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Factors Influencing C−ON Bond Homolysis in Alkoxyamines: Unexpected Behavior of SG1 (*N*-(2-methyl-2-propyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*N*-oxyl)-Based Alkoxyamines

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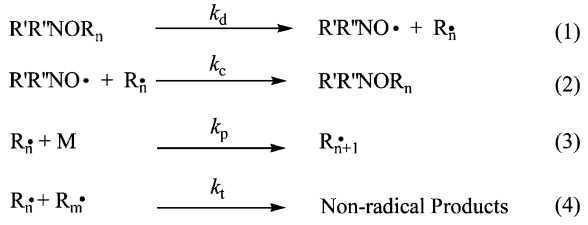
Alkoxyamines and persistent nitroxides are important regulators of nitroxide-mediated radical polymerization (NMP). Since the polymerization time decreases with the increasing equilibrium constant K (k_d/k_c), i.e., the increasing rate constant k_d of the homolysis of the C−ON bond between the polymer chain and the nitroxide moiety, the factors influencing the cleavage rate constants are of considerable interest. SG1-based alkoxyamines have turned out to be the most potent alkoxyamine family to use for NMP of various monomers. Therefore, it is of high interest to determine the factors which make SG1 derivatives better regulators than TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) derivatives. Contrary to what we had observed with TEMPO derivatives, we observed two relationships for the plot E_a vs BDE(C−H), one for the nonpolar released alkyl radicals (E_a (kJ/mol) = −133.0 + 0.72BDE) and the other one for the polar released alkyl radicals (E_a (kJ/mol) = −137.0 + 0.69BDE). However, for both families (SG1 and TEMPO derivatives), the rate constants k_d of the C−ON bond homolysis were correlated to the cleavage temperature T_c ($\log(k_d(s^{-1})) = 1.51 - 0.058T_c$). Such correlations should help to design new alkoxyamines to use as regulators and to improve the tuning of NMP experiments.

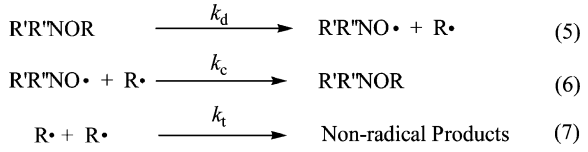
Introduction

Thanks to the seminal works of Rizzardo[1] and Georges,[2] it is now possible to obtain polymers with definite molecular weights and architectures as well as low polydispersity indices using the process called nitroxide-mediated radical polymerization (NMP).[3] Such free radical polymerization can be performed through the reversible deactivation of the growing polymeric radical by stable or persistent radicals such as nitroxyl radicals.[4] The easiest way to trigger the polymerization is to use thermally unstable alkoxyamines prepared beforehand (reaction 1 with $n = 0$). The growth of the polymeric radicals (reaction 3 with k_p the propagation rate constant) involves successive deactivation dissociation cycles (reactions 2 and 1 with k_c and k_d the deactivation and dissociation rate constants, respectively), which transform them into macroalkoxyamines (called dormant species), which are alternately reactivated into polymeric radicals by thermal homolysis. The self-termination reaction (reaction 4 with k_t the self-termination rate constant) is kept at a low level (Scheme 1).

SCHEME 1



SCHEME 2



Due to the persistent radical effect (PRE, Scheme 2),[5] the rate of polymerization in this type of system depends on the constant of equilibrium $K = k_d/k_c$, k_d being the C−ON bond homolysis rate constant and k_c the reformation rate constant. If K is too small, the polymerization can be very sluggish or even inhibited, while if K is too large, the polymerization is too rapid—the control is loosened—or a noncontrolled radical polymerization occurs.[6]

