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Alkoxyamine-Initiated Living Radical Polymerization: Factors Affecting Alkoxyamine Homolysis Rates

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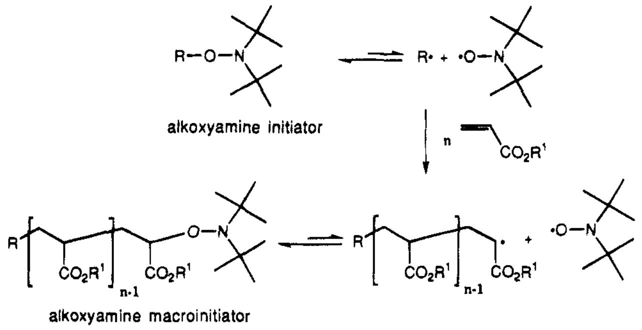
ABSTRACT: Previous work from these laboratories has shown that the success of alkoxyamine-initiated living radical polymerization (polydispersity of product, rate of polymerization) is critically dependent on the rate of homolysis of the C−O bond of the alkoxyamine initiator. Half-lives for a range of alkoxyamines based on initiator-derived radicals or low molecular weight propagating species have been measured experimentally. The values show a marked dependence on the structure of both the nitroxide and radical components. In this work, we demonstrate that semiempirical molecular orbital calculations provide a reliable, though qualitative, prediction of the experimentally observed trends in alkoxyamine homolysis rates. For example, for a series of alkoxyamines based on nitroxides $(R(CH_3)_2C)_2NO^•$, C−O bond dissociation energies are predicted to decrease with an increase in ring size or the C−N−C angle (*i.e.*, 5-membered > 6-membered > open chain > 7-membered), which is in accord with experimental results (5-membered > 6-membered > open chain). More importantly, calculations allow an assessment of the relative importance of steric and polar factors and radical stability in determining the order of alkoxyamine homolysis rates. In the case of secondary and tertiary alkoxyamines, steric factors appear to be the dominant influence. The calculations have application in the design of new initiators for living radical polymerization.

Introduction

Living polymerization methods offer perhaps the best chance for precise control of polymer molecular weight distribution and structure. Unfortunately, the propensity of free radicals to undergo self-reaction at diffusion controlled rates precludes living polymerization in the conventional sense (as is possible for anionic or cationic propagating species). However, radical polymerizations with reversible termination by radical−radical combination or chain transfer are possible.[1,2] Such polymerizations may be considered living if certain conditions are met. First, one (or both) of the radicals formed on initiator decomposition must be both long-lived and unable or slow to initiate polymerization. Second, primary radical termination (by combination) and transfer to initiator (by group transfer) should be the only significant mechanisms for the interruption of chain growth. Third, the bond to the end group formed in these termination reactions must be thermally or photochemically labile. It must be able to undergo reversible homolysis under the reaction conditions to regenerate the propagating radical (*i.e.*, the product is itself an initiator).

In earlier work,[2,3] we showed that certain alkoxyamine-initiated polymerizations meet these criteria. The alkoxyamine initiators are thermally labile and on heating decompose to form a stable nitroxide and a reactive carbon-centered radical ($R^•$). The latter species ($R^•$) may add monomer before recombining with nitroxide to give a new alkoxyamine. The mechanism of acrylate polymerization initiated by these species is illustrated below (Scheme 1).

Scheme 1



Alkoxyamine-initiated living radical polymerization was first described in our patent[3] in 1983, and we have subsequently reported on the general details[2,4,5] and kinetics[6] of these polymerizations. The method has utility in the synthesis of block and graft copolymers and narrow polydispersity homopolymers with designed architecture and end group functionality.[3] The alkoxyamines used in the process may be pre-prepared, or they can be generated *in situ* from a source of carbon-centered radicals and a suitable nitroxide.[3]

Recently, alkoxyamine-initiated living radical polymerization has begun to attract wide interest.[7−15] In particular, Georges *et al.*[7−10] and Hawker[14,15] have applied the methodology to the synthesis of narrow polydispersity homopolymers based on styrene.

