4a)—Yield: 67% (pink solid). ¹H NMR (DMSO-*d*₆): δ (ppm) 10.1 (s, 2H, ArNH), 8.2 (s, 2H, ArH), 7.8 (d, 2H, ArH, *J* = 7.5 Hz), 7.10 (d, 2H, ArH, *J* = 8.0 Hz), 2.5 (t, 4H, CH₂), 2.3 (t, 4H, CH₂, *J* = 5.0 Hz), 1.70 (m, 8H, CH₂), 1.30 (b, 12H, CH₂), 0.90 (t, 6H, CH₃, *J* = 5.0 Hz). IR (NaCl, cm⁻¹): 3040–2700 (COOH), 3330 (NH), 1750 (C=O, ester), 1690 (C=O, amide I), 1650 (amide II). MS (M + Na⁺) *m/z* Calcd. for C₃₄H₄₄O₁₀N₂Na 663.7, Found 663.3; *T*_d = 225 °C, mp: 174–176 °C.

1,12-Bis-5-nonanamidosalicyl-dodecanoate (4b)—Yield: 90% (gray solid). ¹H NMR (DMSO-*d*₆): δ (ppm) 10.1 (s, 2H, ArNH), 8.2 (s, 2H, ArH), 7.85 (d, 2H, ArH, *J* = 10.0 Hz), 7.10 (d, 2H, ArH, *J* = 10.0 Hz), 2.5 (t, 4H, CH₂), 2.3 (t, 4H, CH₂, *J* = 5.0 Hz), 1.70 (b, 8H, CH₂), 1.40 (b, 32H, CH₂), 0.90 (b, 6H, CH₃). IR (NaCl, cm⁻¹): 3270–2700 (COOH), 3320 (NH), 1750 (C=O, ester), 1660 (C=O, amide I), 1540 (amide II). MS (M + Na⁺) *m/z* Calcd. for C₄₄H₆₄O₁₀N₂Na 804.0, Found 803.6; *T*_d = 218 °C, mp: 164–166 °C.

1,12-Bis-5-dodecanamidosalicyl-dodecanoate (4c)—Yield: 25% (brown solid). ¹H NMR (DMSO-*d*₆): δ (ppm) 10.1 (s, 2H, ArNH), 8.2 (s, 2H, ArH), 7.85 (d, 2H, ArH, *J* = 8.0 Hz), 7.15 (d, 2H, ArH, *J* = 8.0 Hz), 2.5 (t, 4H, CH₂), 2.3 (m, 4H, CH₂), 1.70 (m, 8H, CH₂), 1.40 (b, 44H, CH₂), 0.90 (b, 6H, CH₃). IR (NaCl, cm⁻¹): 3050–2800 (COOH), 3260 (NH), 1750 (C=O, ester), 1660 (C=O, amide I), 1540 (amide II). MS (M⁺) *m/z* Calcd. for C₅₀H₇₆O₁₀N₂ 865.2, Found 865.3; *T*_d = 216 °C, mp: 152–154 °C.

Synthesis of Poly(anhydride-esters) (5, 6)

For all polymers, a solution polymerization method was used for each diacid (**3**, **4**). For example, **3a** (1.1 mmol) was dissolved in 20% (w/v) CH₂Cl₂ and triethylamine (3.3 mmol) for 1 h at 0 °C. Triphosgene (1.7 mmol) was dissolved in minimum amount of CH₂Cl₂ at 50 (w/v) and added into the reaction mixture with one drop every 4 s at 0 °C. After 1 h, the reaction was diluted with 3 N HCl solution (20 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The organic layer was washed with saturated NaCl solution (20 mL), dried over MgSO₄,

and evaporated to dryness except (**5a**, **6a**, and **6b**). For these polymers, the solvent was evaporated to dryness with a rotary evaporator and the resulting solid was ground. The polymers (**5a**, **6a**, and **6b**) were washed with 3N HCl (3×20 mL) to remove salts, filtered, and dried under vacuum oven.

