Homolysis of N–alkoxyamines: A Computational Study

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Anouk Gaudel Siri
Aix-Marseille Université

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Aix-Marseille Université

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Homolysis of *N*-alkoxyamines: A Computational Study

Anouk Gaudel-Siri, Didier Siri,* and Paul Tordo[a]

During nitroxide-mediated polymerization (NMP) in the presence of a nitroxide $R^2(R^1)NO^•$, the reversible formation of N-alkoxyamines [P–ON(R^1)R^2] reduces significantly the concentration of polymer radicals (P•) and their involvement in termination reactions. The control of the livingness and polydispersity of the resulting polymer depends strongly on the magnitude of the bond dissociation energy (BDE) of the C–ON(R^1)R^2 bond. In this study, theoretical BDEs of a large series of model N-alkoxyamines are calculated with the PM3 method. In order to provide a predictive tool, correlations between the calculated BDEs and the cleavage temperature (T_c), and the dissociation rate constant (k_d), of the N-alkoxyamines are established. The homolytic cleavage of the N–OC bond is also investigated at the B3P86/6-311++G(d,p)//B3LYP/6-31G(d), level. Furthermore, a natural bond orbital analysis is carried out for some N-alkoxyamines with a O–C–ON(R^1)R^2 fragment, and the strengthening of their C–ON(R^1)R^2 bond is interpreted in terms of stabilizing anomeric interactions.

Introduction

Controlled/"living" radical polymerizations enable the design of polymers with complex architectures and polydispersities well below the theoretical limit for conventional free-radical polymerization processes. Among controlled/"living" radical polymerization procedures, nitroxide-mediated polymerization[1] (NMP) is based on the reversible trapping of growing polymer radicals by a stable nitroxide to form dormant *N*-alkoxyamines (Scheme 1). The thermally labile *N*-alkoxyamines decompose on heating to release nitroxide molecules and reactive polymeric chains that may add monomers before recombining with the nitroxide to give *N*-alkoxyamines with higher molecular weights.
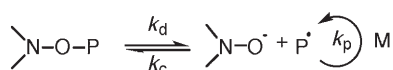
Scheme 1. Controlled/"living" polymerization in the presence of nitroxide.

The process is based on the persistent radical effect[2] and the efficiency of the control depends on the ratio of the dissociation and recombination rate constants, k_d/k_c [Eq. (1)]:

$$k_d/k_c = (A_d/A_c)\exp(-\Delta H_r^o/RT) \tag{1}$$

where A_d and A_c are the Arrhenius prefactors for the *N*-alkoxyamine dissociation and recombination, respectively. It is commonly assumed that A_d/A_c is roughly constant for a set of similar compounds. Thus, the polymerization process is partly controlled by the magnitude of $-\Delta H_r^°$, which is the bond dissociation enthalpy (BDE) of the NO–C bond. If the NO–C bond is too labile, the polymerization process is not controlled; whereas it is inhibited if the NO–C bond is too strong. The experimental determination of BDE (NO–C) for a given *N*-alkoxyamine is a tedious task that requires the determination of E_{ad} and E_{ac}, the activation energies for the *N*-alkoxyamine dissociation and recombination respectively. So, the strength of the NO–C bond is often indirectly studied with the help of k_d or the cleavage temperature T_c. The determination of k_d requires many kinetic runs at a given temperature and, to determine T_c values, a precise protocol[3m] using electron spin resonance (ESR) was followed: the temperature of the sample was increased stepwise by 5°C, and the rough T_c corresponds to the temperature where the ESR signal of the nitroxide appears. Cleavage temperatures of *N*-alkoxyamines are also directly correlated to the strength of the NO–C bond, since the stronger the NO–C bond is, the higher the temperature of dissociation should be. E_{ac} for the combination of carbon-centered radicals with nitroxides are small and, if we assume that they are not significantly influenced by the structure of the trapped radical,[4] then Equation (2) is obtained:

$$\log k_d \propto -E_{ad}/RT \propto -\text{BDE (NO–C)}/RT \tag{2}$$

A correlation similar to Equation (2) between the experimental values of $\log k_d$ and T_c has already been reported.[3m]

[a] Dr. A. Gaudel-Siri,+ Prof. D. Siri, Prof. P. Tordo
UMR-CNRS 6517, Universités d'Aix-Marseille 1 et 3
Faculté des Sciences de St-Jérôme, Case 521
13397 Marseille Cedex 20 (France)
Fax: (+33) 491-288-841
E-mail: didier.siri@up.univ-mrs.fr

[+] Current address:
UMR-CNRS 6178, Université Paul Cézanne-Aix-Marseille
Faculté des Sciences et Techniques, Case D12
13397 Marseille Cedex 20 (France)

Many experimental[3] but few theoretical[3a,f–g,j–k,m–o,5] studies have been performed to estimate factors influencing the BDE (NO—C) of *N*-alkoxyamines. Experimental results show that narrow polydispersities and high polymerization rates depend on the ease of the NO—C bond homolysis.[3f] Both experimental and theoretical results have established that the more stabilized the released radical is, or the more destabilized the starting *N*-alkoxyamine is, the easier is the dissociation of the NO—C bond.[3b,f,m,5] Nitroxides such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, **I**), di-*tert*-butylnitroxide (DTBN, **II**), and *N,N*-(2-methylpropyl-1)-(1-diethylphosphono-2,2-dimethyl-propyl-1)-*N*-oxyl (SG1, **III**) (Scheme 2) have been extensively used for NMP of styrene. Nitroxide **III** was shown to be efficient also during

three other main reasons supported the choice of the PM3 method:

- the better description[9] of nitroxides and *N*-alkoxyamines obtained with PM3, compared to MNDO,[10a] AM1,[10b] or SAM1[10c]
- the satisfactory parametrization of the phosphorus atom in PM3
- among semiempirical methods, PM3 gives the most satisfying calculated bond lengths and BDEs. In a recent study[11a] with a series of 28 compounds, the mean absolute error value for the calculated BDEs of X—X and X—Y bonds was 7 kJ mol^{-1} at the B3P86/6-311G(2d,2p)//PM3 level and 10 kJ mol^{-1} at the B3P86/6-311G(2d,2p)//AM1 level. This result can be accounted for by the better accuracy of the PM3 calculated bond lengths.
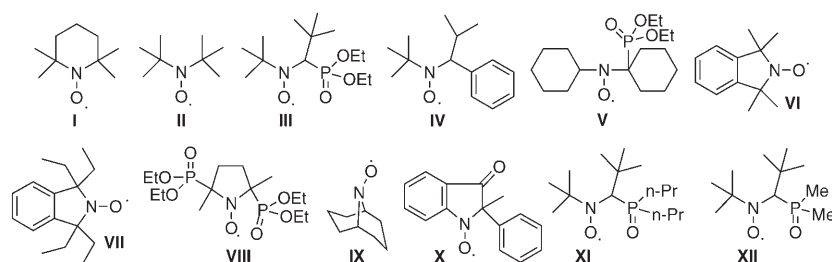
Scheme 2. Chemical structures of the nitroxides **I–XII**.