In the previous work, we concluded that narrow polydispersities[6] and rapid polymerization rates[3,5,6] were controlled by the facility of the C−O bond homolysis for the alkoxyamine initiator and macroinitiator (see Scheme 1). This finding is supported by work from other laboratories, and a similar requirement appears general for other living polymerization systems which involve reversible termination.[2,7,16,17]

It is also known that the rate constants for C−O bond homolysis for alkoxyamines are strongly dependent on the structure of the nitroxide (and the carbon-centered radical) formed (for example, see Table 1).[3,5,18] Rate constants for the reverse coupling reaction show a corresponding dependence on nitroxide structure.[19−21] This dependence of the rate parameters on nitroxide structure (for both the forward and reverse reactions) has previously been ascribed to steric factors,[2,5,20] with

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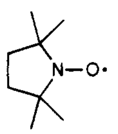
the implication that thermodynamic and polar considerations are of secondary importance. Nonetheless, the findings of solvent dependence for both coupling[22] and homolysis rates,[3,18] and of trends in rate constants with stability of the carbon-centered radical,[3,20] suggest that other factors also contribute.

In carrying out the work described in this paper, we have sought to understand more fully the factors affecting the rate of these reactions, with the aim of providing some criteria for the design of new systems. Molecular orbital calculations have been carried out on a series of alkoxyamines and for the homolysis reaction. The calculations shed light on how the alkoxyamine structure determines the C−O bond strength and what is required for these species to be successful initiators of living radical polymerization.[23]

As this paper was being readied for submission, a paper by Kazmaier *et al.*[24] appeared on the use of semiempirical molecular orbital calculations as a criterion for selecting stable free radical terminators for use in living polymerization. As part of their study, Kazmaier *et al.*[24] carried out a scan of alkoxyamine structures based on various nitroxides and found that alkoxyamines formed with di-*tert*-butyl nitroxide (**7**) should have a lower C−O bond dissociation energy than those formed with TEMPO (**5**). This conclusion is in accord with the findings of the present study and with our previously published experimental results[3−5,23]—see below. No analysis was carried out to establish the factors influencing the value of the bond dissociation energies, and no comparison with previous experimental data in the field was reported.[24]



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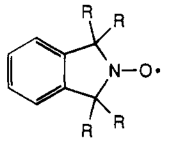
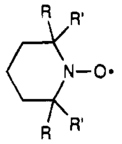
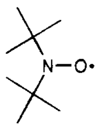


2 R=CH_3
3 R=C_2H_5
4 R=n-C_3H_7



5 R=R'=CH_3
6 R=CH_3, R'=n-C_3H_7



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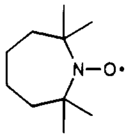

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Results

Alkoxyamine Homolysis Rates. For rapid polymerization rates and narrow polydispersities, the nitroxide portion of the alkoxyamine initiators must be chosen so as to give a rapid C−O bond homolysis rate and few side reactions at the desired polymerization temperature.[3,6] Half-lives of alkoxyamines formed between various nitroxides (**1**−**7**) and radicals (see Table 1) have been measured by following the rate of consumption of the alkoxyamine (or appearance of product) when it is heated with an excess of nitroxide (**2** or **5**) in ethyl acetate solution (for example, see Scheme 2).[3,25]

The reaction between the carbon-centered radicals and the latter scavengers (**2** or **5**) is essentially irreversible under the measurement conditions, and the course of the reaction may be conveniently determined by reverse phase HPLC analysis. The concentrations of added nitroxide were chosen such that the rate of disappearance of alkoxyamine is a true measure of the homolysis rate constant (*i.e.*, no significant recombination to the original alkoxyamine).

Table 1. Half-Lives (min) of Alkoxyamines[a] in Ethyl Acetate Solution

	radical (temp)					
nitroxide	$(CH_3)_2C^{\bullet}CN$ (60 °C)	AMS[b] (60 °C)	S[b] (80 °C)	AN[b] (90 °C)	MAN[b] (60 °C)	MMA[b] (60 °C)
1	280					
2	780					
3	33	75	>1000		55	123
4	31					
5	65					
6		10	400			
7		~2[c]	70[d]	105		

[a] Alkoxyamines formed between nitroxide and radical indicated. [b] Radicals formed by tail addition of *tert*-butoxy radical to the monomer indicated: AMS, α-methylstyrene; S, styrene; AN, acrylonitrile; MAN, methacrylonitrile; MMA, methyl methacrylate. [c] Half-life is 18 min at 40 °C. [d] Half-life is 22 min at 90 °C.

