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Influence of the Nitroxide Structure on the Homolysis Rate Constant of Alkoxyamines: A Taft−Ingold Analysis

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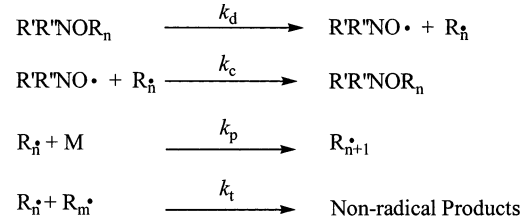
Alkoxyamines and persistent nitroxyl radicals are important regulators of living radical polymerizations. Because polymerization times decrease with the increasing rate of the homolytic C−O bond cleavage between the polymer chain and the nitroxide moiety, the factors influencing the homolysis rate are of considerable interest. Here, we present an analysis of the cleavage rate constants for 28 alkoxyamines carrying the styryl (PhEt) group as leaving alkyl radical in terms of polar inductive/field (σ_L) and steric (E_s) effects of the nitroxide substituents, using the Taft−Ingold equation, i.e., $\log(k/k_0) = \rho_L\sigma_L + \delta E_s$. The rate constants are shown to increase with the increasing electron-donating capacities, the steric demand, and the intramolecular (hydrogen) bonding capabilities of the substituents. A good correlation, ($R^2 = 0.95$, 23 data) $\log k_d = -3.07\sigma_L - 0.88E_s - 5.88$, is obtained, which should facilitate the design of new nitroxyl radicals and alkoxyamine regulators.

Introduction

Thanks to the seminal works of Rizzardo[1] and Georges[2a,b] it is now possible to prepare polymers with definite weights and architectures and low polydispersity indices (PDI), using the so-called nitroxide-mediated polymerization (NMP) process.[3a−l] 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. The easiest way to trigger the polymerization is to use thermally unstable alkoxyamines prepared beforehand. The growth of polymeric radicals involves successive deactivation-dissociation cycles, by which they are alternatively transformed into alkoxyamines (so-called dormant species) and reactivated by thermal homolysis (Scheme 1). Then, several groups have developed and applied the method by fundamental investigations on the synthesis and the mechanism[4,5] of new initiators/controllers.[6−10] Recently, Fischer et al.[11] and other groups[12] have presented the kinetics ruling the NMP. They showed that the core equations involve a combination of the dissociation rate constant k_d of the initiator and the

SCHEME 1



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intermediate so-called "dormant species", the recombination rate constant k_c of the propagating radical with the persistent species, the propagating rate constant k_p of the propagating radical, and the termination rate constant, k_t (Scheme 1).

They also showed that the values of k_d are crucial for the success of NMP. Because little was known on the effects influencing the homolysis of the C−ON bond in alkoxyamines,[13,14] thorough studies of those effects have been undertaken.[3h,15−17] Early studies mainly focused on the effect of the leaving alkyl group on the C−O bond homolysis but attained only a general view of the influence of the structure of the nitroxyl moiety.[3h,13−19] It appeared that polar and steric effects are strongly intertwined in the nitroxide moiety and affect markedly the values of k_d. Because the synthesis of new nitroxides may be a difficult work and the knowledge of k_d is crucial for NMP, it would be highly advantageous to have a means of designing new nitroxyl radicals or alkoxyamines and of predicting accurate and reliable k_d values. To separate polar and steric effects in the nitroxide moiety, we present here an approach involving the Taft−Ingold equation[20] (TIE).

Results

Activation energies, E_a, and rate constants, k_d, for alkoxyamines **1**−**27** (Table 1) have already been published in the literature.[14,16,17,21] Alkoxyamines[14,16] **11**−**14** (Table 1) did not carry the PhEt group, and therefore their E_a values (Table 1) were converted by using increments, as previously determined.[16] Moreover, because not all frequency factors (A) had been determined and because the difference observed between the known values of A was low and mainly due to the compensation error effect, all E_a were reestimated using a mean frequency factor of 2.4×10^{14} s^{-1} and used to calculate the dissociation rate constants k_d gathered in Tables 1 and 2.[16,17]

TIE is well-known and is used to separate polar and steric effects in a reaction series.[20,22,23] It has already been applied successfully in the homolysis of C−C or O−O bonds.[24−26] In eq 1, the polar effects are related to the Hammet σ coefficients σ_G, whereas the steric effects are related to the steric constant E_s(G), both belonging to the G group located on the atoms of the cleaved bond involved in the change of reactivity (here the G group is the RR′N part of the nitroxide moiety). They are equated to the logarithms of the rate constants corresponding to the influence of the (G) group (k(G)) and to the influence of the standard substituent (k_0 R = R′ = H being generally taken as standard).

$$\log \frac{k(\mathrm{G})}{k_0} = \rho\sigma_{\mathrm{G}} + \delta E_{\mathrm{s}}(\mathrm{G}) \qquad (1)$$

To simplify the problem, all alkoxyamines carried the same leaving alkyl group, namely, the styryl group (PhEt). Its electronic and steric effects were assumed constant for each alkoxyamine, and thus any difference observed should be due to the nitroxyl moiety.

The R substituents are bound to a tetrahedral carbon (Scheme 2), which inhibits any resonance effect (delocalized polar effect) with the reactive region.[27,28] Therefore σ_L is used in eq 1 as Hammet σ constant for localized polar effects, i.e., field/inductive polar effects.[29] As the nitroxide moiety in alkoxyamines carries various groups, the value of σ_L (Table 1) will be merely the sum (eq 2 and Scheme 2) of the individual $\sigma_L(\mathrm{R}_i)$.[26,30]

$$\sigma_{L,\mathrm{n}} = \sum_{i=1}^{6} \sigma_L(\mathrm{R}_i) \qquad (2)$$

It must be pointed out that for symmetrical reasons, for piperidin-*N*-oxyl derivatives such as molecule **10** (Scheme 2), the value of $\sigma_L(\mathrm{R}_i)$ for the group in position 4′ will be taken as equal to the half value of the $\sigma_L(\mathrm{R}_i)$ for $CH_3C(O)CH_2$.[20,27] The same will be applied to molecules **12**−**14**, where the phenyl ring is fused in position 3′−4′ of a pyrrolidin ring, that is, the half value of the $\sigma_{L,\mathrm{Ph}}$ for the phenyl ring will be used (Scheme 2).

