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Notes

A Living Free Radical Exchange Reaction for the Preparation of Photoactive End-Labeled Monodisperse Polymers

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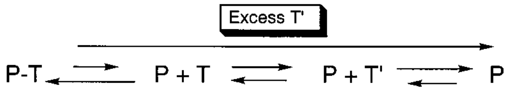
Introduction

During the past decade a number of reports have appeared on the subject of "living free radical" polymerizations which are characterized by a critical feature of reversible termination of growing polymer chains that are capable of stepwise chain growth.[1] Some of the more successful systems employ a nitroxide-stable, free radical to produce a "pseudo-living" free radical polymerization system and to produce polymers with low polydispersity.[2] The reversible nature of the poly(styrene)−nitroxide system has been established[3] by EPR and exchange[4] studies. The usual irreversible termination of two living chains to form a dead polymer is inhibited by the continuous capture of growing chains by nitroxides, which exist in relatively large excess compared to the stationary concentration of growing chains. The concentration of nitroxide is controlled by the reversible equilibrium of the capped living polymer with the growing chain and free nitroxide radical.[5] The equilibrium is controlled, in the main, by the strength of the key, weak NO−C(polymer) bond. In the case of poly(styrene)−TEMPO (cf. structure **2,** Chart 1), the bond strength of the key bond is ca. 130 kJ/mol.[6] For other poly(styrene)−nitroxide systems, the bond energies are in the range 130−100 kJ/mol. The dissociation of these living polymers shows *A* factors[6] in the range of 10^{13-14} s^{-1}.

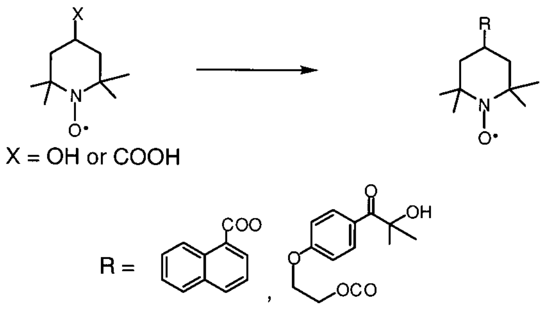
We have synthesized a number of nitroxides covalently attached to photochemically and photophysically active groups for investigations of chemically induced dynamic electron polarization.[7] It occurred to us that the "living" free radical method allows a convenient method for the preparation of "monodisperse" polymers with a wide variety of end groups by a simple nitroxide exchange under equilibrium conditions. This synthetic strategy, if successful, would offer an alternative to the classical living anionic methods of synthesizing monodisperse end-labeled polymers. The basic strategy of this synthetic method is to first synthesize a monodisperse nitroxide (e.g., T = TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxyl) capped polymer in the usual way with an appropriate alkoxylamine initiator such as **1** (e.g., eq 1, where P denotes a monodisperse polymer, T represents a Tempo cap, and T′ represents the desired cap to replace T). Previous studies have demonstrated that effective initiators must possess an α-methyl substituent at the benzylic carbon in order to generate monodisperse polymer chains.[1,8] An alternative approach to the synthesis of end-labeled monodisperse polymers starts with the end-labeled nitroxide as part of the alkoxyamine initiator. This method has the advantage of not requiring an exchange of the labeled nitroxide but the disadvantage of having to run a series of polymerizations if a family of monodisperse end-labeled polymers is desired. In practice, it is expected that the latter method, in addition to the one reported here will be useful, once the appropriate end-labeled nitroxide is synthesized. The method reported will be particularly useful when the comparison of a family of identical monodisperse polymers with different end groups is desired.



$$\text{P-T} \rightleftharpoons \text{P} + \text{T} \rightleftharpoons \text{P} + \text{T}' \rightleftharpoons \text{P-T}' \qquad (1)$$

T = Tempo, T' = substituted tempo.

Using this synthetic strategy, a single monodisperse polymer, P−T, serves as the precursor for an exchange reaction that will substitute any desired nitroxide (without the structural limitations of the original initiator addend) which is added to the system, in excess, at equilibrium conditions. Since TEMPO nitroxides can be readily prepared with a wide variety of groups in the 4 position (cf. eq 2),[7] the overall substitution reaction provides a general strategy for preparing a range of photoactive, monodisperse polymers that take advantage of controlled macromolecular architectures.



(2)

Results

The validity of the concept of employing eqs 1 and 2 to synthesize monodisperse polymers end-labeled with photoactive groups was demonstrated by attaching a fluorescence label and a photocleavable label. The overall reactions are shown in eqs 3 and 4 of Scheme 1.