Scheme 2[25]

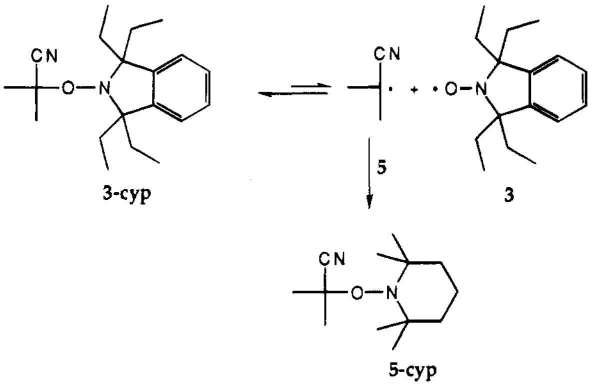


Table 2. Sovent Dependence of Half-Life at 60 °C for Alkoxyamine 3-cyp

solvent	half-life (min)	solvent	half-life (min)
hexane	38	methanol	17
ethyl acetate	33	10% (v/v) water in methanol	16
acetonitrile	22	10% (v/v) acetic acid in methanol	15
dimethylformamide	20		

The results of these experiments are summarized in Tables 1 and 2.[26] The experiments show that homolysis rates increase with ring size of the nitroxide fragment (for the cyclic nitroxides) and that alkoxyamines based on the open chain nitroxide (**7**) offer the fastest homolysis rates. An increase in size of the substituents α to the nitroxide nitrogen also results in enhanced homolysis rates.

The reaction medium was also found to have a significant effect on the rate constant for C−O bond homolysis. Half-life data at 60 °C for the alkoxyamine formed between nitroxide **3** and cyanoisopropyl radical are presented in Table 2. There is a clear trend for a decrease in half-life with increasing solvent polarity.

Molecular Orbital Calculations. There have been a number of recent studies[7,24,27−29] on nitroxides, alkoxyamines, and their reactions using semiempirical methods, although none of these have sought to address directly the issues covered in the present work. In this study, semiempirical molecular orbital calculations have been conducted for a series of alkoxyamines to establish a correlation between structure and C−O homolysis rates. The calculated heats of formation (ΔH_f) and C−O bond dissociation energies (D_{C-O}) and features of the

Table 3. Calculated Heats of Formation for Nitroxides (kJ mol^{-1})

	method						
nitroxide	AM1-UHF	AM1-RHF	AM1-CI	PM3-UHF	PM3-RHF	3-21G[a]	exptl
1	−73.3	−60.9	−62.8	−119.7	−114.8	28.3	
2	115.2	128.3	128.3	37.0	41.7		
5	−90.0	−77.1	−79.5	−121.2	−115.2	29.3	27.2[37]
7	−65.1	−52.7	−54.8	−115.0	−110.2	31.0	
8	−89.1	−77.1	−78.6	−113.9	−109.0		

[a] UHF calculation with 3-21G basis set performed with Gaussian 92.[33] Corrected for zero point vibrational energy: **1**, 653.3 kJ mol^{-1}; **5**, 738.1 kJ mol^{-1}; **7**, −713.4 kJ mol^{-1}.

ground and transition state geometries are summarized in Tables 3−5.

The use of semiempirical calculations to obtain ΔH_f values for radical species has been questioned.[30] Part of the problem is that the semiempirical methods often underestimate ΔH_f for free radicals.[31,32] However, because many of the errors are systematic, it is believed that the geometries and trends in ΔH_f for series of structurally analogous compounds may be reliably predicted.

Various options for calculating the ΔH_f for radical species were investigated (AM1 or PM3; half-electron approximation, UHF calculation or minimal CI, Gaussian 92).[33] Previous workers have observed a significant difference between estimates of ΔH_f (and derived D_{C-O}) for radicals provided by the AM1 and PM3 methods, with the AM1 values being generally closer to experimental (but still significantly lower).[24,32,34,35] For example, ΔH_f for *tert*-butyl radical is underestimated by at least 25 kJ mol^{-1} (AM1-UHF −26.0 kJ mol^{-1}; AM1-RHF −11.3 kJ mol^{-1}; AM1-CI −11.3 kJ mol^{-1}; PM3-UHF −39.1 kJ mol^{-1}; PM3-RHF −25.6 kJ mol^{-1}; PM3-CI −24.8 kJ mol^{-1}; experimental values are in the range 16−35 kJ mol^{-1}).[31,36] However, consistent with the earlier findings,[32,34,35] the AM1 method was found to provide the best estimate.