the NMP of various acrylic monomers. Nevertheless, to extend NMP to other types of monomers, or to improve the previous reported results, the development of appropriate nitroxides is still a challenge. Molecular modeling could be of great help to estimate, before their synthesis, the efficiency of new nitroxides for NMP. Moreover, a rapid procedure to estimate a priori the BDE (NO—C) or the dissociation rate constant k_d of new *N*-alkoxyamines may help organic and polymer chemists in the design of suitable controllers.

The present work is a theoretical study of the dissociation reactions of various *N*-alkoxyamines. In the first section, we give the results of our BDE (NO—C) calculations for various *N*-alkoxyamines. We show that good correlations exist between their calculated BDE (NO—C) and their T_c and k_d values. These correlations provide a valuable tool for evaluating the ability of new nitroxides to control the NMP of styrene and acrylate monomers. Furthermore, for *N*-alkoxyamines, the competition between two different dissociation pathways is studied and shows the limitations of NMP procedures. The results are completed by a natural bond orbital (NBO) analysis[6] for three *N*-alkoxyamines. The NBO analysis allows the separation of the energy contributions due to hyperconjugation from those caused by electrostatic and steric interactions, so that the influence of hyperconjugative interactions can be studied separately.

Computational Section

Semiempirical calculations were performed with the PM3[7] method of the AMPAC software.[8] In addition to its low computational cost,

In the first step, for each *N*-alkoxyamine, the lowest-energy geometry was determined by simulated annealing[12] and highest occupied molecular orbital/lowest unoccupied molecular orbital (HOMO/LUMO) configuration interaction. The energy of the radical species was calculated with a minimal configuration interaction over the HDOMO (highest doubly occupied MO), singly occupied MO SOMO, and LUMO frontier orbitals. All minima were confirmed by the calculation of vibrational frequencies. Bond dissociation enthalpies were calculated from Equations (3) and (4):

$$BDE_{CO}(298\,K) = \Delta H_f^{\circ}(\text{nitroxide}) + \Delta H_f^{\circ}(R^{\cdot}) - \Delta H_f^{\circ}(\textit{N}\text{-alkoxyamine})$$

(3)

$$BDE_{NO}(298\,K) = \Delta H_f^{\circ}(\text{aminyl}) + \Delta H_f^{\circ}(RO^{\cdot}) - \Delta H_f^{\circ}(\textit{N}\text{-alkoxyamine})$$

(4)

where the energy of the open-shell species is recalculated with a minimal configuration interaction over the two SOMOs (keywords OPEN(2,2) C.I. = 2) in order to minimize size-consistency problems. Density functional theory (DFT) calculations were performed with the Gaussian 03 package.[13] In some recent studies,[4a,11] various standard functionals have been tested to calculate the BDEs of C—X and X—Y bonds belonging to a large panel of compounds. The best results were obtained with the B3P86 functional and the best correlation constants between the experimental and calculated values were obtained[11c] at the B3P86/6-311++G(d,p)//B3LYP/6-31G(d) level: 0.991 for all the compounds, 0.969 for C—X bonds, and 0.945 for X—Y bonds with a systematic underestimation of the BDEs. Herein, the geometry optimization and the calculation of vibrational frequencies were performed at the B3LYP/6-31G(d) level and a single point at the B3P86/6-311++G(d,p) level was used to calculate the energy. All minima were confirmed by a calculation of vibrational frequencies. For thermodynamic calculations, as recommended by Wong,[14] a scale factor of 0.9804 was applied to vibrational frequencies. Bond dissociation enthalpies were calculated by Equation (5):

$$BDE = \Delta H_r^{\circ}(298\,K) = D_e + \Delta ZPE + \Delta H_{trans} + \Delta H_{rot} + \Delta H_{vib} + RT$$

(5)

where D_e is the classical electronic bond dissociation energy; ΔZPE is the difference in zero-point energy between products and the *N*-alkoxyamine; ΔH_{trans}, ΔH_{rot}, ΔH_{vib} are the contributions from translational, rotational, and vibrational degrees of freedom.

An NBO analysis was performed at the B3P86/6-31+G(d) level, using the NBO 3.1 program[15] included in the Gaussian 03 package.

Results and Discussion

Experimental and Calculated BDE (NO—C)