The main steric constants used are the E_s family[20,31−33] and the υ parameter of Charton.[34] Because all of the

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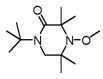
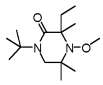
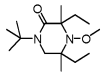
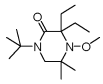
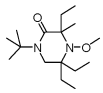
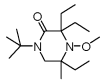
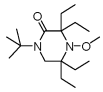
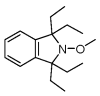
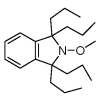
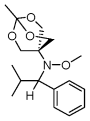
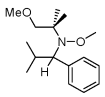
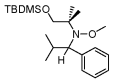
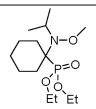
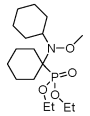
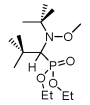
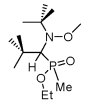
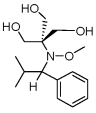
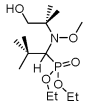
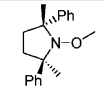
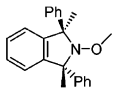
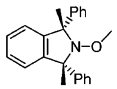
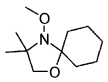
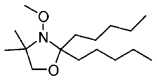
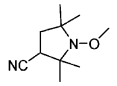
TABLE 1. Reestimated Activation Energy E_a and Rate Constants k_d, Polar Constant σ_L, Steric Energy Constants E_s, Steric Strain E_N and E_N' for the Nitroxyl Moiety of Alkoxyamines Used for NMP[a]

Entry	Alkoxyamine RR'NO-PhEt	E_a[b]	k_d[b]	σ_L[c]	E_s[d]	E_N[e]	E'_N[f]
1		137.7[g]	$1.2\ 10^{-4}$	0.33	-3.5	-2.79	129.5
2		135.7[g]	$2.2\ 10^{-4}$	0.33	-3.7	-2.53	129.3
3		133.4[g]	$4.5\ 10^{-4}$	0.33	-3.9	-2.22	125.6
4		129.5[g]	$1.5\ 10^{-3}$	0.33	-4.5	-1.70	121.3
5		129.7[g]	$1.4\ 10^{-3}$	0.33	-4.7	-1.73	121.5
6		126.8[g]	$3.4\ 10^{-3}$	0.33	-4.7	-1.34	118.9
7		124.2[g]	$7.4\ 10^{-3}$	0.33	-5.5	-1.00	116.0
8		132.9[h]	$5.2\ 10^{-4}$	-0.06	-2.7	-3.49	134.4
9		127.9[i]	$2.4\ 10^{-3}$	-0.06	-3.6	-2.82	129.4
10		127.7[j]	$2.6\ 10^{-3}$	0.13	-3.9	-2.14	124.5
11		137.0[i]	$1.5\ 10^{-4}$	-0.06	-2.1	-4.04	138.5
12		139.8[h,i]	$6.3\ 10^{-5}$	0.08	-2.1	-3.93	137.8
13		131.1[h,i]	$9.0\ 10^{-4}$	0.08	-4.1	-2.78	129.1
14		130.9[i]	$9.6\ 10^{-4}$	0.08	-5.6	-2.75	128.9
15		137.2[k]	$1.4\ 10^{-4}$	0.46[l]	-4.1	-2.28	125.7
16		130.2[k]	$1.2\ 10^{-3}$	0.22	-4.1	-2.16	124.7
17		128.2[k]	$2.2\ 10^{-3}$	0.11[m]	-4.1	-2.28	125.5
18		127.1[h]	$3.1\ 10^{-2}$	0.10	-4.1	-2.12	124.6
19		122.4[h]	$1.3\ 10^{-2}$	-0.06	-4.2	-2.10	123.9
20		126.6[h]	$3.6\ 10^{-3}$	0.28	-5.0	-1.49	119.6
21		125.8[h]	$4.6\ 10^{-3}$	0.28	-5.0	-1.38	118.8
22		125.5[h]	$5.0\ 10^{-3}$	0.28	-5.0	-1.34	118.5
23		120.4[h]	$2.4\ 10^{-2}$	0.27	-5.7	-0.69	113.7
24		118.5[h] 116.9[h]	$4.3\ 10^{-2}$ $7.0\ 10^{-2}$	0.26	-6.0[n]	-0.48 -0.27	112.0 110.4
25		127.5[h]	$2.7\ 10^{-3}$	0.22	-4.1	-1.82	121.3
26		125.4[h]	$5.2\ 10^{-3}$	0.46	-4.1	-0.71	113.9
27		121.3[h]	$1.8\ 10^{-2}$	0.40	-5.0	-0.37	111.3

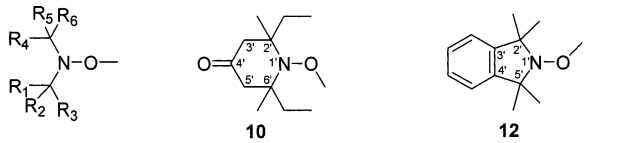
[a] E_a and E_N' in kJ mol^{-1} and k_d in s^{-1} at 393 K. [b] See Results Section. [c] Estimated with eq 2. Individual values taken from Table 3 unless otherwise noted. A positive value denotes an electron-withdrawing group (EWG). [d] Estimated from eqs 3 and 13. Individual values are gathered in Table 3. [e] Estimated with eq 12a. [f] Estimated with eq 12b. [g] $E_{a,n}$ converted from ref 21. [h] $E_{a,n}$ converted from ref 16. [i] E_a converted from refs 14 and 16. [j] Unpublished data from S. Marque. [k] $E_{a,n}$ converted from ref 17. [l] Ortho ester group is assumed to show the same polar effect as three $MeOCH_2$ groups, i.e., $\sigma_{L,(CH_2O)_3CMe} = 3\sigma_{L,CH_2OMe}$. [m] Rescaled individual value from ref 42 for $OSiMe_2tBu$ group assuming $\sigma_{L,CH_2OSiMe_3} \approx \sigma_{L,CH_2OSiMe_2tBu} \approx 0.0$. [n] Equations 12a and 4 cannot take into account the difference in k_d due to the diastereoisomers of **24**.

