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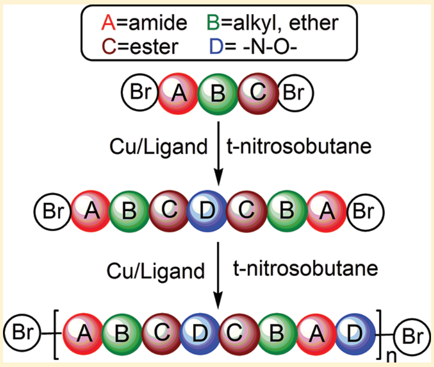
Radical Addition-Coupling Polymerization (RACP) toward Periodic Copolymers

Chengyu Zhang, Jun Ling, and Qi Wang*

Key Laboratory of Macromolecular Synthesis and Functionalization (Ministry of Education), Department of Polymer Science & Engineering, Zhejiang University, Hangzhou 310027, P. R. China

S *Supporting Information*

ABSTRACT: We synthesize periodic copolymers possessing [ABAC], [ABCD], and [ABCDBCAD] repeating structure by radical addition-coupling polymerization (RACP) based on the reaction between α,ω-biradicals derived from α,α'-dibromo compound and 2-methyl-2-nitrosopropane.



INTRODUCTION

Natural macromolecules, such as proteins and nucleic acids, have various properties originating from their perfectly sequence-regulated chain structures. Periodic copolymer[1−3] as a counterpart in synthetic chemistry, in which a particular arrangement of the different units repeats along the polymer chain, has attracted much attention. However, the sequence regulation of synthetic polymers is still beyond the current state of the art in polymer synthesis. Therefore, sequence regulation is one of the most challenging objectives in contemporary polymerization science. For this purpose, various synthetic pathways have been developed to achieve this ultimate goal, although it has not yet been perfectly achieved. Most copolymers synthesized by chain-growth copolymerization have statistical or random monomer sequence distribution, although a few alternating copolymers can be obtained by specific monomer pairs.[4,5] Recently, some novel methods have been developed to produce such polymer via chain-growth[6−12] and step-growth polymerization.[13−16] By condensation polymerization, various polymers with precise periodic structure, such as amide, ester, ether, and so on, in main chain can be obtained by various building blocks.[4] Oligoamides, oligoesters, oligoureas, oligocarbamates, and oligosaccharides can be produced by Merrifield's solid-phase condensation and nonenzymatic template polymerization.[17,18]

Generally, radical coupling reaction is scarcely used in polymerization[19] although it is a rapid reaction because radical still undergo disproportionation and transfer reactions by themselves, which makes it impossible to produce polymer with high molecular weight.[4] Radical cross-coupling reaction based on persistent radical effect or Ingold−Fischer effect[20,21] has been widely applied in organic synthesis. The cross-coupling reaction between carbon-centered radical and stable nitroxyl radical have been reported to prepare alkoxyamine[22] and diblock copolymer with alkoxyamine as joint unit.[23,24] Recently, we applied such reaction with combination of the Ingold−Fischer effect to polymerization. As shown in Scheme 1, in situ formation of nitroxyl radical via addition of carbon-centered radical generated by redox reaction between α,α'-dibromo compound and Cu/ligand to N═O double bond of C-nitroso compound followed by cross-coupling of carbon-centered radical (**3**) and nitroxyl radical (**4**) produces alternating copolymers.[25] The so-called radical addition-coupling polymerization (RACP) can be applied to synthesize periodic copolymer with alternative monomer sequence from saturated and unsaturated monomers together with multisegmented polymer.[26]

In this article, we apply RACP to the synthesis of some new types of periodic copolymers from dibromo compounds containing amide, ester, ether, and phenyl groups with *tert*-nitrosobutane, which possess [ABAC], [ABCD], and [ABCDBCAD] periodic structure.

RESULTS AND DISCUSSION

As shown in Scheme 1, various dibromo compounds (**1**) containing amide, ester, and ether groups were prepared by a general method (see Supporting Information). They were treated with copper powder and ligand (2,2′-bipyridine, bpy; *N*,*N*,*N*′,

