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The synthesis, characterization and antibacterial activity of quaternized poly(2,6-dimethyl-1,4-phenylene oxide)s modified with ammonium and phosphonium salts

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ABSTRACT

A new class of antimicrobial polymers consisting of PPO (polyphenylene oxide) was synthesized, and the antimicrobial activities of these polymers were investigated. This was accomplished by selective α-bromination of PPO (BPPO) followed by quaternization reactions with various tertiary amines or phosphines. Two types of BPPO were prepared, and the antimicrobial activities of the quaternized polymers were tested against Gram-positive bacteria (*S. Epidermidis*) and Gram-negative bacteria (*Escherichia. coli*). The triphenylphosphonium-modified polymer showed excellent antibacterial activity against both types of bacteria. Generally, the thermal stability of phosphonium-modified BPPO was superior to that of the ammonium analog, and the increase in the functionalization of the polymer backbone resulted in improved antimicrobial activity.

1. Introduction

Nosocomial, or hospital-acquired, infection is a serious global public-health issue. The sterilization procedure in hospitals generally involves application of heat, chemicals, irradiation, high pressure or filtration. However, these conventional ways of hospital sterilization can alter the chemical structure and physical properties of materials and reduce equipment lifetime. There is a keen interest in materials capable of killing or preventing micro organisms. The previous approach to making materials bactericidal is to blend or coat materials with antibacterial agents such as antibiotics, silver ions, fluoroquinolones and quaternary ammonium compounds, but these antibacterial agents are gradually released over time [1]. Recent studies have focused on the non-release strategy for creating a permanent antibacterial effect, and various methods have been used to synthesize polymers with antimicrobial activity [2–5]. Besides the biguanide-containing polymers, which are known to exhibit intrinsic antibacterial activities [6,7], most polymers possessing biocides in their pendant groups are synthesized from the polymerization of acrylate [8–13], styrene [14–17], or norbornene [18,19] monomers. Immobilization of the antibacterial moiety through chemical anchoring by post-polymerization modification has also been applied in copolymer systems such as vinylbenzyl chloride cross-linked with 2-chloroethyl vinyl ether (CEVE) or with methylmethacrylate (MMA), poly(ethylene-co-vinyl alcohol) and poly(styrene-co-maleic anhydride) [20–27]. The antibacterial moieties in polymers include antibiotics, organotin, *N*-halamines, silver ions and various types of quaternary ammonium and phosphonium salts. Compared with conventional antibacterial agents of low molecular weight, polymeric antibacterial agents have advantages such as non-volatilization, inability to permeate the skin and reduced toxicity to the environment. Moreover, cationic polymers with quaternary ammonium or biguanide groups generally exhibit higher antimicrobial activities than the corresponding low-molecular-weight model compounds because of the much higher charge density carried by the polycations, which can initiate stronger interactions with the negatively charged bacterial cell surfaces [28,7,29].

Despite extensive research efforts, most of the resulting copolymers consist of an ethylene backbone, whereas only a few non-ethylene main chain skeletons, such as cellulose [30], chitosan [31–35], polysiloxanes [36,37] or polyamide [38] have been reported and little work has been conducted on their thermal stability. Poly(phenylene oxide) (PPO), also known as poly(phenylene ether) (PPE), is one of the most important engineering plastics and is widely used in electrical appliances due to their balanced physical, chemical and electrical properties. Because PPO is also a nontoxic, Food and Drug Administration (FDA) compliant material and readily available from the commercial market, it is of great interest to develop these non-ethylene-backbone polymers, which

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lead to new antimicrobial materials with applications for which known polymers are unsuitable. In this study, a series of quaternary ammonium- and phosphonium-modified PPOs were synthesized, and the objective of the present study is to explore how this structural modification of the PPO polymer will influence material properties such as thermal stability and the antibacterial properties against Gram-positive and Gram-negative bacteria.

2. Experimental

2.1. Materials

All reagents and solvents were of reagent grade. Poly(2,6-dimethyl-1,4-phenylene oxide) (intrinsic viscosity = 0.4×10^{-3} $m^3\ kg^{-1}$, i.e., 0.4 dL g^{-1}) in chloroform at 25 °C was obtained from General Electric Plastics and purified before use by precipitation from a chloroform solution into methanol. *N*-Bromosuccinimide (NBS; Acros), 2,2′-azobisisobutyronitrile (AIBN; Showa), triphenylphosphine (PPh_3; Lancaster), triethylamine (TEA; RDH), tributylamine (TBA; Acros), dimethylsulfoxide (DMSO; Sigma), triethylenediamine (TEDA; Sigma), tributylphosphine (PBu_3; Kanto), toluene, chlorobenzene, diethyl ether, chloroform, *n*-hexane (all from Tedia), tetrahydrofuran (THF; J.T. Baker), Peptone (AMRESCO), beef extract (MP Biomedicals), LB broth (Lab M Limited) and agar (CONDA) were purchased from commercial companies and used as received.

