Polymer Journal, Vol. 33, No. 9, pp 704—707 (2001)

NOTES

Preparation of New Polymer from 18β-Glycyrrhetintic Acid Derivative

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(Received April 12, 2001; Accepted June 21, 2001)

KEY WORDS 18β-Glycyrrhetintic Acid (GA) / 18β-Acrylglycyrrhetintic Acid (AGA) / Homo- and Co-Polymerization /

In recent years, many research efforts have been devoted to the development of polymeric materials with natural compound (Example: Bile Acid) used in biomedical and pharmaceutical fields.[1–7] Since these polymers contain natural compound skeleton, they may overcome the shortcomings of the pure synthetic materials and have better biological compatibility and acceptability.

Glycyrrhetintic acid (GA) is pentacyclic triterpenoid prepared from ammonium glycyrrizate which was isolated and prepared from liquoric root (*Glycyrrhiza uralensis* Fisch., *G. inflata* Bat. and *G. glabra* L.). It is the mixtures of 18α- and 18β-glycyrrhetintic acid. 18α−glycyrrhetintic acid has smaller content and lower biological activity.[8] 18β-glycyrrhetintic acid has biological activity like adrenocorticotrpic hormone (ACTH),[9] it is used as an anti-inflammatory agent in the clinical practice to treat the rheumatic arthritis, the dermatitis and the gastrelceosis etc.[10–13] Moreover, 18β-glycyrrhetintic acid has the antitumor activity,[14,15] scavenging effects on oxygen free radical and protective effects on CCl_4-injured hepatocytes.[16] It could also protect myocardium and treat ischemic cardiac disease.[17]

To synthesize a new polymeric drug, we have attempted to prepare new polymer from 18β-glycyrrhetintic acid derivative. The β-OH group on the C-3 position of GA can readily react with acryloyl chloride to form the new monomer (18β-acrylglycyrrhetintic acid) (AGA) (Figure 1) which can then be polymerized. Although GA contain a free carboxy group, it is slightly soluble in water. All GA, AGA, and homopolymer of AGA exhibite hydrophobicity. There is an obvious way to improve the hydrophilicity of the polymer: the copolymerization of AGA with monomer of higher hydrophilicity such as *N*-isopropylacrylamide (NIPAAm) and acrylamide (AAm), which are often used in the preparation of polymeric hydrogels. In addition, the comonomers are repected to improve the flexibility of polymer chains since they are smaller in size.[7] In this article, we report the synthesis of 18β-acrylglycyrrhetintic acid (AGA) and the preparation of its homo- and co-polymer.

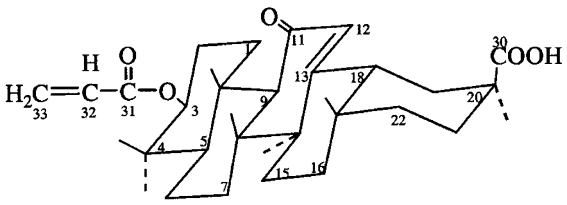

Figure 1. The chemical structure of 18β-acrylglycyrrhetintic acid (AGA).

EXPERIMENTAL

Materials

18β-Glycyrrhetintic acid (GA) was obtained from Lanzhou medical college (It was isolated and prepared from *Glycyrrhiza glabra* L.) and recrystallized in ethanol. *N*-Isopropylacrylamide (NIPAAm) was synthesized from acrylonitrile and isopropyl alcohol.[18] Acryloyl chloride was always freshly prepared from acrylic acid and phosphorus trichloride.[19] 2,2′-Azobisisobutyronitrile (AIBN), Acrylamide (AAm) and other reagents were purified by routine methods.

Synthesis of 18β-Acrylglycyrrhetintic Acid (AGA)

The GA (9.42 g, 20 mmol) and triethylamine (3.04 g, 30 mmol) were added to dry chloroform (100 mL) in a

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three-neck flask. Acryloyl chloride (2.72 g, 30 mmol) was dissolved in dry chloroform (20 mL) in a dropper funnel. The flask was cooled to 0°C with an ice-water bath and the acryloyl chloride solution was added dropwise. It was stirred at 0°C for 2 h and the temperature was increase gradually to 25°C during a period of 30 min and stirring was continued for 24 h. The solvent was removed by vacuum and ethyl acetate was added to precipitate the salt. After removing the salt by filtration, the product was obtained by recrystallization from ethanol (6.34 g, 60.5%). Mp : 226–227°C.

^{1}H NMR ($DCCl_3$, ppm): δ = 4.63 (t, 3-H), 5.69 (s, 12-H); 6.15 (m, 32-H); 5.85 and 6.32 (m, 33-H_2).

