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Fast conversion of terminal thiocarbonylthio group of RAFT polymer to "clickable" thiol group *via* the versatile sodium azide

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This work reports a facile and fast way of removing thiocarbonylthio end groups of RAFT-made polymers by the utilization of sodium azide (NaN_3) without deoxygenation. Within several minutes (1~5 minutes), the terminal thiocarbonylthio group of RAFT-made polybutylacrylate (PBA) was completely removed upon NaN_3 treatments as revealed by nuclear magnetic resonance. Careful identification of the chain end structure of the resultant polymer was implemented by matrix-assisted laser desorption ionization time-of-flight mass spectrum, the results unambiguously proved that the terminal thiocarbonylthio group was converted to the "clickable" thiol group by NaN_3 *via* nucleophilic process. Polystyrene, poly(methyl methacrylate) and poly(vinyl acetate) prepared by RAFT technique with different kinds of RAFT agents have been also examined under identical conditions. Similar results were obtained, demonstrating a good universality of this approach. This work provides an alternative and effective approach for removing/modifying thiocarbonylthio end groups of RAFT-made polymers, while producing "clickable" thiol-terminated polymers for many post-modification possibilities.

In 1998, a newborn reversible–deactivation radical polymerization (RDRP) technique termed as reversible addition–fragmentation chain transfer polymerization (RAFT) mediated by a thiocarbonylthio-containing compound was discovered.[1] Shortly after it's advent, RAFT technique has been widely used to design and synthesis of a variety of polymers, such as star, block, microgel and hyperbranched structures and so on. Up to date, RAFT polymerization has been one of the most popular tools for fabricating diverse well-defined polymeric materials, including bio-related and optoelectronic materials. RAFT polymerization relies on a reversible chain transfer equilibrium between the thiocarbonylthio-terminated polymer and propagating polymeric radical. Hence, the resultant RAFT-made polymers are captured by thiocarbonylthio groups with high-degree chain end functionality. In most cases, RAFT-made polymers are coloured due to the terminal thiocarbonylthio chromophores. Also, RAFT polymers usually emit unpleasant odors arising from the decomposition of thiocarbonylthio groups. These negative factors may limit the pratical applications of RAFT-made polymers in some areas, such as biological and photoelectricity applications. Polymer scientists have made tremendous efforts in removing or modifying the terminal thiocarbonylthio end groups, such as reaction with nucleophiles (amines,[2] thiols,[3] hydroxides[4]), reaction with oxidizing agents (ozone, air[5], hydrogen peroxide, hydroperoxides and peracids[6]), radical-induced reduction,[7] radical addition–fragmentation–coupling[8] and thermolysis[9]. Among them, the removal of thiolcarbonylthio groups *via* nucleophilic reaction is an effective approach and has been most frequently used. Primary amines, such as butylamine and hexylamine, are commonly used for the nucleophilic aminolysis of thiocarbonylthio-terminated RAFT polymers,[10] converting thiocarbonylthio group to the "clickable" thiol group for further modification by implementing thiol–ene (yne) addition, thiol-bromo or thiol–isocyanate reactions. Usually, several to dozens of hours are needed for the complete conversion of thiocarbonylthiol to thiol by the utlization of primary amines. An *et al*. reported that the strong nucleophilic and antioxidative hydrazine can induce a fast and effective conversion of thiocarybonylthio to thiol within minutes without deoxygenization.[11] It is well known that sodium azide (NaN_3), a strong nucleophile, can effectively convert the terminal halogen group to azide, which can undergo "click" reaction with alkyne-bearing molecule or polymer for preparing end-group modified atom transfer radical polymerization (ATRP) polymer or multiblock copolymer.[12] It is expected that the strong nucleophile NaN_3 can also readily react with thiocarbonylthio termini to produce "clickable" thiol-terminated polymer. Therefore, for the polymer terminated with both halogen from ATRP and thiocarbonylthio from RAFT, the treatment with NaN_3 may simutaneously convert the both terminates to "clickable" azide and thiol, respectively. This work aims at providing an alternative thiocarbonylthio removal/modification approach by the utlization of NaN_3. Typical RAFT-made polymers, including poly(alkyl (meth)acrylate), poly(styrene) and poly(vinyl acetate) will be explored for verifying the versatility of this approach. The resultant polymer will be fully characterized by nuclear magnetic resonance, size exclusion chromatograph and matrix-assisted laser desorption ionization time-of-flight mass spectra for hard evidence and a comprehensive understanding of this method.

