JOC The Journal of Organic Chemistry

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pH-Sensitive C—ON Bond Homolysis of Alkoxyamines of Imidazoline Series with Multiple Ionizable Groups As an Approach for Control of Nitroxide Mediated Polymerization

Mariya V. Edeleva,[*,†,‡] Igor A. Kirilyuk,[§] Irina F. Zhurko,[§] Dmitry A. Parkhomenko,[†,‡] Yuri P. Tsentalovich,[†] and Elena G. Bagryanskaya[*,†]

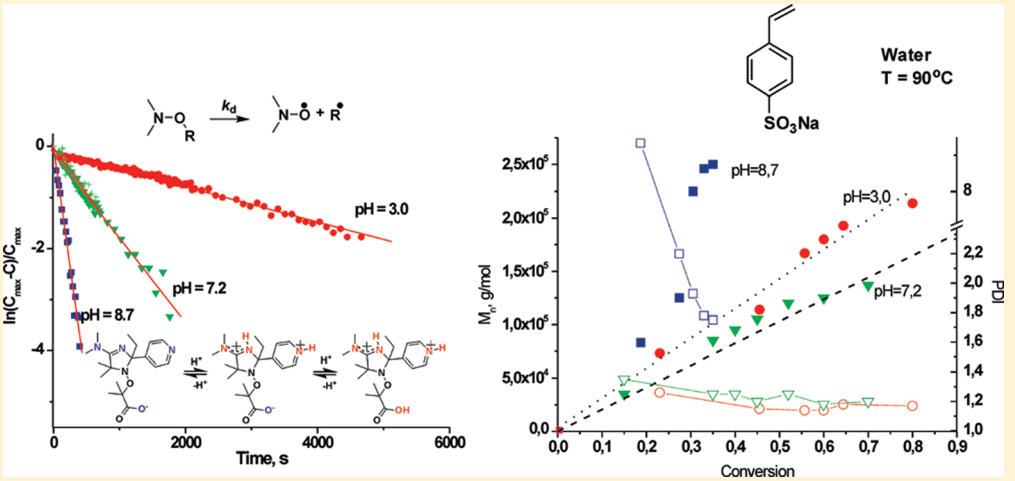
[†]International Tomography Center SB RAS, Institutskaya 3A, Novosibirsk, 630090, Russian Federation

[‡]Novosibirsk State University, Pirogova 2, Novosibirsk, 630090, Russian Federation

[§]Novosibirsk Institute of Organic Chemistry SB RAS, Pr. Lavrentjeva 16, Novosibirsk, 630090, Russian Federation

Supporting Information

ABSTRACT:



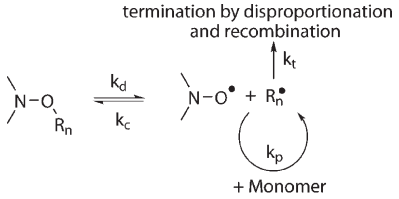
Recently, a new concept of pH-switchable agents for reversible addition—fragmentation chain transfer (RAFT) polymerization has been introduced by Benaglia et al. (*J. Am. Chem. Soc.* **2009**, *131*, 6914—6915). In this paper we extended the concept of pH-switchable mediators to nitroxide mediated polymerization (NMP) by employing nitroxides with basic or acidic groups as controlling agents. Four alkoxyamines, the derivatives of 2-(4-(dimethylamino)-2-ethyl-5,5-dimethyl-2-(pyridin-4-yl)-2,5-dihydro-1*H*-imidazol-1-oxyl and 2-(2-carboxyethyl)-5,5-diethyl-2,4-dimethyl-2,5-dihydro-1*H*-imidazol-1-oxyl, have been prepared. The influence of pH on alkoxyamine homolysis rate constants (k_d) and on the nitroxide-alkyl radical recombination rate constants (k_c) was studied. All alkoxyamines under study as well as the parent nitroxides have several basic groups, which under pH variation can undergo consecutive protonation. It was shown that the k_d value under basic conditions are significantly (up to 15-fold) higher than in acidic solution at the same temperature, whereas the k_c value in basic solutions decrease by a factor of 2 only. The efficiency of NMP is known to be dependent on k_d and k_c, both constants being dependent on the monomer structure; therefore the performance of NMP of different monomers in the controlled mode requires different conditions. It is shown that the pH value crucially affects the polymerization regime, changing it from the controlled to the uncontrolled mode. The controlled regime of NMP of different hydrophilic monomers (sodium 4-styrenesulphonate and acrylamide) in aqueous solution under mild conditions (90 °C) can be achieved using the same alkoxyamine by the variation of the pH value. The chain length of polymers depends on pH value during the polymerization.

INTRODUCTION

Nitroxide mediated radical polymerization (NMP) is a versatile technique for the preparation of homo- and co-polymers with controlled molecular weight, complex architecture, and reactive end groups.[1−7] The analysis of NMP kinetics shows that the polymerization efficiency depends on the rate constant k_d of the dormant species (alkoxyamines) homolysis and on the rate constant of nitroxyl and alkyl radicals recombination k_c (Scheme 1).[8] The rate constants k_d and k_c depend on the monomer structure,

Received: March 2, 2011
Published: June 02, 2011

Scheme 1. Simplified Reaction Scheme of NMP



therefore the polymerization of various monomers requires different conditions to perform NMP in the controlled mode.[9−12]

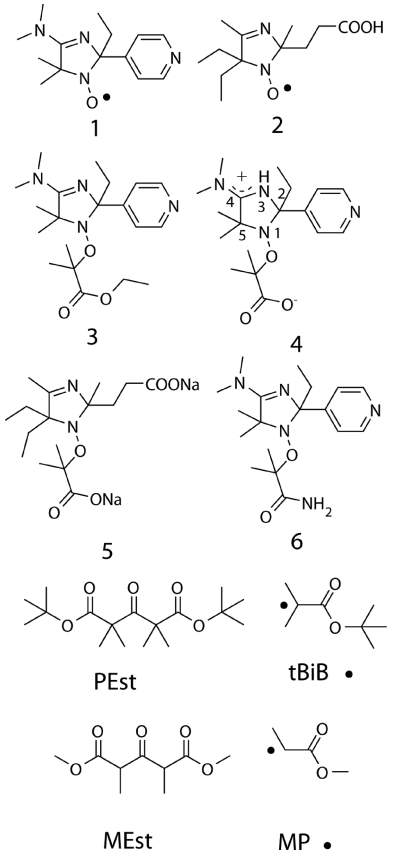
Recently, a new concept of pH-switchable agents for reversible addition−fragmentation chain transfer (RAFT) polymerization has been introduced.[13,14] It was shown that the activation/deactivation parameters of the RAFT agents can ary upon the protonation of functional groups in the structure of dithiocarbamates used as control agents. Using this effect, the polymerization of so-called "more activated monomers" and "less activated monomers" can be performed in a controlled manner with the same initiator/controlling agent. This opens a facile route to the preparation of block co-polymers. Marx et al.[15] used *N-tert*-butyl-*N*-[(1-(2-pyridyl)-2-methyl)-propyl] nitroxide (pyridyl-modified TIPNO) for the polymerization of styrene and acrylates and noted that alkoxyamines with the protonable groups could be of interest for NMP. To describe their unexpected results of polymerization, Mazarin et al.[16] proposed that the protonation of the nitroxides moiety can decrease k_d value dramatically. However, no experimental evidence of the effect of protonation on k_d value was provided.

In this paper we extended the concept of pH-switchable mediators to NMP by employing nitroxides with basic or acidic groups as controlling agents. It is known[17] that the variation of k_d and k_c values can significantly affect the polymerization. It was shown that the values of k_d and k_c strongly depend on the structure of substituents.[18,19] The presence of electron-withdrawing groups in the structure of nitroxyl fragment results in the increase of the activation energy of alkoxyamine homolysis and, therefore, in the decrease of the homolysis rate constant k_d.[18,20] The reversible protonation of functional groups in alkoxyamine changes the polarity of the nitroxyl or alkyl moieties of the alkoxyamine. Thus, it is expected that the value of k_d should be pH-dependent. The dependence of k_d on the protonation of alkyl moiety of alkoxyamine was recently observed by Bremond et al.[21] One can also expect the changes of k_c due to the reversible protonation of functional groups in nitroxide.

Variation of pH causes strong changes in the EPR spectra of imidazoline nitroxides[22] due to the proximity of the basic center at the nitrogen atom N3 (Chart 1) of the heterocycle to the nitroxide group. Introduction of yet another basic center into the side chain can further increase the effect of pH on EPR spectra due to the consecutive protonation of basic groups.[23,24] One could expect that the cross-coupling rate constants k_c for these nitroxides and k_d for corresponding alkoxyamines with several basic groups would also demonstrate the strongest dependence on pH, with the multistep "switching" (variation) upon pH changes. This may permit the regulation of the parameters for the various polymerization processes via pH variation.

The efficiency of imidazoline nitroxides as polymerization mediators for acrylates and styrene has recently been demonstrated.[25−28] The controlled polymerization of methyl

Chart 1. Structures of Compounds under Investigation

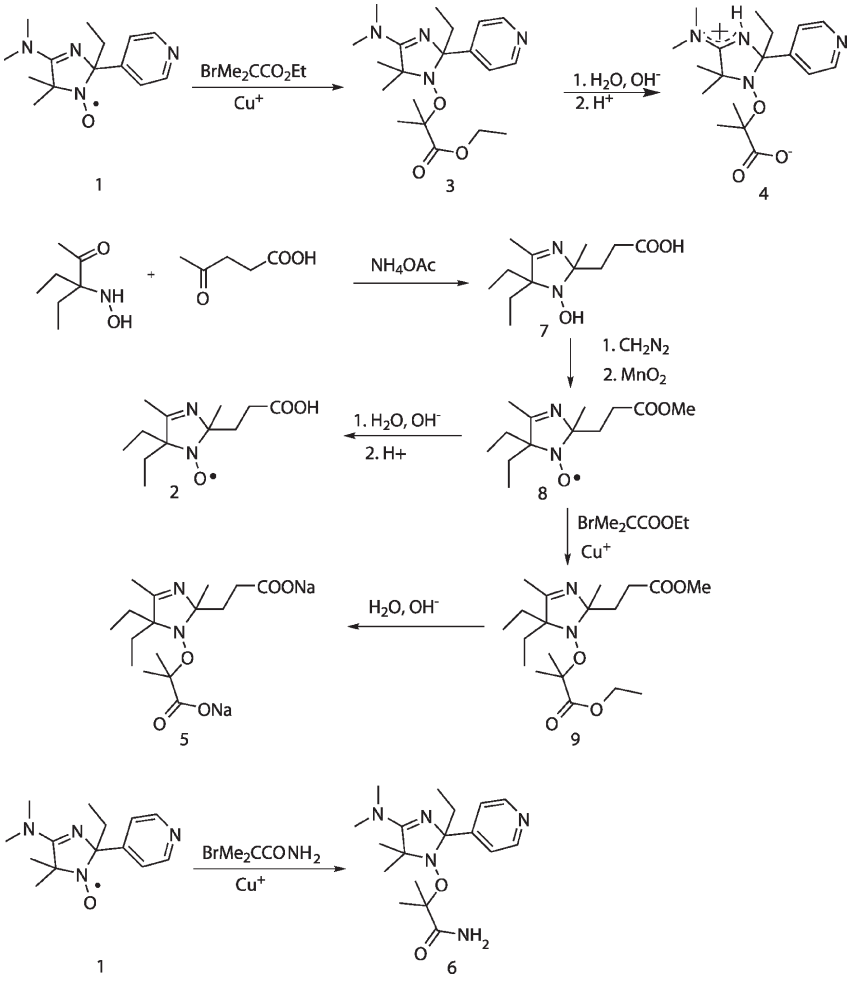


methacrylate (MMA) up to moderate conversion was performed in the presence of imidazoline-based alkoxyamine; however, the polymerization was not living due to the instability of the mediator.[29] Since imidazoline nitroxides are water-soluble, they could be used as mediators of NMP of hydrophilic monomers. In most cases, the polymerization of hydrophilic monomers by controlled techniques requires the chemical protection of functional groups,[30] and the polymerization temperature has to exceed the water boiling point.[31] Only recently, the development of new types of nitroxides made it possible to conduct NMP in aqueous solutions at temperatures as low as 85−95 °C.[32,33]