^{13}C NMR($DCCl_3$, ppm): δ = 80.89 (3-C); 200.06 (11-C); 128.41 (12-C); 169.32 (13-C); 177.05 (30-C); 166.08 (31-C); 129.15 (32-C); 130.62 (33-C).

Anal. Calcd for $C_{33}H_{48}O_5$: C, 75.54%; H, 9.22%; found: C, 76.08%; H, 9.47%.

Preparation of Homo- And Co-polymer

Homopolymerization. The AGA (0.524 g, 1 mmol) was dissolved in chloroform (or ethanol) (15 mL) in an ampoule equipped with a magnetic stirrer. AIBN (6.7 mg, 4 mol%) was added to the solution. Then the solution was degassed with N_2 before it was sealed. The temperature was raised slowly to 60°C (or 70°C in ethanol) during a period of 2 h, and the mixture was continuously stirred for 36 h. The mixture in chloroform was completely dissolved during whole period, the polymer was precipitated in methanol, filtered, washed with methanol, and dried.

The mixture in ethanol was dissolved at the first period, as the polymerization proceeded, a precipitate formed, which was then filtered, washed with ethanol and dried.

Copolymerization. The copolymers were prepared by a similar procedure. The comonomer was mixed in appropriate molar ratios and dissolved in chloroform. The mixtures were continuously stirred at 60°C for 36 h. Copolymers of new monomer with NIPAAm were very soluble in chloroform and can be precipitated from methanol and filtered, washed and dried.

For the copolymerization of new monomer with AAm, the mixtures were dissolved at the first period, as the reaction proceeded, a precipitate formed, which was then filtered, washed and dried.

Measurements

The NMR spectra were recorded on a BRUKER AM 400 spectrometer (400 MHz) in deuterated chloroform. IR spectra were measured on a Nicolet AVATAR 360 FT-IR instrument. The chemical composition of the copolymers were determined by analysis of nitrogen element on an element Vario.EL instrument. The molecular weight of the polymers were determined by gel-permeation chromatography (GPC) on a WATERS 150Cv system using polystyrene as the standard. The samples were measured at 30°C using THF as the mobile phase (flow rate 1 mL min^{-1}), the samples concentration was 5% w/v in THF.

RESULT AND DISCUSSION

The AGA was synthesized from the reaction of acryloyl chloride with the 3β-hydroxy of GA, and the chemical structure was established by elemental analysis, IR spectroscopy and NMR analysis. The absorption band at 1031 cm^{-1}, which is assigned to the flexural vibration of OH group on the C-3 position of GA, could be seen in the IR spectra of GA but disappeared in the IR spectra of AGA (Figure 3). The absorption band at 1726 cm^{-1}, which is assigned to the –CO–O– group at C-3 position of AGA, could be found in the IR spectra of AGA. The chemical shifts of the proton and the carbon at C-3 position changed from 3.26 and 78.63 ppm to 4.63 and 80.89 ppm, since the 3β-hydroxy of GA had reacted with acryloyl chloride.

The AGA can readily undergo radically-initiated homopolymerization in chloroform or ethanol. The formation of the polymer was confirmed by solution ^{1}H NMR (Figure 2), which showed the disappearance of the double bonds (–C=C–) of acrylate group and also broadening of the ^{1}H NMR signals. The GPC results showed that the number- and weight-average molecular weights M_n and $M_w$of polymer prepared in chloroform are 11800 and 25600, and the ratio of weight- to number-average molecular weight (M_w/M_n) is 2.17. M_n and M_w of polymer prepared in ethanol could not be determined by GPC, because this polymer is partially dissolved in organic solvents such as THF, benzene and chloroform. The insoluble part did not swell in the solvents, so the cross-link could not be defined. For the insolubility of polymer prepared in ethanol, further studies are necessary.

To alter the properties of the polymer and improve its hydrophilicity, the copolymers of AGA with NIPAAm/AAm were made by free radical polymerization in chloroform. The products were characterized by ^{1}H NMR and IR spectra (Figures 2 and 3). In addition to the absorption band of PNIPAAm at 1548 cm^{-1}, typical for amides, the absorption band at 1726 could be seen, which is typical for the –CO–O– group of the chain element of poly(AGA), and the broad absorption band at 1659 cm^{-1}could be also found, which is typical for amides of PNIPAAm and carbonyl (–CO–) at C-11 position of GA skeleton. The chemical shift at 5.70 ppm

