Steric and Polar Effects of the Cyclic Nitroxyl Fragment on the C−ON Bond Homolysis Rate Constant

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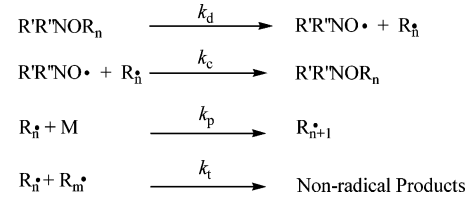
ABSTRACT: Alkoxyamines and persistent nitroxyl radicals are important regulators of nitroxide mediated radical polymerization (NMP). Because polymerization times decrease with increasing rate constant of the homolysis of the C−ON bond between the polymer chain and the nitroxyl moiety, the factors influencing the cleavage rate constant are of considerable interest. Here, we present the measurements of the rate constants (k_d) of the C−ON bond cleavage in new cyclic alkoxyamine models. The homolysis rate constants of 9 new alkoxyamines and 33 others given by the literature are analyzed with regards to the contributions of the polar inductive/field (σ_I) effect, the steric (E_s) effect and the intramolecular hydrogen bonding (IHB) effect of the nitroxyl moieties, using the multiparameter equation established by Marque, i.e., $\log(k_d/k_{d,0}) = -3.07\sigma_I - 0.88E_s - 5.88$. Cyclic steric constants $r(R_i)$ for seven- and eight-membered rings are developed. Analysis of the results provides new insight on the importance of the conformation of the alkoxyamine on the values of k_d.

Introduction

Since the pioneering work of Rizzardo[1] and Georges,[2] nitroxide mediated free radical polymerizations (NMP) have often been used for the synthesis of living polymers and copolymers with low polydisperties, controlled molecular weights, and elaborate architectures.[3,4] The ideal mechanism is outlined in Scheme 1. Nitroxide-capped chain molecules cleave into propagating alkyl and persistent nitroxyl radicals (k_d). The propagating radicals grow by monomer addition (k_p) and re-form longer dormant chains by cross-coupling with the nitroxyl radicals (k_c). Simultaneously, the usual self-termination of the propagating radicals into unreactive polymer products takes place (k_t). This removes the propagating radicals and increases nitroxyl radical concentration in time; the cross-coupling reaction therefore dominates over self-termination. For long reaction times, a quasi-equilibrium of the reversible cleavage is reached, characterized by weakly time-dependent concentrations and a large excess of the persistent over the propagating radicals.[5−9]

For the well-controlled and living radical polymerization of a given monomer with propagation and termination constants k_p and k_t, the rate constants of the reversible cleavage k_d and k_c must fall into proper ranges.[6,8−12] Several studies have shown that k_d is a crucial parameter because it varies within a broad range, i.e., from 2.4 to 10^{-10} s^{-1}, whereas the range for k_c is rather narrow (10^6−10^9 L mol^{-1} s^{-1}).[7,8,10−15] Furthermore, at a given time, the polydispersity index is lower for a larger k_d.[8,10,11,13,15] Consequently, the determination of k_d has recently found considerable attention for both polymeric[16−22] and low molecular weight model systems.[23−45]

Scheme 1



Among other factors, the polar and steric effects of the substituents of both the leaving alkyl[23−25,27−36] and the nitroxyl[23−26,29,36−46] radicals affect the homolysis rate constant k_d. Nevertheless, although systematic studies on the nitroxyl moiety are scarce,[36,38,40,46] one of us[46] has recently developed a Taft−Ingold approach that separates the polar and steric effects of the substituents on the nitroxyl moiety in the sum (eq 1) of the universal electrical Hammett constant[47−51] σ_I and the Taft steric constant[52,53] E_s.

$$\log k_d = -3.07\sigma_{I,n} - 0.88E_{s,n} - 5.88 \qquad (1)$$

We present hereafter the Arrhenius parameters and the k_d values for eight piperidine−squeleton-based (**11**, **25**, **26**, **32**−**34**, **36**, **36a**) one PROXYL−squeleton-based (**18**), and two diazepanone-based (**20**, **44**) alkoxyamines (Table 1). Those values, along with the k_d of 33 alkoxyamines from the literature[36−42,54] (Scheme 2), are analyzed with eq 1 to determine the influence of the polar effect, the ring size effect, the ring substitution and the ring sp^2/sp^3 hybridization effects, the leveled steric effect, and the intramolecular hydrogen bonding (IHB) effect.

Experimental Section

The syntheses of alkoxyamines **11**, **18** **20**, **25**, **26**, **32**−**34**, and **44** have recently been described.[55−59]

Remarks. Due to the presence of several diastereoisomers, the ^1H and ^{13}C NMR spectra are extremely complicated, and comprehensive assignment of individual resonances was therefore not possible. Hence, only unambiguous signals were

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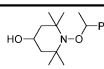
Table 1. Arrhenius Parameters (A, E_a), Rate Constants (k_d) at 120 °C for C−ON Bond Homolysis in Alkoxyamines 11, 18, 20, 25, 26, 32−34, 36, 36a, and 44, and Nitrogen Hyperfine Coupling Constants a_N of the Corresponding Nitroxyl Radicals

Alkoxyamines		runs	T (°C)	A (10^{14} s^{-1})[a]	E_a (kJ·mol^{-1})[b]	$k_{d,393}$ (s^{-1})	a_N (mT)[c]
11		3	119 - 140	(2.4)	135	$3.1\ 10^{-4}$	-
18		17	71 – 111	3.5	115[d]	0.16	1.420
20		2	121 – 122	(2.4)	132	$6.6\ 10^{-4}$	1.506
25		6	50 – 90	3.4	113[e]	0.34	1.470
26		5	91 - 148	1.5	128	$1.5\ 10^{-3}$	1.382
32		3	115 - 125	(2.4)	128	$2.7\ 10^{-3}$	1.450
33		8	80 – 126	2.8	128	$3.0\ 10^{-3}$	1.466
34		14	80 – 132	1.6	125	$3.5\ 10^{-3}$	1.412
36		3	100 - 120	(2.4)	126	$3.8\ 10^{-3}$	1.472
36a		3	110 - 130	(2.4)	135	$2.8\ 10^{-4}$	1.472
44		2	100 – 120	(2.4)	122	$1.3\ 10^{-2}$	1.506

