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Copper-Catalyzed Bimolecular Coupling of α,ω-Dibromide-Functionalized Poly(γ-caprolactone)

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ABSTRACT: α,ω-Dibromide-functionalized poly(γ-caprolactone) was synthesized by reacting α,ω-dihydroxy-terminated poly(γ-caprolactone) with an excess of 2-bromoisobutyryl bromide, leading to above 99% esterification. The resulting dibromide end-functionalized polycaprolactone (Br-PCL-Br) was found to "polymerize" in the presence of an excess of copper(I) chloride catalyst without the addition of vinyl monomers. Size exclusion chromatography (SEC) clearly revealed that the molecular weight of the "polymerized" macroinitiator shifts to higher values, and a broad peak was obtained with the main peak centered at a molecular weight which was twice that of the Br-PCL-Br precursor, suggesting that the main reaction is bimolecular coupling (~80%), while a shoulder at molecular weights about 6−7 times that of the macroinitiator was also observed attributed to multimolecular coupling. The effects of the reaction temperature and the presence of copper(II) catalyst on the radical coupling reactions were also studied. A higher temperature or a lower copper(II) catalyst concentration favored the bimolecular as opposed to the multimolecular coupling, suggesting the possible occurrence of side reactions such as disproportionation and elimination, which hindered further coupling of the free chain ends.

Introduction

The synthesis of polymers with well-defined compositions, architectures, and functionalities has long been pursued by polymer chemists. Recently, with the development of controlled/living radical polymerization methods,[1−5] atom transfer radical polymerization (ATRP)[6,7] has proved to be a versatile technique to the controlled synthesis of polymers and copolymers of various architectures.

The ATRP technique originated from an organic reaction, the atom transfer radical coupling (ATRC), which contains the initiator and catalysts to form the reversible activation and deactivation of a dormant species R−X to radical R, as shown in Scheme 1. Based on this reaction equilibrium, the radicals produced can be kept at a very low concentration in an ATRP process, at the early stages of the polymerization, and can quickly initiate the polymerization of the large amount of monomer(s) to form the polymer chains while the radical termination reactions can be ignored due to the "persistent radical effect".[7] Polymers or copolymers with well-controlled structures bearing functional groups have been obtained via the ATRP technique.

Recently, studies of the ATRC reaction have attracted much attention for understanding the mechanism of the ATRP process and for its special applications.[8−14] Following the development of a detailed study of the ATRP and ATRC techniques, α,ω-telechelic polymers, multiblock copolymers, or polymers of different architectures were obtained using the simple combination of ATRP and ATRC, which obviously avoid the complicated synthesis protocol used before.[9−22] The polymers or block copolymers containing functional groups were first prepared via the ATRP technique, and then the telechelic polymers were formed by the radical coupling reaction of these macromolecules via an ATRC reaction catalyzed by copper salt (or/and copper) and the appropriate ligand. It should be noted that this method is very simple and versatile for the preparation of polymers with controlled architectures as compared to other polymer radical coupling methods reported in the literature.[23−29]

In the application of the ATRC reaction, Fukuda et al.[8] first reported the polystyrene coupling with 90% coupling efficiency from polystyryl bromide using a Cu(I)Br/tris(2-(dimethylamino)ethyl)amine (Me_6TREN)/Cu(0) catalyst system. In this study, the concentrations of precursor, polystyrene macroinitiator (PS-Br or Br-PS-Br), and Cu(0) were very high, and the formed polystyrene radicals underwent a coupling reaction under a high radical concentration in the ATRC reaction. The results are consistent with the radical coupling reaction of polystyrene reported by different methods. Radical termination normally occurs to an appreciable extent only when the concentration of polymer radicals is unusually high without the presence of monomer, which means that the contribution of polymer radical termination can be expected to be more significant at high initiator concentration and low monomer concentration.[23] Following his pioneered work, Yagci and coworkers[9] reported the preparation of α,ω-telechelic functional polystyrene via ATRP and ATRC techniques, and Hocker et al.[16] reported the fabrication of triblock and multiblock copolymers from PPO-*b*-PS and PS-*b*-PPO-*b*-PS, respectively, where the PPO is poly(propylene oxide) via ATRC technique. Matyjaszewski et al.[10,12] expanded the ATRC study from PS to poly(methyl acrylate) (PMA) and found that the radical coupling efficiency of PMA was lower compared to that of PS coupling and that the general coupling reaction for the PMA system is not viable. However, when a small amount of styrene monomer was introduced into the PMA coupling

