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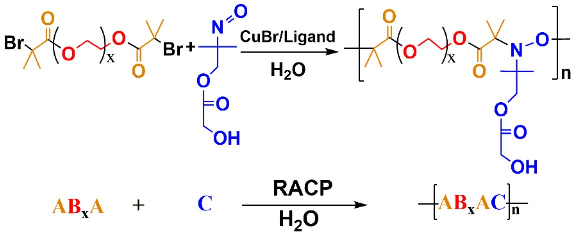

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# Aqueous Radical Addition-Coupling Polymerization for Synthesis of Hydrophilic Periodic Polymer

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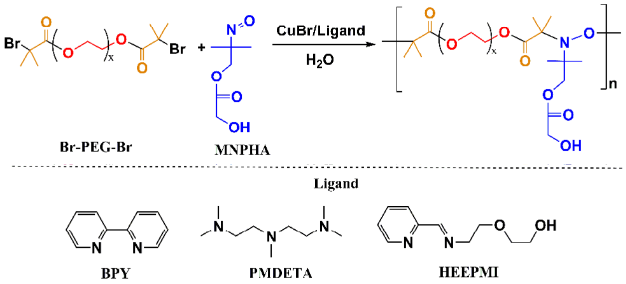
**Hydrophilic polymer possessing $[AB_xAC]_n$ (A=ester, B=ethylene oxide, C=N-O) repeating sequence was synthesized by aqueous radical addition-coupling polymerization using water-soluble dibromide and nitroso compound in the presence of CuBr/ligand. This opens a new pathway to synthesize water-soluble periodic polymer with regular sequence.**

Natural macromolecules, such as proteins and nucleic acids, have unique properties generating from their precisely sequence-regulated chain structures. As a counterpart in synthetic polymer, periodic copolymer[1-3], which has a particular arrangement of the different units repeating along the polymer chain, has attracted much attention. Control on the unit sequence and the molecular weight of the product is two challenging targets in chain-growth polymerization. The "living" radical polymerizations, such as ATRP[4] and RAFT[5] polymerization, achieve perfect control on the molecular weight distribution, but the control on sequence-regulated chain structure in radical polymerization is far from satisfaction.

Chain-growth copolymerization produces polymer with statistical or random monomer sequence distribution, although a few alternating copolymers can be obtained by specific monomer pairs.[6-7] Condensation polymerization based on the two or more kinds of bifunctional monomers with different groups is a suitable method to produce sequence-regulated chain, but its low reaction rate, precise feed ratio and high reaction content for high molecular weight limit its application. Recently, some novel methods have been developed to produce periodic polymers via chain-growth[8-14] and step-growth polymerization[15-18]. We have also developed radical addition-coupling polymerization (RACP)[19-20], 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.

Most of above methods are performed in organic media. The natural macromolecules are waterborne and mostly synthesized in aqueous media. 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. Polymerization in water is also an environment-friendly and low-cost process. These advantages have stimulated efforts to conduct various kinds of polymerization in aqueous media. 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, here we report the aqueous RACP for synthesis of periodic polymer with regular unit sequence $[AB_xAC]$, which can be applied to synthesis of well-controlled hydrophilic periodic polymer from water-soluble monomer.



**Scheme 1**. Aqueous radical addition-coupling polymerization (aRACP) of Br-PEG-Br.

RACP involves consecutive addition of carbon-centered radical generated by redox of telechelic dibromide by Cu/ligand 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[19-20]. To conduct aqueous RACP, all components, including monomer, ligand and nitroso compound, need to be soluble in water. Poly(ethylene glycol) diisobutyryl bromide (**Br-**PEG-Br) can be easily prepared by reaction of α-bromo isobutyryl bromide with α,ω-dihydroxyl poly(ethylene glycol) (HO-PEG-OH). By using HO-PEG-OH with different molecular weights, several Br-PEG-Br were prepared and used as monomer. 2-Methyl-2-nitroso propane (MNP) used in organic RACP does not dissolve in water very well. We synthesized the novel nitroso compound, 2-methyl-2-nitroso propyl 2-hydroxyl acetate (MNPHA), as shown in Scheme 1. It is more soluble than MNP in water due to its hydroxyl group. It is a better choice for aqueous RACP compared with MNP. The hydrophilic pyridyl methanimine ligands were reported to be suitable for aqueous ATRP of hydrophilic methacrylates[21]. N-(2-hydroxyl ethoxyethyl) 2-pyridyl methanimine (HEEPMI) in Scheme 1 was readily synthesized by the reaction between 2-pyridine carbaldehyde and 2-(2-aminoethoxy) ethanol. HEEPMI is more soluble in water than N-ethyl pyridyl methanimine. $^1H$ NMR spectroscopy was used to confirm chemical structures and purity of synthesized compounds.