In this work, we present the first study of the effect of pH on the rate constants k_d and k_c and the first example of the application of this effect to the polymerization of water-soluble monomers. Four alkoxyamines, the derivatives of 2-(4-(dimethylamino)-2-ethyl-5,5-dimethyl-2-(pyridin-4-yl)-2,5-dihydro-1*H*-imidazol-1-oxyl (**1**) and 2-(2-carboxyethyl)-5,5-diethyl-2,4-dimethyl-2,5-dihydro-1*H*-imidazol-1-oxyl (**2**) were synthesized. The pH-dependent reversible protonation of basic functional groups of alkoxyamines **3**−**6** and nitroxide **2** was studied using NMR and EPR, correspondingly. The homolysis rate constants for alkoxyamines **3**−**6** (Chart 1) based on nitroxides **1** and **2** and the rate constants k_c for the nitroxides **1** and **2** recombination with different alkyl radicals were measured at different pH values. We have demonstrated that the pH regulation of the controlled regime of polymerization is possible using different types of hydrophilic monomers in aqueous solution at 90 °C. It is also shown that the pH variation can be used for controlling the polymer chain length.

dx.doi.org/10.1021/jo200341m |*J. Org. Chem.* 2011, 76, 5558–5573

Scheme 2. Reaction Scheme for Alkoxyamines Preparation



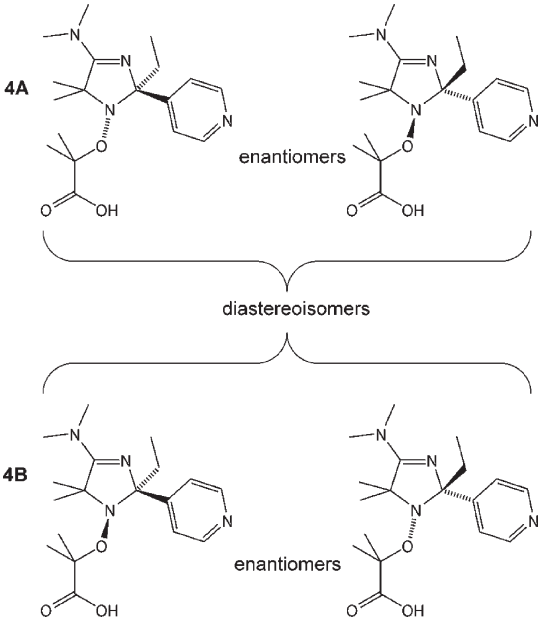
RESULTS AND DISCUSSION

Nitroxides and Alkoxyamines Synthesis. The alkoxyamines **3**, **4**, **5**, and **6** and the nitroxide **2** were prepared according to Scheme 2. It should be noted that the alkoxyamines **3** and **9** coordinate copper ions, and therefore the solutions of **3** obtained using the standard Matyjaszewski's procedure were dark-green due to the copper complexes. The complexes were stable in chromatography columns, so the treatment with diethylene triamine pentaacetic acid (DTPA) was needed to remove copper and to prepare the pure samples of **3** and **9**. The following alkali hydrolysis yielded the alkoxyamines **4** and **5**.

NMR spectra of the alkoxyamines **3**, **4**, **5**, and **6** show a double set of signals implying formation of a mixture of two isomeric forms; the transition between these forms is slow in the NMR time scale. The ratio of the isomers was solvent-dependent. The observed phenomena are accounted for by slow inversion at the N1 atom of the heterocycle.[34−37] Asymmetric centers at C2 and N1 produce two diastereomers (Chart 2), which, however, cannot be separated chromatographically due to the relatively high inversion rate. Similar effect was observed earlier for some alkoxyamines of imidazoline and imidazolidine series.[27,29]

Acid−Base Equilibria in the Solutions of Nitroxides 1 and 2 and Alkoxyamines 4−6. The EPR spectrum of **1** is known to

Chart 2. Two Diastereomers with Asymmetric Centers at C2 and N1



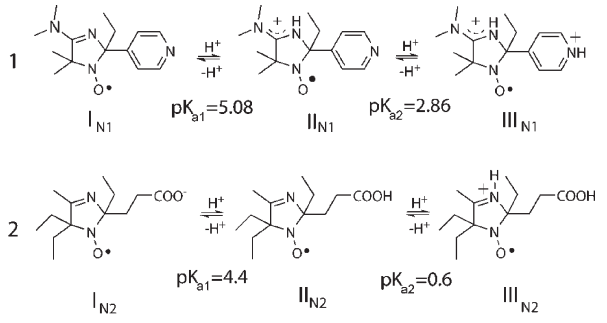
dx.doi.org/10.1021/jo200341m |J. Org. Chem. 2011, 76, 5558–5573

be sensitive to the protonation, showing a gradual increase of the observed hyperfine constant from 1.396 to 1.530 mT upon pH changes from 1 to 7.5. Analysis of the titration curve reveals two pK_a values of 5.08 and 2.86, assigned to the protonation of amidine and pyridine groups, respectively (Scheme 3).[25] pK_a values of nitroxide **2** were obtained using the experimentally measured dependence of EPR spectra on pH shown in Figure 1. Analysis of the titration curve was performed in the same way as in ref 23 using two pK_a values of 0.6 and 4.4, assigned to the protonation of amidine and carboxylate groups, respectively (Scheme 3).

NMR spectra of the alkoxyamines **4**, **5**, and **6** in D_2O also demonstrate pH dependence (see Figure 2, Scheme 4, Table 1SI in Supporting Information). The observed changes are in agreement with the equilibria shown in Scheme 4. The exchange between different protonated/deprotonated forms is fast in the NMR time scale and produces narrow or moderately broadened signals at the averaged position in the NMR spectrum. The signals of diastereomers **4A** and **4B** are clearly resolved. This allows for the monitoring of pH-associated changes for each isomer separately.

At pH 12.5 the deprotonated form I of alkoxyamine **4** is observed in the NMR spectrum. The increase of the pH value does not lead to the spectral changes. When the solution was acidified to pH = 7 the chemical shift of the Me protons in amidine group (signal *b* in figure 1 a) changed from 2.8 ppm up to 3.1 ppm.

Scheme 3. Protonation of Functional Groups in Nitroxides 1 and 2



This indicates the protonation of amidine group. In this case the form II is predominant. The value of pK_a obtained from the titration curve is 9.8. Decrease of the pH value from 7 to 4 leads to the protonation of pyridine ring and subsequent changes in the chemical shift of *c* and *c*′ signal. The value of pK_a assigned to the protonation of pyridine group is 5.25. The analysis of signals in the aliphatic zone is complicated due to the presence of 8 different diastereoisomeric forms of alkoxyamine **4**, and therefore no titration curve was built for the signals in this zone. It should be noted that the carboxylate group of alkoxyamine **4** is protonated at pH close to 3.8 for alkoxyamine **5** (see below). Thus, the form IV is predominant at this pH range.

The titration curves for alkoxyamine **6** are similar. The values of pK_a assigned to the protonation of amidine and pyridine groups were found to be 8.0 and 5.0, respectively (Figure 2e and f).

Similar analysis was carried out for the titration curves of alkoxyamines **5**. The value of pK_a for protonation of imidazoline ring was found to be 5.7 (curve b on figure 2 d). The signal of methyl groups isobutyric moiety undergoes downfield shift upon protonation of adjacent carboxylate group (pK_a = 3.7, curve a in Figure 2d). Signal d is affected by the protonation of the imidazoline ring and carboxylic group, and therefore the titration curve exhibits two values of pK_a values (curve d in Figure 2d)

Homolysis Rate Constant k_d. The observed homolysis rates of the alkoxyamines **3**, **4**, **5**, and **6** are pH-dependent (Figure3, Table 1) in a good agreement with the expected consequences of the consecutive protonation of their basic groups. The pH-associated changes in the k_d values are observed for both polar (water) and nonpolar (chlorobenzene) solvents, and therefore the effect cannot be attributed to the variation of the polarity of the reaction medium. It should be noted that the addition of acid has no effect on the value of k_d for TEMPO-based alkoxyamines in organic media.[20] However, DFT calculation performed by Mazarin et al.[16] showed that the protonation of alkoxyamine nitrogen may result in the increase of the activation barrier for C−O bond cleavage. Presumably, that protonation does not take place within the pH region used in the present study.

Figure 3 shows the kinetics of homolysis of **4** in aqueous solution at different pH and in chlorobenzene in the presence or absence of acid. Alkoxyamine **4** shows much higher homolysis rate constants k_d at pH 8.7 when deprotonated form is predominant:

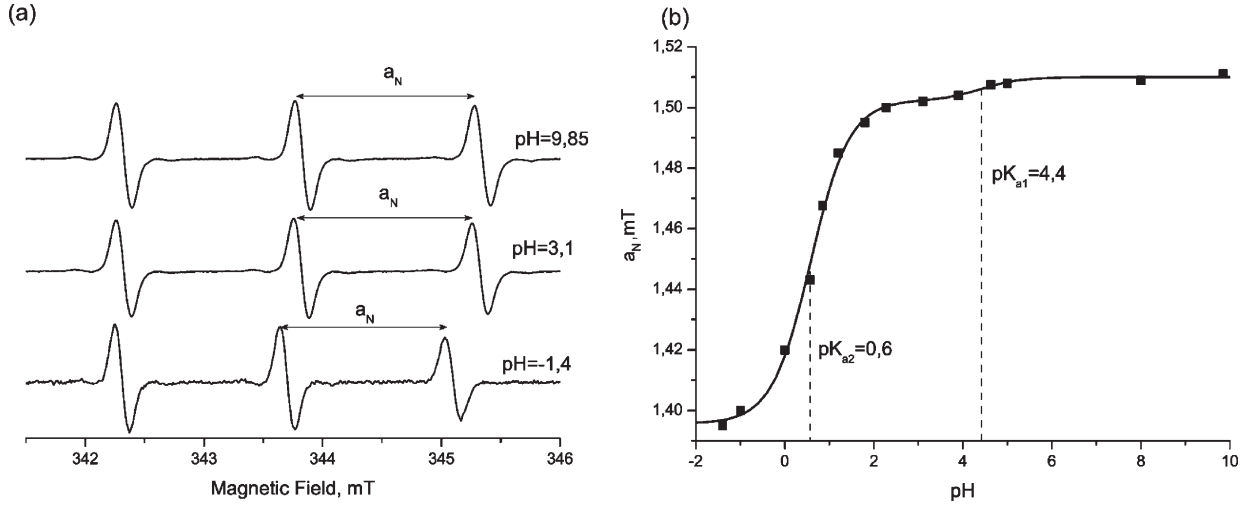


Figure 1. (a) EPR spectra of nitroxide **2** obtained at different pH values (room temperature, 10^{-4} M nitroxide aqueous solution); a_N (pH −1.4) = 1.395, a_N (pH 3.1) = 1.502; a_N (pH 9.85) = 1.51 (b) pH-dependence of nitrogen hyperfine constant for nitroxide **2** (titration curve).