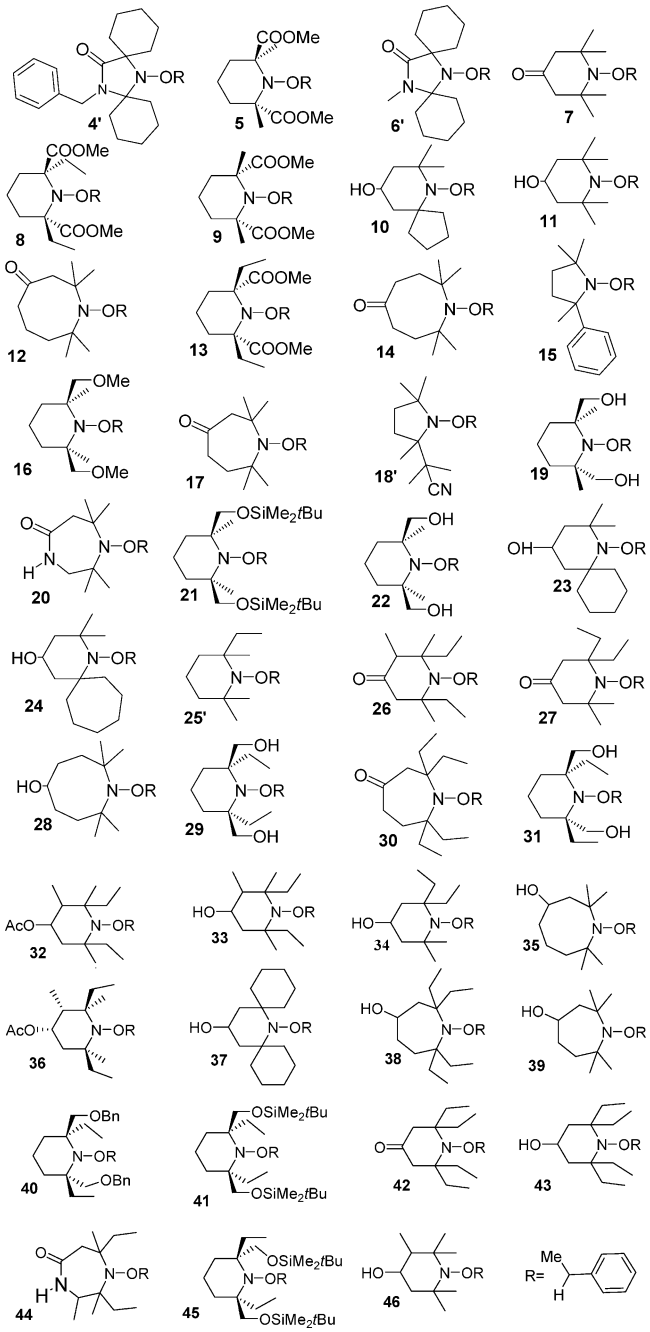
[a] Statistical error smaller than a factor of 2. Values in brackets are the average of all experimentally accessible frequency factors given in refs 23, 24, 36, and 38. [b] Statistical error between 2 and 3 kJ/mol. [c] EPR nitrogen hyperfine coupling constant a_N in *tert*-butylbenzene. The corresponding nitroxyl radicals **18**• **20**•, **25**•, **26**•, **32**•, **33**•, **34**•, **36**•, and **44**• are displayed in Scheme 6. [d] The reestimated value of E_a with $A = 2.4 \times 10^{14}$ s^{-1} is of 114 kJ/mol. [e] The reestimated value of E_a is of 112 kJ/mol with $A = 2.4 \times 10^{14}$ s^{-1}.

individually assigned. The identification of the new compounds rests on these typical ^{1}H and ^{13}C NMR assignments, combined with very good elemental analysis and gas chromatography coupled with mass spectrometer (GC−MS) analysis.

General Data. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.37 MHz) spectra were recorded in $CDCl_3$ on a Bruker 300 spectrometer. IR spectra were taken on a Nicolet Magna-IR 750 spectrometer in KBr pill, MS spectra on a Finnigan SSQ 710 apparatus using isobutane for chemical ionization (CI). Elemental analyses were performed on a Leco CHNS-932 apparatus. Gas chromatography was performed on Agilent 6850 Series chromatograph on a HP-1 methyl siloxane capillary column (30 m × 320 μm × 0.25 μm) with He carrier gas (3 mL/min) and FID detector, injector temperature 250 °C, starting temperature 100 °C, and gradient 20°/min to 300 °C.

Materials. The following reagents and solvents were acquired from Fluka and were used as received: acetanhydride (≥99%), *tert*-butyl hydroperoxide (70% in water), copper(I) chloride (≥97%), copper(I) bromide (≥98%), 2-chloropropionic acid methyl ester (≥97%), 4-(dimethylamino)pyridine (≥98%), ethyl acetate (≥99.5), ethylbenzene (≥98%), hexane (≥99.5%), methyl *tert*-butyl ether (≥99%), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylene-triamine (≥98%), pentane (≥99.5%), sodium borohydride (≥96%), tetrabutylammonium bromide (≥98%), and toluene (≥99.7%). Peracetic acid (40% in acetic acid, Peraclean) was from Degussa. All other chemicals were from Fluka and were ≥98% pure. Silica gel (0.063−0.2 mm) for column chromatography was from Merck.

Scheme 2



2,6-Diethyl-2,3,6-trimethylpiperidin-4-ol (2). A 50% aqueous solution of NaOH (40 mL) was added to a solution of 197.3 g (1.0 mol) 2,6-diethyl-2,3,6-trimethylpiperidin-4-one[57] (**1**) in 2-propanol (160 mL). Sodium borohydride (22.7 g, 0.60 mol) was added, and the stirred mixture was heated to reflux under nitrogen for 5 h. Water (80 mL) was then added, and the mixture was refluxed for 5 min, cooled to 50 °C, and extracted with toluene (2 × 100 mL). The organic layer was washed with water (3 × 100 mL) and an aqueous NaCl solution (10%, 3 × 80 mL), dried over $MgSO_4$, and then evaporated on a rotary evaporator to afford **2** (193.7 g, 97.2%) as a slightly yellow oil. Capillary GC: six closely spaced peaks at 3.635 min (4.36%), 3.656 min (10.93%), 3.708 min (39.95%), 3.767 min (17.91%), 3.791 (19.40%), 3.842 min (6.73%), sum of all peaks = 99.28%. Anal. Calcd for $C_{12}H_{25}NO$ (199.34): C, 72.31; H, 12.64; N, 7.03. Found: C, 72.07; H, 12.62; N, 6.99. GC−MS(CI), *m*/*e*: six peaks with identical spectra: 200 (42, $[M + H]^+$), 182 (100). IR (cm^{-1}): 3341 s, 2964 s, 2933 s, 2879 s, 1460 s, 1373 s. ^{1}H NMR (300 MHz, $CDCl_3$), mixture of diastereoisomers: δ = 4.30−3.60 (m, 1 H, −C*H*(OH)−), 1.80−0.80 (m, 24 H, 1 OH, 1 NH,