Some calculated ΔH_f for nitroxides are presented in Table 3. There are only a few reports of experimental ΔH_f values for nitroxides in the literature. The ΔH_f for **5** has been reported[37] as 27.2 kJ mol^{-1} (in benzene). This is substantially higher than the predictions made using all semiempirical methods but is closer to the AM1 values. It was decided to use the AM1 method for all studies and to employ minimal CI for calculations on radicals.[38]

Activation energies for C−O bond rupture were also calculated with the AM1 method by a "path calculation" (for example, see Figure 1). Those for **1-tBu**, **5-tBu**, **7-tBu**, and **8-tBu** are 107.2, 103.4, 100.5, and 98.4 kJ mol^{-1}, respectively. Limited experimental data are available for comparison.[18] The activation energy for C−O homolysis of **7-tBu** is reported to be 96 kJ mol^{-1}, which appears close to the value predicted by the calculation. On the other hand, calculated activation energies for the coupling reaction of nitroxides with *tert*-butyl radicals, while displaying the expected trend, appear to be substantially overestimated. The value of E_a for trapping of a tertiary alkyl radical by nitroxide (**2**) in a nonpolar solvent (cyclohexane) should lie in the range 2−8 kJ mol^{-1}.[19] This value does not compare favorably with our predicted "gas phase" values, which are in the range 60−80 kJ mol^{-1} and seem unreasonably high. This problem is attributed to the tendency for semiempirical methods to significantly underestimate ΔH_f for free radicals (see above).

The possibility of conducting calculations using *ab initio* methods was also investigated. Heats of formation of several nitroxides were calculated using Gaussian 92[33] (see Table 3), and the predicted ΔH_f for **5** appears in good agreement with experiment. However, the size of the systems precluded a full calculation on the alkoxyamines. It was possible to calculate energies for points on the AM1 reaction coordinate by carrying out single point *ab initio* calculations (Gaussian 92 with 3-21G basis set). The total energies were found to show a similar trend to the ΔH_f obtained with the semiempirical methods.

Discussion

Effects of Ring Size and Nitroxide CNC Angle. The calculations confirm the experimentally observed trend for a decrease in the C−O bond strength with increasing ring size or CNC angle (see Table 4). The findings also predict that an alkoxyamine derived from a 7-membered ring nitroxide (**8**) may show a faster C−O homolysis rate than those from analogous 6-membered (**5**) or open chain (**7**) nitroxides.

We have previously indicated that the relative rates of C−O bond homolysis for alkoxyamines are likely to be determined by steric factors.[2] The calculations predict that values of D_{C-O} do decrease in the series where the nitroxide is **1** > **5** > **7** > **8**. The calculated geometries and molecular models of the *tert*-butoxyamines based on nitroxides **1**, **5**, **7**, and **8** show that steric interactions between the alkyl radical and the nitroxide methyls should increase in this series along with the increase in the C−N−C bond angle (see (Figure 2).

If steric factors were important in determining the bond dissociation energies, it might be anticipated that this should be reflected in longer lengths for the breaking C−O bond in the ground state for the systems for which steric factors are greatest. This is known to be the case for C−C bond homolysis reactions of highly substituted ethanes.

In line with this proposition, it is found that there is a correlation between calculated C−O bond lengths and the size of the radical formed. For example, C−O bond lengths for the *tert*-butoxyamines based on nitroxides **1**, **2**, **5**, **7**, and **8** (1.470 ± 0.002 Å) are significantly longer than those for the corresponding methoxyamines (1.440 ± 0.001 Å). The value for the methoxyamines is only slightly greater than the standard C−O single bond length of 1.43 Å.[36] A crystal structure for an alkoxyamine based on the isoindoline nitroxide (**2**) and a secondary alkyl radical has been reported and shows a C−O bond length of 1.425 Å.[39]

However, the C−O bond lengths appear almost invariant with structure within each series of alkoxyamines. The very slight increase in bond length with decrease in D_{C-O} for the *tert*-butoxyamines where the nitroxide fragment is **2** > **5** > **1** > **7** ~ **8** (1.468−1.472 Å, see Table 4) is well within experimental error. Calculated C−O bond lengths in the transition state were also found to be essentially invariant within the accuracy of the calculations (1.93 ± 0.02 Å).[40]

A better measure of the influence of steric factors is the C−N distance in the C−O−N fragment (see Figure 2). This distance encompasses changes in the C−O and N−O bond lengths and the C−O−N bond angle. An increase in any of these parameters can reduce steric interactions between the alkyl and nitroxide fragments. The correlation between the C−N distance and D_{C-O} is