TABLE 2. Reestimated Activation Energy E_a and Rate Constants k_d, Polar Constant σ_L, Steric Energy Constants E_s, for the Nitroxyl Moiety of Alkoxyamines Used for NMP[a]

Entry	Alkoxyamine RR'NO-PhEt	PDI[b]	σ_L[c]	E_s[d]	k_d[e]	E_a[f]
28		1.17	0.20	-3.9	$8.7\ 10^{-4}$	131.2
29		1.49	0.28	-3.9	$4.9\ 10^{-4}$	133.1
30		1.71	0.28	-3.9	$4.9\ 10^{-4}$	133.1
31		1.72	0.38[g]	-3.1	$4.8\ 10^{-5}$	140.7
32		1.65	0.38	-4.3[h] -3.1[i]	$5.5\ 10^{-4}$ $4.8\ 10^{-5}$	132.7 140.7
33		1.25	0.05[j]	-2.1	$6.5\ 10^{-5}$	139.7

[a] E_a in kJ mol^{-1} and k_d in s^{-1} at 393 K. [b] PDI for 18-h styrene polymerization at 120 °C from ref 7. [c] Estimated with eq 2. Individual values taken from Table 3 unless otherwise noted. Positive value denotes an electron-withdrawing group (EWG). [d] Estimated from eqs 3 and 4. Individual values are given in Table 3 unless otherwise noted. [e] Estimated from eq 15. [f] See Results. [g] $\sigma_{L,MeO} = 0.30$.[27,41] [h] $r^{pentyl} = -0.83$.[35] [i] When pentyl groups are assumed to be no more efficient than ethyl groups, i.e., $r^{pentyl} \approx r^{Et}$. See text. [j] Using $\sigma_{L,CH_2CH_2CN} = 0.09$, $\sigma_{L,CH_2CN} = 0.2$ and assuming an increment of around −0.1 for each methyl group on the carbon bearing the cyano group, $\sigma_{L,MeCHCNCH_2} \approx -0.01$ and $\sigma_{L,MeCNCH} \approx 0.1$.[27,41]

SCHEME 2



10 $\sigma_L = 2\sigma_{L,Me} + 2\sigma_{L,Et} + \sigma_{L,CH3COCH2}/2 + \sigma_{L,CH3COCH2}/2$

12 $\sigma_L = 4\sigma_{L,Me} + \sigma_{L,Ph}/2 + \sigma_{L,Ph}/2$

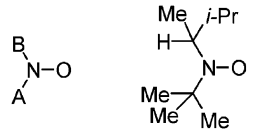
steric constants of the various groups in the nitroxide moiety are not given in the literature, the versatile approach of Fujita,[35] using modified E_s,[36] is the most adapted to our compounds. Fujita et al.[35] have shown that steric effects can be represented with a linear combination (eq 3) of the individual steric constants for a group X, noted here r_i(X) with i being the rank related to the value of r(X), i.e., its size (the more negative r(X) is, the larger X is; example in Scheme 3).

$$E_s(CR_1R_2R_3) = c_0 + c_1r_1(R_1) + c_2r_2(R_2) + c_3r_3(R_3) \quad (3)$$

with $c_0 = -2.104$, $c_1 = 3.429$, $c_2 = 1.978$, and $c_3 = 0.649$

(35) Fujita, T.; Takayama, C.; Nakajima, M. *J. Org. Chem.* **1973**, *38*, 1623.

SCHEME 3



α

$$E_s^A(\alpha) = E_s(\text{CHMe}i\text{-Pr}) = c_0 + c_1 \times r_1(\text{H}) + c_2 \times r_2(\text{Me}) + c_3 \times r_3(i\text{-Pr}) = -1.7$$

$$E_s^B(\alpha) = E_s(\text{CMeMeMe}) = c_0 + c_1 \times r_1(\text{Me}) + c_2 \times r_2(\text{Me}) + c_3 \times r_3(\text{Me}) = -2.1$$

$$E_s(\alpha) = -3.8$$

and $r_1 \geq r_2 \geq r_3$ (such equation is also used when all X groups are identical). As in the nitroxyl moiety, two alkyl parts (A and B in Scheme 3) are attached to the nitrogen, and a linear combination of these two alkyl parts with a and b as coefficients is assumed, a priori. Then, E_s (Table 1), generally negative because of the negative values of r(X), is given by eq 4 and by definition E_s^A corresponds to the moiety carrying the bulkiest group, i.e., with the smallest r_i(X).

$$E_s = aE_s^A + bE_s^B \quad (4)$$

For the sake of simplicity, it is assumed $a = b = 1$, as is given in the example in Scheme 3 (values for r(X) are given in Table 3).[24,37]

Then, eq 5a or its energetic variant eq 5b is used to separate the influences of polar and steric effects due to the structure of the nitroxyl moiety on the C−O bond homolysis in alkoxyamines.

$$\log k_d = \rho_L\sigma_L + \delta E_s + \log k_0 \quad (5a)$$

$$E_s = L\sigma_L + \delta' E_s + E_0 \quad (5b)$$

Here, k_0 refers to the homolysis of dimethylnitroxide phenylethyl alkoxyamine (Me_2NO-PhEt, $\sigma_L = 0$ and $E_s = 0$ from eq 3) taken as standard, and ρ_L and δ are the slopes of the correlation lines representing the influences of the polar and steric effects, respectively. For eq 5b, $L = -\rho_L RT$ ln 10 and $\delta' = \delta RT$ ln 10, and $E_{a,0}$ is the unknown activation energy for the standard, which is assumed to be the dimethylnitroxyl moiety. Values of k_d at 120 °C, E_a, σ_L, E_s, E_N, and E_N' are stored in Table 1. From calculations[14] and from the assumption of a polar transition state,[17] we expect a delaying polar effect increasing with the electron-attracting strength, i.e., a

(36) We used E_s^c simply for easiness, although Hancock's correction seems to have no meanings (see refs 33, 54).

