

In-Situ Nitroxide-Mediated Radical Polymerization (NMP) Processes: Their Understanding and Optimization

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In-Situ Nitroxide-Mediated Radical Polymerization (NMP) Processes: Their Understanding and Optimization

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1. Introduction

Nowadays, controlled (“living”) radical polymerization (C(L)RP) is rapidly expanding as assessed by a large number of publications, reviews, and patents on this topic.^{1–22} This evolution is in response to the steadily increasing need for new and/or improved organic materials. The success of CRP relies on the robustness of radical chemistry and the capacity to control the polymer structure (predetermined molecular weight, narrow molecular weight distribution, well-defined end groups, and architecture) under milder experimental conditions than living ionic polymerization.^{23–28} Control of the macromolecular characteristic features is a prerequisite for designing the profile of macroscopic properties and for polymers to penetrate a variety of domains, such as nanotechnology (electronics, computer science), materials technology (compatibilizers, stabilizers, adhesives, dispersing agents, polymer toughening agents, thermoplastic elastomers, hybrid materials, etc.), and biomaterials (bio-related polymers, drug delivery systems, etc.).^{1–3,5,29–31} The most recent developments in materials research are mainly devoted to the use of highly efficient and selective organic reactions for the chemical modification of well-defined polymer architectures. This organic/polymer synergy is required to enable functional groups to be introduced at defined locations of the polymer chain and thus control every facet of macromolecular structure. This unique combination of disciplines allows designing nanomaterials with a high degree of structural order and defined properties.^{32,33}

Nitroxide-mediated polymerization (NMP)^{5,34–56} is a very attractive CRP system because it is metal free and effective in the polymerization of a broad range of monomers with various functionalities. This system provides colorless and odorless polymers with no demanding purification. This control of the NMP process relies on the reversible capture of the propagating species by nitroxides with formation of dormant chains (alkoxyamines) (Scheme 1). Whenever this equilibrium is shifted toward the dormant form, the stationary concentration of the active species is low and the irreversible chain termination is limited.

Either bimolecular or unimolecular initiators can be used in NMP.^{5,57} The bimolecular initiation requires combining a traditional free radical initiator (e.g., benzoyl peroxide (BPO) and 2,2'-azobis(isobutyronitrile) (AIBN)) with a nitroxide

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Valérie Sciannamea was born in Liège, Belgium, in 1979. She studied chemistry at the University of Liège, where she started undergraduate research in the Center for Education and Research on Macromolecules (CERM) under the supervision of Professor R. Jérôme. The topic of the project was on-situ nitroxide-mediated radical polymerization (in-situ NMP) using nitrones as precursors of nitroxides. She extended this research program in her Ph.D. thesis, which she defended with the highest mark in 2006. She is now working with the "Belgian Science Policy" in Brussels, Belgium.



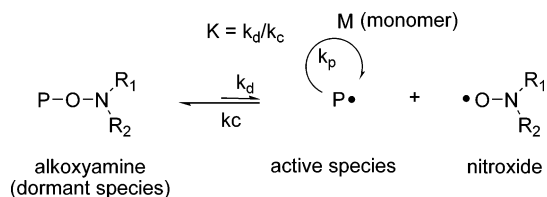
Robert Jérôme studied chemistry at the University of Liège, Belgium, where he obtained his graduate degree ("licence") in 1964 and Ph.D. degree (1970) in Physical Chemistry. His doctoral thesis focused on the preparation and electrochemical properties of ion-exchange membranes under the supervision of the late Professor Victor Desreux. Then he joined Professor Philippe Teyssié and collaborated with him to develop the laboratory of "Macromolecular Chemistry and Organic Catalysis". He was director of the laboratory of "Macromolecular Chemistry and Organic Materials" (1989–1994) and of the "Center for Education and Research on Macromolecules" (CERM) (1994–2006) (approximately 40 persons). He was also president of the Department of Chemistry at the University of Liège. Throughout his scientific career, he has focused his attention on macromolecular engineering based on living anionic polymerization, controlled radical polymerization, and controlled ring-opening polymerization. This research effort is oriented toward the development of novel or at least improved multiphase polymeric materials, including block and graft copolymers and their supramolecular assembly, polymer blends, filled polymers with a special emphasis on nanocomposites, porous materials, and biomaterials. Nowadays he is paying attention to macromolecular chemistry without using organic solvents, thus in the melt or with the assistance of supercritical fluids. He is co-author of several hundreds of scientific papers and several tens of patents. He is a member of the editorial board of several international scientific journals. He was holder of a "Chaire Francqui" in Belgium in 2006.

(e.g., 2,2,6,6-tetramethylpiperidinyloxy (TEMPO)).³⁷ The limitation of this system is the poorly defined structure and concentration of the initiating species. In contrast, thermolysis of a well-defined unimolecular initiator,^{57–62} typically an alkylated nitroxide or alkoxyamine, releases both the initiat-



Christophe Detrembleur was an undergraduate student at the University of Liège (Belgium), where he conducted a research project on structure/polarizability relationships in a novel type of push–pull conjugated system. In 1996, he started his Ph.D. thesis under the supervision of Professor R. Jérôme at the Center for Education and Research on Macromolecules (CERM), University of Liège, Belgium. His major research topic was the search for new regulators for the controlled radical polymerization of (meth)acrylic monomers. He was an invited researcher at IBM, Almaden Research Center, CA, for 3 months in 1998. He received his Ph.D. degree in 2001. Then, he joined the Research Center of Bayer AG in Leverkusen (Germany), where he worked on materials synthesis, polymer processing, and development of high-performance UV coatings. In October 2003, he was awarded a permanent Research Associate position at CERM under the auspices of the National Fund for Scientific Research (FNRS). His main research projects are in the field of new controlled radical polymerization techniques, preparation of new polymeric materials by these techniques, and contribution of macromolecular engineering to nanotechnology.

Scheme 1

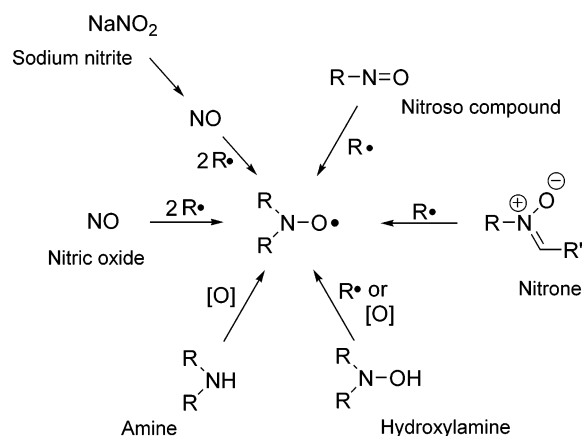


ing radical and the nitroxide in a 1/1 molar ratio. Therefore, the initiator efficiency is close to unity, and the structure of the chain ends is well defined with the initiating fragment of the alkoxyamine being attached at the α -chain end and the nitroxide at the ω -chain end of the chains.

Originally, NMP mediated by TEMPO was limited by slow polymerization (~ 25 – 70 h), high polymerization temperature (125 – 145 °C), and a limited range of suitable monomers, mainly styrene and derivatives.^{34–38,63} NMP was extended to acrylates with success with the assistance of additives^{64–66} or duly substituted TEMPO.^{67–69} The discovery of new types of nitroxides (such as *N-tert-butyl-N*-(1-diethylphosphono-2,2-dimethylpropyl)-*N*-oxyl or DEPNO, 2,2,5,5-tetramethyl-4-phenyl-3-azahexane-3-oxyl or TIPNO, and *N-tert-butyl*-(1-*tert-butyl*-2-ethylsulfinyl)propyl nitroxide or BESN)^{1–5,39–56} also contributed to overcoming the original limitations. For a detailed discussion of traditional NMP, the reader is referred to an excellent review by Hawker et al.⁵

Although NMP is now extremely efficient for the preparation of a variety of well-defined (co)polymers, availability and cost of nitroxides and/or alkoxyamines remain a concern. Indeed, alkoxyamines are commonly synthesized by coupling of an alkyl radical to a nitroxide that must be synthesized (usually by a multistep reaction scheme) and purified.

Scheme 2



As an alternative strategy, several researchers have contemplated the direct formation of nitroxides and alkoxyamines in the polymerization medium from readily and/or commercially available and inexpensive precursors. Both the initiating radicals and the mediators would be produced in a one-pot technique, designated as in-situ nitroxide-mediated polymerization (in-situ NMP). A large variety of nitroxide precursors has been considered, which includes nitrones, nitroso compounds, hydroxylamines, amines, sodium nitrite, and nitric oxide (Scheme 2). Most of these precursors are known as inhibitors of radical polymerization.^{70–78}

This review focuses on the major progress made in (i) the one-pot radical preparation of alkoxyamines from nitroxide precursors and (ii) the development of in-situ NMP processes and their understanding and optimization. The major advantage of in-situ versus traditional NMP is a less costly implementation, which is highly desirable when producing commodity polymers.

2. Common Radical Synthesis of Alkoxyamines Active in NMP

This section is an overview of the most common synthetic methodologies for the preparation of a variety of alkoxyamines. As a rule, they rely on the generation of carbon-centered radicals that are trapped by a preformed nitroxide.

There are several routes for the production of alkyl radicals, including thermolysis of a free radical initiator,^{57,58,79} hydrogen removal from an appropriate substrate,^{57,59–62,79,80} and addition of a radical to an olefin.^{57,58} Organomagnesium compounds ($R-MgX$)⁵⁷ are also precursors of alkyl radicals, which can also be produced by atom transfer radical addition (ATRA);^{81–94} thus, reaction between an activated alkyl halide and a transition-metal complex.

One of the first methods of production of alkoxyamines was reported by Hawker et al. in 1994.⁵⁸ A mixture of benzoyl peroxide (BPO) and TEMPO was heated with an excess of styrene at 80–90 °C under inert atmosphere (Scheme 3). At this temperature, benzoyloxy radicals were released by BPO, which added one styrene unit with formation of the parent carbon-centered free radicals, finally trapped by TEMPO. The yield, after purification, of the expected alkoxyamine was about 40%. Because of the reactivity of the ester group, derivatives of this alkoxyamine were made available.⁵⁷

Alkoxyamines active in NMP were also prepared by thermal decomposition of azo-initiators, for example, azo-

bis(isobutyronitrile) (AIBN), in the presence of a nitroxide, such as *tert*-butyl-(dimethyl-*tert*-butylaminocarbonyl-methyl)-amine-*N*-oxyl (Scheme 4).⁷⁹

According to a similar approach, styryl radicals were generated by hydrogen abstraction from ethylbenzene by *tert*-butyl peroxide in the presence of TEMPO (Scheme 5).^{57,59–62,79} The yield in this unimolecular initiator was about 40%.

The same strategy was used for preparing alkoxyamines based on noncyclic nitroxides (open-chain alkoxyamines).⁷⁹ Photochemical activation of ethylbenzene by peroxides was also successfully carried out for the preparation of a broad range of alkoxyamines active in CRP with the advantage of a low reaction temperature (i.e., room temperature) and the high-yield synthesis (~90%) of less thermally stable alkoxyamines.⁸⁰

Alkyl free radicals were also produced by the halogen abstraction of alkyl halides by silyl radicals (Scheme 6). Alkoxyamines, including hydroxyl- or carboxyl-functional *N*-alkoxyamines were prepared by the reaction of these radicals with nitroxides.⁹⁵ The main steps are shown in Scheme 6: (i) thermal cleavage of the O–N bond of *tert*-butyl hyponitrite, (ii) hydrogen abstraction from tris(trimethylsilyl)silane by the *tert*-butoxy radicals, (iii) halogen abstraction from the alkyl halide by the silicon-centered radicals, (iv) coupling of the alkyl radicals with the nitroxide.

Reaction of Grignard reagents with a nitroxide (usually TEMPO) was also studied in detail (Scheme 7).⁵⁷ The best yields (~85%) were reported at low temperature (i.e., –78 °C), however in relation to the R group of the Grignard reagent. The major disadvantage of this route was the restricted tolerance of the Grignard reagent toward several organic functions, which limited the range of the alkoxyamines made available.

Matyjaszewski et al. synthesized alkoxyamines from organic halides and a nitroxide (TEMPO) in the presence of a copper complex (Scheme 8).^{81–83} The alkoxyamine was prepared at a moderate temperature (75 °C) by atom transfer radical addition (ATRA) within a high yield (70–95%). The process was improved when Cu(I) was regenerated by reduction of Cu(II) by Cu(0).⁸³ Indeed, in the absence of metallic copper, the concentration in the Cu(II) halide complex increased over time, which shifted the reaction equilibrium in such a way that the conversion of the organic halide was less complete.