A TEMPO end-labeled poly(styrene) was synthesized according to a published method.[8] The initiator **1** (see Chart 1 for the structures described in this section) was

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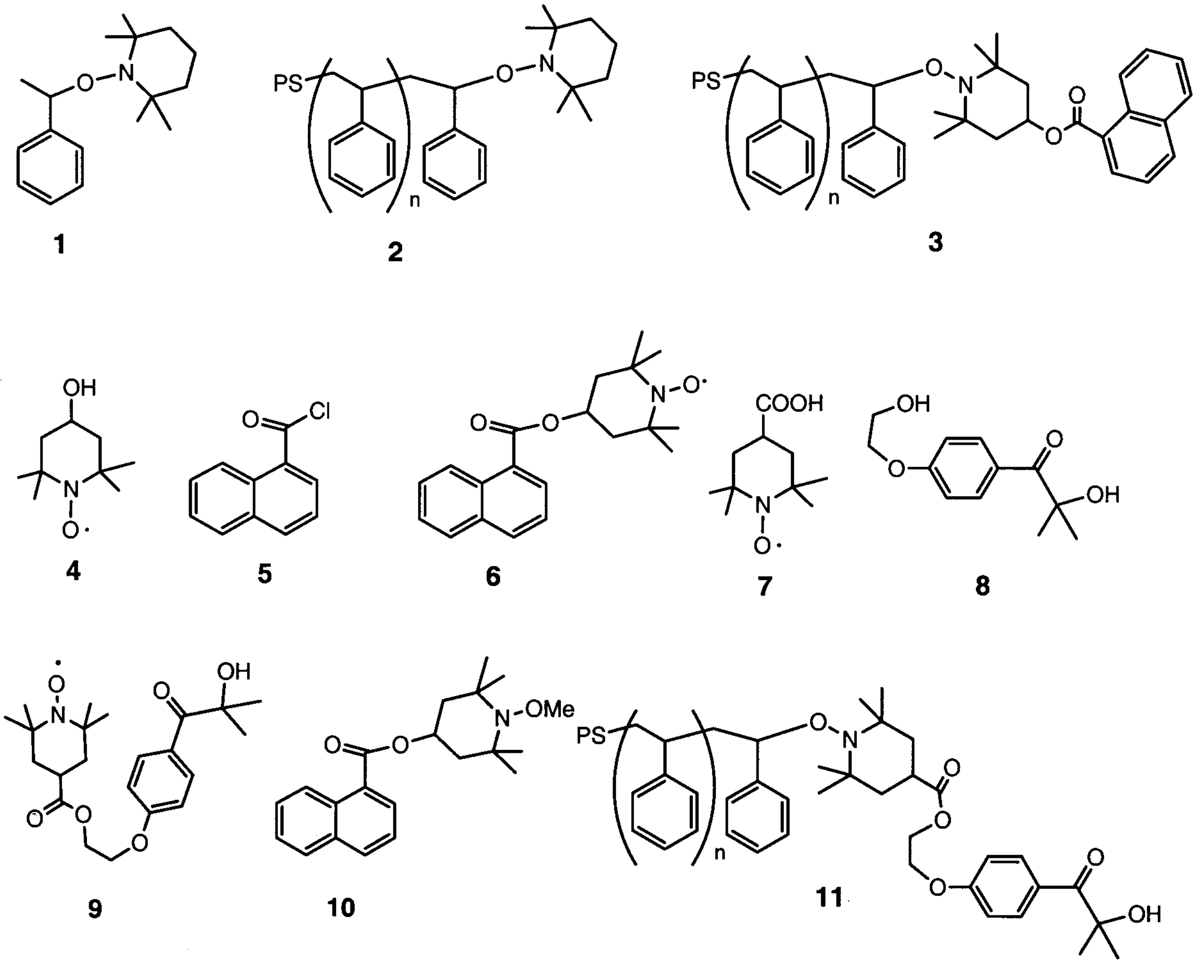
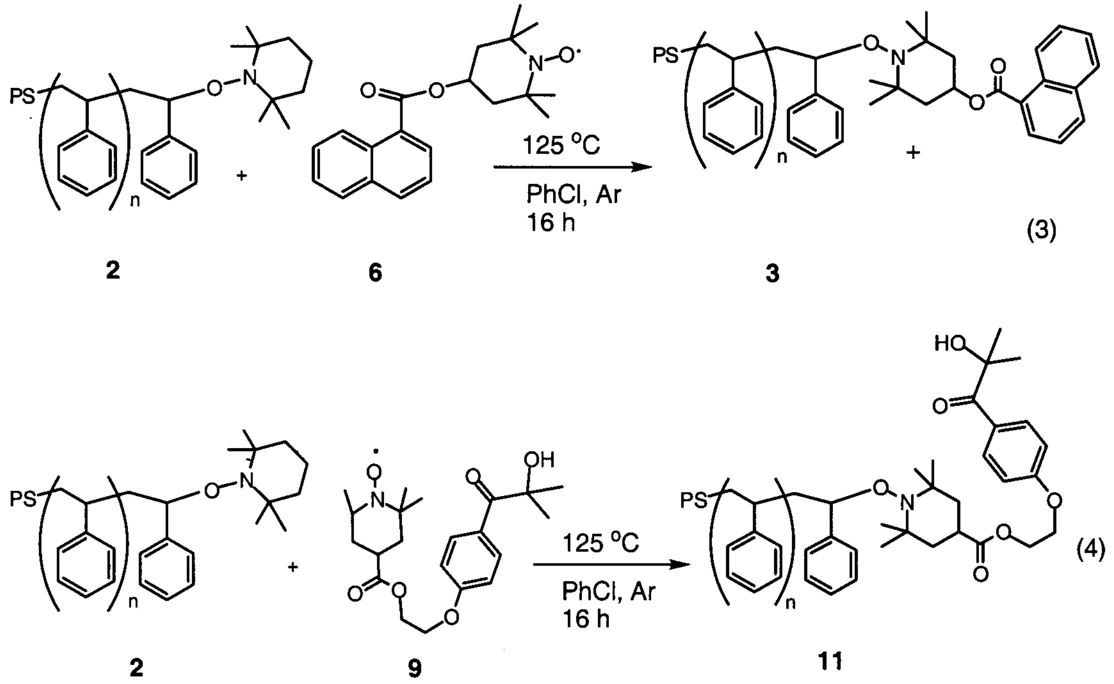
Chart 1. Structures Employed in This Investigation