(37) a and b could be determined using eqs 17−19 and compounds **1**−**3**, assuming same $\sigma_{L,n}$ (see Table 1).

$$E_N(\mathbf{1}) - E_N(\mathbf{3}) = -\delta a(c_2 + c_3)r(\text{Et}) \quad (17)$$

$$E_N(\mathbf{3}) - E_N(\mathbf{7}) = -\delta b(c_2 + c_3)r(\text{Et}) \quad (18)$$

$$\frac{a}{b} = \frac{E_N(\mathbf{1}) - E_N(\mathbf{3})}{E_N(\mathbf{3}) - E_N(\mathbf{7})} = 1.5 \quad (19)$$

Intuitively and taking into account a probable distortion of the ring due to the substitution (see compounds **5** and **6** in Table 1, which show different E_a for an expected equivalent steric strain), the ratio a/b can be assumed close to 1. Consequently, being the simplest solution, $a = b = 1$ should be used with each nitroxyl moiety; any other possibility involves simply a scaling factor of δ.

TABLE 3. Individual Steric Constants *r* and Polar *σ* Constants σ_L

group[a]	r^b	$\sigma_L(R_i)^c$	group[a]	r^b	$\sigma_L(R_i)^c$
H	0.32	+0.00	$CR_2(CH_2)_3CR_2$	0.22[d,e]	−0.02[f]
Me	0.00	−0.01	$CR_2C(O)NRCH_2CR_2$	0.11[d,e]	0.33[h]
Et	−0.38	−0.01	$CR_2CH_2C(O)CH_2CR_2$		0.13[i]
Pr	−0.67	−0.01	CH_2OMe	−0.45[j]	0.11
i-Pr	−1.08	+0.01	CH_2OH	−0.33[j]	0.11
t-Bu	−2.46	−0.01	$P(O)(OEt)_2$	−1.22[d,e]	0.32
Ph	−1.40[d]	+0.12	P(O)Me(OEt)	−1.58[d,e]	0.31
$CR_2(CH_2)_2CR_2$	0.31[d,e]	−0.02[f]	$P(O)Me_2$	−1.72[d,e]	0.30
$(CH_2)_5$	−0.38[g]	−0.02[f]			

[a] Groups attached to the nitroxide moiety. [b] Individual steric constants *r*(X) from ref 35 unless otherwise noted. [c] Individual polar constants σ_L from refs 27 and 41 unless otherwise noted. [d] See Results. [e] In text, *r*(C5) is used for $CR_2(CH_2)_2CR_2$, *r*(C6) for $CR_2(CH_2)_3CR_2$, *r*(C6′) for $CR_2C(O)NRCH_2CR_2$ and $CR_2CH_2C(O)CH_2CR_2$, $r(PO_3)$ for $PO(OEt)_2$, $r(PO_2)$ for P(O)(OEt)(Me), and *r*(PO) for $P(O)Me_2$. [f] We assumed that a ring does not exhibit a more polar effect than a linear alkyl group, i.e., $\sigma_{(CH_2)4or5} = 2\sigma_{Et}$. References 27 and 41. [g] From ref 38, used with compounds **20** and **21**. [h] We assumed $\sigma_{L,CH_2NtBuAc} \approx \sigma_{L,CH_2NHAc} = 0.09$ and $\sigma_{L,CH_2NtBuCO} \approx \sigma_{L,Me_2NCO} = 0.28$ from refs 27 and 41. [i] We assumed $\sigma_{L,CH_2COCH_2} \approx \sigma_{L,CH_2COMe} \approx 0.17$ from ref 43; $\sigma^* = 0.60$ rescaled with equations of ref 42. [j] From refs 39 and 43.

negative slope ρ_L, and an accelerating steric effect increasing with the bulkiness of the substituents, i.e., a negative slope δ (E_s being generally negative). First, the slope δ is determined using molecules **1**−**7**, then the slope ρ_L is determined using series **15**−**18**, and then log k_0 is estimated using molecule **19**, for which σ_L and E_s are known unambiguously. Then, the missing *r*(X) constants are calculated, and eq 5a is checked using the remaining molecules. Finally, the estimated values *r*(X) and their effect on the steric strain in our alkoxyamines are discussed, and then an example of the help of eq 5 in the understanding of the NMP is given.

Although many *r*(X) values are known from the work of Fujita[35,38] or can be deduced from the literature,[33,39] *r*(X) for phosphorus groups ($r(PO_3)$ for $PO(OEt)_2$, $r(PO_2)$ for P(O)(OEt)(Me), and *r*(PO) for $P(O)Me_2$) are not known and will have to be determined. Moreover, the *r*(X) established by Fujita[38] for piperidine (*r*(C6)) and pyrrolidine (*r*(C5)), for the hydrogen-bond formation of tertiary and secondary amines with $CHCl_3$, are nearly equal to the values of *r*(Et) because of a similar reactivity of the cyclic amines and of their linear homologues, whereas a strong difference of reactivity was observed with our compounds (see compounds **8**, **11**, and **19** in Table 1). Consequently, the values of *r*(C6) and *r*(C5) have to be reestimated for our molecules. In **8** and **19**, σ_L is the same and thus the difference in reactivity observed is due to steric changes. Thus, log k_d of molecule **8** is proportional to eq 6 when *r*(C6) > *r*(Me) and to eq 7 when *r*(C6) < *r*(Me). Moreover, for **19**, log k_d is proportional to eq 8:

$$\log k_d \approx \delta(2c_0 + 2c_1r_1(C6) + 2c_2r_2(Me) + 2c_3r_3(Me)) \quad (6)$$

$$\log k_d \approx \delta(2c_0 + 2c_1r_1(Me) + 2c_2r_2(Me) + 2c_3r_3(C6)) \quad (7)$$

$$\log k_d \approx \delta\,(2c_0 + 2c_1r_1(Me) + 2c_2r_2(Me) + 2c_3r_3(Me)) \quad (8)$$

In eq 9, the difference (Δ log k_d) between eq 8 and eq 7 gives a positive left-hand side and, since δ is negative (vide supra), a negative right-hand side. On the other hand, in eq 10, Δ log k_d between eq 8 and eq 6 gives a positive value for both the left-hand side and right-hand side.