2.2. Characterization

^{1}H spectra were recorded on a 300-MHz Varian–Mercury$^+$300 spectrometer using deuterated solvent. Gel permeation chromatography (GPC) was carried out with polymer solutions in THF. Thermogravimetric analysis (TGA) was performed with a TGA Q50 (TA Instruments) thermogravimetric analyzer under a nitrogen atmosphere. Samples (10–15 mg) were placed in platinum pans and put in an oven at 30 °C. The temperature was raised from 30 to 105 °C at 10 °C/min, maintained for 20 min, and raised to 800 °C under nitrogen. Degradation temperature at 5% weight loss was measured ($T_{d5\%}$) and the char yield (Char %) at 800 °C was recorded on TGA.

2.3. Synthesis

2.3.1. Synthesis of methyl-brominated poly(2,6-dimethyl-1,4-phenylene oxide) (BPPO)

NBS (4.70 g, 26.6 mmol) and AIBN (0.20 g, 1.2 mmol) were added to a stirred solution of 4.80 g of PPO in chlorobenzene (200 mL). The mixture was stirred under refluxing conditions for 4 h, and the reaction mixture was added to a ten-fold excess of *n*-hexane to precipitate the product. After filtration and washing with methanol, the polymer was dissolved in chloroform and re-precipitated in a methanol solution. The polymer was collected as a light-yellow powder and dried under vacuum overnight (BPPO-1: 5.80 g, yield: 92%, bromination ratio: 46.4%). ^{1}H NMR ($CDCl_3$, δ ppm): Ar-C**H**$_3$ (2.08 ppm, s, 9H), Ar-C**H**$_2$-Br (4.34 ppm, s, 2H), Ar-**H** of a PPO repeat unit (6.47 ppm, s, 2H), Ar-**H** of a bromomethylated PPO unit (6.5–6.7 ppm, m, 2H).

Using the same procedure, 2.84 g (10 mmol) of NBS and 0.2 g (1.2 mmol) of AIBN gave BPPO-2 (5.40 g, yield: 91%, bromination ratio: 24.8%).

2.3.2. Synthesis of the triethylammonium salt of PPO (TEA-PPO)

TEA (0.64 g) was added to a stirred solution of BPPO-1 (0.52 g) in 15 mL of THF and 5 mL of MeOH. The mixture was stirred for 16 h at reflux temperature, and the reaction mixture was added to a sixfold excess of diethyl ether. The product was filtered, washed several times with diethyl ether, and dried under a vacuum at room temperature to give 0.49 g of 1. (TEA-PPO-1, ammonium salt ratio: 35.8%, yield: 83.2%). ^{1}H-NMR: Ar-C**H**$_3$ (2.02 ppm, s, 9H), Ar-**H** of a non-substituted PPO unit (6.51 ppm, s, 2H), Ar-**H** of a PPO unit with an ammonium-salt pendant group (7.10 ppm, m, 2H), Ar-C**H**$_2$-N$^+$-(CH_2CH_3)$_3$ (4.24 ppm, m, 2H), Ar-CH_2-N$^+$-(C**H**$_2$$CH_3$)$_3$ (3.16 ppm, m, 6H), Ar-CH_2-N$^+$-(CH_2C**H**$_3$)$_3$ (1.10 ppm, m, 9H). ^{13}C NMR (75 MHz, DMSO-d_6, δ (ppm)): 155.5, 146.4, 133.5, 123.5, 115.5, 53.0, 40.2, 17.4, 8.6.

A similar procedure was used for all polymers 2–10, except that the type and quantity of the quaternization reagent were different.

2: BPPO-2 (0.51 g) and TEA (0.48 g) were used. (TEA-PPO-2, 0.36 g, yield: 69.6%, ammonium salt ratio: 19.8%).

