DOI: 10.1070/RCR4765

Imidazoline and imidazolidine nitroxides as controlling agents in nitroxide-mediated pseudoliving radical polymerization

Mariya V. Edeleva,[a, b] Sylvain R. A. Marque,[a, c] Elena G. Bagryanskaya [a, b] *

[a] *N.N.Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences*
pr. Akademika Lavrentieva 9, 630090 Novosibirsk, Russian Federation
[b] *Novosibirsk State University*
ul. Pirogova 1, 630090 Novosibirsk, Russian Federation
[c] *Aix-Marseille University, National Center for Scientific Research, Institute of Radical Chemistry Laboratory 7273, building 551, avenue Escadrille Normandie-Niemen, 13397, Marseille, France*

Controlled, or pseudoliving, radical polymerization provides unique opportunities for the synthesis of structurally diverse polymers with a narrow molecular-weight distribution. These reactions occur under relatively mild conditions with broad tolerance to functional groups in the monomers. The nitroxide-mediated pseudoliving radical polymerization is of particular interest for the synthesis of polymers for biomedical applications. This review briefly describes one of the mechanisms of controlled radical polymerization. The studies dealing with the use of imidazoline and imidazolidine nitroxides as controlling agents for nitroxide-mediated pseudoliving radical polymerization of various monomers are summarized and analyzed. The publications addressing the key steps of the controlled radical polymerization in the presence of imidazoline and imidazolidine nitroxides and new approaches to nitroxide-mediated polymerization based on protonation of both nitroxides and monomers are considered.
The bibliography includes 154 references.

Contents

1. Introduction 329
2. Mechanism of controlled radical polymerization 330
3. Imidazoline and imidazolidine nitroxides as probes to study the mechanism of key reactions in controlled radical polymerization 332
4. Use of imidazoline and imidazolidine nitroxides as controlling agents for controlled radical polymerization 341
5. Conclusion 346

M.V.Edeleva. PhD (Chemical Sciences), Senior Researcher at the NIOCH SB RAS and the Laboratory for Organic Compounds Structure, Properties and Reaction Mechanisms of the Department of Natural Sciences (DNS) at the NSU.
E-mail: edeleva@nioch.nsc.ru
Current research interests: controlled radical polymerization, nitroxide radicals, synthesis of macromolecules with complex architecture, application of NMR spectroscopy, EPR and gel permeation chromatography in studies of macromolecules.
S.R.A.Marque. Professor, Leading Researcher at the NIOCH SB RAS, Head of a laboratory at the Aix-Marseille University.
Telephones: +33 (491)28 – 8640, +7 (383)330 – 5530,
e-mail: sylvain.marque@univ-amu.fr
Current research interests: radical chemistry; nitroxide-mediated controlled polymerization; alkoxyamines, approaches to controlling homolysis of alkoxyamines, use of alkoxyamines and nitroxides in biology and medicine; theranostics.

E.G.Bagryanskaya. Doctor of Physical and Mathematical Sciences, Professor, Director of the NIOCH SB RAS, Head of the Laboratory for Organic Compounds Structure, Properties and Reaction Mechanisms of the DNS at the NSU.
Telephone: +7(383)330 – 8850, e-mail: egbagryanskaya@nioch.nsc.ru
Current research interests: nitroxide-mediated polymerization; application of nitroxide and triarylmethyl radicals as spin probes and spin labels in structural biology, radicals and in supramolecules; EPR of molecular magnets; EPR imaging, development of new high-sensitive magnetic resonance-based techniques; study of short-lived radical species; reactivity of organic radicals.

Received 18 July 2017
Translation: T.N.Safonova

© 2018 Uspekhi Khimii, Russian Academy of Sciences and Turpion Ltd.

1. Introduction

Controlled/living radical polymerization (CRP) was described for the first time by Moad and Rizzardo [1] about 30 years ago. The CRP is a powerful tool for the synthesis of unique polymer materials. In the past decades, CRP was considered in quite a number of papers and surveyed in several reviews [2 – 10] and monographs,[11, 12] which are devoted to various aspects of this process: the synthesis of controlling agents and initiators,[2, 5, 7] the mechanism and kinetics of polymerization,[10 – 17] the polymerization of various monomers [3, 4, 7, 12] and practical applications.[3, 7, 12, 18 – 20] The most popular pseudoliving radical polymerization techniques are the atom transfer radical polymerization (ATRP), the reversible addition – fragmentation chain transfer (RAFT) polymerization and the nitroxide-mediated polymerization (NMP). Pseudoliving radical polymerization is a process, in which the irreversible quadratic termination of growing chains is suppressed by reversible chain termination or transfer using various controlling agents for each of the three types of polymerization. Main kinetic features of nitroxide-mediated pseudoliving radical polymerization are analyzed in detail in the recent review by Zaremski [10] and in a special chapter in a monograph by Bagryanskaya and Marque.[17] Besides, the review by Zaremski describes methods for the determination of the rate constants of reinitiation and reversible chain termination in polymerization systems and presents an analysis of the relevant results.

On the one hand, CRP occurs under relatively mild conditions typical of conventional radical polymerization, exhibits broad tolerance to functional substituents in monomers and does not require high-purity reagents. On the other hand, CRP techniques allow for the preparation of polymers in a specified molecular-weight range with a narrow molecular-weight distribution (typical values 1.05 – 1.5). Besides, CRP methods are suitable for the synthesis of polymers with different architectures (linear polymers, graft polymers, polymer brushes, star-like polymers and dendrimers) and macromolecules with a complex composition (block copolymers, gradient polymers, alternating polymers) (Fig. 1). Therefore, CRP techniques can be used in industrial synthesis of macromolecules for high-tech applications. Nitroxide-mediated pseudoliving radical polymerization is most suitable for the synthesis of macromolecules for biomedical purposes because it employs nontoxic organic compounds as controlling agents, which can be purified to a high degree in the course of the preparation. In this review, the nitroxide-mediated pseudoliving radical polymerization will be called the controlled radical polymerization for the sake of brevity.

The present review does not aim to duplicate all available data on the CRP. The major focus is given to studies devoted to the use of two families of nitroxide radicals (NRs) — imidazoline and imidazolidine nitroxides — as controlling agents for CRP. The application of pyrrolidine nitroxides and the SG1 nitroxide [SG1 is *N*-*tert*-butyl-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*N*-oxyl] is briefly considered.

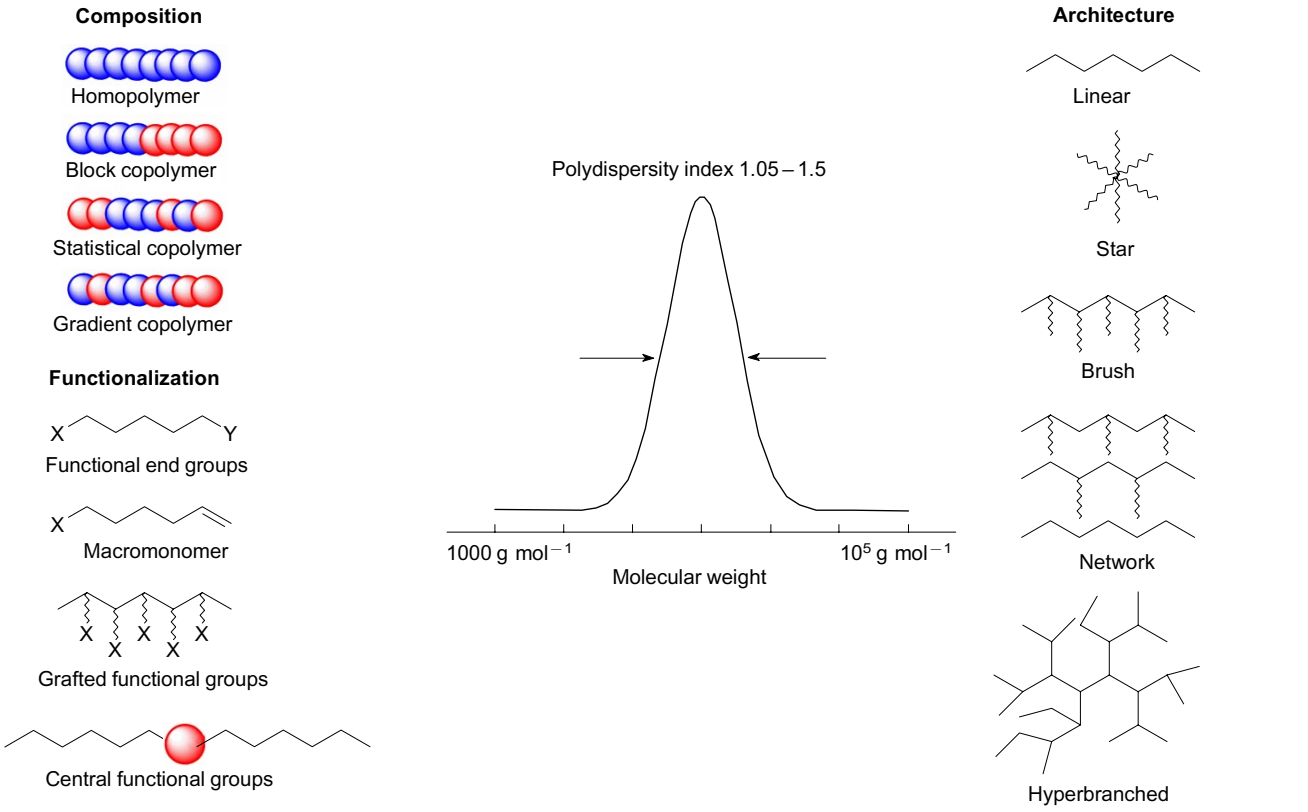


Figure 1. Synthetic opportunities of controlled radical polymerization.

2. Mechanism of controlled radical polymerization

The mechanism of CRP is based on the so-called persistent (long-lived) radical effect,[21] which was independently described by Fischer and co-workers[22, 23] and by Goto and Fukuda.[15] This effect may be better explained by the homolysis of alkoxyamine R–Y (the adduct generated *via* recombination of nitroxide with a carbon-centred radical), where R$^{\bullet}$ is a carbon-centred radical, Y$^{\bullet}$ is a persistent nitroxide radical, which cannot be involved in bimolecular recombination with the second persistent radical. Carbon-centred radicals generated *via* homolysis [reaction (1), Scheme 1] recombine both with each other [reaction (3)] and with nitroxide radicals [reaction (2)], while nitroxide radicals are involved in the reaction only with alkyl radicals [see reaction (2)]. As a result, the concentration of nitroxide radicals becomes several orders of magnitude higher than that of alkyl radicals in a short time after the beginning of the reaction, and, in the absence of other reactions, the reversible homolysis of alkoxyamine R–Y is the major process.

Scheme 1

$$R-Y \longrightarrow R^{\bullet} + Y^{\bullet} \quad (1)$$

$$R^{\bullet} + Y^{\bullet} \longrightarrow R-Y \quad (2)$$

$$2R^{\bullet} \longrightarrow P \quad (3)$$

In 1987, Fischer and Paul[24] solved kinetic equations that describe reactions involving stable and short-lived radicals. A few years later, Daikh and Finke suggested the term 'persistent radical effect'.[21] The synthesis of polymers with precisely specified molecular weight by nitroxide-mediated pseudoliving radical polymerization was described in patents.[25, 26] Almost at the same time, Otsu *et al.*[27] proposed a model of nitroxide-mediated living polymerization. Subsequently, it was demonstrated that other molecules can also be used as controlling agents for controlled radical polymerization, *e.g.*, transition metal complexes, which were described by Wang and Matyjaszewski[28] and by Sawamoto and co-workers,[29] and dithiobenzoic and dithioacetic acid derivatives proposed by Rizzardo and co-workers.[30]

The mechanism and kinetics of CRP were described in detail in a number of reviews.[31–33] Therefore, we will only briefly outline the main aspects required for the presentation of the data in this review. The CRP is generally described by a scheme that includes the reversible inhibition reaction of growing polymer radicals with a stable species X, which does not react with alike species (Scheme 2). It should be noted that the nature of the species X can be different. Thus, a stable nitroxide radical, other stable organic radicals or variable-valence metal complexes can serve as such species.[11] This approach is relevant because the active radical – deactivated radical equilibrium plays a key role in the system; besides, the addition of a monomer to an active radical gives a structurally equivalent radical.

Scheme 2

$$X-R \underset{k_c}{\overset{k_d}{\rightleftharpoons}} X^{\bullet} + R^{\bullet} \xrightarrow{k_p} + M$$

M is monomer

Recent studies devoted to the kinetics of polymerization initiation and the influence of termination reactions and side reactions demonstrated that the initiation and addition of the monomer to the active growing radical may have a very significant effect on the polymerization and the characteristics of the resulting polymer. Hence, in our opinion, it is appropriate to consider the detailed scheme, which distinguishes the steps of chain initiation and propagation, reversible recombination of the controlling agent with the active chain and various chain termination reactions.[7, 12, 16, 34] For nitroxide-mediated CRP, the chain initiation and propagation steps involve the reversible recombination of the nitroxide radical with the C-centred radical of the growing polymer chain. This reaction leads to a decrease in the concentration of carbon-centred radicals and reduces the contribution of the chain termination reaction. This results in that most polymer chains carry the alkoxyamine end group after the completion of the polymerization. Such non-terminated chains are called living polymers.

Two main approaches are used to accomplish nitroxide-mediated radical polymerization. In one case, a bimolecular initiating system composed of a nitroxide radical and a radical initiator is used (Scheme 3). Generally, the temperature required for the formation of alkoxyamine is specified

Scheme 3

Initiation

Initiation by alkoxyamine initiators

$$R'R''NOR \longrightarrow R'R''NO^{\bullet} + R^{\bullet} \qquad k_d$$

$$R'R''NO^{\bullet} + R^{\bullet} \longrightarrow R'R''NOR \qquad k_c$$

$$R^{\bullet} + M \longrightarrow R-M^{\bullet} \qquad k_{add}$$

Initiation of radical polymerization by conventional initiators

$$I_2 \longrightarrow 2I^{\bullet}$$

$$I^{\bullet} + M \longrightarrow I-M^{\bullet}$$

Reversible inhibition

$$R'R''NO^{\bullet} + RM_n^{\bullet} \longrightarrow R'R''NOM_nR \qquad k_{c,ds}$$

$$R'R''NOM_nR \longrightarrow R'R''NO^{\bullet} + RM_n^{\bullet} \qquad k_{d,ds}$$

Chain propagation

$$RM_n^{\bullet} + m\,M \longrightarrow RM_{n+m}^{\bullet} \qquad k_p$$

Chain termination

$$R^{\bullet} + RM_n^{\bullet} \longrightarrow \text{dead chains} \qquad k_t$$

$$RM_m^{\bullet} + RM_n^{\bullet} \longrightarrow \text{dead chains} \qquad k_{t,ds}$$

Side reactions

$$R'R''NOR \longrightarrow R'R''NOH + \text{alkene} \qquad k_{dD}$$

$$R'R''NO^{\bullet} + R^{\bullet} \longrightarrow R'R''NOH + \text{alkene} \qquad k_{cD}$$

k_p is the rate constant of chain propagation, k_t and $k_{t,ds}$ are the rate constants of recombination/disproportionation of C-centred radicals, k_{dD} is the rate constant of intramolecular hydrogen transfer reaction, k_{cD} is the rate constant of radical hydrogen transfer between the nitroxide, initiating radical or growing chain radicals.

in the initial step, and then the temperature optimal for controlled polymerization is maintained. Another approach is based on the use of alkoxyamines as initiators. The chain initiation and propagation steps involve the reversible homolysis of alkoxyamine (in the case of initiation) or of the polymer chain bearing the alkoxyamine end group, the so-called dormant polymer chain. The polymerization mode (controlled or uncontrolled) strongly depends on the rate constants of homolysis and recombination of low- and high-molecular-weight alkoxyamines (k_d, $k_{d,ds}$, k_c and $k_{c,ds}$), which, in turn, are determined by the structure of the nitroxide moiety, the size and polarity of the substituents and stability of the resulting nitroxide and alkyl radicals.[17, 35]

The equations describing the time (t_χ) needed to reach a certain conversion χ ($0 \leqslant \chi \leqslant 1$) [equation (4)], the polydispersity index at infinite time (PDI_∞) [equation (5)] and the number of living chains (φ) [equation (6)] using the rate constants of elementary steps were reported by Fischer and co-workers [13, 14, 36] and by Goto and Fukuda.[15] It should be noted that these equations are valid only if there are no side reactions and if the nitroxide radical is sufficiently stable under polymerization conditions.

$$t_\chi = \frac{\{2\ln[1/(1-\chi)]\}^{3/2}}{3k_p^{3/2}} \left(\frac{k_t k_{c,ds}}{[I]_0 k_{d,ds}}\right)^{1/2} \quad (4)$$

$$PDI_\infty = 1 + \frac{[I]_0}{[M]_0} + \left(\frac{\pi k_p^3 [I_0]}{k_{d,ds} k_{c,ds} k_{t,ds}}\right)^{1/2} \quad (5)$$

$$\varphi = \left(\frac{2k_{d,ds}k_{t,ds}\ln[1/(1-\chi)]}{k_{c,ds}k_p[I]_0}\right)^{1/2} \quad (6)$$

where $[I]_0$ and $[M]_0$ are the initial concentrations of the initiator and the monomer, respectively.