Only few experimental BDEs of *N*-alkoxyamines or hydroxylamines have been reported in the literature.[3a–d, 5a, 16] When these scarce experimental data were compared to calculated BDEs (Table 1), we first noted that, in most cases, PM3 calculations slightly overestimated the BDE values (mean error value of 5 kJ mol^{-1}), while B3P86/6-31G(d)//HF/6-31G(d) calculations underestimated them (mean error value of 16 kJ mol^{-1}). BDEs calculated at the DFT level offered a better correlation (Figure 1 a) with experimental data ($r^2 = 0.999$), but PM3 results were also satisfactory ($r^2 = 0.962$). Steric effects were well-described with a decrease in BDE (NO—C) from a primary (—CH$_2$Ph, Table 1, entry **4**) to a secondary (—styryl, Table 1, entry **5**), and a tertiary (—cumyl, Table 1, entry **6**) leaving group (Scheme 3 shows the structures of the leaving groups used in this study). Moreover, with a given leaving group, the BDE (NO—C) of *N*-alkoxyamines derived from **III** were always lower than those of *N*-alkoxyamines derived from **I**. These results for alkyl leaving groups are in very good agreement with experimental data. However, at the PM3 level of calculation, some BDEs were overestimated, while others were underestimated (Table 1): then, individual absolute values must be considered carefully. Consequently, the PM3 method appears to be a valuable tool for estimating relative BDEs of a series of *N*-alkoxyamines with alkyl leaving groups within reasonable calculation times, while a higher-level method is recommended for calculating accurate BDEs. In order to also validate the PM3 method for *N*-alkoxyamines with electron-withdrawing groups, we compared PM3 results with those obtained at the B3P86/6-311++G(d,p)//B3LYP/6-31G(d) level (Table 2, Figure 1 b). PM3 predicts BDEs in good agreement with B3P86 results ($r^2 = 0.995$). In most cases, PM3 BDEs were slightly underestimated; the particular case of *N*-alkoxyamine **40** will be discussed below.
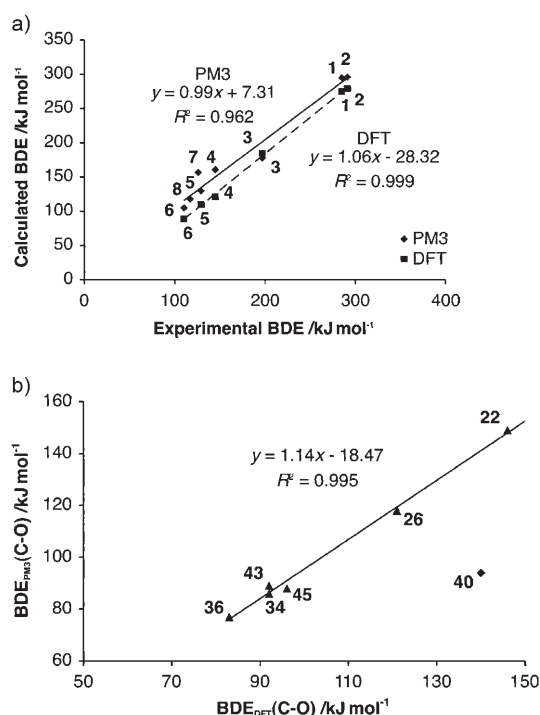
Correlations Between Experimental Data and Calculated BDE (NO—C)

The *N*-alkoxyamine T_c values were determined by experimental chemists in our laboratory.[3m] As expected, they were strongly

Table 1. Comparison between experimental and calculated BDE (O—R) for various hydroxylamines and *N*-alkoxyamines with an alkyl leaving group at 298 K.

N-alkoxyamine or hydroxylamine	BDE$_{PM3}$ [kJ mol^{-1}]	Signed error[b] [kJ mol^{-1}]	BDE$_{DFT}$[c] [kJ mol^{-1}]	Signed error[b] [kJ mol^{-1}]	BDE$_{exp}$ [kJ mol^{-1}]
1 II—H	295	10	275	−10	285[16b]
2 I—H	296	5	279	−12	291[16a]
3 I—Me	178	−19	185	−12	197[3a]
4 I—CH$_2$Ph	161	16	121	−24	145[5a]
5 I—styryl	130	1	110	−19	129[5a]
6 I—cumyl	105	−5	89[d]	−21	110[3d]
7 III—CH$_2$Ph	157	31	–	–	126[5a]
8 III—styryl[a]	118	1	–	–	117[5a]
mean signed error		5		−16	

[a] Mean value for the SR/RS and RR/SS diastereomers. [b] Signed errors in calculated BDE (O—R). [c] Ref. [5a] with B3P86/6-31G(d)//HF/6-31G(d) method. [d] *T* was set to 358 K.

Figure 1. a) Correlation between experimental and theoretical BDEs for the NO—C homolytic cleavage of various *N*-alkoxyamines with an alkyl or a π-delocalized alkyl leaving group. (■) PM3 calculations. (◆) B3P86/6-31G(d)//HF/6-31G(d) calculations. b) Comparison between BDEs calculated with PM3 and BDEs calculated at the B3P86/6-311++G(d,p)//B3LYP/6-31G(d) level for the NO—C homolytic cleavage of various *N*-alkoxyamines with an electron-withdrawing leaving group.
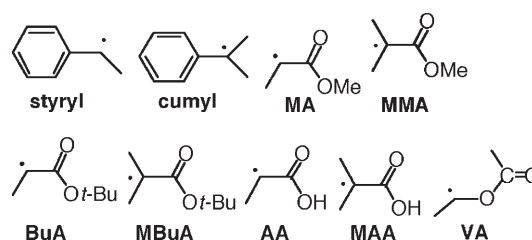
Scheme 3. Chemical structures of leaving groups.

Table 2. Comparison between the PM3 method and the B3P86/6-311++ G(d,p)//B3LYP/6-31G(d) level at 298 K for various *N*-alkoxyamines with an electron-withdrawing leaving group.

N-alkoxyamine	BDE$_{PM3}$ (OR) [kJ mol^{-1}]	BDE$_{DFT}$ (OR) [kJ mol^{-1}]	Signed error[a] [kJ mol^{-1}]
22 I–CH$_2$C(O)OMe	149	146	3
26 I–MA	118	121	−3
34 I–MMA	86	92	−6
36 II–MMA	77	83	−6
40 IX–MMA	94	140	−46
43 I–CMe$_2$CN	89	92	−3
26 VI–CMe$_2$CN	88	96	−8

[a] BDE$_{PM3}$ (OR)−BDE$_{DFT}$ (OR).

Table 3. Comparison between T_c determined by ESR, k_d measured by ESR (393 K), and BDE (NO–C) calculated by PM3 at 298 K.

