

STUDY ON THE SYNTHESIS OF COPOLYMER CONTAINING N-SUBSTITUTED ACRYLAMIDE COMPONENT*

LI Xuefen (李学芬), WANG Shenguo (王身国) and LI Zhifen (李执芬)

(Institute of Chemistry, Academia Sinica, Beijing)

ABSTRACT

In this paper the synthesis of linear and crosslinked N-substituted acrylamide copolymer is reported. In order to obtain the terpolymer with appropriate hydrophilicity, the conditions of aminolysis of St-MMA copolymer have been selected.

It is shown that the copolymer with predictable hydrophilicity possesses good blood compatibility.

INTRODUCTION

The copolymers, containing amino group have much high reactivity and, hence, they have been found many important applications, such as chelating agent, coagulating agent, dispersion agent etc. Recently, polyacrylamide and its derivatives as a kind of hydrogel has been found wide application in the field of biomedicine^[1]. However, because of the toxicity of acrylamide monomer, application of its polymer as biomedical material would be limited, if the monomer could not be completely removed. J. Kopecek and coworkers carried out a series of research works on N-substituted and N,N-disubstituted polyacrylamide, mainly in studying on blood compatibility of those polymers, their stability in vivo, penetration for metabolite and mechanical property of the polymer^[2-7]. They found that those N-substituted (or N,N-disubstituted) polyacrylamides not only have no toxicity, but also possess the good biocompatibility and the high stability in vivo.

This paper deals with the synthesis of a new type material — N-substituted acrylamide copolymer with predictable hydrophilicity by macromolecular reaction. Because of the difficulty in preparing the monomer with multi-amino and hydroxyl groups the procedure of aminolysis of St-MMA (styrene-methyl methacrylate) copolymer has been chosen^[8]. First of all styrene and methyl methacrylate were copolymerized then the obtained St-MMA copolymer aminolyzed. Thus, two kinds of copolymers — the linear and the crosslinked spherical copolymers possessing hydrophilicity and hydrophobicity have been synthesized.

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The condition of aminolysis was studied and the properties of the copolymers before and after aminolysis were discussed.

EXPERIMENTAL

1. Materials

Monomers St and MMA were distilled in vacuum before use. 2-hydroxyethyl ethylene diamine used as aminolysis agent was purified by vacuum distillation.

Initiator azobisisobutyronitrile (AIBN) was recrystallized twice from ethanol.

2. Synthesis of St-MMA copolymer

(1) Preparation of linear copolymer: Copolymerization of St with MMA was carried out under Ar in benzene as solvent with AIBN as initiator in a sealed ampoule at $60^{\circ}\text{C} \pm 1^{\circ}\text{C}$ for 24 hrs. White powder product was precipitated from methanol twice at -30°C and then dried by freezing with a 50% yield.

(2) Preparation of crosslinked St-MMA copolymer sphere^[9]: A mixture of monomers (St and MMA) with crosslinking agent divinyl benzene (DVB) and initiator (AIBN) was added to an aqueous solution containing a small amount of vinyl alcohol (PVA). For getting suitable size of suspension particles of monomer the stirring velocity was controlled and then stabilizer bontonite added to the system.

After stirring for 15 min. the polymerization was started under Ar at 60°C for 24 hrs. Crosslinked product obtained was washed with plenty of water for removing the stabilizer and sieved after being dried in vacuum.

3. Aminolysis of St-MMA copolymer

In an Erlenmeyer flask with reflux condenser, St-MMA copolymer (PSM) was dissolved in tetrahydronaphthalene (or triglycol), and aminolyzing agent 2-hydroxyethyl ethylene diamine and catalyst triethylenediamine were added. Under magnetic stirrer the reaction proceeded at $160^{\circ} \pm 1^{\circ}\text{C}$ for 72 hrs. The light yellow powder product precipitated twice in ether at -50°C and then followed by freeze drying.

4. Analysis

(1) Elementary analysis by Carlo Erba Elemental Analyzer mod. 1102.

IR spectrum by JASCO-IR-A100.

^1H -NMR by 250 MH NMR spectroscopy.

