Synthesis of pH-Responsive Block Copolymer By ATRP

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Abstract The block copolymer, poly(4-vinylpyridine)-b-poly(tert-butylmethacrylate) (P4VP-b-PtBMA), was synthesized by atom transfer radical polymerization (ATRP) in two steps. Firstly, macroinitiator P4VP-C1 was prepared via ATRP with the conversion of monomer 66.3%. The result of GPC illustrated that the $M_n$ of P4VP-C1 could be controlled by adjusting polymerization conditions. Then, P4VP-b-PtBMA was synthesized by ATRP using P4VP-C1 as macroinitiator. The effects of polymerization reaction parameters such as solvent and polymerization time on the $M_n$ and $M_n/M_w$ were investigated. Then the pH-responsive block copolymer poly(4-vinylpyridine)-b-poly(methacrylic acid) (P4VP-b-PMAA) was obtained by hydrolyzing the P4VP-b-PtBMA copolymer.

1. Introduction

The double-hydrophilic BCPs were prepared by Armes\textsuperscript{1} and Smith\textsuperscript{2}, poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) were reported by Luo and Liu et al.\textsuperscript{3,6} Such systems are particularly attractive for biological applications that can be found in normal or infected tissues. For the micellization and applications of the copolymers, the further development is to control the molecular characteristics of the pre-block copolymer and to develop appropriate conditions to achieve the required size and microstructure of the micelle. ATRP is one of the Controlled Radical Polymerization (CRP) processes which could enable precise control over the $M_n$ and $M_n/M_w$ of the polymers.\textsuperscript{1} It can be applied in many kinds of polymerization conditions, including water solvent at room temperature, and is tolerant of most functional groups.

Therefore, in this paper, ATRP method was firstly applied to synthesize macroinitiator P4VP-C1 with high active tris[2-(dimethylamino) ethyl]amine (Me\textsubscript{3}TREN) as ligand and CuCl as catalyst, then the block copolymer P4VP-b-PtBMA was also synthesized by ATRP of tBMA, CuC/Me\textsubscript{3}TREN as catalyst and ligand, respectively. P4VP-b-PMAA, abstained from hydrolyzing P4VP-b-PtBMA, which could be promisingly used in industrial catalysis, nanomicelle-supported medicine and heavy metals composites, rubber, dyes and many other fields.
2. Experimental

2.1 Materials
4-Vinylpyridine (4VP, Acros Organics) was dried over CaH₂ and distilled at 55 °C before use. tert-butylmethacrylate (tBMA, Tokyo, Japan) was refined by vacuum distillation in nitrogen atmosphere. Ethyl-2-chloropropionate (ECP, Acros Organics) and CuCl (ECP, Acros Organics) was used without further purification. Me₆TREN was synthesized and purified according to the reference. All the other solvents and materials were purchased from Shanghai Chemical Reagent Station without further purification.

2.2 Synthesis of P4VP-Cl macroinitiator
The macroinitiator P4VP-Cl was synthesized by ATRP using 4VP as monomer, ECP as initiator, CuCl as catalyst and high active Me₆TREN as ligand. The detailed addition ratio in the polymerization was listed as follows: \( n[4VP]:n[ECP]:n[Me₆TREN]:n[CuCl]=50:1:2:1 \) and 2 mL 2-propanol solvent were added into the reaction system. The sample was firstly degassed by nitrogen, then, 2 g monomer was added into the reaction system. The polymerization was carried out at 40 °C to a predetermined time, the solution were passed through Al₂O₃ column which could remove the CuCl catalyst in the reaction system to purify the polymers, then the purified polymers P4VP-Cl were precipitated in cold ether. Such process was repeated twice and P4VP-Cl could be obtained after dried in an oven at 30 °C.

2.3 Synthesis of P4VP-b-PrBMA
Then P4VP-b-PrBMA was synthesized using tBMA as monomer, the synthetic P4VP-Cl as macroinitiator, CuCl as catalyst and high active Me₆TREN as ligand by ATRP. The detailed addition ratio in the polymerization was listed as follows: \( n[tBMA]:n[P4VP-Cl]:n[Me₆TREN]:n[CuCl]=50:1:2:1 \) with the addition amount of tBMA was 2g were added into the reaction system. The sample was also firstly degassed by nitrogen, and then the the synthetic P4VP-Cl was added into the synthetic system. Then the polymerization system was heated to 70 °C. When the polymerization was carried out for a scheduled time, the solution were passed through Al₂O₃ column which could remove the CuCl catalyst in the reaction system to purify the polymers, then the purified copolymers P4VP-b-PrBMA was precipitated in cold ether. Such process was repeated twice and such process was repeated twice, and the P4VP-b-PrBMA obtained after the copolymers were dried in an oven at 30 °C. The synthetic procedure of the polymers by ATRP was illustrated in Scheme 1.
Scheme 1 Synthetic procedure of the polymers by ATRP

2.4 Hydrolysis of P4VP-b-PtBMA
The synthetic copolymer P4VP-b-PtBMA was firstly dissolved in solvent CH₂Cl₂ with the addition ratio was 1mg copolymer: 2mL solvent CH₂Cl₂ and then the system were added by CF₃COOH with the addition ratio was fivefold molar to the tert-butyl group. Then the solution was stirred for 24 h at room temperature. When the reaction was finished the solvent were removed by rotating evaporation, and then the solution were deposited in hexamethylene. The pH-responsive block copolymer P4VP-b-PMAA was obtained after the filter was dried in an oven.

2.5 Measurements
The parameter of nuclear magnetic resonance (¹H NMR) was list as follows: Bruker AVANCE III, 400 MHz. The parameter of gel-permeation chromatography (GPC) was list as follows: Agilent-1100, USA which could used to determine the Mₘ and Mₘ/Mₘ of the polymers.