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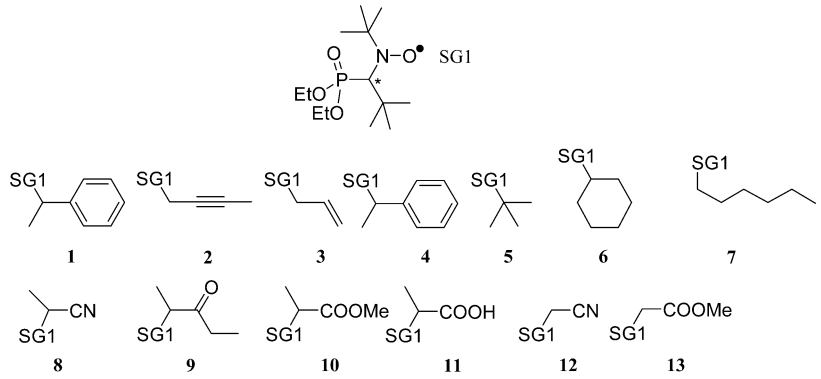
SCHEME 3



Fischer et al.[6,7a−e] and Fukuda et al.[7f−i] have shown that, for NMP to be efficient—short polymerization time, low polydispersity indices PDI, and high livingness—the equilibrium constant $K = k_d/k_c$ should vary roughly between 10^{-7} and 10^{-11} M and the product k_dk_c should be as large as possible to reach low PDI's. Therefore, k_d and k_c have to be in a narrow range, i.e., 10^{-3} s^{-1} < k_d < 1 s^{-1} and 10^6 L mol^{-1} s^{-1} < k_c < 10^9 L mol^{-1} s^{-1}. Since k_d and k_c depend on the alkoxyamine structure and k_c varies in general within a narrow range (10^5 to 10^9 L mol^{-1} s^{-1} from room temperature to 120 °C), while k_d varies within a wide range (10^{-9} to 1 s^{-1} at 120 °C),[8] it is crucial to know the effect of the alkoxyamine structure on k_d. Almost all NMPs performed with TEMPO[9] or DBNO[9] (di-*tert*-butyl-*N*-oxyl)-based alkoxyamines are known to suffer severe limitations.[3b,10] This has led our group[8c,11] to develop a new family of alkoxyamines (Scheme 3) based on a nitroxyl moiety carrying a phosphoryl group in the β position, called SG1 (*N*-(2-methyl-2-propyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*N*-oxyl).

Inspired by numerous studies on NMP using TEMPO-based alkoxyamines, several groups[8a−i,11c,d,12−18] have undertaken thorough studies of the effect of the alkoxyamine structure on the values of k_d. A linear plot E_a vs bond dissociation energies BDE(C−H) or BDE(C−O) of the released alkyl radical was obtained in the case of TEMPO-based alkoxyamines,[8b,d,19] which means that the more stabilized the released alkyl radical, the higher k_d. However, there were some outlying alkoxyamines, due to the anomeric effect of the heteroatom in α position to the C−ON bond.[8d,19] As for the tertiary released alkyl radicals, they slightly deviated from the general trend.[8b,d]

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Our group[8c,11d,e,18] obtained very promising results concerning the polymerization of styrene, acrylates, and methacrylates. Because SG1-based alkoxyamines are the most potent family to achieve the control of several monomers via NMP, it is timely to check whether the same effects occur as those observed with the TEMPO series. Unfortunately, little is known on the effect of the structure of SG1-based alkoxyamines on k_d and thus on K. We present hereafter the synthesis of a series of SG1-based alkoxyamines **1**−**13**, the values of their C−ON bond homolysis rate constants k_d and the cleavage temperatures T_c (see the Experimental Section).