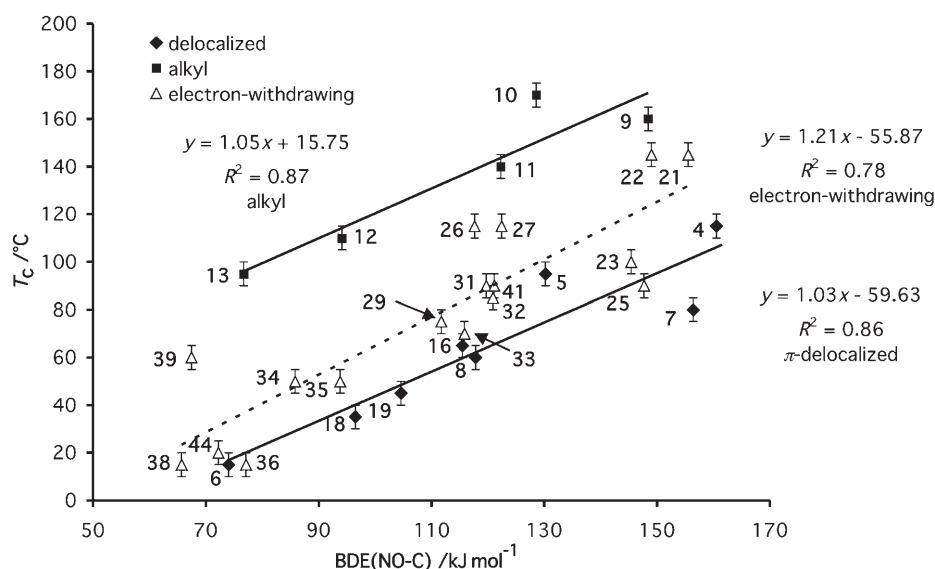| *N*-alkoxyamine	T_c[b] [°C]	BDE$_{PM3}$ [kJ mol^{-1}]	k_d[e] [s^{-1}]	logk_d
9 III–(CH$_2$)$_5$CH$_3$	160[3m]	148	8.00E−09[3m]	−8.10
10 I–*cy*–Hex	170[3m]	129	< 2.80E−08[3m]	> −7.55
11 III–*cy*–Hex	140[3m]	122	6.40E−08[3m]	−7.19
12 I–*t*-Bu	110[3m]	94	1.00E−05[3m]	−5.00
13 III–*t*-Bu	95[3m]	77	6.50E−05[3m]	−4.19
4 I–CH$_2$Ph	115[3m]	161	1.10E−05[3m]	−4.96
14 II–CH$_2$Ph	121[c]	162	1.90E−04[3l]	−3.72
7 III–CH$_2$Ph	80[3m]	157	3.30E−04[3m]	−3.48
5 I–styryl	95[3m]	131	5.20E−04[3m]	−3.28
15 II–styryl	84[c]	131	1.40E−02[3l]	−1.89
8 III–styryl[a]	60[3m]	118	5.50E−03[3m]	−2.26
16 VI–styryl[a]	65[3m]	116	3.30E−03[3m]	−2.48
17 VIII–styryl	100[17]	123	–	–
18 XI–styryl	35[17]	97	1.80E−01[f]	−0.74
19a XII–styryl (SR/RS)	49[c]	113	4.60E−02[3l]	−1.34
19b XII–styryl (SS/RR)	46[c]	109	7.50E−02[3l]	−1.12
8 I–cumyl	45[3m]	105	8.50E−02[3m]	−1.07
20 III–cumyl	≈ 15[3m]	74	1.99[f]	0.30
21 I–CH$_2$C(O)O*t*-Bu	145[3m]	156	8.10E−08[3m]	−7.09
22 I–CH$_2$C(O)OMe	145[18]	149	8.10E−08[18]	−7.09
23 III–CH$_2$C(O)OMe	100[3m]	145	3.60E−06[3m]	−5.44
24 III–CH$_2$C(O)OH	100[d]	146	2.30E−06[h]	−5.64
25 III–CH$_2$CN	90[i]	148	2.00E−04[h]	−3.70
26 I–MA	115[18]	118	3.40E−05[18]	−4.47
27 I–BuA	115[3m]	122	3.40E−05[3m]	−4.47
28 II–BuA	96[d]	119	1.10E−03[3l]	−2.96
29 III–MA[a]	75[3m]	112	–	–
29a III–MA (RS/SR)	–	113	3.00E−03[3m]	−2.52
29b III–MA (RR/SS)	–	110	1.00E−03[3m]	−3.00
30 III–AA	64[d]	111	5.30E−04[h]	−3.28
31 IV–MA[a]	90[3m]	120	4.50E−04[3m]	−3.35
32 V–MA	85[i]	121	5.10E−04[g]	−3.29
33 III–CH(Me)CN[a]	70[17]	116	2.80E−03[3l]	−2.55
34 I–MMA	50[18]	86	2.20E−02[18]	−1.66
35 I–MBuA	50[3m]	94	2.20E−02[3m]	−1.66
36 II–MMA	15[19]	77	4.80E−01[g]	−0.32
37 II–MBuA	39[d]	84	3.10E−01[3l]	−0.51
38 III–MMA	≈ 15[3m]	66	8.00[i]	0.90
39 VIII–MMA	60[19]	67	–	–
40 IX–MMA	165[19]	94	–	–
41 X–MMA	90[19]	121	6.50E−05[g]	−4.19
42 III–MMA	18[d]	66	2.80E−01[h]	−0.55
43 I–CMe$_2$CN	46[d]	89	1.30E−01[3l]	−0.89
44 III–CMe$_2$CN	20[i]	72	1.31[h]	0.12
45 VI–CMe$_2$CN	46[d]	88	1.90E−02[3l]	−1.72
46 VII–CMe$_2$CN	35[d]	81	1.60E−01[3l]	−0.80

[a] T_c or k_d measured for the racemic and mean value of BDE calculated for the two diastereomers. [b] The error in T_c measurements is ±5 °C. [c] Estimated T_c values obtained from the correlation of Fig. 4. [d] Estimated T_c values obtained from the correlation of Figure 6. [e] The error in k_d measurements is ±10%. [f] Estimated k_d values obtained from the correlation of Figure 5. [g] Estimated k_d values obtained from the correlation of Figure 7. [h] S. Marque, D. Gigmes, personal communication. [i] To be published.

dependent on the structure of the leaving radical (Table 3). From a qualitative point of view:

- T_c decreased when the substitution at the radical center of the leaving radical increased (see for example, *N*-alkoxyamines entries **9**, **11** and **10**, **12**)
- for a given released radical, *N*-alkoxyamines derived from **III** exhibited a lower T_c than those derived from **I** (see for example, *N*-alkoxyamines entries **10**, **11** or **12**, **13**).

These results are in agreement with the BDE values of the NO–C bond calculated with the PM3 method. However, no direct correlation between T_c and BDE (NO–C) was found for the whole series of *N*-alkoxyamines, because the polar effects of the nitroxide moiety and the leaving radical must be also considered. Hence, we first defined three sets of *N*-alkoxyamines according to the nature of the radical released during the dissociation: an alkyl radical, a π-delocalized alkyl radical, and a radical bearing an electron-withdrawing group.