Other research groups used this strategy to prepare other alkoxyamines active in NMP.^{84–91} Alkoxyamines bearing a polymerizable group were also prepared by ATRA between a nitroxide and an activated alkyl halide bearing an acrylate group (Scheme 9).⁹²

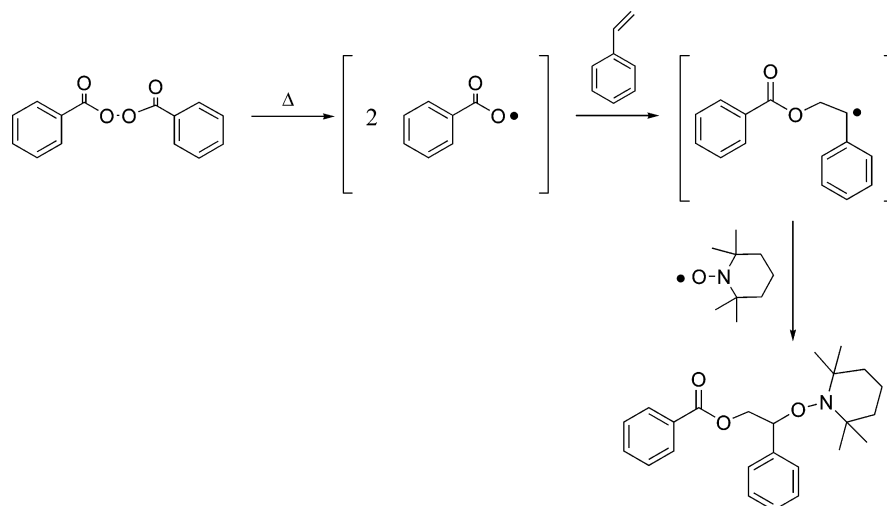
Polyalkoxyamines, mainly di- and trialkoxyamines, based on DEPn were synthesized by ATRA of polyalkyl halides with DEPn (Scheme 10).^{93,94} They were successfully used for the preparation of ABA triblock and star-shaped copolymers.

Another approach for the preparation of dialkoxyamines was based on the reaction of a DEPn-type alkoxyamine with a diacrylate according to Scheme 11.⁹⁶

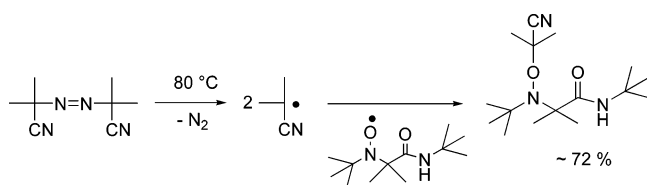
In 2004, the ATRA reaction was nicely adapted to the polycondensation of an activated alkyl bromide bearing a nitroxide with formation of original polymeric alkoxyamines active in NMP (Scheme 12).⁹⁷

Another convenient way toward alkoxyamines consisted of adding styrene derivatives to the oxomanganese center of manganese oxo derivatives.^{5,46,98–100} The free radical generated could react with a preformed nitroxide, and the

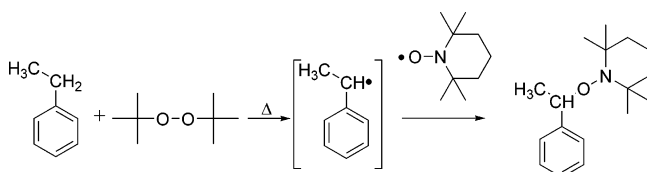
Scheme 3



Scheme 4



Scheme 5



alkoxyamine was released by reduction of the oxometal substituent (Scheme 13).

Alkoxyamines were also prepared with a high yield by saponification of an azo compound, followed by photolysis of the salt in the presence of a nitroxide (DEPN).^{101,102} Photolysis generated radicals which were trapped by the nitroxide (Scheme 14).

More recently, photolysis of dithiocarbamates in the presence of nitroxides led to the synthesis of alkoxyamines at room temperature with a high yield (~90%; Scheme 15).^{103,104} These two photochemical synthetic pathways are very well suited for the synthesis of thermosensitive alkoxyamines.

From an economic point of view, these techniques may suffer from the cost of (i) ligands and transition-metal-based catalysts, (ii) synthesis and purification of nitroxides, (iii) possible tedious purification of the final product.

3. Nitrones: Precursors of Nitroxides for the Synthesis of Alkoxyamines and in-Situ NMP

3.1. Nitrones as Precursors of Nitroxides

For many years, nitrones have been known to be effective spin traps that convert transient radicals into long-lived nitroxides (Scheme 16).^{105–117} Nitrones can however react further with an excess of free radicals with formation of alkoxyamines by 1,3-addition (Scheme 16). In fact, one free radical is added to the C atom and another to the O atom of the nitrone.^{107–109}

Moreover, several nitrones, such as *N*-*tert*-butyl- α -phenylnitron (PBN), 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), and *N*, α -diphenylnitron (DPN), are commercially available (Scheme 17). Other nitrones can be prepared using one of the three following methods: (i) acid-catalyzed condensation of carbonyl compounds with *N*-monosubstituted hydroxylamines, (ii) zinc-mediated reduction of nitro compounds in the presence of an aldehyde, or (iii) oxidation of *N*,*N*-disubstituted hydroxylamines.^{118–142} Nitrones are thus attractive precursors of nitroxides and alkoxyamines to be used in in-situ NMP.

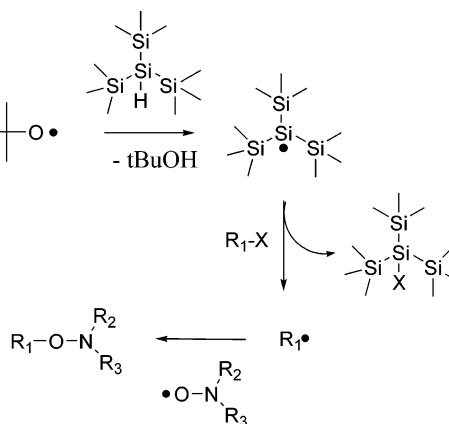
3.2. Contributions of Nitrones to the in-Situ NMP

Nesvadba et al. were the first to use nitrones for the controlled radical polymerization of vinyl monomers and launch the in-situ NMP concept.^{143,144} In a very first approach, alkoxyamines were prepared by reaction of free radicals released by thermolysis of azo-initiators [AIBN and ACCN (1,1'-azobis(cyclohexanecarbonitrile))] with the selected nitrones (Scheme 18).

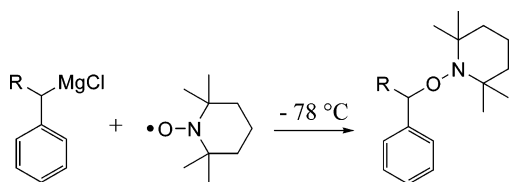
After purification, the alkoxyamines were tested in the radical polymerization of acrylates and styrene in bulk or in solution between 100 and 145 °C. Low molecular weight polymers (3000–14 000 g/mol) were formed rapidly (from 1 to 6 h) with, however, a rather high polydispersity ($1.2 \leq M_w/M_n \leq 3.4$). Additional data were reported for the styrene and nBuA polymerization initiated by compound **A** (Scheme 18). High styrene conversion was observed together with a low polydispersity. Nevertheless, the radical polymerization of nBuA led to chains with a broad molecular weight distribution, and the experimental molecular weight exceeded the theoretical value.¹⁴⁵

In a second approach, nitroxides and parent alkoxyamines were directly formed in the polymerization medium (in-situ NMP) by reaction of the nitrone with the free radical initiator. Two situations must be distinguished depending on whether this reaction was carried out before monomer addition (version 1) or after (version 2) (Scheme 19). Whatever the case, a prereaction was systematically performed at a temperature of about 60–80 °C, thus before polymerization was initiated at a higher temperature (130 °C). The in-situ-formed nitroxides and alkoxyamines were able to control the radical polymerization of *n*-butylacrylate (nBuA), although only low molecular weight poly(nBuA) ($M_n < 10\,000$ g/mol) with a polydispersity in the 1.65–2.0 range was

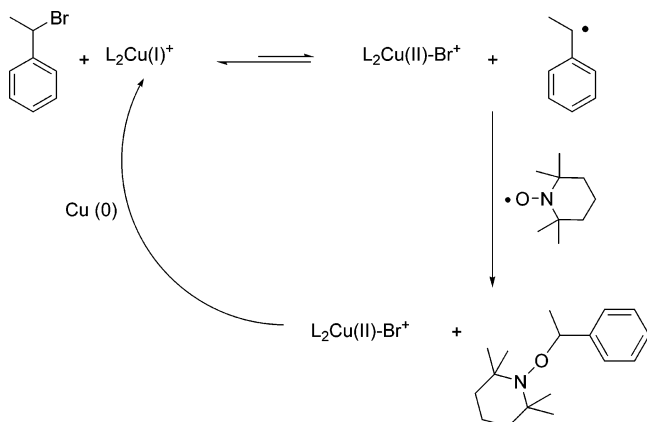
Scheme 6



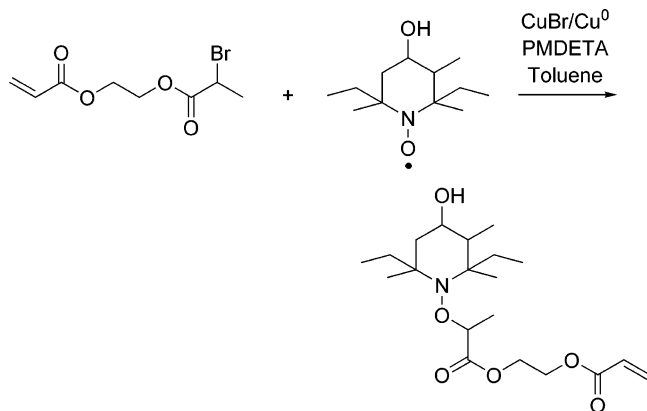
Scheme 7



Scheme 8



Scheme 9



produced. As a rule, the polydispersity was higher compared to the case where the alkoxyamine was preformed and purified before being added to the polymerization medium.

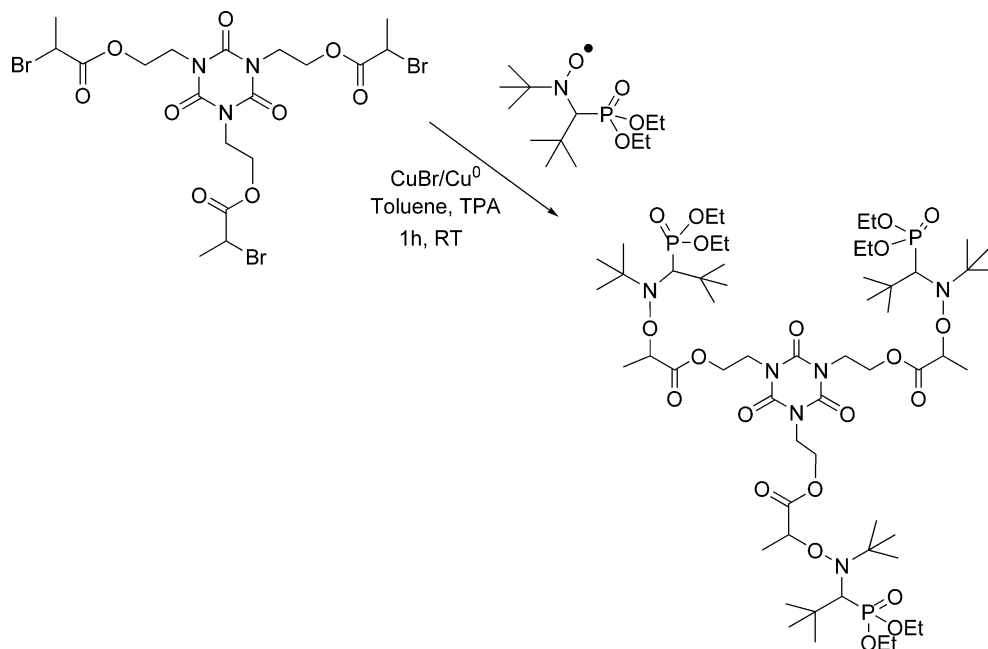
Subsequently, Asada and Lee polymerized styrene in the presence of a nitroxide (mainly PBN) and a mixture of substituted BPO (*m*-toluyl and benzoyl peroxides).¹⁴⁶ Nitroxide and the benzoyl peroxide mixture were prereacted in the presence of styrene at 95°C for 3.5 h, followed by an

increase in temperature up to 120°C for the polymerization. High polymerization rates were observed (85% monomer conversion after 7.5 h), molecular weights were increasing with the monomer conversion, and the polydispersity was moderately high (~ 1.6).

