Polymer Communication

Synthesis of a novel pH-responding polymer with pendant barbituric acid moieties

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Abstract

A simple method for the synthesis of pH-responding polymers containing barbituric acid moieties is described. The synthesis involves N-methyl-N'-(4-vinylbenzyl) urea (**2**) preparation and its polymerization in DMF using AIBN as the initiator to give poly(N-methyl-N'-(4-vinylbenzyl)urea) (**4**) with a number average molecular weight of 4.9×10^5 as determined by GPC. Cyclocondensation of urea with malonic acid in acetic acid/acetic anhydride affords the polymer (**5**) with pendant barbituric moieties. The pH-responding behavior of polymer **5** in water indicates that it has excellent pH-sensitivity at pH $6 \sim 7$. The potential and the versatility of this work are exciting and include the potential preparation of water-soluble polymers by modification of polyureas, metal chelating materials, and "smart" hydrogels upon crosslinking. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: pH-responding polymer; Poly(barbituric acid); Polyureas

1. Introduction

Polymers responsive to solvent composition [1,2], pH [1–4], electric fields [5,6], and temperature [4,7–13] are being utilized for potential applications in chemical or mechanical engineering systems such as chemical valves [14], shape memory [15,16], as well as biomedical applications including artificial organs [17] and drug delivery systems [11,18–20]. Among them, pH-sensitive polymers have attracted much attention due to their wide range of potential applications. For example, Peppas et al. [4] reported the synthesis and characterization of a pH-responding hydrogel for which the pH dependent swelling cycle can be repeated for several times by incorporation of carboxylic acid groups into the gel network. Osada et al. [21] recently synthesized a novel water-soluble polymer containing carboxylic acids with a conjugated rigid polythiophene main chain and their results indicate these polymers undergo abrupt conformational changes upon pH changes. Carboxylic acid groups were also incorporated into polypeptide membranes to control the water permeation rate [22].

Barbituric acid has a lower pk_a (4.0) than a carboxylic acid ($pk_a \sim 4.8$). Thus, the barbituric acid moiety can be deprotonated at a lower pH than a carboxylic acid and possibly lead a phase transition of the polymer. Interest in and

technological demand for external stimuli-responding polymers led us to explore the synthesis of novel pH-responding polymers [23–26] and we report here the synthesis of a novel polymer with pendant barbituric acid moieties (Scheme 1) and its reversible phase transition upon pH changes. To the best of our knowledge, polymers containing barbituric acids have not been reported. The low pk_a of barbituric acid may give the resulting polymer interesting features, for example metal chelation in acidic media.

2. Experimental

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a QE-300 instrument (General Electric, NMR-Instruments, Freemont CA) in CDCl$_3$/DMSO-d_6 using TMS as internal standard. Fourier transform infrared spectroscopy (FTIR) measurements were performed on a Galaxy 3000 FTIR (Mattson, Madison, WI) using KBr disks at a resolution of 2 cm^{-1}. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60F$_{254}$ (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany).

The molecular weight characteristics of homopolymer **4** was investigated by gel permeation chromatography (GPC) on a Varian-9002 liquid chromatography equipped with refractive index detector (RI-4) by Polymer Sources, Inc. A Supelco Column TSK-GEL G5000 was used, employing

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DMF as the eluent with a flow rate of 1.0 ml/min at 40°C. Molecular weight was calculated using polystyrene as the standard.

4-Vinylbenzylisocyanate (1). Compound **1** was prepared as described earlier [27].