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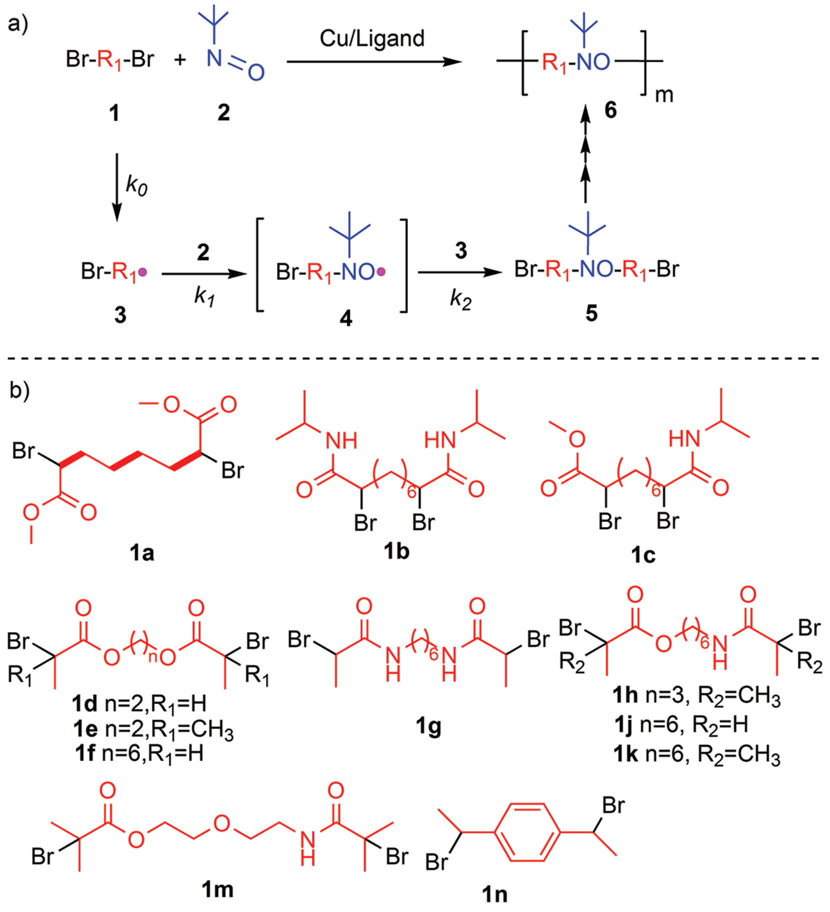
Scheme 1. Concept of Radical Addition-Coupling Polymerization (RACP) (a) and the Structure of Various Monomers 1 (b)



N'',N''-pentamethyldiethylenetriamine, PMDETA; tris[2-(dimethylamino)ethyl]amine, Me_6TREN) in the presence of equivalent amount of *tert*-nitrosobutane (**2**) in tetrahydrofuran (THF) or toluene/dimethyl sulfoxide (DMSO) at 25 °C. After separation of residual copper complex, the polymer was obtained. The polymerization results given in Table 1 indicate that polymers with high molecular weight and unimodal molecular weight distribution are obtained.

From monomers **1a**−**1c**, the periodic copolymers with same or different pendent functional groups can be obtained. For example, the copolymer prepared from **1a** has the repeating unit of (acrylate−ethylene−acrylate−**2**), which can be considered as the alternating copolymer of corresponding vinyl monomers with [ABAC] sequence. The polymer prepared from **1c** has the repeating unit of [acrylate−tetramethylene−amide−**2**], which is the periodic copolymer with [ABCD] sequence. From monomers **1d**−**1m**, the periodic copolymers, such as polyester, polyamide, poly(ester−amide), and poly(ester−ether−amide), can be prepared by using different monomers with same or different functional groups in the main chain of polymer. All copolymers have high molecular weight and unimodal molecular weight distribution. The molar ratio [**1**]/[**2**] of copolymer measured by ^{1}H NMR is close to unit, except polymer 12 in Table 1, which indicates that monomer sequence of copolymer is strictly alternative.

The variation of molecular weight distribution of polymer obtained from **1c** and **2** was monitored by gel permeation chromatography (GPC) by direct sampling at different times. As shown in Figure 1a, a clear shift of the molecular weight distribution toward high molecular weight indicates that the polymerization follows the step-growth mechanism, which was proposed and proved in our previous paper.[25] At 15 min (curve 2), the monomer **1c** completely disappeared and a main peak with molecular weight of 870 was found. This peak is assigned to oligomer with **1c**−**2**−**1c** sequence, which is identified by peaks of m/e = 759.0 ([**1c**−**2**−**1c**+H]$^+$) and 780.8 ([**1c**−**2**−**1c**+Na]$^+$) in its mass spectrum (Figure 1b). In addition, the peaks of m/e = 1122.8 and 1465.0 suggest the existence of oligomers with **1c**−**2**−**1c**−**2**−**1c** and **1c**−**2**−**1c**−**2**−**1c**−**2**−**1c** sequence, which can be also detected as two small shoulder peaks in its GPC curve (curve 2).