**Table 1.** Aqueous RACP of Br-PEG600-Br and nitroso compound (MNPHA) under different initiation systems.[a]

| run | Initiation system | $M_n$[b] (g/mol) | PDI[b] |
|---|---|---|---|
| 1 | Cu/PMDETA | 3700 | 2.62 |
| 2 | Cu/HEEPMI | 7900 | 2.79 |
| 3 | CuBr/BPY | 1900 | 1.87 |
| 4 | CuBr/PMDETA | 2100 | 2.07 |
| 5 | CuBr/HEEPMI | 12000 | 2.29 |

[a] Polymerization condition: [Br-PEG600-Br]:[MNPHA]: [Cu or CuBr]:[ligand]=1:1.1:2.2:2, [Br-PEG600-Br]=0.1 M, $H_2O$, 40 °C, 4 h. [b] Number-averaged molecular weight ($M_n$) and polydispersity index (PDI) of polymer measured by gel permeation chromatography.

The Br-PEG-Br can be well polymerized by RACP in THF in the presence of Cu/ N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA), which was same as α,α'-dibromoesters monomers reported by previous papers.[19-20] Two ligands, PMDETA and HEEPMI were screened for their performance in water. The polymerization were conducted at [Br-PEG600-Br]:[MNPHA]:[Cu]:[ligand] =1:1.1:2.2:2 and [Br-PEG600-Br]=0.1 M in water at 40 °C for 4 hours and the number-average molecular weight ($M_n$) and polydispersity index (PDI) of products were given in **Table 1**. HEEPMI resulted the higher $M_n$ of polymer than PMDETA, although both ligands gave low $M_n$. 2,2'-bipyridinyl (BPY)[22-23], 1,1,4,7,10,10-hexamethyltriethylenetetramine[22], tris(2-pyridylmethyl)amine[24] and N-alkyl pyridyl methanimine[21, 25] were reported to be used in aqueous ATRP, but their low solubility in water limits their application in aqueous RACP.

The $M_n$ of product of aqueous RACP is much lower than organic RACP. The reason is probably the relative low concentration of radical during the polymerization. For RACP, relative high radical concentration is crucial, which is achieved by high concentration of dibromide monomer (0.5M or so). In organic RACP, radical is in-situ generated by the efficient and rapid single electron transfer redox reaction between dibromide and Cu/polyamine. The in-situ generated radical undergoes further reaction with N=O double bond.[19-20] It is evident that the initiator system applied for organic RACP does not work well in the water.

Water is a very strong ligand that can coordinate to metal ion, resulting in competition with the nitrogen ligand. It is clear that water greatly affects the equilibrium between $Cu^I/Cu^{II}$ complexes and stability of the complex in aqueous ATRP[26]. In aqueous RACP, the concentrations of monomer (also termed as initiator in ATRP) and ligand are around $10^{-2}$-$10^{-1}$ M, which are much higher than the concentration of the initiator and the ligand in normal aqueous ATRP. Besides the effect of water on the formation of radical species from alkyl halide, the influence of interaction between monomer and ligand on aqueous RACP should be considered as well. Since the ligands are tertiary polyamines and the monomer is bromide, the quaternization reaction must be considered. In organic RACP[19-20], PMDETA is a good ligand and can be applied for many monomers containing α-bromoester group. Precipitation occurred when PMDETA and α,α'-dibromo *p*-xylene were mixed together in THF, which is due to quaternization reaction. If the quaternization process occurs, the generation of radical from the halide is hindered, which results termination of the growth of polymer chain in RACP.

The $^1$H-NMR spectra of the mixture of Br-PEG600-Br with PMDETA and HEEPMI at 50 °C in water for 1 hour were recorded. At the similar reaction condition as RACP, the quaternization reaction took place in water for both ligands. The quaternization percentage of Br-PEG-Br was 48 mol% for PMDETA and 31 mol% for HEEPMI.(see Figs S15,S16) We believe this is the main reason accounting for the poor performance of Cu/ligand in aqueous RACP compared with organic RACP, because no quaternization process is observed in THF.