N-Methyl-N′-(4-vinylbenzyl) urea (2). A 25 ml, one-necked, round-bottomed flask was equipped with a magnetic stir bar and charged with 5 ml of 40% methylamine aqueous solution (1.80 g, 58.1 mmol). The solution was cooled to 0°C in an ice bath while stirring for ca. 30 min. Isocyanate **1** (1.21 g, 7.6 mmol) was added, and the ice-cooled reaction mixture was vigorously stirred for 16 h. After this time, some white solid which was formed during the reaction was filtered and the collected solid was vacuum dried at 50°C. The crude urea product was purified by silica gel chromatography (100% EtOAc) to afford 1.08 g of **2** as a white solid (81%), mp 132.5–133.5°C; TLC (EtOAc) R_f 0.45; ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 2.72 (d, $J = 4.8$ Hz, 3H), 4.30 (d, $J = 5.7$ Hz, 2H), 4.65 (b, 1H), 5.00 (b, 1H), 5.22 (d, $J = 10.9$ Hz, 1H), 5.71 (d, $J = 17.6$ Hz, 1H), 6.68 (dd, $J = 17.6$, 10.9 Hz, 1H), 7.22 (d, $J = 7.8$ Hz, 2H), 7.34 (d, $J = 7.8$ Hz, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ(ppm) 27.24, 44.36, 44.39, 113.78, 126.47, 127.64, 136.41, 138.83, 158.86. IR (KBr disk): 3352, 3044, 2938, 1625, 1423, 1267, 992, 907, 826 cm^{-1}. Anal. Calcd for C$_{11}$H$_{14}$N$_2$O: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.42; H, 7.43; N, 14.69.

1-Methyl-3-(4-vinylbenzyl)barbituric acid (3). Urea **2** (47.6 mg, 0.27 mmol) and malonic acid (28.2 mg, 0.27 mmol) were dissolved in 1 ml of acetic acid under N$_2$ in a 5 ml flask fitted with a reflux condenser and a magnetic stir bar. Acetic anhydride (0.1 ml) was added through a syringe while the reaction temperature was kept at 65°C for 30 min. The temperature was then raised to 90°C for 4 h at which time the solvent was removed under vacuum. Preparative TLC was used to isolate the desired compound (**3**) as a yellow solid. TLC (EtOAc:hexane:AcOH = 30:70:1) R_f 0.39. ^{1}H NMR (300 MHz, CDCl$_3$): δ(ppm) 3.30 (s, 3H), 3.70 (s, 2H), 5.03 (s, 2H), 5.25 (d, $J = 10.9$ Hz, 1H), 5.73 (d, $J = 17.6$ Hz, 1H), 6.69 (dd, $J = 17.6$, 10.9 Hz, 1H), 7.36 (d, $J = 8.3$ Hz, 2H), 7.41 (d, $J = 8.3$ Hz, 2H).

Poly(N-methyl-N′-(4-vinylbenzyl) urea) (4). Under an inert N$_2$ atmosphere, a 25 ml, two-necked, round-bottomed reaction flask was charged with 13 ml of degassed DMF (freeze/pump/thaw cycles) and a small magnetic stir bar. Monomer **2** (0.76 g, 4.31 mmol) was added to make a solution and the flask was placed in a oil bath at 70°C. After thermal equilibrium had been reached, AIBN (6.5 mg, 0.04 mmol) was added to the mixture. After 48 h, the flask was removed from the oil bath, DMF was partially removed under vacuum, and resulting solution was precipitated in ethyl acetate, washed and dried under reduced pressure to constant weight. A white polymer material (**4**) was obtained (0.46 g, 60%). GPC measurement showed that polymer **4** had a number average molecular weight (M_n) of 4.9×10^5, a weight-average molecular weight (M_w) of 1.2×10^7 and a

high molecular weight polydispersity ($M_w/M_n = 24$). ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 6.93 (brd, ArH, 2H), 6.40 (brd, ArH, 2H), 5.94 (brd, NHCO, 1H), 4.12 (brd, ØCH$_2$–, 2H), 2.57 (brd, CH$_3$, 3H), 1.10–1.71 (brd, CH$_2$CHØ). IR (KBr disk): 3359 (brd), 3016, 2921, 1638, 1568, 1267 cm^{-1}.