Equations (4) – (6) were deduced taking into account only the chain propagation and termination steps because the initiation in CRP is much faster compared to the overall polymerization process. An analysis of the kinetics shows that, in early stages of CRP, the concentrations of nitroxide and alkyl radicals increase at the same rate proportionally to time. The recombination and disproportionation of alkyl radicals, which make significant contributions at short polymerization times, give rise to a large excess of nitroxide radicals compared to alkyl ones. After that, the recombination of nitroxide and alkyl radicals (k_c or $k_{c,ds}$) becomes dominant, resulting in the formation of alkoxyamine. Subsequently, the kinetics for nitroxide and alkyl radicals changes and remains $t^{1/3}$ and $t^{-1/3}$ dependent, respectively, over a long period of time (from several hours to several centuries depending on the structure of alkoxyamine and experimental conditions). During this period of time, the alkoxyamine concentration changes only slightly. As a result, this time interval is long enough for the polymerization to occur (usually 6 – 8 h) to form high-molecular-weight alkoxyamine in a yield of about 90%. These polymer chains bearing an alkoxyamine end group are the target products of the CRP reaction because they enable the reinitiation of polymerization and the synthesis of block copolymers with desired properties.[7, 14, 15]

Equations (4) – (6) are used to calculate the kinetics of polymerization [13, 14, 36] and predict CRP behaviours.[7, 16, 17] The plots for equations (4) – (6) in $k_c - k_d$ coordinates consist of three intersecting straight lines, which divide the plane into several regions, which can contain the coordinates of the (k_c, k_d) point for a particular nitroxide radical – alkyl radical pair (Fig. 2). Each region characterizes a certain polymerization mode. In the region D, the polymerization occurs in a controlled manner with a high percentage of living chains; the region X corresponds to non-living uncontrolled polymerization; in the region C , the polymerization affords a highly dispersed polymer; the region A is characterized by controlled polymerization but it occurs over a long period of time; the region B corresponds to slow polymerization giving a dispersed polymer. Obviously, Fischer's diagram provides only an estimate of the polymerization mode; however, it is often useful for choosing the optimal temperature profile for the polymerization process.

It is important to bear in mind that the polymerization under actual conditions generally follows monoexponential kinetics, and the $t^{1/3}$ law is not met, which is a consequence of the contribution of side reactions, resulting in polymer chain termination. The kinetics and mechanism of CRP are considered in more detail in reviews [4, 7, 10, 14, 15] and publications.[37, 38]

The equilibrium constant of the homolysis of high-molecular-weight alkoxyamine and the recombination of radical chains with nitroxide radicals play a key role in chain propagation. It should be noted that all effects typical of initiation and reversible homolysis of low-molecular-weight alkoxyamine are true in this case as well. In addition, one should consider the effect of the penultimate monomer unit in the high-molecular-weight alkyl radical — the so-called penultimate unit effect consisting in that the structure (polarity and steric characteristics) of the substituent in the penultimate unit affects the activation energy of homolysis. This effect was shown to be significant only in the presence of a tertiary penultimate unit [39 – 43] and it plays a significant role only in the polymerization of methacrylate monomers.[44] The chain length can also affect polymerization, particularly, in the case of polymer chains containing polar substituents.[16, 17, 45]

The addition of a C-centred radical to the alkene double bond is the main process in the chain propagation step. This reaction is described in detail in the literature (see, for example, Ref. 46). The rate constants for this process strongly depend on the alkene structure and may vary

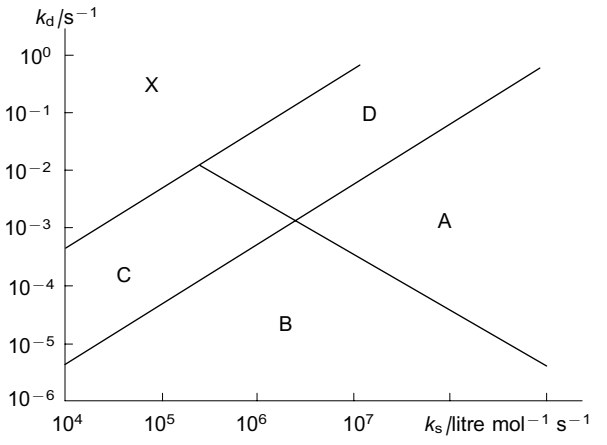


Figure 2. General layout of Fischer's diagram.

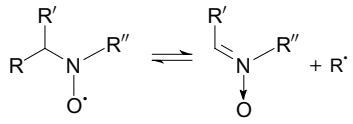
from a few units to 10^5 litre mol^{-1} s^{-1} at one and the same temperature. The effects that influence the chain propagation are comprehensively described in the review by Buback[47] and the publication by Barner-Kowollik and co-workers.[48]

The chain termination step involves recombination and disproportionation of simple alkyl radicals and polymer radicals and is considered in a number of reviews.[10, 24, 49, 50] Reactions of alkyl and nitroxide radicals lead not only to recombination giving alkoxyamine but also to chain termination: 1) in the reaction between nitroxide and the C-centred radical accompanied by hydrogen abstraction from the latter and the formation of alkene and hydroxylamine (hydrogen transfer reaction)[51] and 2) in intramolecular proton transfer in alkoxyamine.

The CO – N bond cleavage is yet another side reaction in CRP. Despite the fact that this reaction can significantly affect the kinetics of polymerization, it has not been adequately explored as yet.[52–55] Since the CO – N bond cleavage is competitive with C – ON bond cleavage, this side reaction would be expected to occur in the case of alkoxyamines with the C – ON bond dissociation energy higher than 140 kJ mol^{-1}. It should be noted that such alkoxyamines are not applicable in CRP.[56] The CO – N and C – ON homolysis in alkoxyamines was theoretically studied by Coote and co-workers.[54] They showed that, regardless of the reaction conditions, the C – ON bond cleavage is 50 kJ mol^{-1} more favourable, and the free energies (ΔG) of both reactions are not correlated. The CO – N homolysis will occur only if the resulting aminyl radical is stable, while the alkyl radical generated *via* C – ON homolysis is unstable.

Another side reaction in CRP is irreversible decomposition of nitroxides, which leads to uncontrolled polymerization. Stability of nitroxides under different conditions was studied in detail.[57] In some cases, CRP involves thermal decomposition of NR to alkyl radical as the side reaction (Scheme 4). This reaction is in essence reverse to the formation of the nitroxide radical from nitrone. The NR decomposition leads to a decrease in the polymerization time because the probability of the formation of dormant chains is reduced and the polydispersity index increases due to an increase in the probability of irreversible reactions involving growing polymer radicals.

Scheme 4



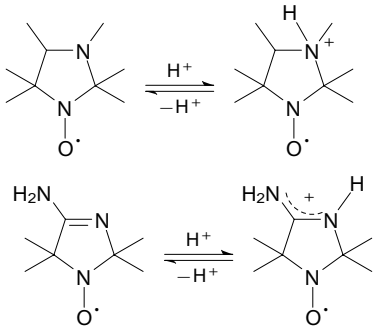
Another side reaction is the chain transfer to monomer,[33] resulting in an increase in the polydispersity index of the polymer and also in an increase in the concentration of dead chains.[58, 59] Investigations of the hydrogen transfer and other side reactions in the nitroxide-mediated polymerization, in particular, the elucidation of factors that interfere with this reaction, are currently an important issue in this area. Ultimately, these studies provided an approach to nitroxide-mediated controlled polymerization of methacrylate monomers.

Therefore, in order for the CRP to be successfully accomplished, the rate constants of homolysis of alkoxyamine and the rate constants of recombination of nitroxide and alkyl radicals should be in certain ranges, while the contribution of side reactions leading to chain termination should be insignificant. To evaluate the prospects of the employment of nitroxide radicals having a particular structure as a controlling agent for CRP, it is necessary to know the factors affecting the constants k_d, $k_{d,ds}$, k_c and $k_{c,ds}$. The next section gives examples of the use of imidazoline and imidazolidine radicals for the investigation of these factors.

3. Imidazoline and imidazolidine nitroxides as probes to study the mechanism of key reactions in controlled radical polymerization

Imidazoline and imidazolidine nitroxides were synthesized for the first time by Volodarsky and co-workers.[60–62] Methods for the preparation of these species were described in detail in the literature.[60–64] The synthesis of nitroxide radicals and, in particular, of imidazoline derivatives is a rapidly growing field in organic chemistry. An important feature of imidazoline and imidazolidine radicals is that their rings include a nitrogen atom, which can be reversibly protonated depending on the pH of the medium. This leads to a change in the spin density on the nitroxide nitrogen atom, resulting in a change in the *g*-factor, and the hyperfine coupling (HFC) constant can change by 0.1 – 0.15 mT. The protonation reactions of tetramethyl imidazolidine and imidazoline radicals are shown as an example in Scheme 5. For the imidazolidine radical, the difference between the HFC constants for the protonated and unprotonated forms is 0.127 mT, $pK = 4.7$; for the imidazoline radical, the difference is 0.079 mT, $pK = 6.1$. The changes in the HFC constants can be detected by EPR spectroscopy and can be used to measure the pH values.[65] Therefore, since the discovery, imidazoline and imidazolidine radicals have been considered and widely employed as functional spin probes for proton electron double resonance imaging (PEDRI), which combines EPR imaging with Overhauser-enhanced magnetic resonance imaging (MRI).[66] In this case, the major parameter providing the functionality of these radicals is resistance to reduction in living cells. The introduction of bulky substituents at positions 2 and 5 of the ring leads to a considerable increase in stability of NRs and a decrease in the rate constant of their reduction by ascorbic acid.[67] Recently, Kirilyuk *et al.*[68] demonstrated that there is a good correlation between the rate constants of recombination of these NRs with alkyl radicals and the

Scheme 5



rate constants of their reduction by ascorbic acid. Moreover, the approach, which was used to analyze the rate constants of recombination taking into account the steric energy and polarity of NRs, proved to be applicable to the analysis of reduction rate constants. This is evidence that the rate constants of these reactions are determined by similar factors. Methods employed for the synthesis of alkoxyamines based on imidazoline and imidazolidine nitroxides are the same as for other radicals. In particular, the procedure developed by Matyjaszewski *et al.*[69] can be used for this purpose.

As mentioned above, it is necessary to know the rate constants of reversible inhibition and to explore the key reactions in CRP under different conditions for the practical application of CRP. Imidazoline and imidazolidine nitroxides and related alkoxyamines serve as a good model for this purpose, because the available procedures for the synthesis allow one to substantially vary the structure of nitroxide radicals and, as a consequence, the kinetic parameters of the key reactions in CRP.

There are four main areas of investigation of processes involving imidazoline and imidazolidine nitroxides and related alkoxyamines.

1. Factors that affect the rate constants of alkoxyamine homolysis and the rate constants of recombination of nitroxide and alkyl radicals with different structures were studied in relation to imidazoline and imidazolidine nitroxides. The controlled mode of polymerization mediated by the same nitroxide was shown to depend on the k_p/k_d ratio, which should be taken into account in the development of efficient polymerization initiators.[70, 71]

2. Using alkoxyamines based on imidazoline and imidazolidine nitroxides and methacrylate monomers, approaches for the exploration of hydrogen transfer reactions as side processes were tested and the main characteristic features of this process were revealed.[72]

3. The RAFT and ATRF methods are suitable for the controlled polymerization of methyl methacrylate (MMA). However, the nitroxide-mediated radical polymerization of MMA was a difficult problem for many years because of the contribution of the hydrogen transfer reaction or because the constants k_c and k_d do no satisfy the controlled polymerization conditions.[73] Charleux and co-workers[44, 74] succeeded in developing an approach to the CRP of methyl methacrylate using small additives of styrene or acrylonitrile. The block copolymerization by CRP of this monomer in the living chain mode in the absence of additives was successfully performed for the first time in the presence of imidazoline nitroxide.[75]

4. Imidazoline nitroxides were employed for the development of new 'controlled' initiators/controlling agents for CRP. In 2011, Brémond and Marque proposed to use the protonation of the 4-pyridylalkyl group of alkoxyamine based on SG1 to influence the kinetics of alkoxyamine homolysis.[76] It was also shown[77] that the protonation of the nitroxide moiety of alkoxyamines based on imidazoline radicals has a significant effect on the reaction rate of alkoxyamine homolysis and the recombination rate constants of these NRs and alkyl radicals. This effect underlies the regulation of the controlled polymerization. The same effect was observed by Marx and co-workers.[78] These studies represent a new area of research on CRP related to switchable initiators/controlling agents for polymerization.

3.1. Investigation of factors that affect the rate constants of alkoxyamine homolysis and the rate constants of recombination of nitroxide and alkyl radicals with different structures

3.1.1. Homolysis of alkoxyamines

Two methods are currently employed for measurements of the rate constant k_d. One method is based on the analysis of changes in the molecular-weight distribution of polymerization products synthesized in the presence of macroinitiators.[15, 79, 80] The drawback of this method is that it is difficult to estimate the contributions of the starting macroinitiator and the product. In recent years, another method based on competitive inhibition has been increasingly used.[81, 82] The homolysis of alkoxyamine is reversible. Therefore, regarding the measurements of the rate constant k_d, it is necessary to suppress the recombination of nitroxide and alkyl radicals. Experimentally, this is achieved by adding an alkyl radical scavenger. Oxygen, nitroxide with a different structure at a higher concentration, benzenethiol, galvinoxyl, monomers which can add to a growing polymer chain with a high rate constant (k_p), and so on were described as such scavengers in the literature. In the presence of a sufficiently large excess of a scavenger, the alkoxyamine homolysis follows the pseudo-first order kinetics, because the contribution of the recombination of alkyl and nitroxide radicals can be disregarded. In this case, the kinetics of consumption of alkoxyamine and the kinetics of accumulation of nitroxide (provided that it does not react with the scavenger) are described by a monoexponential function with the decay parameter k_d. Experimental methods used to measure the constant k_d include EPR spectroscopy, NMR spectroscopy (^{1}H and ^{31}P NMR for phosphorus-containing alkoxyamines), high-performance liquid chromatography and gel permeation chromatography. The choice of a particular method depends on the availability of instruments and reagents.

The factors that affect the rate constants of homolysis and recombination of NRs with alkyl radicals are discussed in a number of reviews.[16, 17, 35, 38] The main factors are the polarity, stability of nitroxide and the C-centred radical and their steric hindrance. Minor factors include the formation of intramolecular hydrogen bonds, hyperconjugation, conformational effects and solvent effects. All these factors affect the energy levels for the starting reactants, the transition state and reaction products, which dictates the rate constant of alkoxyamine homolysis (k_d) and the rate constant of recombination of nitroxide and alkyl radicals (k_c). The influence of each factor on the rate constants k_d is schematically shown in Fig. 3.

Since the constant k_d for structurally different alkoxyamines varies in a wide range, it is a common practice to compare the activation energies (E_a) of homolysis. The homolysis is a monomolecular process and, correspondingly, the temperature dependence of its rate constant is described by Eqn (7).

$$k_d = A_0 e^{-E_a/RT} \quad (7)$$

where A_0 is the pre-exponential factor, R is the universal gas constant, T is temperature.