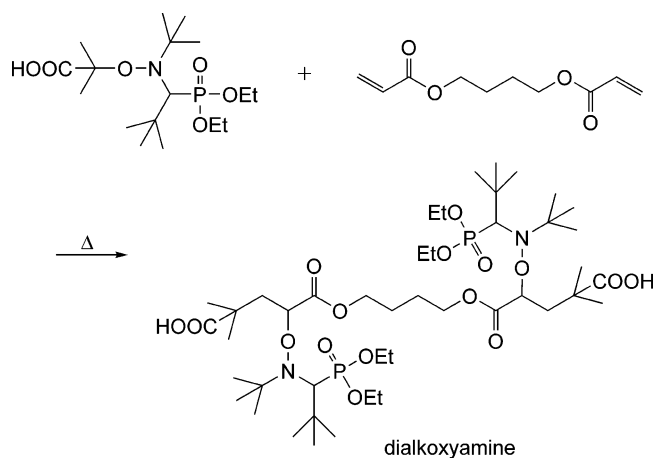
The ability of *N-tert*-butyl- α -phenylnitroxide (PBN) (Scheme 17) to mediate the controlled radical polymerization of methyl methacrylate (MMA) was studied by Grishin et al., who used AIBN as a free radical initiator at 50 and 65°C .¹⁴⁷ In contrast to Nesvadba et al., the mixture of nitroxide, initiator, and monomer was directly heated at the polymerization temperature without PBN/AIBN prereaction. A tentative proposal for the mechanism was as follows: (i) polymerization initiation by AIBN and propagation (P^\bullet), (ii) trapping of the growing radicals P^\bullet by the nitroxide (N) with formation of the macronitroxide (PN^\bullet), (iii) reversible trapping of the growing chains by the macronitroxide with formation of dormant species (alkoxyamine) (PNP) as in classical NMP (Scheme 20). According to Grishin et al. the C–ON bond of the macronitroxide-based alkoxyamine would be more labile compared to the commonly used alkoxyamine based on low molar mass nitroxides as a result of higher steric hindrance. A lower polymerization temperature could thus be used.

The MMA polymerization was better controlled at high PBN/AIBN molar ratio (8/1), although the polydispersity ($M_w/M_n \approx 1.7\text{--}2$) and molecular weight ($M_n \approx 3 \times 10^5$ to 7.5×10^5 g/mol) were very high. Substitution of dicyclohexyl peroxydicarbonate (CPC) for AIBN,¹⁴⁸ all other conditions remaining the same, modified the molecular characteristic features of PMMA, thus emphasizing the crucial role of the nitroxide/initiator pair on the course of the radical polymerization. Other monomers were also considered, such as vinyl chloride (VC),^{149,150} styrene (Sty),^{151,152} acrylonitrile (AN),¹⁵² *n*-butylacrylate (nBuA), and butylmethacrylate (BMA),¹⁵³ with the same PBN/AIBN pair, in the $50\text{--}70^\circ\text{C}$ temperature range. Nevertheless, the molecular weight increased only slightly with the monomer conversion (being extremely high for PBMA and PnBuA), the molecular weight distribution was high, and the polymer was rapidly formed at the initial stage of the process. Resumption of the VC polymerization (polydispersity = 2.5) and random copolymerization of styrene and acrylonitrile ($1.5 \leq M_w/M_n \leq 2.3$) were also reported. Moreover, polymerization of nBuA required temperatures higher than 50°C , and the monomer conversion was limited at 35%. The PBN/AIBN molar ratio was changed in relation to the monomer to be polymerized. This ratio was 0.1/1 for the styrene polymerization, whereas an equimolar

Scheme 10



Scheme 11



ratio was used in the case of acrylic monomers, and a much higher ratio (8/1) was used when methacrylic monomers were concerned. The reason for so different molar ratios was not clearly established. Finally, Grishin et al. substituted *N*, α -diphenylnitron (DPN) (Scheme 17) for PBN in the radical polymerization of MMA and nBuA initiated by either CPC or AIBN.¹⁵⁴ The results were reported at low temperature (40–50 °C), and the polydispersity was very high ($M_w/M_n > 2$), more likely as a result of irreversible termination reactions. Emulsion polymerization of styrene was also carried out in the presence of the ammonium persulfate/PBN pair and an ionic surfactant in the 70–90 °C temperature range.¹⁵⁵ Not only a latex was formed, but the polymerization was fast with 60% of monomer converted within only 30 min even in the presence of an excess of nitron.

Golubev et al.¹⁵⁶ focused on the bulk radical polymerization of styrene with the PBN/BPO pair (molar ratios from 0.7/1 to 10/1) according to the same strategy as Grishin et al., except for a higher temperature (90–120 °C). The reaction time was long (several days) at 90 °C, and the polydispersity was high ($1.6 \leq M_w/M_n \leq 3.5$). Nevertheless, molecular weight increased linearly with the monomer conversion, and PS-*b*-PnBuA block copolymers were syn-

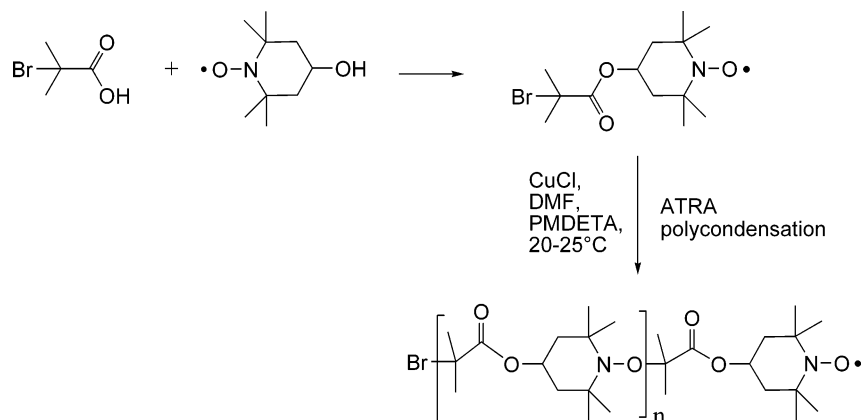
thesized with styrene first polymerized. In contrast, polymerization of nBuA with the PBN/BPO pair was limited in conversion (~30%) and poorly controlled. According to Golubev et al., a high temperature (≥ 90 °C) was required for the styrene polymerization to be controlled. Under these conditions, the initiator was rapidly decomposed, whereas at the lower temperatures used by Grishin et al. the initiation occurred during the whole polymerization process, continuously creating new polymer chains and leading to broad molecular weight distributions.

With the purpose of improving control of the in-situ NMP, Detrembleur et al.¹⁵⁷ addressed the question of the importance of the prereaction step between the nitron and the initiator in the presence or not of the monomer at a moderate temperature. They investigated in detail the impact of this preliminary step on the polymerization initiated at a higher temperature.

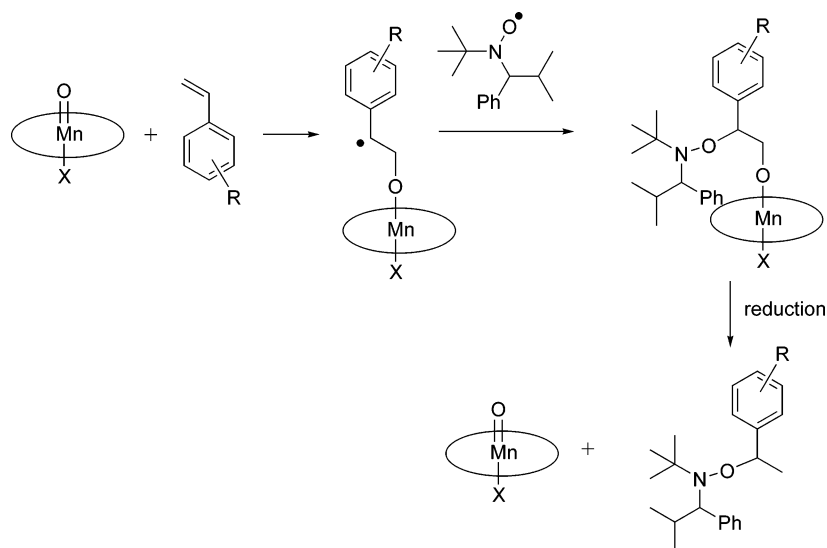
Attention was first paid to the *N-tert*-butyl- α -isopropyl nitron (Scheme 21)/BPO pair for the controlled radical (co)-polymerization of styrene and a styrene/acrylonitrile mixture.¹⁵⁷

When the styrene polymerization was concerned, a pre-reaction between the nitron and BPO (nitron/BPO: 1/0.5) was carried out in the presence of styrene at 85 °C for 4 h followed by polymerization at 110 °C. Under these conditions, no polymer was formed during the prereaction at 85 °C; polymerization was controlled at 110 °C. Moreover, polystyrene with a narrow polydispersity was prepared ($M_w/M_n \approx 1.25$) for the first time by an in-situ NMP system based on nitron. Although the initiation efficiency ($f = M_{n,theor}/M_{n,exp} \approx 0.2$) was low, the molecular weight was controlled by the styrene/nitron molar ratio, keeping constant the nitron/BPO ratio. However, an induction period of 4–10 h was observed after the prereaction, more likely because of the consumption of free nitroxides formed at the end of the prereaction. When most of these nitroxides were consumed, the nitroxide-mediated polymerization could start. However, addition of a free radical initiator (0.25 equiv of AIBN compared to the nitron) at the end of the prereaction suppressed this induction period. The structure of the

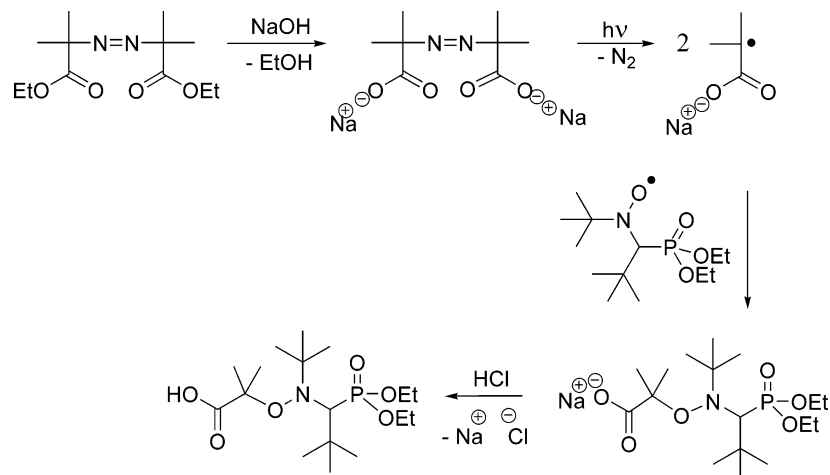
Scheme 12



Scheme 13



Scheme 14



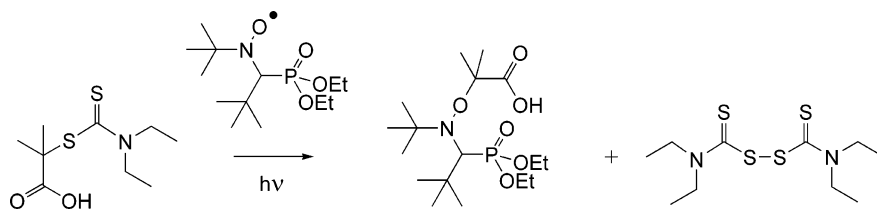
nitroxides and alkoxyamines formed in situ was however very difficult to elucidate because of the complexity of the prereaction as illustrated by Scheme 22.

Copolymerization of styrene and acrylonitrile was also investigated.¹⁵⁷ In order to control this copolymerization, acrylonitrile had to be added after the prereaction between the nitronium and BPO in styrene. Poly(styrene-*co*-acrylonitrile)-*b*-poly(styrene) (PSAN-*b*-PS) copolymers of high molecular weight ($M_n = 10\,4000$ g/mol) were also prepared with reasonably low polydispersity ($M_w/M_n = 1.40$).

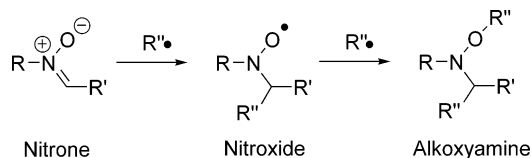
Although this system was not effective for the homopolymerization of nBuA and isoprene, well-defined poly(styrene)-*b*-poly(*n*-butylacrylate) (PS-*b*-PnBuA) and poly(styrene)-*b*-poly(isoprene) (PS-*b*-PIP) copolymers were successfully prepared. These results paved the way to the synthesis of well-defined copolymers by in-situ NMP, which had until then been limited to the preparation of copolymers with a high polydispersity.