Results

Due to re-formation (PRE, Scheme 2) of the alkoxyamine, k_d cannot be measured directly from the alkoxyamine decay under normal conditions.[8b−d,20] Instead, the conditions have to be chosen so that either the transient radical or the persistent species is rapidly converted into other nonreactive species before re-formation.[8b−d,20,21] We[8b−d,11d,22] and others[13a,23] have previously shown that k_d can be measured by ESR monitoring of the nitroxide build-up using dioxygen, the galvinoxyl radical, TMIO (2,2,10,10-tetramethylisoindolin-*N*-oxyl), and TEMPO as alkyl radical scavengers or by ^{31}P NMR monitoring of the alkoxyamine evolution[21] using TEMPO, phenylhydrazine, or thiophenol as scavengers for the transient radical and/or the nitroxyl radical. The experiments were carried out in *tert*-butyl benzene, and the rate constants k_d were measured using either the plateau (eq 8) or the initial slope (eq 9) methods[8b−d,20] from the curve giving the time dependence of the nitroxide concentration. We also considered the decay (eq 10) of the alkoxyamine.[21]

$$\ln\left(\frac{[\mathrm{SG1}]_\infty - [\mathrm{SG1}]_t}{[\mathrm{SG1}]_\infty}\right) = -k_d \times t \qquad (8)$$

$$\frac{[\mathrm{SG1}]_t}{[\mathrm{SG1}]_\infty} = k_d \times t \qquad (9)$$

$$\ln\left(\frac{[\mathrm{SG1-R}]_t}{[\mathrm{SG1-R}]_0}\right) = -k_d \times t \qquad (10)$$

The results were reproducible, and the rate constants did not change upon varying alkoxyamine concentrations. We had previously shown that the frequency factor A for the homolysis of the alkoxyamine C−ON bond did not vary much when the alkoxyamine structure varied and ranged between 10^{13} and 10^{15} s^{-1}, with an average value of 2.4 10^{14} s^{-1}.[8b,d] When the dissociation rate constant was determined at only a few temperatures this average value was used to estimate the energies of activation (E_a). The estimated E_a values ranged within an interval of 2 kJ/mol and their average was taken. For alkoxyamines **6**, **7,** and **13**, k_d and E_a may be subject to larger errors, because at higher temperatures SG1 is less persistent and the measurements were performed at very low alkoxyamine conversions (<5%). The values of E_a, k_d, A, and T_c are collected in Table 1.

Discussion

In preliminary studies,[8b] we showed that SG1-based alkoxyamines follow grossly the same trend as TEMPO ones. To confirm this observation, we undertook the synthesis of new SG1-based alkoxyamines, so that no anomeric effect could occur, measured their k_d (Table 1), and drew a plot E_a vs BDE(C−H).[24] To our great surprise, the plot turned out to be more complicated than in the case of the TEMPO series (eq 13).[8b] Indeed, the SG1-based alkoxyamines are split into two families which are correlated to the BDE(C−H) of the released alkyl radical (Figure 1). Along a first line (eq 11) alkoxyamines **1**−**4**, **6** and **7**, that is, weakly or nonpolar ($-0.01 < \sigma_U < 0.12$)[25] released alkyl radicals were gathered. A second line (equation 12) gathered alkoxyamines **8** − **13**, which carry polar ($0.30 < \sigma_U < 0.57$)[25] released alkyl radicals. Furthermore, the smaller slopes (0.72 and 0.69 in eqs 11 and 12, respectively) observed for SG1 derivatives than the slope (0.97 in eq 13) for TEMPO derivatives point out that the reaction enthalpy is not the major influence involved in the C−ON bond homolysis of SG1 − based alkoxyamines.

$$E_a\ (\mathrm{kJ/mol}) = -133.0\ (\pm 25.0) + 0.72\ (\pm 0.07) \times \mathrm{BDE(C\text{-}H)} \qquad (11)$$

$R^2 = 0.97$ N = 6 $s = 3.7$

$$E_a\ (\mathrm{kJ/mol}) = -137.0\ (\pm 52.0) + 0.69\ (\pm 0.13) \times \mathrm{BDE(C\text{-}H)} \qquad (12)$$

$R^2 = 0.77$ N = 10 $s = 4.1$

$$E_a\ (\mathrm{kJ/mol}) = -226.0\ (\pm 43.0) + 0.97\ (\pm 0.12) \times \mathrm{BDE(C\text{-}H)} \qquad (13)$$

