



Synthesis of ammonium bisphosphonate monomers and polymers



N. Hu, L.M. Johnson, Nikorn Pothayee, Nipon Pothayee, Y. Lin, R.M. Davis, J.S. Riffle*

Macromolecules and Interfaces Institute, Virginia Tech, Blacksburg, VA 24061, USA

ARTICLE INFO

Article history:

Received 28 February 2013

Received in revised form

11 April 2013

Accepted 13 April 2013

Available online 19 April 2013

Keywords:

Polyphosphonate

Polyelectrolyte

Bisphosphonate

ABSTRACT

Ammonium bisdiethylphosphonate acrylate and methacrylate monomers were synthesized by an aza-Michael addition of 3-aminopropanol across the double bond of bisdiethylphosphonate, followed by acylation with (meth)acryloyl chloride. Free radical copolymerizations of the monomers with an acrylate-functional poly(ethylene oxide) (PEO) macromonomer produced graft copolymers. Quantitative deprotection of the alkylphosphonate groups, then adjustment of the pH to 7.74 ± 0.03 , yielded graft copolymers with zwitterionic ammonium bisphosphonate backbones and PEO grafts. Copolymerization kinetic studies showed that the ammonium bisdiethylphosphonate methacrylate incorporated into the copolymers with PEO-acrylate well, but that the corresponding acrylate monomer reacted too slowly. The zwitterionic copolymers spontaneously assembled into aggregates in aqueous media.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

Phosphorus-containing polymers have been widely investigated as flame retardants, adhesion promoters, components of dental resins, and as substrates for binding calcium or calcium phosphates [1–10]. Polymers containing phosphate and phosphonate pendent groups are of interest for potential orthopedic and dental applications. Stancu et al. [5] investigated copolymers of methacryloyloxyethyl phosphate with (2-diethylamino)ethyl methacrylate and found enhanced calcium-binding capacity with increasing amounts of the phosphate-containing monomer. Mineralization of such substrates with calcium phosphates, however, was complicated and did not correlate well with calcium binding. Phosphoric and phosphonic acid-bearing polymers have been studied as potential components of dental adhesives and resins, where their acidity can etch tooth enamel to increase adhesion of filler materials [6,7]. Chougrani et al. [8,9] reported a series of *N,N*-bis(methylene diphosphonate) methacrylate monomers as precursors for polymers that promote adhesion. Moszner et al. [6,10] synthesized phosphonic acid-containing (meth)acrylamides and novel acrylic ether phosphonic acids for potential self-etching dental adhesives with increased hydrolytic stability over phosphorus-containing methacrylates.

Only a few investigations of block copolymers containing phosphonic acids and PEO have been carried out. Penczek et al. prepared PEO–polyglycidol diblock copolymers that were post-

modified with phosphonates and carboxylates on the same pendent carbon [11]. This group also modified PEO–polyglycidol block copolymers with phosphate groups and showed that they could mediate crystallization of calcium carbonate [12]. Hollow spheres with hybrid calcium carbonate–polymer compositions comprised of layers of smaller spheres were formed with these materials.

Self-assembly of phosphonate- and phosphate-containing monomers and polymers have been reported [13–15]. Francová and Kicelbick [16,17] synthesized methacrylate-functional amphiphiles with alkyl spacers terminated with phosphonate and phosphate groups that formed micelles in water, then crosslinked the micelles in UV- or thermally initiated free radical polymerizations. Dynamic light scattering (DLS) measurements showed a distribution of spheres ranging from 30 to 400 nm in diameter. Tew and Eren [18] prepared polyoxanorbornene copolymers where one block had pendent phosphonic acids and the other was relatively hydrophobic. A series of these materials had mean hydrodynamic radii ranging from 123 to 301 nm as measured by DLS.

This paper focuses on synthesis of ammonium bisdiethylphosphonate acrylates and methacrylates and their copolymerization with acrylate-functional PEO macromonomers to yield poly(ammonium bisdiethylphosphonate (meth)acrylate)-*g*-PEO copolymers. Subsequent removal of the ethyl groups on the phosphonates produced zwitterionic poly(ammonium bisphosphonate (meth)acrylate)-*g*-PEO copolymers. The properties of these copolymers in aqueous media are of interest because of their potential utility as components of drug delivery and bioimaging vehicles.