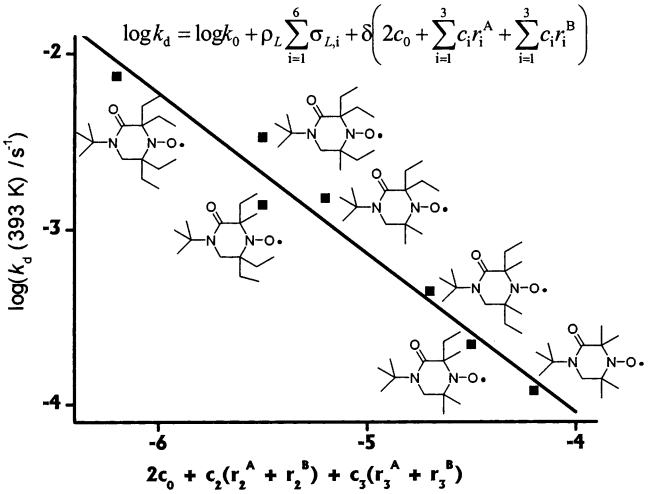


FIGURE 1. log k_d vs eq 4 with $r_1 = r$(C6′), unknown for compounds **1**−**7**.

$$\Delta \log k_d \approx \delta 2c_3(r_3(Me) - r_3(C6)) \quad (9)$$

$$\Delta \log k_d \approx \delta 2c_1(r_1(Me) - r_1(C6)) \quad (10)$$

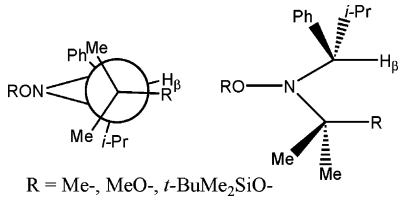
The same result is also observed with alkoxyamine **11**. The same approach holds for five-membered ring molecules, and therefore a positive value is assumed for *r*(C5) and *r*(C6) for the other cyclic compounds listed in Tables 1 and 2.

In a recent paper, with molecules **1**−**7**,[21] and although *r*(C6) was undetermined, it has been shown that the change in E_a or log k_d values was accounted for by an increase of steric hindrance from molecule **1** to **7**. Plotting log k_d vs E_s gives a straight line with a slope $\delta = -0.91 \pm 0.09$ ($R^2 = 0.95$, 7 data), which represents the steric effect in that series (Figure 1) and for the other alkoxyamines used in that study.[21,40]

Although many $\sigma_L(R_i)$ values are available from the literature,[27,30,41−43] the very scattered plot log k_d vs σ_L suggests polar and steric effects strongly intertwined in

(38) Takayama C.; Fujita, T.; Nakajima, M. *J. Org. Chem.* **1979**, *44*, 2871.
(39) Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, 91.
(40) Equivalent values were found with couple (**12**,**13**) and (**8**,**9**), −0.61 and −0.83, respectively.
(41) Charton, M. *Prog. Phys. Org. Chem.* **1987**, *16*, 287.
(42) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

SCHEME 4



R = Me-, MeO-, *t*-BuMe$_2$SiO-

our series of alkoxyamines. It is known that the electron paramagnetic resonance (EPR) coupling value of the hydrogen in the β position is sensitive to the steric hindrance in the nitroxyl radical.[44] Consequently, the unchanged EPR hyperfine coupling constant values $a_{H\beta}$ for molecules **15**−**18** suggest no change in steric strain.[17] That is, it implies that the steric strain in the B moiety is the same throughout the series, i.e., CH_2OMe, CH_2-$OSiMe_2t$-Bu, and ortho ester groups are sterically equivalent. Hence, we can assume a locked conformation for molecules **16**−**18**, as depicted in Scheme 4, where H_β is eclipsed by the R group (Me, MeO, or *t*-BuMe$_2$SiO) on the other side.

Consequently, series **15**−**18** should be a good model for the estimation of the inductive/field effect, $\rho_L\sigma_L$. Indeed, plotting log k_d vs σ_L gives a good straight line with a slope $\rho_L = -3.60 \pm 0.30$ ($R^2 = 0.98$, Figure 2). Hence, an averaged value of all possible ρ_L (6 couples) is taken, i.e. $\rho_L = -3.40$, and is applied to the whole set of molecules. Thus, with **19** ($\sigma_L = -0.06$ and $E_s = -4.2$) and eq 11, a value of log $k_0 = -5.92$ ($E_{a,0} = 152.7$ kJ/mol) is obtained.

$$\log k_d = -3.40\sigma_L - 0.91E_s + \log k_0 \qquad (11)$$

Assuming a late transition state and the same influence of the H atom and of the PhEt group on the homolysis of the O−H and O−C bonds, the close values of ΔE_a (ca. 25 kJ/mol)[45] and ΔBDE_{O-H} (ca. 33 kJ/mol)[46] between *t*-Bu_2NO-PhEt (**19**) and Et_2NO-PhEt and between *t*-Bu_2NO-H (hydroxylamine of molecule **19**) and Et_2NO-H, respectively, support the results obtained above ($E_{a,0} = 152.7$ kJ/mol for Me_2NO-PhEt).

The electronic effect $\rho_L\sigma_L$ being known, the steric influence (E_N or E_N', when E_a is used, see Table 1) of the surroundings of the nitroxide moiety on the k_d or E_a values (see discussion part) is estimated with eq 12:

$$E_N = \log k_d + 3.40\sigma_L \qquad (12a)$$

$$E_N' = E_a - 25.0 \times \sigma_L \qquad (12b)$$

From eq 12b, E_N'(**18**) is very close to E_N'(**19**) (Table 1), suggesting only small differences in steric strain, i.e., E_s-(**18**) $\approx$ E_s(**19**). Moreover, the value of *r*(Ph) depends strongly on the position of the phenyl group with regard to the reactive center, that is, *r*(Ph) is 0.23 when the phenyl group is orthogonal to the reactive center and

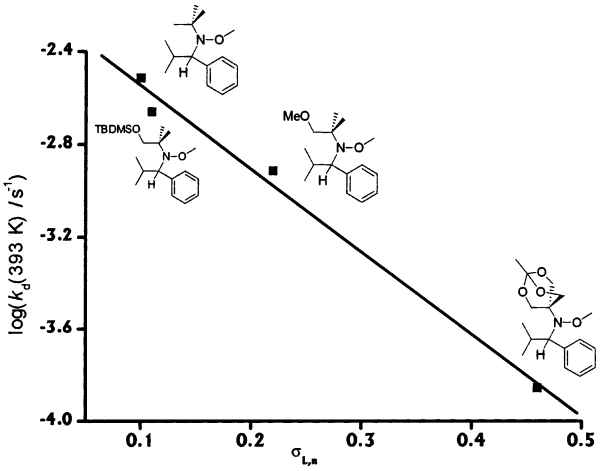


FIGURE 2. Logarithm of the rate constant k_d for the C−ON bond cleavage of (**15**−**18**)-PhEt-derived alkoxyamines vs σ_L given in Table 1.