3. Results and Discussions

3.1 Synthesis of P4VP-Cl macroinitiator
The macroinitiator P4VP-Cl was synthesized by ATRP using 4VP as monomer, ECP as initiator, CuCl as catalyst and high active Me₆TREN as ligand in the solvent 2-propanol. The solvent 2-propanol which was proved to be suitable for the polymerization of 4VP.⁹ The conversion of monomer increases from 19.2% to 66.3% with the polymerization time prolongs from 1 h to 5 h. As shown in Fig.1, the MₘGPC that the Mₘ measured by GPC of P4VP-Cl increases linearly with the monomer 4VP conversion, but it was bigger than the theory we calculated due to the polystyrene standard which was used in GPC. Then as shown in Fig.1, Mₘ/Mₘ of macroinitiator P4VP-Cl was relatively broad when the conversion of the monomer 4VP was low and gradually kept around 1.23 when the conversion of the monomer 4VP reaches about 45%.
Fig. 1 Dependence of $M_n$ and $M_n/M_w$ on conversion of 4VP

$M_{\text{elv}}=([M]_0/[ECP]_0) \times M_{4VP} \times \text{Conversion} + M_{ECP}$, where $[M]_0$ and $[ECP]_0$ are initial concentrations of 4VP and ECP, respectively, $M_{4VP}$ and $M_{ECP}$ are the molecular weights of 4VP and ECP, respectively.

3.2 Synthesis of P4VP-b-PtBMA

3.2.1 Structure of P4VP-b-PtBMA

As shown in Fig. 2, the structure of the copolymer P4VP-b-PtBMA was determined by $^1$H NMR, we could see the integration of ortho- and meta-protons of pyridine ring in the P4VP units with the spectra peaking at 6.4 (q) and 8.3 (r) ppm. The weak absorption peaks at e, f, g are corresponding to the methyl and methylene in group of tBMA units. The entire results mean the synthesis of the copolymers by ATRP were success.

3.2.2 Effect of the solvents on the synthesis of copolymer P4VP-b-PtBMA by ATRP

Generally, in the polymerization reaction of ATRP, the solvents play an important role. The solvents in the polymerization reaction affect the solubility of system and affect the redox reaction of Cu(I)/Cu(II) and equilibrium reactions between active species and dormant species. Therefore, in the
ATRP system of copolymer P4VP-b-PrBMA, we used the macroinitiator P4VP-Cl with the $M_n = 3150$, the high active ligand Me₆TREN in different solvents. The result was list in Table 1, we could see that the conversion of tBMA in solvent 2-propanol was only 25% after the copolymerization performed for 24 h, whereas, in solvent DMF, conversion of tBMA reached the highest, which is due to the solubility of the ATRP system in DMF was the best. $M_n$ of P4VP-b-PrBMA in different reaction solvents varies from 9600 to 5940 which is measured by GPC as shown in Table 1.

Table 1 Effect of solvents on the synthesis of the P4VP-b-PrBMA copolymer

| Solvent   | $M_n$(GPC) | Conversion of tBMA/% |
|-----------|------------|----------------------|
| DMF       | 9600       | 60                   |
| 1,4-dioxane | 6700       | 32                   |
| 2-propanol | 5940       | 25                   |

Fig.3 shows the relationship of $M_n$ and $M_n/M_w$ with conversion of tBMA in solvent DMF. $M_n$ of P4VP-b-PrBMA increases with the conversion of tBMA, and the values correspond with $M_n$(th). $M_n/M_w$ keeps around 1.48.

Fig.4 shows the relationship between the reaction time and the ln([M]₀/[M]). When the conversion of tBMA was below 25%, we could see the results in Fig.4, the dynamics of the copolymerization was in accordance with ATRP characteristics. However, when the conversion was above 30%, we could obviously see it deviated from the straight line with the copolymerization rate downward. The increase of the viscosity of copolymer with the conversion leads the rate of monomer-proliferation decreased. Thus, the copolymerization rate declines. The number of free radicals relatively decreases and some free radicals become inactive in the process of copolymerization, which also change the copolymerization rate.
3.3 *The hydrolysis of P4VP-b-PtBMA*

As shown in Fig.5, the composition of pH-responsive block copolymer P4VP-b-PtBMA was determined by $^1$H NMR spectra, we could see the result from Fig.5, the the peak at 12.25 (f) belongs to the carboxyl proton peak formed by hydrolysis, while the proton peak of tert butyl at the δ1.2 almost disappears. The entire results implied the synthesis of the P4VP-b-PMAA was success.

4. Conclusions

P4VP was prepared via ATRP with the conversion of monomer 66.3% and the $M_n$ of St-P4VP could be controlled by adjusting polymerization reaction conditions. Then, the copolymers P4VP-b-PtBMA were prepared by ATRP using P4VP-C1 as macroinitiator by ATRP, the polymerization reaction parameters such as solvent and polymerization time on $M_n$ and $M_w/M_n$ were investigated, we found the conversion in DMF was highest, $M_n$ of P4VP-b-PtBMA increases with the conversion of tBMA, and the values correspond with $M_{m(b)}$, $M_w/M_n$ keeps around 1.48. Then the pH-responsive block copolymer P4VP-b-PMAA was obtained by hydrolyzing the P4VP-b-PtBMA in the presence of CF$_3$COOH which could be promisingly used in industrial catalysis, nanomicelle-supported medicine and heavy metals composites, rubber, dyes and many other fields.
Acknowledgments
The authors would like to thank Qinglan project of Jiangsu Province of China, Postdoctoral research funding program of Jiangsu Province 2019K007 and Soft science research project of Wuxi Association for science and technology KX-20-C116 for financially supporting this research.

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