When the same strategy was applied to the *N*-*tert*-butyl- α -isopropyl nitronium/AIBN pair, “uncontrolled” polymerization

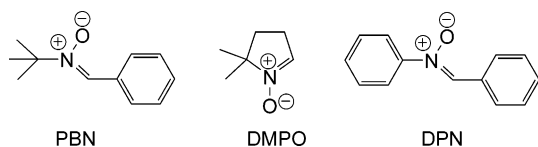
Scheme 15



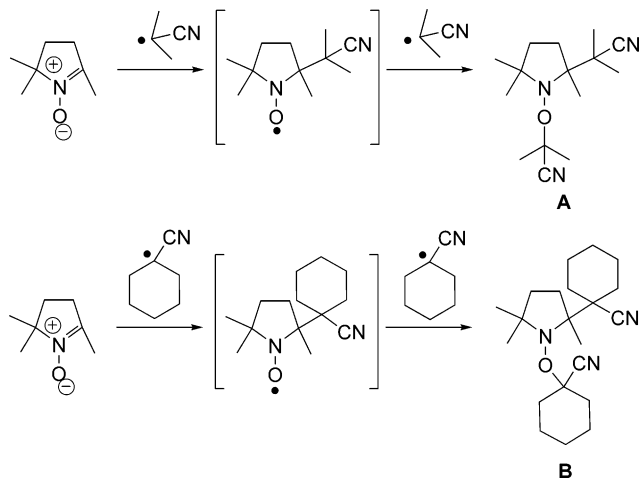
Scheme 16



Scheme 17



Scheme 18



of styrene already occurred during the prereaction step.^{157,158} This observation emphasized the crucial role of the initiator on the course of the prereaction and, ultimately, on polymerization control. Indeed, this control was directly dependent on the nitroxide structure, which was dictated by the structure of both the nitronium and the initiator, and on the rate of addition of the initiating radicals onto the nitronium and the monomer.

A series of nitroniums (Scheme 23) combined with AIBN were screened for their ability to control the radical polymerization of styrene.¹⁵⁸

To avoid the uncontrolled polymerization of styrene during the prereaction at 85 °C, no styrene was added to the nitronium/AIBN mixture and the prereaction was carried out in toluene. Styrene was then added and polymerized at 110 °C. Under these conditions, only one type of nitroxide and alkoxyamine should have formed (Scheme 24).

This comparative study showed that the PBN/AIBN system was the most appropriate nitronium/initiator pair to impart control to the solution and bulk polymerization of styrene at 110 °C with formation of low-polydispersity chains. The crucial role of the prereaction was emphasized by the very poor polymerization control observed when all

the constitutive components (nitronium, initiator, and monomer) were directly mixed and heated at 110 °C, in contrast to the conclusions by Grishin et al.^{151,152} The molecular weight of the polymers was governed by the total amount of the alkoxyamine formed in situ during the prereaction and the first stage of the polymerization whenever AIBN persisted in the medium.¹⁵⁹ The in-situ formation of the nitroxide was confirmed by electron spin resonance (ESR) (Scheme 25), and monitoring of its concentration with time showed the establishment of a pseudo-stationary state at 110 °C.¹⁵⁹ Polymerization of styrene was also carried out at 100 and 90 °C.¹⁵⁹

Recently, nBuA was successfully polymerized by the PBN/AIBN pair at 110 °C.¹⁶⁰ Similarly, well-defined PnBuA-*b*-PS copolymer was prepared with nBuA polymerized first, all the previously investigated systems being unsuccessful.

In 2005, Wertmer et al. patented the controlled radical (co)polymerization of vinyl monomers mediated by nitroniums substituted by longer alkyl groups (R and R' being C₁₈, Scheme 16).¹⁶¹ The nitronium was heated in the presence of BPO and the monomer (e.g., styrene) at 130 °C for 24 h without any prereaction, similar to the strategy of Golubev et al.¹⁵⁶ Polystyrene of high molecular weight (98 000–146 000 g/mol) was prepared, but polydispersity was undisclosed. PS-*b*-PnBuA diblock copolymers were also prepared with a high polydispersity ($M_w/M_n \geq 2$).

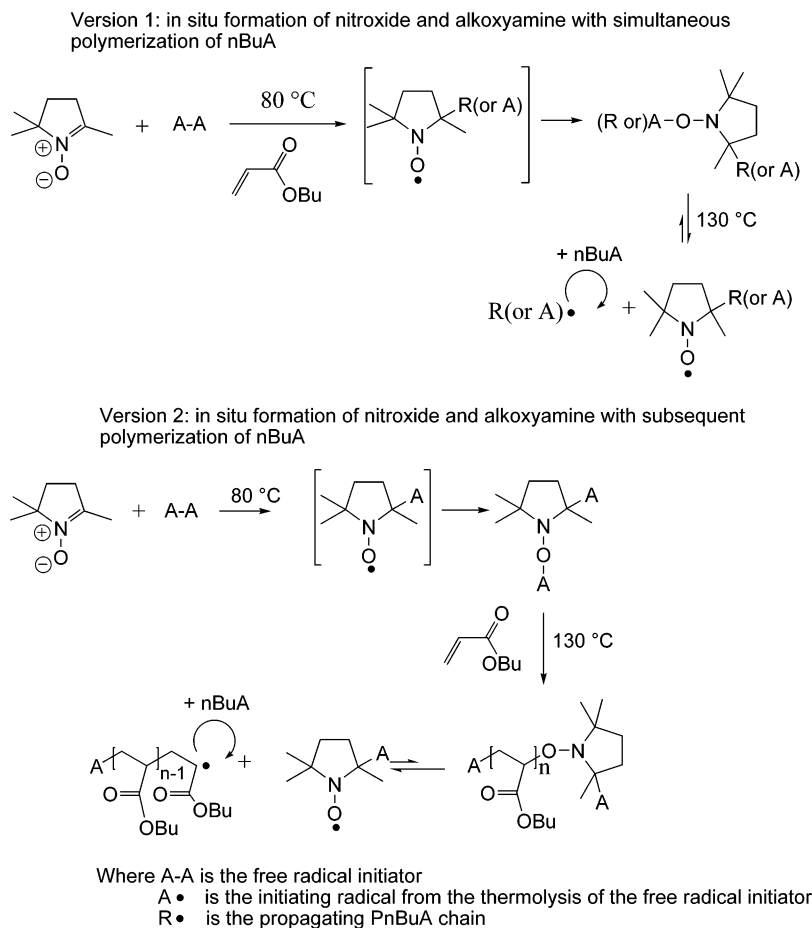
3.3. Cyclic Oxazolidine as Initiator and Regulator for the Radical Polymerization of Vinyl Monomers

Nitroniums are typical 1,3-dipoles prone to 1,3-dipolar cycloaddition onto carbon–carbon double and triple bonds with formation of five-membered heterocyclic compounds, i.e., isoxazolidines and isoxazolines, respectively (Scheme 26).^{118,121,162–171} Isoxazolines are commonly unstable, in contrast to isoxazolidines, which are usually stable and can be isolated from the reaction medium. It must be noted that monosubstituted alkenes like styrene, acrylonitrile, acrylate, and isoprene lead to 5-substituted isoxazolidines,¹⁶² which are nothing but cyclic alkoxyamines. The C–ON bond of isoxazolidine is labile at high temperature and releases a carbon-centered radical able to initiate polymerization and a nitroxide moiety able to control polymerization. The conditions are thus fulfilled for a classical NMP to occur (Scheme 27).

Cardi et al. patented the use of isoxazolidines as initiator/controlling agents for the radical polymerization of unsaturated monomers between 100 and 130 °C.¹⁷² 2-(1,1-Dimethylethyl)-3,3-dimethyl-5-phenyl-isoxazolidine (Scheme 27) was synthesized by 1,3-dipolar cycloaddition of the parent nitronium onto styrene and used to control the radical polymerization of styrene at 110 and 125 °C and prepare poly(styrene)-*b*-poly(styrene-*co*-acrylonitrile) block copolymers.

Under these conditions, the reaction time was short (4–6 h), although including an induction period of less than 1 h,

Scheme 19



and the monomer consumption increased linearly with time. However, no information was reported on the molecular weight distribution, the structure, and the composition of the block copolymers.

Other isoxazolidines (Scheme 28) were synthesized and tested in the radical polymerization of styrene at 100 °C, 110 and 125 °C and the synthesis of PS-*b*-PSAN block copolymers. A very high molecular weight ($M_n > 100\,000$ g/mol) was observed very rapidly at 125 °C with no significant dependence on monomer conversion. A decrease in the polymerization temperature was beneficial, although not enough to make this polymerization extensively controlled.

The main disadvantage of this strategy is the multistep synthesis and purification of the required heterocycles together with a limited mediating efficiency in radical polymerization.

3.4. Advantages and Drawbacks of the Nitronium Systems

Although well-defined (co)polymers can be prepared in the presence of properly chosen nitronium/radical promoter pairs, the in-situ conversion of the nitroniums into nitroxides and/or alkoxyamines must be improved. Indeed, experimental molecular weights are usually higher than the theoretical values. Moreover, the availability of nitroniums is limited, and in the case of large-scale production of polymers, use of significant amounts of free radical initiator calls for care, which might be a barrier to industrial developments. The

thermal stability of nitroniums is another concern. The choice of the nitronium and pre-reaction and polymerization temperatures must thus be optimized for each monomer, which means that a nitronium/free radical initiator pair is effective under specific conditions. In-situ NMP based on nitroniums thus not merely consists of mixing and heating all the components (nitronium, initiator, and monomer) at the polymerization temperature. A pre-reaction of the nitronium with the radical initiator at a temperature lower than the polymerization temperature is usually required for the control to be effective and to prepare polymers with a low polydispersity.

4. Nitroso Compounds

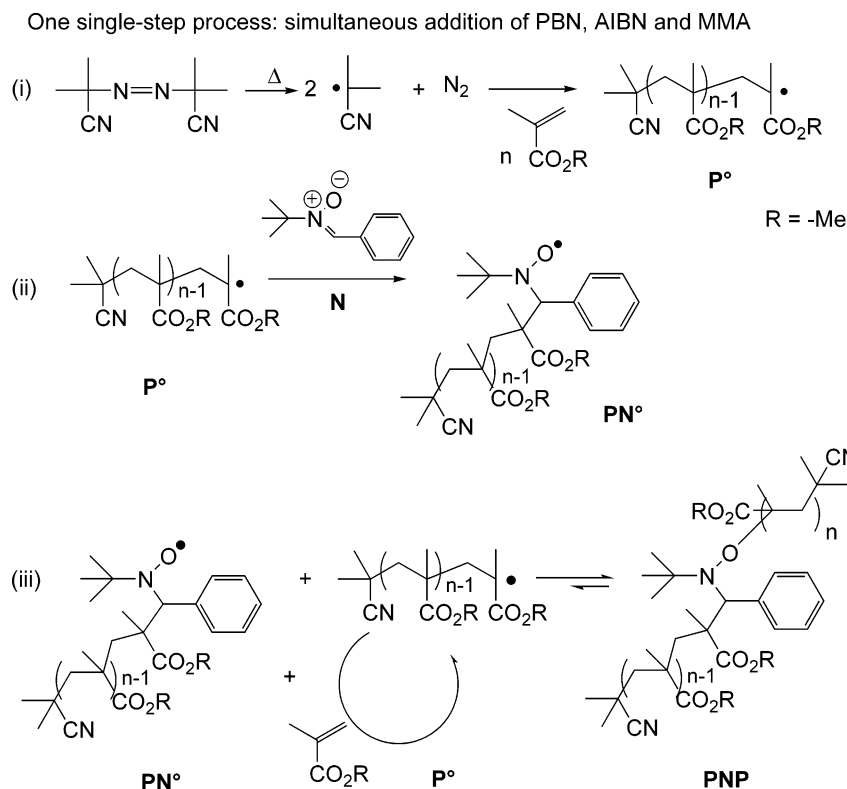
4.1. Reaction of C-Nitroso Compounds with Free Radicals

Nitroso compounds are well-known radical scavengers. They react rapidly with free alkyl radicals with formation of the parent nitroxides capable of reacting further with formation of alkoxyamines (Scheme 29).

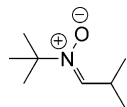
Gingras and Waters¹⁷³ observed this reaction when nitrosobenzene was reacted with an excess of AIBN (Scheme 30). That this reaction pathway is general was assessed by spin-trapping experiments with different nitroso compounds.^{113,174–182}

Some nitroso compounds are commercially available or quite easily prepared^{179,183–185} by oxidation of amines and hydroxylamines, by reduction of nitro compounds,^{179,183–186}

Scheme 20



Scheme 21



from alkyl nitrites,^{184,185,187} and by free radical addition onto nitric oxides.^{173,177,188–192} For more details, the reader is referred to a recent review by Gowenlock and Richter-Addo.¹⁸⁵

In 1953, Waters et al. studied the reaction of nitric oxide with cyanoisopropyl radicals and isolated the addition product of three cyanoisopropyl radicals onto nitric oxide (Scheme 31).¹⁸⁸

The ability of nitrogen monoxide to react with free radicals and form sequentially the parent nitroso compound, nitroxide, and alkoxyamine was investigated by Vertommen et al.¹⁹³ and Nesvadba et al.¹⁹⁴

Availability and radical scavenging properties of nitroso compounds make them well suited to the one-pot formation of alkoxyamines and in-situ NMP process.