Polymer chemists have proposed many ingenious ways to remove the thiocarbonylthio end groups of RAFT-made polymers.[13] Compared with ever reported methods, NaN_3 as nucleophile to modify the thiocarbonylthio group shows its advantage since that NaN_3 can also effectively convert terminal halogen of ATRP-made polymer to azide group. If the NaN_3 can effectively remove or modify the terminal thiocarbonylthio of RAFT-made polymer, it can be seemed as a versatile agent for the terminal group modification since that ATRP plus RAFT-made polymers contain the largest proportion of polymers prepared by RDRP techniques. Firstly, RAFT-made poly(butyl acrylate) (PBA, $M_{n,SEC}$ = 7,500 Da, M_w/M_n = 1.06) dissolved in DMF was treated by NaN_3 ($[PBA]_0/[NaN_3]_0$ = 1/10) without deoxygenation, and the ampoule was kept in opening. Upon the addition of NaN_3, the molecular weight (MW) of most of the polymers immediately changed to its twice (within 1 min). With time increasing from 5 min, through 10 min, 30 min to the final 120 min, the MW of the original PBA gradually increased to its twofold value (Figure 1), and a bimodal MW distribution (MWD) displayed. The formation of the twofold MW was probably due to the oxygen-facilitated coupling reaction of thiol-terminated polymers generated from the nucleophilic reaction in the open system. At different time intervals, the treated polymers were monitored by ^1H NMR spectrum. The characteristic ^1H NMR signals of the naphthyl's protons arising from CPDN moieties (7.30-8.20 ppm) almost disappeared (Figure 2b) after 1 min of NaN_3 treatment. The colour of the solution also became light immediately after the addition of NaN_3 (ESI, Figure S1b). After 5 min, the characteristic ^1H NMR signals of naphthyl's protons diappeared completely. Combining with the NMR results and the almost colourless of the precipitate polymer, the color of the reaction solution was supposed from the detached small molecules. After 120 min, the colour of solution became obviously lighted (ESI, Figure S1b). Lowing the amount of NaN_3 to $[PBA]_0/[NaN_3]_0$ = 1/1, the time needed for the complete removal of thiocarbonylthio groups prolonged to 1440 minutes; Further reducing NaN_3 to $[PBA]_0/[NaN_3]_0$ = 1/0.1, 2880 minutes were insufficient for the thorough convertion of thiocarbonylthio group (ESI, Figure S2).

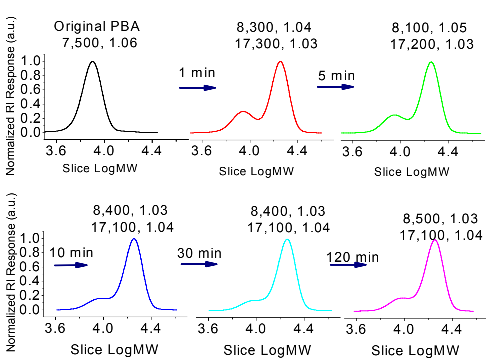


Fig. 1 SEC traces of PBA before and after the treatment by NaN_3. Original PBA: $[BA]_0/[CPDN]_0/[AIBN]_0$ = 500/5/1, time = 4.5 h, conversion = 45.9 %, 60 °C, BA = 10.0 mL, toluene = 4.0 mL; Treated conditions: $[PBA]_0/[NaN_3]_0$ = 1/10, PBA = 0.2000 g, DMF = 1.0 mL, 25 °C, 1 min, 5 min, 10 min, 30 min, 120 min.