$R^2 = 0.86$ N = 13

Alkoxyamine **5** lies on the polar released alkyl radical line (Figure 1) although the *t*-Bu group must be considered as a nonpolar group ($\sigma_U = -0.01$).[25] Such shift to the nonpolar line is certainly due to the steric effect[8b,d]

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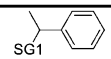
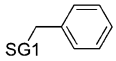
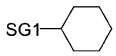
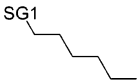
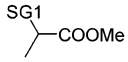
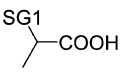
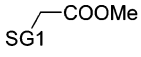
TABLE 1. Activation Parameters, Rate Constants k_d at 120 °C, and Cleavage Temperatures T_c for SG1-Based Alkoxyamines

	SG1 – based alkoxyamines	Runs	T^a (°C)	A^b (10^{14} s^{-1})	E_a^c (kJ·mol^{-1})	$k_{d,393}{}^d$ (s^{-1})	$E_a^{corr\ e}$ (kJ·mol^{-1})	T_c (°C)	Ref.
1		20[f]	60 - 137	1.9	124.5	$5.5\cdot10^{-3}$	125.2	60	8b
2		3	90 - 120	(2.4)	130.0	$1.3\cdot10^{-3}$	-	60	this work
3		3	100 - 130	(2.4)	131.9	$7.1\cdot10^{-4}$	-	70	this work
4		3	110 - 131	(2.4)	134.4	$3.3\cdot10^{-4}$	-	80	8b
5		3	120 - 140	(2.4)	139.7	$6.5\cdot10^{-5}$	-	95	11d
6		1[g]	150	(2.4)	162.3	$6.4\cdot10^{-8}$	-	140	11d
7		1[g]	150	(2.4)	169.2	$7.8\cdot10^{-9}$	-	160	11d
8		1[h]	100	(2.4)	118.5	$4.3\cdot10^{-2}$	-	70	this work
		1[h]	100	(2.4)	126.1	$4.2\cdot10^{-3}$			
		2[i]	110	(2.4)	127.4	$2.8\cdot10^{-3}$			21
9		6	100 - 137	(2.4)	126.4	$3.8\cdot10^{-3}$	-	-[l]	this work
10		12[j]	80 - 132	3.5	128.4	$3.0\cdot10^{-3}$	127.2	75	8b, 21, 31
		4[k]	90 - 129	(2.4)	130.8	$1.0\cdot10^{-3}$	-		
11		1	120	(2.4)	132.9	$5.2\cdot10^{-4}$	-	-[l]	21
					130.7	$1.0\cdot10^{-3}$			
12		3	120 - 140	(2.4)	136.0	$2.0\cdot10^{-4}$	-	90	this work
13		3	130 - 150	(2.4)	149.1	$3.6\cdot10^{-6}$	-	100	this work

[a] $T \pm 1$ °C. [b] Statistical errors smaller than a factor of 2. The value in parentheses is the average of all experimentally accessible frequency factors. [c] Statistical errors around 2 kJ mol^{-1}. [d] Values calculated with parameters from columns 4 and 5. [e] Rescaled values of E_a using an averaged frequency factor (see text) when it was necessary, i.e., A different from 2.4×10^{14} s^{-1}. [f] Both diastereoisomers showed the same rate constant. [g] The value may be affected by errors due to a side reaction; see ref 31. [h] The two isomers were not isolated separately. The rate constants were estimated from a plot of eq 8 showing two slopes. [i] Only one isomer could be measured. ^{31}P NMR (C_6D_6) $\delta = 21.8$ ppm. [j] Isomers *RS* and *SR*, ^{31}P NMR (C_6D_6), $\delta = 22.3$ ppm. [k] Isomers *RR* and *SS*, ^{31}P NMR (C_6D_6), $\delta = 23.0$ ppm. [l] Not determined.

