Synthesis of a novel poly(anhydride-ester)

Michael L. Beaton* and Kathryn Uhrich
Department of Chemistry and Chemical Biology, Rutgers University,
610 Taylor Road, Piscataway, New Jersey 08854-8087

*Rutgers Undergraduate Research Fellow

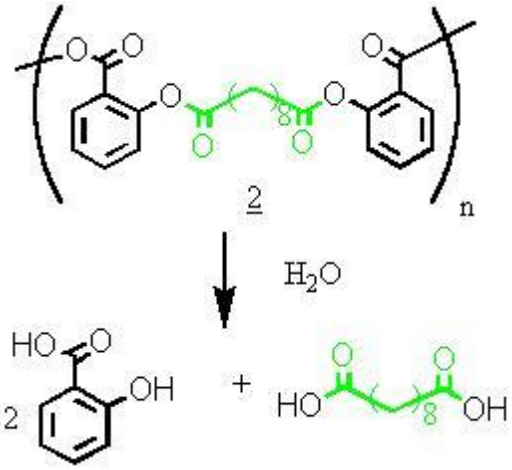
Keywords: polymer, poly(anhydride-ester), aminosalicylate

Abstract

A poly(anhydride-ester) containing 4-benzamidosalicylic acid was synthesized by melt-condensation polymerization. The polymer and its intermediates were characterized by NMR and IR spectroscopies, gel permeation chromatography, differential scanning calorimetry, and thermogravimetric analysis. The polymer had an average molecular weight of 3700, a glass transition temperature (T_g) of 103°C, and a thermal decomposition temperature (T_d) of nearly 400°C.

Background

Hydrolysis of acetylsalicylic acid, (a.k.a., aspirin) generates salicylic acid (1), an anti-inflammatory analgesic. Similarly, poly(anhydride-ester) (2), upon hydrolytic degradation, releases salicylic acid (1) and another biocompatible product, sebacic acid (3).



salicylic acid 1 — sebacic acid 3

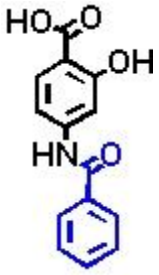
The release of salicylic acid in this fashion opens up the possibility of using poly(anhydride-esters) as controlled drug delivery systems, especially as an alternative to aspirin. Aspirin taken orally is rapidly metabolized in the stomach to salicylic acid. However, unlike aspirin, polymer 2 hydrolyzes most rapidly in a basic

environment [1]. These degradation characteristics are appropriate for site-specific release of salicylic acid into a patient's lower intestine, where the environment is typically more basic (pH ~ 8).

Other applications for poly(anhydride-esters) include their use as dental implants or tissue scaffolds. Upon degradation, the polymers reduce inflammation and promote new tissue growth. Preliminary studies have shown that poly(anhydride-ester) (2) stimulates new bone formation in vivo [2].

Methods

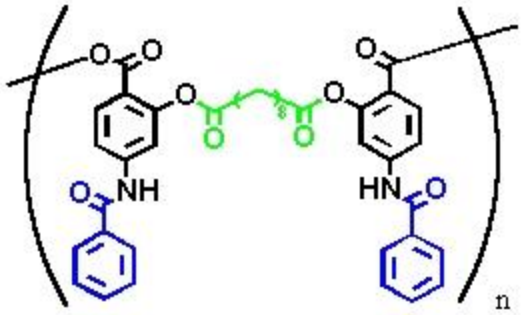
Our research aims at developing a series of related polymers, each of which degrades into therapeutic compounds. Specifically, we have designed and synthesized a polymer that contains 4-benzamidosalicylic acid (4).



4-benzamidosalicylic acid
4

4-Benzamidosalicylic acid (4) reacts with water to form 4-aminosalicylic acid, which is used to treat tuberculosis and also exhibits anti-inflammatory properties [3].

Two different methods were employed for the synthesis of (5), a polymer that should hydrolyze into 4-benzamidosalicylic acid (4).



5

A one-step procedure for the formation of an important intermediate from 4 was

used in Method A, while Method B used a protection/deprotection route to arrive at the same intermediate.