dx.doi.org/10.1021/jo200341m |*J. Org. Chem.* 2011, 76, 5558–5573

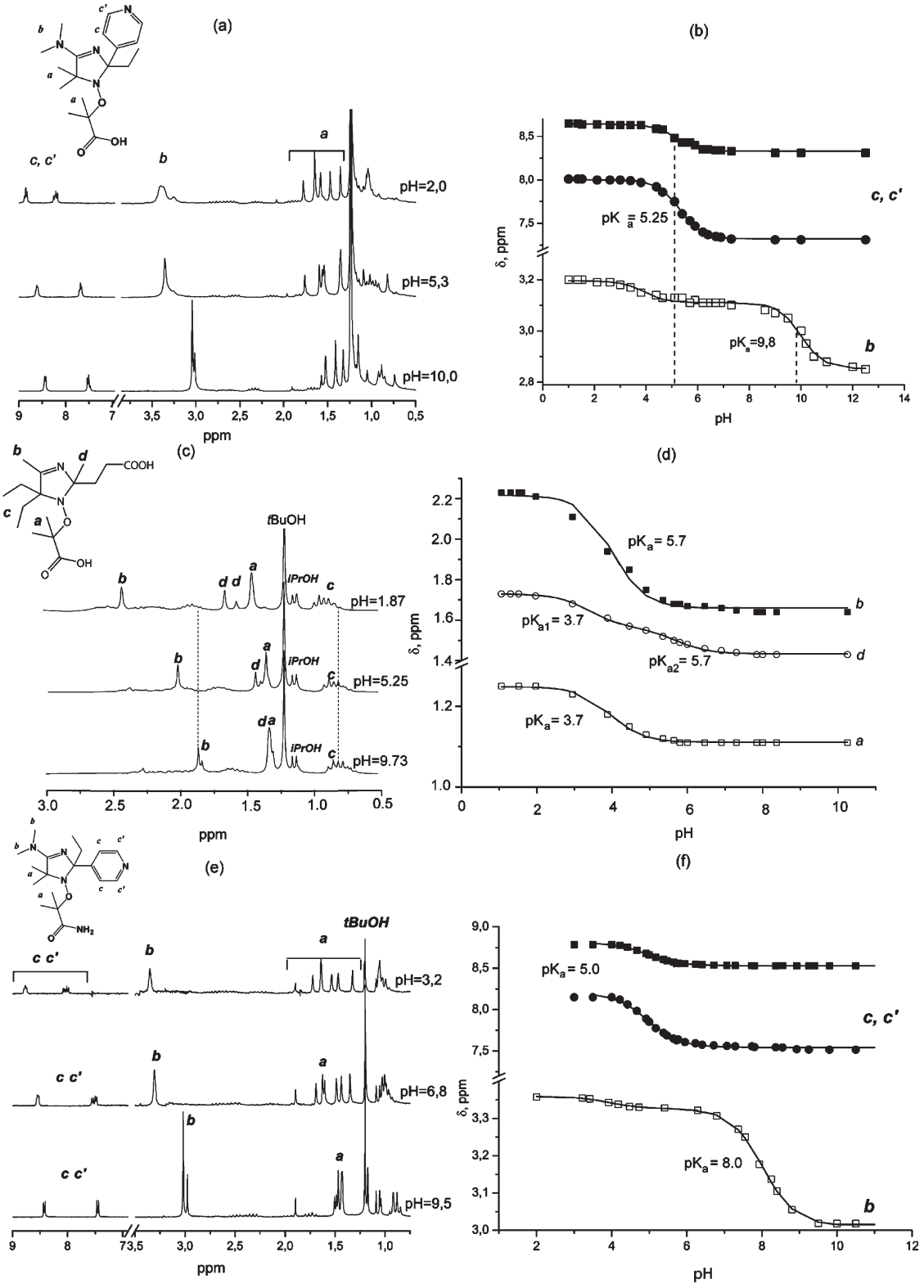


Figure 2. pH dependence of the ^{1}H NMR spectra of alkoxyamines **4**, **5**, and **6** (left side) and titration curves (right side) of alkoxyamines **4**, **5**, and **6** obtained for 0.02 M alkoxyamine solutions in D_2O at room temperature. *t*BuOH signal was used as reference.

at the same temperature, the k_d value at acidic pH is 15-fold lower than that for basic medium (Table 1). Table 1 summarizes the results of the k_d measurements for alkoxyamines **3**−**6** in media of different acidity. For comparison, the activation energy of homolysis E_a was estimated using the averaged frequency factor $A = 2.4 \times 10^{14}$ s^{-1} (Table 1).[38] One can see that all alkoxyamines exhibit pH-dependence of the observed values of k_d. Indeed, k_d measurements at pH = 11 in water, when the form I of the

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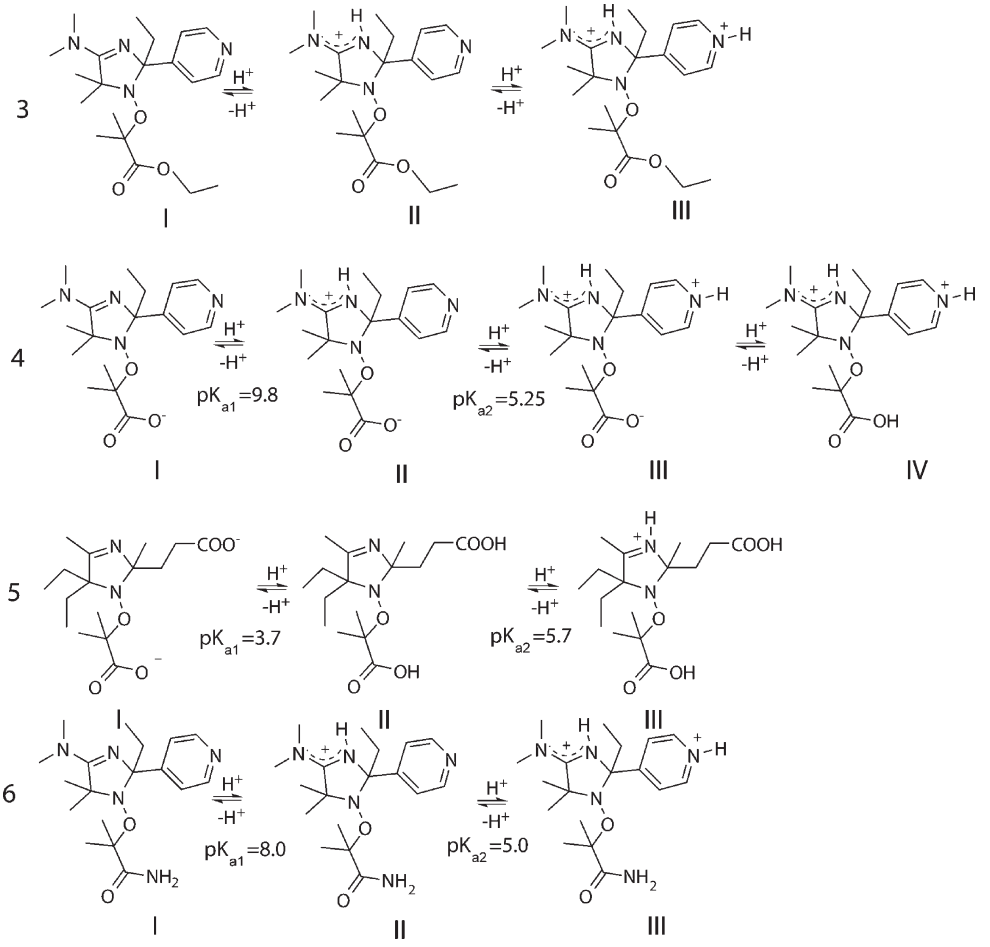
Scheme 4. Forms of Alkoxyamines 3−6 at Different pH



alkoxyamine **4** is predominant, give the highest k_d values. Acidification to pH = 8.7 leads to a decrease in k_d value due to the predominance of form II. In pure chlorobenzene solution alkoxyamine **4** is expected to be in the form II, which is confirmed by the close values of k_d observed in water at pH = 8.7 and in pure chlorobenzene solution. The addition of 1 or 2 equiv of CF_3COOH to the solution of **4** in chlorobenzene gives similar results, indicating that the acidity of the media may lead to the protonation of amidine, while the pyridine nitrogen presumably remains deprotonated (form III). The addition of 4 mM concentration of CF_3COOH leads to further decrease in k_d value, which is obviously caused by alkoxyamine dication (form IV) predominance (Figure 3b, Table 1). The protonation of the nitroxide fragment results in the decrease of k_d by a factor four: namely such effect was observed for **3** and **6** (Table 1), for which the protonation of the nitroxide fragment is unambiguous. A 15-fold effect is observed for **4**, but that likely involves synergetic effect due to the protonation of both alkyl and nitroxide fragments. It should be mentioned that in the organic solution pure alkoxyamine **4** exists in the zwitterionic form, which is indicated by good agreement between the values of k_d for pure **4** in C_6D_5Cl and **4** in water at pH = 8.7.

It is known that diastereomers may exhibit the same or different k_d values.[39] In our experiments, the integration of several NMR lines corresponding to different diastereomers was used to determine the k_d values. The difference observed for different diastereomers was within the range of the experimental error at all pH values.

According to the literature data, the values of the rate constant k_d are usually similar for alkoxyamines based on carboxylic acid and carboxylate alkyl fragment[40] unless the case hyperconjugation effect takes place. Since protonation of carboxylic and pyridine groups occurs at the close pH values, the hyperconjugation effect cannot be separated clearly from the electron withdrawing effect.

A similar difference in k_d values for the protonated and deprotonated forms was observed for alkoxyamine **5** and **6**. Unlike **4**, alkoxyamines **5** and **6** are poorly soluble in benzene. Therefore the k_d values were measured for aqueous solutions only. In basic solution alkoxyamines **5** and **6** showed larger k_d than in acidic media, demonstrating the same trend as for alkoxyamines **3** and **4**. It should be mentioned that the values of k_d for the protonated/deprotonated forms of **6** are at least 10 times smaller than those for alkoxyamine **4**, indicating the influence of the amide residue on the homolysis of C−O bound. Note, that the possible protonation of NH_2 group should be excluded as it would increase the value of k_d as observed by Bremond et al.[21]

Recombination Rate Constant k_c. The rate constants k_c of the radical cross-coupling were measured by LFP method. Alkyl radicals were generated by photolysis of the corresponding symmetric ketones, and their decay was monitored at the absorption maximum of 315 nm.[41] In the absence of nitroxides,

dx.doi.org/10.1021/jo200341m |*J. Org. Chem.* 2011, 76, 5558–5573

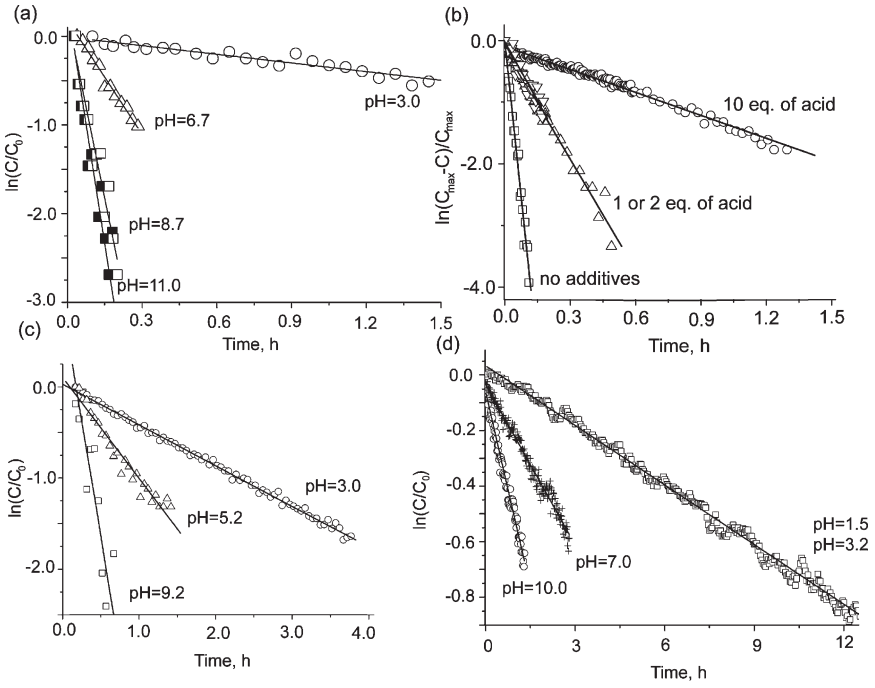


Figure 3. Kinetics of homolysis of alkoxyamine **4** (a), alkoxyamine **5** (c), and alkoxyamine **6** (d) in D_2O (0.02 M solution) at 368 K measured by ^1H NMR in the presence of 40 equiv of ascorbic acid/ascorbate at different pH. Kinetics of homolysis of alkoxyamine **4** (b) in chlorobenzene (10^{-4} M solution) at 373 K measured by ESR in the presence of oxygen as a scavenger. Experimental conditions are presented in the figure.