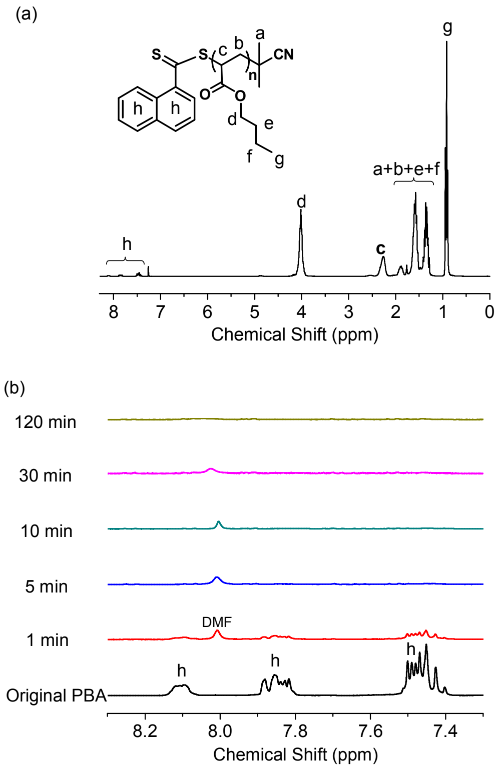


Fig. 2 Full ^1H NMR spectrum of original PBA (a) and enlarged ^1H NMR signals of thiocarbonylthio groups (b) before and after the treatment of PBA by NaN_3. Original PBA: $[BA]_0/[CPDN]_0/[AIBN]_0$= 500/5/1, time = 4.5 h, conversion = 45.9 %, 60 °C, BA = 10.0 mL, toluene = 4.0 mL; Treated conditions: $[PBA]_0/[NaN_3]_0$ = 1/10, PBA = 0.2000 g ($M_{n,SEC}$ = 7,500 Da, M_w/M_n = 1.06), DMF = 1.0 mL, 25 °C, 1 min, 5 min, 10 min, 30 min, 120 min.

To get a clear idea about the exact mechanism of the removal of thiocarbonylthio groups under NaN_3, matrix-assisted laser desorption ionization time-of-flight mass spectrum (MALDI-TOF MS) was used to analyze the resultant PBA with bimodal MWD (8,500 Da, 17,100 Da in Figure 1). MALDI-TOF MS of original PBA was also performed for an easy identification. As presented in the insets of Figure 3(a), the MALDI-TOF MS (linear mode) of the original PBA showed only one series of peak with a regular MW difference of BA unit (128.17 Da). And, the MS peak data complied with the theoretical values with thiocarbonylthio end-capped PBA, denoting a high chain fidelity of PBA obtained from RAFT polymerization. After 120 min of NaN_3 treatment, a bimodal MWD displayed in MALDI-TOF MS (Figure 3a), agreeing with the SEC results (Figure 1a, 120 min). As for the enlarged low-molecular-weight spectra (~4,000-10,000 Da), two series of peak can be found. One series of peak was assigned to the thiol terminated PBA stemmed from the nucleophilic process. The other agreed well with the MW with disulfide bond (−S−S−) centered polymer generated from the terminal thiol-thiol oxidation coupling reaction. With respect to the high-molecular-weight spectra (~10,000-16,000 Da), there was only one series of peak corresponding to the polymer generated from the terminal thiol-thiol oxidation coupling reaction. These results provided solid evidence that NaN_3 can effectively convert the terminal thiocarbonylthio group of RAFT-made polymer to thiol group. Since that NaN_3 has no reducing ability, the nascent thiol groups readily formed disulfide groups *via* thiol-thiol oxidation coupling reation under open circumstance. As a consequence, a doubled MW with gradually increased intensity in SEC traces were found (Figure 1). Considering that the disulfide groups can be easily reduced to thiol groups under reducing environments, the resultant PBA with bimodal MWD (8,500 Da, 17,100 Da) was subjected to reduction by utlization of dithiothreitol (DTT). Obviously, after the reduction by DTT, almost all of the twofold MW reduced to its half value (Figure 3b), validating further that the polymers with twofold MW were centered by disulfide bonds originated from the thiol-thiol oxidation coupling. These results clearly demonstrated that NaN_3 can effectively convert thiocarbonylthio groups of RAFT-made polymers to thiol groups *via* a nucleophilic reaction. The mechanism of the nucleophilic process with NaN_3 as nucleophile was illustrated in Scheme 1.[14]