1 CH, 1 CH_2, 3 CH_3 , 2 C_2H_5). ^{13}C NMR(75.38 MHz $CDCl_3$): a mixture of diastereoisomers, 48 poorly resolved signals clustered between 69.79 and 27.29 ppm.

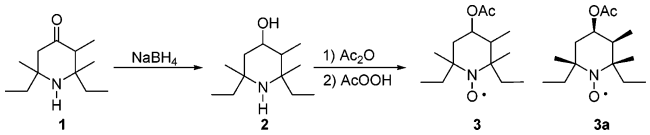
4-Acetoxy-2,6-diethyl-2,3,6-trimethylpiperidin-*N*-oxyl (3 and 3a). Acetanhydride (55.9 g, 0.5475 mol) was added dropwise over 30 min to a stirred solution of 4-(dimethylamino)pyridine (0.56 g) in 2,6-diethyl-2,3,6-trimethyl-piperidin-4-ol (**2**) (99.67 g, 0.50 mol). The temperature during the addition was kept below 45 °C. The mixture was then stirred for another 30 min at 45 °C, cooled to room temperature, and diluted with methyl-*tert*-butyl ether (250 mL). A solution of sodium hydroxide (23.8 g, 0.595 mol) in water (125 mL) was then added, and the organic layer was separated, washed with water (30 mL) and an aqueous NaCl solution (10%, 2 × 30 mL), dried over $MgSO_4$, and evaporated on a rotary evaporator to afford 117.64 g (97.5%) of the O-acetylated **2** as a slightly yellow oil. Capillary GC: six closely spaced peaks at 4.166 min (6.80%), 4.196 min (9.89%), 4.233 min (32.73%), 4.249 min (24.06%), 4.273 min (19.83%), 4.310 min (5.72%), sum of all peaks = 99.03%. Anal. Calcd for $C_{14}H_{27}NO_2$ (241.38): C, 69.66; H, 11.28; N, 5.80. Found: C, 69.55; H, 11.24; N, 5.75. GC−MS(CI), *m/e*: six peaks with identical spectra ($C_{14}H_{27}NO_2$ (241.38)) 242 (20, $[M + H]^+$), 182 (100). ^1H NMR (300 MHz, $CDCl_3$), mixture of diastereoisomers, δ = 5.30−4.60 (*m*, 1H, −C*H*(OAc)−), 1.95 (*bs*, 3H, $OCOCH_3$), 1.80−0.40 (*m*, 23 H, 1 NH, 1 CH, 1 CH_2, 3 CH_3, 2 CH_2CH_3). ^{13}C NMR(75.38 MHz $CDCl_3$), mixture of diastereoisomers, δ ($OCOCH_3$) = 170.64, 170.62, 170.43, 170.38, additionally 53 signals clustered between 73.33 and 30.08 ppm.

Water (75 mL) and solid $NaHCO_3$ (63.0 g, 0.75 mL) were added to a solution of 60.34 g (0.250 mol) of the O-acetylated **2** in hexane (150 mL). A 40% solution of peracetic acid in acetic acid (76.05 g, 0.40 mol) was then added dropwise to the stirred mixture at 25−30 °C over 90 min. The red mixture was stirred for 150 min at room temperature, then the organic layer was separated, washed with water (100 mL), with aqueous Na_2CO_3 (1 M, 50 mL), and finally with a NaCl solution (10%, 2 × 50 mL), dried over $MgSO_4$, and evaporated on a rotary evaporator to afford 63.45 g (99%) of **3** as a red oil which partly solidified on standing. Capillary GC: eight closely spaced peaks at 4.903 min (6.02%), 4.944 min (9.82%), 4.996 min (5.21%), 5.050 min (17.71%), 5.090 min (35.47%), 5.108 min (17.24%), 5.133 min (5.81%), 5.194 min (1.36%), sum of all peaks = 98.64%. Anal. Calcd for $C_{14}H_{26}NO_3$ (256.37): C, 65.59; H, 10.22; N, 5.46. Found: C, 65.60; H, 10.15; N, 5.40. GC−MS (CI), *m/e*: eight peaks with identical spectra 256 (3, $[M]^+$), 168 (24), 137 (67). IR (cm^{-1}): 2975 m, 2938 m, 2882 w, 1738 s.

Crystallization of the Diastereoisomer 3a. The diastereoisomeric mixture **3** (30 g) was dissolved in pentane (15 mL) and left at −30 °C for 15 h. The crystals (7.55 g) were filtered off, washed with cold pentane, and recrystallized once again from pentane (80 mL) at −30 °C to afford 7.05 g of the pure isomer **3a** as large red crystals, mp 86−89 °C. Capillary GC: 1 peak at 5.090 min (98.6%).

