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ARTICLE TYPE

Aqueous Radical Addition-Coupling Polymerization Using Nitroso Benzene/Cyclodextrin Complex for Synthesis of Hydrophilic Periodic Polymer

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Hydrophilic periodic polymer possessing $[AB_xAC]_n$ (A=ester, B=ethylene oxide, C=N-O) repeating sequence was synthesized by aqueous radical addition-coupling polymerization using water-soluble inclusion complex of nitrosobenzene and Me_2-β-cyclodextrin together with poly(ethylene glycol) bis(α-bromoisobutyrate) in the presence of Cu/ligand.

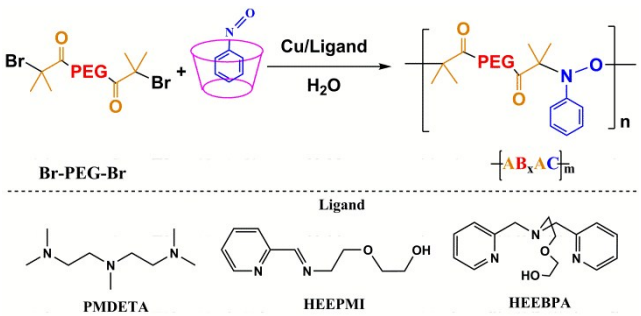
Introduction

Control on the molecular weight and unit sequence of the polymer chain is two challenging targets in radical polymerization. Perfect control on the molecular weight distribution was achieved by the "living" radical polymerizations, such as ATRP[1] and RAFT[2] polymerization, but the control on unit sequence in radical addition polymerization is far from satisfaction.

Condensation polymerization is a simple method to synthesize sequence-regulated chain, but its low reaction rate, precise feed ratio and high reaction content to achieve high molecular weight limit its application. Recently, some novel methods have been developed to produce periodic polymers via chain-growth[3-9] and step-growth polymerization[10-13].

We have developed radical addition-coupling polymerization (RACP)[14-15], which can be applied to synthesis of periodic polymer with regular unit sequence, such as [ABAC], [ABCD] and [ABCDCBAD], by using dibromide and C-nitroso compounds. RACP involves consecutive addition of carbon-centred radical generated by redox of telechelic dibromide to N=O double bond of C-nitroso compound followed by cross-coupling of carbon-centered radical and in situ formed nitroxyl radical, which produces periodic polymers with high molecular weight.[14-15]

Most of above methods are performed in organic media. Polymerization in water is also an environment-friendly and low-cost process. Development of polymerization conducted in water that produces periodic hydrophilic polymer is of the great importance, and is still a big challenge in polymer synthesis. Although condensation polymerization is a suitable method to synthesize polymer with periodic unit sequence, the method is not applicable in aqueous media due to either hydrolysis reaction or the tolerance of functional group. Followed the successful organic RACP, aqueous RACP was realized and hydrophilic polymer with $[AB_xAC]_n$ (A=ester, B=ethylene oxide, C=N-O) repeating sequence was synthesized by using water soluble nitroso compound and dibromide.[16]



Scheme 1. Aqueous radical addition-coupling polymerization (aRACP) via cyclodextrin complex.

Although aqueous RACP can be realized by using water soluble nitroso compound, the synthesis of special nitroso compound is not easy. Methyl nitrosopropane (MNP) and nitrosobenzene (NB) are two commercial available nitroso compounds, but their low solubility in water prevent them to be used in aqueous RACP.

Cyclodextrin has a hydrophobic cavity and hydrophilic exterior, so it is able to host hydrophobic molecules and form water-soluble host-guest complex.[17] It has been applied to solubilize hydrophobic monomers in water for aqueous radical polymerization.[18] In this paper, cyclodextrin was applied to "solubilize" hydrophobic nitroso compound by formation guest-host complex. The water-soluble inclusion complexes of Me_2-β-cyclodextrin (CD) and NB allows us to conduct aqueous RACP by using hydrophobic nitroso compound.

Experimental Section

Materials

Copper powder (Cu, 3.25-4.75μm, 99.9%, Alfa Aesar), 2-bromo-2-methylpropionyl bromide (98%, Aldrich), nitrosobenzene (NB, 98%, TCI), 2,6-dimethyl-β-cyclodextrin (CD, average M_n=1310, aladdin), N, N, N', N'', N'' -pentamethyldiethylenetriamine (PMDETA, 98%, Alfa Aesar), pyridine-2-carboxaldehyde (99%, Aldrich), 2-(2-aminoethoxy)ethanol (98%, Alfa Aesar) and 1-

ethylpiperidinehypophosphite (EPHP, 95%, Aldrich) were used as received. The water used in all experiments was deionized and doubly distilled prior to use. Poly(ethylene glycol) bis(α-bromoisobutyrate) (Br-PEG-Br) and N-(2-hydroxyl ethoxyethyl) 2-pyridyl methanimine (HEEPMI) were synthesized according to our published method[16] and stored under anhydrous conditions prior to use.