Table 4. Predicted Properties of Alkoxyamines from AM1-CI Calculations

alkoxyamine[a]	ΔH_f (kJ mol^{-1}) radical	nitroxide	alkoxyamine	D_{C-O}[b] kJ mol^{-1})	C–O[c] (Å)	N–O[c] (Å)	C–N[c] (Å)	C–N–C (deg)
2-Me	130.8	128.3	93.3	165.8	1.441	1.347	2.331	107.8
1-Me	130.8	−62.8	−93.9	161.9	1.440	1.348	2.332	107.8
5-Me	130.8	−79.5	−111.2	162.5	1.439	1.355	2.341	116.1
7-Me	130.8	−54.8	−83.6	159.6	1.439	1.357	2.347	119.1
8-Me	130.8	−78.6	−104.4	156.6	1.439	1.358	2.349	119.7
2-Et	75.9	128.3	70.2	134.0	1.454	1.344	2.337	107.8
1-Et	75.9	−62.8	−117.0	130.1	1.454	1.346	2.338	107.8
5-Et	75.9	−79.5	−134.1	130.5	1.453	1.353	2.347	116.0
7-Et	75.9	−54.8	−106.6	127.7	1.453	1.355	2.353	119.2
8-Et	75.9	−78.6	−127.5	124.8	1.453	1.356	2.355	119.8
2-Pr	27.9	128.3	50.6	105.6	1.461	1.343	2.350	107.5
1-Pr	27.9	−62.8	−135.9	101.0	1.460	1.345	2.354	107.9
5-Pr	27.9	−79.5	−149.7	98.1	1.459	1.353	2.370	115.3
7-Pr	27.9	−54.8	−119.2	92.3	1.460	1.354	2.376	118.0
8-Pr	27.9	−78.6	−137.4	86.7	1.460	1.352	2.402	119.3
2-tBu	−11.3	128.3	41.1	75.9	1.468	1.341	2.379	107.3
1-tBu	−11.3	−62.8	−140.3	66.2	1.471	1.341	2.394	107.6
5-tBu	−11.3	−79.5	−147.3	56.5	1.470	1.351	2.421	115.3
7-tBu	−11.3	−54.8	−118.0	51.9	1.472	1.351	2.424	117.5
8-tBu	−11.3	−78.6	−138.8	48.9	1.472	1.353	2.426	118.4

[a] Alkoxyamines comprised of the nitroxide and radical indicated.25 [b] Heat of reaction for C–O bond homolysis. [c] Atoms in >C–O–N fragment (see Figure 1).

Table 5. Effect of Leaving Radical on Geometric Parameters and Bond Dissociation Energies for Alkoxyamines (12)

alkoxyamine[a]	R^1	R^2	R^3	C–N–C (deg)	C–O[b] (Å)	O–N[b] (Å)	N–C[b] (Å)	D_{C-O}[c] (kJ mol^{-1})
1-tBu	CH_3	CH_3	CH_3	107.6	1.471	1.341	2.394	75.9
1-cyp	CH_3	CH_3	CN	107.6	1.460	1.347	2.379	61.7
1-php	CH_3	CH_3	Ph	107.6	1.474	1.344	2.441	60.5
1-Pr	CH_3	CH_3	H	107.9	1.460	1.345	2.354	101.0
1-phe	CH_3	Ph	H	107.7	1.462	1.346	2.354	96.9
1-cye	CH_3	CN	H	108.4	1.454	1.349	2.348	95.6
1-Et	CH_3	H	H	107.8	1.454	1.346	2.338	130.1
1-Me	H	H	H	107.8	1.440	1.348	2.332	165.8

[a] Alkoxyamines comprised of the nitroxide and radical indicated.[25] [b] Atoms in >C–O–N fragment (see Figure 1). [c] Heat of reaction for C–O bond homolysis.

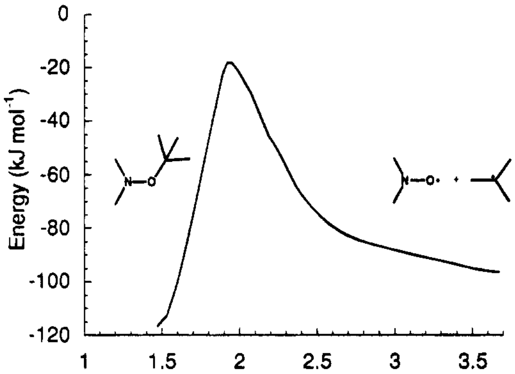


Figure 1. Reaction profile for C–O bond homolysis reaction of alkoxyamine (**7**) as obtained from AM1 calculation.

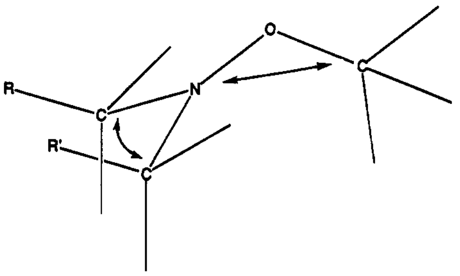


Figure 2.