Scheme 1



synthesized in 30% yield by refluxing a mixture of TEMPO, ethylbenzene, and di-*tert*-butyl peroxide for 16 h under an argon atmosphere. **1** (1 equiv) was reacted with 100 equiv of stabilizer free styrene at 125 °C for 36 h under an argon atmosphere. The polymer was precipitated through the addition of methanol and then washed with 2 L of methanol to remove the styrene monomer. After drying in an oven, **2** (MW 7500, $M_W/M_N = 1.11$) was isolated in 87% yield. The latter may be a maximum calculated value, since in addition to **2**,

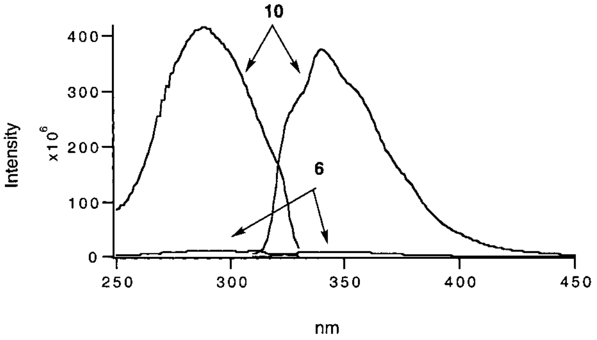


Figure 1. Fluorescence ($\lambda_{excitation} = 280$ nm, $OD_{280} = 0.2$) and excitation ($\lambda_{emission} = 340$ nm) spectra of **6** and **10** in hexanes.

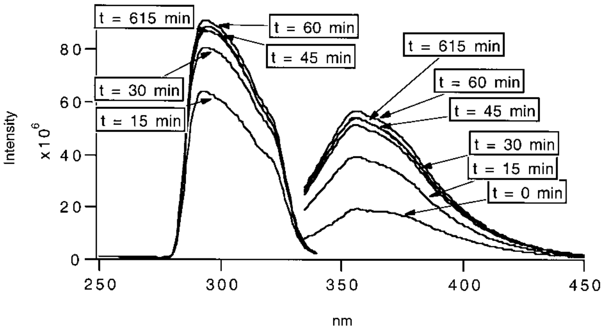


Figure 2. Fluorescence ($\lambda_{excitation} = 280$ nm, $OD_{280} = 0.2$) and excitation spectra ($\lambda_{emission} = 340$ nm) of the exchange reaction between **2** and 15-fold excess of **6** at 125 °C in PhCl.

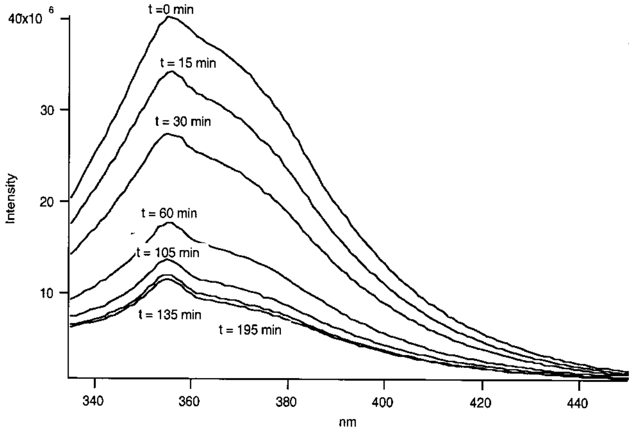


Figure 3. Fluorescence profile of the exchange reaction between **3** and a 10-fold excess of TEMPO at 125 °C in chlorobenzene over a period of 3 h.

the isolated polymer may contain trace amounts of unlabeled polymer chains arising from macroradical termination processes.