Characterization

Number-average molecular weight (M_n) and molecular weight distributions (PDI) were determined by gel permeation chromatograph (GPC) on a PL GPC220 equipped with two PLgel 5 μm MIXED-C columns using polystyrene standards and THF as the eluent at a flow rate of 1.0 mL/min at 40°C. ^{1}H NMR spectra were recorded at room temperature by a Bruker (400 MHz) spectrometer using tetramethylsilane as the internal standard and $CDCl_3$ or D_2O as the solvent.

Synthesis of 2,6-dimethyl-β-cyclodextrin/Nitrosobenzene complex (CD/NB)

NB (11.8 mg, 1.1 ×10^{-4} mol), CD (157.7mg, 1.21×10^{-4} mol) and doubly deionized water (0.5 ml) were added into a Schlenk-tube with a stirring bar. The mixture was ultrasonicated at ambient temperature for 30 min to form a blue homogeneous solution.

Synthesis of N-(2-hydroxyl ethoxyethyl)-bis(2-picolyl) amine (HEEBPA)

N-(2-hydroxyl ethoxyethyl)- bis(2-picolyl) amine (**HEEBPA**) was synthesized according to literature method.[19] Pyridine-2-carboxaldehyde (0.5356 g, 5.0×10^{-3} mol), 2-(2-aminoethoxy) ethanol (0.2629 g, 2.5×10^{-3} mol) and acetic acid (0.29 ml, 5.0×10^{-3} mol) were dissolved in dry THF (20 ml). Then sodium triacetoxyborohydride (1.415 g, 6.7×10^{-3} mol) was added and the reaction mixture was stirred at room temperature for 3 days under nitrogen atmosphere. After removing the solvent, the residue was dissolved in CH_2Cl_2 (15 ml) and washed with aqueous solution of Na_2CO_3 (10 wt%, 3×30 ml), and dried over anhydrous $MgSO_4$. Evaporation of the solvent and purification by flash column chromatography (CH_2Cl_2:CH_3OH = 9:1) to give an dark-yellow oil (23%). ^{1}H-NMR (400 MHz, D_2O) δ (in ppm): 7.08-8.20 (m, $C_5\boldsymbol{H}_5N$), 3.61 (s, $(C_5H_5N\text{-}C\boldsymbol{H}_2)_2N$), 3.45 (q, $C\boldsymbol{H}_2\text{-}O\text{-}C\boldsymbol{H}_2$), 3.28 (t, $O\text{-}CH_2C\boldsymbol{H}_2\text{-}OH$), 2.62 (t, $(C_5H_5N\text{-}CH_2)_2N\text{-}C\boldsymbol{H}_2$).

Aqueous radical addition coupling polymerization

In a typical procedure of aqueous RACP, CD (157.7 mg, 1.21×10^{-4} mol), NB(11.8 mg, 1.1×10^{-4} mol) and doubly deionized water (0.5 mL) were added into a 10 ml Schlenk flask which was equipped with a stirring bar. The mixture was ultrasonicated for 30 min to form a blue homogeneous solution. Subsequently, Br-PEG-Br (1.1×10^{-4} mol) and HEEPMI (4×10^{-4} mol) were added. After four freeze-pump-thaw cycles, Copper powder (14.1 mg, 2.2×10^{-4} mol) was added under nitrogen to start the polymerization. The reaction solution became dark brown gradually. After for predetermined time, the mixture was diluted with CH_2Cl_2/CH_3OH (20:1) and purified by passing through a neutral alumina column. The polymer solution was concentrated and dried under vacuum at 40 °C to yield crude product as a light yellow tacky gum, and it was analyzed by GPC.

Dialysis of crude product

The crude product was dialysed with a dialysis membrane (MWCO = 3500 Da) at ambient temperature for a given time. The solvent was removed in vacuum to yield the pure polymer.

Thermal fragmentation of polymer in the presence of 1-ethylpiperidinehypophosphite (EPHP)

The dialyzed polymer (33 mg), EPHP (996 mg) were charged to a 10 ml Schlenk flask which was equipped with a stir bar, and they were dissolved in anisole (1.5 ml). After three freeze-pump-thaw cycles, the Schlenk tube was placed in an oil bath thermostated at 130 °C. After 60 h the product was diluted with 80 ml CH_2Cl_2 and washed with deionized water for three times. The polymer solution was concentrated. It was finally dried under vacuum at 40 °C, the resulting product was analyzed by GPC.