Polymer (**5**) [28]. Polymers with different barbituric moiety contents were synthesized by varying the ratio of urea to malonic acid. A typical procedure is as follows: into a 10 ml round bottom flask was added polyurea **4** (0.25 g, 4.9 mmol of urea functionality), malonic acid (0.17 g, 5.8 mmol), and 3.5 ml of acetic acid. The solution was stirred at 65°C for 1 h during the time 3.5 ml of acetic anhydride was added. The reaction mixture was raised to 90°C for 2 days at which time the reaction mixture was cooled to room temperature and then precipitated in methanol, washed and dried under reduced pressure to constant weight. Polymer **5** was obtained as an amorphous yellow powder (0.31 g). Polymer **5** had a number average molecular weight of 3.1×10^7, a weight-average molecular weight of 1.25×10^8 and a low molecular weight polydispersity ($M_w/M_n = 4.0$). ^{1}H NMR (300 MHz, DMSO-d_6): δ(ppm) 7.00 (brd, ArH), 6.40 (brd, ArH), 4.83 (brd, $\varnothing$CH$_2$–), 3.76 (brd, COCH$_2$CO), 3.09 (brd, NCH$_3$), 1.10–1.71 (brd, CH$_2$CH$\varnothing$). IR (KBr disk): 3446, 2923, 1679, 1569, 1422 cm^{-1}.

pH-Responding studies. Polymer **5** (22.5 mg) was mixed with 3.47 ml of deionized water in a 4 ml UV cuvette charged with a small magnetic stir bar. Aqueous HCl and NaOH solutions (0.5, 2.0, and 4.0 N) were used to adjust the pH of the mixture and pH was measured using a pH meter (Orion 310). The absorbency of the solution was acquired on a HITACHI U-2000 spectrophotometer at a wavelength of 500 nm. Polymer **6** was isolated as a yellow powder by precipitation in methanol after adjusting the pH to 7. IR (KBr disk): 3431, 2923, 2855, 1617, 1423, 786 cm^{-1}.

Thermal studies. Differential scanning calorimetry (DSC) (Shimadzu, DSC-50) was performed at a heating rate of 10°C/min in nitrogen atmosphere using crimped aluminum pans. Measurement of the glass transition temperatures were carried out with a sample weight of ca. 5 mg. The sample was first heated from room temperature to 140°C, followed by cooling to room temperature in the DSC cell, and then equilibrated at room temperature for 10 min. The sample was then re-scanned and the midpoint of specific heat increment in the second scan was taken as the glass transition of these polymers.

Thermal stability studies of the dry gel samples were performed using a thermogravimetric analyzer (TGA) (TGA-50, SHIMADZU, Japan) with a sample weight of ~5 mg. The temperature range in these experiments encompassed 25–600°C at a heating rate of 20°C/min using a dry nitrogen purge at a flow rate of 30 ml/min. The degradation temperature (T_{deg}), defined as the point of intersection of the tangents, in the thermogram was taken.
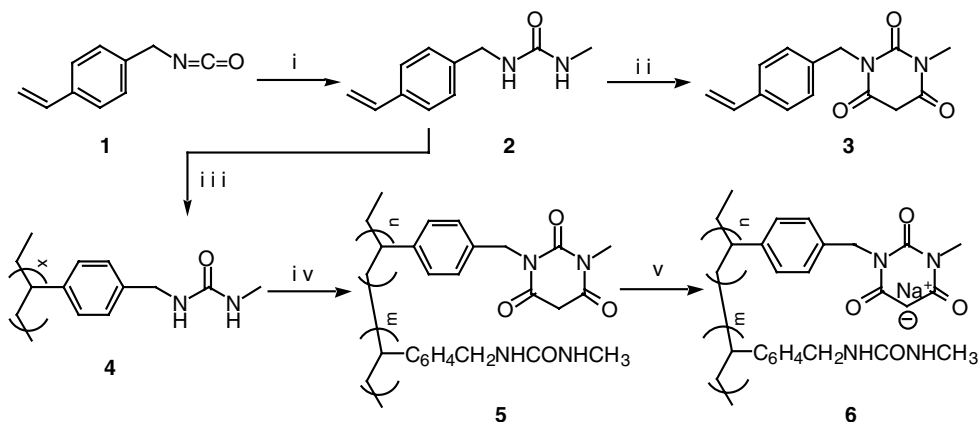
Scheme 1. Reagents and conditions: (1) CH_3NH_2, H_2O, 0°C, 16 h. (ii) $CH_2(COOH)_2$, $AcOH/Ac_2O$, 65°C, 30 min; then 90°C, 4 h. (iii) AIBN, DMF, 70°C, 48 h. (iv) $CH_2(COOH)_2$, $AcOH/Ac_2O$, 65°C, 1 h; the 90°C, 48 h. (v) H_2O, NaOH.