Table 1. Observed Dissociation Rate Constants k_d and Evaluated Activation Energies of Dissociation E_a for Alkoxyamines 3−6[a]

alkox	method	predominant form	solvent	conditions	T, K	k_d, 10^4 s^{-1}	$E_a \pm 0.5$, kJ mol^{-1}
3	EPR	III	C_6H_5Cl	4×10^{-3} M of CF_3COOH	373	7.2 ± 0.3	125.0
		II		10^{-3} M of CF_3COOH	373	10 ± 0.1	124.0
		I		pure solution	373	27 ± 3	121.0
		I		treated with NaOH	373	30 ± 3	120.5
	NMR	III	D_2O/CD_3OD = 1:1	pH = 3.0	363	0.5 ± 0.05	129.0
		II		pH = 6.7	363	3.0 ± 0.5	124.0
		I		pH = 8.7	363	5.0 ± 0.5	123.0
4	EPR	IV	C_6H_5Cl	4×10^{-3} M of CF_3COOH	373	3.4 ± 0.1	127.4
		III		C_6H_5Cl, 10^{-4} M of CF_3COOH	373	17 ± 1	122.0
		III		C_6H_5Cl, 2×10^{-4} M of CF_3COOH	373	18 ± 1	122.0
		II		C_6H_5Cl, pure	373	43 ± 5	119.5
		II		C_6H_5Cl, treated with NaOH	373	52 ± 3	119.0
	NMR	IV		pH = 3.0	368	26 ± 0.1	126.5
		III		pH = 6.7	368	12 ± 0.5	121.8
		II		pH = 8.7	368	35 ± 2	118.5
		I		pH = 11	368	45 ± 2	117.8
	NMR	III		pH = 3.0	368	1.2 ± 0.2	128.9
		II		pH = 5.2	368	4.2 ± 0.2	125.0
		I		pH = 9.5	368	14 ± 0.5	121.4
6	NMR	IV	D_2O	pH = 1.5	363	0.2 ± 0.02	132.5
				pH = 3.2	363	0.2 ± 0.02	132.5
		II		pH = 7.0	363	0.55 ± 0.01	129.5
		I		pH = 10.0	363	1.3 ± 0.1	126.0

[a] Concentration of alkoxyamine was 20 mM for NMR experiments and 1 mM in EPR experiments.

the carbon-centered radicals decay in the reactions of dimerization and disproportionation by second-order kinetics with the parameter $k_t/\varepsilon = 7 \times 10^6$ cm s^{-1} for methyl propionyl radical (MP) and $k_t/\varepsilon = 6 \times 10^6$ cm s^{-1} for *t*-Bu-isobutiryl radical (*t*BiB), where ε is the extinction coefficient of the corresponding alkyl radicals. In the presence of nitroxides, the decay becomes

dx.doi.org/10.1021/jo200341m |*J. Org. Chem.* 2011, 76, 5558–5573

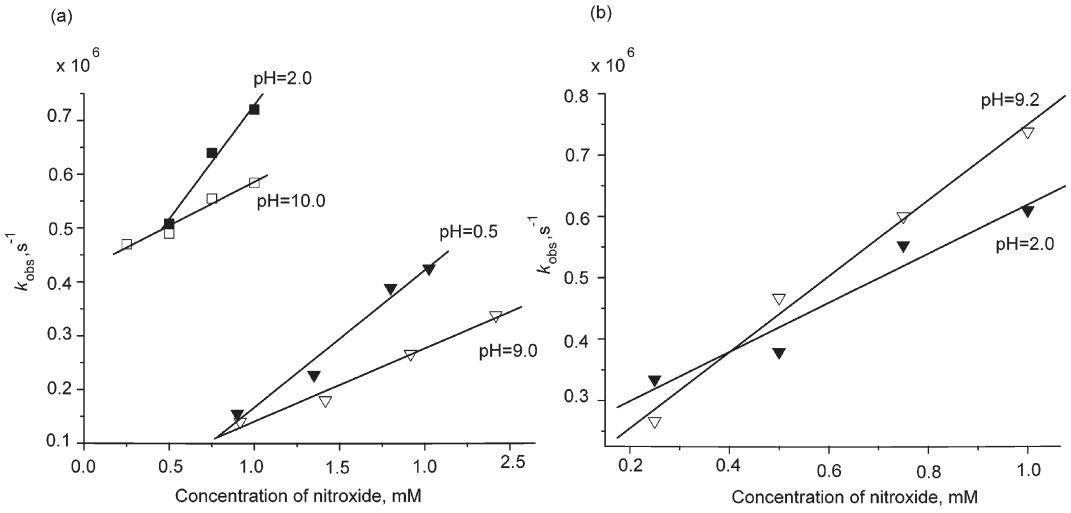


Figure 4. Dependence of the pseudo-first-order decay rate constant k_{obs} of alkyl radicals *t*BiB (a) and MP (b) on the concentration of nitroxides **1** and **2** at room temperature, observed during the photolysis of PEST and MEST ketones. Acetonitrile/water mixture (1:1): (▼) **1** in completely protonated form III; (▽) **1** in deprotonated form I; (■) **2** in completely protonated form III; (□) **2** in deprotonated form I.

Table 2. pH Dependencies of the Rate Constant k_c of Cross-Coupling of Nitroxides 1 and 2 with MP and *t*BiB Alkyl Radicals

		entry	k_c, 10^8 M^{-1} c^{-1}	pH
1$^{\bullet}$	MP$^{\bullet}$	1	5.3 ± 2	2
		2	9.3 ± 3	9.2
	tBiB$^{\bullet}$	3	4.2 ± 0.7	2
		4	1.6 ± 0.4	10
2$^{\bullet}$	tBiB$^{\bullet}$	5	2.6 ± 0.4	0.5
		6	1.4 ± 0.3	9

exponential, the observed pseudo-first-order rate constant k_{obs} is proportional to the nitroxide concentration $k_{obs} = k_0 + k_c[NO^{\bullet}]$ (Figure 4).

It was shown that the values of cross-coupling rate for constants of different nitroxides k_c are markedly below the diffusion-controlled limit of about 5×10^9 M^{-1} s^{-1} and only slightly depend on temperature, showing very small, or even negative, activation energy.[19,42] In general, radical coupling reactions exhibit very low (below 10 kJ mol^{-1}) E_a values. Therefore, the variations of k_c with T are weak. This indicates the entropy control of the reaction, i.e., the hindered approach of the alkyl radical to the oxygen-centered radical. Thus, the measurements of k_c were performed at room temperature, and k_c values at T ≈ 90−100 °C were assumed to be approximately the same.

The values of k_c were obtained for the nitroxyl radicals **1** and **2** at different pH (Table 2, Figure 3). It should be noted that the absolute values of k_c are close to the ones reported for such types of nitroxides, i.e., $1.0-8.0 \times 10^8$ M^{-1} s^{-1}.[19] Figure 4 and Table 2 demonstrate that the values of k_c for the protonated forms of nitroxides **1** and **2** and tBiB$^{\bullet}$ are approximately two times larger than for the deprotonated forms. Thus, the observed influence of protonation on k_c is not large, and it is opposite to that on k_d. The exception is the case of nitroxide **1** and MP$^{\bullet}$ alkyl radical, where the value of k_c for the protonated state is slightly lower than for the deproponated state, but it should be mentioned that in this case the values of k_c are close to diffusion limit, which causes large experimental error. It was previously shown[44,43] that k_c is influenced by the same effects as k_d, i.e., stabilization, steric, and polar effects, and they are expected to be anticorrelated to those observed for k_d. The effect of polar group on k_c was previously clearly observed for the several nitroxides, but the difference in k_c values due to the polar effect is not large.[44] Thus, the observed results are in a good agreement with our expectations based on the literature data and the structural changes in nitroxides upon protonation.

Thermal Stability of Nitroxides. The thermal instability of a nitroxide mediator can sometimes destroy the controlled regime of polymerization.[29] The presence of acid in the reaction medium can favor the decomposition of nitroxides.[45] Thus, the thermal stability of nitroxides **1** and **2** at different pH (in acidic and basic media) has to be verified. The measurements were performed for 10^{-4} M degassed solutions of nitroxides **1** and **2** in chlorobenzene in the presence of 1−20 equiv of CF_3COOH or excess of base. The EPR signals of nitroxides were monitored at 363 K for 3−6 h. No changes in the intensities of EPR signals were observed, so one can conclude that the imidazoline nitroxides **1** and **2** are sufficiently stable under acidic and basic conditions.

Polymerization. Taking into account the values of alkoxyamine homolysis rate constants k_d and of nitroxide and alkyl radical recombination rate constants k_c, one can predict the controlled and "living" regimes of polymerization of particular monomer using a Fischer diagram.[46] Figure 5 shows the diagram for the polymerization of styrene (Sty) at 140 °C and acrylamide (AAm) at 90 °C. Since the reactivities of monomers and polymers differ, the values of the rate constants k_d and k_c measured for monomers in the Fisher diagram need to be adjusted. Typically, the activation energy of homolysis for imidazoline-based alkoxyamines with the isobutyrate alkyl fragment is by 5 kJ mol^{-1} smaller than that with the ethylbenzyl fragment.[27] The value of k_c measured for the recombination of **1** and *t*BiB alkyl radical was divided by 30 in agreement with the literature data.[47] Since the chain length effect for styrene was found to be negligible,[48−50] the rate constants k_d(Sty) and k_c(Sty) were used without further adjustment. In the construction of Fischer's diagram for acrylamide the values of k_c for alkoxyamine **6** and the values for nitroxide **1** and MP alkyl radical recombination were taken. To take into account the chain length

dx.doi.org/10.1021/jo200341m |*J. Org. Chem.* 2011, 76, 5558–5573

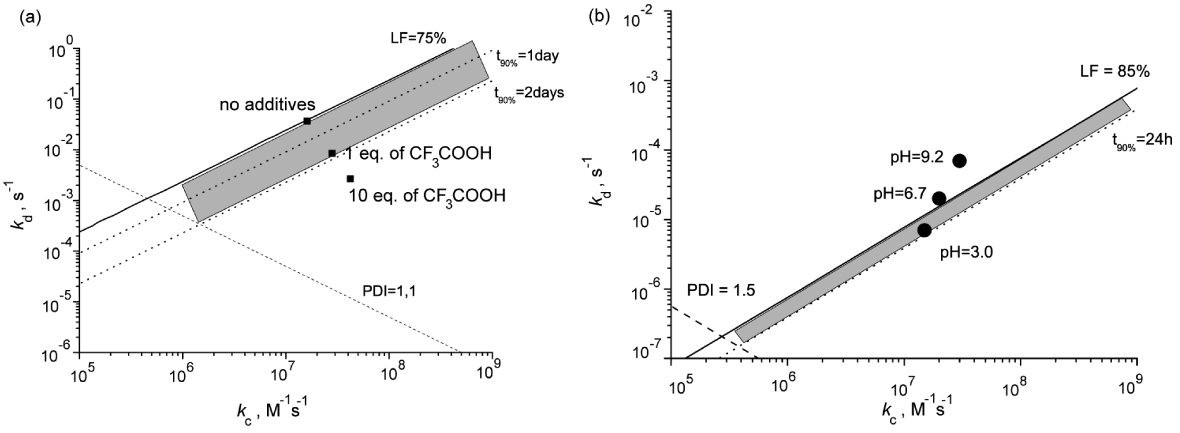


Figure 5. Fischer diagrams[46] for the polymerization of monomers (a) Sty at 140 °C controlled by nitroxides I (with the correction of rate constants), the monomer to initiator ratio is 1000/1, $k_p = 10^3\ M^{-1}\ s^{-1}$, $k_t = 1.7\ 0 \times 10^8\ M^{-1}\ s^{-1}$;[54] (b) AAm at 90 °C controlled by nitroxides **1**:, the monomer to initiator ratio is 1000/1, $k_p = 6.6 \times 10^3\ M^{-1}\ s^{-1}$, $k_t = 1.6 \times 10^8\ M^{-1}\ s^{-1}$.[55] The gray region corresponds to the controlled and "living" polymerization. In both diagrams polymerization time corresponds to 90% of conversion.

and the penultimate unit effect on the values of k_d and k_c, it was assumed that in the pAAm alkyl chain the value of k_d is 2 time greater[51] and the value of k_c is 10 times smaller[52] than it was measured for the alkyl radical, as observed with TEMPO-based macro-alkoxyamines. Since there is no literature data on the chain length and penultimate effect for AAm polymerization, the Fischer's diagram can be used for the qualitative evaluation of the influence of protonation on polymerization.

Two main challenges were addressed in these experiments: (i) polymerization temperature below 100 °C for the polymerization in aqueous media and (ii) relatively high molecular weight of the final polymer ($\sim 10^5$ g mol^{-1} at high monomer conversion). These two factors shrink the controlled region in the Fischer's diagram making the achievement of the controlled regime rather complicated.

Figure 5a shows that one can expect the controlled polymerization of Sty mediated by forms I_{N1} and II_{N1} (Scheme 3) of the nitroxide **1**. The Sty polymerization mediated by the protonated form III_{N1} (Scheme 3) of the nitroxide **1** is expected to be slow. Figure 5b shows that the polymerization of AAm mediated by the nitroxide **1** in the protonated form III_{N1} should be controlled and living, while the polymerization mediated by the nitroxide **1** in the deprotonated form I_{N1} is too slow and, consequently, not controlled.

Figure 6 and Table 2SI in Supporting Information demonstrated the result of the Sty polymerization initiated by the different forms of alkoxyamine **4**. As it is expected from the Fischer diagram analysis the polymerization of Sty initiated by the form II of alkoxyamine **4** proceeds faster than initiated by form IV (Figure 6b). In all cases the polymerization of Sty is controlled: the linear increase of M_n with conversion is observed and the PDI values for the polymers obtained are low (Figure 6b, Table 2SI in Supporting Information). In the presence of acid the polymerization proceeds slower since the homolysis of macroalkoxyamine based on the protonated form of nitroxide **1** is slow. Slow monomer conversion can be also attributed to the suppression of self-initiation process of Sty in the presence of acid as reported by Buzanowski et al.[53] Slow dissociation of the protonated form of macroalkoxyamine during polymerization of Sty under acidic conditions results in the slight increase of PDI to 1.6 (Figure 6, Table 2SI, entry 3).