Investigations of alkoxyamines with different structures demonstrated that the pre-exponential factor A_0 varies within one order of magnitude and is, on average, 2.4×10^{14} s^{-1} (see Ref. 83). Therefore, the activation ener-

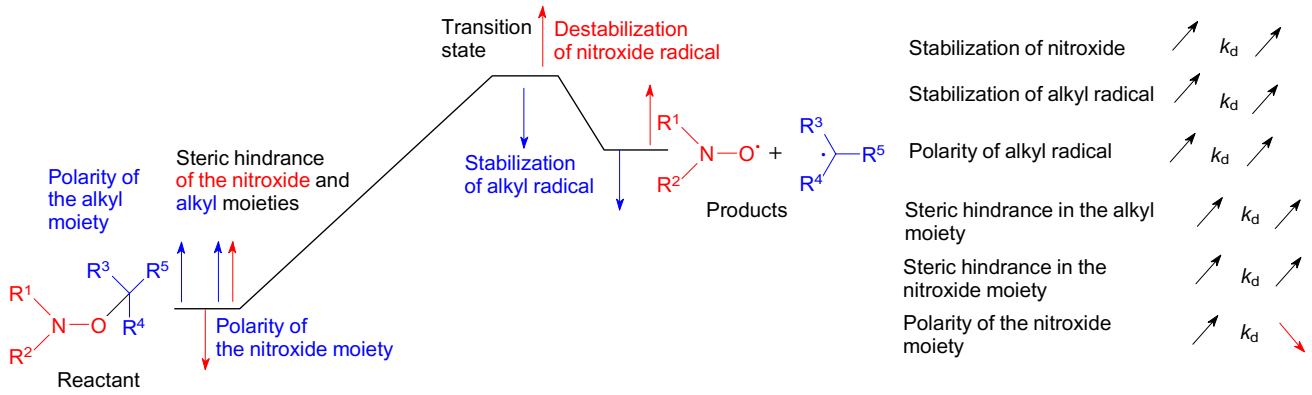
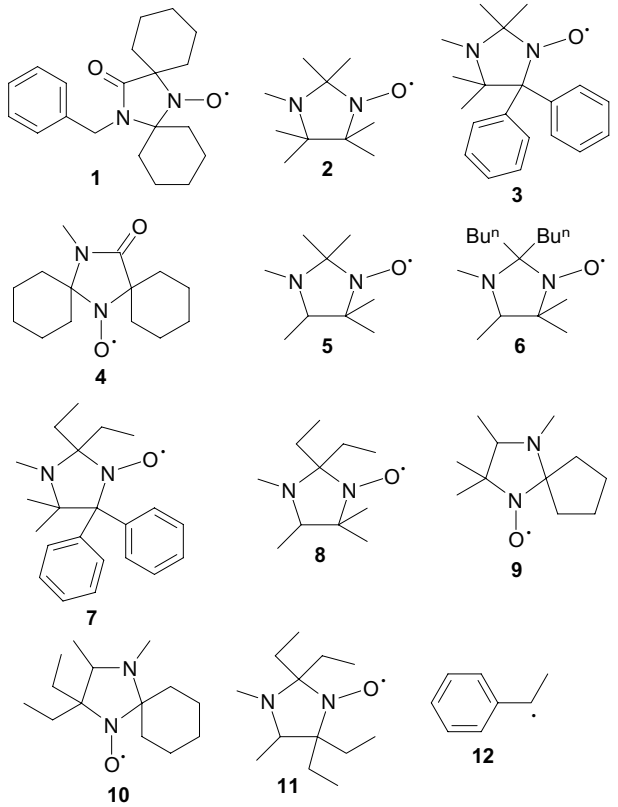


Figure 3. Energy profile for C–ON bond homolysis and the factors that affect the rate constant of alkoxyamine homolysis (k_d).[17] Except the polarity of the nitroxide moiety, an increase in all parameters leads to an increase in the constant k_d.

gies for homolysis are generally compared using this value of the pre-exponential factor. For a series of alkoxyamines containing imidazoline, imidazolidine and pyrrolidine nitroxides with different structures and MMA, the rate constants of homolysis and the energies E_a were measured by Zubenko *et al.*[70,71] and by Edeleva *et al.*[72] The activation energies of homolysis vary from 140 kJ mol^{-1} for tetramethyl-substituted alkoxyamines to 114 kJ mol^{-1} for the diethylcyclohexyl-substituted imidazoline radical. The constants k_d were considered at the same temperature for structurally different alkoxyamines based on nitroxides **1**–**11** and the phenethyl radical (**12**) depending on the polarity parameters (Hammett constants σ_L) and steric

Structures 1–12



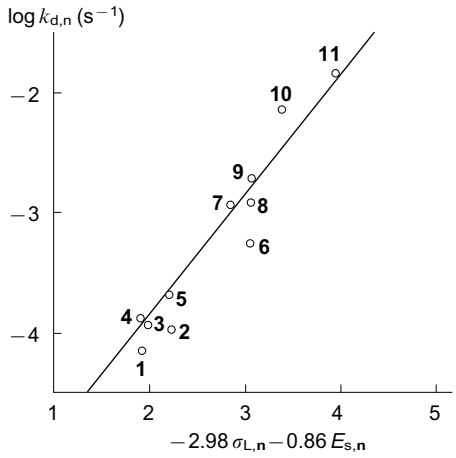


Figure 4. Plot for $\log k_d$ according to Eqn (8) for alkoxyamines based on nitroxides **1**–**11** and phenethyl radical **12**.[70] (Only 11 date points are shown.)

hindrance (E_s).[71] The linear correlation (Fig. 4) between the values of k_d and the steric energy and polarity parameters was obtained according to Eqn (8).[70]

$$\log k_d\,(s^{-1}) = \qquad (8)$$

$$= -2.98\,(\pm 0.14)\cdot\sigma_{L,n} - 0.86\,(\pm 0.03)\;E_{s,n} - 5.83\,(\pm 0.10)$$

$$R^2 = 0.96,\; s = 0.14,\; N = 11$$

where R^2 is the square of the linear regression coefficient, s is the standard deviation, N is the number of experimental data used to obtain the correlation equation.

The coefficients in Eqn (8) are similar to those determined by Fischer and co-workers,[83] which made it possible to use this dependence for the evaluation of k_d for alkoxyamine with arbitrary structure.

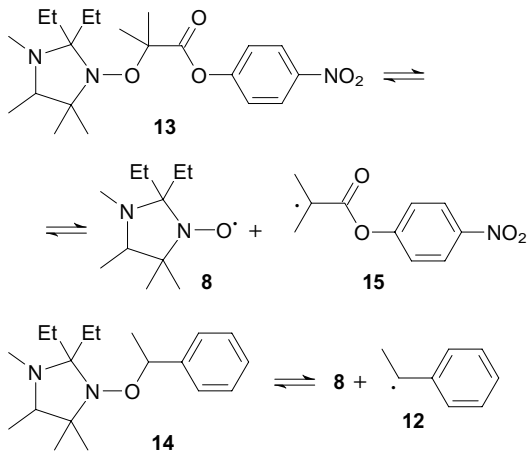
In the study of styrene polymerization initiated by alkoxyamines, the constant k_d was measured for a broad range of alkoxyamines containing imidazoline and imidazolidine nitroxide radicals and the phenethyl radical.[70] The

constant k_d was shown to decrease with increasing electron-donating ability of substituents in the nitroxide moiety, but it increases in the presence of sterically hindered groups.

The constant k_d exerts a significant effect on the rate of initiation of polymerization and then on the time of achievement of the controlled mode. For instance, Chauvin *et al.*[84] employed alkoxyamines characterized by different values of k_d and investigated the conversion of the monomer at which the controlled polymerization is achieved. It was shown that, in the case of high k_d, controlled polymerization can be obtained in a very short time. Depending on the structures of nitroxide and alkyl moieties, the rate constant of alkoxyamine homolysis varies in a broad range, and the constant of k_d correlates well with the polarity and steric hindrance of alkoxyamine.[85]

Apart from the rate constant of alkoxyamine homolysis and the rate constant of recombination of alkyl and nitroxide radicals, the result of controlled polymerization depends on the efficiency of initiation of chain propagation by a primary alkyl radical. The study of styrene polymerization initiated by alkoxyamines **13** and **14** based on imidazolidine radical **8** (Scheme 6)[70] demonstrated that the initiation step significantly affects the kinetics and success of CRP (Fig. 5). For instance, at 120 °C the polymerization occurred in a controlled manner only in the presence of alkoxyamine **14** as the initiator, while in the presence of alkoxyamine **13**, the polymerization was uncontrolled and stopped at low conversions. Noteworthy is that the rate constant of homolysis for compound **13** is several times higher than that for alkoxyamine **14** and, consequently, the former compound is characterized by a higher rate of initiation. Besides, nitroxide radical **8** served as the controlling agent for CRP in both cases. This unusual behaviour is attributed to the hydrogen transfer reaction,[72] the contribution of which is ~3%, upon the recombination of alkyl radical **15** with the nitroxide radical.

Scheme 6



The effect of the rate of addition of alkene to the initiating C-centred radical (k_{add}) on the polymerization was described by Fischer and co-workers.[36] This step is particularly important if the polymerization process involves hydrogen transfer as the side reaction along with the main reactions, such as the decomposition of the initiator and the addition to alkene. The key role of the addition step was demonstrated by Zubenko *et al.*,[71] who

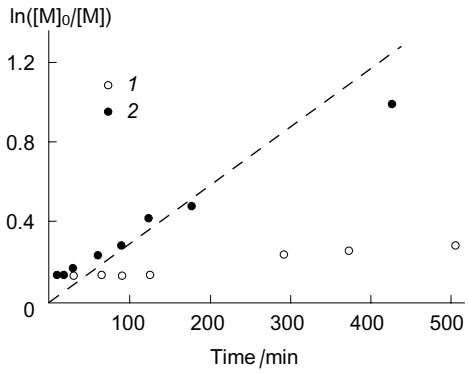


Figure 5. Conversion *vs.* time for styrene polymerization at 120 °C initiated by alkoxyamines **13** (*1*) and **14** (*2*) based on imidazolidine nitroxide radical **8**.[70]

studied the styrene polymerization initiated by two alkoxyamines. One of these processes involved the hydrogen transfer reaction, resulting in a decrease in the efficiency of initiation and had a detrimental effect on the overall polymerization process.

As mentioned above, different rate constants of alkoxyamine homolysis (k_d) and recombination of alkyl and nitroxide radicals (k_c) are optimal for the polymerization of different monomers. Consequently, the polymerization of different monomers should be accomplished using different nitroxide radicals as controlling agents, while it is impossible to change the structure of the nitroxide during its use. It is not always possible to achieve the controlled polymerization for different monomers by varying the temperature. The steric hindrance, which can also lead to a change in the constant k_d, cannot be reversibly changed.

The polarity is another parameter that affects the constant k_d. The polarity can be reversibly varied by protonation – deprotonation of functional groups in alkoxyamines, because the protonation changes the polarity of nitroxide and alkyl moieties. The protonation of the nitroxide moiety of alkoxyamine leads to an increase in the polarity of the nitroxide moiety, resulting in an increase in the polarity of the C—O bond due to an increase in the δ— charge on the oxygen atom (Fig. 6). This leads to destabi-

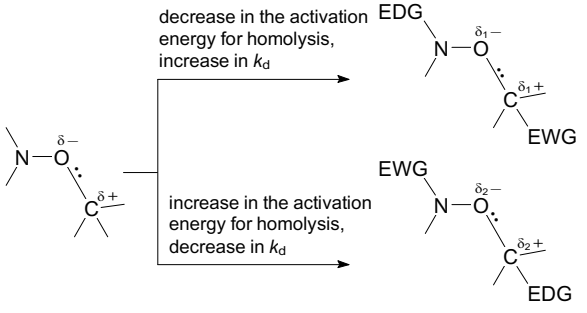


Figure 6. Influence of electron-donating (EDG) and electron-withdrawing (EWG) groups on the polarity of the C—O bond in alkoxyamines and the corresponding changes in the rate constants of C—O bond homolysis (k_d).

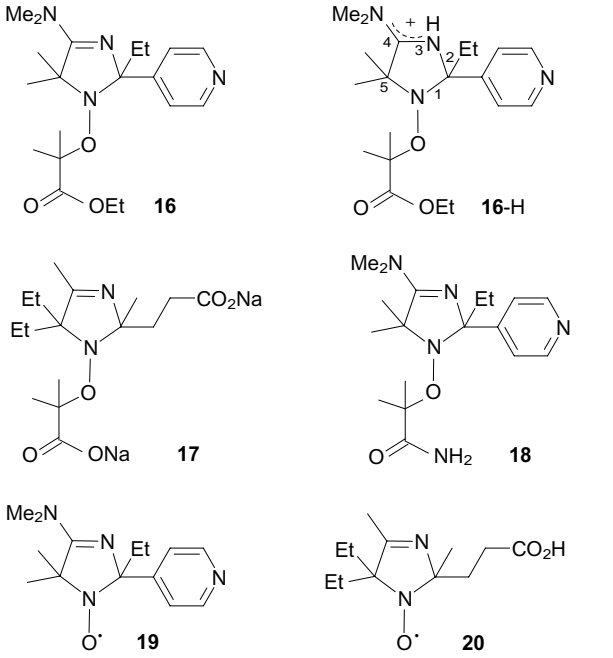
lization of the transition state of the alkoxyamine homolysis *via* the destabilization of the generated nitroxide. This hinders the C—O bond homolysis and leads to an increase in the activation energy for homolysis (decrease in k_d). On the contrary, the deprotonation of pH-sensitive groups of nitroxide leads to a decrease in the polarity of the latter, resulting in a decrease in δ− on the oxygen atom and a decrease in the polarity of the C—O bond. Therefore, the transition state of the alkoxyamine homolysis is stabilized, resulting in a decrease in the activation energy for homolysis and an increase in k_d. It should be noted that the experimental study provided evidence that the addition of acid does not cause a change in k_d for alkoxyamines based on the nitroxide radical TEMPO [TEMPO is (2,2,6,6-tetramethylpiperidin-1-yl)oxyl], which has no moieties capable of protonation.[86] Calculations performed by Mazarin *et al.*[87] demonstrated that the protonation of the nitrogen atom of the alkoxyamine moiety can lead to an increase in the activation barrier to alkoxyamine homolysis.

In recent studies, Rizzardo and co-workers[88,89] proposed a method for the reversible change in the electron-donating properties of controlling agents for the RAFT polymerization *via* protonation of functional substituents. The authors employed this approach to perform the polymerization of so-called 'more active' and 'less active' monomers using one agent but in different (protonated or deprotonated) forms. Brémond and Marque[76] extended this approach to the nitroxide-mediated polymerization. In particular, they synthesized alkoxyamine based on the nitroxide radical SG1 containing a protonatable functional group in the alkyl moiety. It was demonstrated that the protonation of this group leads to a 15-fold change in the rate constant of alkoxyamine homolysis in a non-polar solvent. In aqueous media, the increase in the rate constant of alkoxyamine homolysis in going from the unprotonated to protonated form is even larger (64-fold). Subsequently, different effects emerging from the protonation and quartenization of the N atom in substituents of alkoxyamines were investigated.[90–97]

However, the protonation of the alkyl group affects only the initiation step of polymerization. The rate of reversible alkoxyamine homolysis can be influenced throughout the polymerization process *via* protonation of the nitroxide moiety of alkoxyamine. Since, as mentioned above, imidazoline and imidazolidine nitroxides can be subjected to protonation,[67] these nitroxides were proposed[77] as controlling agents for the polymerization of hydrophilic and lipophilic monomers (alkoxyamines **16**–**28** based on NRs **19** and **20**). Nitroxide radicals containing two basic centres, which were synthesized in the cited study, undergo stepwise protonation caused by changes in the pH value, which is easily detected based on the change in the hyperfine coupling constant (a_N) in the EPR spectrum depending on the pH of the medium. The rate constant of recombination of nitroxide and alkyl radicals also depends on the protonation of functional groups of NRs, while alkoxyamines based on such NRs have different rate constants of homolysis depending on pH; the values of k_d vary 10–15-fold.

To further develop this approach (protonation of initiating alkoxyamines and nitroxide radicals as controlling agents of CRP), Parkhomenko *et al.*[98] studied the effect of acidity of the medium on the energy parameters of the alkoxyamine homolysis by the density functional theory. The protonation of functional substituents in the nitroxide part of alkoxyamine was demonstrated to cause an increase

Structures 16 – 20



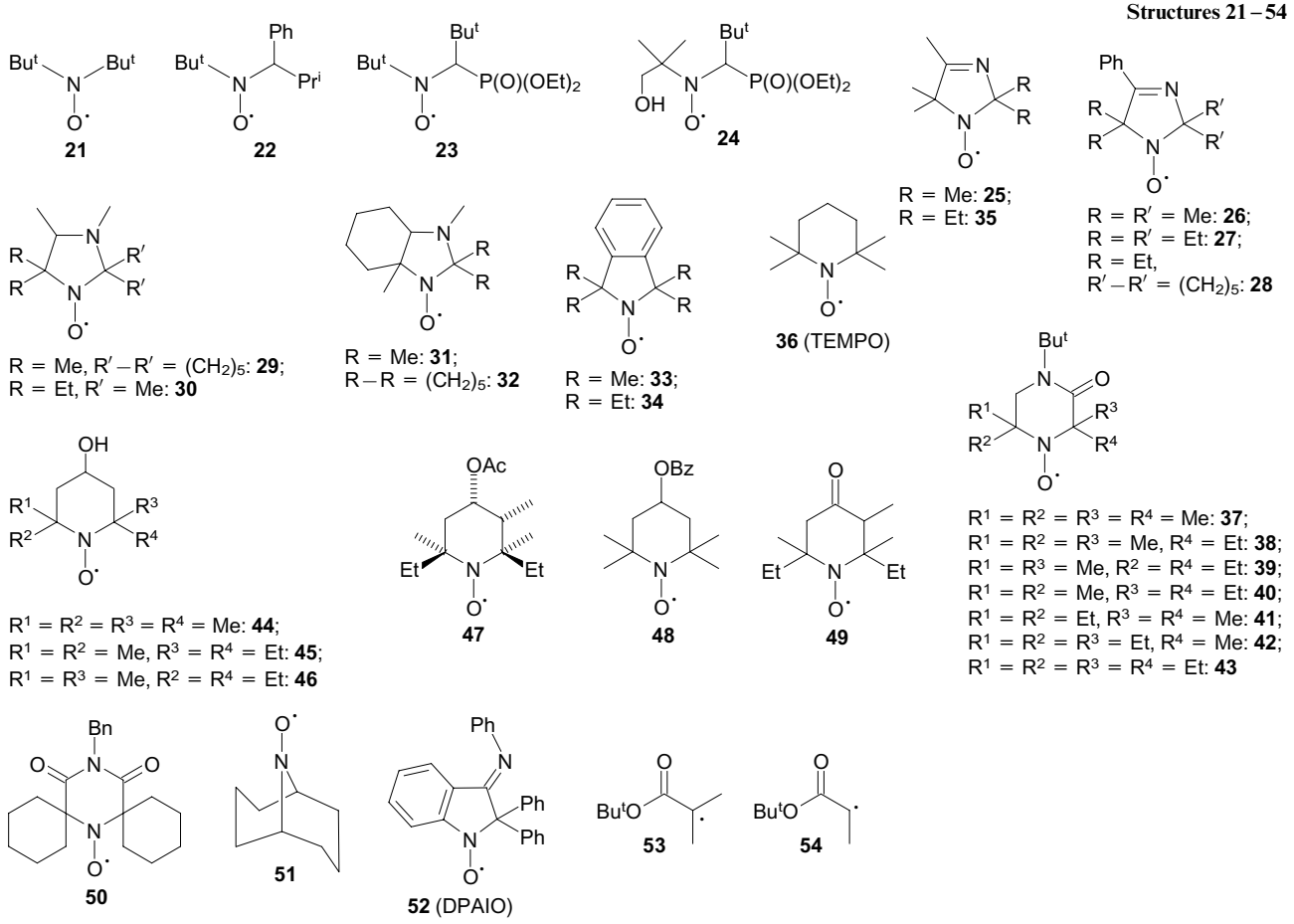
in the Gibbs free energy of alkoxyamine homolysis; the protonation of the alkyl moiety decreases this energy. Calculations demonstrated that the protonation of the nitroxide moiety stabilizes the final homolysis products, resulting in an increase in the activation barrier of the reaction. Therefore, the results of calculations are in good agreement with the experimental data and provide insight into the mechanism of influence of protonation on the rate constants of alkoxyamine homolysis and recombination of alkyl and nitroxide radicals.