4.2. Use of C-Nitroso Compounds in Controlled Radical Polymerization

Matyjaszewski et al.¹⁹⁵ polymerized MMA at 80 °C with AIBN combined with 2-methyl-2-nitrosopropane (MNP) and 2,4,6-tri(*tert*-butyl)nitrosobenzene (TBNB) (Scheme 32). The main information reported was that the polymerization rate changed with the nitroso compound at constant nitroso compound/initiator molar ratio.

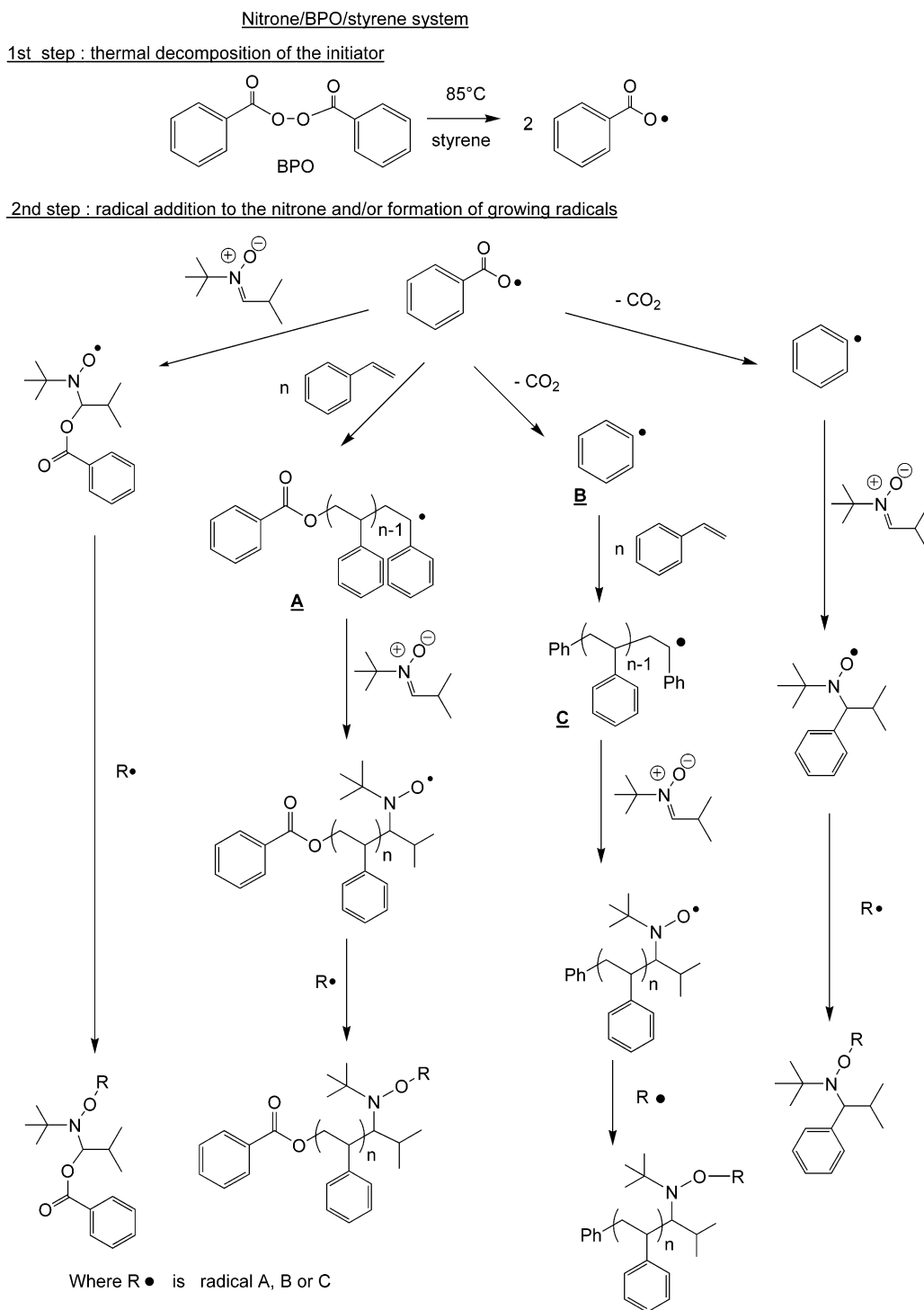
In 1998, Vertommen et al. prepared an alkoxyamine from nitrosobenzene and AIBN (Scheme 33). After purification, this alkoxyamine was used for the NMP of styrene, MMA, and nBuA at temperatures between 120 and 140 °C in the presence of camphor sulfonic acid (CSA).¹⁹³

Later, Nesvadba et al. patented the use of nitroso compounds as regulators for the controlled radical polymerization of vinyl monomers by NMP.^{143–145} Two procedures were claimed in the patent: (i) preparation of alkoxyamines by reaction of free radicals with nitroso compounds (Scheme 34), isolation, purification, and use as initiators and regulators for the NMP of various vinyl monomers and (ii) in-situ formation of alkoxyamines by addition of nitroso compounds and free radical initiators to the polymerization medium with a prereaction in the presence or not of the monomer at a temperature lower than the polymerization temperature.

Preformed alkoxyamines were tested in radical polymerization of styrene, nBuA, MMA, MADMAEE (methacrylic acid-2-diamino-ethylester), and MAGE (methacrylic acid-glycidylester) in the 100–130 °C temperature range and in random and block copolymerization of these monomers. When the in-situ process was concerned, only the nBuA polymerization was investigated. Regardless of the strategy, the experimental observations were comparable to those reported for the nitroxide system. The collected polymers were of a low molecular weight (<10 000 g/mol) with a high polydispersity (1.4–3.5).

Vertommen et al.¹⁹³ and Nesvadba et al.¹⁹⁴ also synthesized alkoxyamine initiators (Scheme 35) active in NMP by reaction of a free radical initiator (AIBN, ACCN, and 2,2'-azobis(2-methylbutyronitrile) (AMBN)) with gaseous nitric oxide.

Grishin et al. reported the controlled radical polymerization of MMA initiated by AIBN at 50–65 °C in the presence of 2-methyl-2-nitrosopropane (MNP) with no prereaction (Scheme 32).¹⁹⁶ Chains with very high molecular weight were formed (10^5 to 3×10^6 g/mol). Polydispersity was 1.6 at low monomer conversion (<10%) and increased up to 2.0–2.5 with increasing monomer conversion. MNP was also tested in the radical polymerization of vinyl chloride and styrene in combination with CPC and BPO, respec-

Scheme 22^a

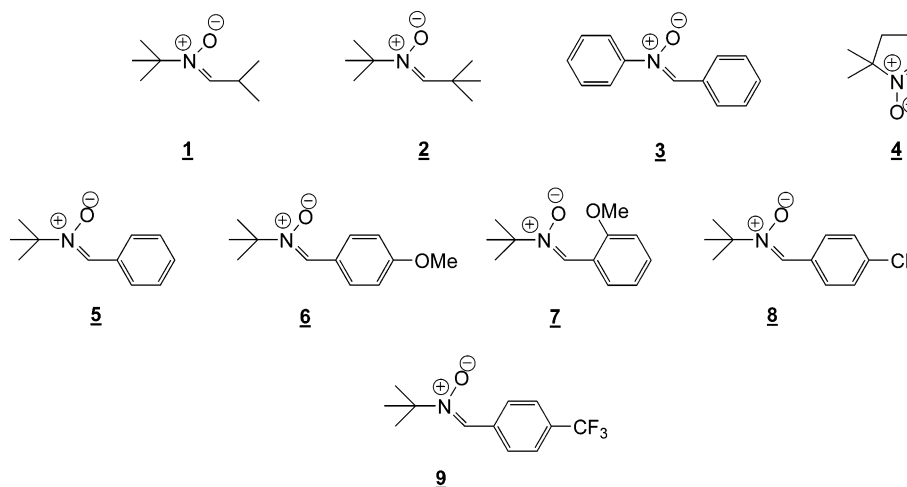
^a Where R• is radical A, B, or C.

tively.^{150,151,197} In contrast to PBN, MNP behaves as a conventional inhibitor, at least under the experimental conditions used. Later, MNP was used to copolymerize styrene and acrylonitrile at 100 °C with BPO as an initiator. The molecular weight distribution of the copolymer was however broad (mainly, $M_w/M_n > 2$).¹⁹⁸ Radical polymerization of styrene¹⁵¹ and copolymerization of styrene with acrylic monomers (e.g., MMA, nBuA)¹⁹⁹ were also conducted in the presence of the nitrosodurene (Scheme 36)/AIBN pair at 70 °C. Compared to MNP, the molecular weight of polystyrene increased more significantly with

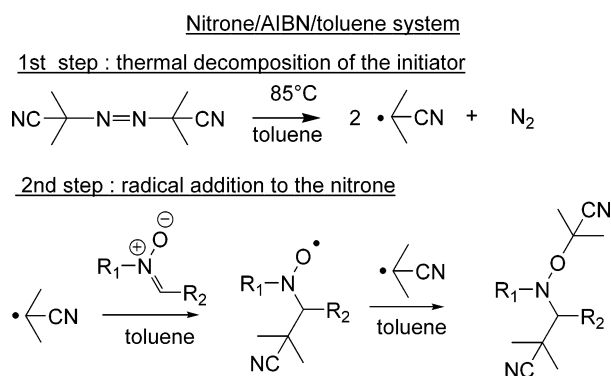
monomer conversion, and this was also the case for polydispersity (1.5–1.7).

A mixture of *m*-toluyl and benzoyl peroxides with 2-methyl-2-nitrosopropane was used by Asada and Lee¹⁴⁶ to polymerize styrene. These compounds were prereacted with styrene at 95 °C for 3.5 h before the temperature was increased and maintained at 130 °C. A high polymerization rate was observed (70% monomer conversion after 7.5 h), and the molecular weight increased linearly with monomer conversion. The polydispersity was reported as low (~1.25). The random copolymerization of styrene and acrylonitrile

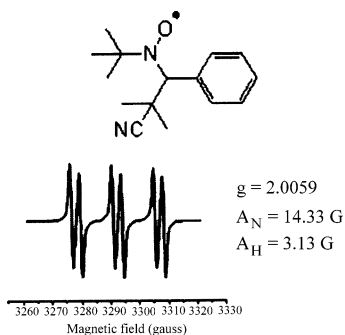
Scheme 23



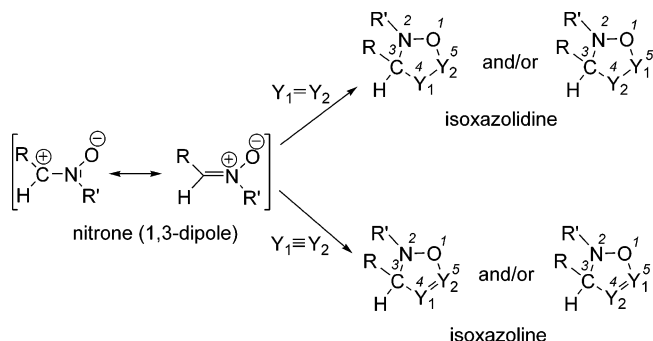
Scheme 24



Scheme 25



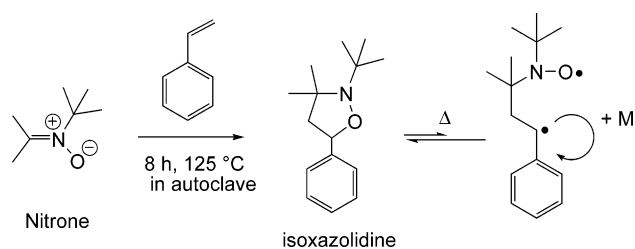
Scheme 26



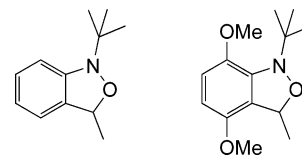
was successful under the same conditions. In the absence of prereaction, styrene polymerization remained controlled with, however, a higher polydispersity ($M_w/M_n \approx 1.35-1.4$).