Acetic Acid 2,6-Diethyl-2,3,6-trimethyl-1-(1-phenylethoxy)piperidin-4-yl Ester (36). Tetrabutylammonium bromide (0.075 g, 23.3 mmol) and Cu^IBr (0.032 g, 0.223 mmol) were added to a solution of 5 g (0.0195 mol) of **3a** in 10.3 g (0.0970 mol) of ethylbenzene, and the mixture was deoxygenated by four vacuum (0.1 bar)/argon cycles. An aqueous solution (70%) of *tert*-butyl hydroperoxide (5.3 g, 41.2 mmol) was then added dropwise at 45−50 °C over 10 min. The mixture was stirred at 45−50 °C for 5 h, then diluted with 20 mL ethylbenzene, washed successively with 20 mL each of aqueous Na_2SO_3 (20%), saturated $NaHCO_3$, and saturated NaCl, and then dried over Na_2SO_4. Evaporation of the solvent on a rotary evaporator and chromatography on silica gel column with hexanes−EtOAc (20:1) afforded 6.4 g (90.8%) of **36** as colorless oil. Anal. Calcd for $C_{22}H_{35}NO_3$ (361.53): C, 73.09; H, 9.76; N, 3.87. Found: C, 72.87; H, 9.64; N, 3.85. MS-(APCI), *m/e*: 362 (45, $[M + H]^+$). IR (cm^{-1}): 2973 s, 1736 s, 1452 m, 1367 s, 1239 s. ^1H NMR (300 MHz, $CDCl_3$), two diastereoisomers, δ = 7.39−7.22 (m, 5H, C_6H_5), 5.35−5.10 (m, 0.4H, −C*H*(OAc)−, first diastereoisomer), 5.10−4.88 (m, 0.6H, −C*H*(OAc)−, second diastereoisomer), 4.77 (q, J = 6.6 Hz, 1H, $CH_3CHC_6H_5$), 2.35−0.35 (m, 25 H, 1 CH, 1 CH_2, 4 CH_3, 2 C_2H_5), 2.07 (bs, 3H, $OCOCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), two diastereoisomers, δ = 170.96 ($OCOCH_3$), 147.00 ($CH_3CHC_6H_5$), 128.40 (C_6H_5), 127.19 (C_6H_5), 126.48 (C_6H_5), additionally ∼33 poorly resolved signals clustered between 84 and 8.47 ppm.

Scheme 3



Acetic Acid 2,6-Diethyl-1-methoxycarbonyloxy-2,3,6-trimethylpiperidin-4-yl Ester (36a). CuCl (1.98 g. 0.020 mol) was added to a solution of **3a** (2.564 g, 0.010 mol) and 2-chloropropionic acid methyl ester (1.348 g, 0.0110 mol) in ethyl acetate (20 mL) under nitrogen. Thereafter, *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (3.466 g, 0.020 mol) was added dropwise over 20 min. The mixture was stirred at room temperature for 4 h, diluted with ethyl acetate (50 mL), and then filtered over a filtration aid (Hyflo). The filtrate was washed with water (3 × 10 mL) and then with an aqueous solution of EDTA disodium salt (1%, 3 × 10 mL) and water (3 × 10 mL). Drying over $MgSO_4$ and evaporation on a rotary evaporator afforded 3.40 g (99%) of **36a** as colorless oil. Anal. Calcd for $C_{18}H_{33}NO_5$ (343.47): C, 62.95; H, 9.68; N, 4.08. Found: C, 63.25; H, 9.75; N, 4.04. GC−MS (APCI), *m/e*: 344, (100, $[M + H]^+$). IR (cm^{-1}): 2987 m, 2951 m, 1735*s*. ^1H NMR (300 MHz, $CDCl_3$), two diastereoisomers, δ = 5.20−5.09 (bs, 0.3H, −C*H*(OAc)−, first diastereoisomer), 4.98−4.82 (bs, 0.7H, −C*H*(OAc)−, second diastereoisomer), 4.45−4.25 (m, 1H, $CH_3CHCOOCH_3$), 3.72 (s, 3H, OCH_3), 2.20−0.70 (m, 25 H, 1 CH, 1 CH_2, 4 CH_3, 2 C_2H_5), 2.06 (bs, 3 H, $OCOCH_3$). ^{13}C NMR-(75.38 MHz $CDCl_3$), two diastereoisomers, δ = 174.72 (CH_3-$CHCOOCH_3$), 170.72 ($OCOCH_3$), 82.51, 80.48, 72.72, 68.34, 66.56, 66.08, 65.30, 65.10, 64.15, 63.66, 61.18, 60.80, 51.65 ($COOCH_3$), 38.18, 37.09, 36.95, 36.49, 34.42, 31.86, 31.44, 29.65, 29.10, 27.39, 26.43, 25.49, 21.55, 21.36, 19.14, 18.88, 18.76, 12.77, 10.36, 8.38, 7.89, 7.74.

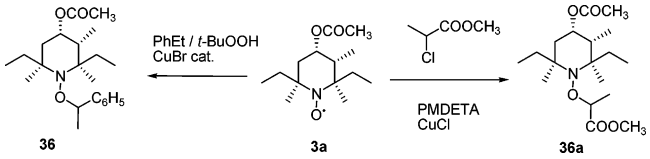
Kinetic Experiments. The solvent *tert*-butylbenzene (Fluka, >99%) was purified following a known procedure.[60] Rate constants k_d were obtained from the appearance of the nitroxyl radical ESR signal recorded in the presence of various scavengers such as galvinoxyl, oxygen, and TMIO−$^{15}ND_{12}$ used to remove irreversibly the released alkyl radicals.[7,24] The evolution of the nitroxyl radical signal was recorded with either a EMX Bruker or a MS100 Magnettech EPR spectrometer. The nitroxyl radical growth obeyed the expected first-order kinetics and ended at the concentration expected for full decomposition of the alkoxyamine. Measurements at different temperatures yielded the frequency factors A and the activation energies E_a by Arrhenius analysis.

Results

Preparation of Alkoxyamines 36 and 36a. Compounds **36** and **36a** were prepared from the easily available[57] 2,6-diethyl-2,3,5-trimethylpiperidin-4-one, **1**, which was transformed into nitroxyl radicals **3** and **3a** as depicted in Scheme 3.

Ketone **1** contains three asymmetric carbon atoms; hence four diastereoisomers may be expected. GC−MS analysis revealed only two isomeric peaks in a 2.2:1 ratio. However, four distinct C-carbonyl resonances in the ^{13}C NMR spectrum of **1** indeed indicated the presence of four diastereoisomers.[57] Nevertheless, given the very narrow boiling range of **1** and its appearance as a single spot on TLC, the separation of the isomers by distillation or chromatography was not attempted. Therefore, the formulas in Scheme 3, with the exception of **3a**, represent all possible diastereoisomers. Sodium borohydride reduction of **1** followed by acetylation and

Scheme 4



peracetic acid oxidation afforded nitroxyl radical **3** as a diastereomeric mixture. Crystallization of the isomeric mixture of **3** from *n*-pentane afforded a single diastereomer **3a**. Its structure was determined by X-ray analysis.[61] Nitroxyl radical **3a** was then transformed into alkoxyamine **36** using Cu-catalyzed *t*-butylhydroperoxide-promoted coupling[62] with ethylbenzene. The slightly adapted protocol[31] of Matyjaszewski was used for the coupling of **3a** with methyl chloropropionate to afford **36a** (Scheme 4).