−2.58 when it is on the same plane.[39,47] Here, from the X-ray structure of **18**,[48] the phenyl group lies in an intermediate position, thus the use of a mean value of −1.4 for *r*(Ph) seems reasonable, but it gives E_s(**18**) markedly larger than E_s(**19**), which is not what we expected. However, it is known that, because of some congestion in the molecule, the orientation of several groups can be limited ("*gear effect*") and the "*effective*" steric constants *r*(X) might differ from their original values (vide infra).[35] Consequently, a term ϵ taking into account a steric interaction between the two parts, A and B, of the nitroxyl moiety must be added:

$$E_s = aE_s^A + bE_s^B + \epsilon \qquad (13)$$

Experimentally, rules of thumb are defined: (i) if the nitroxyl moiety shows some symmetry (like in molecules **8**, **11**, **19**, etc.) or pseudosymmetry (like in cyclic molecules such as **2**, **6**, etc.), ϵ is equal to zero; (ii) if the nitroxyl moiety does not show any symmetry or pseudosymmetry, ϵ is equal to $-bE_s^B$.[49] For the time being, it seems that rule (i) applies when E_s (estimated with eqs 3 and 4) does not exceed −6.

Such rules were applied to the whole set of alkoxyamines.[50] Thus, using eqs 3, 13, and 11 and molecules **8**, **11**, and **22**−**24**, the values of *r*(C6), *r*(C5), $r(PO_3)$, $r(PO_2)$, and *r*(PO) were estimated. They are collected in Table 3. When log k_d of molecules **15**−**18**, **21** and **9**, **12**, **13**, and **22** (**14** was omitted, vide infra) were reported in eq 11, a good agreement was observed with the fitted eq 14:

$$\log k_d = -3.20(\pm 0.36)\sigma_L - 0.89(\pm 0.05)E_s - 5.93(\pm 0.19) \qquad (14)$$

$$R^2 = 0.96; \quad s = 0.17; \quad F_{15,0.01\%} = 157$$

When compounds **1**−**7** and **10** were plotted with eq 14

(43) Hansch, C.; Leo, A. In S*ubstituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley-Interscience Publication: John Wiley & Sons: New York, 1979.

(44) Janzen, E. G. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley-Interscience: New York, 1971; Vol. 6, pp 177−217.

(45) The value of 147 kJ/mol for E_a of Et_2NO-PhEt was estimated with eqs 3, 4, and 11, $\sigma_L = -0.02$ and $E_s = -0.75$.

(46) Bordwell, F. G.; Liu, W.-Z. *J. Am. Chem. Soc.* **1996**, *118*, 10819.

(47) Kutter, E.; Hansch, C. *J. Med. Chem.* **1969**, *12*, 647.

(48) X-rays data (personal communication of Prof. P. Tordo) of **2** show the phenyl group on the nitroxide moiety in an intermediate position, which supports our feeling for the value of *r*(Ph).

(49) The limits of the thumb rules are truly well highlighted by the small but significant and unexpected difference observed in E_a for molecule **5** and **6**, in Table 1.

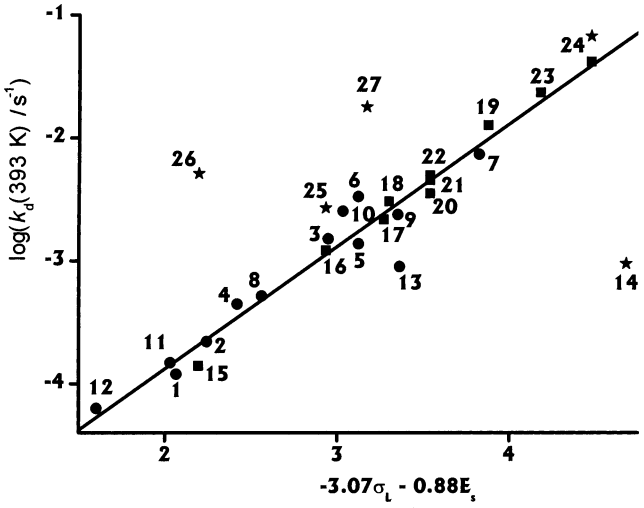


FIGURE 3. log k_d for the C−ON bond cleavage of nitroxide-PhEt-derived alkoxyamines vs eq 15. Circles are for cyclic nitroxyl moieties (**1**−**13**), squares for linear nitroxyl moieties (**15**−**24**), and stars for outliers (**25**−**27** and **14**).

and using r(C6), a clear discrepancy was observed between data **1**−**7** and **10** and eq 14. It points out that the *exo* cyclic double bond sufficiently distorts the ring to change the value of r(C6). Therefore, it was assumed that **1** fulfilled eq 14, and the r(C6) constant for a ring with an *exo* cyclic double bond, $r(C6') = 0.11$, was estimated and then applied to data **1**−**7** and **10**. Subsequently, data **1**−**7** and **10** fit eq 14 well, and a reevaluation gave eq 15, whose ρ_L and δ coefficients are in good agreement with the equations established above (Figure 3).

$$\log k_d = -3.07(\pm 0.28)\sigma_{L,n} - 0.88(\pm 0.04)E_{s,n} - 5.88(\pm 0.16) \quad (15)$$

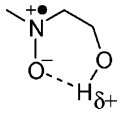
$$R^2 = 0.95; \quad s = 0.17; \quad F_{23,0.01\%} = 210$$

The negative value of ρ_L observed with electron-withdrawing groups supports a partial positive charge generated in the transition state, as it can be expected from the mesomeric forms of nitroxyl radical,[17] while the expected negative value of δ indicates an increase of k_d with increasing steric strain. Using the relationships given by Shorter,[51] the respective weights of polar (35%) and steric (65%) effects were estimated. This points out a strong delaying influence of the electrical effect (σ_L) of the nitroxyl moiety on the value of the cleavage rate constant k_d.