Poly[1,10-bis-5-butanamidosalicylic sebacate] (5a)—Yield: 88% (orange powder). ^1H NMR ($\text{DMSO}-d_6$): δ (ppm) 10.35 (s, 2H, ArNH), 8.35 (s, 2H, ArH), 8.10 (d, 2H, ArH, $J = 10.0$ Hz), 7.25 (b, 2H, ArH), 2.50 (t, 4H, CH_2), 2.25 (b, 4H, CH_2), 1.60 (m, 8H, CH_2), 1.30 (m, 8H, CH_2), 0.90 (b, 6H, CH_3). IR (NaCl, cm^{-1}): 3400 (NH), 1750–1540 ($\text{C}=\text{O}$, anhydride, ester, and amide I,II). $T_g = 58$ °C, $T_d = 200$ °C, M_w : 57,000 Da; PDI, 1.2.

Poly[1,10-bis-5-nonanamidosalicylic sebacate] (5b)—Yield: 64 % (yellow solid). ^1H NMR ($\text{DMSO}-d_6$): δ (ppm) 10.20 (s, 2H, ArNH), 8.24 (s, 2H, ArH), 8.00 (d, 2H, ArH, $J = 15.0$ Hz), 7.20 (m, 2H, ArH), 2.50 (t, 4H, CH_2), 2.25 (b, 4H, CH_2), 1.60 (b, 8H, CH_2), 1.20 (b, 28H, CH_2) 0.8 (b, 6H, CH_3). IR (NaCl, cm^{-1}): 3300 (NH), 1810 ($\text{C}=\text{O}$ anhydride), 1770–1660 ($\text{C}=\text{O}$, anhydride, ester, and amide I), 1530 (amide II). $T_g = 83$ °C, $T_d = 191$ °C, M_w : 54,000 Da; PDI, 1.0.

Poly[1,10-bis-5-dodecanamidosalicylic sebacate] (5c)—Yield: 66% (brown solid). ^1H NMR ($\text{DMSO}-d_6$): δ (ppm) 10.10 (s, 2H, ArNH), 8.20 (s, 2H, ArH), 7.85 (d, 2H, ArH, $J = 5.0$ Hz), 7.10 (d, 2H, ArH, $J = 5.0$ Hz), 2.50 (t, 4H, CH_2), 2.25 (m, 4H, CH_2), 1.60 (m, 8H, CH_2), 1.3 (m, 40H, CH_2) 0.85 (b, 6H, CH_3). IR (NaCl, cm^{-1}): 3400 (NH), 1800–1620 ($\text{C}=\text{O}$, anhydride, ester, and amide I), 1600 (amide II). $T_g = 97$ °C, $T_d = 217$ °C, M_w : 19,000 Da; PDI, 1.1.

Poly[1,12-bis-5-butanamidosalicylic dodecanoate] (6a)—Yield: 24% (orange powder). ^1H NMR ($\text{DMSO}-d_6$): δ (ppm) 10.3 (s, 2H, ArNH), 8.4 (s, 2H, ArH), 8.1 (d, 2H, ArH, $J = 10.0$ Hz), 7.25 (b, 2H, ArH), 2.50 (t, 4H, CH_2), 2.30 (b, 4H, CH_2), 1.70 (m, 8H, CH_2), 1.30 (m, 8H, CH_2), 0.95 (b, 6H, CH_3). IR (NaCl, cm^{-1}): 3400 (NH), 1800 ($\text{C}=\text{O}$, anhydride), 1780 ($\text{C}=\text{O}$, anhydride and ester), 1680 ($\text{C}=\text{O}$, anhydride, and amide I), 1550 (amide II). $T_g = 131$ °C, $T_d = 212$ °C, M_w : 57,000 Da; PDI, 1.1.