Kinetic Measurements. Because of the persistent radical effect (PRE),[5] measurements of k_d were performed in the presence of an excess of scavengers such as galvinoxyl, TMIO−$^{15}ND_{12}$, or oxygen.[7,24] Plots of nitroxyl concentration evolution with time and Arrhenius plots were already well exemplified in previous works and do not need further reports and comments.[7,24] As expected, frequency factors A of molecules **18**, **25**, **26**, **33**, and **34** lie in the range 10^{13}−10^{15} s^{-1} and are centered ca. 10^{14} s^{-1}.[23−25,27,32,36,38,39] Therefore, the 33 values of A measured by Marque et al.[23−25,36,38] give an averaged value of 2.4×10^{14} s^{-1}, and this value is used to estimate and to reestimate the values of E_a (Tables 1 and 2). While this work was in progress, the k_d of **11** and **20** were published by Fukuda et al.[63] and Studer et al.,[54] respectively, and the values obtained by the authors agree well with these reported values. The E_a of **36a** (135 kJ/mol, Table 1) falls close to the expected value (132 kJ/mol) when applying the increment ($\Delta E_{a,PhEt\rightarrow EEst} = +5.7$ kJ/mol) given by Marque et al.[24]

Taft—Ingold Approach. Recently, one of us[46] showed for 24 nitroxyl moieties that the effects of the substituents on the nitroxyl moiety are rationalized in terms of the Taft−Ingold equation (eq 1) where $\sigma_{I,n}$ and $E_{s,n}$ are the universal electrical (polar inductive/field effect) and steric substituent constants for a given alkoxyamine n. Thus, the ring substituent and ring size effects in molecules **4′**−**45** were analyzed with eq 1. All the values of E_a given in Table 2 were reestimated with an averaged frequency factor A of 2.4×10^{14} s^{-1} and for the PhEt group (R group in Scheme 2) as released alkyl radical. For molecules **18′** and **25′**, the values of E_a for a nitroxyl moiety carrying a PhEt group were estimated using the increment[64] ($\Delta E_{a,PCN\rightarrow PhEt}$) of +18.0 kJ/mol to give 132.3 and 129.7 kJ/mol, respectively. The values of k_d at 120 °C, $\sigma_{I,n}$, $E_{s,n}$, and $E_{N,n}'$ (global steric strain of nitroxyl moiety given by eq 2) are gathered in Table 2.

$$E_{N,n}' = E_a - 25.0\sigma_{I,n} \quad (2)$$

$$\sigma_{I,n} = \sum_{i=1}^{i=6} \sigma_I(R_i) \quad (3)$$

$$\sigma_{I,R_1CH_2} = 0.416\sigma_{I,R_1} - 0.0103 \quad (4)$$

$$\sigma_{I,R_1R_2CH} = 0.297\Sigma\sigma_{I,R} + 0.00482 \quad (5)$$

The values of $\sigma_{I,n}$ were given[46] by eq 3 where $\sigma_I(R_i)$ is the individual Hammett constant[65,66] σ_I of each R group bonded to the tetrahedral carbon in the positions α to the nitroxyl function. All individual σ_I constants were not known, and the missing ones were estimated[67] with eqs 4 and 5. The values of $E_{s,n}$ were given by eq 6 assuming $a = b = 1$ and $\epsilon = 0$, because all molecules were cyclic and therefore exhibited symmetry or pseudosymmetry.[46] The values of E_s^A and E_s^B were given[53] by eq 7 and the individual steric constant $r(R_i)$ with i being the rank related to the value of $r(R_i)$ i.e., its size (the more negative $r(R_i)$ is, the larger R_i is) and $r_1 \geq r_2 \geq r_3$. All individual $\sigma_I(R_i)$ and $r(R_i)$ values are listed in Table 3. Unknown values of $r(R_i)$ were estimated either by analogy[68] like for $r(CMe_2CN)$[69] and $r(CH_2OCH_2Ph)$ or assuming that the value of k_d obeyed eq 1 like for r(C7), r(C7′), r(C8), r(C8′), r(COOMe), and $r(CH_2OSiMe_2t\text{-Bu})$. The value of r(C7‴) was estimated

Table 2. Reestimated Activation Energies (E_a) and Rate Constants (k_d) at 120 °C, Universal Electrical (Polar) Hammett Constants $\sigma_{I,n}$, Steric Constants $E_{s,n}$, and Global Steric Strain $E_{N,n}'$ for the Nitroxyl Fragments of Alkoxyamines 4′−45[a]