2.3.3. Synthesis of the tributylammonium salt of PPO (TBA-PPO)

3: BPPO-1 (0.51 g) and TBA (1.16 g) were used. (TBA-PPO-1, 0.50 g, yield: 64.6%, ammonium salt ratio: 44.9%). ^{1}H-NMR of TBA-PPO (Acetone-d_6, δ ppm): Ar-C**H**$_3$ (2.02 ppm, s, 9H), Ar-**H** of a non-substituted PPO unit (6.51 ppm, s, 2H), Ar-**H** of a PPO unit with an ammonium-salt pendant group (7.10 ppm, m, 2H), Ar-C**H**$_2$-N$^+$-($CH_2CH_2CH_2CH_3$)$_3$ (4.32 ppm, m, 2H), Ar-CH_2-N$^+$-(C**H**$_2$$CH_2CH_2CH_3$)$_3$ (3.11 ppm, m, 6H), Ar-CH_2-N$^+$-(CH_2C**H**$_2$$CH_2CH_3$)$_3$ (1.57 ppm, m, 6H), Ar-CH_2-N$^+$-(CH_2CH_2C**H**$_2$$CH_3$)$_3$ (1.22 ppm, m, 6H), Ar-CH_2-N$^+$-($CH_2CH_2CH_2$C**H**$_3$)$_3$ (0.88 ppm, m, 9H). ^{13}C NMR (75 MHz, Acetone-d_6, δ (ppm)): 155.5, 148.3, 146.3, 133.1, 125.5, 115.1, 59.8, 25.2, 20.4, 16.7, 13.9.

4: BPPO-2 (0.52 g) and TBA (0.88 g) were used. (TBA-PPO-2, 0.47 g, yield: 78.4%, ammonium salt ratio: 21.4%).

2.3.4. Synthesis of the triethylenediamine ammonium salt of PPO (TEDA-PPO)

5: BPPO-1 (0.52 g) and TEDA (0.77 g) were used. (TEDA-PPO-1, 0.43 g, yield: 66.6%, ammonium salt ratio: 36.9%). ^{1}H-NMR of TEDA-PPO (DMSO-d_6, δ ppm): Ar-C**H**$_3$ (2.02 ppm, s, 9H), Ar-**H** of a non-substituted PPO unit (6.51 ppm, s, 2H), Ar-**H** of a PPO unit with an ammonium-salt pendant group (6.96 ppm, m, 2H), Ar-C**H**$_2$-N$^+$-(CH_2CH_2)$_3$–N (4.32 ppm, m, 2H), Ar-CH_2-N$^+$-(C**H**$_2$$CH_2$)$_3$–N and Ar-$CH_2$-N$^+$-($CH_2$C**H**$_2$)$_3$–N (3.15 ppm, m, two peaks overlapped, 12H). ^{13}C NMR (75 MHz, DMSO-d_6, δ (ppm)): 154.2, 146.8, 144.1, 133.8, 132.2, 122.2, 114.5, 62.9, 51.8, 44.8, 16.44.

6: BPPO-2 (0.51 g) and TEDA (0.40 g) were used. (TEDA-PPO-2, 0.50 g, yield: 85.9%, ammonium salt ratio: 21.4%).

2.3.5. Synthesis of the triphentlphosphonium salts of PPO (PPh_3-PPO)

7: BPPO-1 (0.52 g) and PPh_3 (1.23 g) were used in 40 mL of methanol solution. (PPh_3-PPO-1, 0.70 g, yield: 87.2%, phosphonium salt ratio: 45.5%). ^{1}H-NMR of PPh_3-PPO (DMSO-d_6, δ ppm): Ar-C**H**$_3$ (2.02 ppm, s, 9H), Ar-**H** of a non-substituted PPO unit (6.51 ppm, s, 2H), Ar-**H** of a PPO unit with a phosphonium-salt pendant group (6.23 ppm, m, 2H), Ar-C**H**$_2$-P$^+$-Ph_3 (4.84 ppm, m, 2H), Ar-CH_2-P$^+$-**Ph**$_3$ (7.65–7.86 ppm, m, 15H). ^{13}C NMR (75 MHz, DMSO-d_6, δ (ppm)): 155.3, 146.3, 136.0, 134.8, 133.1, 131.1, 123.3, 119.1, 117.9, 115.4, 24.6, 16.3.

8: BPPO-2 (0.52 g) and PPh_3 (0.93 g) were used in 40 mL of methanol solution. (PPh_3-PPO-2, 0.64 g, yield: 97.6%, phosphonium salt ratio: 20.9%).

2.3.6. Synthesis of the tributylphosphonium salts of PPO (PBu_3-PPO)

9: BPPO-1 (0.51 g) and PPh_3 (0.93 g) were used in 15 mL THF and 5 mL MeOH solution. (PBu_3-PPO-1, 0.42 g, yield: 58.0%, phosphonium salt ratio: 40.2%). ^{1}H-NMR of PBu_3-PPO-1 (DMSO-d_6, ppm): Ar-C**H**$_3$ (2.02 ppm, s, 9H), Ar-**H** of a non-substituted PPO unit (6.51 ppm, s, 2H), Ar-**H** of a PPO unit with an ammonium-salt pendant group (6.82 ppm, m, 2H), Ar-C**H**$_2$-P$^+$-($CH_2CH_2CH_2CH_3$)$_3$ (3.58 ppm, m, 2H), Ar-CH_2-P$^+$-(C**H**$_2$$CH_2CH_2CH_3$)$_3$ (2.15 ppm, m,