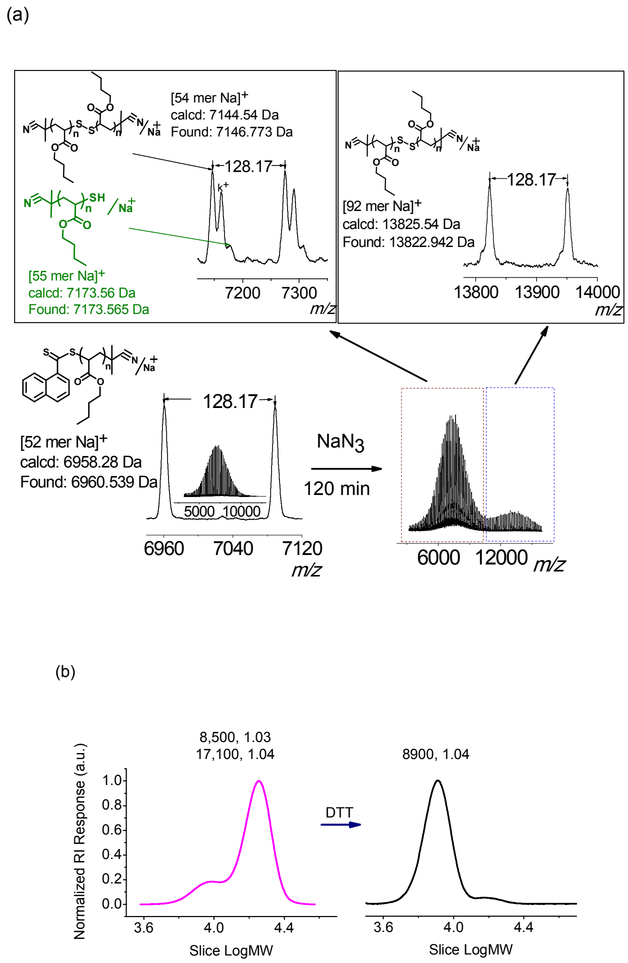
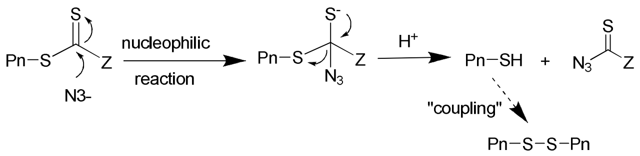


Fig. 3 Matrix assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry of Original PBA and PBA treated by NaN_3 ($[PBA]_0/[NaN_3]_0 = 1/10$, 25 °C, 120 min) (a); SEC traces the PBA before and after reduction by dithiothreitol (DTT) (b).



Scheme 1. The mechanism of the reaction of the RAFT-made polymers with NaN_3.

To test the versatility of thiocarbonylthio modification by NaN_3, different RAFT-made polymers with various MWs, monomer and RAFT agent were examined. In the presence of NaN_3, the convertion of thiocarbonylthio of poly(methyl methacrylate) (PMMA) from 2-cyanopropan-2-yl dithiobenzoate (CPDB)-mediated RAFT polymerization was completed within 1 min, as presented in Figure 4. Similarly, the SEC traces showed a bimodal MWD with time evolution (Figure 4c) and the twofold MW can completely shift to its half under DTT reduction (ESI, Figure S3c). Also, after 1 min's treatment, the UV absorption of thiocarbonylthio group at about 300 nm was remarkably decreased to a very low level (ESI, Figure S4b). The results indicated a same nucleophilic mechanism with that of PBA. Upon NaN_3 treatments, the terminal thiocarbonylthio of polystyrene (PS) (7,200 Da, 1.10) prepared with CPDN as chain transfer agent was effectively converted to thiol as confirmed by SEC (Figure 5c), NMR (ESI, Figure 5b) and DTT reduction (ESI, Figure S5b). Explorations of different MWs of RAFT-made PS (4,400 Da, 12,800 Da) testified that the NaN_3 was valid for modifying the thiocarbonylthio group of polymers with different MWs (ESI, Figures S6 and S7). Since that the generated thiol group can undergo various “click” reactions, such as Michael addition reactions with acrylate or maleimide. The formed thiol-terminated PS by NaN_3 treatment and DTT reduction was then immediately subjected to Michael addition reaction with N-propylmaleimide. From the results of SEC traces and MALDI-TOF MS (ESI, Figure S8), it was clear that the Michael addition reaction was successfully implemented, demonstrating the “clickable” reactivity of the generated thiol group. The results of NaN_3 converting thiocarbonylthio group of poly(vinyl acetate) (PVAc) from (S)-2-(ethyl propionate)-(O-ethyl xanthate)-mediated RAFT polymerization proved that NaN_3 can be used for the terminal modification of RAFT-made PVAc (ESI, Figure S9), illustrating a good versatility of this approach.