CuBr/ligand was also tested for in-situ generation of radical in water, since large ATRP equilibrium constant in aqueous media may generate high concentration of radical[26]. It was also reported that alkyl halide was much more rapidly activated by $Cu^I$ than by Cu in the water[27]. The BPY can be used since its complex with CuBr is well soluble in the water. The $M_n$ and PDI of resulting polymers were given in Table 1. The ligands BPY and PMDETA gave almost the same $M_n$. PMDETA results slight lower $M_n$ paired with CuBr than Cu. Only HEEPMI in combination with CuBr gave the highest $M_n$, which was much higher than with Cu.

**Table 2.** Aqueous RACP of Br-PEG600-Br and MNPHA with CuBr/HEEPMI as initiation system.[a]

| run | [Br-PEG-Br](M) | Temp[b] | $M_n$[c] | PDI[c] | Yield[d] |
|---|---|---|---|---|---|
| 1 | 0.1 | 40 | 12.1 | 2.71 | 99% |
| 2 | 0.1 | 50 | 14.5 | 2.48 | 99% |
| 3 | 0.1 | 60 | 9.7 | 2.47 | 97% |
| 4 | 0.1 | 50 | 14.7 | 3.09 | 98% |
| 5 | 0.05 | 50 | 15.1 | 3.06 | 98% |
| 6 | 0.02 | 50 | 12.4 | 3.14 | 98% |

[a] Polymerization condition: [Br-PEG600-Br]:[MNPHA]:[CuBr]:[HEEPMI] =1:1.1:2.2:4, $H_2O$, 1 h. [b] Polymerization temperature in °C. [c] Number-averaged molecular weight ($M_n$ in $10^3$ g/mol) and polydispersity index (PDI) of polymer (excluding the minor peak of the monomer) measured by gel permeation chromatography. [d] Polymer yield calculated by the integrity area of GPC curve of polymer.

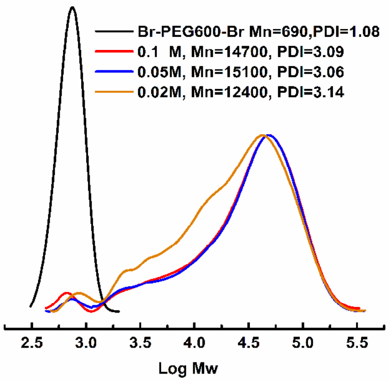


**Fig.1.** GPC curves of polymers prepared by aqueous RACP under different monomer concentrations.

Following these observations, CuBr/HEEPMI initiator system was chosen for further investigation for screen of polymerization condition, and the results were listed in **Table 2**. The polymerization temperature was varied from 40 to 60 °C, the $M_n$ of polymer was maximum at 50 °C. When the monomer concentration varied from 0.1 M to 0.05 M, the polymer with similar molecular weight distribution was obtained as shown in

**Fig. 1**. When the concentration was further reduced to 0.02 M, a much lower molecular weight fraction was found in the GPC curve of the product, resulting a reduced $M_n$ and broad distribution. In the GPC curves of all products, the trace monomer can be detected, which is due to the non-full functionality of Br-PEG-Br or cyclization of the monomer. From the GPC curves, the conversion of the monomer can be calculated based on the ratio of the peak areas of monomeric and polymeric fractions. As shown in Table 2, the conversions were more than 97% for all polymerizations.

**Table 3.** Polymers prepared by aqueous RACP with different Br-PEG-Br.[a]

| Run | Monomer | Polymer | | | |
|---|---|---|---|---|---|
| | | $M_n$[b] | PDI[b] | DP[c] | [PEG]/[MNPHA][d] |
| 1 | Br-PEG600-Br | 14.7 | 3.09 | 21.6 | 1.00 |
| 2 | Br-PEG1000-Br | 16.6 | 1.69 | 12.8 | 0.98 |
| 3 | Br-PEG2000-Br | 25.5 | 1.67 | 8.8 | 0.97 |

[a] [Br-PEG-Br]:[MNPHA]:[CuBr]:[HEEPMI]=1:1.1:2.2:4, Br-PEG-Br =0.1M, $H_2O$, 50 °C, 1 h. [b] Number-averaged molecular weight ($M_n$ in $10^3$ g/mol) and polydispersity index (PDI) (excluding the minor peak of the monomer) of polymer measured by gel permeation chromatography. [c] $DP=M_n/(M_{Br\text{-}PEG\text{-}Br} + M_{MNPHA} - 2M_{Br})$ , $M_n$ of Br-PEG600-Br, Br-PEG1000-Br and Br-PEG2000-Br are 690, 1300 and 2900 g/mol respectively. [d] Composition of polymer measured by $^1$H-NMR spectra..