In 2001, Catala et al. studied the radical polymerization of styrene initiated by AIBN in the presence of nitroso-*tert*-

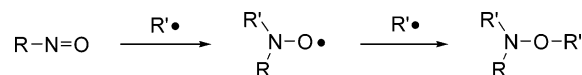
Scheme 27



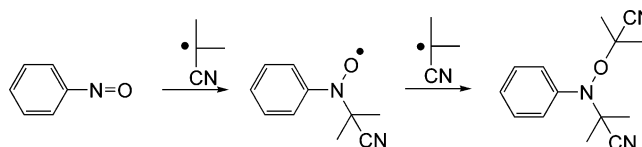
Scheme 28



Scheme 29



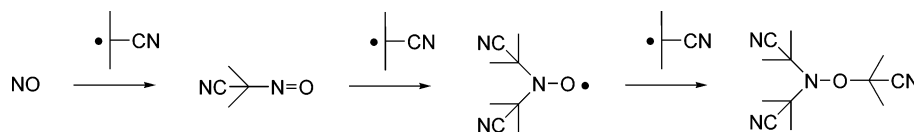
Scheme 30



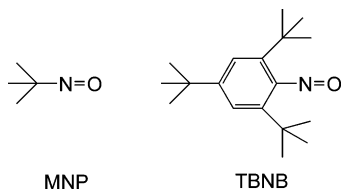
octane at 90 and 110 °C without any prereaction (Scheme 37).²⁰⁰ On the basis of kinetic data and ESR measurements, polymerization appeared to be controlled up to 50% of monomer conversion. The in-situ formation of nitroxide end-capped polystyrene chains (Scheme 37) was confirmed by ESR.

Recently, Grubbs et al. synthesized an alkoxyamine active in NMP by reaction of 2-methyl-2-nitrosopropane with 1-bromoethylbenzene by ATRA catalyzed by PMDETA-ligated CuBr in the presence of Cu(0) (Scheme 38).²⁰¹ Compared to the classical synthesis of alkoxyamines by ATRA, a commercially available precursor of nitroxide was used instead of a preformed nitroxide. The purified alkoxyamine was used to initiate the radical polymerization of styrene and isoprene. Well-defined polymers were prepared with a low polydispersity ($M_w/M_n = 1.14$ for polystyrene and 1.28 for polyisoprene). More recently, Grubbs

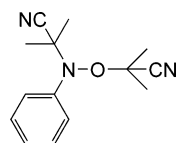
Scheme 31



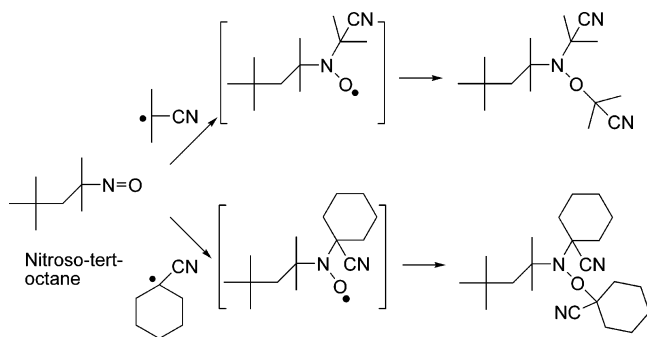
Scheme 32



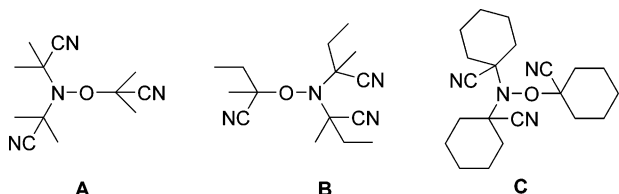
Scheme 33



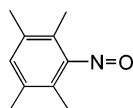
Scheme 34



Scheme 35



Scheme 36



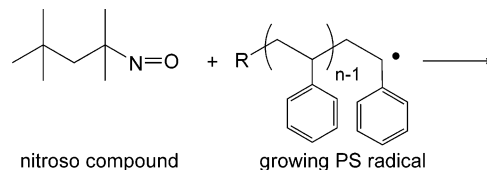
et al. used this alkoxyamine and successfully controlled the radical polymerization of *n*-butyl acrylate at 125 °C.²⁰² Lower polydispersity was observed when the alkoxyamine was preheated at temperatures up to 125 °C for 30 min prior to adding the monomer. This prereaction was needed for an excess of free nitroxide to be formed in situ and for polymerization to be controlled at best.²⁰²

4.3. Limitations of C-Nitroso Compounds

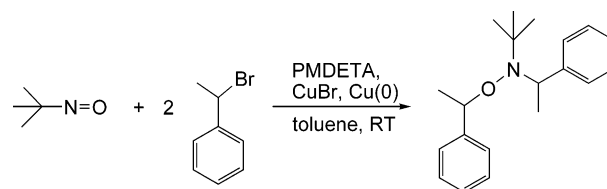
Thermal instability and high toxicity are the main limitations for the use of C-nitroso compounds as precursors of nitroxides in in-situ NMP. Moreover, nitroso compounds are known to form dimers (Scheme 39), which are unable to trap free radicals and be converted into nitroxides.^{178,181}

Upon thermolysis and photolysis, nitroso compounds are decomposed into a variety of products depending on their

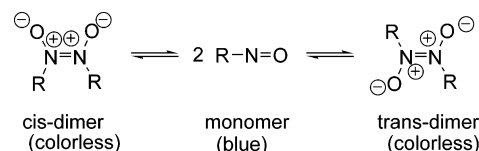
Scheme 37



Scheme 38



Scheme 39



Scheme 40



structure.¹⁸⁴ Reaction with mono-olefins and conjugated dienes is also possible.¹⁸⁴ The in-situ formation of these byproducts might be deleterious to the polymerization control.

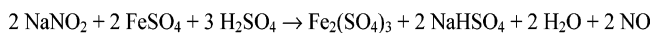
5. Sodium Nitrite and NO/NO₂ Mixtures for the in-Situ NMP

5.1. Preliminary Results and Mechanistic Considerations

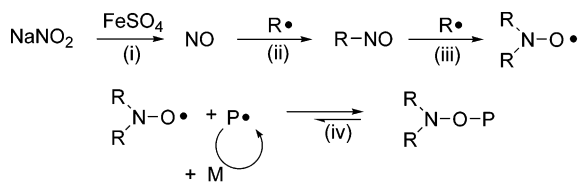
Sodium nitrite (NaNO₂) is known as an inhibitor for polymerization of water-soluble monomers at room temperature. Bortel et al. were the first to use NaNO₂ for imparting control to polymerization of the sodium salt of acrylic acid initiated by ammonium persulfate in water at 90 °C.²⁰³ Although the polymerization rate decreased and the number-average molecular weight slightly increased over time, the polydispersity was extremely high ($M_w/M_n > 6.5$). The authors proposed that sodium nitrite was reversibly decomposed, however, in water in relation to temperature and pH (Scheme 40).

Nitric oxide and nitrogen dioxide are paramagnetic species able to trap propagating chains with formation of nitroso compounds and nitro compounds, respectively. The nitro

Scheme 41



Scheme 42



Where $\text{R}\cdot$ is the propagating chain or the initiating radical
 $\text{P}\cdot$ is the propagating chain
 M is the monomer

compounds can be further converted into nitroso compounds by reaction with an additional radical. According to these authors, the ammonium persulfate radicals and growing polymer radicals would be capped by a nitroxide that would participate in an equilibrium between active and dormant species. No structure was however proposed for the assumed nitroxide.

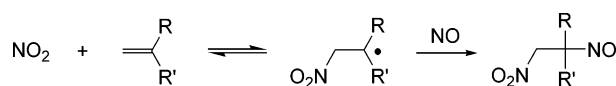
Later, Detrembleur et al. demonstrated that the radical polymerization of *tert*-butylmethacrylate initiated by a conventional initiator (AIBN or potassium persulfate ($\text{K}_2\text{S}_2\text{O}_8$)) could be controlled by a combination of sodium nitrite (NaNO_2) and iron(II) sulfate (FeSO_4) at 80 °C in water.^{204–207} PtBMA was prepared with a controlled molecular weight, whereas the polydispersity, which was initially low ($M_w/M_n \approx 1.1–1.2$), increased with the reaction time. At the same time, $\ln([M]_0/[M])$ deviated from the linearity, consistent with a loss of the polymerization control. Interestingly, the molecular weight was dictated by the initial amount of sodium nitrite rather than by the amount of iron(II) sulfate. However, FeSO_4 had to be added to NaNO_2 , even in a low amount, for the control to be observed.

Reduction of sodium nitrite by an acidic solution of FeSO_4 is known to release NO (Scheme 41), which is able to trap free radicals with formation of nitroxides and parent alkoxyamines.^{208,209}

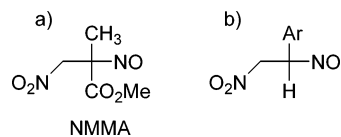
A four-step mechanism was accordingly proposed (Scheme 42): (i) formation of NO by reduction of NaNO_2 by iron(II) sulfate, (ii) reaction of NO with the initiating and/or growing radicals with formation of a nitroso compound ($\text{R}-\text{NO}$), (iii) conversion of the nitroso compound into the parent nitroxide ($\text{R}_2\text{NO}\cdot$), and (iv) reversible trapping of the propagating chains by the nitroxide with establishment of an equilibrium between active and dormant species at the origin of the polymerization control. Therefore, three initiating/propagating radicals per NO molecule were required to form the alkoxyamine responsible for the control. The yield in alkoxyamine was difficult to estimate because the initiation efficiency strongly depended on the solvent, temperature, dilution, and free volume of the reaction flask. Moreover, the limited solubility of NO in the liquid phase and possible loss of NO when samples were picked out from the polymerization flask were additional factors that affected the yield.

It must be noted that although NO is paramagnetic, it does not add to alkenes with acceptor or donor substituents with formation of β -nitrosoalkyl radicals.^{210,211} In contrast, addition of NO_2 to the less sterically hindered carbon of double bonds leads to β -nitroalkyl radicals.^{212,213} Therefore, if a mixture of NO and NO_2 is added to alkenes, NO can add to the β -nitroalkyl radicals formed by addition of NO_2 to the

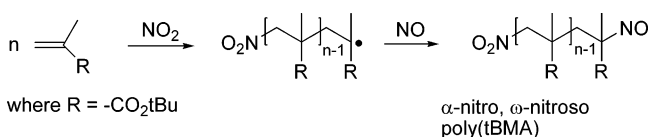
Scheme 43



Scheme 44



Scheme 45



where $\text{R} = -\text{CO}_2\text{tBu}$

α -nitro, ω -nitroso
poly(tBMA)

alkenes and leads to α -nitroso- β -nitro compounds as shown in Scheme 43.

Alkyl methacrylates and styrene were involved in the synthesis of α -nitroso- β -nitro derivatives.^{212,213} Shechter et al.²¹² were the first to report on the synthesis of methyl 2-methyl-3-nitro-2-nitrosopropionate (NMMA) (Scheme 44a) by reaction of methyl methacrylate (MMA) with a sodium nitrite/sulfuric acid mixture (this mixture being precursor of a NO and NO_2 mixture). Similarly, another research group synthesized the α -nitroso- β -nitro styrene derivative (Scheme 44b) by passing a NO/ NO_2 mixture (1/1 molar ratio) through a styrene solution.²¹³

These α -nitroso- β -nitro derivatives were converted into the parent nitroxides by addition of free radicals as confirmed by ESR.^{213–216}

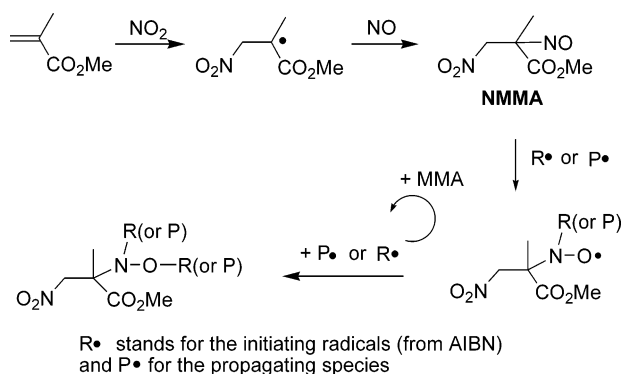
Detrembleur et al. emphasized the simultaneous formation of NO and NO_2 when sodium nitrite was reduced by FeSO_4 . When the reaction occurred in the presence of tBMA, α -nitro- ω -nitroso poly(tBMA) was formed (Scheme 45).^{204–207} Because this nitroso compound was a precursor of nitroxide by reaction with alkyl radicals, it was involved in the NMP polymerization as will be reported in the next section.