alkoxyamines	E_a[b]	k_d	$\sigma_{I,n}$[c]	$E_{s,n}$[d]	$E_{N,n}'$[e]
4′	139.4[f,g]	7.1×10^{-5}	0.50	−3.62[f]/*−2.87*[f,h,i]	123.2
5	138.5[j]	9.4×10^{-5}	0.60	−4.71	125.5
6′	137.4[f,g]	1.3×10^{-4}	0.50	−3.62[f]/*−2.87*[f,h,i]	124.9
7	137.3[k]	1.4×10^{-4}	0.07	−2.70	135.7
8	135.6[j]	2.3×10^{-4}	0.60	−6.21	122.6
9	135.5[j]	2.3×10^{-4}	0.60	−4.71	122.5
10	135.0[l]	2.7×10^{-4}	−0.01	−2.80	135.3
11	134.6[f]	3.1×10^{-4}	−0.02	−2.70	134.9
12	134.6[k]	3.1×10^{-4}	0.08	−2.90	132.6
13	134.1[j]	3.6×10^{-4}	0.60	−6.21	121.1
14	133.6[k]	4.2×10^{-4}	0.00	−2.90	133.6
15	133.5[f,m]	4.3×10^{-4}	0.07	−2.99	131.8
16	133.3[j]	4.6×10^{-4}	0.18	−3.34	128.8
17	133.1[k]	4.9×10^{-4}	0.11	−3.32	130.4
18′	132.3[f]	6.2×10^{-4}	0.09	−3.44	130.1
19	132.1[j]	6.6×10^{-4}	0.18	−2.74	127.6
20	132.1	6.6×10^{-4}	0.15	−3.32	127.6
21	131.6[j]	7.7×10^{-4}	−0.04	−3.09	132.6
22	131.3[j]	8.5×10^{-4}	0.18	−2.74	126.8
23	130.9[j]	9.6×10^{-4}	−0.01	−3.09	131.2
24	130.4[l]	1.1×10^{-3}	−0.01	−3.41	130.7
25′	129.7[f]	1.4×10^{-3}	−0.06	−2.95	131.3
26	129.4	1.5×10^{-3}	0.06	−3.95[f]	126.1
27	128.7[k]	1.9×10^{-4}	0.07	−3.70[f]/*−4.45*[f,h,n]	127.0
28	128.6[k]	1.9×10^{-3}	−0.02	−3.59	129.1
29	128.4[j]	2.1×10^{-3}	0.18	−3.31	123.9
30	128.1[k]	2.3×10^{-3}	0.11	−5.30	125.4
31	128.0[j]	2.3×10^{-3}	0.18	−3.31	123.5
32	127.5	2.7×10^{-3}	0.00	−3.95[f]/*−3.19*[f,h,o]	127.5
33	127.2	3.0×10^{-3}	−0.02	−3.95[f]/*−3.19*[f,h,p]	127.7
34	126.7	3.5×10^{-3}	−0.01	−3.70	127.0
35	126.7[k]	3.5×10^{-3}	−0.03	−3.59	127.5
36	126.4	3.8×10^{-3}	0.00	−3.95[f]/*−3.19*[f,h,q]	126.4
37	125.7[l]	4.7×10^{-3}	−0.01	−3.49	126.0
38	125.7[k]	4.7×10^{-3}	−0.02	−6.20	126.2
39	124.3[k]	7.2×10^{-3}	−0.02	−4.20	124.3
40	124.2[j]	7.4×10^{-3}	0.18	−4.85	119.7
41	123.8[j]	8.4×10^{-3}	−0.04	−4.38	124.8
42	123.7[k]	8.7×10^{-3}	0.07	−4.70[f]/*−5.45*[f,h,r]	122.0
43	122.8[j]	1.1×10^{-2}	−0.01	−4.70	123.1
44	122.4	1.3×10^{-2}	0.15	−5.06[f]/*−3.81*[f,h,s]	118.7
45	122.2[j]	1.4×10^{-2}	−0.04	−4.38	123.2

[a] E_a and $E_{N,n}'$ in kJ/mol and k_d in s^{-1} at 393 K. [b] E_a was reestimated with a frequency factor of 2.4×10^{14} s^{-1} (see text) and for an alkoxyamine carrying a PhEt as leaving alkyl radical, unless otherwise mentioned. [c] Estimated with eqs 3−5. [d] Estimated with eqs 6 and 7. [e] Estimated with eq 2. [f] See text. [g] Given in ref 75. [h] Italized values are for triangles in Figure 1. [i] $E_{s,4'}$ and $E_{s,6'}$ were estimated with r(C5) and r(C6″). [j] Given in ref 45. [k] Given in ref 40. [l] Given in refs 42 and 43. [m] Given in refs 41 and 70. [n] $E_{s,27}$ was estimated with r(C6′). [o] $E_{s,32}$ was estimated with r(C6). [p] $E_{s,33}$ was estimated with r(C6). [q] $E_{s,36}$ was estimated with r(C6). [r] $E_{s,42}$ was estimated with r(C6′). [s] $E_{s,44}$ was estimated with r(C7).

Table 3. Individual Steric Constants *r* and Electrical Universal (Polar) Constants σ_L

group[a]	r[b]	$\sigma_I(R_i)$[c]	group[a]	r[b]	$\sigma_I(R_i)$[c]
$CR_2(CH_2)_2CR_2$	0.31[d,e]	−0.02	$CR_2CH_2C(O)NHCHMeCR_2$	0.02[d,f]	0.19[g]
$CR_2NMeC(O)CR_2$	0.20[d,f,h]	0.54[i]	$CR_2(CH_2)_2CHOHCH_2CR_2$	0.00[d,f]	0.04[j]
$CR_2CH_2C(O)CH_2CR_2$	0.22[d,f]	0.11[k]	Me	0.00	−0.01
$CR_2CH_2CHOHCH_2CR_2$	0.22[d,f]	0.03[l]	$(CH_2)_4$	−0.04[d]	−0.02
$CR_2(CH_2)_3CR_2$	0.22[d,e]	−0.02[e]	CH_2OH	−0.06[f]	0.11
$CR_2(CH_2)_3C(O)CH_2CR_2$	0.19[d,f]	0.12[m]	$(CH_2)_5$	−0.15[d]	−0.02
$CR_2(CH_2)_2C(O)(CH_2)_2CR_2$	0.19[d,f]	0.04[n]	$(CH_2)_6$	−0.27[d]	−0.02
$CR_2(CH_2)_2COCH_2CR_2$	0.13[d,f]	0.15[o]	CH_2OSiMe_2t-Bu	−0.30[f]	0.00[e]
$CR_2CH_2NRCOCR_2$	0.11[d,e]	0.37[e]	Et	−0.38	−0.01
$CR_2CH_2COCMeHCR_2$	0.11[d,e]	0.10[p]	CH_2OMe	−0.50[f]	0.11
$CR_2CH_2CHOAcCHMeCR_2$	0.11[d,f]	0.04[q]	CH_2OCH_2Ph	−0.50[f]	0.11[f,r]
$CR_2CH_2CHOHCHMeCR_2$	0.11[d,f]	0.02[s]	Ph	−1.40[e]	0.12
$CR_2(CH_2)_3CHOHCH_2CR_2$	0.09[d,f]	0.02[t]	COOMe	−1.55[f]	0.64
$CR_2(CH_2)_2CHOH(CH_2)_2CR_2$	0.09[d,f]	0.01[u]	CMe_2CN	−2.10[v]	0.14