Figure 7a demonstrates the plot of molecular weight versus conversion for the polymerization of AAm initiated by the alkoxyamine **4** at acidic pH in aqueous solution T = 90 °C at the monomer to initiator ration 1000/1 (see also Table 3, entry 1). The polymerization of AAm was stopped at high monomer conversions (50−70%) because the reaction mixture became viscous. The M_n versus conversion plot is linear, which indicates that the number of propagating radicals remains constant. The final molecular weight $M_n = 3.4\ 0 \times 10^4$ g mol^{-1} (relative to PEO standards) is in good agreement with the theoretical value $M_{n,th} = 3.9 \times 10^4$ g mol^{-1}. The final dispersity index is 1.16, which is far below the theoretical limit for the noncontrolled radical polymerization. This means that the polymerization of AAm initiated by alkoxyamine **4** under acidic conditions proceeds in the controlled mode. It should be mentioned that the polymerization of AAm performed under basic conditions for 4 h does not result in the monomer conversion (Table 3, entry 2).

The same influence of pH on the polymerization of AAm was observed for different monomer/initiator ratios. At acidic pH, controlled regime of polymerization was observed, that led to lower PDI value and high monomer conversion (Figure 7a and c, Table 3 entries 1, 3, 4). The controlled regime of AAm polymerization at acidic pH can occur for several reasons. First, Fischer's diagram predicts controlled regime of polymerization only in acidic medium. Second, this might be due to some unexpected effect of pH on the intra- and intermolecular H-transfer reaction occurring with alkoxyamine. The influence of pH on the intra- and intermolecular H-transfer reaction in alkoxyamines is the topic of future investigations.

The polymerization of sodium 4-vinylbenzenesulfonate (SS) initiated by the alkoxyamines **4** and **5** was also performed at different pH with the same monomer to initiator ratio and temperature. The polymerization of SS in aqueous solution at 90 °C at pH = 9.2 (Table 3, entry 8, Figure 8b) in the presence of alkoxyamine **4** with monomer to initiator ratio 1000/1 was characterized by a linear growth of molecular weight and decrease of dispersity with conversion. After 1 h, the monomer conversion stopped with the final value of 40%. The polymer obtained has the dispersity index 1.75. Thus, it can be concluded

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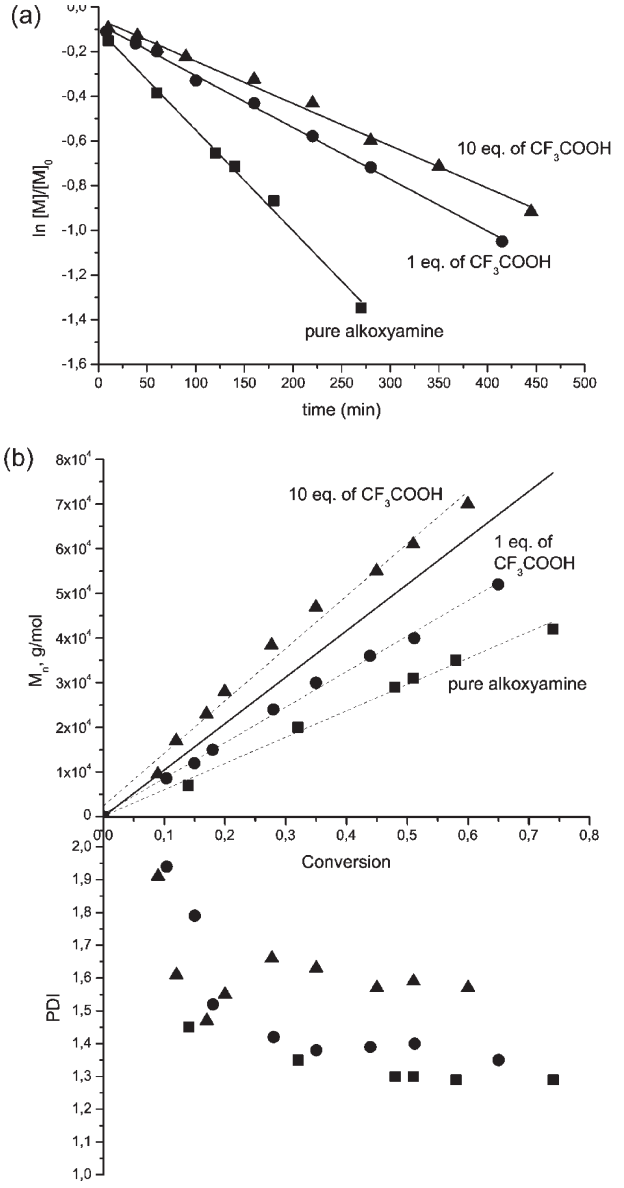

Figure 6. Polymerization of Sty at 140 °C initiated by protonated/deprotonated forms of alkoxyamine **4** and controlled by nitroxides **1**. Monomer to initiator ratio is 1000/1. (a) Kinetics plot for polymerization; lines represent linear fit of the experimental data points. (b) Evolution of molecular weight and dispersity. (■) pure alkoxyamine, form II; (●) alkoxyamine in the presence of 1 equiv of CF_3COOH, form III; (▲) alkoxyamine in the presence of 10 equiv of CF_3COOH, form IV. Solid line shows the theoretical M_n, dashed lines represent linear fit of the experimental data points.

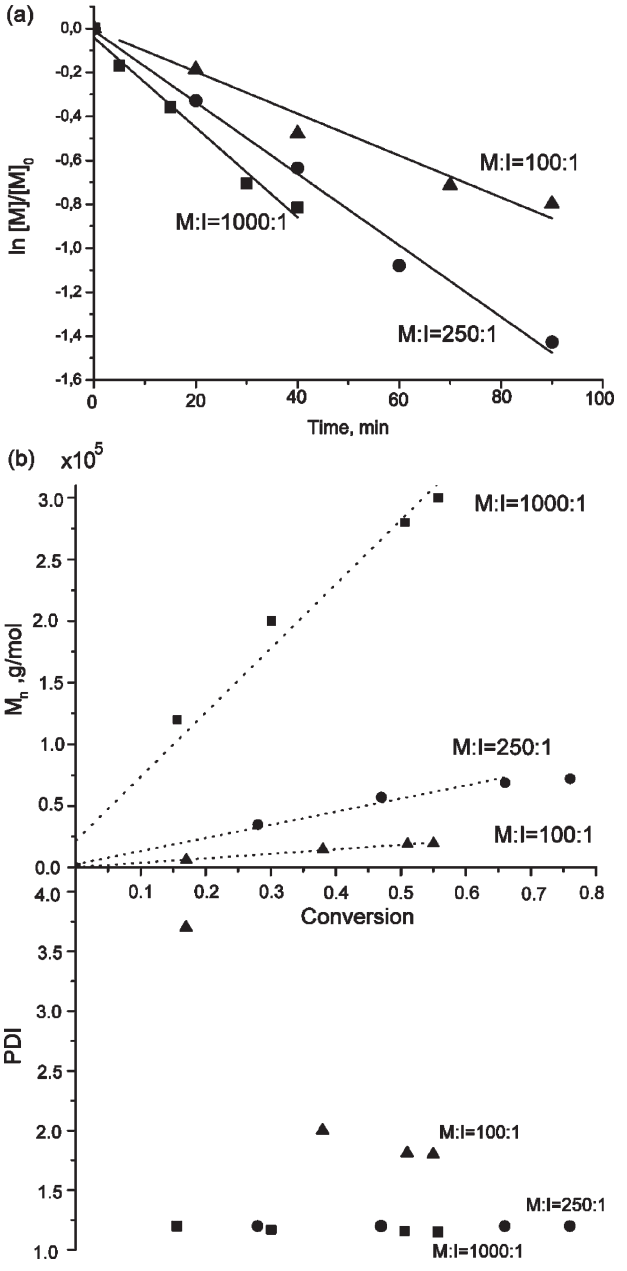

Figure 7. (a) Kinetics of acrylamide polymerization at T = 90 °C initiated by the alkoxyamine **4** and controlled by the nitroxide **1** in form III at pH = 3.0 with different monomer to initiator ratio (M:I), lines represent linear fit of the experimental data points. (b) Evolution of molecular weight and dispersity. Dotted line is the linear fit of the experimental data points.

that the conditions of polymerization were not optimal. In the case of the monomer to initiator ratio equal to 500/1, higher conversion (65%) and lower PDI (1.32) were observed (Table 3, entry 12). When the polymerization of SS was carried out at pH = 7.3 and the monomer to initiator ratio 1000/1 (Table 3, entry 10, Figure 8b), 70% of monomer conversion was reached in 3 h. A linear growth of molecular weight was observed up to ca. 50% of the monomer conversion. Later on, the rate of the molecular weight growth decreases, which can probably be attributed to the viscosity increase. Nevertheless, the final dispersity index of the polymer obtained was 1.15, which is far below the theoretical limit of 1.5 for the controlled radical polymerization. This demonstrates that the acceptable conditions for the controlled regime of polymerization were achieved. It should be noted that the self-initiation process for SS at 90 °C is negligible and cannot affect the kinetics of polymerization.

The results obtained can be compared with the data reported by Phan et al.[32] and Nicolay et al.[33] The authors of these works described NMP of SS up to 63% of conversion and low dispersity, but the molecular weights of the polymer were smaller. Under acidic conditions, the evolution of M_n with

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Table 3. Experimental Conditions and Characteristics of the Polymers Obtained for the Polymerization of Hydrophilic Monomers at 90 °C Initiated by Alkoxyamines in Different Forms

entry	initiator	monomer	M:I	pH	conversion %	PDI	M_n[a] 10^{-5} g mol^{-1}	$M_{n,th}$ 10^{-5} g mol^{-1}
1	4	AAm	1000/1	3.2	55.7	1.16	0.34	0.40
2	4	AAm	1000/1	9.9	0			
3	4	AAm	250/1	3.0	76.0	1.20	0.72	0.8
4	4	AAm	100/1	3.0	55.0	1.80	0.21	0.20
5	5	AAm	1000/1	5.2	0			
6	5	AAm	1000/1	2.7	20.0	4.0	2.0	0.14
7	5	AAm	500/1	6.5				
8	4	SS	1000/1	9.2	40.0	1.75	1.5	0.82
9	4	SS	1000/1	6.7	51.7	1.2	1.2	1.07
10	4	SS	1000/1	7.3	70.0	1.15	1.37	1.40
11	4	SS	1000/1	3.0	80.0	1.2	2.0	1.70
12	4	SS	500/1	10.1	65	1.32	1.0	0.70
13	5	SS	1000/1	6.3	35	1.80	1.1	0.72
14	5	SS	1000/1	2.5	35	1.60	4.3	0.72

[a] Relative to PEO standards.

conversion is linear for the polymerization of SS initiated by the alkoxyamine **4** (Table 3, entry 11, Figure 6b), though the molecular weight of the polymer is slightly higher than the calculated values. The polymerization was controlled up to 80% of the monomer conversion with the low dispersity of the polymer obtained.

The livingness of the polymer was verified by reinitiation experiments. Poly-Sty obtained in the experiments 1−3 (Table 3SI in Supporting Information) was precipitated in cold methanol and used for the polymerization of new portion of Sty. In all cases the increase of molecular weight and the absence of macroinitiator traces were observed by means of GPC indicating the living character of the polymerization (Figure 9). Figure 9a presents the results of the reinitiation test for poly-Sty obtained with the form II of alkoxyamine **4** (Table 2SI in Supporting Information, entry 1). The traces of the low molecular weight poly-Sty observed in GPC can probably be due to the self-initiation process at 140 °C. In the presence of acid self-initiation of polymerization of styrene is suppressed,[53] and thus the low molecular weight peak is absent in Figure 9b. The analysis of experimental results taking into account three contributions (polymer formed from macroinitiator, dead polymer chains and low molecular weight polymers determined by self-initiation of styrene) allows us to evaluate the fraction of living chains to be larger than 85%. Thus, a higher molecular weight than expected (Figure 8b) could be explained by some loss of living ends.

The poly-(SS) obtained by the polymerization in the presence of alkoxyamine **4** under neutral conditions at 70% of conversion (Table 3, entry 10) was precipitated in cold methanol, dried in vacuum, and used as a high molecular weight initiator for the polymerization of AAm. Acidic conditions and temperature 90 °C were chosen for the polymerization of AAm. Under these conditions, 69% of AAm conversion were achieved with the final molecular weight $M_n = 4.3 \times 10^5$ g mol^{-1} and dispersity 1.24. No traces of poly-(SS) were observed in the final reaction mixture. This indicates that the polymerization of SS in the presence of alkoxyamine **4** is living. The evaluated fraction of the living chain was higher than 95%. The GPC traces obtained for macroinitiator and co-polymer are presented in Figure 9.