Contamination of PtBMA by iron was a severe drawback of the $\text{NaNO}_2/\text{FeSO}_4$ system. Therefore, nonmetallic activators for the decomposition of sodium nitrite were sought. In this respect, ascorbic acid proved to be a successful alternative for activation of the NaNO_2 decomposition.²¹⁷ Acetic acid, formic acid, hydrochloric acid, and sulfuric acid could also be used for this purpose.²¹⁸ Additional contributions dealt with the radical polymerization of (i) MMA at 95 °C by the $\text{NaNO}_2/\text{FeSO}_4$ system in the presence of acetic anhydride²¹⁹ and (ii) styrene by the sodium nitrite/iron(II) sulfate pair.²²⁰ Polydispersity was ~ 1.5 at the early stage of the styrene polymerization and increased over time, as observed for the alkyl methacrylate polymerization.

5.2. Controlled Radical Polymerization of Alkyl Methacrylates in the Presence of the In-Situ-Formed α -Nitro- ω -nitroso Adducts

Detrembleur et al. demonstrated that the bulk polymerization of MMA and tBMA conducted in the presence of methyl 2-methyl-3-nitro-2-nitrosopropionate (NMMA) (Scheme 46) was controlled when initiated by AIBN at 60 °C.^{204,221} However, the polydispersity increased from 1.15 to 1.95

Scheme 46



when the monomer conversion was increased. The nitroso compound was synthesized by reaction of MMA with the NO/NO₂ mixture in situ released by the sodium nitrite/sulfuric acid system²¹² and purified before use. A PMMA-*b*-PtBMA copolymer with a rather low polydispersity (~1.4) was synthesized, although contaminated by unreacted PMMA prepared in the first step.²⁰⁴

α -Nitro- ω -nitroso poly(tBMA) and poly(MMA) were also prepared by bubbling NO and NO₂ in tBMA and MMA, respectively. These chains contributed to control of the bulk polymerization of alkyl methacrylates initiated by AIBN at 60 °C.^{207,221} They slowed down the polymerization, whereas the polydispersity was initially low (~1.15) but increased with the reaction time (1.8–1.95).

From this short overview, it appears that the nitrite system is intrinsically complex because several species are formed in situ as a result of the addition of both the initiating radicals and the propagating radicals (initiated by AIBN and NO₂ gas) onto NO. Therefore, several nitroso compounds and thus nitroxides and alkoxyamines coexist in the polymerization medium (Scheme 47).

5.3. NO/NO₂ Mixtures: An Alternative Way to the Nitroso Compounds as Precursors of Nitroxides

Instead of using sodium nitrite as a precursor of nitric oxides, NO and NO₂ were simultaneously bubbled in the monomer (MMA and tBMA) at room temperature for 5 min.^{207,221} The α -nitro- ω -nitroso poly(MMA) and poly-(tBMA) thus formed (Scheme 48) were regulators for the polymerization initiated by AIBN at 60 °C. Again, the polydispersity increased with time. Molecular weight was basically controlled by the amount of NO/NO₂.

Random copolymerization of MMA and 2-hydroxyethyl methacrylate (HEMA) was also controlled provided that NO and NO₂ were bubbled first in MMA at room temperature for 5 min before HEMA and AIBN were added and the temperature increased to 60 °C.²²¹

5.4. Advantages and Limitations of the Sodium Nitrite and NO/NO₂ Systems

The main advantage of the sodium nitrite system is in the availability and very low cost of the reagents: sodium nitrite, iron(II) sulfate, ascorbic acid, acetic acid, and the free radical initiator (AIBN or K₂S₂O₈). It is a one-pot process that occurs in water at quite a low temperature. Moreover, a metal-free system can be implemented using ascorbic acid or acetic acid instead of iron(II) sulfate as an activator for decomposition

of NaNO₂. Last but not least, the process is well suited to the radical polymerization of alkyl methacrylates, even though other monomers can also be polymerized. This is a major improvement because NMP is known to work well for the polymerization of styrene and derivatives, acrylates, and 1,3-dienes but not efficiently for methacrylates. The nitrite system is thus raising new prospects, although the polymerization control of alkyl methacrylates still needs to be improved because the polydispersity is too high and the polymerization rate decreases with the reaction time, more likely for several reasons, such as heterogeneity of the system, number of steps leading to the dormant species, and formation of several nitroso compounds, nitroxides, and alkoxyamines of different reactivity and stability.^{204,217}

Although the polymerization control is not ideal, a gaseous mixture of NO/NO₂ is a potential substitute for nitroxides and alkoxyamines commonly used in NMP. However, handling of toxic and corrosive nitrogen monoxide and dioxide is a deleterious problem. The in-situ formation of nitric oxide from decomposition of sodium nitrite is an interesting alternative. Another way to control the radical polymerization of vinyl monomers by the in-situ production of nitric oxide from an organic precursor was also reported. Indeed, *tert*-butylnitrite combined with 2-mercaptoethanol could impart some control to the tBMA radical polymerization initiated by potassium persulfate at 80 °C in water even though the control was not ideal.^{206,207} The polymer polydispersity which was initially low (1.1–1.2) increased up to 1.7 with increasing monomer conversion. A thermally unstable *S*-nitrosothiol (or thionitrite)^{222,223} was assumed to be formed in situ at the early stage of the reaction. These thionitrites are well-known precursors of nitric oxide under thermal treatment. Nitric oxide would thus be the key molecule for formation of the nitroxide responsible for the polymerization control (Scheme 49).

The main disadvantage of this technique is the use of thiols responsible for a nasty smell and undesired color. In addition to nitric oxide, thermolysis of thionitrite also leads to disulfide (RSSR) (Scheme 49), which might interfere with the NMP mechanism.

6. Hindered Secondary Amines and the in-Situ NMP

6.1. Oxidation of Secondary Amines into Nitroxides

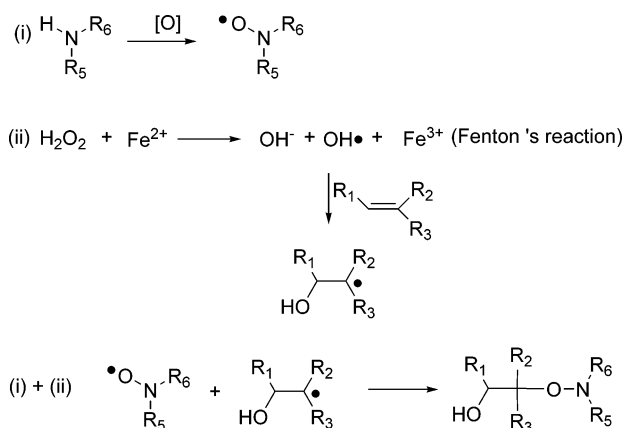
Oxidation of hindered secondary amines (Scheme 50) is a very useful way to prepare nitroxides because of the high reaction yield and availability of the secondary amines (commercial or easily synthesized²²⁴).

A series of oxidizing agents have been used, including peracids,^{87,225–233} dimethyldioxirane,^{234–236} peroxides,^{113,237–242} lead(IV), mercury and silver oxide,^{113,243} Oxone and Caro's acid^{113,244} (KHSO₅·KHSO₄·K₂SO₄ or potassium peroxy-monosulfate), combination of KMnO₄/OH[–],²⁴⁵ molecular oxygen¹¹³ and ozone, and peroxy radicals R–O–O[•].¹¹³ Peracetic acid and hydrogen peroxide are however preferred because of availability, low cost, mild reaction conditions, and high oxidation yield of secondary amines.²³³

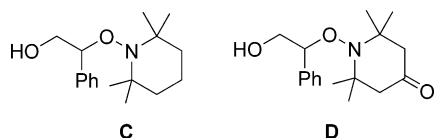
6.2. One-Pot Processes for the Preparation of Alkoxyamines Active in NMP

Alkoxyamines **A** and **B** active in NMP (Scheme 51) were synthesized in a one-pot process by oxidizing first the parent

Scheme 52



Scheme 53



monomer conversion increased. Block copolymerization could also be carried out, e.g., PSAN-*b*-PnBuA.^{248,249}

These two new approaches for the synthesis of alkoxyamines in biphasic media are thus very effective. Significantly, purification of the alkoxyamines after synthesis was not required for the aforementioned achievements to be made.

Compared to the classical formation of an alkoxyamine by reaction of a preformed and purified nitroxide with an alkyl radical, these synthetic pathways are more direct and time saving, which makes them very attractive for industrial applications.

6.3. In-Situ NMP Using Hindered Secondary Amines and Oligomeric Secondary Amines

In 2001, it was shown that the polymerization of styrene could be controlled by 2,2,6,6-tetramethylpiperidine (TMP) used as a nitroxide precursor according to the following strategy: (i) TMP was first oxidized into TEMPO by *m*-chloroperbenzoic acid (mCPBA) at room temperature for 5 h, (ii) styrene and BPO were then added to the TEMPO-containing reaction medium followed by a prereaction at 95 °C for 3.5 h in order to form the alkoxyamine, and (iii) styrene polymerization was then carried out at 123 °C (Scheme 54).²⁵⁰ Although polystyrene was formed with a low polydispersity ($M_w/M_n \approx 1.25$), the polymerization rate was low (90% monomer conversion after 69 h) and a long induction period (~ 15 h) was observed.

When carried out in a single step without pre-reactions i and ii, Detrembleur et al. emphasized the exothermicity and thus the related risks of this polymerization that was out of control.^{251,252} However, when a mixture of styrene, TMP, or 4-oxo-TMP and peracetic acid was heated at the polymerization temperature without any free radical initiator, the exothermicity was moderate and polymerization was controlled with relatively low polydispersity until high molecular weights. Interestingly, no free radical initiator had to be added before polymerization. Copolymers of styrene and acrylonitrile and styrene and *n*-butylacrylate were prepared with the 4-oxo-TMP/peracetic acid pair. The in-situ-formed TEMPO derivatives were clearly responsible for the controlled polymerization.

PS oligomers end capped by a more sterically hindered secondary amines (Scheme 55) triggered unusually fast controlled radical polymerization of different vinyl monomers (styrene, styrene/acrylonitrile) when combined with peracetic acid without additional free radical initiator.^{253,254} For instance, the random copolymerization of styrene and acrylonitrile was almost complete after only 2.5 h at 95–100 °C, and the molecular weight distribution was rather narrow ($M_w/M_n \approx 1.4$). This was the first example of a fast NMP at a rather low temperature. It should be noted that the polymer molecular weight was controlled by the amount of secondary amine with respect to the monomer at a constant amine/oxidizing agent molar ratio.

Star-shaped and grafted (co)polymers were also reported to have been formed by this strategy using multifunctional oligomeric secondary amines.

Grishin et al. also combined di-*tert*-butylamine (DBA) and *tert*-butylamine (TBA) with dicetylperoxy dicarbonate (DCP) and BPO, respectively, in order to control the styrene polymerization.^{197,255} DCP and BPO initiated the radical polymerization of styrene and simultaneously oxidized the amine to the parent nitroxide. Polymerization occurred at 65 °C, and chains of high molecular weights were formed with a rather high polydispersity ($M_w/M_n \approx 2$).

6.4. Advantages and Limitations

The main advantages of amines of low molecular weight as precursors of nitroxides are their availability and low cost, which is of the utmost importance for industrial development of the process. Although most of the hindered oligomeric or polymeric secondary amines have to be prepared, some of them are commercially available at low cost and commonly used as stabilizers of polymers, which makes the process attractive.

The choice of the oxidizing agent in this in-situ NMP process is also crucial for the success or failure of the process. Indeed, oxidation of the secondary amine into nitroxide must be fast however without forming too many initiating radicals; otherwise, the polymerization would be exceedingly exothermic and uncontrolled.

7. Hydroxylamines and the in-Situ NMP

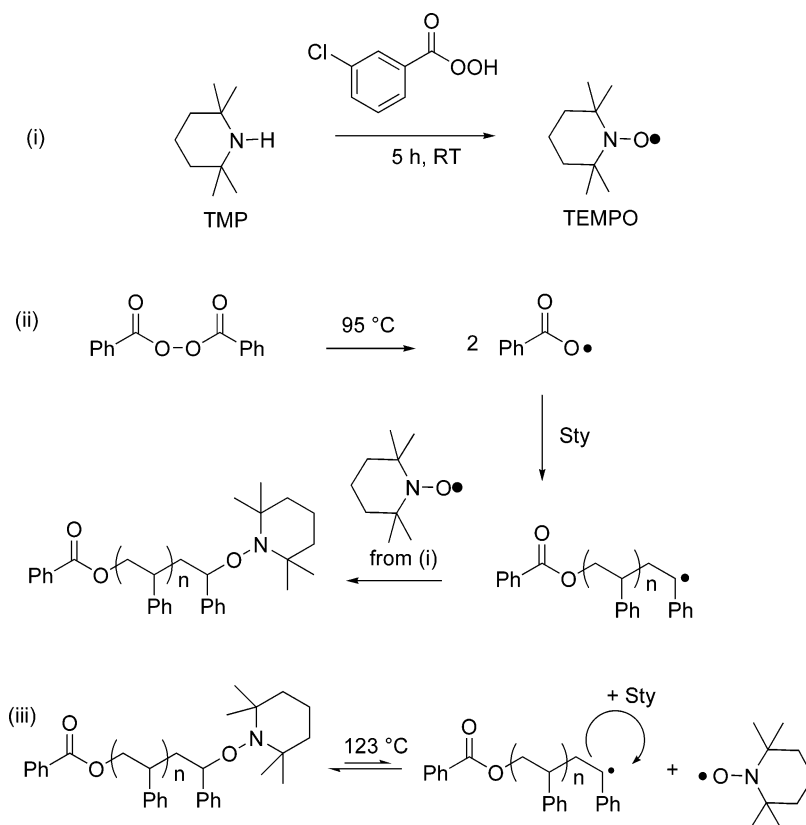
7.1. Oxidation of Hydroxylamines into Nitroxides

Hydroxylamines are well-known radical scavengers and thus stabilizers for material sensitive to radical attacks.^{256–258} Their stability to heat and storage largely depends on their substitution (degree and type of substituents).¹⁸⁴ N,N-Disubstituted hydroxylamines are oxidized into nitroxides either in contact with air or when reacting with silver oxide, Fremy's salt ($(\text{KO}_3\text{S})_2\text{NO}$), peroxides, or free radical initiator able to abstract the hydrogen atom (Scheme 56).^{46,47,184,259–262} Formation of nitroxides from hydroxylamines is however less common in industry than from amines.