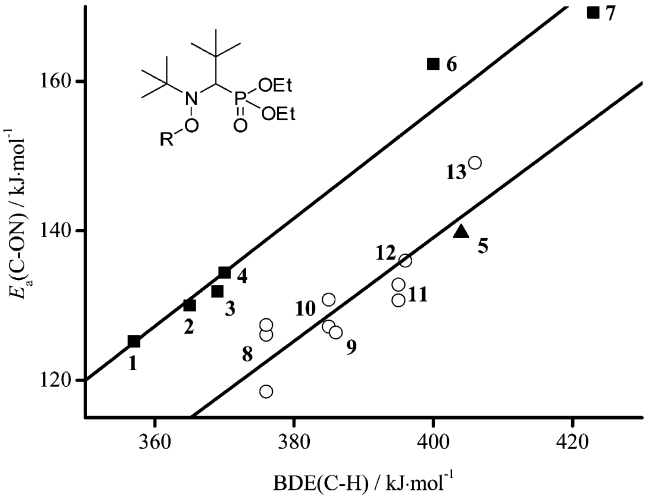


FIGURE 1. Plot of E_a(CO−N) bond homolysis in SG1-based alkoxyamines against BDE(C−H) of the corresponding released alkyl radical: (■) weakly or nonpolar, (○) polar, and (▲) tertiary alkyl fragments.

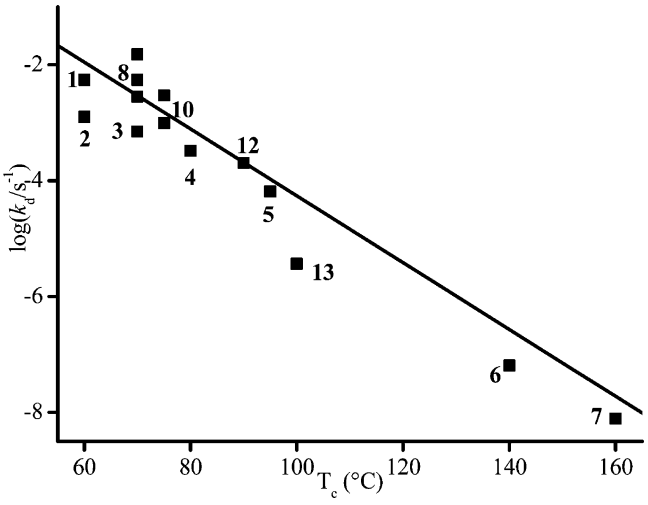


FIGURE 2. Plot of log k_d vs T_c.

of the second methyl group (*t*-Bu is the only tertiary group of the series) which increases the steric hindrance and thus enhances k_d, i.e., lowers E_a. However, at the moment, such assumption is hard to verify because only a few tertiary SG1-CMe_2COOR alkoxyamines have been prepared.[26] And due to the size effect of the R group, the E_a's of such alkoxyamines cannot be directly correlated to the BDE(C−H).[27] It is now clear that the structures of both nitroxyl radical and released alkyl radical strongly influence the values of k_d in a more complex way than earlier expected. So far, it is not clear whether the polar effect destabilizes the ground state or stabilizes the transition state although it is established that the stabilization of the nitroxyl radical decreases with the increasing polarity of the substituents.[28] Consequently, the predictive tables built in a previous work[8b] to give k_d as function of the nitroxyl radical and the released alkyl radical have to be used with care. It seems that the nitroxyl moiety family should be split into two families, i.e., one for the polar structures (SG1 family and homologues) and one for the nonpolar nitroxyl structures (TEMPO, DBNO...). These results show that the trend observed for TEMPO derivatives cannot be directly extended to any type of alkoxyamine.