Discussion

As explained in the Results section, we built a Taft−Ingold equation using seven compounds to generate six new steric constants r(X). In Figure 3, it can be seen that substituted cyclic (five- to six-membered rings) and linear nitroxyl moieties are described by eq 15. Using r(C6) = +0.22 (Table 3) gave poor results with **1**−**7** and **10**, which suggests that a substitution in position 3′ and 4′ (Scheme 2) on the ring can influence the steric hindrance around the nitroxyl moiety. Indeed, with $r(C6') = +0.11$ (vide supra) a good agreement was observed with eq 11 (Figure 3 and eq 15). A perfect behavior being assumed for all molecules except for **25**, **26**, **27**, and **14** (outliers in Figure 3, vide infra), the steric constants r(X) were reestimated (Table in Supporting Information) and are in good agreement with the data listed in Table 3. The averaged value of r(Ph) ($\langle r(\mathrm{Ph})\rangle = -1.40$) agrees well with the value (−1.2) used in the literature.[26,52,53] The reestimated value of $r(PO_3)$ for **22** is close to that of r(Ph) (slightly smaller than $\langle r(\mathrm{Ph})\rangle = -1.40$), which implies that the difference between E_N'(**22**) and E_N'(**18**) is mainly due to the *t*-Bu group in **22**.

SCHEME 5



The abrupt change in steric effect observed between symmetric or cyclic alkoxyamines and asymmetric acyclic alkoxyamines seems extremely close to the so-called "*leveled steric effect*" described by Dubois et al.,[54] who showed that the overcrowded *i*-Pr_3COOR ester hydrolyzed faster than the sterically less hindered *i*-Pr_2EtCOOR ester. This observation was explained by conformation effects generating "*active*" and "*inactive*" steric sites. Here, the small EPR hyperfine coupling constants[17,55] of H_β suggest that the situation illustrated in Scheme 4, where H_β eclipses the large alkyl group (B group in Scheme 3) bonded to the nitrogen atom, is common in acyclic nitroxyl radicals and then by analogy surely also in alkoxyamines. Indeed, the positioning of the H_β might create a "*hole*" that would *swallow up* the B group and then provoke a "*leveled steric effect*". Such effect is presently under investigation.

Dubois et al.[54] have observed that sometimes the propyl group is as encumbering as the ethyl group. Therefore, if r(Pr) is assumed equal to −0.27, E_s(**14**) = −3.5, which is in a good agreement with eq 15. From Figure 3, molecules **25**,[56] **26**, and **27** (Table 1) are outliers and cannot be accounted for simply by a larger steric strain. Indeed, in a previous work,[17] it has been shown that an intramolecular hydrogen bond (IHB in Scheme 5) occurred in molecules **25** and **26**. As a result of this IHB, E_a(**25**) is smaller than E_a(**16**) (**16** is a homologue of **25**) by 2.6 kJ mol^{-1} and E_a(**26**) is smaller than E_a(**15**) (**15** is a homologue of **26**) by 11.8 kJ mol^{-1}. Thus, the difference between E_a(**27**) (**27** being the homologue of **25**) and E_a(**22**)

(50) r(Ph), $r(PO_3)$, $r(PO_2)$, and r(PO) can be estimated using original values of respective B parts, but estimated values of −0.20, −0.15, −0.55, and −0.65, respectively, infer that a phosphoryl group generates less steric strain than ethyl group. It means that a nitroxide carrying an ethyl group instead a phenyl or phosphored groups should be as good than these latter.

(51) Shorter, J. In *Correlation Analysis of Organic Reactivity*; D, B., Ed.; Research Studies Press: J. Wiley & Sons: New York, 1982; p 73.

(52) Hendrickson, W. H.; Nguyen, C. C.; Nguyen, J. T.; Simons, K. T. *Tetrahedron Lett.* **1995**, *36*, 7217.

(53) It is not clear how the authors in refs 26 and 47 reached the value of r(Ph), so some cautions have to be taken. Furthermore, different values of r(Ph) can be also estimated from ref 35.

(54) Dubois, J.-E.; MacPhee, J. A.; Panaye, A. *Tetrahedron* **1980**, *36*, 919.

(55) (a) Tordo, P.; Boyer, M.; Friedmann, A.; Santero, O.; Pujol, L. *J. Phys. Chem.* **1978**, *82*, 1742. (b) Dembrowski, L.; Finet, J.-P.; Fréjaville, C.; Le Moigne, F.; Maurin, R.; Mercier, A.; Pages, P.; Stipa, P.; Tordo, P. *Free Rad. Res. Communs.* **1993**, *19 Suppl.*, S23.

(56) Although **25** does not lie outside of the correlation in Figure 3, it will be considered as an outlier because it is capable of IHB as **26** and **27**.

(**22** being the homologue of **27**) was expected to be smaller than the obtained value of 4.2 kJ mol^{-1} (it was expected to be ca. 0.4 kJ mol^{-1}, which is the difference between E_a(**25**) and E_a(**18**)). Furthermore, for EPR hyperfine coupling constants, we expected[17] $a_N^{27} \approx a_N^{22}$, $a_{P\beta}^{27} \approx a_{P\beta}^{22}$ and $a_{H\beta}^{27} \approx a_{H\beta}^{22}$ and not $a_{P\beta}^{27} = 40.7$ G and $a_{P\beta}^{22} = 46.6$ G. The amplitude of $a_{P\beta}$ is related, by the McConnell relationship (eq 16), to the dihedral angle θ_P between the phosphonyl group and the π orbital of the NO moiety where the odd electron is located.

$$a_{P\beta} = B_P \rho_N \cos^2\theta_P \qquad (16)$$

In eq 16, B_P is the constant for the phosphonyl group and ρ_N the spin density on the nitrogen atom for a given nitroxide family. Therefore, if we take $B_P\rho_N \approx 60$ G,[55] eq 16 gives $\theta_P \approx 28°$ for **22** and $\theta_P \approx 35°$ for **27**, which indicates the presence of unexpected strain on the phosphonyl group. This strain can hardly be explained with an IHB,[17] as depicted in Scheme 5. A dipole−dipole interaction between hydroxyl and phosphoryl groups or a hydrogen bonding between these two groups are two possible explanations.[57]