Synthesis

4-Aminosalicylic acid (4-ASA) (6) (48.9 g, 319 mmol) was dissolved in 200 mL distilled tetrahydrofuran (THF) and 25 mL pyridine. The solution was cooled in an external ice/water bath to approximately 5°C and with stirring, benzoyl chloride (7) (74.1 mL, 738 mmol) was added dropwise over the course of 30 minutes. After stirring 2 hours at room temperature, the solution was added to water made basic (pH 12) with NaOH for a total volume of 1000 mL. The solution was stirred for 2 hours at room temperature, acidified with HCl (pH 2), and the solid collected by vacuum filtration. Solid was recrystallized in ethanol/water (2:1 vol:vol) and left to form crystals overnight at room temperature. Crystals were vacuum filtered and washed once with water. After drying, 4-benzamido salicylic acid (4-ASA-Bz) (4) (45.3g, 55 % yield) was collected as white needles with the following properties.

- melting point: 251-252°C (lit. 253°C) [4]
- ^{1}H NMR (DMSO-d_6): 10.45 (s, 1H, N-H), 7.95 (d, 2H, Ar-H), 7.80 (d, 1H, Ar-H), 7.60 (m, 4H, Ar-H), 7.35 (d, 1H, Ar-H).
- IR (neat, cm^{-1}): 3399 (N-H), 1675 (C=O), 1638 (C=O).

4-ASA-Bz (4) (8.50 g, 33.0 mmol) was dissolved in 150 mL DMF and sodium bicarbonate (5.55 g, 66.1 mmol). With stirring, benzyl bromide (10) (19.5 mL, 165 mmol) in 150 mL DMF was added dropwise over the course of 1.5 hours. After 18 hours at room temperature, the solution was gently heated to ~60°C for 1 hour. In two portions, the solution was added to 200 mL water and then extracted with 2 x 100 mL ethyl acetate. The ethyl acetate fractions were combined and washed once with 30 mL water, then dried over magnesium sulfate. Ethyl acetate was removed by rotary evaporation to yield a dark brown oil. The oil was washed repeatedly with hexanes until a sandy product formed, which was vacuum filtered, and washed with hexanes to yield benzyl-4-benzamide salicylic acid (Bn-4-ASA-Bz) (11) (8.94g, 78% yield) as a tan solid with the following properties.

- melting point: 160-161°C.
- ^{1}H NMR (DMSO-d_6): 10.65 (s, 1H, O-H), 10.55 (s, 1-H, N-H), 7.95 (d, 2H, Ar-H), 7.80 (d, 1H, Ar-H), 7.50 (m, 10H, Ar-H), 5.40 (s, 2H, CH_2).
- IR (neat, cm^{-1}): 3376 (N-H), 1666 (C=O).

Bn-4-ASA-Bz (11) (3.2 g, 9.2 mmol) was dissolved in 150 mL distilled THF and cooled to approximately 5°C in an external ice/water bath. With stirring, 60% sodium hydride (0.36 g, 9.2 mmol) was added over the course of 5 minutes. The solution was allowed to cool, then sebacoyl chloride (8) (1.2 mL, 5.5 mmol) was added dropwise over the course of 1 hour. After 12 hours at room temperature, the solution was heated to reflux temperature for 3.5 hours. The solution was gravity filtered to remove NaCl and the THF was removed by rotary evaporation to yield a pink solid.

The solid was washed with ethyl acetate and vacuum filtered. (Bn-4-ASA-Bz)2SA (2.9 g, 74% yield) (12) was collected as a white solid.

- melting point: 175-178°C.
- ^{1}H NMR (DMSO-d_6): 10.90 (s, 2H, N-H), 8.05 (d, 4H, Ar-H), 7.90 (d, 2H, Ar-H), 7.50 (m, 20H, Ar-H), 5.30 (s, 2H, CH_2), 2.40 (m, 4H, CH_2), 1.55 (m, 4H, CH_2), 1.30 (s, 8H, CH_2).
- IR (neat, cm-1): 3358 (N-H), 1753 (C=O), 1694 (C=O), 1664 (C=O).