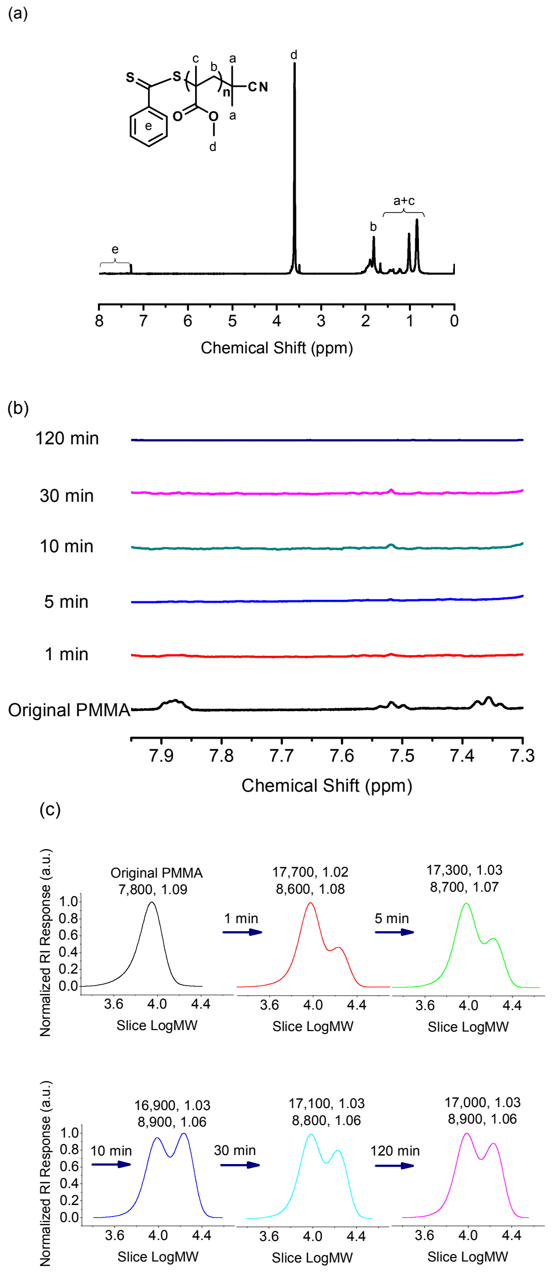


Fig. 4 Full ^{1}H NMR spectrum of original PMMA (a), enlarged ^{1}H NMR signals of thiocarbonylthio groups (b) and SEC traces (c) before and after the treatment of PMMA by NaN_3. Original PMMA: $[MMA]_0/[CPDB]_0/[AIBN]_0$ = 500/5/1, time = 10 h, conversion = 51.2 %, 60 °C, MMA = 10.0 mL, toluene = 4.0 mL; Treated conditions: $[PMMA]_0/[NaN_3]_0$ = 1/10, PMMA = 0.2000 g, DMF = 1.0 mL, 25 °C, 1 min, 5 min, 10 min, 30 min, 120 min.