The polarity of alkoxyamine can also be reversibly affected by the complexation with metal ions. In recent studies, Audran *et al.*[99,100] synthesized complexes of copper hexafluoroacetylacetonate and alkoxyamines based on the nitroxide SG1 containing the pyridine substituent in the alkyl group. The complexation was found to significantly affect the rate of C—ON bond homolysis in alkoxyamine. Thus, the constant k_d for the complex form is 21 times higher than that for the free form.

3.1.2. Recombination between nitroxide and alkyl radicals

There are currently no methods for the direct determination of the rate constants of recombination of polymer radicals with nitroxides. Generally, these values are calculated relative to the rate constant of chain propagation or relative to the already known rate constants of adduct decomposition and the equilibrium constant. Methods for measurements of rate constants for polymer radicals and nitroxides are considered in a review of Zaremski.[10] These are a method for the measurement of the degree of polymerization of a product prepared at a given concentration of a nitroxide free radical under conditions in which the reinitiation reaction can be ignored,[101] and a simpler method of competitive inhibition.[102] In the latter case, the polymerization is performed in the presence of two nitroxide radicals, with a known rate constant of recombination for one of them.

Structures 21 – 54



The first measurements of the rate constants of recombination between carbon-centred radicals (low-molecular-weight analogues of polymer radicals) and nitroxides were reported by Ingold and co-workers.[103, 104] In these studies, the rate constants of recombination of alkyl radicals with nitroxides were measured by a direct method — nanosecond laser flash photolysis.[105] The constants k_c were shown to be smaller than the diffusion rate constants. Besides, the constants k_c depend on the polarity and viscosity of the solvent. Thus, the constants k_c may decrease by an order of magnitude in going from nonpolar to polar and from nonviscous to viscous solvents.[106] The recombination of two radical species usually occurs through a barrierless process, due to which the rate constants k_c are weakly temperature-dependent. Besides, in some cases, the constant k_c decreases with temperature, which is attributed to a negative activation entropy of the recombination of these radicals.[106] Other methods for measurements of the constants k_c in these systems are the time-resolved chemically induced dynamic nuclear polarization (CIDNP) techniques[107, 108] and the switched external magnetic field CIDNP technique.[109]

The results of measurements of the rate constants of recombination of imidazoline and imidazolidine nitroxide radicals with different C-centred radicals were reported by Zubenko *et al.*[110, 111] The authors studied the factors that affect the constant k_c and revealed correlations of the steric and polar parameters with the rate of recombination of nitroxides with alkyl radicals. The measured k_c values for different nitroxides and alkyl radicals were substantially lower than the diffusion-controlled limit and were weakly temperature-dependent. For a large series of imidazolidine and imidazoline nitroxides, the rate of radical recombination was shown to decrease with increasing bulkiness of substituents in the vicinity of the nitroxide group. Besides, the polarity of substituents in the nitroxide radical was demonstrated to significantly affect the constant k_c. Therefore, in the synthesis of new nitroxide radicals promising for controlled polymerization, the rate of their recombination with alkyl radicals can be varied by changing the polarity of the substituents with the retention of steric hindrance.

Measurements of the constants k_c for a broader range of nitroxides **21** – **52**, including a large series of imidazoline and imidazolidine nitroxides,[112] allowed for a multiparameter analysis of the factors that affect the rate constants of recombination (Fig. 7). Based on these results, the following trends were elucidated: 1) stabilization of an alkyl radical and an increase in steric hindrance of nitroxide lead to a decrease in k_c; 2) the presence of an electron-donating group in nitroxide leads to an increase in the electron density on the nitroxide oxygen atom, thereby increasing k_c; 3) steric effects of substituents in the nitroxide moiety are provided by the ⟨ONCR⟩ dihedral angle $< 90°$. The constants k_c can be rather precisely estimated using the correlations derived from the structural data for nitroxide radicals. The influence of each factor on the rate constants k_c is schematically presented in Fig. 8.

The effect of the structures of nitroxide and alkyl radicals and the solvent effects on the rate of their recombination k_c for a wide range of nitroxides are integrated in the

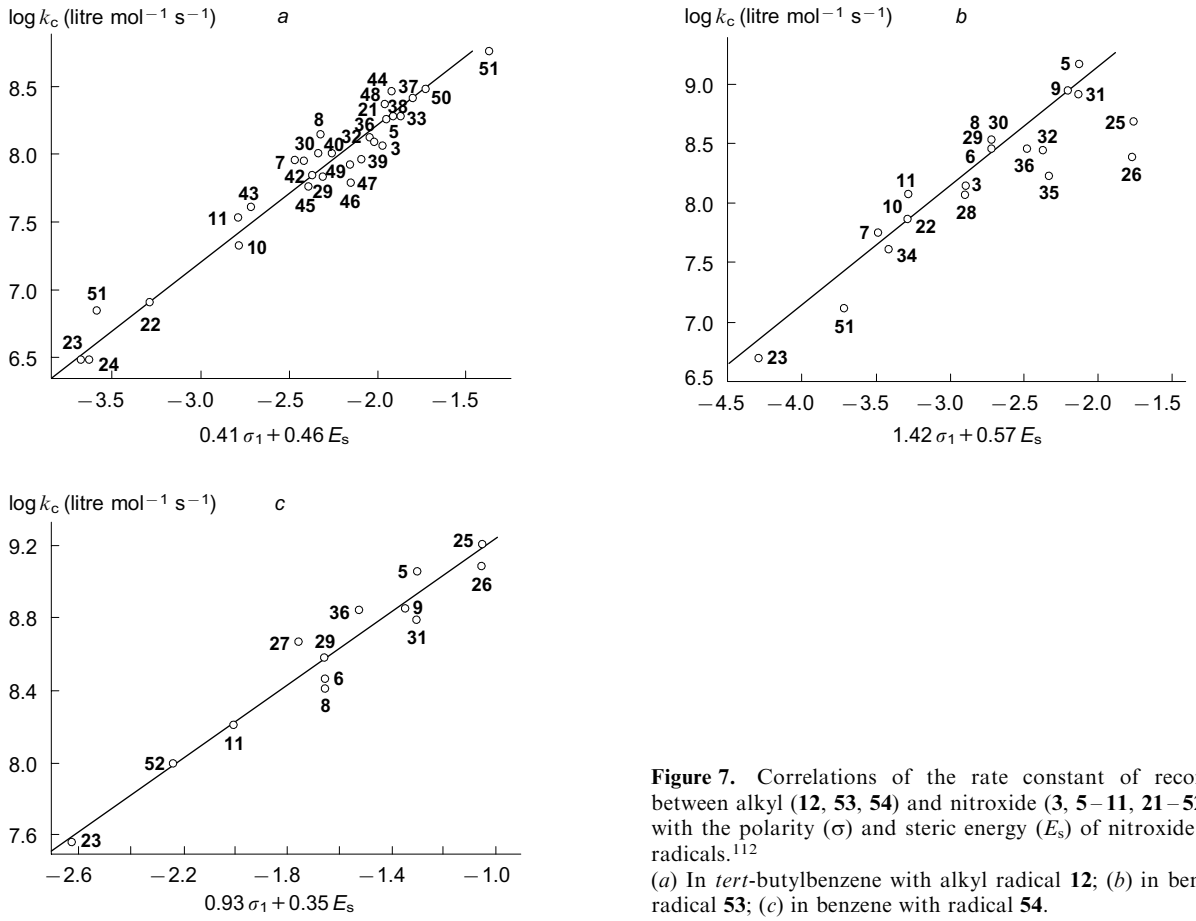


Figure 7. Correlations of the rate constant of recombination between alkyl (**12**, **53**, **54**) and nitroxide (**3**, **5** – **11**, **21** – **52**) radicals with the polarity (σ) and steric energy (E_s) of nitroxide and alkyl radicals.[112]
(*a*) In *tert*-butylbenzene with alkyl radical **12**; (*b*) in benzene with radical **53**; (*c*) in benzene with radical **54**.

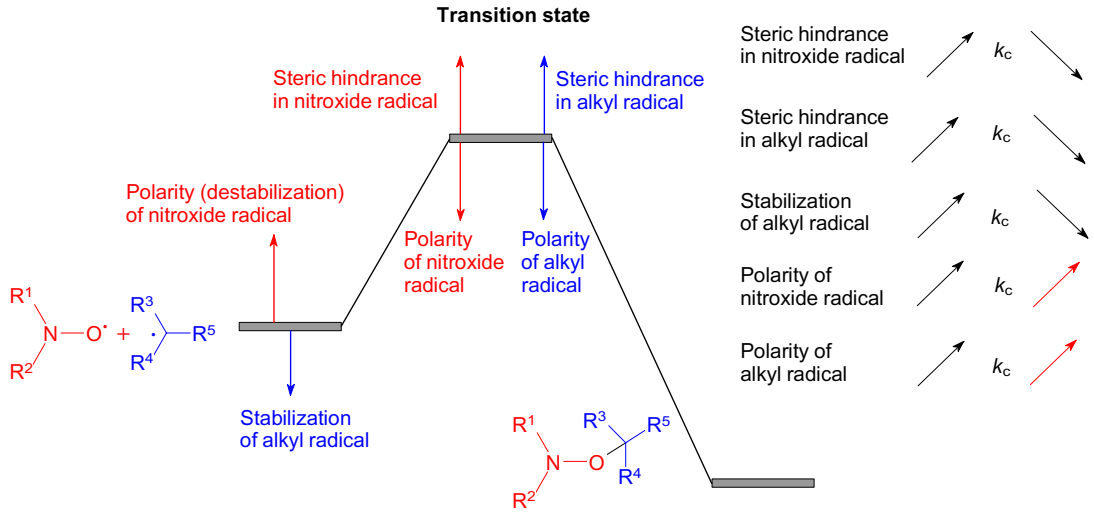


Figure 8. Influence of different factors (polarity, steric hindrance of nitroxide and alkyl radicals) on the energy levels and the reaction rate of recombination between nitroxide and the alkyl radical.[112]

review by Bagryanskaya and Marque,[106] where, in particular, data for 20 imidazoline and imidazolidine nitroxides and a large series of C-centred radicals are summarized. In this review, the k_c values are reported and the factors that affect the rate of recombination between nitroxides and C-centred radicals are thoroughly discussed.

3.2. Hydrogen transfer and intramolecular proton transfer reactions in alkoxyamines

Chain termination reactions involving the recombination and disproportionation of simple alkyl radicals and polymer radicals are considered in a number of reviews.[24, 49, 50] The reactions of alkyl and nitroxide radicals lead not only

to recombination giving alkoxyamine but also to chain termination in 1) the reaction between nitroxide and C-centred radical accompanied by the hydrogen abstraction from the latter giving rise to alkene and hydroxylamine (radical hydrogen transfer reaction)[51] and 2) the intramolecular proton transfer in alkoxyamine. Both reactions afford the same products, though following different mechanisms: the radical mechanism in the former case and the intramolecular (ionic) mechanism in the latter case. It was shown that the experimental conditions used may sometimes lead to erroneous conclusions concerning the reaction mechanism. The reaction that proceeds *via* an intramolecular mechanism was studied for the first time by Skene *et al.*[113] It is worth noting that the mechanism of intramolecular hydrogen transfer reaction is similar to that of Cope elimination.[72, 114] Different approaches should be employed to affect these processes in order to decrease their contribution to the polymerization process. Hydrogen transfer reactions were investigated for the most commonly used nitroxides, such as TEMPO,[115] DPAIO (2,2-diphenyl-3-phenylimino-2,3-dihydroindol-1-yloxyl, **52**)[116] and SG1;[117] meanwhile, investigations of imidazoline and imidazolidine nitroxides made the most substantial contribution to the understanding of these processes.

The mechanism of the hydrogen transfer reaction in the polymerization of methyl methacrylate is shown in Scheme 7.[72] There are two pathways for this reaction. One of them involves the reaction of the nitroxide radical Y$^{\bullet}$ with the polymer alkyl radical R$^{\bullet}$ affording hydroxylamine YH and alkene R(−H) — the radical hydrogen transfer (k_{cD}). Another mechanism involves the non-radical decomposition of the starting alkoxyamine to form alkene R(−H) and hydroxylamine YH — the intramolecular proton transfer *via* the Cope elimination mechanism (k_{dD}). The occurrence of the side reaction giving rise to dead chains R(−H) plays a significant role in the polymerization and changes its character. Thus, the amount of nitroxide radicals Y$^{\bullet}$ and propagating radicals R$^{\bullet}$ decreases and finally the polymerization stops.

A theoretical study of the ideal CRP mechanism and the influence of the hydrogen transfer side reaction on the polarization parameters was performed by Souaille and Fischer.[118] Equations (9)–(11) derived in this study describe the kinetics of changes in the amount of living chains and radical species for the hydrogen transfer reaction (Fig. 9). In the absence of side reactions, the amount of living chains slightly decreases during the polymerization (curve [I] in Fig. 9) with high monomer conversion (curve [M] in Fig. 9 *a*). A small contribution of the hydrogen transfer reaction to the chain termination step leads to a rapid decrease in the amount of living chains, and the monomer conversion stops (curves [I] and [M] in Fig. 9 *b*).

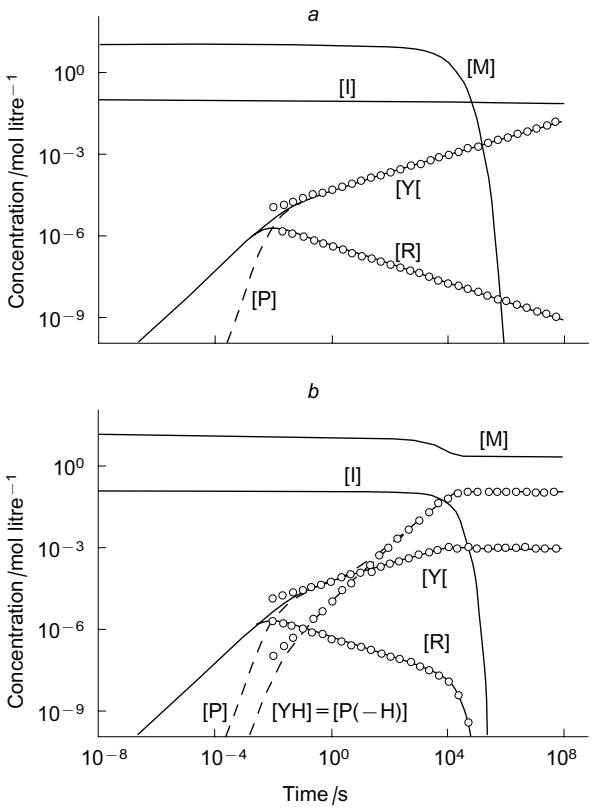


Figure 9. Concentrations of the monomer [M], nitroxide radical [Y], alkyl radical [R], dormant chains [I], products of recombination and disproportionation of alkyl radicals [P] and hydrogen transfer products [YH] = [P(−H)] *vs.* time in the absence of hydrogen transfer (*a*) and in the case of hydrogen transfer (*b*).[118] The lines represent the numerical solutions of kinetic equations.