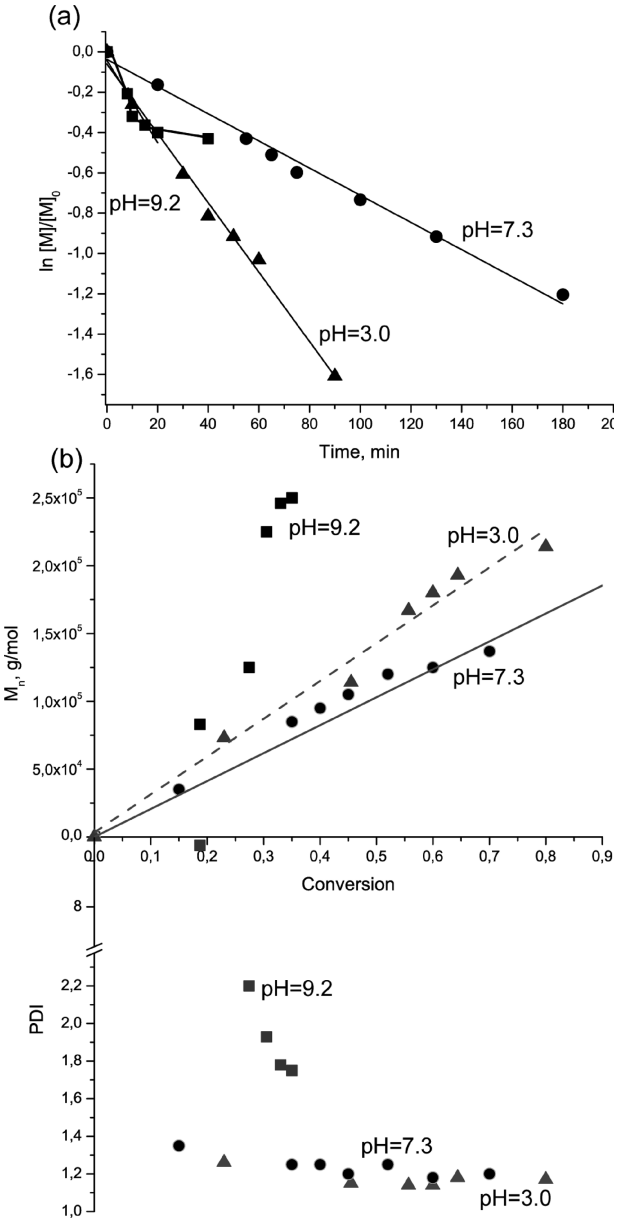

Figure 8. (a) Kinetics of 4-vinylbenzenesulfonate polymerization at 90 °C initiated by the different forms of alkoxyamine **4** and controlled by the nitroxide **I**, monomer to initiator ratio 1000/1, at pH = 9.2 (■, form I of nitroxide **1**), pH = 7.3 (●, form II of nitroxide **1**), and pH = 3.0 (▲, form III of nitroxide **1**), lines represent linear fit of the experimental data points. (b) Evolution of molecular weight and dispersity. Solid line shows the theoretical M_n, dotted line is the linear fit of the experimental data points.

The polymerization of both AAm and SS initiated by alkoxyamine **5** and controlled by nitroxides **1** in acidic, basic or neutral media was not successful (Table 3, entries 5−7 and 13, 14, Figure 2SI in Supporting Information). Polymerization of AAm was uncontrolled giving low monomer conversion (~20%) with high dispersity index of the polymer obtained. In the polymerization of SS initiated by alkoxyamine **5**, the molecular weights deviated from the calculated values, the dispersity index was above 1.5, and only low monomer conversions could be achieved. The M_n versus conversion and PDI versus conversion plots are presented as Supporting Information.

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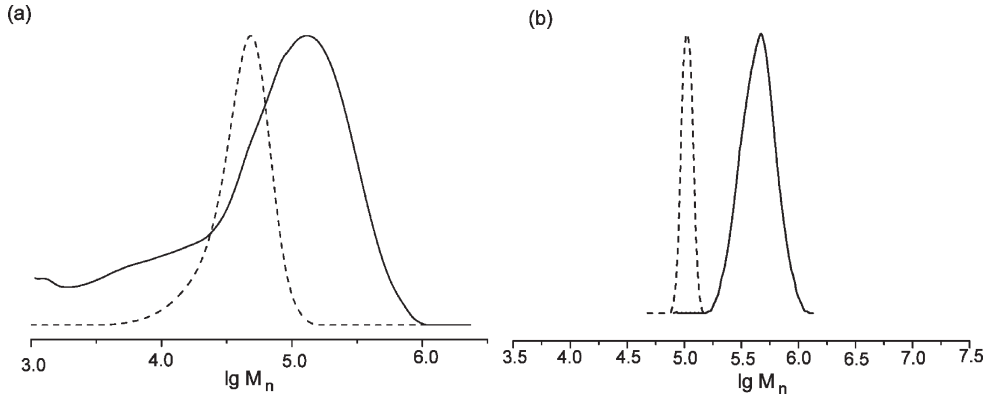

Figure 9. Normalized GPC traces of (a) poly-Sty (entry 1, Table 2SI in Supporting Information) (dashed line) and poly-SS obtained in reinitiation experiment (solid line); (b) poly-(SS) (entry 10, Table 3) (dashed line) and poly-(SS)-*b*-poly-(AAm) (after reinitiation experiment) (solid line).

CONCLUSION

Imidazoline alkoxyamines with functional groups containing multiple ionizable centers were synthesized to quantify the influence of reversible protonation on the dissociation rate constant k_d and on the cross-coupling rate constants of nitroxide and alkyl radicals k_c. Using the polymerization of three representative monomers (styrene, alcrylamide, and styrene sulfonate) mediated by nitroxides with protonable groups, we have clearly demonstrated that the pH value crucially affects the polymerization regime, changing it from the controlled to the uncontrolled mode. In the case of the controlled radical polymerization, the pH dependence of the polymer length chain was observed.

It is shown that the pH-induced switching of k_d and k_c opens an easy and convenient way for the preparation of block co-polymers via NMP since it allows the achievement of controlled regime of polymerization for different monomers at the same temperatures and monomer to initiator ratios. Note that alkoxyamine **4** is well-soluble in organic solvents and water, which makes the polymerization of different types of hydrophobic/hydrophilic monomers possible. The controlled polymerization of acrylamide and 4-styrenesulphonate initiated by **4** was observed in water. The polymerization of Sty initiated by different forms of **4** was controlled and living, affording different rates of polymerization and lengths of polymer chain depending on protonation. Successful preparation of SS-AAm block co-polymers in the controlled and living fashion in aqueous solutions requires different parameters of polymerization at different stages of the process, which cannot be achieved with the use of conventional nitroxides such as TEMPO, TIPNO, and SG1. However, the use of alkoxyamines with pH-switchable proton made it possible: the SS polymer was prepared at pH 7 (form II of **4**), and the polymerization of AAm block was performed at pH 3 (form IV of **4**). The polymerization proceeded in a controlled manner, and the polymers obtained were "living" making the preparation of block co-polymers possible. Thus, for the first time the concept of pH-switchable alkoxyamines was successfully applied to the controlled polymerization of hydrophobic and hydrophilic monomers in aqueous solutions at temperatures below 100 °C to obtain high molecular weight polymers and block co-polymer.

EXPERIMENTAL SECTION

Alkoxyamines and Nitroxides Synthesis. The IR spectra were recorded in KBr pellets (the concentration was 0.25%, the pellet thickness was 1 mm). The ^{1}H and ^{13}C NMR spectra were recorded for 5−10% solutions using the signal of the solvent as a standard (400.134 MHz for ^{1}H and 100.624 MHz for ^{13}C). All chemicals were used as received. The nitroxide **1** was prepared according to the previously published procedures.[25]

To confirm the NMR peak assignments of alkoxyamines **3**−**7**, **9** we used ^{1}H NMR, ^{13}C NMR J-mod spectrum and COSY 45, 200 MHz for ^{1}H. ^{1}H and ^{13}C NMR spectra of compounds **3**−**5**, **9**. ^{1}H NMR spectra of alkoxyamine **3**, **4**, **6**, **7**, **9** were recorded in $CDCl_3$; ^{1}H NMR spectrum of alkoxyamine **5** was recorded in $CDCl_3/CD_3OD$; ^{13}C NMR J-mod spectra of alkoxyamines **3**, **4**, **6**, **7**, **9** were recorded in $CDCl_3$; ^{13}C NMR J-mod spectrum of alkoxyamine **5** was recorded in $CDCl_3/CD_3OD$; COSY 45 NMR spectra of alkoxyamines **4**, **5** were recorded in D_2O; COSY 45 NMR spectrum of alkoxyamine **6** was recorded in DMSO-d_6.

2-(2-Carboxyethyl)-5,5-diethyl-2,4-dimethyl-2,5-dihydro-1*H*-imidazol-1-oxyl (2). Prepared from 3-ethyl-3-hydroxyaminopentan-2-one[56] according to Scheme 2 (see Results).

3-(5,5-Diethyl-1-hydroxy-2,4-dimethyl-2,5-dihydro-1*H*-imidazol-2-yl)propanoic Acid (7). Suspension of 3-ethyl-3-hydroxyaminopentan-2-one hydrochloride (1.00 g, 5.5 mmol), levulinic acid (2.00 g, 17 mmol), and ammonium acetate (2.00 g, 26 mmol) in methanol (5 mL) was bubbled with argon and then stirred under argon for 4 days. Reaction mixture was diluted 5-fold with brine and extracted with chloroform (10 mL × 3 times). The combined extract was washed with brine and dried with $MgSO_4$. Chloroform was removed under reduced pressure. The residue was triturated with ether/hexane mixture 1:1. The precipitate was filtered off and recrystallized from ethyl acetate/hexane mixture 1:1 to yield 0.92 g (70%) of **7** as colorless crystals, mp 179−183 °C (hexane/ethylacetate 1:1). Found: C, 59.42; H, 9.15; N, 11.32; calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. IR (KBr), ν, cm^{-1}: 3187 (br), 2926 (br), 1706, 1654, 1462 (br), 1375, 1303, 1263, 1220, 1169, 1144, 1107, 1038, 946 (br), 888. ^{1}H NMR δ 400 MHz ($CDCl_3$, CD_3OD)/ppm: 0.62 and 0.67 both 3H t, J = 7 Hz (2 × CH_3, Et-C), 1.08 3H s (C^2-CH_3), 1.27 and 1.76 both 1H ABt, J_{AB} = 15 Hz J_t 7 Hz (C^2-CH_2), 1.42 1H m and 1.50 3H m (2 × CH_2, Et-C), 1.64 3H s (C^4-CH_3), 2.03 and 2.11 both 1H ABt, J_{AB} = 15 Hz J_t 7 Hz (CH_2-CO). ^{13}C NMR δ 100 MHz ($CDCl_3$, CD_3OD)/ppm: 7.46 and 9.15 (CH_3, Et-C), 15.88 (CH_3, C4-Me), 21.08 (CH_3, C^2-Me), 24.47 (CH_2, CH_2CO), 28.05 and 28.69 (CH_2, Et-C), 35.48 (CH_2, C^2-CH_2), 77.63 (C^5), 90.00 (C^2), 175.94 (COOH), 176.80 (C=N).

5,5-Diethyl-2,4-dimethyl-2-(2-methoxycarbonylethyl)-2,5-dihydro-1*H*-imidazol-1-oxyl (8). The crystalline powder of **7** (0.9 g, 3.7 mmol) was added portionwise to 0.1 M solution (100 mL) of diazomethane in ether. The suspension was stirred until a homogeneous

dx.doi.org/10.1021/jo200341m |*J. Org. Chem.* 2011, 76, 5558–5573

solution was obtained and kept for 16 h. Then manganese dioxide (2,0 g, 23 mmol) was added and the suspension was stirred vigorously for 1 h. The precipitate of manganese oxides was filtered off, and the filtrate was evaporated under reduced pressure. The residue was separated via column chromatography on silicagel, eluent chloroform/hexane (1:1), to yield 0.8 g (85%) **8** as orange oil. Found: C, 61.42; H, 9.08; N, 10.82; calced for $C_{13}H_{23}N_2O_3$: C, 61.15; H, 9.08; N, 10.97. IR (neat), ν, cm^{-1}: 2967, 2879, 1739, 1638, 1458, 1437, 1380, 1290, 1197, 1175, 1073, 990, 879, 845, 785, 747.