(2) Water absorption: About 1 g. copolymer sphere was immersed in water at 40°C for 100 hrs. After filtration the sphere was centrifugalized for 10 min. (2000 rpm) and then weighed before and after dried at 60°C in vacuum. Water absorption was calculated by the following formula:

$$\text{Water adsorption \%} = \frac{W_1 - W_2}{W_2} \times 100\%$$

where W_1 and W_2 were the weight of copolymer before and after drying respectively.

RESULTS AND DISCUSSION

1. *Determination of composition of St-MMA copolymer and its aminolysis degree*

At first, the content of C element in St-MMA copolymer was determined by elementary analysis and the ratio of signal area of hydrogen in benzene ring and out of benzene ring was measured in H^1 -NMR. Thus the composition ratio of copolymer can be calculated. According to the content of N element the aminolysis degree can be determined by the following formula:

$$\text{Aminolysis degree \%} = \frac{\text{Mole of aminolyzed MMA}}{\text{Mole of MMA in copolymer}} \times 100 \%$$

The results of analysis are given in Tables 1 and 2.

Table 1 Composition of St-MMA linear copolymers and their aminolysis degree

Sample	Composition of copolymer			Aminolysis degree (%)
	Ratio of monomer St:MMA (mole)	Elementary analysis St:MMA (mole)	H^1 -NMR St:MMA (mole)	
SM-1	80 : 20	70 : 30	—	86.4
SM-2	60 : 40	56 : 44	55.5 : 43.5	
SM-3-1	40 : 60	45 : 55	46.1 : 53.9	
SM-3-2	40 : 60	45 : 55	46.1 : 53.9	
SM-4	20 : 80	26 : 47	—	

It was shown in Table 1 that the composition of copolymer given from elementary analysis and H^1 -NMR spectra agreed with each other very well.

Table 2 Composition of crosslinked spheric St-MMA copolymers and their aminolysis degree

Sample	Composition of copolymer		Aminolysis product	
	Ratio of monomer St:MMA (mole)	Elementary analysis St:MMA (mole)	Elementary analysis N content (%)	Aminolysis degree (%)
SM-S-1	80:20	82:18	2.82	62.3
SM-S-2	60:40	67:33	4.81	61.0
SM-S-3	40:60	50:50	6.50	56.8
SM-S-4	20:80	30:70	9.31	63.1

It was revealed in Tables 1 and 2 that although the same ratio of monomers was used in copolymerization in both cases of reaction the composition was different in linear and cross-linked copolymers, because of different medium for the polymerization. Linear copolymer was obtained from organic solvent, while the crosslinked one from aqueous solution.

2. The effect of temperature on aminolysis reaction

In order to select the suitable condition for the aminolysis reaction, St-MMA crosslinked copolymer has been aminolyzed by 2-hydroxyethyl ethylene diamine at different temperatures and the aminolysis degree has been determined at certain interval. It was shown in Fig. 1 that the rate of reaction was increased with increase of temperature. When the aminolysis reaction proceeded for 48 hrs. the degree of aminolysis at 160°C was 5 times of that at 100°C. So that higher temperature promoted rate of aminolysis reaction. At too high temperature certain by-reaction was liable to take place. It was shown from Fig. 1 that in all cases the rate of reaction was high at beginning and then approached an equilibrium value.

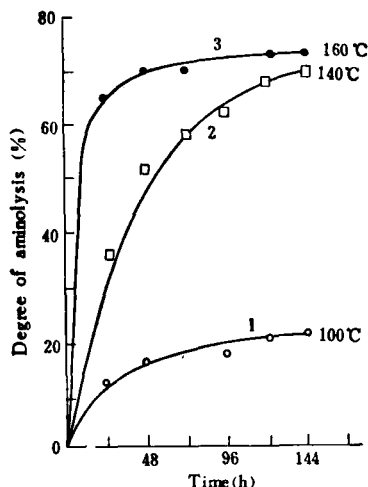


Fig. 1 Effect of temperature on aminolysis degree
 1—100°C; 2—140°C; 3—160°C.
 Composition of copolymer: St:MMA = 51:49 (mole); Size of sphere: 40 mesh;
 Crosslinking degree: 2%; Aminolysis agent: 2-hydroxyethyl ethylene diamine.