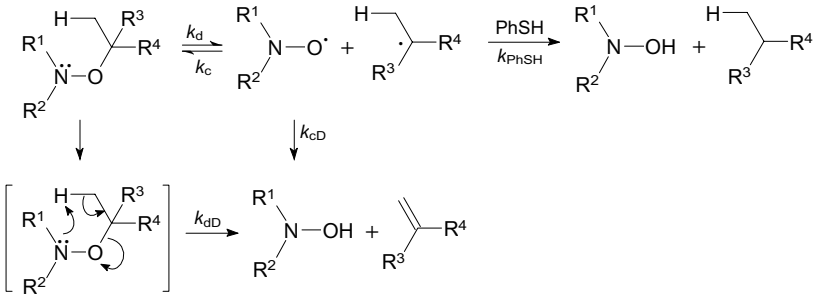
It was found that the character of polymerization is not significantly changed if the contribution of the hydrogen transfer reaction is $<0.7\%$ of the recombination reaction; in other words, the hydrogen transfer is observed only in seven of 1000 recombining pairs.

$$[YH] = [I]_0(1-e^{-f_D k_d t}) \quad (9)$$

$$[I] = [I]_0\, e^{-f_D k_d t} \quad (10)$$

$$f_D = \frac{k_{cD}}{k_c + k_{cD}} \quad (11)$$

Scheme 7



Ananchenko *et al.*[82] established that the hydrogen transfer does not occur in the polymerization of MMA in the presence of the nitroxide radical SG1. Therefore, it would be expected that this radical will be a promising controlling agent for MMA polymerization. Unfortunately, a high value of the measured equilibrium constant $K = k_d/k_c$ for the corresponding alkoxyamine leads to an increase in the concentration of active chains and, consequently, to uncontrolled MMA polymerization.

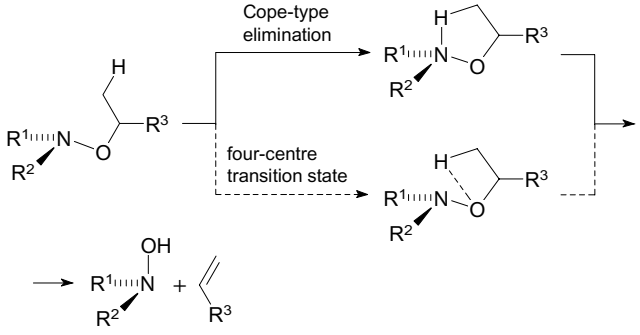
The factors that affect the hydrogen transfer side reaction for alkoxyamines with different structures were studied by experimental methods. The results of these investigations are important because the knowledge of the dependence of the hydrogen transfer reaction on the structure of the nitroxide radical allows the proper selection of the controlling agent for the controlled polymerization of MMA. The hydrogen transfer in alkoxyamines, including those based on imidazolidine radicals, was experimentally investigated by Edeleva *et al.*[72, 119] In these studies, NMR and CIDNP techniques were applied to analyze the mechanism of this reaction and elucidate the influence of different factors. The hydrogen transfer reaction was explored by theoretical methods in a number of works.[120, 121] The three-dimensional geometry of the transition state and the energy barriers for the hydrogen transfer reaction are difficult to calculate because of the complex structures of the starting molecules.

The investigation of side reactions in the nitroxide-mediated CRP includes the analysis of the end groups in the resulting polymer by different methods, such as ^{1}H NMR spectroscopy and mass spectrometry (MALDI TOF technique). Burguière *et al.*[115] studied the hydrogen transfer reaction in the TEMPO-mediated polymerization of n-butyl methacrylate at a variable TEMPO concentration using either a low-molecular-weight alkoxyamine initiator or a TEMPO-capped polystyrene macroinitiator. In both cases, the complete consumption of the initiator was observed, but the monomer conversion was low. The end groups of the polymer were analyzed by ^{1}H NMR spectroscopy and MALDI TOF mass spectrometry. The end group in the poly(n-butyl methacrylate) was found to be the attached initiator, *i.e.*, the block copolymer was synthesized *via* the reaction with the polystyrene macroinitiator. The other terminal functionality of the polymer was not a TEMPO-based alkoxyamine but unsaturated methylene. Meanwhile, a saturated polymer, which could be formed by disproportionation, was absent among the reaction products. From this result, it has been concluded[115] that the β-hydrogen transfer from a propagating radical to TEMPO is the main chain termination reaction (disproportionation reaction). A similar procedure was employed to detect the hydrogen transfer reaction in the MMA polymerization in the presence of a large excess of SG1.[122] Another approach is based on gel permeation chromatography.[58] Zetterlund *et al.*[58] evaluated the role of the chain transfer to monomer in the kinetics of styrene polymerization by molecular-weight distribution analysis. Spin trapping is the most appropriate technique for the detection of intermediate radicals generated during the thermolysis of alkoxyamines.[53] In this case, the EPR spectrum of adducts of structurally different radicals to a spin trap is simulated and compared with the experimental spectrum. The structures of the radical products of alkoxyamine thermolysis can be established from the correspondence between the simulated and experimental spectra.

An original method for investigating side reactions was described by Edeleva *et al.*,[116] who studied the mechanism and kinetics of intramolecular and radical hydrogen transfer reactions for nitroxide-based alkoxyamine using ^{1}H NMR spectroscopy. The approach is based on the examination of kinetics and investigation of alkoxyamine thermolysis products in a pure solution and in the presence of benzenethiol as a reducing agent for alkyl and nitroxide radicals. In the presence of benzenethiol, the reactions of nitroxide and alkyl radicals in solution, including the radical hydrogen transfer reaction, are suppressed. Therefore, the appearance of alkene in the reaction mixture in such experiments is evidence that hydrogen transfer occurs *via* an intramolecular mechanism. The nature and mechanism of side reactions can be revealed by analyzing the alkoxyamine homolysis products obtained in the absence of benzene thiol. This approach was employed to analyze the kinetics and mechanism of side reactions for alkoxyamines based on the nitroxide radicals TEMPO and DPAIO.[116] Subsequently, this method was used to experimentally study the reaction mechanism of the hydrogen transfer reaction for imidazoline nitroxide-based alkoxyamines with different structures.[72] It was shown that the contribution of both radical and intramolecular hydrogen transfer reactions decreases with increasing steric hindrance of the nitroxide moiety.

Parkhomenko *et al.*[123] performed a theoretical study of the factors that affect the hydrogen transfer reaction for a series of nitroxide radicals, including imidazoline and imidazolidine radicals. The calculations confirmed that if the hydrogen transfer reaction follows an intramolecular mechanism, the process occurs in two steps. Two possible geometries of the transition state are shown in Scheme 8. According to the calculations, the transition state includes a five-membered ring, the structure and geometric parameters of which are independent of the substituents in the nitroxide moiety of alkoxyamine. The results of this study provide an explanation for the experimental observation that the presence of sterically hindered substituents causes a decrease in the contribution of the proton transfer reaction: this side reaction always competes with alkoxyamine homolysis. In the case of sterically hindered alkoxyamines, the activation energy for homolysis significantly decreases due to stabilization of the corresponding reaction products. This leads to an increase in the difference between the activation energies for homolysis and hydrogen transfer,

Scheme 8



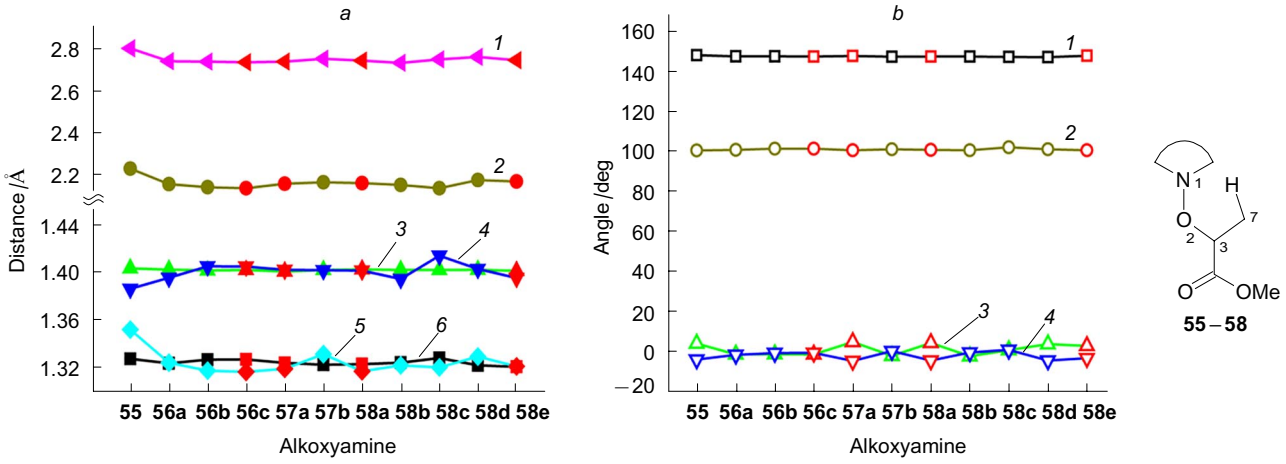
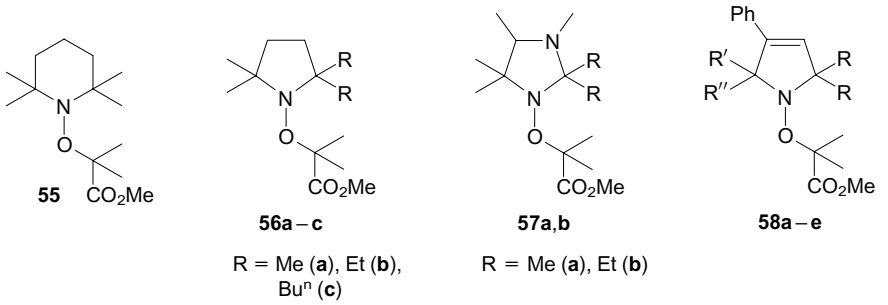


Figure 10. The C(3)–O(2) (*1*), N(1)–O(2) (*2*), C(3)–C(7) (*3*) and C(7)–H bond lengths (*4*) and the intermolecular N(1)···C(3) (*5*) and N(1)···H (*6*) distances (*a*); the C(3)–O(2)–N(1) (*1*) and N(1)–H–C(7) bond angles (*2*) and the N(1)–O(2)–C(3)–C(7) (*3*) and O(2)–C(3)–C(7)–H(4) dihedral angles (*4*) for alkoxyamines **55**–**58**.[124] Compounds in which the intramolecular hydrogen transfer was experimentally observed are marked in red.

Structures 55 – 58



R = R′ = R″ = Me (**a**),
R = Et, R′ = R″ = Me (**b**),
R–R = $(CH_2)_5$: R′ = Bu^n,
R″ = Bu^t (**c**), R′ = R″ = Et (**d**),
R′ = Me, R″ = Ph (**e**)

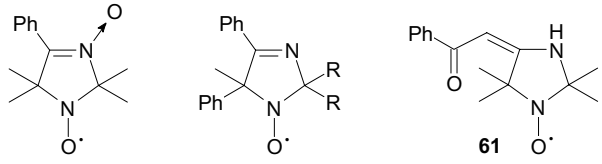
resulting in that the side reaction is virtually absent (Fig. 10).

4. Use of imidazoline and imidazolidine nitroxides as controlling agents for controlled radical polymerization

4.1. Polymerization of styrene

Styrene is the simplest monomer, which serves as a model for the nitroxide-mediated polymerization, because side reactions make an insignificant contribution to the kinetics of CRP of styrene, while the rate constants k_d and k_c suitable for controlled polymerization of styrene vary in wide ranges. The utilization of imidazoline nitroxides for the CRP of styrene was described for the first time by Grishin and co-workers.[125–128] The authors studied the effect of various sterically hindered amines and their derivatives on the kinetics of styrene polymerization.[125] The introduction of such compounds into the polymerization process was shown to slow down the polymer chain propagation, while the molecular weight of the polymers linearly depends on the conversion, resulting in the formation of a polymer with a narrow molecular-weight distribution. This was attributed to the fact that the polymerization *via* a radical mechanism *in situ* produces a nitroxide radical, which mediates the polymerization process. Lazarev *et al.*[126] performed styrene polymerization using nitroxide radicals **26** (TPIO) and **59**. These radicals proved to be efficient controlling agents for polymerization. Styrene polymers with molecular weights of 3000–6000 Da and the polydispersity index (PDI) of 1.3–1.5 were synthesized. Subsequently, this research group[127] explored the applicability of a series of five imidazoline nitroxides [**25** (PMIO), **26**, **35**, **60a**,**b**] to styrene polymerization. Each nitroxide was examined in the styrene polymerization under different conditions. The optimal initiator, the temperature profile and the optimal monomer to initiator ratio were chosen, which allowed the authors to prepare polymers with molecular weights of 3–48 kDa and the polydispersity index of 1.23–3.68. A good agreement between the calculated and experimental molecular weights of the polymer was achieved using benzoyl peroxide as an initiator (Fig. 11).

Structures 59 – 61



R = Me (**a**),
R–R = $(CH_2)_5$ (**b**)

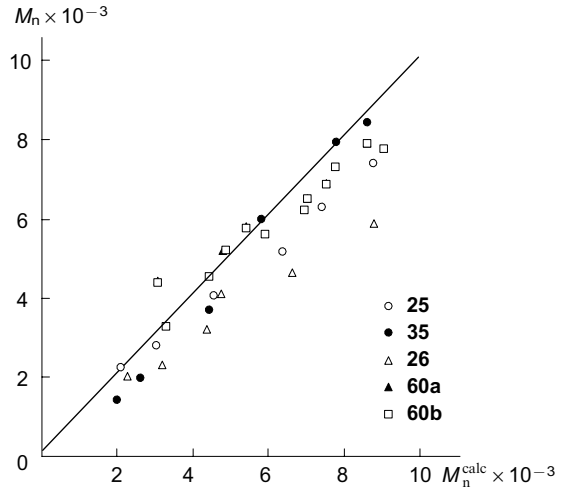


Figure 11. Correlation between the experimental and calculated values (M_n and M_n^{calc}, respectively) for polystyrene at different degrees of monomer conversion in the benzoyl peroxide-initiated polymerization at 120 °C.[127]
$[Styrene]_0 = 8.71$ mol litre^{-1}, the ratio $[styrene]_0 : [initiator]_0 : [nitroxide]_0 = 100 : 1 : 1.5$.

Apart from styrene homopolymers, Grishin *et al.*[128] successfully synthesized copolymers of styrene, methyl methacrylate, butyl acrylate and acrylonitrile using the same NRs.

Zhu *et al.*[129] used imidazoline nitroxides **25**, **59** and **61** as controlling agents for CRP of styrene. The authors succeeded in performing the controlled polymerization at 135 °C up to a conversion of 80% and prepared a polymer with a narrow molecular-weight distribution (the polydispersity index was 1.32) and a rather high molecular weight (29 kDa). The resulting polymer was suitable for the reinitiation of polymerization, which is indicative of a high percentage of living chains.

Alkoxyamines containing an imidazoline or imidazolidine moiety and an alkyl isopropionate or isobutyrate moiety were also used as initiators of CRP of styrene.[70] In the cited study, the rate constants of homolysis and recombination of alkoxyamines, as well as of hydrogen transfer side reactions, were measured. Taking into account the measured parameters, the polymerization temperature was chosen and the styrene polymerization was explored. The hydrogen transfer side reaction in the initiation step was found to lead to considerable deviations of the experimental molecular weight from the theoretically calculated value. These results are in good agreement with the data published by Zubenko *et al.*,[71] who studied the styrene polymerization initiated by various alkoxyamines based on imidazoline nitroxides and alkyl moieties of different nature and demonstrated that the initiating moiety significantly affects the CRP process. Therefore, the polymerization occurs in a controlled manner only in the absence of side reactions in the initiation step.

4.2. Polymerization of (meth)acrylates

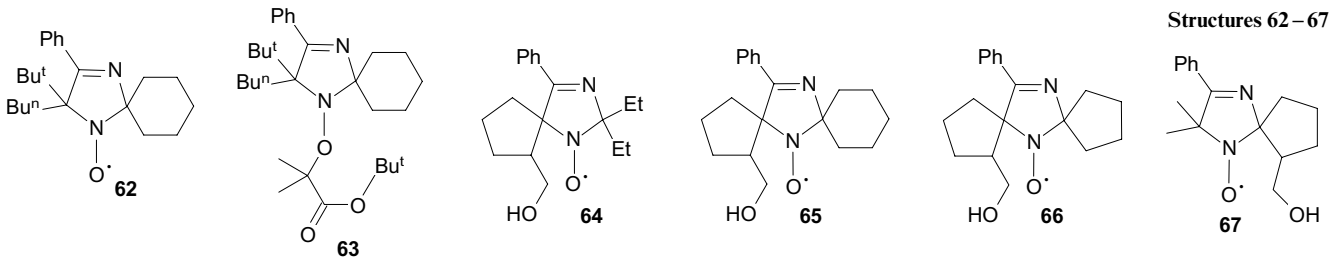
The living radical polymerization can be used to polymerize various vinyl monomers — styrene and acrylate derivatives.[130] However, until recently, attempts to perform the controlled polymerization of methacrylate monomers to form a living polymer failed. The polymerization stops at a low monomer conversion, is non-living and affords a polymer with high dispersity.[34, 113, 131 – 134] This polymerization character is attributed to the side reaction — the hydrogen abstraction from the alkyl radical by nitroxide.[132] Besides, the thermolysis of high-molecular weight alkoxyamine involves the C – O bond homolysis along with intramolecular proton transfer.