Since the asymmetric monomer **1c** contains two different functional groups, the reactivity of two C−Br bonds must be different, which is convinced by the fact that polymerization rate of **1b** is rather slower than **1a**. From the ^{1}H NMR spectrum of product obtained at 15 min, the peak of α-protons (H_a in Figure 2) adjacent to ester group of monomer **1c** (noted as head) almost disappeared and the peak of α-proton (H_b in Figure 2) adjacent to amide group (noted as tail) remained the same as monomer **1c**, which indicates the reactivity of C−Br bond adjacent to the head of monomer **1c** is more active than the tail. These evidence clearly demonstrate that the first stage of polymerization is the coupling reaction of radical generated from α-bromo ester group of asymmetric monomer **1c** (see Scheme 2),

Table 1. Step-Growth Radical Addition-Coupling Polymerization of α,α'-Dibromo Compounds (1) and 2-Methyl-2-nitrosopropane (2) Promoted by Cu/Ligand

polymer	monomer **1**	ligand[d]	time (h)	M_n[e] (g/mol)	M_w/M_n[e]	DP[f]	[**1**]/[**2**][g]	$T_{d,10}$[h] (°C)
1[a]	**1a**	PMDETA	1	10 200	3.16	35	1.01	224
2[b]	**1b**	Me_6TREN	2	6 600	3.69	18	–[i]	–[i]
3[a]	**1c**	PMDETA	5	11 900	1.94	68	1.02	238
4[a]	**1d**	PMDETA	1	7 100	1.89	28	1.02	219
5[a]	**1e**	bpy	23	7 900	1.83	28	1.05	–[i]
6[a]	**1f**	PMDETA	1	8 100	1.86	28	1.00	–[i]
7[b]	**1g**	Me_6TREN	2	4 800	1.32	15	–[i]	–[i]
8[c]	**1h**	PMDETA	1	24 900	1.76	82	0.99	–[i]
9[a]	**1j**	Me_6TREN	1	11 200	1.90	36	1.01	234
10[c]	**1k**	PMDETA	1	21 000	1.85	61	0.99	171
11[c]	**1m**	PMDETA	1	11 100	1.64	33	0.99	187
12[a]	**1n**	PMDETA	1	12 200	1.91	56	1.09	204

[a] General conditions: $[\mathbf{1}]_0:[\mathbf{2}]_0:[\mathrm{Cu}]_0:[\mathrm{ligand}]_0$ = 1:1:2.2:2, $[\mathbf{1}]_0$ = 0.5 M, THF = 1 mL, temperature = 25 °C. [b] Solvent: toluene/DMSO = 7/3. [c] $[\mathbf{1}]_0:[\mathbf{2}]_0:[\mathrm{Cu}]_0:[\mathrm{ligand}]_0$ = 1:1:2.2:1. [d] Ligands: PMDETA = *N,N,N′,N″,N″*-pentamethyldiethylenetriamine, Me_6TREN = Tris((*N,N*,-dimethylamino)ethyl)amine, bpy = 2,2′-bipyridine. [e] Number-averaged molecular weight (M_n) and polydispersity index (M_w/M_n) were measured by gel permeation chromatography (GPC). [f] Degree of polymerization is calculated by DP = $M_n/(M_1 + M_2 - 2M_{Br})$. [g] The [**1**]/[**2**] of copolymer was calculated by the ratio of peak area of selected groups of ^{1}H NMR spectra of **1** and **2**. [h] Temperature at 10 wt % weight loss. [i] Not measured.