3. Results and discussion

We recently synthesized a new isocyanate monomer (**1**) under mild conditions in 90% yield from 4-vinylbenzyl chloride [27]. Reaction of **1** with methylamine aqueous solution at 0°C affords monomer urea **2** in 81% as a white powder after silica flash chromatography. ^{1}H NMR spectra of **2** clearly shows two broad protons (NHCONH) at 4.65 and 5.00 ppm and the methylene ($\varnothing CH_2N$) and methyl (NCH_3) protons at 2.72 and 4.30 ppm, respectively, as doublets. Barbituric acid (**3**) can be synthesized from urea (**2**) by reaction with malonic acid using acetic anhydride as the dehydration reagent [28]. Reaction indeed taken place and barbituric acid **3** could be isolated on preparative TLC on a small scale. ^{1}H NMR spectra of **3** token immediately after the TLC indicates the methylene ($\varnothing CH_2N$, 2.72 ppm) and methyl (NCH_3, 4.30 ppm) protons of **2** were shifted to 3.30 and 5.03 ppm, respectively, upon barbituric formation. In addition, a new singlet at 3.70 ppm (2H) was assigned as the methlyene protons (COCH_2CO) from the barbituric moiety. Unfortunately, we were unable to separate monomer **3** on a large scale by normal silica chromatography since barbituric acid is a known photoinitiator [29]. The formed barbituric acid (**3**) could initiate polymerization by an intermolecular addition.

Thus, another approach to polymers with pendant barbituric moieties was attempted by polymerization of urea **2** first and subsequent cyclocondensation of the urea moiety with malonic acid to give the desired polymer. Polymerization of urea **2** in DMF at 70°C using AIBN as the initiator led to polymer **4** in 60% yield as a white powder. GPC analysis showed that the resulting polymer has a number average molecular weight of 4.9×10^5 with a high molecular weight polydispersity ($M_w/M_n = 24$) (Fig. 1) and a glass transition temperature of 143°C as determined by DSC. Reaction of **4** with malonic acid in acetic acid/acetic anhydride mixture at 90°C led to polymer **5**. The success of **4** → **5** was confirmed by ^{1}H NMR, IR, and weight gain analysis. ^{1}H NMR of polymer **5** shows the methyl protons

(NCH_3) at 3.09 ppm, the benzylic methylene protons ($\varnothing CH_2-$) at 4.83 ppm, and the acidic methylene protons (COCH_2CO) at 3.76 ppm, respectively. Integration of the corresponding peaks indicates that about 89% of the urea moieties were transformed into barbituric derivatives with a reaction ratio of 1:1.2 (urea/malonic acid). Polymer **5** has a number average molecular weight of 3.1×10^7, a weight-average molecular weight of 1.25×10^8 with a molecular weight polydispersity of 4.0. The high molecular weight of polymer **5** indicates that barbituric moiety formation indeed causes polymer branching (Fig. 1). Polymer **5** has a T_g of 147°C. The higher T_g of polymer **5** compared to polymer **4** is because the cyclic barbituric moieties are rigid and the samples are above the critical molecular weight for all T_g measurement, even after removing the urea hydrogen bonding.