The data on the employment of various NRs as controlling agents for MMA polymerization are available in the literature. The TEMPO-mediated MMA polymerization proceeds to a monomer conversion of 3%.[34] This process affords a polymer with the end double bond (macromonomer) and hydroxylamine (TEMPO-H) as the major products, which attests to the hydrogen transfer reaction. The quantitative formation of the macromonomer in the TEMPO-mediated methacrylate polymerization was used to create the functional ω-unsaturated polystyrene-block-poly(n-butyl methacrylate) copolymer.[115] The nitroxide SG1 is of limited use in the MMA polymerization because of a high equilibrium constant.[52] This results in a significant contribution of recombination of two alkyl radicals to the polymerization process and in the accumulation of an excessive amount of NR that inhibits polymerization. Charleux and co-workers[44, 74] succeeded in performing controlled MMA polymerization giving a living polymer in the presence of small amounts of styrene and acrylonitrile (4.4 mol.% – 8.8 mol.%). However, the presence of a comonomer sometimes changes the properties of the resulting polymer. Therefore, this method is undesirable. The nitroxide radical DPAIO (**52**) can be employed as a controlling agent of the controlled MMA polymerization in the absence of an additive of the comonomer.[135] This process occurs with high conversion (80%) and affords a polymer with a narrow molecular-weight distribution. However, the percentage of living chains in the resulting polymer is low. Later, it was shown that the DPAIO-mediated MMA polymerization involves the N – O bond cleavage in alkoxyamine as the side reaction.[116]

It should be noted that, although such CRP techniques as ATRP and RAFT are suitable for the controlled polymerization of methacrylates and the synthesis of polymers with good characteristics,[136 – 141] investigations on the nitroxide-mediated CRP of methacrylates are still ongoing since there remains a need to synthesize polymers that would be free from metal traces and would have no offensive odour caused by the presence of sulfur compounds. This task is difficult to accomplish using ATRP or RAFT. Detailed studies of side reactions and the elucidation of the factors playing a key role in these reactions have enabled some advances in developing controlling agents for polymerization of MMA and analogues. Examples of the nitroxide-mediated controlled polymerization of methacrylate monomers are given below.

The first attempt to employ imidazoline radicals for the MMA poymerization[128] was unsuccessful: the polymerization was uncontrolled due to hydrogen transfer side reactions. Subsequently, the CRP of methyl methacrylate was achieved using imidazoline radicals with bulky substituents as controlling agents:[72] n-butyl-*tert*-butyl-substituted imidazoline nitroxide **62** and related alkoxyamine **63**. The contributions of both the radical and intramolecular hydrogen transfer reactions to the thermolysis of this alkoxyamine were found to be small. Thus, the polymerization

Structures 62 – 67



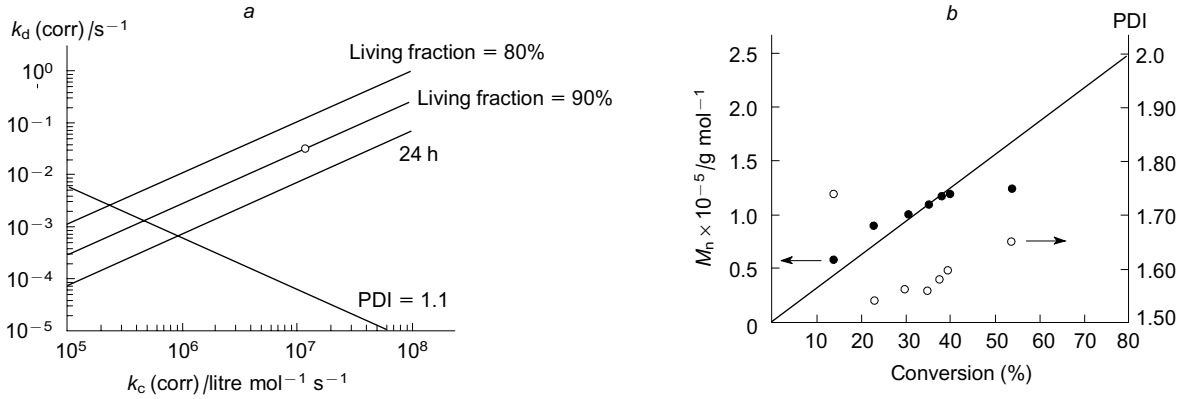


Figure 12. Fischer's diagram for MMA polymerization initiated by alkoxyamine **63** (represented by a point in the diagram); the rate constants of homolysis (k_d) and recombination (k_c) are corrected for the effects of the chain length and the penultimate unit (*a*). Changes in the molecular weight and the polydispersity index during MMA polymerization initiated by alkoxyamine **63** at 80 °C (*b*).[72]

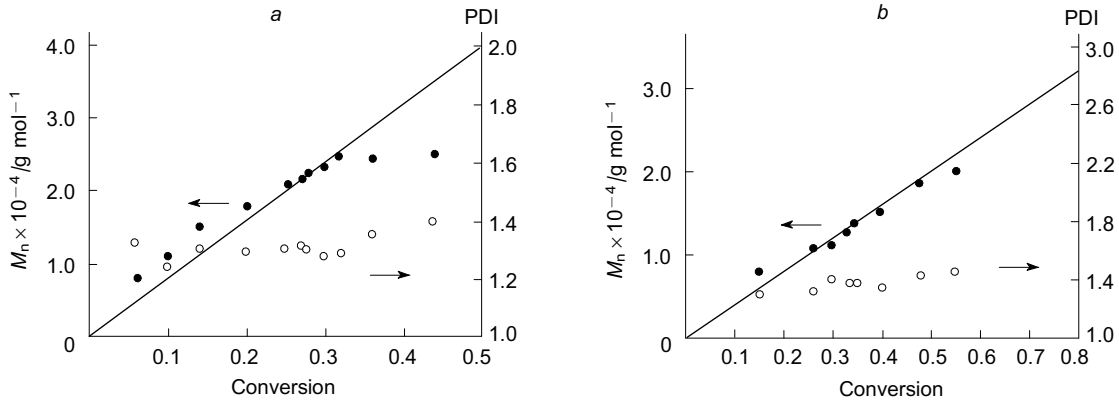


Figure 13. Plots of M_n and the polydispersity index *vs.* the monomer conversion for MMA polymerization in the presence of nitroxide **64** at 80 °C and different ratios [initiator] : [monomer] = 800 : 1 (*a*), 350 : 1 (*b*).[75]

occurs in a controlled manner up to the conversion of 40%; however, at higher conversions, the molecular weight of the polymer stops to grow (Fig. 12). This is due to thermal instability of the nitroxide. The latter decomposes by a radical mechanism on heating during the polymerization process, which makes the polymerization uncontrolled.

In a more recent study, Edeleva *et al.*[75] utilized thermally stable nitroxides **64** – **67** containing a spirocyclic substituent, for which the contribution of hydrogen transfer was negligible. In the presence of radical **64** as a controlling agent for MMA polymerization, the monomer conversion was 55% and the polymerization produced a narrow-disperse (PDI = 1.45) polymer (Fig. 13). A macroinitiator was used for styrene polymerization affording the corresponding block copolymer. Hence, the polymerization was shown to be living, and it was demonstrated that poly(methyl methacrylate)-block-polystyrene copolymers can be synthesized in the presence of imidazoline nitroxide as a single controlling agent.

4.3. Polymerization of vinyl chloride

Grishin and co-workers [142, 143] employed imidazoline nitroxides to accomplish polymerization of such functional monomers as vinyl chloride. Nitroxides **26**, **60a**,**b** and

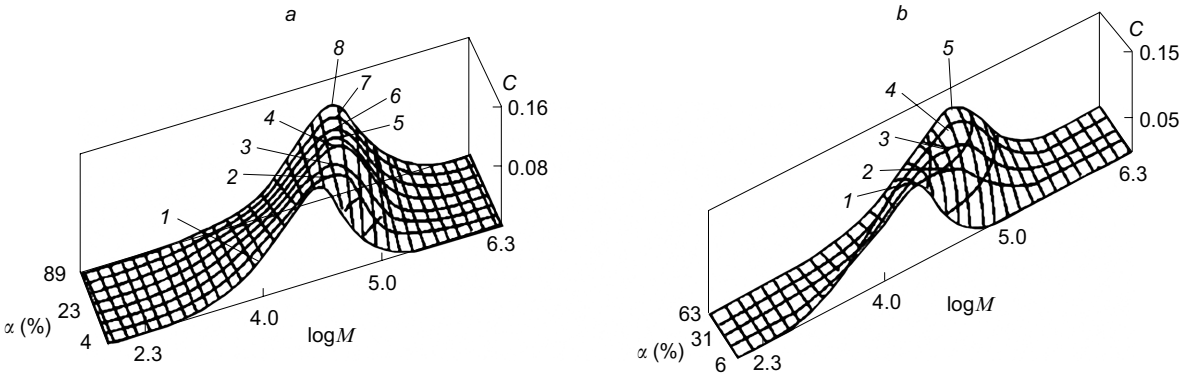


Figure 14. Gel permeation chromatography data for PVC samples which were synthesized at 50 °C in the presence of dicyclohexyl peroxydicarbonate and *C*-phenyl-*N*-*tert*-butyl nitrone (PBN);[143] α is conversion, *C* is weight fraction, *M* is molecular weight. The PBN concentration (mol.%): 0.1 (*a*) and 0.5 (*b*). Conversion (%): (*a*) 4 (*1*), 7 (*2*), 23 (*3*), 48 (*4*), 62 (*5*), 89 (*6*), 94 (*7*), 114 (*8*) (samples *7* and *8* were prepared by post-polymerization); (*b*) 6 (*1*), 12 (*2*), 31 (*3*), 41 (*4*), 63 (*5*).

C-phenyl-*N*-*tert*-butyl nitrone (PBN) were used as controlling agents. This polymerization produced polymers with a molecular weight of up to 20 kDa and a polydispersity index of up to 1.7 (Fig. 14). The resulting macromolecules were utilized as high-molecular-weight initiators for styrene polymerization and the synthesis of poly(vinyl chloride)-block-polystyrene copolymers.

4.4. Polymerization of hydrophilic monomers

Polymers prepared from hydrophilic monomers are widely used in different areas. Polymers based on such monomers as acrylamide, sodium acrylate, sodium 4-styrenesulfonate, 4-hydroxymethyl methacrylate and vinylpyrrolidone are of great practical importance and are employed in medicine,[144, 145] oil industry for enhanced oil recovery from oil fields, mining industry for mineral recovery and processing, industrial wastewater treatment, as additive in the paper industry and so on.[146] Hence, the synthesis of high-quality polymers from hydrophilic monomers is a challenge. One way to achieve this goal is to perform controlled living polymerization in an aqueous medium.

The nitroxide-mediated polymerization of water-soluble monomers was performed in a monomer medium and in an aqueous-organic emulsion using TEMPO and its water-soluble analogues (4-hydroxy and 4-amino derivatives) as controlling agents.[147 – 149] For instance, the 4-hydroxy-TEMPO-mediated polymerization of sodium styrenesulfonate followed by the partial replacement of the sulfo groups by the porphyrin ring produced a polymer capable of absorbing light in the visible region. In aqueous solutions, this polymer forms nanospheres that can serve as nanoreactors. The polymerization of acrylic acid was described by Ladavière *et al.*;[150] Bian and Cunningham [151] performed the SG1-mediated polymerization of 2-hydroxyethyl acrylate. Many examples of the application of macroinitiators based on water-soluble polymers for the emulsion and

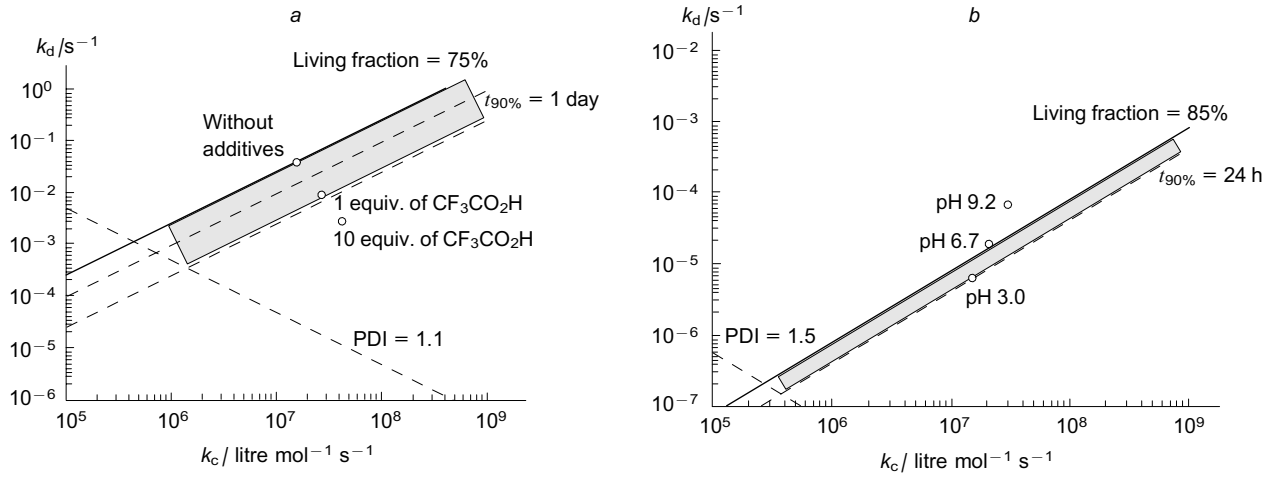


Figure 15. Fischer's diagrams for polymerization of styrene (*a*)[77] and acrylamide (*b*).[77] (*a*) Styrene polymerization at 140 °C initiated by different forms of alkoxyamine **16**, the rate constants k_d and k_c were corrected to take into account changes in the macroalkoxyamine structure; the ratio monomer : initiator = 1000 : 1, $k_p = 10^3$ litre mol^{-1} s^{-1}, $k_t = 1.7 \times 10^8$ litre mol^{-1} s^{-1}; (*b*) acrylamide polymerization initiated by alkoxyamine **16**, the ratio monomer : initiator = 1000 : 1, $k_p = 6.6 \times 10^3$ litre mol^{-1} s^{-1}, $k_t = 1.6 \times 10^8$ litre mol^{-1} s^{-1}. The grey-shaded regions correspond to controlled polymerization.