By means of a plot of initial rate of aminolysis reaction at different temperature versus reciprocal of temperature according to the Arrhenius equation, the activation energy of reaction system was obtained (11.4 Kcal/mole).

3. The effect of composition of copolymer on the aminolysis reaction and the properties of product

The results of aminolysis of St-MMA copolymer with different composition by 2-hydroxyethyl ethylene diamine at the same condition have been shown in Table 1 and Fig. 2.

The aminolysis degree of copolymer remained at a constant value when the content of MMA in copolymer increased from 18% to 70%.

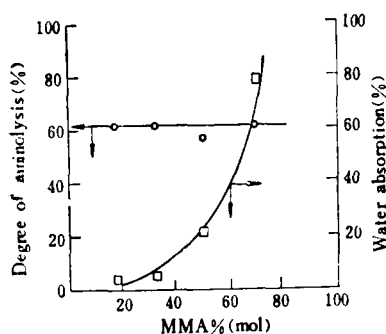


Fig. 2 The effect of copolymer composition on aminolysis degree and water absorption of aminolysis product

Crosslinking degree: 2%;

Aminolysis agent: 2-hydroxyethyl ethylene diamine;

Condition of aminolysis: 140°C, 70 hrs.

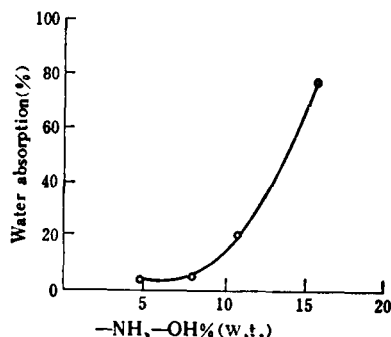


Fig. 3 The relationship of content of hydrophilic groups with water absorption

At this condition the aminolysis agent could enter into the beads of crosslinked copolymer, therefore copolymer sphere can be aminolyzed uniformly and the aminolysis degree was independent on the content of MMA in copolymer. But the water absorption of aminolyzed copolymer with the same crosslinking degree and aminolysis degree increased rapidly with increasing MMA content in copolymer. Because of increase of MMA component in copolymer the amount of aminolyzed MMA unit increased even at the same aminolysis degree. Therefore the hydrophilic $-\text{NH}-$ and $-\text{OH}$ groups increased and consequently the water absorption was enhanced. The relation of content of hydrophilic groups in wt. % in copolymer versus the water absorption is shown in Fig. 3. The water absorption went up remarkably with content of $-\text{NH}-$ and $-\text{OH}$ groups showing that the water absorption of copolymer is dependent not only on the hydrophilic groups but also on the hydrophobic one. With decreased St content the resistance of hydrophobic St to the volume expansion of aminolysis product was reduced and therefore the product of aminolysis can be swelled freely and water absorption increased considerably.

4. The effect of crosslinking degree of copolymer on the aminolysis reaction and properties of product

St-MMA copolymer with the same composition but different crosslinking extent was aminolyzed under the same condition. The result showed that due to the homogeneous aminolysis reaction system with high aminolysis efficiency the linear copolymer had highest aminolysis degree.

In case of crosslinked copolymer, the aminolysis reaction took place in heterogeneous system and the higher the extent of crosslinking, the lower the efficiency of aminolysis reaction and aminolysis degree of product.

It was shown in Fig. 4 that in the interval of 5–10% crosslinking the aminolysis degree remained unchanged because of the same swelling extent. The water absorption of aminolysis

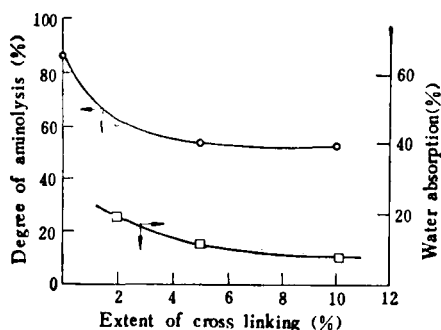


Fig. 4 The effect of crosslinking degree on the aminolysis reaction

Composition of copolymer: St:MMA = 45:55 (mole);
Size of sphere: 40–60 mesh;
Aminolysis agent: 2-hydroxyethyl ethylene diamine;
Condition of aminolysis: 140°C, 96 hrs.