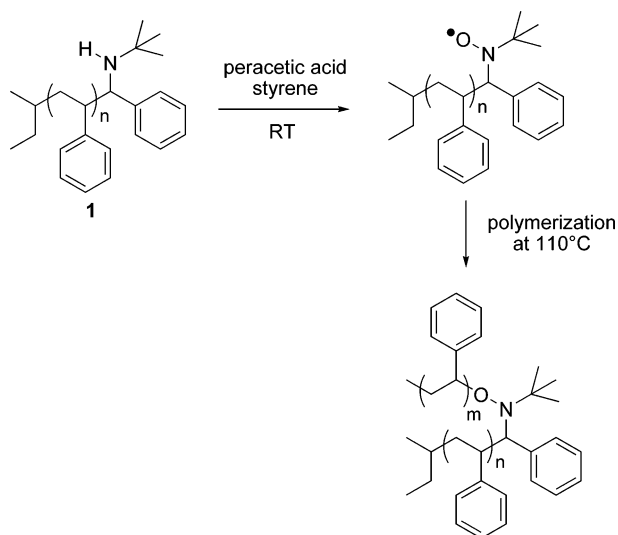
7.2. Hydroxylamines and the in-Situ NMP

In 2001, N,N-disubstituted aliphatic or cyclic hydroxylamines were reported in the synthesis of vinyl polymers.^{261,262} The strategy consisted of mixing the hydroxylamine, the monomer, and a free radical initiator (e.g., a peroxide, an azo compound, and a hydroperoxide) in the 90–150 °C temperature range. As an example, styrene was

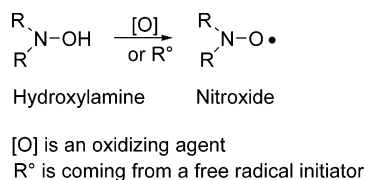
Scheme 54



Scheme 55



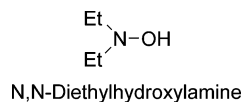
Scheme 56



polymerized in the presence of *N,N*-diethylhydroxylamine (Scheme 57) with BPO as a free radical initiator.

Whenever a prereaction of the three components was carried out at 95 °C for 3.5 h before the polymerization was initiated at 130 °C, a polystyrene with a high molecular weight ($M_n = 78\,000 \text{ g/mol}$) and a low polydispersity (M_w/M_n

Scheme 57



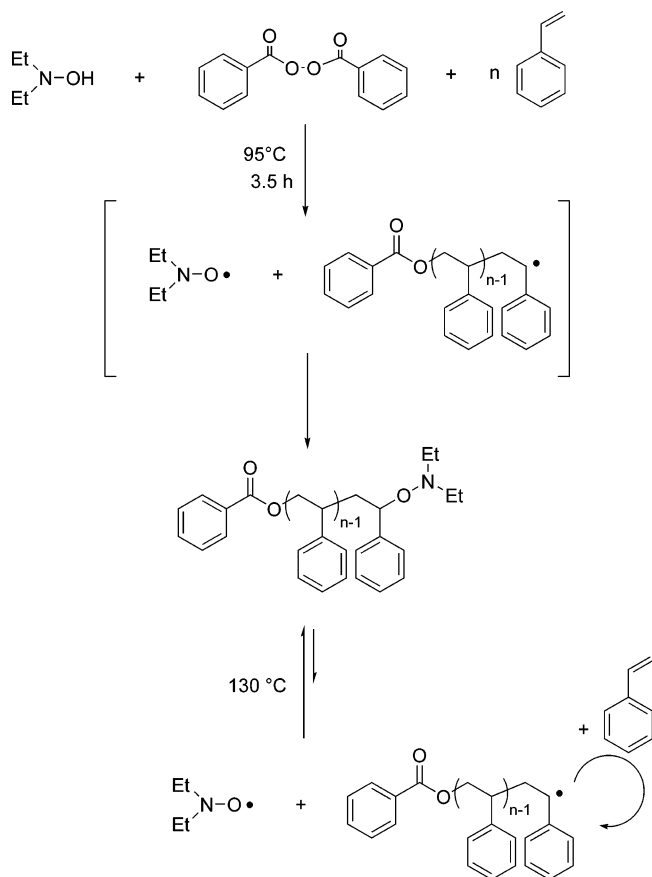
$M_n = 1.3$) was formed in a controlled manner (75% monomer conversion after 4.5 h). It must be noted that styrene started to be polymerized at 95 °C with a polydispersity of 1.55 that however decreased during the polymerization at 130 °C. These observations suggested that nitroxides and parent alkoxyamines were formed during the prereaction at 95 °C and thus contributed to the polymerization control at 130 °C (Scheme 58).

The control was less effective when the polymerization was carried out at 130 °C without prereaction at 95 °C. A higher polydispersity ($1.65 \leq M_w/M_n \leq 2.00$) was then observed. At 130 °C, oxidation of the hydroxylamine into nitroxide competed with initiation of the polymerization. In this process, BPO had a dual role: it oxidized the hydroxylamine into nitroxide and initiated the styrene polymerization.

Although the radical polymerization of styrene was reported as well controlled, the “livingness” of the polymer chains was not confirmed by, e.g., polymerization resumption and synthesis of block copolymers. The stability of the nitroxide formed by oxidation of *N,N*-diethylhydroxylamine is another pending question.

In 2004, Grishin et al. used di-*tert*-butylhydroxylamine (DBHA) in combination with BPO (or AIBN and DPC) for control of the radical polymerization of styrene and methyl methacrylate. Styrene was polymerized at 100 °C with BPO and at 70 °C with AIBN, whereas the polymerization temperature was 50 °C for MMA.²⁶³ Although PMMA of very high molecular weight ($M_n > 150\,000 \text{ g/mol}$) and

Scheme 58

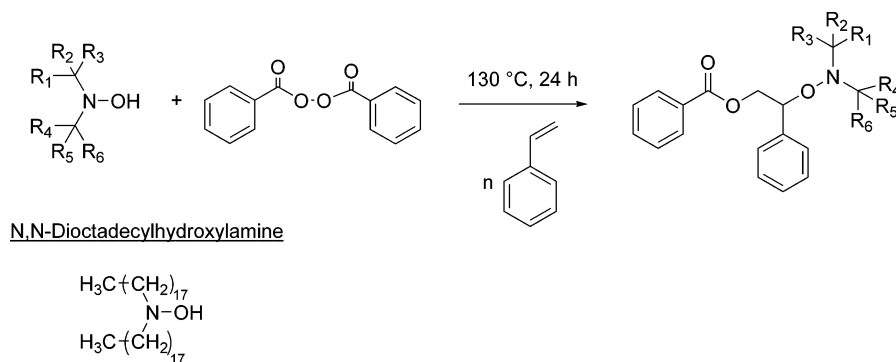


polydispersity (from 1.7 to 2.9) was formed, shorter PS chains were collected in the presence of the DBHA/BPO ($5000 \text{ g/mol} \leq M_n \leq 15\,000 \text{ g/mol}$) and the DBHA/AIBN pair ($20\,000 \text{ g/mol} \leq M_n \leq 30\,000 \text{ g/mol}$). Nevertheless, the polydispersity of PS was also high ($1.5 \leq M_w/M_n \leq 1.9$). Peroxides (DPC and BPO) had a dual role of polymerization initiator and oxidizing agent of the hydroxylamine into the parent nitroxide. When AIBN was used, the nitroxides were formed in situ by H abstraction from DBHA by the propagating chain.

7.3. High Molecular Weight Hydroxylamines for the Polymerization of Vinyl Monomers and Synthesis of Block Copolymers

In 2005, Wermter et al. extended the previous method based on low molecular weight hydroxylamines to hydroxylamines containing a long alkyl chain.¹⁶¹ The same technique

Scheme 59



was used except that no prereaction at a lower temperature was performed (Scheme 59).^{261,262}

For instance, styrene was polymerized in a single step with *N,N*-dioctadecyl-hydroxylamine and BPO at 130 °C for 24 h (Scheme 59). PS of a high molecular weight ($85\,100 \leq M_n \leq 138\,500 \text{ g/mol}$) was formed with a high monomer conversion (from 65% to 98%). The time required for high conversion at this temperature was long, and no information was provided about the molecular weight distribution. PS was used in a subsequent step as a macroinitiator for the *n*BuA polymerization at 130 °C with the purpose to prepare PS-*b*-P*n*BuA diblock copolymers. High polydispersity was reported ($1.8 \leq M_w/M_n \leq 2.3$). Although no quantitative information on the diblock copolymer formation was disclosed, the authors stated that the efficiency of block copolymerization was higher when a high molecular weight hydroxylamine (*N,N*-dioctadecyl-hydroxylamine) was substituted for a small one (*N,N*-diethylhydroxylamine). The reason might be that low molecular weight hydroxylamines were partly lost at the polymerization temperature (130–150 °C), such that not enough nitroxide was available to control all the initiated chains.

7.4. Advantages and Limitations

The use of hydroxylamines (of low or high molecular weight) as precursors of nitroxides is an easy and inexpensive alternative for the controlled radical polymerization of vinyl monomers because these compounds are synthesized with a large spectrum of structure by standard methods at a low cost.^{264,265} Compared to in-situ NMP based on hindered secondary amines, oxidants, such as peracids, are no longer needed because the hydroxylamine is transformed into nitroxide by the free radical initiator itself.

The polymerization control must however be improved in order to decrease the polydispersity and increase the block copolymerization efficiency.

Although the dual role of the free radical initiator is beneficial, oxidation of the hydroxylamine must be much faster than the polymerization, which explains why a two-step process is the best strategy; thus, conversion of the hydroxylamine into nitroxide at a temperature where the monomer is stable followed by polymerization at a higher temperature.

8. Conclusions

This review indicates that the main methods recently proposed for the preparation of alkoxyamines in a one-pot process from low-cost nitroxide precursors are valuable alternatives to the expensive alkoxyamines available on the market.

The so-called in-situ NMP methods rely on conversion of readily available and low-cost starting products into mediating nitroxides and alkoxyamines directly in the polymerization medium. Nevertheless, in most cases, just mixing all the components and heating them at the polymerization temperature does not lead to an effective control. The technique in fact consists of premaking the polymerization regulators (nitroxides and alkoxyamines) in the reaction medium before starting the polymerization at a higher temperature. The way to proceed depends on several factors, including the monomer and precursors of nitroxides, although no rule has emerged. In addition to the economic advantage, these NMP systems are very attractive because the structure of the nitroxides and alkoxyamines formed in situ depends on the structure of both the nitroxide precursor and the free-radical initiator and on the experimental conditions (pre-reaction or not in the presence or not of the monomer(s)) as well. Therefore, the process can be highly flexible and tunable.

For the time being, several issues are pending and must be addressed for the in-situ NMP to be applicable on an industrial scale. First, the underlying mechanisms must be well understood, particularly the structure and amount of the regulating species (nitroxides and alkoxyamines) and their dependence on the main experimental parameters. This is a prerequisite for the process to be optimized. Any secondary reactions that can compete with the in-situ formation of the nitroxides/alkoxyamines should also be identified and minimized as much as possible. The stability of both the precursors (nitrones, nitroso compounds, hydroxylamines, etc.) and the in-situ-formed regulators is also a major issue to be considered.

For in-situ NMP processes to be implemented on a large scale, not only their efficiency and control should be improved but also their safe nature must be taken into account because of the possible high exothermicity and contamination of the final polymers by toxic residues.

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