Interesting correlations were obtained within the three sets of *N*-alkoxyamines (Figure 2 and Figure 3). Slightly better correlations were obtained between logk_d and BDE (NO–C) than between T_c and BDE (NO–C). The same slope was obtained for the correlations corresponding to leaving groups expected to exert similar polar effects, such as alkyl groups and π-delocalized alkyl groups. We noted a slightly larger slope for leaving groups bearing an electron-withdrawing substituent, such as −CN or −C(O)OR. The combination of both steric and electron-withdrawing effects for the released radical (e.g., methylmethacrylate MMA) led to a significant increase in the dissociation rate. In addition to experimental T_c and k_d values, calculated T_c and k_d values are reported in Table 3 (italic). These values were calculated with the correlations of Figures 4 and 6, and Figures 5 and 7, respectively. The predicted k_d value for entry **20** (1.99 s^{-1} at 120 °C) is in agreement with the value estimated by Marque and co-workers[3m] (1.7 s^{-1} at 120 °C).

The whole series of *N*-alkoxyamines studied in this work can be represented by the three general formula shown in Scheme 4. If the transition state of the NO–C bond homolysis is stabilized by polar contributions, the homolysis of *N*-alkoxyamines B (Scheme 4) is expected to be favored, while no signifi-

cant influence of polar contributions is expected for *N*-alkoxyamines A and C.

In Figure 4, only π-delocalized alkyl leaving groups of similar electronegativities were considered, and two satisfactory corre-
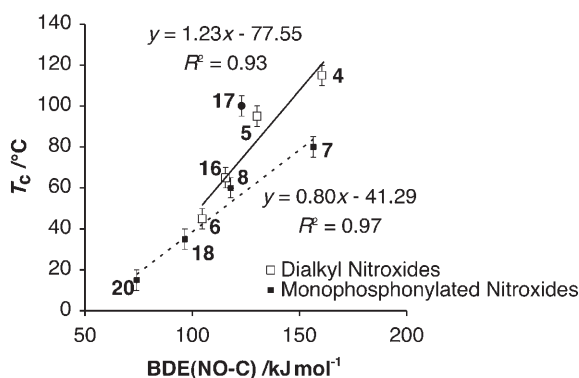
Figure 2. Correlations between BDE (NO—C) calculated with the PM3 method and available experimental T_c considering three series of leaving groups: alkyl, π-delocalized alkyl, and electron-withdrawing moieties.
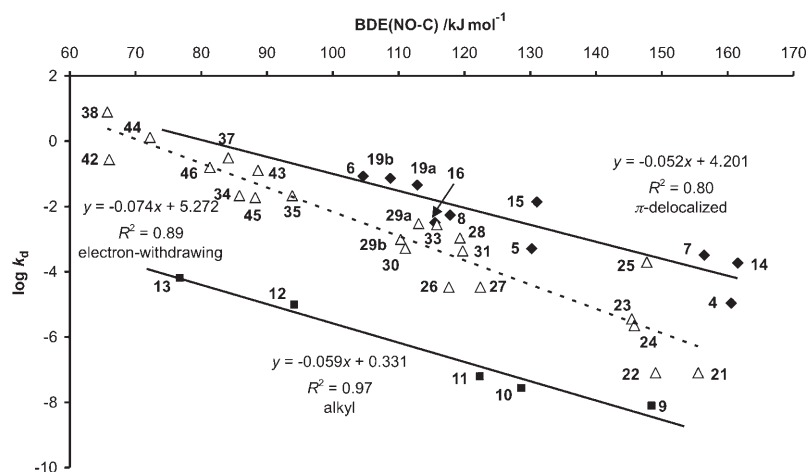
Figure 3. Correlations between BDE (NO—C) calculated with the PM3 method and available experimental k_d values considering three series of leaving groups: alkyl (■), π-delocalized alkyl (◆), and electron-withdrawing (△) moieties.

Figure 4. Correlations between BDE (NO—C) calculated with the PM3 method and experimental T_c considering alkyl π-delocalized leaving groups and dialkyl or monophosphonylated nitroxides.

lations were obtained according to the presence or the absence of an electron-withdrawing substituent on the nitroxide moiety. A better correlation, and a significantly smaller slope, was obtained for monophosphonylated nitroxides (**III**, **XI**, **XII**) than for dialkyl ones (**I**, **IV**). The polar contribution represented by B is expected to be more stabilizing than that represented by A and, as observed, a smaller slope was expected for the correlation involving the *N*-alkoxyamines based on monophosphonylated nitroxides (**III**, **XI**, **XII**). The diphosphonylated cyclic *N*-alkoxyamine **17** (**VIII**-styryl) did not correlate to any linear fit. As already pointed out by Moad and Rizzardo,[3f] a decrease in the θ(CNC) valence angle leads to a higher BDE (NO—C) and then, an increase in T_c. However, more experimental data from a series of cyclic and acyclic diphosphonylated nitroxides should be analyzed in order to draw any conclusions on the effect of the two phosphonyl substituents. In Figure 5, a slightly larger slope was also obtained for dialkyl nitroxides (**I**, **II**, **IV**) than for the monophosphonylated ones (**III**, **XI**, **XII**).
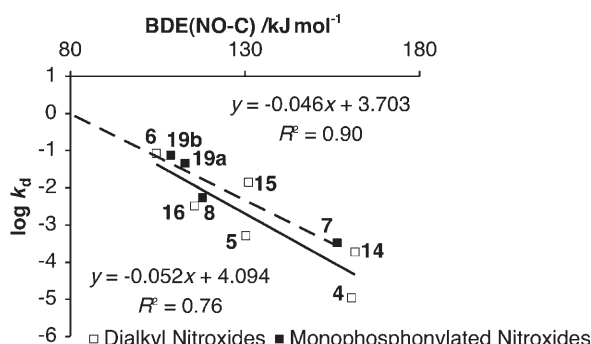
The *N*-alkoxyamines considered in Figures 6 and 7 are A and C types. Good correlations were obtained. Note again the synergy of the polar and steric effects of the leaving group with a larger slope in the case of dialkyl nitroxides (**I**, **II**, **IV**, **VI**, **VII**). The lower slope for *N*-alkoxyamines based on **III** and **V** is due to the larger steric hindrance of the nitroxide moiety (Figure 6). *N*-alkoxyamines **39** and **40** were considered (BDE (NO—C) = 67 kJ mol⁻¹, T_c = 60 °C and BDE (NO—C) = 94 kJ mol⁻¹, T_c = 165 °C,[19] respectively), but neither correlated with a linear fit. For *N*-alkoxyamine **17**, we note significant differences in the valence angle θ(CNC) for **39** and **40**, compared to **34** and **36** (Table 4), and an increase in the BDE (NO—C) and in the cleavage temperature was again observed.