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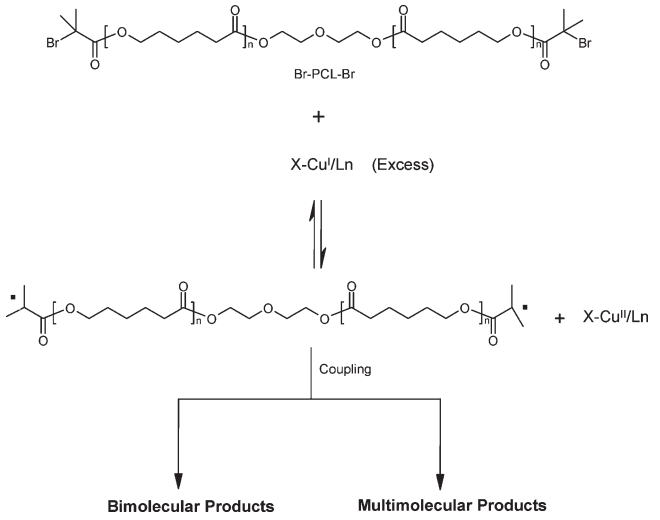
Scheme 1. Schematic Representation for the Bimolecular and Multimolecular Coupling Reactions of Dibromide End-Terminated Poly(γ-caprolactone) in an Excess of Copper(I) Catalyst



system, the produced styrene-terminated PM radicals could undergo the coupling reaction with high efficient coupling. Using the same principle, Luo et al.[20] reported the synthesis of H-shaped ABCAB terpolymers composed of PS (A), poly(ethylene oxide) (B), and poly(*tert*-butyl acrylate) (C) by an ATRC reaction using ABC star terpolymers as precursors and a small quantity of styrene monomer.

The above reports show clearly that the Cu(0)-mediated radical termination method is a facile technique to synthesize longer polymer chains or polymers of complex architecture without employing a complicated synthetic process. Notably, in all the above ATRC studies, the precursor adduct and the zerovalent copper concentrations were high, leading to the formation of the polymer radicals at high concentration and to the dramatic shift of the equilibrium shown in Scheme 1 to the right (high concentration of active radical species). The key point for the ATRC reaction of PS was to keep the concentration of polymer radicals formed to a maximum to increase the radical coupling reactions. However, there are a lot of questions that should be addressed, and the research should be extended as the general ATRC coupling of (meth)acrylate systems seems problematic; the adduct used, Cu(0), was not dissolved in the organic solvent, and the systems studied so far focused mainly on the coupling reactions of PS and PMA.

Poly(γ-caprolactone) (PCL) is a biocompatible polymer and can be easily functionalized to form a precursor that can undergo ATRC reaction. Moreover, the ATRC of PCL would be interesting and useful for the preparation of telechelic PCL polymers. Herein, we report the radical coupling reaction of a dibromide end-functionalized poly(γ-caprolactone) by a copper(I) chloride catalyzed process in the absence of Cu(0) (Scheme 1). First, an ATRP α,ω-macroinitiator was synthesized by reacting α,ω-dihydroxy-terminated poly(γ-caprolactone) with an excess of 2-bromoisobutyryl bromide to obtain a dibromide end-functionalized polymer. Next, the radical coupling reactions of the dibromide end-functionalized poly(γ-caprolactone) adduct were investigated in the presence of an excess of copper(I) catalyst. The effects of the reaction temperature and the presence of Cu(II) on the bimolecular coupling reactions were studied.