2-(2-Carboxyethyl)-5,5-diethyl-2,4-dimethyl-2,5-dihydro-1*H*-imidazol-1-oxyl (2). Aqueous solution of NaOH 20% (1.0 mL) was added to the solution of nitroxide **2** (200 mg, 0.78 mmol) in ethanol (0.5 mL) and the reaction mixture was kept for 6 h at +20 °C. Ethanol was evaporated under reduced pressure, then water (3 mL) and diethyl ether (5 mL) were added. The mixture was acidified to pH 3 with $NaHSO_4$ upon stirring, organic layer was separated and dried with Na_2SO_4. Ether was evaporated under reduced pressure and the residue was recrystallized from ethylacetate/hexane mixture 1: 2 to give **2** as yellow crystals, mp 147−148 °C. Found: C, 59.51; H, 8.63; N, 11.61; calcd for $C_{12}H_{21}N_2O_3$: C, 59.73; H, 8.77; N, 11.61. IR (KBr), ν, cm^{-1}: 3426 (br), 2971, 2934, 2884, 2746, 2680, 2539 (br), 1719, 1641, 1454, 1423, 1388, 1296, 1200, 1160, 1111, 1033, 947, 888.

Ethyl 2-(4-(Dimethylamino)-2-ethyl-5,5-dimethyl-2-(pyridin-4-yl)-2,5-dihydro-1*H*-imidazol-1-yloxy)-2-methylpropanoate (3). Prepared according to Matyjaszewski's method.[57] A mixture of 2-(4-(dimethylamino)-2-ethyl-5,5-dimethyl-2-(pyridin-4-yl)-2,5-dihydro-1*H*-imidazol-1-oxyl (**1**)[25] (300 mg, 1.15 mmol), 2-bromo-2-methylpropionic acid ethyl ester (300 mg, 1.54 mmol), Cu powder (350 mg, 5.52 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (12 mg, 0.045 mmol), $Cu(OTf)_2$ (12 mg, 0.033 mmol), and benzene (5 mL) was placed in a Schlenk flask and degassed by three freeze−pump−thaw cycles. The solution was stirred for 5 h at 60 °C. The benzene was removed under reduced pressure, the residue was treated with ethyl acetate, and the inorganic precipitate was filtered off. The solution was carefully washed with basified 10% solution of diethylene triamine pentaacetic acid (DTPA) potassium salt (pH 8) in water to remove copper and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was separated using column chromatography on silicagel, eluent chloroform, to yield **3** (346 mg, 80%) as colorless crystals, mp 67−70 °C (hexane). Found: C, 64.21; H, 8.57; N, 15.03. Calcd for $C_{20}H_{32}N_4O_3$: C, 63.80; H, 8.57; N, 14.88. IR (KBr), ν, cm^{-1}: 3083, 2982, 2931, 2866, 1728, 1606, 1593, 1466, 1447, 1409, 1399, 1379, 1364, 1291, 1228, 1176, 1145, 1107, 1071, 1029, 981, 910, 812, 652. ^{1}H NMR δ 400 MHz ($CDCl_3$), isomer A (60%) 0.83 3H t, J = 7 Hz (CH_3, Et-C), 1.08, 1.31, 1.37, and 1.53 each 3H s ((CH_3)$_2$C-N and (CH_3)$_2$C-O), 1.22 3H t, J = 7 Hz (CH_3, Et-O), 1.81 and 2.08 each 1H ABq, J_{AB} = 14 Hz J_q 7 Hz (CH_2, Et-C), 3.00 6H s ((CH_3)$_2$N), 4.09 2H m (CH_2, Et-O), 7.30 and 8.45 each 2H AA′BB′ (Py); isomer B (40%) 0.90 3H t, J = 7 Hz (CH_3, Et-C), 0.94, 1.22, 1.29, and 1.50 each 3H s ((CH_3)$_2$C-N and (CH_3)$_2$C-O), 1.20 3H t, J = 7 Hz (CH_3, Et-O), 1.85 and 2.38 each 1H ABq, J_{AB} = 14 Hz, J_q = 7 Hz (CH_2, Et-C), 2.95 6H s ((CH_3)$_2$N), 4.02 2H q, J = 7 Hz (CH_2, Et-O), 7.30 and 8.45 each 2H AA′BB′ (Py). ^{13}C NMR δ 100 MHz ($CDCl_3$), isomer A 7.94 (CH_3, Et-C), 13.87 (CH_3, Et-O), 19.11, 23.32, 26.21, and 27.03 ((CH_3)$_2$C-N and (CH_3)$_2$C-O), 31.76 (CH_2, Et-C), 38.75 (N-CH_3), 60.77 (OCH_2), 67.50 (CMe_2), 81.87 (O-CMe_2), 89.76 (N-C-N), 123.59 (C^3-Py), 148.38 (C^2-Py), 152.28 (C^4-Py), 168.11 (C═O), 174.21 (C═N); isomer B 9.19 (CH_3, Et-C), 13.87 (CH_3, Et-O), 20.60, 23.55, 25.28, and 27.81 ((CH_3)$_2$C-N and (CH_3)$_2$C-O), 27.52 (CH_2, Et-C), 38.93 (NCH_3), 60.66 (OCH_2), 68.65 (CMe_2), 81.50 (O-CMe_2), 91.39 (N-C-N), 122.41 (C^3-Py), 149.10 (C^2-Py), 155.21 (C^4-Py), 167.63 (C═O), 174.23 (C═N).

2-(4-(Dimethylamino)-2-ethyl-5,5-dimethyl-2-(pyridin-4-yl)-2,5-dihydroimidazol-1-yloxy)-2-methylpropanoic Acid (4). A solution of NaOH (0.25 g, 6.25 mmol) in water (2 mL) was added to the solution of alkoxyamine 3 (376 mg, 1 mmol) in ethanol, and the mixture was stirred for 2 h and left overnight. Then the solution was evaporated under reduced pressure. The residue was triturated with ethyl acetate (5 mL), and the solution was filtered and evaporated under reduced pressure. The residue was triturated with diethyl ether, and the precipitate was filtered off and dissolved in chloroform/CCl_4 1:1 mixture. Then diethyl ether was added dropwise with stirring. The crystalline precipitate was filtered off and washed with dry diethyl ether to give **4** (300 mg, 63%, zwitterionic form, crystalline solvate with chloroform) as colorless crystals, mp 86−89. Found: C, 48.40; H, 6.18; N, 12.00, Cl 22.57. Calcd for $C_{18}H_{28}N_4O_3 \cdot CHCl_3$: C, 48.78; H, 6.25; N, 11.98, Cl, 22.74. IR (KBr), ν, cm^{-1}: 3431 br, 2982, 2939, 2876, 1601 br, 1467, 1447, 1403, 1365, 1289, 1225, 1180, 1144, 1068, 1015, 815, 789, 910, 764. ^{1}H NMR δ 400 MHz ($CDCl_3$), isomer A (60%) 0.82 3H t, J = 7 Hz (CH_3, Et-C), 1.00 3H s, 1.32 6H s and 1.40 3H s ((CH_3)$_2$C-N and (CH_3)$_2$C-O), 1.77 and 2.11 each 1H ABq, J_{AB} = 14 Hz, J_q = 7 Hz (CH_2, Et-C), 2.99 6H s ((CH_3)$_2$N), 7.38 and 8.37 each 2H AA′BB′ (Py); isomer B (40%) 0.84 3H t, J = 7 Hz (CH_3, Et-C), 0.99, 1.03, 1.27and 1.44 each 3H s ((CH_3)$_2$C-N and (CH_3)$_2$C-O), 1.89 and 2.38 each 1H ABq, J_{AB} = 14 Hz, J_q = 7 Hz (CH_2, Et-C), 2.95 6H s ((CH_3)$_2$N), 7.33 and 8.37 each 2H AA′BB′ (Py). ^{13}C NMR δ 100 MHz ($CDCl_3$), isomer A 8.00 (CH_3, Et-C), 19.10, 24.49, 26.20, and 27.02 ((CH_3)$_2$C-N and (CH_3)$_2$C-O), 31.74 (CH_2, Et-C), 38.78 (N-CH_3), 67.31 (CMe_2), 82.80 (O-CMe_2), 89.25 (N-C-N), 124.05 (C^3-Py), 147.36 (C^2-Py), 153.71 (C^4-Py), 168.38 (C═O), 179.55 (C═N); isomer B 9.28 (CH_3, Et-C), 20.86, 24.90, 25.42, and 27.77 ((CH_3)$_2$C-N and (CH_3)$_2$C-O), 27.72 (CH_2, Et-C), 39.05 (NCH_3), 68.79 (CMe_2), 82.31 (O-CMe_2), 91.25 (N-C-N), 122.71 (C^3-Py), 148.09 (C^2-Py), 156.27 (C^4-Py), 167.89 (C═O), 179.78 (C═N).

Sodium 2-(2-(2-Carboxylatoethyl)-5,5-diethyl-2,4-dimethyl-2,5-dihydro-1*H*-imidazol-1-yloxy)-2-methylpropanoate (5). Synthesized from **8** via alkoxyamine **9** (Scheme 2) by analogy with compounds **3** and **4**.

Ethyl 2-(5,5-Diethyl-2-(2-methoxycarbonylethyl)-2,4-dimethyl-2,5-dihydro-1*H*-imidazol-1-yloxy)-2-methylpropanoate (9). The degassed mixture of **8**, 2-bromo-2-methylpropionic acid ethyl ester, Cu powder, 4,4′-di-*tert*-butyl-2,2′-bipyridine, Cu $(OTf)_2$, and benzene was stirred for 5 h at 40 °C. After processing the reaction mixture the residue was separated using column chromatography on silicagel, eluent chloroform, to give **9** in 72% yield as a colorless oil, a mixture of diastereomers. Found: C, 62.19; H, 9.27; N, 7.56; calcd for $C_{19}H_{34}N_2O_5$: C, 61.60; H, 9.25; N, 7.56. IR (neat), ν, cm^{-1}: 3455 (br), 2984, 2950, 2876, 1739 (br), 1667, 1451, 1437, 1378, 1285, 1231, 1174, 1145, 1102, 1027, 994, 953, 909, 887, 877, 838, 767, 685, 620, 596, 565. ^{1}H NMR δ 300 MHz ($CDCl_3$)/ppm: isomer A (70%): 0.71 and 0.79 both 3H t, J = 7 Hz (2 × CH_3, Et-C), 1.21 3H t, J = 7 Hz (CH_3, Et-O), 1.29 3H s (CH_3, C^2-Me), 1.32 6H s (2 × CH_3, OC(Me)$_2$), 1.08−1.58 3H m and 1.67−2.03 3H m (CH_2, Et-C, CH_2-C^2), 2.29 and 2.50 each 1H m (CH_2, CH_2-C═O), 3.56 3H s (CH_3, Me-O), 4.08 2H q, J = 7 Hz (CH_2−O); isomer B (30%): 0.65 and 0.80 both 3H t, J = 7 Hz (2 × CH_3, Et), 1.21 3H t, J = 7 Hz (CH_3, OEt), 1.31 3H s (CH_3, Et-O), 1.33 6H s (2 × CH_3, OC(Me)$_2$), 1.08−1.58 and 1.67−2.03 6H in all both m (CH_2, Et-C, CH_2-C^2), 2.10−2.27 and 2.36−2.58 each 1H m (CH_2, CH_2-C═O), 3.58 3H s (CH_3, Me-O), 4.06 2H q, J = 7 Hz (CH_2−O). ^{13}C NMR δ 75 MHz ($CDCl_3$)/ppm: isomer A: 9.14, 10.54 (CH_3, Et), 13.69 (CH_3, OEt), 16.62 (CH_3, Me-C═), 21.06 (CH_3, Me-C^2), 24.28 and 24.66 (CH_3, C(Me)$_2$CO), 27.19 and 29.12 (CH_2, Et), 30.02 (CH_2, CH_2-C═O), 37.47 (CH_2, CH_2-C^2), 51.12 (CH_3, Me-O), 60.59 (CH_2, OEt-O), 80.88 (C, C(Me)$_2$CO), 81.14 (C^5), 93.27 (C^2), 171.68 (C═N), 173.73 and 174.21 (COOMe, COOEt); isomer B: 8.85, 10.64 (CH_3, Et), 13.69 (CH_3, OEt), 16.42 (CH_3, Me-C═), 24.28 and 24.47 (CH_3, C(Me)$_2$CO), 26.14 (CH_3, Me-C^2), 27.14 and 29.37 (CH_2, Et), 30.29 (CH_2, CH_2-C═O), 31.84 (CH_2, CH_2-C^2), 51.15 (CH_3, Me-O), 60.50 (CH_2, Et-O), 81.04 (C, C(Me)$_2$CO), 81.84 (C^5), 93.21 (C^2), 171.32 (C═N), 173.67 and 174.35 (COOMe, COOEt).