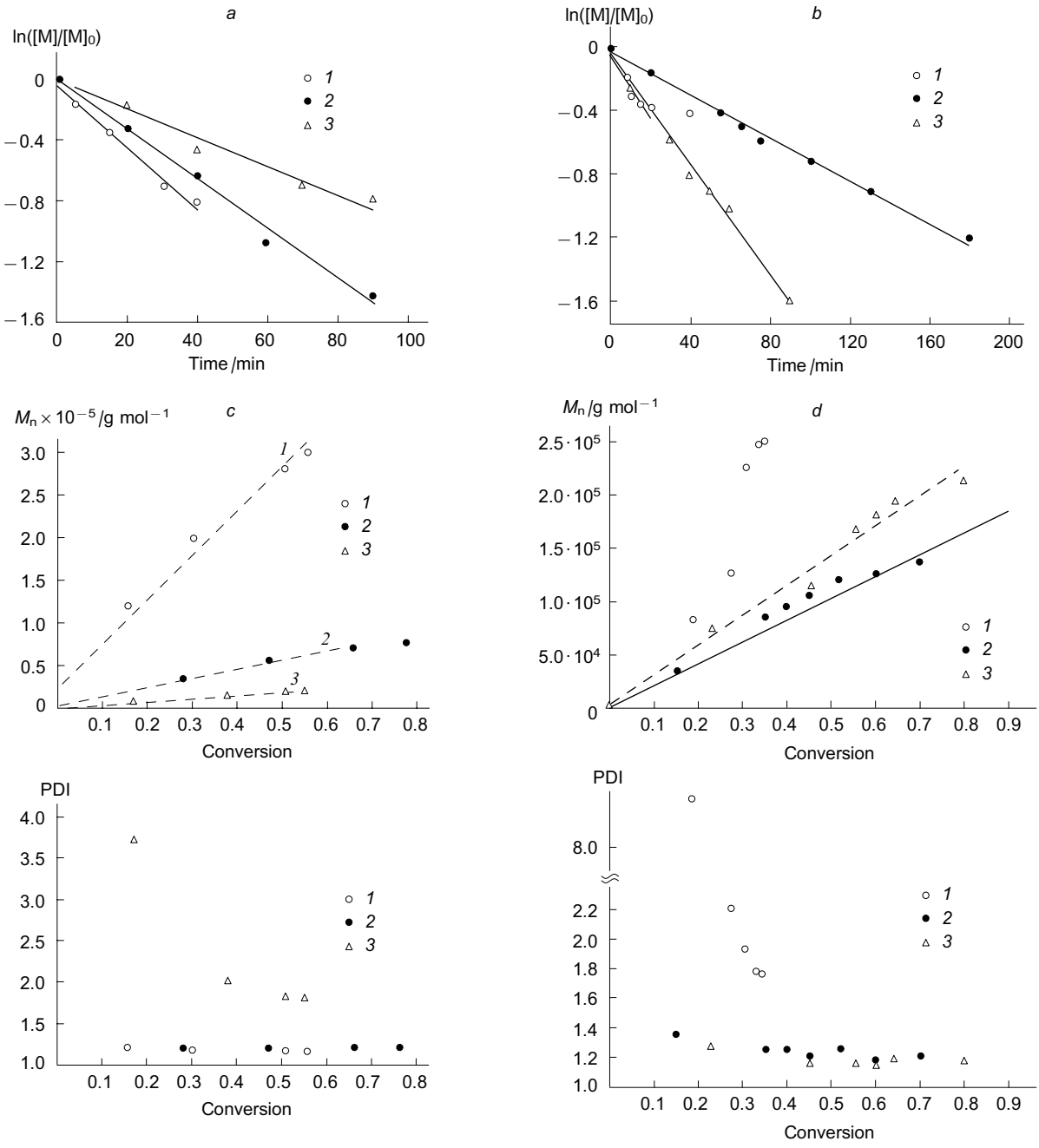


Figure 16. Kinetics of polymerization of acrylamide (*a*) and sodium 4-vinylbenzenesulfonate (*b*) initiated by alkoxyamine **16** at 90 °C.[77] Plots of the molecular weight and dispersity during polymerization of acrylamide at pH 3.0 and different monomer : initiator ratios (*c*) and polymerization of sodium 4-vinylbenzenesulfonate at monomer : initiator = 1000 : 1 and different pH (*d*); (*a*, *c*) the ratio monomer : initiator = 1000 : 1 (*1*), 250 : 1 (*2*), 100 : 1 (*3*); (*b*, *d*) pH 8.7 (*1*), 6.7 (*2*), 3.0 (*3*). The solid lines indicate the calculated molecular weights; the dashed lines show linear approximations of the experimental data.

miniemulsion polymerization of styrene and acrylates have been reported. Delaittre *et al.*[152] prepared copolymers using an acrylic acid-based macroinitiator, which was produced by SG1-mediated living radical polymerization. This method was applied to synthesize an amphiphilic block copolymer. Huang *et al.*[153] demonstrated that nitroxide radicals of the isoindoline and piperidine series are efficient controlling agents for the polymerization of sodium styrenesulfonate and sodium acrylate in an aqueous medium. The polymerization in their presence produced the corresponding polymers and a block copolymer with a narrow molecular-weight distribution (PDI < 1.5). The main drawback of nitroxide-mediated CRP of hydrophilic monomers is the high polymerization temperature (generally > 100 °C) and, consequently, the polymerization should be performed under high pressure or in water – high-boiling solvent mixtures.[154]

Edeleva *et al.*[77] performed the polymerization of hydrophilic and hydrophobic monomers using a single controlling agent. The polymerization of hydrophilic monomers, such

as sodium 4-vinylbenzenesulfonate (SVBS) and acrylamide (AAm), and lipophilic styrene was accomplished in the presence of pH-sensitive imidazoline nitroxide **19**. Fischer's diagrams were applied to select the optimal conditions for the polymerization of each monomer in particular, taking into account changes in the rate constants of alkoxyamine homolysis and recombination between nitroxide and alkyl radicals in the protonation of alkoxyamines and nitroxide radicals (Fig. 15). The polymers poly-SVBS and poly-AAm were synthesized under optimal conditions (pH, temperature and the concentrations of the monomer and the initiator). The polymerization was shown to be living and controlled (Fig. 16). It should be noted that the same nitroxide was employed for the controlled polymerization of styrene. Among other nitroxides, only the nitroxide SG1 is universal with respect to hydrophilic and lipophilic monomers without structural modifications.

5. Conclusion

The data summarized in this review clearly demonstrate that imidazoline and imidazolidine nitroxides hold promise as controlling agents for nitroxide-mediated polymerization. The structural diversity and the available methods for the synthesis make it possible to introduce diverse substituents into the nearest environment of the nitroxide moiety. Therefore, the rate constants of alkoxyamine homolysis can be changed hundred-fold. Besides, the introduction of hydrophilic, protonatable and complexing groups offers routes to directly influencing the reaction rate constants by varying the pH of the solution. Imidazoline and imidazolidine nitroxide radicals can also form complexes with metal ions. Consequently, the complexation would be expected to cause changes in the constants k_d and k_c for these compounds, as it was demonstrated recently for alkoxyamines based on the nitroxide radical SG1.[99, 100]

Currently, the nitroxide-mediated radical polymerization is used not only for research purposes but also in industry. This suggests that there are quite efficient nitroxides, which can be utilized in the large-scale production based on this reaction. The question that arises then is what are the advantages of imidazoline radicals compared to other radicals.

Table 1 presents a brief comparison in relation to several important parameters of imidazoline nitroxides and the radicals TEMPO and SG1 commonly employed in the industry as controlling agents. The evident advantage of the latter radicals is that there are industrial processes using these radicals, while such processes for imidazoline radicals are absent. However, the procedure for the synthesis is quite facile for TEMPO and SG1, as well as for imidazolines. Therefore, the development of industrial processes, if necessary, will not cause a problem.

In terms of the synthesis and variations in the structure, the advantage of imidazoline nitroxides is broad functional group tolerance, while only OH groups can be introduced into SG1; otherwise, unstable radicals are produced.

Another important parameter is the efficiency of controlling agents for the polymerization of different monomers. Above, we have considered examples of the application of imidazoline radicals as controlling agents for the polymerization of various monomers, including styrene and (meth)acrylates. In particular, imidazolines can be used in aqueous media for the polymerization of hydrophilic monomers. Noteworthy is that neither TEMPO nor SG1 can be employed for the polymerization of pure MMA in the absence of additives. Besides, imidazolines are characterized by high thermal stability. They are also stable in the presence of acids and bases. Therefore, nitroxides compare favourably with SG1 and TEMPO (the former has a very short lifetime in an acidic medium). This is why imidazolines are efficient in the design of switchable initiators. For SG1, the polymerization becomes uncontrolled in protonated switchable initiators because of decomposition of the nitroxide. For quite stable TEMPO, the effect of the protonation on the constant k_d is weak, thereby making this radical useless.

Table 1. Comparison of the characteristics of imidazoline nitroxides and the TEMPO- and SG1-based radicals.

Characteristics	Imidazoline nitroxides	TEMPO and its derivatives	SG1
Simplicity of the synthesis	+	+	+
Industrial processes for the synthesis	–	+	+
Possibility of introducing functional groups	+	Limited	Only OH
Green technology	+	+	+
Efficiency of controlling polymerization of different monomers	Styrene and derivatives +, MMA +, MMA derivatives +, acrylates +, hydrophilic monomers +, vinyl acetate –	Styrene and derivatives +, MMA and derivatives – (only in the presence of additives), hydrophilic monomers +/–, vinyl acetate –	Styrene and derivatives +, MMA – (only with a copolymer), MMA derivatives –, hydrophilic monomers +, vinyl acetate –
Stability	Very high thermal stability, including in acidic medium	Low stability, unstable in acidic medium	Low
Possibility of designing switchable initiators	Nitroxide moiety +, alkyl moiety +	Nitroxide moiety –, alkyl moiety + (very weak effect)	Nitroxide moiety +/–, alkyl moiety +

Owing to some properties (stability, ability to undergo protonation and complexation), imidazoline nitroxides can be considered as promising controlling agents for nitroxide-mediated polymerization.

This review has been written with the financial support of the Russian Foundation for Basic Research (Project No. 15-03-05250; E.G.Bagryanskaya) and the Russian Science Foundation (Project No. 15-13-20020; S.R.A.Marque).

Figure 3 is given with permission from Royal Society of Chemistry; Figures 4, 5, 12, 13 and Scheme 7 are given with permission from John Wiley and Sons; Figure 11 is given with permission from Springer; Figures 7, 8, 9, 12 and 16 are given with permission from American Chemical Society.

References

1. G.Moad, E.Rizzardo. *Macromolecules*, **28**, 8722 (1995)
2. D.Gigmes, S.Marque, D.Bertin. *Recent Res. Dev. Org. Chem.*, **10**, 63 (2006)
3. C.J.Hawker, A.W.Bosman, E.Harth. *Chem. Rev.*, **101**, 3661 (2001)
4. K.Matyjaszewski, in *Controlled Radical Polymerization*. (Ed. K.Matyjaszewski). (Washington: ACS Publications, 1998) p. 2
5. R.B.Grubbs. *Polym. Rev.*, **51**, 104 (2011)
6. A.Studer, T.Schulte. *Chem. Rec.*, **5**, 27 (2005)
7. J.Nicolas, Y.Guillaneuf, C.Lefay, D.Bertin, D.Gigmes, B.Charleux. *Prog. Polym. Sci.*, **38**, 63 (2013)
8. M.Yu.Zaremski, A.V.Plutalova, M.B.Lachinov, V.B.Golubev. *Macromolecules*, **33**, 4365 (2000)
9. I.D.Grishin, D.F.Grishin. *Russ. J. Org. Chem.*, **52**, 1541 (2016)
10. M.Yu.Zaremski. *Polym. Sci., Ser. C*, **57**, 65 (2015)
11. *Handbook of Radical Polymerization*. (Eds K.Matyjaszewski, T.P.Davis). (Hoboken: Wiley, 2003)
12. *Fundamentals of Controlled/Living Radical Polymerization*. (Eds N.Tsarevsky, B.S.Sumerlin). (Cambridge: The Royal Society of Chemistry, 2012)
13. H.Fischer. *J. Polym. Sci., Part A: Polym. Chem.*, **37**, 1885 (1999)
14. H.Fischer. *Chem. Rev.*, **101**, 3581 (2001)
15. A.Goto, T.Fukuda. *Prog. Polym. Sci.*, **29**, 329 (2004)
16. D.Bertin, D.Gigmes, S.R.A.Marque, P.Tordo. *Chem. Soc. Rev.*, **40**, 2189 (2011)
17. E.G.Bagryanskaya, S.R.A.Marque, in *Nitroxide Mediated Polymerization: from Fundamentals to Applications in Materials Sciences*. (Ed. D.Gigmes). (Cambridge: The Royal Society of Chemistry, 2016) p. 45
18. K.Matyjaszewski. *Prog. Polym. Sci.*, **30**, 858 (2005)
19. J.Nicolas, B.Charleux, S.Magnet. *J. Polym. Sci., Part A: Polym. Chem.*, **44**, 4142 (2006)
20. M.Destarac. *Macromol. React. Eng.*, **4**, 165 (2010)
21. B.E.Daikh, R.G.Finke. *J. Am. Chem. Soc.*, **114**, 2938 (1992)
22. H.Fischer. *J. Am. Chem. Soc.*, **108**, 3925 (1986)
23. T.Kothe, S.Marque, R.Martschke, M.Popov, H.Fischer. *J. Chem. Soc., Perkin Trans. 2*, 1553 (1998)
24. H.Fischer, H.Paul. *Acc. Chem. Res.*, **20**, 200 (1987)
25. Eur. Patent Appl. EP 135280 (1985); *Chem. Abstr.*, **102**, 221335 (1985)
26. Patent US 4581429 (1986)
27. T.Otsu, M.Yoshida, T.Tazaki. *Macromol. Rapid Commun.*, **3**, 133 (1982)
28. J.S.Wang, K.Matyjaszewski. *J. Am. Chem. Soc.*, **117**, 5614 (1995)
29. M.Kato, M.Kamigaito, M.Sawamoto, T.Higashimura. *Macromolecules*, **28**, 1721 (1995)
30. J.Chiefari, Y.K.Chong, F.Ercole, J.Krstina, J.Jeffery, T.P.Le, R.T.A.Mayadunne, G.F.Meijs, C.L.Moad, G.Moad, E.Rizzardo, S.H.Thang. *Macromolecules*, **31**, 5559 (1998)
31. T.R.Darling, T.P.Davis, M.Fryd, A.A.Gridnev, D.M.Haddleton, S.D.Ittel, R.R.Matheson, G.Moad, E.Rizzardo. *J. Polym. Sci., Part A: Polym. Chem.*, **38**, 1706 (2000)
32. M.H.Stenzel, C.Barner-Kowollik. *Mater. Horizons*, **3**, 471 (2016)
33. M.Yu.Zaremski, V.B.Golubev. *Polym. Sci., Ser. C*, **43**, 81 (2001)
34. G.Moad, A.G.Anderson, F.Ercole, C.H.J.Johnson, J.Krstina, C.L.Moad, E.Rizzardo, T.H.Spurling, S.H.Thang, in *Controlled Radical Polymerization*. (Ed. K.Matyjaszewski). (Washington: ACS Publications, 1998) p. 332
35. D.Gigmes, S.R.A.Marque, in *Encyclopedia of Radicals in Chemistry, Biology and Materials*. (Eds C.Chatgilialoglu, A.Studer). (Chichester: Wiley, 2012) p. 1813
36. B.Knühl, S.Marque, H.Fischer. *Helv. Chim. Acta*, **84**, 2290 (2001)
37. W.Tang, T.Fukuda, K.Matyjaszewski. *Macromolecules*, **39**, 4332 (2006)
38. D.Gigmes, D.Bertin, C.Lefay, Y.Guillaneuf. *Macromol. Theory Simul.*, **18**, 402 (2009)
39. L.C.Li, G.K.Hamer, M.K.Georges. *Macromolecules*, **39**, 9201 (2006)
40. O.Guerret, J.-L.Couturier, F.Chauvin, H.El-Bouazzy, D.Bertin, D.Gigmes, S.Marque, H.Fischer, P.Tordo. *ACS Symp. Ser.*, **854**, 412 (2003)
41. A.Blachon, S.R.A.Marque, V.Roubaud, D.Siri. *Polymers*, **2**, 353 (2010)
42. D.Bertin, F.Chauvin, S.Marque, P.Tordo. *Macromolecules*, **35**, 3790 (2002)
43. M.Zaremski, O.Borisova, C.Xin, V.B.Golubev, L.Billon. *J. Polym. Sci., Part A: Polym. Chem.*, **50**, 3437 (2012)
44. J.Nicolas, C.Dire, L.Mueller, J.Belleney, B.Charleux, S.R.A.Marque, D.Bertin, S.Magnet, L.Couvreur. *Macromolecules*, **39**, 8274 (2006)
45. O.Guerret, J.-L.Couturier, F.Chauvin, H.El-Bouazzy, D.Bertin, D.Gigmes, S.Marque, H.Fischer, P.Tordo, in *Advances in Controlled/Living Radical Polymerization*. (Ed. K.Matyjaszewski). (Washington: ACS Publications, 2003) p. 412
46. S.Beuermann, M.Buback. *Prog. Polym. Sci.*, **27**, 191 (2002)
47. M.Buback. *Macromol. Symp.*, **275 – 276**, 90 (2009)
48. M.Buback, A.Feldermann, C.Barner-Kowollik, I.Lacík. *Macromolecules*, **34**, 5439 (2001)
49. M.Buback, M.Busch, C.Kowollik. *Macromol. Theory Simul.*, **9**, 442 (2000)
50. C.Barner-Kowollik, M.Buback, M.Egorov, T.Fukuda, A.Goto, O.F.Olaj, P.B.Zetterlund. *Prog. Polym. Sci.*, **30**, 605 (2005)
51. J.J.Warren, T.A.Tronic, J.M.Mayer. *Chem. Rev.*, **110**, 6961 (2010)
52. Y.Guillaneuf, D.Gigmes, S.R.A.Marque, P.Tordo, D.Bertin. *Macromol. Chem. Phys.*, **207**, 1278 (2006)
53. D.Gigmes, A.Gaudel, G.Siri, S.R.Marque, D.Bertin, P.Tordo, P.Astolfi, L.Greci, C.Rizzoli. *Helv. Chim. Acta*, **89**, 2312 (2006)
54. J.L.Hodgson, L.B.Roskop, M.S.Gordon, C.Y.Lin, M.L.Coote. *J. Phys. Chem. A*, **114**, 10458 (2010)
55. P.Astolfi, L.Greci, P.Stipa, C.Rizzoli, C.Ysacco, M.Rollet, L.Autissier, A.Tardy, Y.Guillaneuf, D.Gigmes. *Polym. Chem.*, **4**, 3694 (2013)
56. G.Audran, P.Brémond, S.R.A.Marque. *Chem. Commun.*, **50**, 7921 (2014)
57. A.Nilsen, R.Braslau. *J. Polym. Sci., Part A: Polym. Chem.*, **44**, 697 (2006)