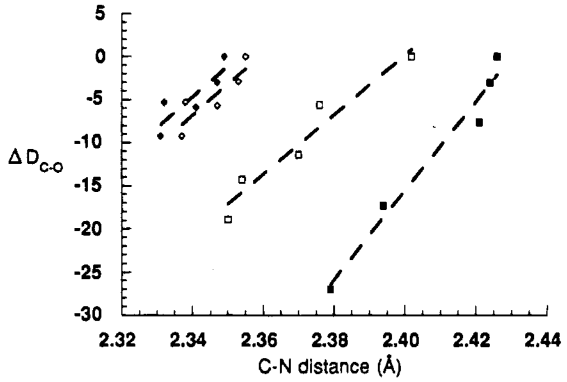
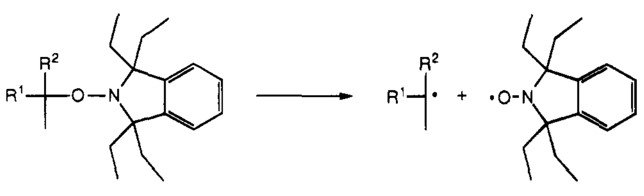


Figure 3. Relative bond dissociation energy ΔD_{C-O} [$=D_{C-O} - D_{C-O}$(**8-R**)] for methoxyamines (R = CH_3) ♦, ethoxyamines (R = C_2H_5) ◇, isopropoxyamines [R = $CH(CH_3)_2$] ☐ and , *tert*-butoxyamines [R = $C(CH_3)_3$] ■. Bond distances increase in the order where the nitroxide fragment is **2** < **5** < **1** < **7** < **8** for each series.

shown in Figure 3. The correlation improves, and the variation in the C–N distance with nitroxide structure increases with increasing size of the alkyl fragment. For methoxy- and ethoxyamines there is significant scatter, indicating that steric factors are relatively unimportant for systems which generate primary alkyl radicals.

It is important to also consider other factors which may influence the values of D_{C-O} in this series of alkoxyamines. The trend in D_{C-O} (and the relative homolysis rates) also correlates with a trend for an increase in thermodynamic stabilities of the nitroxides with an increase in the C–N–C bond angle. There are no experimental data on the thermochemistry of nitroxides as a function of ring size. However, available data on effects of structure on the conformation, properties, and reactivity of nitroxides and their derivatives[37,41–43] suggest this trend. Mahoney *et al.*[37] have reported that >NO–H bond strengths in hydroxylamines increase with a decrease of the C–N–C angle in the nitroxide fragment and ascribe this to a variation in nitroxide stability. Grand and Rey[42] have asserted that the reactivity of nitroxides decreases and the solution stability of nitroxides increases with an increase in the C–N–C bond angle; however, no examples of chemistry were given.

Scheme 3



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a R¹ = CH₂OC(CH₃)₃ R² = CO₂CH₃

b R¹ = CH₂OC(CH₃)₃ R² = Ph

c R¹ = CH₂OC(CH₃)₃ R² = CN

d R¹ = CH₃ R² = CN

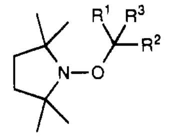
It is possible that steric influences are also reflected in the Arrhenius pre-exponential (*A*) factor or the entropy of activation. Calculations indicate that there are slightly higher barriers for rotation about the $CH_3-CRR'N<$ bonds and the $(CH_3)_3C-ON<$ bonds for *tert*-butoxyamines with larger C−N−C angles (though the difference in the rotational barrier for **1-tBu** *vs* **7-tBu** is only *ca.* 4 kJ mol^{-1}). It is also likely that steric effects will be of greater importance for systems with more bulky substituents α to nitrogen (*e.g.*, alkoxyamines based on nitroxides **3**, **4**, and **6**). Calculations of the entropy of reaction have not as yet been performed but may form part of future work.

It is pertinent to also consider data for the reverse reaction (*i.e.*, coupling) of carbon-centered radicals and nitroxides. The coupling reaction between carbon-centered radicals and nitroxides is known to occur with extremely high rate constants, *ca.* 10^9 M^{-1} s^{-1}.[19-22,44] However, even for these cases, the reactions are not diffusion controlled.[22] Measured activation barriers are small, though nonzero,[19,20,22,44] and rate constants are dependent on solvent (rate constants are highest for polar solvents)[22] and the structure of the nitroxide and radical.