Results and Discussion

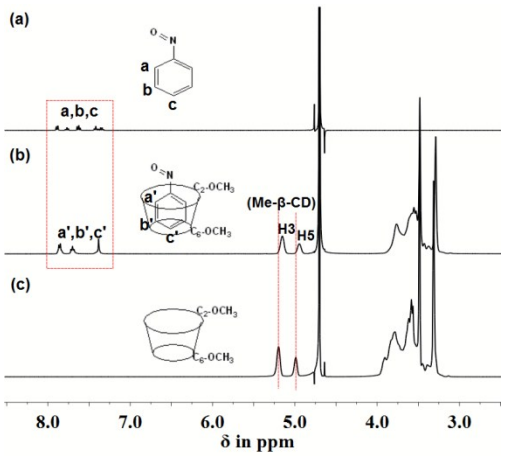


Fig. 1 ^{1}H NMR spectra (in D_2O) of NB(a), CD/NB(b) and CD(c)

Cyclodextrin is able to host hydrophobic molecules in its hydrophobic cavity. The complexation of CD and NB was accomplished via mixing 1 equiv. nitroso compound with 1.1 equiv. CD in water under ultrasonication for 30 minutes. A clear solution was obtained. The product was characterized by ^{1}H-NMR. The formation of inclusion complex was evidenced by the shifting of signals of H3 and H5 protons of CD[20] and aromatic proton of NB as shown in **Fig. 1**. So, NB can be easily solubilized in water by CD and the complex of NB/CD (1:1.1) was used for aqueous RACP.

Poly(ethylene glycol) bis(α-bromoisobutyrate) (Br-PEG-Br) can be easily prepared by reaction of α-bromo isobutyryl bromide with α,ω-dihydroxyl poly(ethylene glycol) (HO-PEG-OH, M_n=600 g/mol).[16] Two ligands, N-(2-hydroxyl ethoxyethyl) 2-pyridyl methanimine (**HEEPMI**) [16] and N-(2-hydroxyl ethoxyethyl)- bis(2-picolyl) amine (**HEEBPA**)[19] in **Scheme 1**, were readily synthesized according to the published methods, which are more soluble in water than PMDETA.

The polymerization were conducted at [CD]:[NB]:[Br-PEG-Br]:[Cu]:[ligand]=1.21:1.1:1:2.2:4 and [Br-PEG-Br]=0.2 M in water at 30 °C for 4 h with three different ligands as shown in Scheme 1. The number-average molecular weight (M_n) and polydispersity index (PDI) of products were given in **Table 1**. Among the three ligands, HEEPMI resulted the highest M_n, which is due to its good solubility in water.

Table 1. Aqueous RACP of Br-PEG-Br and Me_2-β-CD/ NB with different ligands.[a]

run	Ligand	M_n[b] (g/mol)	PDI[b]
1	PMDETA	7500	2.23
2	HEEBPA	6500	1.90
3	HEEPMI	10800	2.08

[a] Polymerization condition: [CD]:[NB]:[Br-PEG-Br]:[Cu]:[ligand] =1.21/1.1/ 1/ 2.2/4, [Br-PEG-Br]=0.2 M, H_2O, 30° C, 4 h. [b] Number-averaged molecular weight (M_n) and polydispersity index (PDI) of polymer (excluding the peak of CD) measured by gel permeation chromatography.

Table 2. Aqueous RACP of Br-PEG-Br and Me_2-β-CD/NB under different conditions[a]

run	[Br-PEG-Br]	Temp[b]	M_n[c] (g/mol)	PDI[c]	Yield (%)
1	0.05	30	13200	2.96	-
2	0.1	30	10200	2.84	-
3	0.2	30	10800	2.08	91
4	0.2	40	9400	2.50	92
5	0.2	50	8200	2.63	86

[a] Polymerization condition: [CD]:[NB]:[Br-PEG-Br]:[Cu]:[HEEPMI] =1.21:1.1:1:2.2:4, H_2O, 4 h. [b] Polymerization temperature in °C. [c] Number-averaged molecular weight (M_n) and polydispersity index (PDI) of polymer (excluding the peak of CD) measured by gel permeation chromatography.

The polymerization temperature and the concentration of monomer were also varied and the results were listed in **Table 2**. When the monomer concentration varied from 0.2 M to 0.1 M, the polymer with similar M_n and broad PDI was obtained. When the concentration was further reduced to 0.05 M, a higher M_n was obtained. As the polymerization temperature increased from 30 to 50 °C, the M_n of polymer gradually decreased. RACP follows the step-growth mechanism. In the RACP, except addition and coupling reactions, all radical reactions, such as the disproportion and transfer reactions, affect the growth of the polymer chain. If the radical concentration is high, the disproportion and transfer reaction of radical lead to the termination of chain growth. This results polymer with low molecular weight at high temperature and high monomer concentration.