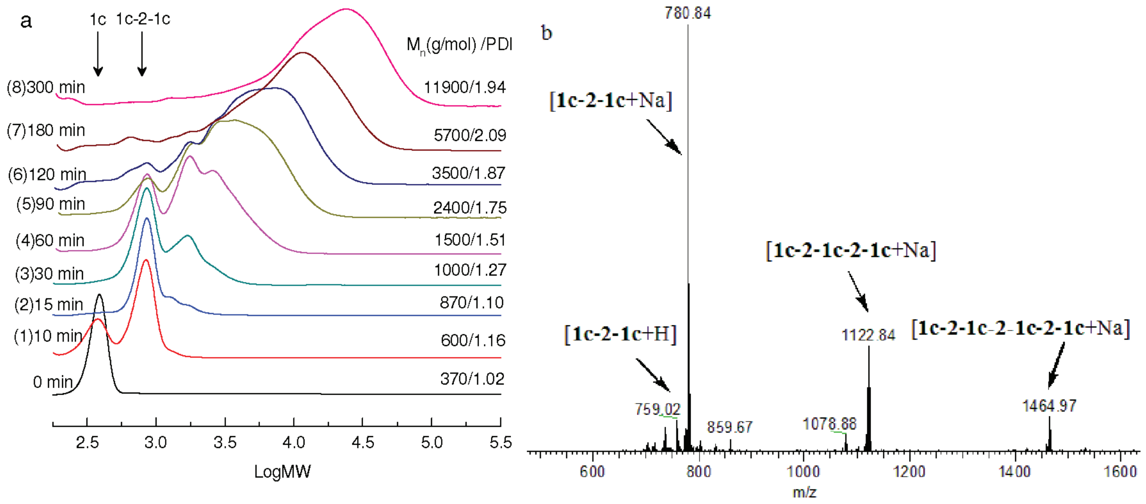


Figure 1. Variation of GPC curves of polymers prepared by RACP of **1c** and **2** promoted by Cu/PMDETA (a) and the ESI-MS spectrum of sample 2 in part a (b) ($[\mathbf{1c}]_0:[\mathbf{2}]_0:[\mathrm{Cu}]_0:[\mathrm{PMDETA}]_0$ = 1:1:2.2:2, $[\mathbf{2}]_0$ = 0.5 M, THF = 1 mL, 25 °C).

resulting trimer with **1c**—**2**—**1c** structure. The in situ formed trimer with two same α,α'-dibromo amide groups then continuously undergoes RACP to produce copolymer with high molecular weight. Therefore, the periodic copolymer **3** in Table 1 has more complicated repeating unit of [ABCDCBAD]. For monomers **1h**—**1m**, the reactivities of the two C—Br bonds are still different. The α-bromo ester group of **1j** generates radical prior to α-bromo amide group, which is confirmed by the ^{1}H NMR spectrum of polymer (Figure S30) synthesized by the feed ratio of $[\mathbf{1j}]_0/[\mathbf{2}]_0$ = 2. So the periodic polymers prepared by asymmetric dibromo compounds must have [ABCDCBAD] repeating sequence. The obtained periodic copolymers have various functional groups in main or side chains; the thermostability was evaluated by TGA, and the results are listed in Table 1 and Figure S35. The temperature at 10 wt % loss of copolymers varied between 171 and 238 °C.

In addition to the reactions proposed in Scheme 1, the radical **3** might undergo self-coupling and disproportionation reactions depicted in Scheme 2 during the polymerization, which are considered as side-reactions in RACP. The self-coupling reaction of **3** will generate [**1**—**1**] diads in polymer with little influence on the molecular weight of the product, while the disproportionation reaction generates one dead chain-end, which might decrease the molecular weight but has no influence on the monomer sequence. For copolymer 12 obtained from monomer **1n**, the copolymer composition indicates that it is not strictly periodic copolymer. From the ^{1}H NMR of copolymer 12 (Figure S34), the diad unit [**1n**—**1n**] could be detected, which suggests that self-coupling of carbon-centered radical generated from **1n** occurs in the polymerization. This is probably due to the rate of formation of carbon-centered radical is so fast and not rather slower than rate of addition reaction, which leads to the self-coupling of carbon-centered radical.

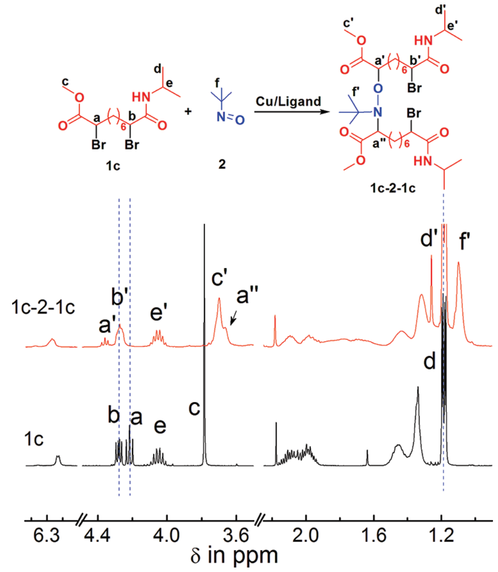


Figure 2. ^{1}H NMR spectra of monomer **1c** and its copolymer (sample **2** in Figure 1a, $[\mathbf{1c}]_0$:$[\mathbf{2}]_0$:$[\mathrm{Cu}]_0$:$[\mathrm{PMDETA}]_0$ = 1:1:2.2:2, $[\mathbf{2}]_0$ = 0.5 M, THF = 1 mL, 25 °C, t = 15 min).

