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Single-Electron-Transfer Nitroxide-Radical-Coupling Reaction at Ambient Temperature: Application in the Synthesis of Block Copolymers

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The "Sharpless-type click chemistry"[1] has attracted considerable attention during the past decade[2] since it provides an easy way to obtain complex macromolecular architectures such as linear,[3] star,[4,5] cyclic,[6] graft polymers,[7] and copolymers as dendrimers.[8−10] However, the polymers with azide group used in "Sharpless-type click chemistry" are difficult to be preserved due to their photosensitivity and thermal instability, which means special care should be taken. Another type of click chemistry, the Diels−Alder reaction[11] (DA) [4 + 2] system, provides a coupling strategy using a diene and dienophile by intra- or intermolecular reaction. This shows great potential based on the macromolecular chemistry particularly providing new materials.[12−16] However, the maleimide or anthracene end-functionalized polymers generally require multistep synthesis and purification. Monteiro[17] also reports a radical coupling method to make high-molecular-weight multiblock copolymers from a difunctional PS, by an outer-sphere electron transfer mechanism. Recently, our group found macroradicals, generated in the presence of metal catalyst and conjugates, could be instantly captured by the 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) group in another polymer chain by formation of alkoxyamine linkage with high effiency.[18,19] This kind of reaction is named as "atom transfer nitroxide radical coupling" (ATNRC) reaction.

Generally, CuBr and *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) were used as the catalyst to generate macroradicals in ATNRC under a relatively high temperature, which could cause side reactions such as cross-link and chain transfer. Some polymers obtained from active monomers, such as methacrylic esters, cannot be conducted in ATNRC due to the significant β-hydrogen transfer from the macroradicals.[20,21] To overcome these disadvantages, the condition of ATNRC should be optimized. Percec[22] reported that an ultrafast synthesis of ultrahigh-molecular-weight polymers from various functional monomers prepared by single-electron-transfer living radical polymerization (SET-LRP) at ambient temperature and Cu^0 was used to substitute the Cu^I to generate the radicals, which provides us a new strategy to generate macroradicals in our ATNRC system.

In this paper, the reaction conditions for SET are applied in the nitroxide radical coupling reaction and the macroradicals generated by SET mechanism at ambient temperature are trapped by nitroxide radicals, named as single-electron-transfer nitroxide-radical-coupling (SET-NRC) reaction (Scheme 1). A living macroradical ($P_n^\bullet$) is generated from P_n−X[23] (halogen-containing polymers) by SET mechanism by the oxidation of Cu^0 to Cu^I, which is efficiently trapped by TEMPO-P_m (TEMPO-containing polymers). Meanwhile, Cu^I is disproportionated into Cu^{II} and Cu^0 to regenerate the Cu^0 in polar solvent (methanol) in the presence of N ligands. However, in THF, no disproportionation of Cu^I was found (see Supporting Information). The coupling reactions were conducted between bromine end polymers, such as polystyrene (PS), poly(*tert*-butyl acrylate) (P*t*BA), poly(methyl acrylate) (PMA), poly(methyl methacrylate) (PMMA), and TEMPO end polymers, poly(ethylene oxide) (PEO), poly(ε-caprolectone) (PCL), in the presence of Cu^0/ *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) under ambient temperature (25 ± 5 °C).

The TEMPO-containing PEO (TEMPO-PEO, $M_{n,NMR}$ (molecular weight from ^{1}H NMR): 3700 g/mol, $M_{n,GPC}$ (molecular weight from GPC): 3500 g/mol, M_w/M_n: 1.08) was prepared by ring-opening polymerization (ROP) of EO in tetrahydrofuran (THF) using diphenylmethylpotassium (DPMK) and 4-hydroxyl-2,2,6,6-tetramethylpiperidinyl-1-oxy (HTEMPO) as initiator.[24] Polystyrene (PS-Br, $M_{n,NMR}$: 4100 g/mol; $M_{n,GPC}$: 4000 M_w/M_n: 1.07) precursor was prepared using the standard ATRP techniques (see Supporting Information).[25] The coupling reaction was carried out as the following procedure: An ampule charged with TEMPO−PEO (0.37 g, 0.1 mmol), Cu(0) (6.4 mg, 0.1 mmol), PMDETA (0.02 mL, 0.1 mmol), and THF (3 mL) was degassed by three freeze−pump−thaw cycles. Then PS-Br (0.41 g, 0.1 mmol) dissolved in THF (2 mL) was introduced into the ampule with additional three freeze−pump−thaw cycles. After 24 h magnetic stirring at ambient temperature, the ampule was immersed in liquid nitrogen. Crude products were diluted with THF, and the solution was passed through neutral alumina to remove copper complex. THF was removed by evaporation, and the crude products were redissolved in CH_3OH. The latter was passed through an ultrafiltration membrane to get rid of the impurities. The pure products were obtained by the concentration of reserved CH_3OH solution to constant weight and dried at 35 °C in vacuo.