Bowry and Ingold[20] found that rate constants for the coupling of carbon-centered radicals with nitroxides display a trend with nitroxide structure which is the inverse of that found for the homolysis reaction; *i.e.*, 5-membered ring (**2**) > 6-membered ring (**5**) > open chain (**8**). This finding is consistent with the trend seen in the present series of AM1 calculations. Bowry and Ingold[20] attributed the trend in rate constants for the coupling reaction to the influence of steric factors.

Effect of Leaving Radical. Half-lives (ethyl acetate, 60 °C) have been determined for the alkoxyamines (**10a−d**) which are based on nitroxide (**3**) and a series of tertiary radicals (**11**), where R¹ = methyl or *tert*-butoxymethyl and R² = CO_2CH_3, Ph, or CN (see Scheme 3). The trend in the half-lives observed (**a** > **b** > **c** ∼ **d**; see Table 1) is not that expected based on individual consideration of either steric effects (steric bulk decreases in order CO_2R ≥ Ph > CN), polar factors (electrophilicity decreases in order CN > CO_2R > Ph), or leaving radical stability (ability to stabilize adjacent radical center decreases in order Ph > CN > CO_2R).

Both theoretically and experimentally, it is found that whether the leaving radical is secondary or tertiary has a more profound effect on the half-life than the nature of the substituent in a tertiary radical. Tertiary alkoxyamines decompose with half-lives orders of magnitude shorter than corresponding secondary alkoxyamines (see Table 1). This observation is in line with the calculated $D_{\mathrm{C-O}}$. The calculations show that the values of $D_{\mathrm{C-O}}$ decrease in the order where the alkyl fragment is H > CH_3 > C_2H_5 > $CHX(CH_3)$ > $CX(CH_3)_2$ and where X is CH_3 > CN > Ph. While the magnitude of the effect may vary, these trends are independent of the nature of the nitroxide fragment. Values of $D_{\mathrm{C-O}}$ for alkoxyamines (**12**) are shown in Table 5.



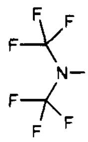
12

Calculated $D_{\mathrm{C-O}}$ values for alkoxyamines based on cumyl and cyanoisopropyl radicals (**1-php** and **1-cyp**, respectively; see Table 5) suggest that, contrary to experiment (Table 1), **1-php** should have the shorter half-life (*i.e.*, values of $D_{\mathrm{C-O}}$ decrease in line with the anticipated stability of the radical formed). However, differences in calculated bond dissociation energies are small and within experimental error for compounds with R² = CN *vs* R² = Ph (<2 kJ mol^{-1}). The opposite order of stability is predicted for the corresponding secondary radicals **1-cye** and **1-phe,** but again the difference is negligibly small.

The stability of the radical formed does not have a substantial influence on the C−N bond length (see Figure 2 and Table 5). The major influence on the C−N bond length is the degree of substitution at the incipient radical center (*i.e.*, steric factors—whether the radical is primary, secondary, or tertiary).

Polar Effects. That polar effects are important in determining the rate of C−O bond homolysis is indicated by the solvent dependence of alkoxyamine half-lives (see Table 2). It is also noteworthy that the rate constants for the coupling reaction[22] and EPR spectral parameters for nitroxides[41] are solvent dependent.

To examine more fully the influence of polar factors on homolysis rates, the values of $D_{\mathrm{C-O}}$ for *tert*-butoxyamines based on nitroxides containing strongly electron withdrawing or donating substituents (**13−15**)-were compared with that for the *tert*-butoxyamine based on nitroxide (**7**). These results are shown in Table 6.



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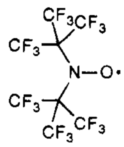

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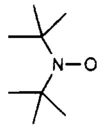

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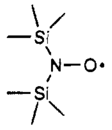

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Replacing the $C(CH_3)_3$ groups of (**7**) with electron withdrawing CF_3 (in **13**) or $C(CF_3)_3$ (in **14**) groups appears to stabilize the C−O bond. Conversely, replacing the $C(CH_3)_3$ groups of (**7**) with electron donating $Si(CH)_3$ groups (in **15**) markedly labilizes the C−O bond.

There are some experimental data on the chemistry of **13** and **15.** The nitroxide (**13**) has been found to be extremely reactive compared to dialkyl nitroxides (*e.g.*, **7**). That it forms strong C−O bonds is indicated by the fact that it adds to unsaturated systems[45,46] and readily abstracts hydrogen.[46-48] This nitroxide is unlikely to be useful in living radical polymerization.