In conclusion, satisfactory correlations were obtained between calculated BDE (NO—C) with the PM3 method and experimental T_c or logk_d. In order to test new nitroxides in NMP, correlations found in this section might help organic chemists, it they first estimate T_c or k_d values for new model *N*-alkoxy-
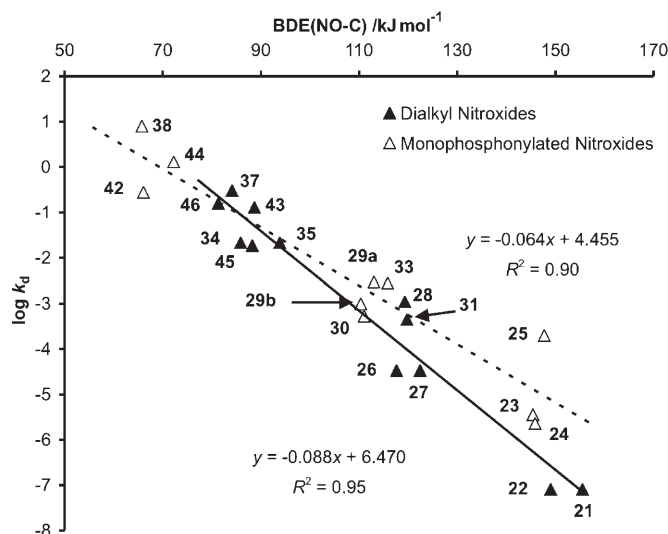
Table 4. Comparison of structural parameters of acyclic (**36**), cyclic (**34**, **39**), and bicyclic (**40**) *N*-alkoxyamines according to PM3 calculations. The ω(CCON) dihedral angle measures the pyramidalization angle of the N atom.

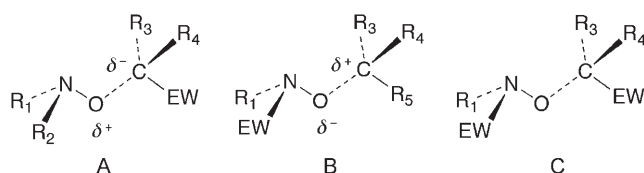| *N*-alkoxyamine	θ(CNC) [deg]	d(NO—C) [Å]	ω(CCON) [deg]
34	119(*118*)[a]	1.436(*1.433*)[a]	29(*32*)[a]
36	121	1.434	28
39	110	1.438	35
40	110(*110*)[a]	1.420(*1.442*)[a]	35(*38*)[a]

[a] Experimental X-ray data values are given in italics.

Figure 6. Correlations between BDE (NO—C) calculated with the PM3 method and experimental T_c considering electron-withdrawing leaving groups and dialkyl or monophosphonylated nitroxides.
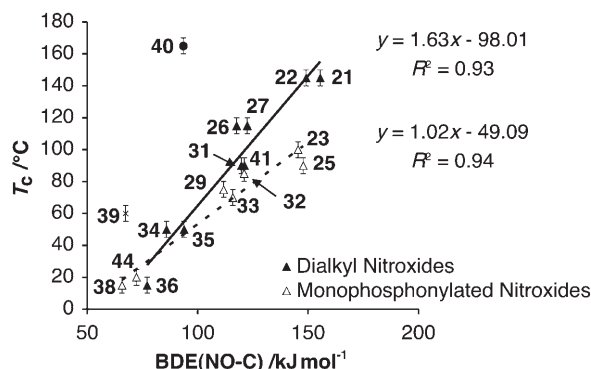

Figure 5. Correlations between BDE (NO—C) calculated with the PM3 method and experimental k_d values considering alkyl leaving radicals and dialkyl or monophosphonylated nitroxides.

amines before their experimental determination, which requires many kinetic runs.

NO—C versus N—OC Bond Cleavage

The cleavage temperature of *N*-alkoxyamines releasing a primary alkyl radical is very high (e.g., **9**). Then, NMP of ethylenic monomers should be conducted at very high temperature and pressure. The NO—C bond in *N*-alkoxyamines is usually considered as the most labile but, at high temperatures, the competitive N—OC homolytic bond cleavage must be also considered. This pathway is not reversible and leads to two reactive radicals: an aminyl radical and an alkoxyl radical (Scheme 5), which are both able to initiate radical reactions. Hereafter, we present our computations on the BDE of the NO—C and N—OC bonds for a series of *N*-alkoxyamines.
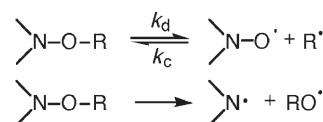
Scheme 5. Competition between homolytic N—OC and NO—C bond cleavage in *N*-alkoxyamines.

At first, some representative *N*-alkoxyamines were chosen to test the ability of the PM3 method to give BDE (N—OC) values in agreement with experimental observations (Table 5).

In agreement with experimental results for *N*-alkoxyamines releasing primary or secondary alkyl radicals, semiempirical BDE (NO—C) were very high (130–155 kJ mol^{-1}). However, BDE (N—OC) of **I**-*n*-hexyl and **III**-*n*-hexyl were significantly lower than BDE (NO—C). This result was not in agreement with the experimental determination of BDE (NO—C) of **I**-Me,[3a] which indicates that BDE (NO—C) < BDE (N—OC) for **I**-*n*-alkyl. *N*-alkoxyamines releasing tertiary radicals (cumyl and MMA) showed highly labile NO—C bonds, in agreement with experimental data. However, spurious results were obtained for primary and secondary π-delocalized radicals. In order to determine if these

Figure 7. Correlations between BDE (NO—C) calculated with the PM3 method and experimental k_d values considering electron-withdrawing leaving radicals and dialkyl or monophosphonylated nitroxides.

**Scheme 4.** General formula of the *N*-alkoxyamines studied.

Table 5. Comparison of BDE (NO—C) and BDE (N—OC) at 298 K calculated with the PM3 method and at the B3P86/6-311++G(d,p)//B3LYP/6-31G(d) level for a series of *N*-alkoxyamines.