The naphthyl-labeled nitroxide **6** was synthesized in 60% yield by reaction of the 4-hydroxy nitroxide, **4**, with the acid chloride **5** in THF and triethylamine. The ketone-labeled nitroxide, **9,** was synthesized in 77% yield from DCC/DMAP catalyzed coupling reaction between the 4-carboxylic acid nitroxide **7** with the dihydroxy ketone **8** in CH_2Cl_2. The nitroxide **6** was converted to the methyl end-capped alkoxyamine **10** (78% yield) by reaction with $FeSO_4$, 30% H_2O_2, in DMSO, under an argon atmosphere.[9]

Preparation of a Fluorescent End-Labeled Monodisperse Poly(styrene), 3. The naphthyl group is generally strongly fluorescent; however, the naphthyl nitroxide **6** is only weakly fluorescent because of intramolecular quenching of naphthalene singlets by the nitroxide group.[10] Although **6** is very weakly fluorescent, the capped nitroxide **10** is strongly fluorescent (Figure 1). Thus, it is expected that the exchange reaction of **6** with the polymer **2** will generate a fluorescent polymer **3** and that the exchange reaction of **9** with the polymer **2** will generate the photoreactive polymer **11**.

Heating of **6** (15 equiv) with **2** (1 equiv) at 125° C in chlorobenzene results in the exchange of nitroxides. The ratio of **6**/**2** can be further optimized, and upon precipitation of the polymer with methanol, unexchanged excess **6** can be isolated and recycled. This exchange can be followed directly by fluorescence spectroscopy (Figure 1), since **6** is only weakly fluorescent, but **3** is expected to be strongly fluorescent. As shown in Figure 2, the fluorescence of the sample increases with time and then saturates after 30−45 min. GPC analysis employing RI detection showed that the molecular weight (MW = 7500 ± 100) of the polymer did not change significantly as a result of reaction. RI detection analyzes all of the polymeric material with and without fluorescence end groups. GPC analysis employing fluorescence detection, which provides a means of detecting only the polymer possessing a fluorescent naphthyl end group, **3**, yielded the same MW as the starting polymer, **2**. Another method, albeit indirect, was also used in an attempt to quantify the exchange efficiency. In this method the UV−vis and fluorescence responses of **10** were correlated with **3** under the approximation that the absorption and emission properties of **3** and **10** were identical. This approach yields an exchange efficiency of ca. 60% by both methods. Separation of **3** from the reaction mixture and treatment with an excess of TEMPO reverses the process shown in Figure 3.

The structure of **3** is also supported by its MALDI-TOF spectrum which displays a cluster of single peaks separated by the mass equal to single styrene units, whereas the spectrum of the crude reaction mixture from the exchange reaction between **2** and excess **6** to form **3** is punctuated by a cluster of double peaks, where each doublet is separated from the next doublet by the mass of single styrene units. A key feature of this spectrum relevant to the structure is the difference of 16 mass units separating each individual peak in a doublet. We believe that this pattern indirectly corresponds to the molecular weights of various polystyrene strands containing the TEMPO end group (**2**) and strands containing the TEMPO−naphthoyl end groups, but where the naphthoyl moiety has been cleaved within the mass spectrum, leaving only polystyrene−TEMPO−oxo strands to be registered by the detector. The ions for which the naphthoyl group has been removed possess an extra oxygen atom (16 mass units) compared to the mass of **2**.

Heating of the ketone-labeled nitroxide **9** (15 equiv) with **2** (1 equiv) at 125° C in chlorobenzene results in the exchange of nitroxides to yield the photoinitiator end-labeled polymer **11**. Precipitation of polymer product from the reaction mixture is achieved by the addition of methanol. The separated polymer showed two broad but characteristic methylene proton NMR signals at 4.22 and 4.40 ppm in $CDCl_3$ solvent, as expected for **11**.

Conclusions

Monodisperse nitroxide end-labeled polymers synthesized from well-developed living free radical methodology may serve as precursors of a range of 4-substituted TEMPO nitroxides through a simple thermal exchange reaction (eq 1). Since TEMPO nitroxides may be synthesized with a variety of groups in the 4-position,[7] the combination of standard monodisperse nitroxide end-labeled polymer preparation by standard living free radical methods and 4-substituted TEMPO exchange provides the advantage of experimental simplicity, functional group tolerance, and flexibility in the preparation of the monodisperse polymer and 4-substituted TEMPOs.

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