Scheme 2. Formation of Periodic Copolymer with [ABCDCBAD] Repeating Unit by RACP of Asymmetric Dibromo Compounds (a) and Influence of Self-Coupling and Disproportionation Reactions of Intermediate Carbon Radical (3) on RACP (b)

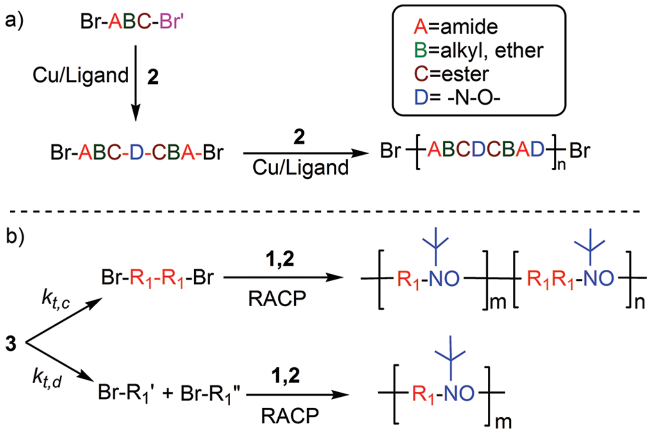


Table 2. Influence of Radical Self-Termination Reaction on Polymerization Degree (DP) and [1−1] Diad Content of Periodic Copolymer Synthesized by RACP Based on Monte Carlo Simulation

entry[a]	k_1/k_t (L mol^{-1} s^{-1})	δ[b]	DP[c]	[**1**−**1**][d]	[**1**]/[**2**][e]
1	$10^5/10^8$	0	50.9	1.82	1.02
2	$10^5/10^8$	0.4	50.5	1.23	1.02
3	$10^5/10^8$	0.7	50.3	0.65	1.02
4	$10^5/10^7$	0.7	50.9	0.06	1.02
5	$10^6/10^8$	0	50.4	0.02	1.02
6	$10^6/10^8$	0.4	50.5	0.01	1.02
7	$10^6/10^8$	0.7	50.5	0.01	1.02
8	$10^6/10^7$	0.7	50.5	0.0	1.02

[a] Kinetics coefficients used in simulation: $k_{0,\mathrm{app}} = 5 \times 10^{-3}$ s^{-1}, $k_2 = 10^8$ L mol^{-1} s^{-1}, $[\mathbf{1}]_0 = [\mathbf{2}]_0 = 0.5$ M, 30 min, at extent of reaction of **1** is 98%. [b] $\delta = k_{t,d}/(k_{t,c} + k_{t,d})$. [c] Degree of polymerization. [d] Numbers of [**1**−**1**] diad per chain on average. [e] The monomer ratio [**1**]/[**2**] of copolymer.

With the consideration of all reactions proposed in Schemes 1 and 2, the polymerization kinetics was simulated by Monte Carlo method with the kinetic parameters obtained from published literature,[27−31] and the results are summarized in Table 2. When the k_1 and k_t are set as 10^5 and 10^8 L mol^{-1} s^{-1}, which are typical values estimated for the current polymerization system, the disproportion reaction of **3** almost has no influence on the degree of polymerization, and the number of [**1**−**1**] diads per chain on average is less than 2.0 when all of the radical **3** undergoes self-coupling reaction. When the k_1 increased to 10^6 L mol^{-1} s^{-1}, the diads [**1**−**1**] in the polymer chain could be neglected. When the k_1 is fixed, the diad content remarkably decreased with the decrement of k_t, which is evidenced by entries 4 and 8 in Table 2. Therefore, the relative difference between k_1 and k_t greatly affects the diads content of the resulting polymer.

CONCLUSIONS

In summary, we have developed an interesting platform for synthesizing periodic polymers with a controlled and complicated microstructure via RACP for the first time. The monomer can be well designed, and the polymerization is tolerated to various functional groups. The biodegradable and thermodegradable functional groups are periodically located in the main or side chain with tunable distance between the groups. Compared with normal condensation polymerization, the RACP has its advantage of achieving high polymerization degree under mild polymerization conditions. This will provide a new strategy for synthesis of sequence-regulated polymer by a simple method.

ASSOCIATED CONTENT

Supporting Information. Experimental details of synthesis and characterization of monomers and polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: wangq@zju.edu.cn. Tel: +86 571 87953754. Fax: +86 571 87952400.

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