Poly[1,12-bis-5-nonanamidosalicylic dodecanoate] (6b)—Yield: 48% (yellow solid). ^1H NMR ($\text{DMSO}-d_6$): δ (ppm) 10.3 (s, 2H, ArNH), 8.4 (s, 2H, ArH), 8.1 (d, 2H, ArH, $J = 10.0$ Hz), 7.25 (m, 2H, ArH), 2.50 (b, 4H, CH_2), 2.30 (b, 4H, CH_2), 1.7 (b, 8H, CH_2), 1.3 (b, 32H, CH_2), 0.95 (b, 6H, CH_3). IR (NaCl, cm^{-1}): 3300 (NH), 1810 ($\text{C}=\text{O}$ anhydride), 1700–1660 ($\text{C}=\text{O}$, anhydride, ester, and amide I), 1530 (amide II). $T_g = 102$ °C, $T_d = 212$ °C, M_w : 57,000 Da; PDI, 1.1.

Poly[1,12-bis-5-dodecanamidosalicylic dodecanoate] (6c)—Yield: 80% (brown solid). ^1H NMR ($\text{DMSO}-d_6$): δ (ppm) 10.35 (s, 2H, ArNH), 8.35 (s, 2H, ArH), 8.10 (d, 2H, ArH, $J = 5.0$ Hz), 7.30 (d, 2H, ArH, $J = 5.0$ Hz), 2.50 (t, 4H, CH_2), 2.20 (m, 4H, CH_2), 1.60 (m, 8H, CH_2), 1.30 (m, 44H, CH_2) 0.90 (b, 6H, CH_3). IR (NaCl, cm^{-1}): 3280 (NH), 1800 ($\text{C}=\text{O}$ anhydride), 1750–1660 ($\text{C}=\text{O}$, anhydride, ester and amide I), 1530 (amide II). $T_g = 70$ °C, $T_d = 207$ °C, M_w : 38,000 Da; PDI, 1.1.

RESULTS AND DISCUSSION

The purpose of this investigation was twofold. First, we sought to generate higher molecular weight polyanhydrides of 5-ASA using milder reaction conditions than the melt condensation previously used.¹² Second, we sought to obtain polyanhydrides of 5-ASA with enhanced solubility in organic solvents to broaden their processing ranges. In this work, we

hypothesized that enhanced solubility in organic solvents could be achieved by increasing polymer hydrophobicity through the use of linear alkyl groups as amine protecting groups, as well as by increasing the length of the linear alkyl moiety that joins the 5-ASA units within the polymer. More carbons within the alkyl chain (i.e., longer alkyl chains) should increase polymer hydrophobicity, thus resulting in increased solubility in organic solvents. Two approaches to increase hydrophobicity were investigated: (i) changing the alkyl chain length (n) between the 5-ASA units (i.e., changing the linker length) and (ii) varying the structure of the amine protecting group (R) as shown in Figure 1.

For the linkage between the 5-ASA units, alkyl chains corresponding to sebacic ($n = 8$) and dodecandioic ($n = 10$) acids were introduced. In addition, the amino group of 5-ASA was protected with linear alkyl chains forming butylamido (four carbons), nonylamido (nine carbons), and dodecylamido (12 carbons) groups (Fig. 1). These linear alkyls are based on fatty acid chains and, thus, should increase hydrophobicity and biocompatibility following polymer degradation.^{41–43} The synthetic scheme to form the various analogs of 5-ASA-containing polyanhydrides backbones are shown in Scheme 1.

The free amines were protected using previously published methods.^{44,45} Briefly, the more nucleophilic amine of 5-ASA attacks the acyl chloride in the presence of pyridine to form the more hydrolytically stable amide bond of compound **2**. Compounds **3a–3c** and **4a–4c** were easily prepared upon coupling of compound **2** with the appropriate diacyl chlorides (sebacoyl chloride and dodecanedioyl chloride) in the presence of pyridine to generate symmetrical diacids containing two 5-ASA units.