Experimental Section

Materials. All reagents were purchased from Sigma-Aldrich unless otherwise noted. α,ω-Dihydroxy-terminated poly(γ-caprolactone) homopolymer (HO-PCL-OH, M_n = 2000 g/mol) was used as received. Triethylamine (TEA, 99%) and methylene dichloride (CH_2Cl_2, 99.5%) were dried over calcium hydride (CaH_2, 95%) and distilled under reduced pressure. Dimethylaminopyridine (DMAP, crystalline) was recrystallized from toluene. 2-Bromoisobutyryl bromide (98%), copper(I) chloride (CuCl, 99.995%), copper(II) chloride ($CuCl_2$, 99.999%), tris(aminoethyl)amine (TREN, 98%), *N*,*N*′-dimethylformamide (DMF, HPLC grade), and neutral alumina oxide were used as received. Me_6TREN was prepared from TREN according to literature procedures.[30]

Synthesis of α,ω-Dibromide-Terminated Poly(γ-caprolactone) (Br-PCL-Br) Macroinitiator. HO-PCL-OH (4 g, 2 mmol) and DMAP (0.4887 g, 4 mmol) were added into a three-neck round-bottom flask, which was vacuum-dried at 80 °C for 2 h to completely remove water. TEA (0.58 mL, 4 mmol) and CH_2Cl_2 (40 mL) were added to the flask under a N_2 atmosphere. 2-Bromoisobutyryl bromide (0.50 mL, 4 mol) was then added dropwise into the above flask at 0 °C. After the addition of 2-bromoisobutyryl bromide, the temperature of the flask was slowly raised to room temperature, and the solution was left stirring overnight. The reaction mixture was filtered and precipitated three times in cold methanol to purify the PCL macroinitiator. The product was finally dried under vacuum at 50 °C. ^{1}H NMR studies in $CDCl_3$ (δ 1.84 (6 H), δ 3.9 (35 H)) indicated the quantitative esterification of the terminal hydroxyl groups of the HO-PCL-OH precursor (see Supporting Information for ^{1}H NMR spectrum of the resulting PCL macroinitiator).

Coupling Reaction of Br-PCL-Br. A typical coupling process is as follows (PCL-3): PCL macroinitiator (0.2443 g, 0.1 mmol), CuCl (0.0495 g, 0.5 mmol), Me_6TREN (0.1150 g, 0.5 mmol), and DMF (1 mL) were added into a round-bottom flask. After three freeze−pump−thaw cycles to remove the oxygen, the flask was placed in an oil bath thermostated at 70 °C for 18 h to allow the coupling reaction to take place. A solution of the crude product was passed through an alumina column to remove the catalyst using chloroform as the elution solvent, and the product was precipitated three times in excess methanol. Finally, the product was dried under vacuum overnight. Size exclusion chromatography analysis of the obtained product revealed a molar mass of 15 100 g/mol and a molecular weight distribution of 2.10.

Different reactions in which the molar ratio of macroinitiator, copper(I) chloride, and Me_6TREN ligand was varied from 1:0.1:0.1, to 1:1:1, and 1:5:5 were carried out. The reaction temperature was also varied (25 and 70 °C) at a constant copper(II) chloride to macroinitiator 1/1 molar ratio to investigate the influence of the reaction temperature and the presence of Cu(II) catalyst on the coupling process.