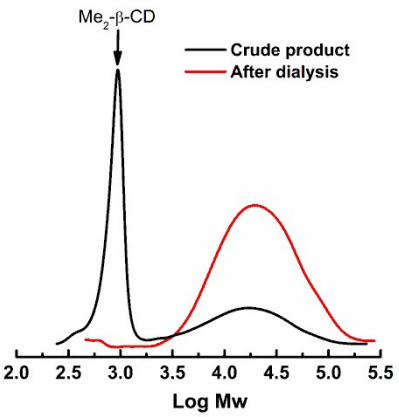


Fig. 2 GPC curves of polymer Run 3 in Table 1 before and after dialysis.

In the GPC curves of all products, peaks corresponding to CD can be detected, which indicated that CD inclusion complex was dissociated after the NB was incorporated into the polymer chain. In order to remove the CD, dialysis was performed using dialysis tubing with a MWCO of 3500 Da at ambient temperature. From the GPC curves shown in **Fig. 2**, the peak derived from CD completely disappeared and the peak of polymer hardly shifted. This indicates that CD can be removed by dialysis and no CD inclusion complex with polymer exists. Based on the weight of the purified polymer, the yields of the RACP were estimated. The yield was lower at 50 °C than 30 and 40 °C, because more low M_n fraction of polymer produced at 50 °C was removed by dialysis.

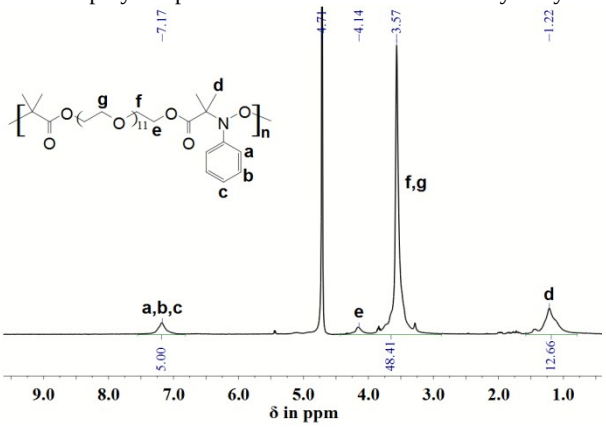


Fig. 3 ^{1}H NMR (D_2O) spectrum of polymer prepared by aqueous RACP of Br-PEG-Br

The ^{1}H-NMR spectra of the Run 3 in **Table 2** after purification by dialysis was shown in **Fig. 3**. The signals from the PEG segment and the nitroso unit can be clearly detected, and no signals from CD unit can be found. The ^{1}H-NMR spectrum of the purified polymer was the same as the ^{1}H-NMR spectrum of polymer prepared by organic RACP using Br-PEG-Br and NB. (see Fig S4) This also demonstrates that CD can be completely removed by dialysis. Although PEG can form complex with CD,[21-22] our result approves that no CD is complexed with PEG segment after polymerization.

The molar ratio of two units incorporated into the polymer chain can be calculated by peak intensity of the methyl groups (H_d) from PEG and phenyl group ($H_{a,b,c}$) from NB. The [PEG]/[NB] molar ratio is 1.06:1, very close to unity, which fits the alternative monomer sequence of the polymer. This is the same as the periodic polymer synthesized by organic[14-15] and aqueous[16] RACP.

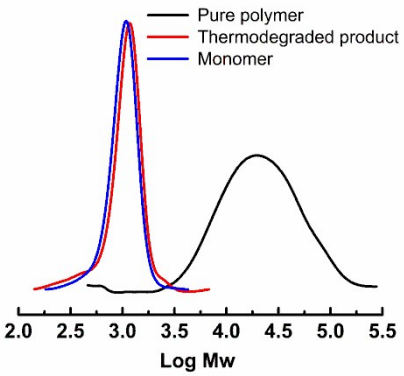


Fig. 4 GPC curves of Br-PEG-Br and periodic polymer prepared by aqueous RACP before and after thermodegradation.

The polymer contains alkoxyamine moiety, which can be thermal degraded. The solution of run 3 in **Table 2** was heated in the presence of 1-ethylpiperidinehypophosphite as hydrogen atom donor. The GPC curve after thermal degradation was almost the same as its monomer, which also clearly demonstrates the perfect alternative monomer sequence of the polymer without PEG-PEG segment generated by self-coupling of carbon radical. The obtained hydrophilic polymer has repeating sequence of $[AB_xAC]_n$ (A=ester, B=ethylene oxide, C=N-O).

Conclusions

We have conduced aqueous RACP using water-soluble inclusion complexes of CD/NB. Compared with water-soluble nitroso compound, the reported system provides a simple method using commercial available nitroso compound to synthesize hydrophilic periodic polymer with regular sequence in aqueous media.

Acknowledgments

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Notes and references

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† Electronic Supplementary Information (ESI) available: GPC and the ^{1}H NMR spectra of obtained polymers. See DOI: 10.1039/b000000x/

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