(Bn-4-ASA-Bz)$_2$SA (12) (2.83 g, 3.29 mmol) was added to 180 mL bulk THF and the solution was heated to 50°C until the solid was completely dissolved. The solution was cooled to room temperature and 10% Pd/C catalyst (0.90 g, excess) was added. Hydrogen gas was bubbled into solution while stirring. After 2.5 hours the solution was filtered through a glass filter with a 1 cm layer of celite, and washed once with warm methanol (~20 ml). Solvent was removed by rotary evaporation to give (4-ASA-Bz)$_2$SA (9) (2.20g, 99% yield) as a white powder.

- melting point: 184.5-185.0°C.
- ^{1}H NMR (DMSO-d_6): 10.65 (s, 2H, N-H), 8.00 (m, 6H, Ar-H), 7.80 (m, 4H, Ar-H), 7.60 (m, 6H, Ar-H), 2.60 (m, 4H, CH_2), 1.70 (m, 4H, CH_2), 1.40 (s, 8H, CH_2).
- IR (neat, cm^{-1}): 3331 (N-H), 1765 (C=O), 1742 (C=O), 1681 (C=O).

(4-ASA-Bz)$_2$SA (9) (1.15 g, 1.69 mmol) was combined with 100 mL acetic anhydride and heated to reflux temperature (149 °C) under nitrogen for 1 hour. The solution was cooled to room temperature upon which a precipitate formed after 1 hour. The solution was further cooled to 0 °C, then vacuum filtered to yield Ac-(4-ASA-Bz)$_2$SA (13) (0.78 g, 60% yield) as a white powder.

- melting point: 117-119°C.
- ^{1}H NMR (DMSO-d_6): 10.80 (s, 2H, N-H), 8.00 (m, 6H, Ar-H), 7.80 (m, 4H, Ar-H), 7.60 (m, 6H, Ar-H), 2.65 (m, 4H, CH_2), 2.25 (s, 6H, CH_3) 1.70 (m, 4H, CH_2), 1.40 (s, 8H, CH_2).
- IR (neat, cm^{-1}): 3343 (N-H), 1795 (C=O), 1760 (C=O), 1729 (C=O).

Ac-(4-ASA-Bz)$_2$SA (13) (0.78 g, 1.0 mmol) was polymerized by melt condensation. The solid was placed in a one-armed test tube and heated with stirring at 180°C under vacuum (2 mm Hg) for 1 hour. Upon cooling, poly[(4-ASA-Bz)$_2$SA] (5) (0.48g, 71% yield) was collected as a rock-hard, glassy brown solid.