In SET, the C−X bond with low dissociation energy is cleaved by the formation of radical anion intermediates via an outer-sphere single-electron-transfer process, which does not show obvious dependency on the nature of the halide group.[26] This means in our system C−Br bond dissociation occurred through the formation and decomposition of the radical anion intermediates. When PS-Br was mixed with TEMPO-PEO in the presence of Cu(0)/PMDETA at room temperature, the formed macroradicals ($PS^\bullet$) were trapped by TEMPO groups immediately by the formation of alkoxyamines. In this process, the feed molar ratio of PS-Br and TEMPO-PEO was controlled at 1:1, and the presence of TEMPO-PEO group may increase the polarity of the solvent[27] to benefit the coupling reaction. However, in the UV spectra of coupling product, only Cu^I at 262 nm was detected; no Cu^{II} at 720 nm was found. It means that when THF was used as solvent in SET, no proportionation of Cu^I was conducted (see Supporting Information for details).

After reaction, the remaining TEMPO-PEO and PS-Br residues were easily removed by membrane separation for TEMPO-PEO and extraction with cyclohexane for PS-Br (see Supporting Information for details) The gel permeation chromatography (GPC) traces of polystyrene with bromine end group (PS-Br), poly(ethylene oxide) with TEMPO end group (TEMPO-PEO), and PS-*b*-PEO are shown in Figure 1 with Gaussian distribution and low polydispersity (M_w/M_n < 1.10). A comparable experiment was carried out by introducing HTEMPO (0.017 g, 0.1 mmol) instead of TEMPO-PEO for the coupling reaction, in order to

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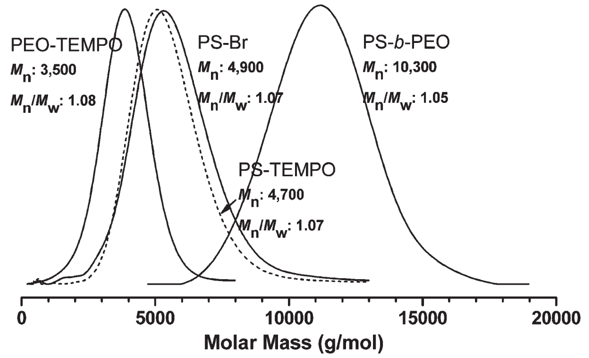
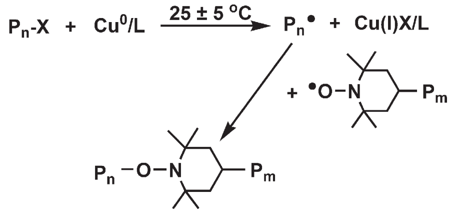


Figure 1. Typical gel permeation chromatography traces of polystyrene with bromine end group (PS-Br), poly(ethylene oxide) with TEMPO end group (PEO-TEMPO), polystyrene capped by HTEMPO (PS-TEMPO), and polystyrene-*block*-poly(ethylene oxide) (PS-*b*-PEO).

Scheme 1. Mechanism of Single-Electron-Transfer Nitroxide-Radical-Coupling (SET-NRC) Reaction



make sure there was no bimacroradical termination in the system. The dot GPC trace in Figure 1 (HTEMPO-capped PS) is unimodal, which means there was no bimacroradical termination. If the latter had occurred, a trace for double molecular weight of PS should be detected.

This process was also supported by ^{1}H NMR spectra. Figure 2 shows the ^{1}H NMR spectra of (A) PS-Br and (B) PS-*b*-PEO. The original resonance observed in region 4.4–4.6 ppm for methine proton of $-CH(Ph)-Br$ in (Figure 2A) is shifted to the higher field after coupling reaction. The resonances for aromatic ring of PS ($-C_6H_5$) are found in the region of 6.30–7.30 ppm and methylene groups ($-CH_2CH_2O-$) of PEO in 3.53–3.78 ppm (Figure 2B). These results indicate the SET-NRC reaction was successful. The molecular weight of PS-*b*-PEO ($M_{n,NMR}$(PS-*b*-PEO)) can be calculated by the integration of peak for aromatic ring $-C_6H_5$ ("b" in both spectrum A and B, repeating unit of PS) against the $-CH_2CH_2O-$ ("c" in spectrum B, repeating unit of PEO), as formula 1 shows:

$$M_{n,NMR}(\text{PS-}b\text{-PEO}) = \frac{5A_{3.4-3.8}}{4A_{6.3-7.3}} \times \frac{M_{n,NMR}(\text{PS})}{104} \times 44 + M_{n,NMR}(\text{PS}) - 80 \qquad (1)$$