dx.doi.org/10.1021/jo200341m |*J. Org. Chem.* 2011, 76, 5558–5573

Sodium 2-(2-(2-Carboxylatoethyl)-5,5-diethyl-2,4-dimethyl-2,5-dihydro-1*H*-imidazol-1-yloxy)-2-methylpropanoate (5). A solution of NaOH (0.5 g, 12.50 mmol) in water (10 mL) was added to the solution of alkoxyamine **9** (627 mg, 1.69 mmol) in ethanol (10 mL), and the reaction mixture was kept at 5 °C overnight. Then the mixture was evaporated under reduced pressure. The residue was diluted with isopropanol (15 mL) and bubbled with CO_2 to pH ~6. The solution was filtered and evaporated again. The residual glassy solid was triturated with diethyl ether, filtered off, and dried in vacuum to give **5** (567 mg, 90%) as a colorless powder. Found: C, 51.49; H, 7.10; N, 7.14; Na, 12.20; calcd for $C_{16}H_{26}N_2Na_2O_5$: C, 51.61; H, 7.04; N, 7.52; Na, 12.35. IR (KBr), ν, cm^{-1}: 3429 (br), 2969, 2943, 2879, 1702, 1662, 1581, 1456, 1398, 1378, 1358, 1301, 1230, 1187, 1154, 1104, 1009, 984, 951, 886, 833, 787, 685, 616, 596, 574, 487, 430. ^{1}H NMR δ 300 MHz ($CDCl_3$, CD_3OD)/ppm: isomer A (70%): 0.85 and 0.93 both 3H t, J = 7 Hz (2 × CH_3, Et), 1.36, 1.41, and 1.47 each 3H s (C^2-CH_3, $(CH_3)_2CO$), 1.52−1.69 3H m and 1.70−2.00 1H m (2 × CH_2, Et), 1.12−1.23, 2.03−2.16, 2.19−2.29 and 2.40−2.57 each 1H m (CH_2-CH_2), 1.88 3H s (CH_3-C═); isomer B (30%): 0.81 and 0.92 both 3H t, J = 7 Hz (2 × CH_3, Et-C), 1.37, 1.38, and 1.40 each 3H s (C^2-CH_3, $(CH_3)_2CO$), 1.70−2.00 4H m (2 × CH_2, Et), 1.12−1.23 1H, 2.03−2.16 1H and 2.40−2.57 2H each m (CH_2-CH_2), 1.87 3H s (CH_3-C═). ^{13}C NMR δ 75 MHz ($CDCl_3$, CD_3OD)/ppm: isomer A: 8.51 and 9.87 (CH_3, Et), 15.56 (CH_3, C^4-Me), 20.90 (CH_3, C^2-Me), 23.83 and 24.72 (CH_3, $OC(Me)_2$), 26.88 and 28.26 (CH_2, Et), 31.23 (CH_2, CH_2CO), 37.93 (CH_2, C^2-CH_2), 80.26 (C^5), 81.23 (C-O−N), 92.53 (C^2), 173.74 (C═N), 178.70 and 178.93 (COO); isomer B: 8.27 and 9.99 (CH_3, Et), 15.55 (CH_3, C^4-Me), 23.94 and 24.58 (CH_3, $OC(Me)_2$), 25.57 (CH_3, C^2-Me), 26.73 and 28.70 (CH_2, Et), 31.51 (CH_2, CH_2CO), 32.46 (CH_2, C^2-CH_2), 80.26 (C^5), 81.43 (C-O−N), 92.62 (C^2), 173.45 (C═N), 178.37 and 178.87 (COO).

2-((4-(Dimethylamino)-2-ethyl-5,5-dimethyl-2-(pyridin-4-yl)-2,5-dihydro-1*H*-imidazol-1-yl)oxy)-2-methylpropanamide (6). Prepared from the nitroxide **1** and 2-bromo-2-methylpropanamide in analogy to the described above procedure. The reaction mixture was diluted with 25% aqueous ammonia and extracted with diethyl ether. The solvent was removed under reduced pressure, and the residue was purified using column chromatography on silicagel, eluent $CHCl_3$/ethanol 25:2, to give 80% of **4** as colorless crystals, mp 154−156 °C (CCl_4). Found: C, 62.19; H, 8.18; N, 19.95. Calcd for $C_{18}H_{29}N_5O_2$: C, 62.22; H, 8.41; N, 20.16. IR (KBr), ν, cm^{-1}: 3312, 3181, 3044, 3019, 2974, 2928, 2876, 2795, 1686, 1593, 1472, 1423, 1407, 1380, 1356, 1288, 1232, 1146, 1113, 1069, 1018, 997, 910, 816, 652. ^{1}H NMR δ 400 MHz ($CDCl_3$), isomer A (60%) 0.90 3H t, J = 7 Hz (CH_3, Et-C), 1.17, 1.40 each 3H s and 1.50 6H s ($(CH_3)_2$C-N and $(CH_3)_2$C-O), 1.92 and 2.20 each 1H ABq, J_{AB} = 14 Hz, J_q = 7 Hz (CH_2, Et-C), 3.04 6H s ($(CH_3)_2$N), 7.27 and 8.49 each 2H AA′BB′ (Py); isomer B (40%) 0.95 3H t, J = 7 Hz (CH_3, Et-C), 0.94, 1.23, 1.42, and 1.45 each 3H s ($(CH_3)_2$C-N and $(CH_3)_2$C-O), 1.90 and 2.32 each 1H ABq, J_{AB} = 14 Hz, J_q = 7 Hz (CH_2, Et-C), 2.99 6H s ($(CH_3)_2$N), 7.27 and 8.49 each 2H AA′BB′ (Py). ^{13}C NMR δ 100 MHz ($CDCl_3$), isomer A 7.94 (CH_3, Et-C), 20.43, 25.26, 25,74 and 27.61 ($(CH_3)_2$C-N and $(CH_3)_2$C-O), 31.10 (CH_2, Et-C), 39.12 (N-CH_3), 68.29 (CMe_2), 82.69 (O-CMe_2), 91.72 (N-C-N), 123.19 (C^3-Py), 148.93 (C^2-Py), 152.47 (C^4-Py), 167.85 (C═O), 176.85 (C═N); isomer B 9.42 (CH_3, Et-C), 21.27, 25.03, 25.32, and 27.93 ($(CH_3)_2$C-N and $(CH_3)_2$C-O), 27.83 (CH_2, Et-C), 39.12 (NCH_3), 68.92 (CMe_2), 82.72 (O-CMe_2), 91.85 (N-C-N), 122.30 (C^3-Py), 149.20 (C^2-Py), 155.01 (C^4-Py), 167.17 (C═O), 177.55 (C═N).

Measurement of Homolysis Rate Constant k_d. Values of the homolysis rate constant k_d were determined either by monitoring the concentration of nitroxide by EPR (electron paramagnetic resonance) or by monitoring the concentration of alkoxyamine by ^{1}H NMR in the presence of nitroxyl radical scavenger/alkyl radical reducing agent during the heating of the corresponding alkoxyamines.

For EPR experiments, 10^{-4} M solutions of alkoxyamine in chlorobenzene were used. To prepare solutions of the corresponding basic forms, the solutions of **4** and **5** in chlorobenzene were stirred with powder of solid NaOH for 1 h. The excess of NaOH was filtered off, and the solution was used for measurements. Oxygen dissolved in chlorobenzene was used for scavenging alkyl radicals. The kinetic measurements of alkoxyamine dissociation were performed with the use of convenient EPR X band spectrometer equipped with a standard liquid nitrogen gas flow temperature controller. The growth of the nitroxyl radical concentration obeyed the first-order kinetic law. The concentration of the nitroxide after thermolysis was measured using 10^{-4} M standard solution of nitroxide **1** or **2** in chlorobenzene.

For NMR experiments, 0.02 M solution of alkoxyamine **3** or **4** in the presence of 0.4 M of ascorbic acid in D_2O was used. The pH was adjusted to basic values 8−13 with NaOD. The kinetics of alkoxyamines homolysis were monoexponential, the parameter k_d was obtained by the exponential fit of the experimental kinetic curve. The value of activation energy was evaluated with the average frequency factor A = 2.4 × 10^{14} s^{-1}.[38]

Measurements of Recombination Rate Constant k_c. The rate constants of recombination of alkyl and nitroxyl radicals were measured by Laser Flash Photolysis (LFP) technique. The detailed description of the LFP setup was published earlier.[58] Symmetric ketones di-*tert*-butyl 2,2,4,4-tetramethyl-3-oxopentanedioate (Pest) and dimethyl 2,4-dimethyl-3-oxopentanedioate (MEst) were synthesized according to standard procedures[59] and purified by column chromatography. The concentration of ketones was 36 mM, and the concentration of nitroxides varied from 0 to 2.5 mM. Solutions of ketones with or without nitroxides in a rectangular cell with the inner dimentions 10 mm ×10 mm were irradiated with a excimer 308 nm laser with pulse energy up to 100 mJ and pulse duration 15−20 ns. The monitoring system included a xenon short-arc lamp connected to a high current pulser, a homemade monochromator, a photomultiplier, and a digitizer. The monitoring light, concentrated in a rectangular of 3 mm height and 1 mm width, passed through the cell along the front of the irradiated window. Thus, in all experiments the excitation optical length was 1 mm, and the monitoring optical length was 8 mm. To obtain one kinetic trace, 15−20 signals were averaged. All solutions were bubbled with Ar for 15 min prior to and all the time during the experiments.

Polymerization. For polymerization of styrene initiated by alkoxyamine **4** (17 mg) was dissolved in 5 mL of distilled styrene. Argon was bubbled through the mixture for 15 min, and then the reaction mixture was placed into a preheated oil bath. Polymerization was performed at 140 °C. The temperature was kept constant within 1 °C. The samples of the polymerization mixture were taken by a syringe at different time intervals from the beginning of the reaction.

For polymerization of hydrophilic monomers initiated by alkoxyamine **4** or **5** (1.7 mg or 1 mg) and monomer (1 g) (sodium 4-vinylbenzenesulfonate or acrylamide) were dissolved in deionized water (4 mL) in a round-bottom flask. The pH value of the solution was adjusted by adding HCl or NaOH aqueous solutions. Argon was bubbled through the mixture for 15 min, and then the reaction mixture was placed into a preheated oil bath. Polymerization was performed at 90 °C. The temperature was kept constant within 1 °C. The samples of the polymerization mixture were taken by a syringe at different time intervals from the beginning of the reaction.

Sample Analysis. The conversion of monomer was determined by ^{1}H NMR using 50 μL samples of polymerization mixture in 550 μL of $CDCl_3$ or D_2O. The molecular weights (M_n) and polydispersities were measured by GPC using a PL-gel Mixed C column (styrene) or PL-aquagel−OH Mixed C column (hydrophilic polymers) and a refractive index detector. THF or water was used as eluent at the flow rate of 1 mL min^{-1}. Calibration was performed with PSt or PEO standards.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR data of alkoxyamine **4** in D_2O at different pH, δ 200 MHz, ppm; experimental conditions and characteristics of the polymers obtained for the polymerization of styrene at 140 °C initiated by alkoxyamine **4** in different forms; evolution of molecular weight and dispersity during polymerization of SS initiated by alkoxyamine **5** at different pH; ^{1}H and ^{13}C NMR spectra of compounds **3**−**5**, **9**; ^{1}H NMR spectra of alkoxyamines **3**, **4**, **6**, **7**, **9** recorded in $CDCl_3$; ^{1}H NMR spectrum of alkoxyamine **5** recorded in $CDCl_3/CD_3OD$; ^{13}C NMR J-mod spectra of alkoxyamines **3**, **4**, **6**, **7**, **9** recorded in $CDCl_3$; ^{13}C NMR J-mod spectrum of alkoxyamine **5** recorded in $CDCl_3/CD_3OD$; COSY 45 NMR spectra of alkoxyamine **4**, **5** recorded in D_2O; COSY 45 NMR spectrum of alkoxyamine **6** recorded in DMSO-d_6. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: elena@tomo.nsc.ru; masha@tomo.nsc.ru.

■ ACKNOWLEDGMENT

Russian Scientific School-7643.2010.3, Division of Chemistry and Material Science (5.1.1), Russian Federal Agency for Education (P1144) are kindly acknowledged for financial support.

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