* Corresponding author.

E-mail address: judyriffle@aol.com (J.S. Riffle).

2. Experimental

2.1. Materials

Diethyl vinylphosphonate (Epsilon-Chimie, >98%) and dichloromethane (EMD Chemicals, anhydrous, 99.8%) were used as received. Methanol (99.9%), hexane (99.9%), dichloromethane (99.9%), chloroform (99.9%), magnesium sulfate (anhydrous, 98%), diethyl ether (anhydrous, 99.8%) and dialysis tubing (Spectra/Por, 3500 MWCO), all from Fisher Scientific, were used as received. *N,N*-Dimethylformamide (DMF, anhydrous, 99.8%), methanol (anhydrous, 99.8%), sodium sulfate (anhydrous, 99%), 3-ammonium-1-propanol (>99%), triethylamine (>99.5%), sodium hydroxide (97%), poly(ethylene oxide) methyl ether ($M_n = 5085$ and 2100 g mol^{-1}), 2,2'-azobisisobutyronitrile (AIBN, 98%), sodium chloride (>99.5%) and benzoylated cellulose dialysis tubing (2100 MWCO) were purchased from Sigma–Aldrich and used as received. Acryloyl chloride (97%), methacryloyl chloride (97%) and bromotrimethylsilane (TMSBr, 97.0%) were fractionally distilled before use.

2.2. Synthesis

2.2.1. Synthesis of hydroxypropyl ammonium bisdiethylphosphonate

3-Aminopropanol (8.0 g, 0.11 mol), diethyl vinylphosphonate (36.0 g, 0.22 mol) and 200 mL of deionized water were charged to a 500-mL round-bottom flask with a magnetic stir bar and sealed with a septum. The reaction was placed in an oil bath and maintained at 60 °C for 24 h. The reaction mixture was extracted with dichloromethane (5 × 80 mL) at room temperature. The combined organic phase was washed with deionized water (2 × 25 mL), dried over anhydrous magnesium sulfate, then the solvent was evaporated to afford 3-hydroxypropyl ammonium bisdiethylphosphonate (**1**, 41 g, 95%).

2.2.2. Synthesis of an ammonium bisdiethylphosphonate acrylate monomer

1 (15 g, 37 mmol), triethylamine (4.1 g, 41 mmol), and 70 mL of anhydrous dichloromethane were charged to a flame-dried, 250-mL round-bottom flask equipped with a septum-sealed dropping funnel and placed in an ice bath. Acryloyl chloride (3.7 g, 41 mmol) was added dropwise. The flask was removed from the ice bath and the reaction was stirred for 4 h at room temperature. The reaction mixture was washed with aq 0.1 N sodium hydroxide (3 × 150 mL) and the organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated and the product (**2**, 11.4 g, 65%) was dried under vacuum at room temperature overnight.

2.2.3. Synthesis of an ammonium bisdiethylphosphonate methacrylate monomer

The ammonium bisdiethylphosphonate methacrylate monomer **3** (9.1 g, 78%) was synthesized in a similar manner to the analogous acrylate monomer using **1** (10.0 g, 25 mmol), triethylamine (2.9 g, 29 mmol), methacryloyl chloride (2.6 g, 29 mmol) and 50 mL of anhydrous dichloromethane. The monomer was dissolved in dichloromethane (18.2 mL) and stored in the refrigerator.

2.2.4. Synthesis of acrylate-functional PEO

Poly(ethylene oxide) methyl ether (25 g, $M_n = 5085 \text{ g mol}^{-1}$, 4.9 mmol) was dried under vacuum at 50 °C overnight in a flame-dried 250-mL round-bottom flask. Triethylamine (2.53 g, 25 mmol) and 70 mL of anhydrous dichloromethane were charged to the flask via syringe. Acryloyl chloride (2.3 g, 25 mmol) was added dropwise to the flask via syringe. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with chloroform and washed 3 × 150 mL with an aqueous solution of sodium

hydroxide (0.1 N). The organic phase was washed with water (2 × 100 mL), dried over anhydrous magnesium sulfate and concentrated by evaporation. The concentrated mixture was precipitated in hexane, filtered and dried under vacuum at room temperature to afford a pale yellow PEO-acrylate powder.