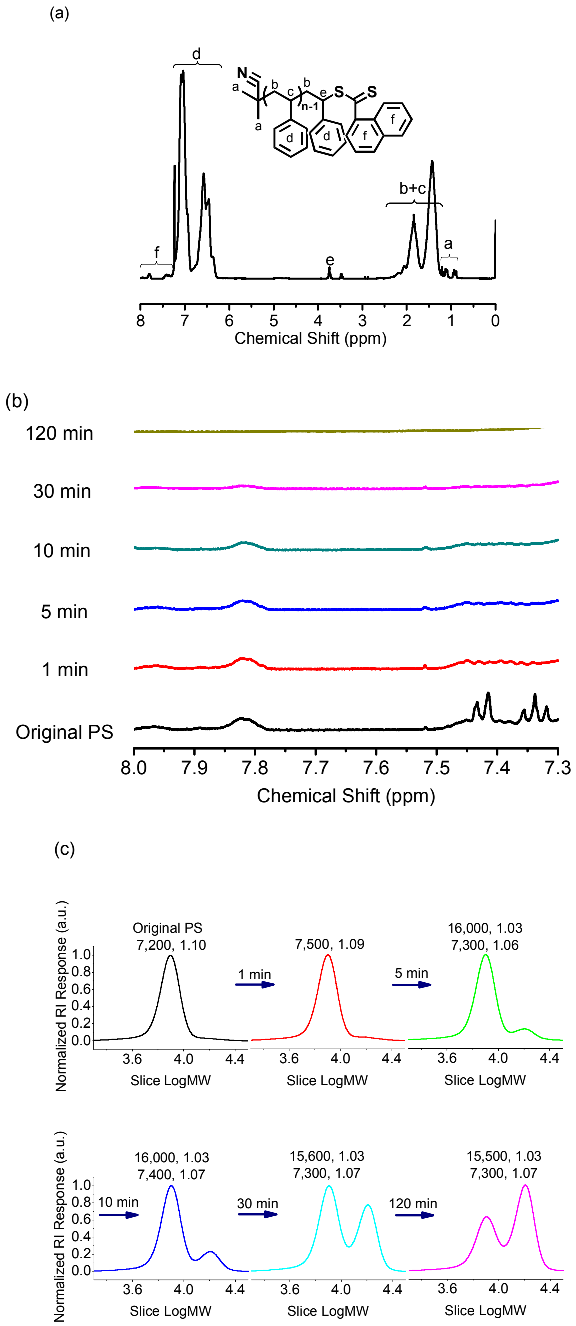


Fig. 5 Full ^{1}H NMR spectrum of original PS (a), enlarged ^{1}H NMR signals of thiocarbonylthio groups (b) and SEC traces (c) before and after the treatment of PS by NaN_3. Original PS: $[St]_0/[CPDN]_0/[AIBN]_0$ = 1000/5/1, time = 94 h, conversion = 29.8 %, 60 °C, St = 10.0 mL, toluene = 4.0 mL; Treated conditions: $[PS]_0/[NaN_3]_0$ = 1/10, PS = 0.2000 g, DMF = 1.0 mL, 25 °C, 1 min, 5 min, 10 min, 30 min, 120 min.

In summary, this work demonstrated a facile and fast approach for converting thiocarbonylthio termini of various RAFT-made polymers to thiol groups by the utilization of NaN_3 in a open system at ambient temperature. Complete conversion of thiocarbonylthio to thiol groups was achieved within several minutes. The approach of conversion of thiocarbonylthio to thiol groups by NaN_3 was confirmed to proceed *via* nucleophilic mechanism. Considering the "clickable" thiol as well as the strong nucleophile of NaN_3 towards epoxy group, terminal halogen of ATRP polymers and so forth, this work undoubtedly offered a promising and efficient end-group removal/modification approach of RAFT polymers with many post-modification possibilities.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section giving materials, instrumentation, and typical recipe details. See DOI:

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Graphical Abstract

Fast conversion of terminal thiocarbonylthio group of RAFT polymer to "clickable" thiol group *via* the versatile sodium azide

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A facile and fast way of converting thiocarbonylthio end groups of RAFT polymers to thiol groups was demonstrated.