Characterization. ^{1}H NMR spectra of the macroinitiator in $CDCl_3$ were recorded on a Varian 200 MHz instrument. The polymer solution was dissolved in *N*,*N*′-dimethylformamide (DMF, Caledon Chemicals) to a concentration of 1 mg/mL. The solution was then filtered over a 0.45 μm nylon syringe filter (Fisher Scientific). Molecular weights and molecular weight distributions were measured with a Viscotek size exclusion chromatograph (SEC) equipped with a model VE 2001 SEC autosampler module, a model VE 270 dual multi-angle light scattering/viscometer detector on line with a model 3180 differential refractometer, and two SEC Viscogel columns (packed with 5 μm fluorinated, highly crossed-linked divinylbenzene (DVB) gel) connected in the following series: I-MBHMW-3078 and I-MBLMW-3078. The columns were used to separate polymer in the molecular weight range between 1000 and 200 000 g/mol with high resolution. DMF (Caledon Chemicals) was used as an eluent at a flow rate of 1.0 mL/min at room temperature. The instrument was calibrated using narrow molecular weight polystyrene standards. The measurements were performed at room temperature. Data acquisition was obtained using Viscotek OmniGPC 4.1 software.

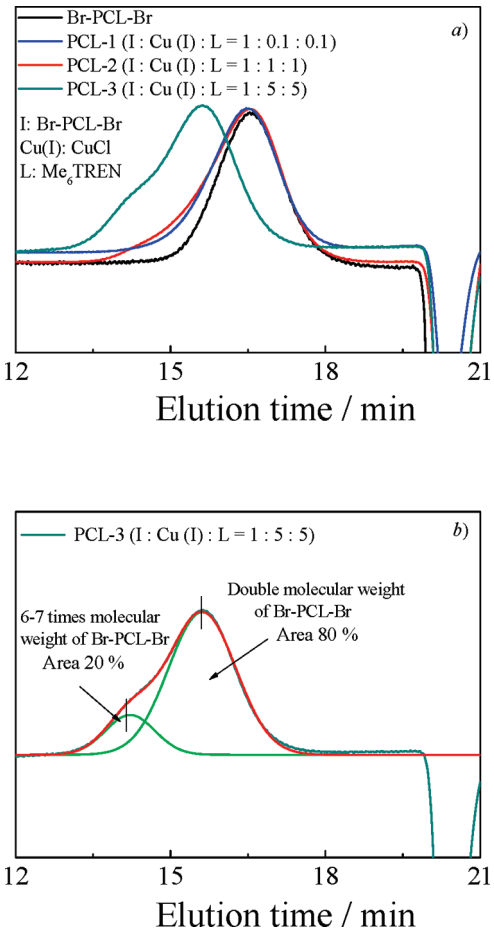


Figure 1. Size exclusion chromatography (SEC) traces for the poly(γ-caprolactone) (PCL) coupling at different copper(I) chloride to macroinitiator molar ratios (a) and peak fitting of the SEC trace of the PCL coupling product using the Gaussian method (b). The reaction temperature was kept constant at 70 °C.

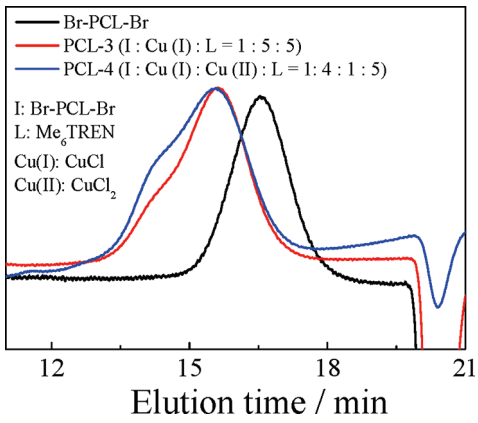


Figure 2. Size exclusion chromatography (SEC) traces of the poly(γ-caprolactone) (PCL) coupling products with and without copper(II) chloride. The reaction temperature was kept constant at 70 °C.

Results and Discussion

Radical Coupling as a Function of Cu(I) Catalyst Concentration. According to the ATRP mechanism, radicals are formed from the reversible redox reaction of a catalyst, such as Cu(I)/ligand, with the bromine- or chlorine-based initiator. Under controlled reaction conditions the radical concentration is kept very low by the reversible redox activation−deactivation process to avoid radical termination. The radicals formed can react with the excess of monomer to generate polymer chains of controlled length. However, if the equilibrium is shifted to the right by enhancing the activation process, the radical concentration increases and the termination reactions become important. Based on this mechanism, the Cu(0)-catalyzed radical coupling reactions have been employed to link functional ATRP macroinitiators in the presence or absence of monomers and obtain longer polymer chains or α,ω-telechelic polymers.