We have recently shown[11d] that the values of k_d of various alkoxyamines can be correlated to the cleavage temperature T_c (eq 14). In Figure 2, only new and old SG1-based alkoxyamines are reported, in good agreement with the correlation observed in a previous work (line in Figure 2).[11d] The new molecules lie close to the straight line and thus, the relationship (eq 14) can be used as a predictive tool.

$$\log(k_d/s^{-1}) = 1.51\ (\pm 0.26) - 0.058\ (\pm 0.003) \times T_c \qquad (14)$$

Conclusion

The observations made with the TEMPO series cannot be directly extrapolated to any type of alkoxyamine. This work shows that three effects—polar, steric, and stabilizing—have an influence on k_d. The strength of each effect depends markedly on the structure of the released alkyl radical as well as on the structure of the nitroxyl moiety, which is an either strongly or weakly polar structure. Consequently, the correlation E_a vs BDE(C−H) cannot be used as a reliable tool to predict accurate values of k_d in the case of alkoxyamines carrying a polar nitroxyl fragment. Consequently, more studies are required to determine accurately the influence of the various effects (polar ground-state effect and steric effect) involved in the homolysis of the alkoxyamine C−ON bond, and they will be published in forthcoming papers.

Experimental Section

Alkoxyamines **1**−**4** and **8**−**13** were synthesized following a modified[11d] procedure (GP1) described by Matyjazewsky.[29] Alkoxyamines **5**−**7** were made following the procedure (GP2) established by Curran.[30]

General Procedure (GP1) for the Alkoxyamine Preparation Using the ATRA Method. A deoxygenated solution of SG1 and alkyl bromide in benzene was added under inert atmosphere to a deoxygenated suspension of Cu(0), CuBr, and ligand [2,2′-dipyridyl (bpy) or *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA)] in benzene. The resulting reaction mixture was stirred between rt and 80 °C for 2−48 h. The solids were then removed by filtration on Celite and washed with Et_2O. When the ligand was 2,2′-bipyridyl (bpy), the filtrate was washed with a 5% w/w aqueous solution of $CuSO_4$ and then with water. With PMDETA as ligand the filtrate was only washed with water. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by silica gel column chromatography afforded pure alkoxyamine.

General Procedure (GP2) for the Alkoxyamine Preparation via an Organometallic Compound. The appropriate magnesium or lithium organometallic compound was added dropwise to a deoxygenated solution of SG1 (0.11 M) in anhydrous THF at −90 °C and under inert atmosphere. The

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(27) Bertin, D.; Gigmes, D.; Marque, S. R. A.; Maurin, R.; Tordo, P. *J. Polym. Sci. Part A: Polym. Chem.* **2004** in press.
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(30) Nagashima, T.; Curran, D. P. *Synlett* **1996**, 330.
(31) Anantchenko, G.; Souaille, M.; Fischer, H.; Le Mercier, C.; Tordo, P. *J. Polym. Sci.: Part A Polym. Chem.* **2002**, *4*, 3264.

reaction temperature was allowed to rise slowly to room temperature. The reaction mixture was then hydrolyzed with a saturated NH_4Cl aqueous solution and extracted three times with Et_2O. The organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Purification of the crude material by silica gel column chromatography afforded pure alkoxyamine.

Kinetic Measurements. Measurements of k_d were carried out following previously described experimental conditions (CW-ESR EMX Bruker[8b−d,20] and 300 MHz Avance Bruker[21] spectrometers).

Measurement of the Cleavage Temperature T_c.[11d] Two ESR probes were filled with 0.01 M *tert*-butylbenzene solution of SG1-based alkoxyamine and degassed with several freeze−pump−thaw cycles. With the first sample, a rough estimation of T_c was made. The temperature was increased stepwise by 5 °C and the rough T_c corresponds to the temperature where the ESR signal of the SG1 appears. Then the second probe was inserted in the ESR cavity (CW-ESR EMX Bruker equipped with a temperature setup Bruker BV 2000) preheated at a temperature 30 °C below the rough T_c. The temperature was increased stepwise by 5 °C, and T_c corresponds to the temperature where the ESR signal recorded at short intervals (1−min) showed a steady increase.

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Supporting Information Available: Preparation and characterization of alkoxyamines **1**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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