In Table 1, the E_N' values, estimated by means of eq 12b, give a good insight on the global steric effect involved in alkoxyamine homolysis. It can be seen that **19** and **18** have close steric strain energies while that of **22** is lower, as it is compensated by a stronger polar effect, i.e., E_a(**19**) < E_a(**22**) < E_a(**18**). Values lower by −4.8 and −6.5 or −8.1 kJ mol^{-1} for E_N'(**23**) and E_N'(**24**), respectively, with regard to E_N'(**22**), point out that P(O)(OEt)Me and P(O)Me$_2$ groups are bulkier than P(O)OEt$_2$. Moreover, replacing the EtO groups in **22** by two Me groups can more or less markedly reduces the value of E_N', depending on the **24** isomer. The E_N' of **11** and **12** are close, with a difference less than 1 kJ mol^{-1}. Therefore, the difference of 2.8 kJ mol^{-1} between E_a(**12**) and E_a(**11**) can only be accounted for by the polar effect of the phenyl group in **12**, while the importance[14] of the steric effect of the phenyl ring in **12** ("*tied-back methyl groups*") is weak and may be discarded. For **1**, **8**, and **11**, the E_N' values decrease when the cyclic hindrance decreases, i.e., E_N'(**11**) > E_N'(**8**) > E_N'(**1**). The presence of an *exo* cyclic double bond in **1** shows that the hybridization of the carbons in positions 3′ or 4′ ($E_N' \approx 129.1$ kJ mol^{-1} is assumed for tetramethylated 2,2,6,6 homologue of **10**) has a clear influence on the E_N' values of cyclic compounds, i.e., smaller than E_N'(**8**) by ca. 5 kJ mol^{-1}. E_N'(**1**−**7**) values show that the strain in position 3′ and the asymmetry induced by the *exo* cyclic double bond generate a clear difference when Et groups are incorporated on the carbons (carbons 2′ and 6′) in α positions of the nitroxide moiety, i.e., a difference of 2.6 kJ mol^{-1} is not expected between the E_N' values for molecules **5** and **6**.

Hawker et al.[7] have observed that polar and steric effects in alkoxyamines play a role in the results of the polymerization of styrene, but they have not assessed their influence. Applying our approach to their alkoxyamines, we tried to determine which effects were involved in the success or failure of their experiments. For molecules **28**−**33**, PDI, $\sigma_{L,n}$, $E_{s,n}$ values, and the estimated cleavage rate constants k_d obtained using eq 15 are listed in Table 2. From **28** to **29**, the decrease in the value of PDI is readily explained by an increase in polarity of the nitroxide moiety, i.e., a decrease of the value of the homolysis rate constant k_d. However, the model cannot explain the difference in PDI observed for **29** and **30**, which is certainly due to a conformation effect (vide supra). Moreover, the value of the recombination rate constant is also conformation dependent[58] and thus the PDI can be modified more than is expected from our model. PDI(**31**) and PDI(**32**) being larger than PDI(**28**) reflects σ_L(**31**,**32**) > σ_L(**28**) and E_s(**31**,**32**) > E_s(**28**), i.e., E_a(**28**) < E_a(**31**,**32**). Moreover, the replacement of a cyclohexyl group by two pentyl groups does not affect the PDI, which indicates that long chains in α-position of the nitroxide moiety do not increase the steric hindrance (vide supra). Molecule **33** is close to molecule **11** in structure, and E_a(**33**) is larger than E_a(**11**) as expected from a larger polar effect due to the presence of the cyano group (Table 2). E_a(**33**) is larger than E_a(**28**), just as PDI(**33**) is larger than PDI(**28**). On the other hand, E_a(**33**) is larger than E_a(**29**) and E_a(**30**), whereas PDI(**33**) is markedly smaller than PDI(**29**) and PDI(**30**) (Table 2). Such results suggest that the phenyl groups are not conformationally locked. However, such assumptions need to be checked with kinetic measurements. Moreover, we should keep in mind that PDI values also depend on k_c, k_p, and k_t values.[11]

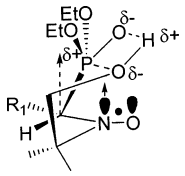
Recently, German et al.[18] have measured the PDI values and the observed polymerization rate constants of the styrene polymerization controlled by *para*-substitued aryl-PROXYL-PhEt alkoxyamines. They claimed that electron-withdrawing groups weakened the C−ON bond homolysis, i.e., that the E_a of homolysis was decreased. However, when we considered their values of PDI, we found that they varied nearly as expected from the results highlighted in our paper, i.e., the C−ON bond is strengthened by electron-withdrawing groups. Because the observed polymerization rate constant in NMP depends on several rate constants, it might be misleading to correlate it to any effect involved in C−ON bond homolysis. Sometimes though, this can suggest some trends, as can be seen in Table 2. Consequently, the results observed on the observed polymerization rate constant by German et al.[18] could be explained either by stereoelectronic effects on the recombination rate constants or a possible polar ground-state effect in the nitroxyl moiety, as already observed by the author on TEMPO alkoxyamines.[17]

Furthermore, the author is pleased to see that Fukuda et al.[19] reached qualitative conclusions, using polystyryl-based alkoxyamines and another method to measure the homolysis rate constants, which are in good agreement with our quantitative conclusions.

Conclusion

It has been shown that polar and steric effects in the homolysis of the C−ON bond of alkoxyamines are sepa-

(57) Recently, X-Ray of **27** were obtained in Tordo's group and corroborate an IHB between hydroxyl and phosphoryl groups as depicted.



(58) Braslau, R.; Naik, N.; Zipse, H. *J. Am. Chem. Soc.* **2000**, *122*, 8421.

rable using a Taft−Ingold approach and that steric strain is the main effect involved. Moreover, the analysis developed here can be used to understand the factors affecting NMP. Despite several drawbacks such as the abrupt change in the steric strain, the possible occurrence of a diastereoisomer effect and of an intramolecular hydrogen bond, which are not easily predictable, and the fact that a few r(X) constants are still unknown, the author believes that the Taft-Ingold approach will be a powerful tool to predict k_d and to help design new nitroxyl radicals for NMP.

Acknowledgment. The author is deeply grateful to Professor Hanns Fischer for guidance and helpful discussions. The author thanks a reviewer for pertinent suggestions on the BDE(O−H) of hydroxylamines. The author thanks the University of Zürich and the University of Provence for their financial support.

Supporting Information Available: Table of reestimated values of r_i(X). This material is available free of charge via the Internet at http://pubs.acs.org.

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