58. P.Zetterlund, Y.Saka, R.McHale, T.Nakamura, S.Aldabbagh, M.Okubo. *Polymer*, **47**, 7900 (2006)
59. D.Greszta, K.Matyjaszewski. *Macromolecules*, **29**, 7661 (1996)
60. L.B.Volodarsky, I.A.Grigor'ev,S.A.Dikanov, V.A.Reznikov, G.I.SHchukin. *Imidazolinovye Nitroksil'nye Radikaly*. (Imidazoline Nitroxides) (Novosibirsk: Nauka, 1988)
61. *Synthetic Chemistry of Stable Nitroxides*. (Eds L.B.Volodarsky, V.A.Reznikov, V.I.Ovcharenko). (Boca Raton, FL: CRC Press, 1993)
62. L.B.Volodarsky, I.A.Grigor'ev, R.Z.Sagdeev, in *Biological Magnetic Resonance* Vol. 2. (Eds L.J.Berliner, J.Reuben). (New York: Plenum Press, 1980) p. 169
63. A.A.Gorodetsky, I.A.Kirilyuk, V.V.Khramtsov, D.A.Komarov. *Magn. Reson. Med.*, **76**, 350 (2016)
64. A.Samouilov, O.V.Efimova, A.A.Bobko, Z.Sun, S.Petryakov, T.D.Eubank, D.G.Trofimov, I.A.Kirilyuk, I.A.Grigor'ev, W.Takahashi, J.L.Zweier, V.V.Khramtsov. *Anal. Chem.*, **86**, 1045 (2014)
65. V.Khramtsov. *Curr. Org. Chem.*, **9**, 909 (2005)
66. A.A.Bobko, T.D.Eubank, J.L.Voorhees, O.V.Efimova, I.A.Kirilyuk, S.Petryakov, D.G.Trofimiov, C.B.Marsh, J.L.Zweier, I.A.Grigor'ev, A.Samouilov, V.V.Khramtsov. *Magn. Reson. Med.*, **67**, 1827 (2012)
67. I.A.Kirilyuk, A.A.Bobko, V.V.Khramtsov, I.A.Grigor'ev. *Org. Biomol. Chem.*, **3**, 1269 (2005)
68. I.A.Kirilyuk, A.A.Bobko, S.V.Semenov, D.A.Komarov, I.G.Irtegova, I.A.Grigor'ev, E.G.Bagryanskaya. *J. Org. Chem.*, **80**, 9118 (2015)
69. K.Matyjaszewski, B.E.Woodworth, X.Zhang, S.G.Gaynor, Z.Metzner. *Macromolecules*, **31**, 5955 (1998)
70. E.Bagryanskaya, D.Bertin, D.Gigmes, I.Kirilyuk, S.R.A.Marque, V.Reznikov, G.Roshchupkina, I.Zhurko, D.Zubenko. *Macromol. Chem. Phys.*, **209**, 1345 (2008)
71. D.P.Zubenko, I.A.Kirilyuk, S.Marque, I.P.Chuikov, E.G.Bagryanskaya. *Polym. Sci., Ser. B*, **52**, 327 (2010)
72. M.V.Edeleva, I.A.Kirilyuk, D.P.Zubenko, I.F.Zhurko, S.R.A.Marque, D.Gigmes, Y.Guillaneuf, E.G.Bagryanskaya. *J. Polym. Sci., Part A: Polym. Chem.*, **47**, 6579 (2009)
73. E.Guégain, Y.Guillaneuf, J.Nicolas. *Macromol. Rapid Commun.*, **36**, 1227 (2015)
74. J.Nicolas, S.Brusseau, B.Charleux. *J. Polym. Sci., Part A: Polym. Chem.*, **48**, 34 (2010)
75. M.V.Edeleva, D.A.Parkhomenko, D.A.Morozov, S.A.Dobrynin, D.G.Trofimov, B.Kanagatov, I.A.Kirilyuk, E.G.Bagryanskaya. *J. Polym. Sci., Part A: Polym. Chem.*, **52**, 929 (2014)
76. P.Brémond, S.R.A.Marque. *Chem. Commun.*, **47**, 4291 (2011)
77. M.V.Edeleva, I.A.Kirilyuk, I.F.Zhurko, D.A.Parkhomenko, Yu.P.Tsentalovich, E.G.Bagryanskaya. *J. Org. Chem.*, **76**, 5558 (2011)
78. Y.Le Du, L.Binet, P.Hémery, L.Marx. *J. Polym. Sci., Part A: Polym. Chem.*, **50**, 2871 (2012)
79. A.Goto, T.Fukuda. *Macromolecules*, **32**, 618 (1999)
80. A.Goto, Y.Kwak, C.Yoshikawa, Y.Tsujii, Y.Sugiura, T.Fukuda, *Macromolecules*, **35**, 3520 (2002)
81. S.A.F.Bon, G.Chambard, A.L.German. *Macromolecules*, **32**, 8269 (1999)
82. G.S.Ananchenko, M.Souaille, H.Fischer, C.Le Mercier, P.Tordo. *J. Polym. Sci., Part A: Polym. Chem.*, **40**, 3264 (2002)
83. H.Fischer, A.Kramer, S.R.Marque, P.Nesvadba. *Macromolecules*, **38**, 9974 (2005)
84. F.Chauvin, P.E.Dufils, D.Gigmes, Y.Guillaneuf, S.R.Marque, P.Tordo, D.Bertin. *Macromolecules*, **39**, 5238 (2006)
85. S.Marque. *J. Org. Chem.*, **68**, 7582 (2003)
86. S.Marque, H.Fischer, E.Baier, A.Studer. *J. Org. Chem.*, **66**, 1146 (2001)
87. M.Mazarin, M.Girod, S.Viel, T.N.T.Phan, S.R.A.Marque, S.Humbel, L.Charles. *Macromolecules*, **42**, 1849 (2009)
88. M.Benaglia, J.Chiefari, Y.Chong, G.Moad, E.Rizzardo, S.Thang. *J. Am. Chem. Soc.*, **131**, 6914 (2009)
89. M.Benaglia, M.Chen, Y.Chong, G.Moad, E.Rizzardo, S.Thang. *Macromolecules*, **42**, 9384 (2009)
90. E.Bagryanskaya, P.Brémond, M.Edeleva, S.R.Marque, D.Parkhomenko, V.Roubaud, D.Siri. *Macromol. Rapid Commun.*, **33**, 152 (2012)
91. P.Brémond, A.Koïta, S.R.Marque, V.Pesce, V.Roubaud, D.Siri. *Org. Lett.*, **14**, 358 (2011)
92. G.Audran, P.Brémond, S.R.Marque, G.Obame. *Polym. Chem.*, **3**, 2901 (2012)
93. G.Audran, P.Brémond, S.R.A.Marque, G.Obame. *J. Org. Chem.*, **77**, 9634 (2012)
94. G.Audran, P.Brémond, S.R.A.Marque, G.Obame. *J. Org. Chem.*, **78**, 7754 (2013)
95. G.Audran, M.B.B.Ibanou, P.Brémond, S.R.A.Marque, G.Obame, V.Roubaud, D.Siri. *J. Phys. Org. Chem.*, **27**, 387 (2014)
96. G.Audran, L.Bosco, P.Brémond, S.R.A.Marque, V.Roubaud, D.Siri. *J. Org. Chem.*, **78**, 9914 (2013)
97. G.Audran, P.Brémond, M.B.B.Ibanou, S.R.A.Marque, V.Roubaud, D.Siri. *Org. Biomol. Chem.*, **11**, 7738 (2013)
98. D.A.Parkhomenko, M.V.Edeleva, V.G.Kiselev, E.G.Bagryanskaya. *J. Phys. Chem. B*, **118**, 5542 (2014)
99. G.Audran, E.Bagryanskaya, I.Bagryanskaya, M.Edeleva, S.R.A.Marque, D.Parkhomenko, E.Tretyakov, S.Zhivetyeva. *ChemistrySelect*, **2**, 3584 (2017)
100. G.Audran, E.Bagryanskaya, I.Bagryanskaya, P.Brémond, M.Edeleva, S.R.A.Marque, D.Parkhomenko, E.Tretyakov, S.Zhivetyeva. *Inorg. Chem. Front.*, **3**, 1464 (2016)
101. E.V.Chernikova, E.A.Leonova, E.S.Garina, M.Yu.Zaremskii, V.B.Golubev. *Polym. Sci., Ser. B*, **43**, 58 (2001)
102. O.V.Borisova, M.Yu.Zaremskii, V.B.Golubev, A.V.Plutalova, O.V.Borisov, L.Billon. *Polym. Sci., Ser. B*, **55**, 508 (2013)
103. V.W.Bowry, K.U.Ingold. *J. Am. Chem. Soc.*, **114**, 4992 (1992)
104. A.L.J.Beckwith, V.W.Bowry, K.U.Ingold. *J. Am. Chem. Soc.*, **114**, 4983 (1992)
105. J.Sobek, R.Martschke, H.Fischer. *J. Am. Chem. Soc.*, **123**, 2849 (2001)
106. E.G.Bagryanskaya, S.R.A.Marque. *Chem. Rev.*, **114**, 5011 (2014)
107. M.Goez. *Annu. Rep. NMR Spectrosc.*, **66**, 77 (2009)
108. L.J.Berliner, E.Bagryanskaya, in *Multifrequency Electron Paramagnetic Resonance*. (Ed. S.K.Misra). (Weinheim: Wiley-VCH, 2011) p. 947
109. N.V.Lebedeva, D.P.Zubenko, E.G.Bagryanskaya, R.Z.Sagdeev, G.S.Ananchenko, S.Marque, D.Bertin, P.Tordo. *Phys. Chem. Chem. Phys.*, **6**, 2254 (2004)
110. D.Zubenko, Yu.Tsentalovich, N.Lebedeva, I.Kirilyuk, G.Roshchupkina, I.Zhurko, V.Reznikov, S.R.A.Marque, E.Bagryanskaya. *J. Org. Chem.*, **71**, 6044 (2006)
111. D.Zubenko, I.Kirilyuk, G.Roshchupkina, I.Zhurko, V.Reznikov, S.R.Marque, E.Bagryanskaya. *Helv. Chim. Acta*, **89**, 2341 (2006)
112. E.G.Bagryanskaya, S.R.A.Marque, Yu.P.Tsentalovich. *J. Org. Chem.*, **77**, 4996 (2012)
113. W.G.Skene, J.C.Scaiano, G.P.A.Yap. *Macromolecules*, **33**, 3536 (2000)
114. G.S.Ananchenko, H.Fischer. *J. Polym. Sci., Part A: Polym. Chem.*, **39**, 3604 (2001)
115. C.Burguière, M.A.Dourges, B.Charleux, J.P.Vairon. *Macromolecules*, **32**, 3883 (1999)
116. M.Edeleva, S.R.Marque, D.Bertin, D.Gigmes, Y.Guillaneuf, S.V.Morozov, E.G.Bagryanskaya. *J. Polym. Sci., Part A: Polym. Chem.*, **46**, 6828 (2008)

117. M.Edeleva, S.R.Marque, K.Kabytaev, Y.Guillaneuf, D.Gigmes, E.Bagryanskaya. *J. Polym. Sci., Part A: Polym. Chem.*, **51**, 1323 (2013)
118. M.Souaille, H.Fischer. *Macromolecules*, **34**, 2830 (2001)
119. M.Edeleva, S.R.Marque, D.Bertin, D.Gigmes, Y.Guillaneuf, E.Bagryanskaya. *Polymers*, **2**, 364 (2010)
120. A.Kaim, E.Megiel. *J. Polym. Sci., Part A: Polym. Chem.*, **44**, 914 (2006)
121. E.Megiel, A.Kaim. *J. Polym. Sci., Part A: Polym. Chem.*, **46**, 1165 (2008)
122. Ch.Dire, J.Belleney, J.Nicolas, D.Bertin, S.Magnet, B.Charleux. *J. Polym. Sci., Part A: Polym. Chem.*, **46**, 6333 (2008)
123. D.Parkhomenko, E.G.Bagryanskaya, S.R.A.Marque, D.Siri. *Phys. Chem. Chem. Phys.*, **15**, 13862 (2013)
124. D.A.Parkhomenko. Candidate Thesis in Physical and Mathematical Sciences, NIOC SB RAS, 2015
125. V.V.Polyanskova, E.V.Kolyakina, D.F.Grishin. *Russ. J. Appl. Chem.*, **79**, 288 (2006)
126. M.A.Lazarev, I.A.Kirilyuk, I.A.Grigor'ev, D.F.Grishin. *Polym. Sci., Ser. B*, **49**, 224 (2007)
127. E.V.Kolyakina, M.A.Lazarev, M.V.Pavlovskaya, I.A.Kirilyuk, I.F.Zhurko, I.A.Grigor'ev, D.F.Grishin. *Russ. Chem. Bull., Int. Ed.*, **59**, 1556 (2010)
128. D.F.Grishin, E.V.Kolyakina, M.V.Pavlovskaya, M.A.Lazarev, A.A.Shchepalov. *ACS Symp. Ser.*, **1024**, 95 (2009)
129. J.Li, X.Zhu, J.Zhu, Z.Cheng. *J. Macromol. Sci., Part A: Pure Appl. Chem.*, **44**, 41 (2007)
130. D.Benoit, V.Chaplinski, R.Braslau, C.Hawker. *J. Am. Chem. Soc.*, **121**, 3904 (1999)
131. J.He, L.Li, Y.Yang. *Macromolecules*, **33**, 2286 (2000)
132. I.Li, B.A.Howell, K.Matyjaszewski, T.Shigemoto, P.B.Smith, D.B.Priddy. *Macromolecules*, **28**, 6692 (1995)
133. B.Y.K.Chong, F.Ercole, G.Moad, E.Rizzardo, S.H.Thang, A.G.Anderson. *Macromolecules*, **32**, 6895 (1999)
134. W.G.Skene, J.C.Scaiano, N.A.Listigovers, P.M.Kazmaier, M.K.Georges. *Macromolecules*, **33**, 5065 (2000)
135. Y.Guillaneuf, D.Gigmes, S.R.A.Marque, P.Astolfi, L.Greci, P.Tordo, D.Bertin. *Macromolecules*, **40**, 3108 (2007)
136. D.A.Shipp, J.-L.Wang, K.Matyjaszewski. *Macromolecules*, **31**, 8005 (1998)
137. J.-S.Wang, K.Matyjaszewski. *Macromolecules*, **28**, 7901 (1995)
138. E.V.Chernikova, A.V.Tarasenko, V.V.Yulusov, V.G.Golubev. *Polym. Sci., Ser. A*, **51**, 212 (2009)
139. L.L.Semenycheva, E.V.Telegina, I.S.Il'ichev, M.V.Pavlovskaya, D.F.Grishin. *Vestn. Nizhegor. Univ. im. N.I.Lobachevskogo. Seriya:Khimiya*, (1), 54 (2001)
140. M.Benaglia, E.Rizzardo, A.Alberti, M.Guerra. *Macromolecules*, **38**, 3129 (2005)
141. E.I.Biryukova, S.V.Amosova, S.A.Zhivet'eva, M.V.Edeleva. *Polym. Sci., Ser. B*, **51**, 438 (2009)
142. L.L.Semenycheva, D.F.Grishin. *Russ. J. Appl. Chem.*, **76**, 851 (2003)
143. D.F.Grishin, L.L.Semenycheva, M.V.Pavlovskaya, K.V.Sokolov. *Russ. J. Appl. Chem.*, **74**, 1594 (2001)
144. P.Dalton, L.Flynn, M.Shoichet. *Biomaterials*, **23**, 3843 (2002)
145. N.S.Melik-Nubarov. Author's Abstract of the Doctoral Thesis in Chemical Sciences, Department of Chemistry, Moscow State University, 2007
146. V.F.Kurenkov. *Soros Educ. J.,* **3** (5), 48 (1997)
147. M.Nowakowska, A.Karewicz, M.Kłos, S.Zapotoczny. *Macromoleculs*, **36**, 4134 (2003)
148. L.Couvreur, C.Lefay, J.Belleney, B.Charleux, O.Guerret, S.Magnet. *Macromolecules*, **36**, 8260 (2003)
149. X.Zhao, W.Lin, N.Song, X.Chen, X.Fan, Q.Zhou. *J. Mater. Chem.*, **16**, 4619 (2006)
150. C.Ladavière, N.Dörr, J.Claverie. *Macromolecules*, **34**, 5370 (2001)
151. K.Bian, M.Cunningham. *Macromolecules*, **38**, 695 (2005)
152. G.Delaittre, J.Nicolas, C.Lefay, M.Save, B.Charleux. *Soft Matter*, **2**, 223 (2006)
153. W.Huang, B.Charleux, R.Chiarelli, L.Marx, A.Rassat, J.-P.Vairon. *Macromol. Chem. Phys.*, **203**, 1715 (2002)
154. *Polymer Handbook*. (Eds J.Brandrup, E.H.Immergut, E.A.Grulke). (Wiley-Interscience, 2003)