Thermal stabilities of polymers **4** and **5** are illustrated in Fig. 2. All of the samples were heated at a steady rate as weight loss was monitored. Clearly, TGA thermograms of polymer **4** showed a two-step decomposition in flowing N_2. The onset of the first thermal decomposition was at 231°C and the second decomposition was at 415°C. The first stage decomposition is due to the urea moieties and the second stage decomposition is due to the polystyrene backbone, which is consistent with our pervious results [30]. On the other hand, TGA thermograms of polymer **5** under N_2 at a heating rate of 20°C/min showed one major decomposition at 338°C due to the low weight percent of the urea moiety in polymer **5**.

The pH-responding behavior of polymer **5** in water was investigated under different pH conditions as adjusted with aqueous HCl or NaOH solutions. We first dissolved **5** in basic aqueous condition and measured the absorption using a spectrometer at a wavelength of 500 nm. Fig. 3 shows one cycle of the pH dependence of the absorption of polymer **5** in water at room temperature in the pH range of 1–13. The absorption of polymer **5** in water was significantly affected by pH. For example, at high pH (>7.0), the polymer was a transparent solution with a yellow color; at
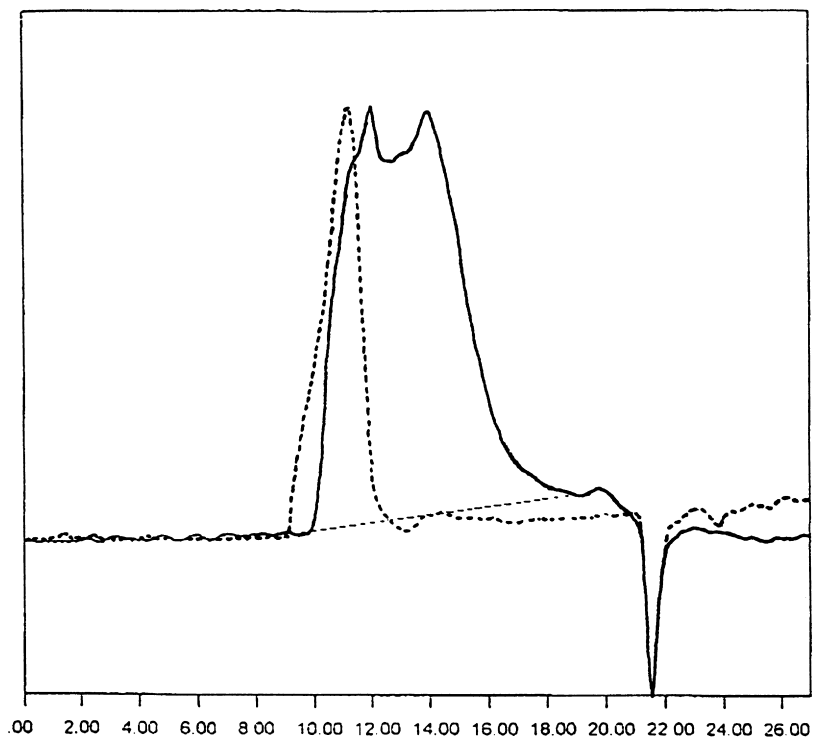
Fig. 1. Gel permeation chromatography chart of polymer **4** (—), and polymer **5** (···).