All polymers were prepared by solution polymerization, using solid triphosgene rather than diphosgene or phosgene to obtain higher molecular weights.¹¹ As shown in Table 1, polymer molecular weights ranged from 19,000 (**5c**) to 57,000 Da (**5a**, **6a**, and **6b**). Interestingly, polymers containing the longer dodecylamido groups (**5c** and **6c**) had consistently lower molecular weights than the polymers containing butylamido or nonylamido groups. These results indicate that increasing the length of the protecting group may introduce increased steric hindrance among the monomer units, leading to decreased degrees of polymerization and decreased molecular weights. However, changing the number of carbons within the linker (Table 1) had significantly less impact on molecular weight, indicating that size and flexibility of monomers with the sebacoyl linker are very similar to the monomers with the dodecacoyl linker. An experimental observation worth noting was that monomer purity, solvent purity, and a slow rate of addition of the triphosgene solution were crucial to success. When compared with the molecular weights of 5-ASA polymers formed by melt polymerization,¹² the advantage of using solution polymerization is readily apparent; aminosalicylate-based polyanhydrides synthesized via melt polymerization had typical molecular weights below 10,000 Da, whereas the molecular weights obtained by solution polymerization averaged ~47,000 Da.

In addition to enhanced molecular weight, solution polymerization produced polymers with measurable glass transition temperatures (Table 1). However, no meaningful trends between glass transition temperatures and linker length/protecting group length are evident. Although increasing protecting group length for the sebacic-linked polymers increased glass transition temperatures, the opposite effect was observed for the dodecanoic-linked polymers. Nonetheless, the reported solution polymerization method is advantageous to melt polymerization as the series of aminosalicylate-based polyanhydrides synthesized via melt polymerization exhibited no measurable glass transition temperatures.¹²

Polymer solubility in common organic solvents is desirable for processing the polymers into appropriate forms dictated by the specific application. Because of this need, qualitative

solubilities of the polymers formed via solution polymerization were established in CH_2Cl_2 . As shown in Table 1, polymer solubility in CH_2Cl_2 generally improved as the alkyl chain length of the amine protecting group increased. By comparison, lengthening the alkyl chain between the 5-ASA units did not influence the solubility properties as much as varying the amine protecting group.

Although the enhanced solubility in CH_2Cl_2 because of the lengthening of the amine protecting group could be explained by increased hydrophobicity of the polymer, water contact angle measurements are not supportive. As shown in Table 1, increasing alkyl chain length did not necessarily increase hydrophobicity. Polymers with the sebacic linker ($n = 8$) only showed increased hydrophobicity by increasing the length of the amine protecting group from four carbons to nine carbons. Further increasing protecting group length to 12 carbons had no effect on hydrophobicity. However, for polymers with the dodecanoic ($n = 10$) linker, the hydrophobicities did not significantly change as the amine protecting group was lengthened.

CONCLUSIONS

5-ASA was incorporated into poly(anhydride-esters) backbones by solution polymerization methods to yield polymers with good solubility in low boiling organic solvents and higher molecular weights than polymers prepared by melt condensation polymerization. Moreover, polymers were prepared by varying the alkyl lengths between 5-ASA units and modifying the alkyl chain protecting groups of the amine. Variations in protecting group length influenced polymer properties such as solubility, molecular weights, and, in some cases, hydrophobicity. Generally, introduction of shorter alkyl chain as protecting groups increased molecular weights, yet decreased solubility. In contrast, longer alkyl protecting groups exhibited lower molecular weight and better solubility in lower boiling organic solvents.

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FIGURE 1.

General chemical structure of 5-ASA polyanhydrides where $n = 8$ for **5** and $n = 10$ for **6**.

SCHEME 1.
Synthesis of 5-ASA polyanhydrides.

TABLE 1

Properties of 5-ASA Polyanyhydrides

Polymers	#C: Linker	#C: Protecting Group	M_w (Da)	T_g (°C)	Contact Angle (°)	Solubility in CH_2Cl_2^a
5a	10	4	57,000	58	65	–
5b	10	9	54,000	83	89	+
5c	10	12	19,000	97	82	+
6a	12	4	57,000	131	81	–
6b	12	9	57,000	102	85	–
6c	12	12	38,000	70	88	++

^a ++very soluble, + soluble, – insoluble.