In this work, we show the Cu(I)-catalyzed radical coupling process (which could also be termed as step-growth polymerization process) of α,ω-dibromide PCL in the absence of monomers. First, a bifunctional bromide end-terminated PCL was synthesized by reacting hydroxy-terminated poly(γ-caprolactone) with an excess of 2-bromoisobutyryl bromide. The esterification reaction was found to proceed to quantitative conversion as determined by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum was run with a relaxation time of 20 s. The methyl protons at ~1.8 ppm and the methylene protons at ~3.9 ppm were used to quantify the esterification (see Supporting Information). It should be noted that the size exclusion chromatography analyses of the HO-PCL-OH and that of the PCL macroinitiator, Br-PCL-Br, using polystyrene standards showed a molar mass of 5800 and 6200 g/mol, respectively.

Next, the dibromide-terminated PCL was reacted with an excess of copper catalyst (copper(I)/macroinitiator = 5/1 molar ratio) in the absence of vinylic monomers, and a clear shift of the SEC traces to higher molecular weights was observed which is indicative of the significant radical coupling reactions between the formed radicals. As shown in Figure 1, the resulting polymer has a bimodal distribution; the molecular weight of the main peak is twice higher than that of the Br-PCL-Br precursor, whereas the molecular weight of the shoulder at lower retention times is approximately 6−7 times higher than that of the Br-PCL-Br adduct (see Scheme 1). These results clearly suggest that in the presence of an excess of copper(I) catalyst and without the addition of a vinyl monomer the primary coupling reaction is the bimolecular radical coupling which occurs to an extend of about 80% (by peak fitting using Origin Software), while multimolecular radical coupling reactions can also take place at ~20%, leading to higher molecular weight products. The formation of such coupling products of various degrees of polymerization has similarly been reported in the literature for α,ω-dibromopolystyrene at reductive conditions using Cu(0) to increase the radical concentration.[8,11] It should be noted that the presence of excess copper(I) catalyst instead of Cu(0) is used for the two points: the Cu(0) was insoluble in organic solvent and results in the heterogeneous reaction, and the key point of radical coupling is the high concentration of formed polymer radical; the excess amount of copper(I) catalyst also shifts the equilibrium to the right to active radical species. So in our studied PCL system, the copper(I) catalyst was used to study the ATRC reaction of the PCL system.

However, when the Br-PCL-Br macroinitiator was subjected to a low concentration of copper chloride catalyst with respect to the difunctional bromide-terminated PCL, no shift in the SEC traces was observed for a copper(I) to macroinitiator molar ratio ≤2 (see Figure 1). This suggests that at a low catalyst concentration no or minimal coupling reactions occur between the radicals formed during the process, possibly due to the low radical concentration. It should also be noted that such radical coupling reactions did not occur with low molecular weight α,ω-dibromide-terminated poly(ethylene glycol) using similar reaction conditions. This

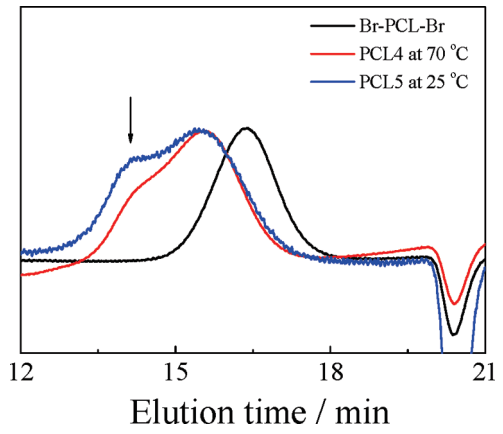


Figure 3. Size exclusion chromatography (SEC) traces for the poly(γ-caprolactone) (PCL) coupling products at different temperatures (25 and 70 °C) and at a constant catalyst to macroinitiator molar ratio (I:Cu(I):Cu(II):L = 1:4:1:5).