low pH (<5.8), the polymer was precipitated as a orange materials and the solution became opaque. The transition pH is about 6–7 for polymer **5** prepared with a reactant ratio of 1:1.2 (urea:malonic acid) with only a small difference between low to high pH and high to low pH directions. The absorption curves shown in Fig. 3 can be repeated for several cycles. That the absorption-pH transition is higher than 4 ($pK_a = 4$) might be due to urea which was not completely transformed into barbituric acid derivatives and/or to electron delocalization of the barbituric moiety and formation of aromatic heterocycles leading to a specific polyelectrolyte. Representative resonance structures of barbituric derivatives (**6**) on depronation leading to aromatic heterocycles is shown in Scheme 2. IR spectra support electron delocalization since polymer **5** has a strong absorption at 1679 cm^{-1} while polymer **6** has a strong absorption at 1617 cm^{-1}. Polymer **6**, with more potential chelating sites and low electron density due to electron delocalization, may find interesting applications in chelating heavy metal ions
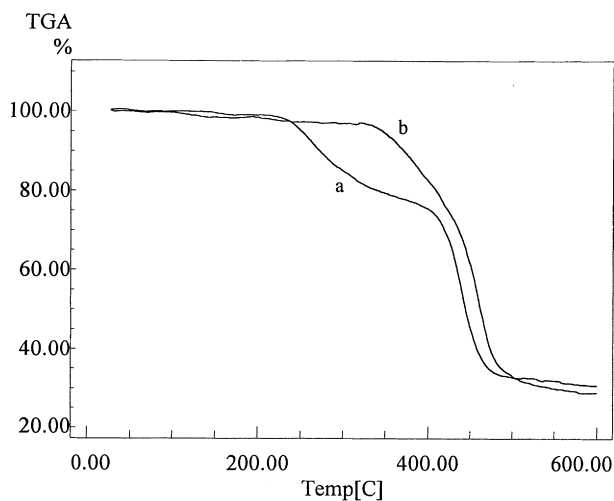

Fig. 2. Thermogravimetric curve for:0 (a) polymer (**4**); (b) polymer (**5**) at a heating rate of 20°C/min under N$_2$.
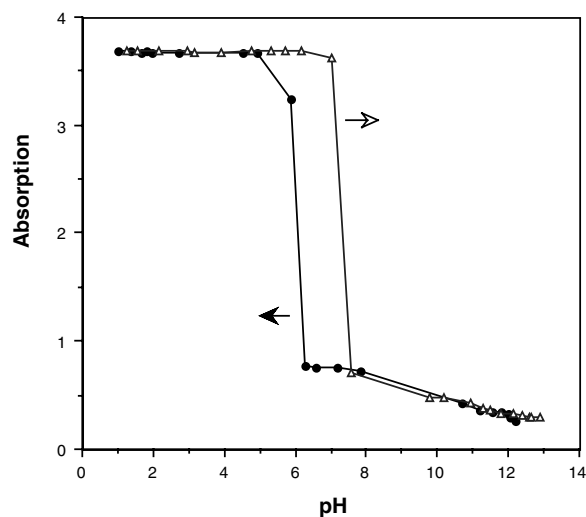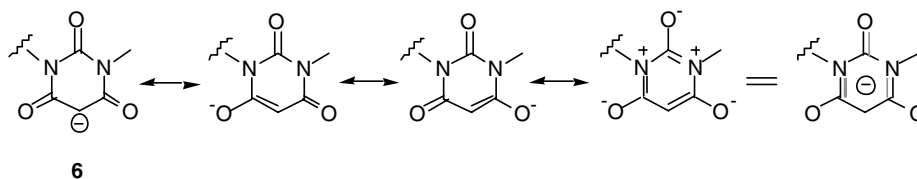

Fig. 3. The pH dependent absorption of polymer (**5**) at 500 nm in water at room temperature in the pH range of 1–13. (X) absorption measured by adjusting the pH from 13 to 1; (K) absorption measured by adjusting the pH from 1 to 13.

Scheme 2.

(Hg^{2+}, Ag$^+$ etc.). Other analogs of **5** prepared with a higher urea/malonic acid ratio (>1:1.2) afford polymers with similar properties as discussed above while a lower urea/malonic acid ratio (1:0.8 or 1:0.5) led to insoluble polymers in a variety of solvents, possibly due to crosslinking.

In summary, a synthetic pathway for the synthesis of pH-responding polymer with pendant barbituric moieties has been developed. The potential and the versatility of this work are encouraging and suggest that attempts can be made to synthesize water-soluble polymers by modification of polyureas, metal chelating materials, and "smart" hydrogels upon crosslinking.

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