N-alkoxyamine		BDE_{PM3} (NO—C) [kJ mol^{-1}]	BDE_{PM3} (N—OC) [kJ mol^{-1}]	BDE_{DFT} (NO—C) [kJ mol^{-1}]	BDE_{DFT} (N—OC) [kJ mol^{-1}]
6	I-cumyl	105	130	87	–
5	I-styryl	130	112	108	174
4	I-CH$_2$Ph	161	107	119	–
26	I-MA	118	–	121	180
34	I-MMA	86	117	–	–
47	I-(CH$_2$)$_5$CH$_3$	151	104	176[a]	189[a]
9	III-(CH$_2$)$_5$CH$_3$	148	77	–	–
48	I-VA	142	107	179	176
49a	III-VA (SR)[b]	135	75	–	–
49b	III-VA (SS)[b]	129	69	–	–

[a] The *n*-hexyl moiety was replaced by a methyl group. [b] The configuration of the nitroxyl chiral center is given first.

discrepancies were due to the use of a semiempirical method, BDE (N—OC) and BDE (NO—C) were calculated with the B3P86/6-311++G(d,p)//B3LYP/6-31G(d) method. Results are reported in Table 5. In order to model the polyethylene chain, the methyl group was taken to reduce calculation times. Table 5 shows that BDEs calculated with the DFT method were in better agreement with experimental data. Only I-MA and I-styryl have a labile NO—C bond (110–120 kJ mol^{-1}). In contrast to the PM3 results, all the *N*-alkoxyamines had strong N—OC bonds (175-190 kJ mol^{-1}) and BDE (NO—C) of I-Me was then lower than BDE (N—OC). For I-VA, BDE (N—OC) and BDE (NO—C) were similar and very high. These values were in agreement with the absence of experimental cleavage temperature for III-VA to 140°C.[20]

This study showed that a comparison of BDE (NO—C) and BDE (N—OC) calculated with the PM3 method did not give reliable relative values. This result can be explained considering the characteristics of the two bonds: a NO—C bond with only one heteroatom and experimental data used in the parametrization of PM3 versus a N—OC bond between two heteroatoms. Moreover, it is known that lone-pair–lone-pair repulsions are not always well represented by semiempirical methods.[21]

## Hyperconjugation in *N*-alkoxyamines: Structural and NBO Analysis

The special cases of the *N*-alkoxyamines I-VA and III-VA is particularly interesting. The steric hindrance in I-VA and I-MA is similar, but their T_c are very different, showing a dramatic strengthening of the NO—C bond in I-VA. Ciriano et al.[3a] have published a study of TEMPO *N*-alkoxyamines derived from tetrahydrofuran and triethylamine. Stronger BDE (NO—C) were attributed to the presence of the heteroatom in the α-position of the NO group. The *N*-alkoxyamine is stabilized by an anomeric interaction[22] between the lone pairs of the heteroatom and the σ*(NO) bond. The NO—C bond is then strengthened while the N—OC bond is weakened. In order to understand the unusual strength of the NO—C bond in I-VA better, a NBO anal-

ysis was carried out where the hyperconjugation in I-VA and I-MA was compared. The hyperconjugation in III-VA was also studied. Starting from the crystal structure of III-VA, the geometry optimization of III'-VA was performed at the B3P86/6-31G(d) level of calculation, and a diffuse function on the nitrogen and oxygen atoms was added to deal with the lone pairs properly. Nitroxide III' differs from III because the ethoxyl moieties attached to the phosphorus atom are substituted by methoxyl groups, in order to reduce the calculation time.

Optimized geometries of I-VA and I-MA are reported in Figures 8 and 9. Some structural variations can be noted in favor
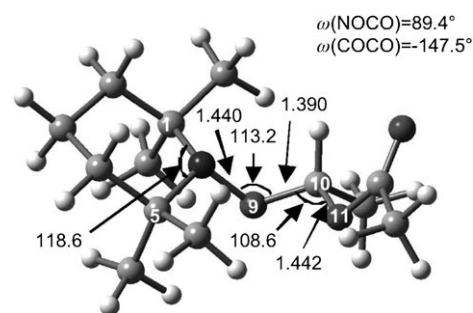
Figure 8. Structural parameters of I-VA optimized at the B3P86/6-31+G(d) level. Bond lengths in angströms, angles in degrees.
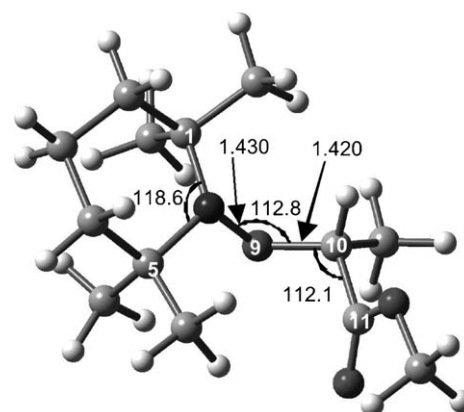
Figure 9. Structural parameters of I-MA optimized at the B3P86/6-31+G(d) level. Bond lengths in angströms, angles in degrees.

of an anomeric interaction in the (N)O9C10O11C moiety of I-VA. At first, the (N)O9—C10 bond of I-VA was significantly shortened (3×10^{-2} Å) while the N—OC bond length did not change. On the other hand, the C10—O11 bond was significantly lengthened (3×10^{-2} Å). Moreover, the ω(NOCO) dihedral angle was close to 90° (89.4°) and the θ(O9C10O11) angle was significantly more acute, compared to the equivalent θ(O9C10C11) angle in I-MA. All these facts support a hyperconjugation between a lone pair of the nitroxyl oxygen O9 and the adjacent antibonding σ* (C10O11) orbital.[3a, 23] In order to confirm this hypothesis, we carried out a NBO analysis[6] of I-VA and I-MA.

Table 6 shows a strong stabilizing interaction (17.9 kcal mol^{-1}) between a p lone pair of O9 and the polar antibonding
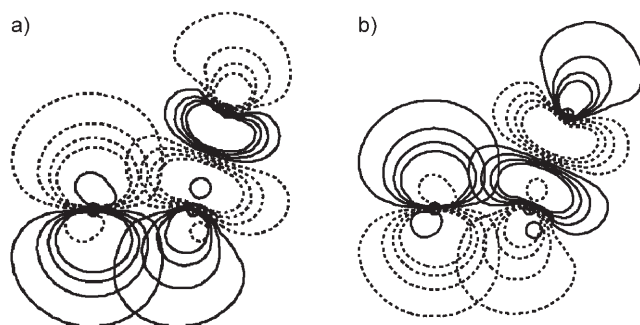
Table 6. Main hyperconjugative interactions in **I**-VA.