Table 1. Experimental Conditions and Molecular Weight Parameters for Bromine-Terminated Poly(γ-caprolactone) (PCL-(Br)$_2$) and Poly(γ-caprolactone) (PCL) Coupling

sample	I:Cu(I):L[b]	Cu(II)	M_n[a] (g/mol)	M_w/M_n[a]
Br-PCL-Br	1:0:0	0	6200	1.25
PCL-1	1:0.1:0.1	0	7000	1.32
PCL-2	1:1:1	0	7100	1.57
PCL-3	1:5:5	0	15100	2.10
PCL-4	1:4:5	1	16200	2.35
PCL-5	1:4:5	1	16750	2.56

[a] Determined by SEC using DMF as eluent at a flow rate of 1.0 mL/min. A series of polystyrene standards were used for the SEC calibration. [b] I, Cu(I), L, and Cu(II) are the (PCL-Br)$_2$, copper(I) chloride, ligand (Me_6TREN), and copper(II) chloride, respectively.

could be attributed to a different radical termination process or to other side reactions which dominate the process. Although the detailed mechanism of ATRC reaction for PEO polymer is not clear, the conformation of the polymer chains may have an effect on the ATRC reaction.

Influence of Cu(II) and the Reaction Temperature on the Radical Coupling Process. In view of controlling the radical concentration and slowing down the coupling reactions, copper(II) chloride was added in the reaction in conjunction with the copper(I) chloride catalyst to decrease the concentration of the radicals formed during the coupling process. As shown in Figure 2, bi- and multimolecular coupling products were obtained in the presence of copper(II) chloride similar to those found without the addition of the Cu(II) catalyst. While the main SEC peak remains at the same position the shoulder peak at higher molecular weights increases in the presence of copper(II) chloride, suggesting that the multimolecular coupling reactions become more pronounced. An increase from 20% to 30% was calculated for the multimolecular coupling via peak fitting. This is attributed to the decrease of the radical concentration with the addition of Cu(II) chloride due to the shift of the reaction equilibrium to the left (see Scheme 1) and to the elimination of radical side reactions which enhances the radical coupling process. It should be noted that the main product of the reaction is still the bimolecular radical coupling adduct (~70% via peak fitting) while the multimolecular coupling product becomes significantly higher. Finally, the effect of the reaction temperature on the radical coupling reactions was also investigated. As shown in Figure 3, the decrease of the reaction temperature from 70 to 25 °C favored the formation of the multimolecular coupling product (about ~40%) compared to the bimolecular coupling. This suggests that the radical side reactions, such as disproportionation and elimination, are more important at 70 °C and are suppressed at the lower reaction temperature, in agreement with the results by Luo et al.[20]

Conclusions

An ATRP dibromide end-functionalized poly(γ-caprolactone) macroinitiator was synthesized and was used as a model compound to study the copper(I)-catalyzed ATRC process in the presence of excess Cu(I) chloride catalyst. The SEC traces clearly show the formation of high molecular weight products at a high catalyst/macroinitiator molar ratio. PCL with molecular weights from 2 to 7 times that of the Br-PCL-Br precursor was formed, suggesting that the main radical termination process is the bimolecular coupling reaction (about 80%), while multimolecular coupling also takes place (about 20%). The extent of coupling was also verified by ^{1}H NMR spectroscopy. The addition of copper(II) chloride and the decrease of the reaction temperature both enhance the multimolecular coupling process due to the decrease of the radical concentration and the suppression of the radical side reactions, although the bimolecular coupling reaction is again the dominant process.

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Supporting Information Available: ^{1}H NMR spectrum of the poly(γ-caprolactone) macroinitiator. This material is available free of charge via the Internet at http://pubs.acs.org.

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