[a] Groups attached to the nitroxyl moiety. [b] Individual steric constants $r(R_i)$ are given in ref 53 unless otherwise mentioned. [c] Individual polar constant $\sigma_I(R_i)$ are given in refs 65 and 66 unless otherwise noted. [d] In text, r(C5) is used for $CR_2(CH_2)_2CR_2$; r(C5′) for $(CH_2)_4$; r(C5″) for $CR_2NMeC(O)CR_2$; r(C6) for $CR_2(CH_2)_3CR_2$, $CR_2CH_2C(O)CH_2CR_2$, and $CR_2CH_2CHOHCH_2CR_2$; r(C6′) for $CR_2CH_2NRC(O)CR_2$, $CR_2CH_2C(O)CMeHCR_2$ $CR_2CH_2CHOAcCMeHCR_2$, and $CR_2CH_2CHOHCMeHCR_2$; r(C6″) for $(CH_2)_5$; r(C7) for $CR_2(CH_2)_2CHOHCH_2CR_2$; r(C7′) for $CR_2(CH_2)_2C(O)CH_2CR_2$ and $CR_2CH_2NHC(O)CH_2CR_2$; r(C7″) for $(CH_2)_6$; r(C7‴) for $CR_2CMeHNHC(O)CH_2CR_2$; r(C8) for $CR_2(CH_2)_2CHOH(CH_2)_2CR_2$ and $CR_2(CH_2)_3CHOHCH_2CR_2$; and r(C8′) for $CR_2(CH_2)_2C(O)(CH_2)_2CR_2$ and $CR_2(CH_2)_3C(O)CH_2CR_2$. [e] Given in ref 46. [f] See text. [g] $\sigma_{I,CH_2NHAc} = 0.09$, assuming $\sigma_{I,CH_2C(O)NHMe} \approx \sigma_{I,CH2C(O)NMe_2}$ given by eq 4 and $\sigma_{I,C(O)NMe_2} = 0.28$. [h] See text for the $PhCH_2$ group. [i] Assuming $\sigma_{I,C(O)NMeH} \approx \sigma_{I,C(O)NMe_2} = 0.28$ and $\sigma_{I,NMeAc} \approx \sigma_{I,NHC(O)Et} = 0.26$. [j] σ_I is estimated with $\sigma_{I,CH_2CH_2CHOHMe} = 0.01$ given by eq 4 and $\sigma_{I,CH_2CHOHMe} = 0.03$. [k] $\sigma_{I,CH_2Ac} = 0.11$ is estimated from eq 4 and $\sigma_{I,Ac} = 0.30$. $\sigma_U = 2 \times (\sigma_{I,CH_2Ac}/2)$; see ref 46. [l] $\sigma_{I,CH_2CHOHMe} = 0.03$, $\sigma_I = 2 \times (\sigma_{I,CH_2CHOHMe}/2)$; see ref 46. [m] σ_I is estimated with $\sigma_{I,CH_2Ac} = 0.11$ (see footnote *k*) and $\sigma_{I,(CH_2)_3Ac} = 0.01$ given by eq 4. [n] $\sigma_{I,(CH_2)_2Ac} = 0.04$ given by eq 4 with $\sigma_{I,CH_2Ac} = 0.11$ (see footnote *k*), and $\sigma_U = 2 \times (\sigma_{I,(CH_2)_2Ac}/2)$; see ref 46. [o] σ_I is estimated with $\sigma_{I,CH_2Ac} = 0.11$ (see footnote *k*) and $\sigma_{I,(CH_2)_2Ac} = 0.04$ (see footnote *n*). [p] $\sigma_{I,CMeHAc} = 0.09$ is estimated with eq 4 and $\sigma_{I,Ac} = 0.30$. $\sigma_I = \sigma_{I,CMeHAc}/2 + \sigma_{I,CH_2Ac}/2$; see ref 46. [q] σ_I is estimated with $\sigma_{I,CH_2CHOAcMe} = 0.04$ given by eq 4 and $\sigma_{I,CMeHCHOAcMe} = 0.04$ given by eq 5. $\sigma_I = \sigma_{I,CH_2CHOAcMe}/2 + \sigma_{I,CMeHCHOAcMe}/2$. [r] Assuming $\sigma_{I,CH_2OMe} \approx \sigma_{I,CH_2OCH_2Ph}$. [s] $\sigma_{I,CMeHCHOHMe} = 0.01$ is estimated with eq 5 and $\sigma_{I,CHOHMe} = 0.04$, and $\sigma_{I,CH_2CHOHMe} = 0.03$. $\sigma_I = \sigma_{I,CMeHCHOHMe}/2 + \sigma_{I,CH_2CHOHMe}/2$; see ref 46. [t] σ_I is estimated with $\sigma_{I,(CH_2)_3CHOHMe} = -0.01$ given by eq 4 and $\sigma_{I,CH_2CHOHMe} = 0.03$. [u] $\sigma_{I,CH_2CH_2CHOHMe} = 0.01$ given by eq 4 and $\sigma_{I,CH_2CHOHMe} = 0.03$. $\sigma_I = 2 \times (\sigma_{I,CH_2CH_2CHOHMe}/2)$; see ref 46. [v] Estimated by analogy with the value of CHF_2 given in ref 69.

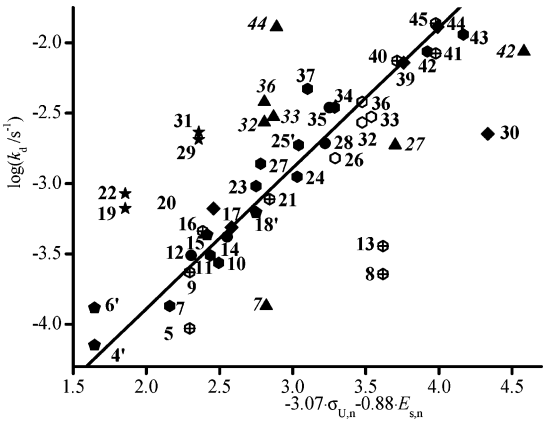


Figure 1. Log k_d vs eq 1 for alkoxyamines **4′**−**45** based on various cyclic nitroxyl fragments, (⬟) for five-membered rings, (●) for six-membered rings and E_s estimated with r(C6), (○) for six-membered rings and E_s estimated with r(C6′), (hexagon with a cross) for six-membered rings carrying polar groups in positions 2 and 6, (★) for six-membered rings carrying groups capable of IHB, (◆) for seven-membered rings, (⬢) for eight-membered rings, (▲) for log k_d estimated with italicized values of $E_{s,n}$.