By using different commercial HO-PEG-OH, α,α'-dibromoester capped PEG can be prepared. Three polymers in **Table 3** were obtained from different Br-PEG-Br. The maximum $M_n$ was obtained by Br-PEG2000-Br and the maximum polymerization degree was obtained by Br-PEG600-Br.

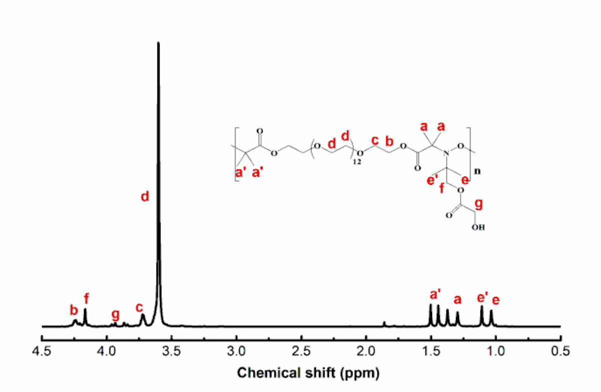
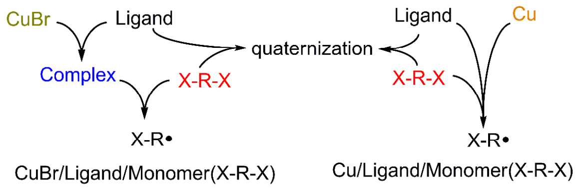


**Fig. 2** $^1$H NMR ($D_2O$, 400MHz) spectrum of polymer prepared by aqueous RACP of Br-PEG600-Br

The $^1$H-NMR of the polymer prepared by Br-PEG600-Br was presented in **Fig. 2**. The signals from the PEG segment and the nitroso unit can be clearly detected. The two groups of double peaks (a and a') clearly indicates the of the two methyl groups of monomer connected to the different sides of -N-O- bond. No other peaks was detected for the methyl group of PEG. According to the two types of methyl groups ($H_{a,a'}$ *vs* $H_{e,e'}$) from two different units, the molar ratio of two units incorporated into the polymer chain can be calculated from the corresponding peaks area. For the three polymers in **Table 3**, the molar ratio of the two units is close to unity (see Figures S12-S14), which demonstrates the alternative monomer sequence of the polymer. This is the same as the periodic polymer synthesized by organic RACP[19-20].

The polymer contains alkoxyamine moiety, which can be thermal degraded. The polymer solution of run 1 in Table 3 was heated in the presence of 1-ethylpiperidinehypophosphite as hydrogen atom donor. The GPC curve (see Figure S18) 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 due to self-coupling of carbon radical. The obtained hydrophilic polymer has repeating sequence of $[AB_xAC]_n$ (A=ester, B=ethylene oxidel, C=N-O), which can be further modified due to its hydroxyl group at the side chain of nitroso unit.

In aqueous ATRP, BPY[22-23], PMDETA, 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA)[22], tris(pyridin-2-ylmethyl)amine[24] and N-alkyl pyridyl methanimine[21, 25] were reported to be used. In the current study, hydrophilic pyridyl methanimine ligand affords the best performance in aqueous RACP.



**Scheme 2** Possible reactions for the different initiation system

As shown in **Scheme 2**, for the polymerization using CuBr/ligand/Br-PEG-Br/MNPHA, the ligand can react with CuBr to generate coordinated complex which is evidenced by change of color. At the same time, the ligand can also reacts with monomer yielding quaternary ammonium salt. The subsequent reaction between the complex and the monomer generates radical based on atom transfer mechanism. For the polymerization using Cu/ligand/Br-PEG-Br/MNPHA, no reaction occurs between ligand and Cu, and the radical is produced by interaction among monomer, Cu and ligand based on single electron transfer mechanism. At the same time, the reaction between ligand and monomer exists as well. If we compare two systems, although the monomer can react with ligand in both systems, but the rapid coordination reaction between ligand and CuBr consumes the ligand quickly resulting in a low concentration of free ligand, which restrains the quaternization reaction between ligand and monomer. This explains the fact that thr CuBr/HEEPMI system is much better than the Cu/HEEPMI for aqueous RACP.

## Conclusions

We have developed aqueous RACP as an efficient tool to prepare hydrophilic periodic polymer using water-soluble components. Hydrophilic pyridyl methanimine ligand presents the best performance in aqueous RACP due to its good solubility and weak ability to generate quaternary ammonium salt in the water. The reported system opens a new pathway to synthesize water-soluble periodic polymer with regular sequence in aqueous media.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, GPC and the $^1$H NMR spectra of obtained polymers. See DOI: 10.1039/b000000x/

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