TEMPERATURE RESPONSIVE METHACRYLAMIDE POLYMERS WITH ANTIBACTERIAL ACTIVITY*

Bor-Kuan Chen**, Shuen-Hung Lo and Shu-Feng Lee
Department of Polymer Materials, Kun Shan University, Tainan 71003, China

Abstract A new methacrylamide monomer, hexylamine methacrylamide (MAHA), was synthesized and used in polymerizations. The homopolymer of MAHA and its copolymers were synthesized by free radical polymerization techniques with N-isopropyl acrylamide (NIPAAm) in two different compositions. The quaternization of the homopolymer and copolymers were carried out using 1-bromopropane. The copolymers with NIPAAm and a low MAHA content showed temperature-responsive behavior in an aqueous environment. The lower critical solution temperatures (LCSTs) of these polymers varied between 32°C and 44°C. The LCSTs of quaternized copolymers were higher than those of neutral copolymers because they were more hydrophilic. The obtained homopolymers and copolymers were tested for antibacterial activities against \textit{S. aureus} and \textit{E. coli}. The quaternized water-soluble copolymers showed antibacterial activities against \textit{S. aureus}. The quaternization resulted in the synthesis of both antibacterial and temperature-responsive copolymers.

Keywords: Methacrylamide; NIPAAm; Antibacterial; Temperature-responsive.

INTRODUCTION

Antibacterial polymers have the advantages of enhanced antibacterial activity, reduced residual toxicity, increased efficiency and improved selectivity\cite{1,2}. Antibacterial polymers have been used as coatings in many areas such as food processing, filters and biomedical devices\cite{3}. They have also been used as preservatives and disinfectants in the pharmaceutical field and in the textile industry in the form of antibacterial fibers. Among the commonly used low-molecular-weight antibacterial agents, quaternary ammonium compounds have been the most widely used agents\cite{4}. They have advantages over other antibacterial agents in terms of better cell membrane penetration, lower toxicity and corrosivity, good environmental stability, lack of skin irritation and extended biological activity\cite{5}. In order to be utilized in biomedical applications, \textit{e.g.}, controlled-release drugs, it would be better to have the lower critical solution temperature (LCST) of the polymer near body temperature. The homopolymer of \textit{N}-isopropyl acrylamide (NIPAAm), PNIPAAm, is one of the most extensively studied polymers with an LCST of 32°C\cite{6,7}. Several copolymers of NIPAAm have been synthesized to change the LCST. It has been found that the use of hydrophilic comonomers with NIPAAm increases the LCST of the copolymers, whereas the use of hydrophobic monomers decreases the LCST\cite{7,8}.

The purpose of this study was to design antibacterial and temperature-responsive polymers. In this study, we first synthesized a new acrylamide monomer, hexylamine methacrylamide (MAHA), then copolymerized it with NIPAAm in two different compositions by conventional free radical polymerization techniques\cite{9,10}. The copolymers with a high NIPAAm content and a low MAHA content showed temperature-responsive behavior in an aqueous environment. We then prepared antibacterial quaternary ammonium salts of methacrylamide

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** Corresponding author: Bor-Kuan Chen (陈伯宽), E-mail: chenbk@mail.ksu.edu.tw
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polymers with temperature-responsive behavior. The quaternization of these polymers was carried out using bromopropane and resulted in the synthesis of both antibacterial and temperature-responsive polymers\(^3\). The obtained polymers were tested for antibacterial activities against \textit{S. aureus} and \textit{E. coli}. The minimum bactericidal concentration values were determined for water-soluble copolymers using broth dilution\(^{12}\) and spread plate methods\(^{13}\).

The synthesized polymers were characterized by FT-IR and NMR to identify the chemical structures. TGA and DSC were used to measure the thermal properties. Their temperature-responsive and antibacterial properties are presented and discussed.

**EXPERIMENTAL**

**Materials**

Chemicals of high purity were purchased from various commercial sources, which include methacrylic anhydride (Aldrich), 1,6-diaminohexane (Aldrich), 2,2'-azobis-isobutyronitrile (AIBN) (Showa, Japan), N-isopropylacrylamide (NIPAAm) (Aldrich), triethylamine (Tedia) and 1-bromopropane (Fluka). Solvents: methanol, ether, dichloromethane, 1,4-dioxane, petroleum ether, N,N-dimethylformamide (DMF) and \(n\)-hexane (all from Acros) were used as received.

**Synthesis of Hexylamine Methacrylamide (MAHA)**

1,6-Diaminohexane (29.1 g, 0.25 mol) and triethylamine (25.3 g, 0.25 mol) were mixed in methylene chloride (80 mL) in a 500 mL round-bottom flask. The flask was kept in an ice bath. Methacrylic anhydride (38.6 g, 0.25 mol) was added to the mixture dropwise over 30 min. The mixture was allowed to react for 30 min at 0°C and at ambient temperature overnight. After completion of the reaction, the reaction mixture was extracted with water, and the organic layer was separated and extracted two more times with water. Finally, the methylene chloride was evaporated using a rotary evaporator to give a solid product. Yield: 89%.

**Synthesis of Homopolymer**

MAHA (18.6 g, 0.1 mol) and AIBN (0.16 g, 1.0 mmol) were dissolved in 80 mL of 1,4-dioxane in a 250 mL round-bottom flask. The flask was purged with nitrogen. The temperature was raised to 70°C, and the mixture was stirred for 24 h. 1,4-Dioxane was evaporated using a rotary evaporator. The product was then reprecipitated from methanol with petroleum ether twice. The final white solid product was dried in a vacuum oven at room temperature to give the homopolymer. Yield: 51%.

**Synthesis of NIPAAm/MAHA Copolymer (90/10 Composition)**

In a 250 mL round-bottom flask, MAHA (1.85 g, 0.01 mol), NIPAAm (10.2 g, 0.09 mol) and AIBN (0.16 g) were dissolved in 120 mL DMF. The flask was purged with nitrogen, the temperature was maintained at 70°C, and the mixture was stirred for 24 h. The final mixture was precipitated into 50 mL of diethyl ether. It was then dissolved in methanol (50 mL), and reprecipitated in petroleum ether. A rotary evaporator was used to remove the solvents. The final product was dried in a vacuum oven at ambient temperature to give the 90/10 copolymer. Yield: 56%.

**Quaternization of NIPAAm/MAHA 90/10 Copolymer**

In a 250 mL round-bottom flask purged with nitrogen, NIPAAm/MAHA 90/10 copolymer (6 g, 0.05 mol) and 1-bromopropane (6.15 g) were mixed in a solvent mixture of methanol (30 mL) and acetonitrile (18 mL). The mixture was stirred at 60°C for 48 h. At the end of the reaction, the mixture was precipitated into diethyl ether. The solid product obtained was dissolved in 50 mL of methanol and reprecipitated in ether. A rotary evaporator was used to remove solvents. Finally, the product was dried in a vacuum oven at 40°C for 8 h and at room temperature overnight.

**Synthesis of NIPAAm/MAHA Copolymer (70/30 Composition)**

In a 250 mL round-bottom flask, MAHA (5.58 g, 0.03 mol), NIPAAm (7.93 g, 0.07 mol) and AIBN (0.16 g) were dissolved in 120 mL DMF. The flask was purged with nitrogen, the temperature was maintained at 70°C,