Here $A_{3.4-3.8}$ is the integral area of the peaks at "c" for methylene group protons on PEO block. $A_{6.3-7.3}$ represents the integral area of the peaks at "b" for aromatic ring protons on PS block. $M_{n,NMR}$(PS) was the molecular weight of PS precursor (calculated by formula S1 from the ^{1}H NMR spectrum, see Supporting Information). The values 104, 44, and 80 were the molecular weights of St, EO, and Br, respectively. Theoretical molecular weight ($M_{n,theo}$(PS-*b*-PEO)) can be calculated by the sum of the separate molecular weight obtained from ^{1}H NMR of precursors PS and PEO, using formula 2.

$$M_{n,theo}(\text{PS-}b\text{-PEO}) = M_{n,NMR}(\text{PEO}) + M_{n,NMR}(\text{PS}) - 80 \qquad (2)$$

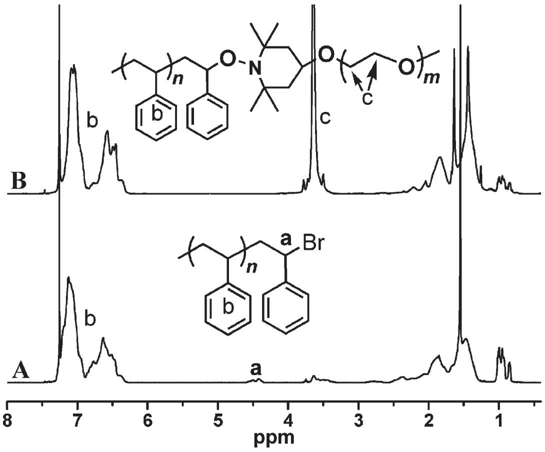


Figure 2. ^{1}H NMR spectra of (A) polystyrene with bromine end group (PS-Br) and (B) polystyrene-*block*-poly(ethylene oxide) (PS-*b*-PEO).

Table 1. Data for the Copolymers Prepared by Single-Electron-Transfer Nitroxide-Radical-Coupling (SET-NRC) Reaction

	block copolymers (g/mol)					
exp	$M_{n,GPC}$[a]	M_w/M_n[a]	$M_{n,NMR}$[b]	$M_{n,theo}$[c]	solvent[d]	EFF (%)[e]
PS-*b*-PEO	8800	1.04	7300	7700	THF	94.8
P*t*BA-*b*-PEO	6300	1.03	6200	6600	ethanol	93.9
PMA-*b*-PEO	8300	1.06	6200	6900	ethanol	89.9
PMMA-*b*-PEO	3850	1.22	5700	6300	methanol	90.5
PS-*b*-PCL	18 300	1.04	8800	9600	THF	92.0
P*t*BA-*b*-PCL	17 700	1.03	7700	8500	THF	90.6
PMA-*b*-PCL	13 500	1.15	8000	8800	THF	90.9
PMMA-*b*-PCL	7800	1.20	8300	9200	THF	90.2

[a] Molecular weight measured by gel permeation chromatography (GPC) in tetrahydrofuran with differential refractive index detector (RID) detector, calibrated with linear PS standards. [b] Calculated from the ^{1}H NMR spectra, using formulas S7–S14 (Supporting Information). [c] Theoretical molecular weight of the blocks calculated by formula 2. [d] Solvents of the coupling reaction. [e] Efficiencies of the formation of blocks, calculated from ^{1}H NMR spectra. (In Table 1, P*t*BA, PMA, PMMA, and PCL are short name of poly(*tert*-butyl acrylate), polymethyl acrylate, poly(methyl methacrylate), and poly(ε-caprolectone), repectively.)

The coupling efficiency of PS-Br and TEMPO-PEO was 94.8% (Table 1) derived from the ratio of $M_{n,NMR}$(PS-*b*-PEO) to $M_{n,theo}$(PS-*b*-PEO).

Other block copolymers obtained by SET-NRC reaction of PS, P*t*BA, PMA, and PMMA with PEO or PCL were also obtained with high efficiencies (90%). The synthetic route and characterization are described in detail (Supporting Information). The reaction efficiency of PS-containing block copolymers have the highest value due to the different activities of formed secondary (tertiary) carbonic radicals, resulting from different substituent groups. The PMMA-containing block copolymers were first synthesized by radical coupling reaction with TEMPO-containing polymer. In common nitroxide-mediated radical polymerization, the β-H of methyl in PMMA macroradical was easily captured by nitroxide radical at high temperature (125 °C),[20] leading to the uncontrollable polymerization. Whereas in SET-NRC reaction, no β-H transfer was found due to the ambient temperature. Meanwhile, SET has been proved a robust method to generate radical, even starting from unpurified monomers, solvents, initiators, and ligands.[28]

In summary, SET-NRC reaction is an alternative effective approach for coupling reaction under ambient conditions, which can be applicable to a variety of halogen-containing polymers including polystyrene, poly(acrylate esters), and poly(methacrylate esters) with any TEMPO-containing polymers. In addition, room temperature inhibits the side reactions such as thermal cross-linking, chain transfer, and the β-H transfer of poly(methacrylate ester) macroradicals especially.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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