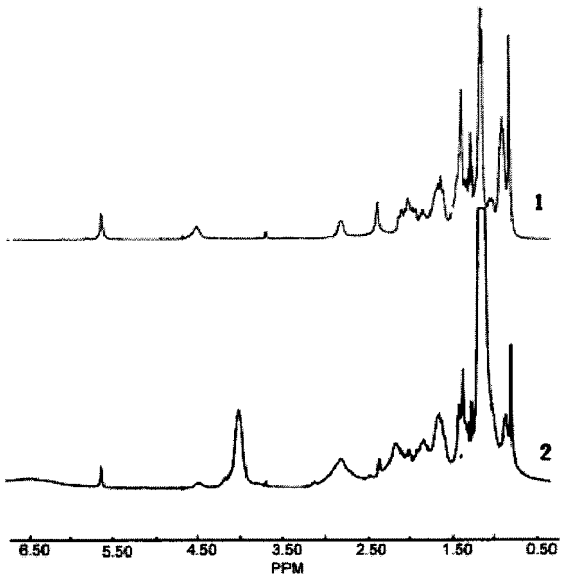

Figure 2. ^{1}H NMR spectra of Homo-, and Co-Polymer with NIPAAm. 1: Homopolymer; 2: Copolymer (The PAGA content (mol%) = 25.2%).

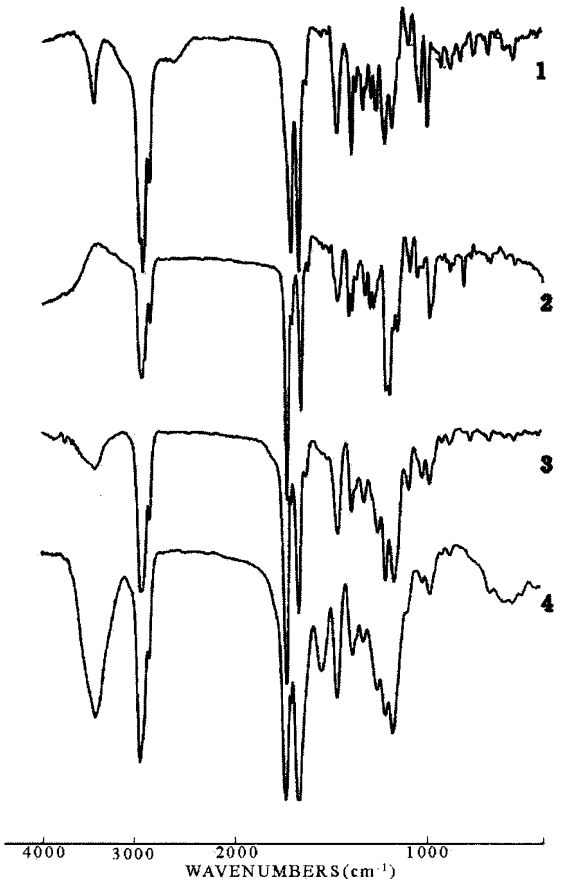

Figure 3. IR spectra of GA, AGA, Homo-, and Co-Polymer with NIPAAm. 1: GA; 2: AGA; 3: Homopolymer; 4: Copolymer (The PAGA content (mol%) = 25.2%).

Table I. Copolymerization of new monomer with NIPAAm/AAm

Sample	PAGA content/mol%		Weight	M_w	M_w/M_n
	Feed	Polymer	conversion		
PAGA/	10.0	8.7	70.6	83600	1.79
PNIPA	30.0	25.4	66.3	117200	2.83
Am	50.0	46.8	73.1	45100	2.01
	70.0	68.1	58.6	52500	2.32
PAGA /	10.0	9.1	81.1		
PAAm	30.0	26.9	85.8		
	50.0	51.3	70.9		
	70.0	66.5	63.3		

in the ^{1}H NMR spectra was assigned to the protons of C-12 of GA skeleton. The chemical shift at 4.01 ppm to the CH-proton of *N*-isopropyl group. All signals of ^{1}H NMR spectra show broadening.

The chemical composition of the copolymers were determined by analysis of nitrogen element (Table I). The data in Table I showed that, the chemical composition of the resulting copolymers are close to the original monomer composition added to the solution prior to polymerization and the total weight conversion of AGA and NIPAAm/AAm decreased with increasing AGA content added.

Since the copolymers of AGA with AAm were not dissolved in THF, chloroform and benzene, the molecular weights of the copolymers of AGA with NIPAAm were only determined by GPC (Table I). The results unequivocally indicate that the molecular weights of copolymers are higher than that of homopolymer because of the small comonomer added.

The studies, for the characteristics of polymer such as the hydrophilicity, the biological activity, the opticity and the glass transition temperatures, are being carried out in our laboratory.

Acknowledgments. The Authors are thankful to Mr. X. X. Zhu (Department de Chimie, Université de Montréal, Canada) for his help.

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