Interaction	Stabilization [kcal mol^{-1}]	Lone-pair delocalization	
n(N)→σ* (C1C$_{axial}$)	7.7	96.1%	sp^3(N)
		0.7%	p(C1)
		0.6%	sp^3(C$_{axial}$)
n(N)→σ* (C5C$_{axial}$)	7.8	96.1%	sp^3(N)
		0.7%	p(C5)
		0.6%	sp^3(C$_{axial}$)
n(O9)→σ*(C10O11)	17.9	95.2%	p(O9)
		2.3%	p(C10)
		0.9%	sp(O11)

ω(NOCO)= 104.2°
ω(COCO)=-142.9°

Figure 11. Structural parameters of **III**′-VA optimized at the B3P86/6-31 + G(d) level with an additional diffuse function for the N and O atoms. Bond lengths in angströms, angles in degrees. For clarity, hydrogen atoms have not been drawn.

σ*(C10O11) orbital. A similar interaction is also noted in **I**-MA, but the stabilizing energy is much weaker and close to that resulting from the delocalization of the N lone-pair in the nonpolar axial σ*(C—Me) orbitals (Table 7, Figure 10). Some structural

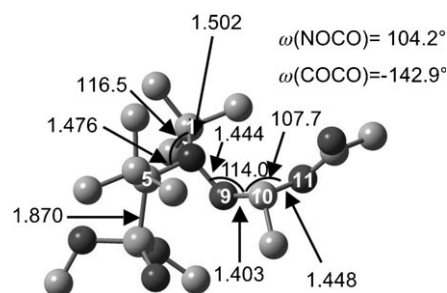**Table 7.** Main hyperconjugative interactions in **I**-MA.

Interaction	Stabilization [kcal mol^{-1}]	Lone-pair delocalization	
n(N)→σ* (C1C$_{axial}$)	7.8	96.0%	sp^3(N)
		0.7%	p(C1)
		0.6%	sp^3(C$_{axial}$)
n(N)→σ*(C5C$_{axial}$)	7.8	96.1%	sp^3(N)
		0.7%	p(C5)
		0.6%	sp^3(C$_{axial}$)
n(O9)→σ*(C10C11)	8.8	96.6%	p(O9)
		0.9%	p(C10)
		0.8%	sp(O11)

Table 8. Main hyperconjugative interactions in **III**′-VA.

Interaction	Stabilization [kcal mol^{-1}]	Lone-pair delocalization	
n(N)→σ* (C1C$_\beta$)	6.9	96.2%	sp^3(N)
		0.6%	p(C1)
		0.5%	sp^3(C$_\beta$)
n(N)→σ*(C5P)	4.7	96.2%	sp^3(N)
		0.7%	p(C5)
		0.5%	s(P)
n(O9)→σ*(C10O11)	15.6	95.3%	p(O9)
		2.1%	p(C10)
		0.8%	sp(O11)

usual lower BDE (NO—C) of **III**-based *N*-alkoxyamines compared to **I**-based *N*-alkoxyamines.

In Table 9 are reported the natural charges of the NOCO and NOCC moieties of **I**-VA, **I**-MA, and **III**′-VA. Natural charges are preferred to Mulliken population analysis, because of instabili-

Figure 10. a) Hyperconjugation in **I**-VA between the O9 lone pair and the antibonding σ* (C10O11) orbital. b) Hyperconjugation in **I**-MA between the O9 lone pair and the antibonding σ* (C10C11) orbital.

Table 9. Comparison of natural charges in **I**-MA, **I**-VA, and **III**′-VA.

Natural charge	N	O9	C10	C11 or O11
I-MA	−0.230	−0.458	−0.009	0.797
I-VA	−0.227	−0.463	0.370	−0.581
III′-VA (SS)[a]	−0.208	−0.461	0.393	−0.582
[a] The configuration of the nitroxyl chiral center is given first.				

variations could also be noted in favor of an anomeric interaction in the (N)O9C10O11C moiety of **III**′-VA (Figure 11). The (N)O9—C10 bond of **III**′-VA is shortened (1.403 Å), while the N—OC and C10—O11 bonds are lengthened, showing a hyperconjugation between a lone pair of the nitroxyl oxygen O9 and the adjacent antibonding σ*(C10O11) orbital. Table 8 shows a strong stabilizing interaction (15.6 kcal mol^{-1}) between a p lone pair of O9 and the polar antibonding σ*(C10O11) orbital. This interaction is similar to the anomeric interaction noted in **I**-VA, but it is less stabilizing. This is in agreement with the

ties with respect to basis expansion and underestimation of ionic character in bonds between atoms with large electronegativity differences.[6d] The charge of either the nitrogen atom or the oxygen atom of the nitroxide moiety is not affected by the nature of the leaving group. On the other hand, the charge of the C10 carbon atom is dramatically modified by the presence of O11 in **I**-VA and **III**′-VA, leading to a highly polarized O9—C10 bond. This charge separation again does not favor the homolytic cleavage of the *N*-alkoxyamine NO—C bond.

The NBO analysis showed that the NO—C bond cleavage in *N*-alkoxyamines releasing a VA radical is not favored, because of an anomeric stabilization and a more polar NO—C bond.

Conclusions

Herein, we reported a semiempirical study of the homolysis of *N*-alkoxyamines. The PM3 method is a valuable tool for estimating relative BDE (NO—C) within a series of *N*-alkoxyamines, and correlations between calculated BDE (NO—C) and the experimental T_c or k_d may be useful for finding new nitroxide controllers for NMP of acrylic or styrenic monomers. These correlations showed the strong influence of steric effects in the NO—C bond cleavage, but polar substituents in the nitroxide are important too, as they modify the polar contributions in the transition state of the homolysis.

PM3 failed to give reliable relative values of BDE (N—OC) and BDE (NO—C). A higher level of theory was necessary to compare the homolytic cleavage of these two bonds. DFT calculations herein were in good agreement with experimental data.

Furthermore, the NBO analysis of two *N*-alkoxyamines releasing a VA radical clearly showed that the control of the polymerization of VA derivatives with nitroxides is unlikely.

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