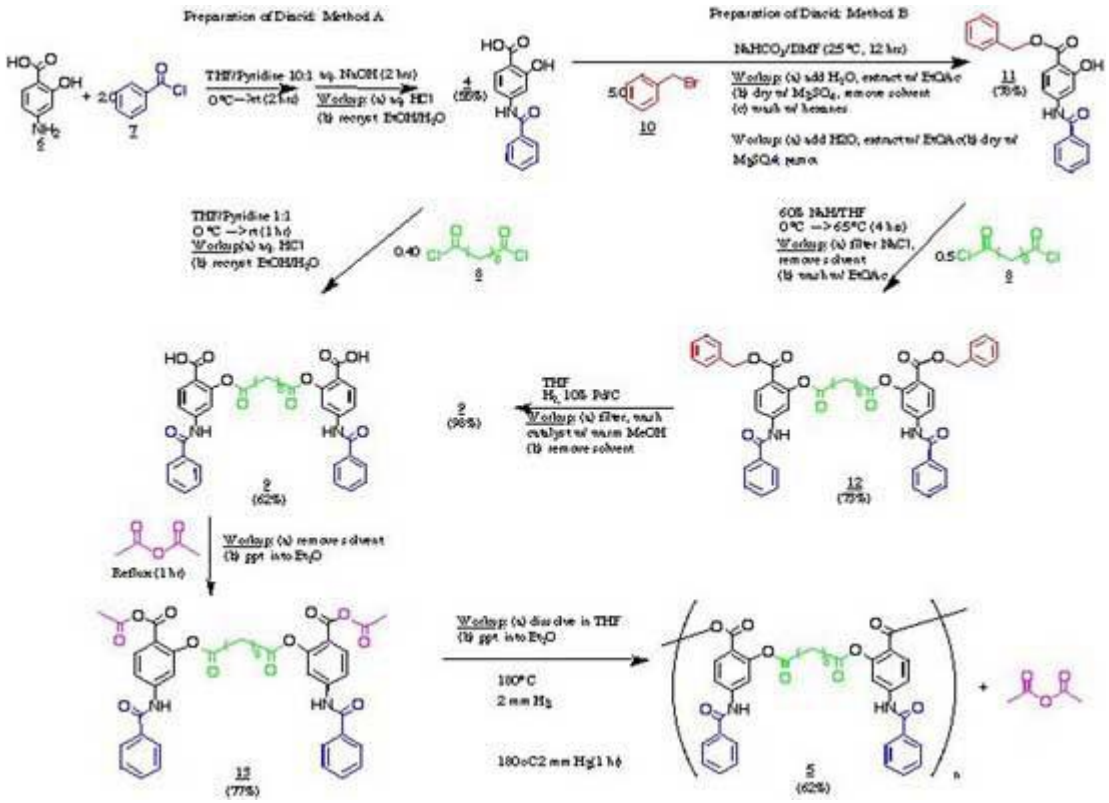
- ^{1}H NMR (DMSO-d_6): 10.80 (b, 2H, N-H), 8.00 (b, 10H, Ar-H), 7.60 (b, 6H, Ar-H), 2.55 (b, 4H, CH_2), 1.60 (b, 4H, CH_2), 1.30 (b, 8H, CH_2).
- IR (neat, cm^{-1}): 3353 (N-H), 1771 (C=O).

Alternate method for the formation of the diacid:

4-ASA-Bz (4) (5.07 g, 19.7 mmol) was dissolved in THF:pyridine (40 mL:35 mL). The solution was cooled in an external ice/water bath and sebacoyl chloride (8) (2.00 mL, 9.38 mmol) in 5 mL THF was added dropwise over the course of 15 minutes. After stirring at room temperature for 2.5 hours, the solution was poured over ice and acidified with HCl/water to pH 2. The solid was collected by vacuum filtration and washed once with hexanes/ethyl acetate (2:1 vol:vol) to give (4-ASA-Bz)$_2$SA (9) (4.51g, 71% yield) as a white solid with a melting point of 175-176°C.

Results and discussion

Two different synthetic routes were explored to give a polymer (5) containing 4-benzamidosalicylic acid (4). The synthetic route for the preparation of diacid 9 gave an overall yield of 16%, whereas Method B gave an overall yield of 15%. Because Method A contains fewer synthetic steps, this approach is advised in future work. However, reaction of 4 with 8 gave a wide range of yields (30% to 70%) of 9. Both procedures are outlined in the following figure.



Conclusions

A poly(anhydride-ester) containing 4-benzamidosalicylic acid was sucessfully synthesized. Future studies will evaluate the degradation characteristics in acidic, neutral, and basic aqueous media.

Acknowledgments

MLB would like to thank Theodore Anastasiou and Robert Schmeltzer for their guidance.

References

[1] Erdmann, L. and Uhrich, K.E. Synthesis and degradation characteristics of salicylic acid-derived poly(anhydride-esters). Biomaterials 2000; 21: 1941-1946.

[2] Erdmann, L., Macedo, B. and Uhrich, K.E. Degradable poly(anhydride ester) implants: effects of localized salicylic acid release on bone. Biomaterials 2000; 21: 2507-2512.

[3] Schreiber, S., Howaldt, S., Raedler, A. Oral 4-aminosalicylic acid versus 5-aminosalcylic acid slow release tablets. Double blind, controlled pilot study in the mainenance treatment of Crohn's ileocolitis. Gut 1994; 35: 1081-1085.

[4] Drain, D.J., Martin, D.D., Mitchell, B.W., Seymour, D.E. and Spring, F.S. 4-Aminosalicylic Acid and Its Derivatives. J. Amer. Chem. Soc. 1949; 1498-1503.