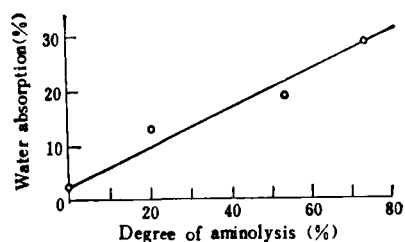


Fig. 5 The relationship between aminolysis degree of crosslinked copolymer sphere and water absorption

Composition of copolymer: St:MMA = 51:49;
Crosslinking degree: 2%;
Size of sphere: 40–60 mesh.

product depended upon the extent of crosslinking. The water absorption increased with decreasing crosslinking degree. After aminolysis the linear copolymer became water soluble, so that its solubility was quite different in comparison with original copolymer. For copolymer sphere with the same extent of crosslinking, the water absorption went up straightly with increasing aminolysis degree and content of hydrophilic groups as shown in Fig. 5.

5. Evidence of aminolysis reaction

Occurrence of aminolysis reaction was identified by elementary analysis, IR spectrum and NMR spectra. IR spectra showed that for the product of aminolysis there appeared some new absorptions at 1655 cm^{-1} and 3350 cm^{-1} of amide group and amino group respectively, at the same time the absorption peak of methyl ester group at 1720 cm^{-1} was reduced obviously. (Fig. 6)

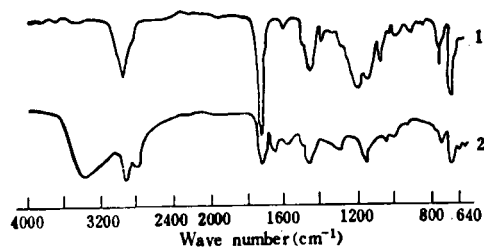


Fig. 6 Comparison of IR of copolymer before and after aminolysis
1. St-MMA copolymer; 2. Aminolysis product by 2-hydroxyethyl ethylene diamine.

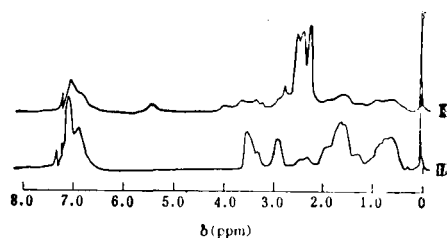
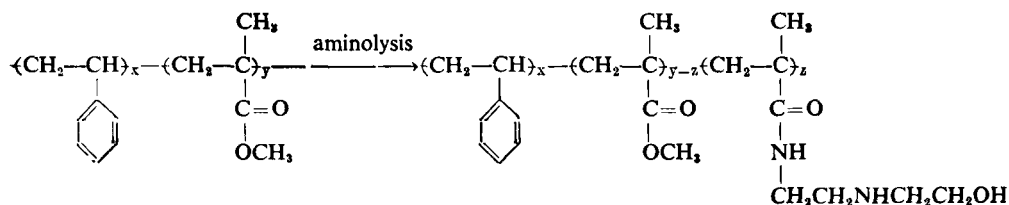


Fig. 7 Comparison of copolymer NMR spectra before and after aminolysis
1. Aminolysis product; 2. St-MMA copolymer.

In the NMR spectra some new signals appeared at $\delta_{2.4}$ and $\delta_{5.45}$ of amide group and hydroxyl group in aminolysis product, but the signal for methyl ester $\delta_{3.5}$ was reduced considerably (Fig. 7).

The aminolysis reaction is represented by:



Consequently, the aminolysis product is a tricomponent copolymer of St-MMA-N-2-hydroxyethyl amino ethylene methacrylamide. The tercopolymer with high aminolysis degree is soluble in ethanol.

The results of minicolumn hemoperfusion on living animal (i.e. dog) revealed that the blood compatibility has been improved greatly for the copolymer with certain ratio of hydrophilicity and hydrophobicity.

In conclusion, the predictable hydrophilic property as well as blood compatibility of copolymer might be controlled by suitable selection of the ratio of components of St-MMA copolymer, crosslinking extent and the degree of aminolysis on the copolymer.

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