2.2.5. Synthesis of a 67:33 wt:wt poly(ammonium bisdiethylphosphonate methacrylate)-g-PEO copolymer

Dichloromethane in the ammonium bisdiethylphosphonate methacrylate monomer solution was removed by rotary evaporation. The monomer **3** (4.3 g, 9.1 mmol) was transferred to a flame-dried, 25-mL Schlenk flask equipped with a stir bar. An acrylate-PEO (2.15 g, 0.42 mmol) solution in degassed DMF (7 mL) was prepared in a 20-mL vial. AIBN (0.15 g, 0.9 mmol) was dissolved in degassed DMF (5 mL) in a separate 20-mL vial. The acrylate-PEO solution and 1 mL of the freshly prepared AIBN solution in DMF were added to the Schlenk flask via syringe. After three freeze–pump–thaw cycles, the reaction mixture was heated at 70 °C for 7 h. The copolymer was precipitated in a cold mixture of 1:1 v:v anhydrous diethyl ether:hexane (2 × 400 mL). The resulting copolymer (**4**) was vacuum dried at room temperature overnight.

2.3. Deprotection of the 67:33 poly(ammonium bisdiethylphosphonate methacrylate)-g-PEO copolymer

A flame-dried, round-bottom flask equipped with a stir bar was charged with dry poly(ammonium bisdiethylphosphonate methacrylate)-g-PEO (1.53 g, 8 meq of phosphonate), TMSBr (1.87 g, 12 mmol) and 10 mL of anhydrous dichloromethane. The reaction was stirred at room temperature for 15 h. Dichloromethane and the excess TMSBr were removed by rotary evaporation at 75 °C and the copolymer was dried under vacuum at room temperature for 1.5 h. Anhydrous methanol (10 mL) was added to the flask via syringe. After 12 h the reaction mixture was precipitated in cold ether (200 mL) and filtered. The copolymer was dissolved in 20 mL of methanol, transferred into 2100 MWCO benzoylated cellulose dialysis tubing and dialyzed against 2 L methanol for 48 h. The solution was freeze-dried to obtain the poly(ammonium bisphosphonic acid)-g-PEO (**6**).

2.4. Kinetic studies of copolymerization

A poly(ammonium bisdiethylphosphonate acrylate)-g-PEO copolymer was synthesized as described above and aliquots were removed at known time intervals during the reaction. The copolymer samples were precipitated in a cold mixture of 1:1 v:v anhydrous diethyl ether:hexane (2 × 100 mL) to remove the unreacted ammonium bisdiethylphosphonate acrylate monomer. The yellow solid was dissolved in THF, transferred to 3500 MWCO dialysis tubing and dialyzed against 4 L of DI water for 48 h to remove unreacted acrylate-PEO.

Copolymers comprised of the ammonium bisdiethylphosphonate methacrylate monomer with the acrylate-PEO were prepared. Samples were taken at known time intervals during the reaction. Monomer conversions and copolymer compositions were measured by ^1H NMR.

2.5. Characterization

^1H NMR spectral analyses were performed on a Varian Unity 400 NMR, a JEOL Eclipse Plus 500 NMR or a Bruker Avance II-500 NMR operating at 399.95 MHz, 500 MHz or 500 MHz, respectively. ^{31}P NMR spectral analyses were obtained on a Varian Inova 400 NMR operating at 161.91 MHz. Parameters utilized for the ^{31}P NMR were a 45° pulse and 1 s relaxation delay with 128 scans. All spectra of

Download English Version:

<https://daneshyari.com/en/article/5182224>

Download Persian Version:

<https://daneshyari.com/article/5182224>

[Daneshyari.com](https://daneshyari.com)