Alkoxyamines based on nitroxide (**15**) are also unlikely to be useful as initiators of living polymerization because the N−Si bond may undergo homolytic cleavage and the compounds are also likely to be effective silylating agents. The nitroxide is also relatively un-

Table 6. Predicted Properties of Alkoxyamines from AM1-CI Calculations

	ΔH_f (kJ mol^{-1})			D_{C-O}[b]	charge (alkoxyamine)[c]			C−O[b]	N−O[b]	C−N[b]	C−N−C
alkoxyamine[a]	radical	nitroxide	alkoxyamine	(kJ mol^{-1})	N	O	C	(Å)	(Å)	(Å)	(deg)
13-tBu	−11.3	1150.3	−1284.7	123.1	−0.125	−0.219	0.100	1.489	1.325	2.390	110.0
14-tBu	−11.3	−3554.8	3621.3	55.2	−0.045	−0.247	0.104	1.508	1.348	2.489	120.7
7-tBu	−11.3	−54.8	−118.0	51.9	−0.099	−0.240	0.090	1.472	1.351	2.424	117.5
15-tBu	−11.3	−475.7	−485.7	1.3	−0.725	0.175	0.041	1.482	1.322	2.448	131.7

[a] Alkoxyamines comprised of the nitroxide and radical indicated.[25] [b] Heat of reaction for C-O bond homolysis. [c] Atoms in >C−O−N fragment (see Figure 1).

stable in solution (compared to **7**) and is extremely air sensitive.[49]

Conclusions

Semiempirical molecular orbital methods may be used to provide a reliable, though qualitative, prediction of the relative stabilities of alkoxyamines used as initiators of living radical polymerization. The rate of alkoxyamine C−O bond homolysis is determined by a combination of polar, steric, and electronic factors. The relative importance of these terms depends on the nitroxide structure. For secondary and tertiary alkoxyamines, steric factors appear to be the dominant influence. It is predicted that an alkoxyamine based on a 7-membered ring nitroxide (**8-tBu**) may show an enhanced homolysis rate over a similarly substituted smaller ring (**1-**, **3-**, or **5-tBu**) or open chain nitroxides (**7-tBu**). Polar influences play an important role when the nitroxide or radical fragment contains heteroatom substituents (*e.g.*, F, Si, CN).

Further work, aimed at more fully exploring the utility of semiempirical and other methods for predicting the dissociation rates for a wider range of alkoxyamines initiators, is underway, and exploitation of this information in the design of new initiators is being actively pursued.

Experimental Section

Molecular Orbital Calculations. Semiempirical molecular orbital calculations (AM1, PM3) were performed using MNDO93 as implemented as part of the Unichem package (Cray Research, version 2.3.1) and the CSIRO Cray YMP-4E. *Ab initio* calculations were carried out with Gaussian 92[33] with the aid of the interface provided by Unichem.

Transition states were located by conducting a "path" calculation, starting with the fully optimized structure for the alkoxyamine and conducting a series of optimizations where the C−O bond length was extended by 0.05 Å increments to 3.0 Å. The structures at the energy maxima (*cf.* Figure 1) were then taken as the starting point for optimization to a transition state.

Alkoxyamine Half-Life Measurements. The synthesis of the alkoxyamines and nitroxides is described elsewhere.[3] A typical experimental procedure for half-life measurement is as follows.

A dilute solution of the alkoxyamine **3-cyp** (16.2 mg), bibenzyl (12.0 mg, internal standard), and an excess of nitroxide **5** (150 mg) in ethyl acetate (5 mL) was degassed by three freeze−evacuate−thaw cycles and held under nitrogen. The reaction mixture was placed in a constant temperature bath at 60.5 °C and sampled at 30 min intervals.

The solvents and temperatures used for other experiments are shown in Tables 1 and 2. The nitroxide was chosen to give an alkoxyamine that was relatively stable under the reaction conditions. Nitroxide **2** was used in most experiments.

The disappearance and formation of the alkoxyamines were monitored by HPLC equipped with a UV detector operating at 270 nm. For the example given above, a DuPont C-18 reverse phase column (25 cm × 6.2 mm i.d.) was employed with an acetonitrile−water gradient as eluent (75−95% over 15 min, flow rate: 2 mL min^{-1}). The compounds eluted as follows: **5**, 290 s; bibenzyl (internal standard), 494 s; **3**, 556 s; **3-cyp**, 887 s.

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