by removing 0.11 from r(C7′) by analogy to the difference between r(C6) and r(C6′).

$$E_{s,n} = aE_s^A + bE_s^B + \epsilon \quad (6)$$

$$E_s(CR_1R_2R_3) = -2.104 + 3.429r_1(R_1) + 1.978r_2(R_2) + 0.649r_3(R_3) \quad (7)$$

For alkoxyamines **15** and **18′** (pentagons in Figure 1), the values of r(C5) and r(Ph) estimated by Marque were used to determine the values of $E_{s,15}$ and $E_{s,18'}$. The value of E_a for **15** was measured by Cameron et al.,[41,70] but it was reestimated with the averaged frequency factor ($A = 2.4 \times 10^{14}$ s^{-1}) and was incremented by 2.7 kJ/mol.[71] For alkoxyamines **4′** and **6′** (pentagons in Figure 1), assuming a small difference of polarity between the methyl and the benzyl group,[72] values of r(C5″) and r(C6″) were used to determine the values of $E_{s,4'}$ and $E_{s,6'}$. The value of r(C5″)[73] was preferred to r(C5) because it yielded a better fit (vide infra).[74] The E_a values of **4′** and **6′** were measured by Aldabbagh et al.[75] for the polystyryl (PS) derivatives. For TEMPO−PS and SG1−PS derivatives, it was shown by Fukuda et al.[20] and Bertin et al.,[16] respectively, that the PS chain increases the value of k_d by a factor of 2 at best. Therefore, the values of k_d for the PS derivatives of **4′** and **6′** were divided by 2, and E_as reestimated with the averaged frequency factor A (vide supra). For alkoxyamines carrying polar groups in positions 2 and 6 on the ring of the nitroxyl fragment (crossed hexagons in Figure 1), the values of $E_{s,n}$ were estimated with r(C6) and with r(COOMe) for **5**, **8**, **9** and **13**, $r(CH_2OMe)$ for **16** and **40**, and $r(CH_2OSiMe_2t$-Bu) for **21**, **41** and **45**. The lower values of E_N' for **5**, and **9** than for **11** (Table 2) indicate that r(COOMe) is larger than r(Me), and assuming that the nitroxyl fragment adopts a preferred conformation, a value of −1.55 was estimated for r(COOMe). For alkoxyamines **16** and **40**, it was assumed that the polar effects of the CH_2OMe and CH_2OCH_2Ph groups were very close, i.e. $\sigma_I(CH_2OCH_2Ph) \approx \sigma_I(CH_2OMe)$,[65−67] as well their steric demands, i.e., $r(CH_2OCH_2Ph) \approx r(CH_2OMe)$, by virtue of the minimum steric interaction (MSI) principle.[68,76] Since the O−Si bond is longer than the O−C bond,[76] the steric demand of the $OSiMe_2t$-Bu group was expected to be smaller than that of the methoxy group; that is, $r(CH_2OSiMe_2t$-Bu) = −0.30 was the best fitting value of eq 1. For alkoxyamines carrying groups capable of intramolecular hydrogen bonding (IHB) in positions 2 and 6 on the ring of the nitroxyl fragment (stars in Figure 1), the $E_{s,n}$ values were estimated with r(C6) and $r(CH_2OH)$ for **19**,

22, **29**, and **31**.[77] For alkoxyamines **7**, **10**, **11**, **23** − **25′**, **27**, **34**, **37**, **42**, and **43** based on a six-membered ring nitroxyl fragment without substituents in position 3 (filled hexagons in Figure 1), the values of $E_{s,n}$ were estimated with r(C6). For alkoxyamines **10**, **23**, **24**, and **37** (filled hexagons in Figure 1), r(C4), r(C5′) r(C6″) were used for the 5-, 6- and seven-membered rings as cyclic substituents in the positions α, respectively. For alkoxyamines **26**, **32**, **33** and **36** based on a six-membered ring nitroxyl fragment carrying one substituent in position 3 (sp^3 hybridized carbon for the methyl group,[78] open hexagons in Figure 1), the $E_{s,n}$ values were estimated with r(C6′). Because of the assumption made in a previous work (see discussion),[46] $E_{s,n}$ values for alkoxyamines **32**, **33**, and **36** were reestimated using r(C6), and $E_{s,n}$ values for alkoxyamines **7**, **27**, and **42** were reestimated using r(C6′). Both families of molecules are the triangles and italicized numbers in Figure 1, and they have $E_{s,n}$ italicized values in Table 2. For alkoxyamines based on a seven-membered ring nitroxyl fragment (diamonds in Figure 1), it was assumed that **17** and **39** obeyed eq 1, and thus values of 0.13 and 0.00 were estimated for r(C7) and r(C7′) for a seven-membered ring containing one sp^2 hybridized carbon atom (**17**) and a seven-membered ring with all sp^3 hybridized carbon atoms (**39**), respectively. These values of r(C7) and r(C7′) were applied to molecules **20** and **30** and molecule **38**, respectively. It has to be mentioned that **30** and **38** are outliers (see leveled steric effect section), and for the sake of simplicity, **38** is not reported in Figure 1 because it deviates markedly from the regression line (coordinates are 5.52 for the x axis and −2.33 for the y axis; see Figure 1SI in Supporting Information). For molecule **44**, r(C7‴) was used to estimate $E_{s,44}$ (vide supra). For alkoxyamines based on a eight-membered ring nitroxyl fragment (circles in Figure 1), because the k_d values are known only for **12**, **14**, **28**, and **35**, it was assumed that **14** and **28** obeyed eq 1, and thus values of 0.19 and 0.09 were estimated for r(C8) and r(C8′) for a eight-membered ring containing a sp^2 hybridized carbon atom (**12** and **14**) and a eight-membered ring with all sp^3 hybridized carbon atoms (**28** and **35**), respectively.

Except for **6′**, **5**, **8**, **13 19**, **22**, **29**−**31**, **37** and **38**, the 31 alkoxyamines left lie very close (eq 8) to the regression line given by eq 1. In eq 9, the regression is performed on all the known alkoxyamines based on cyclic nitroxyl fragments (31 alkoxyamines presented in this work and 12 alkoxyamines previously presented by Marque)[46] and exhibit very good statistical parameters. Very good statistical parameters were again obtained when the biparameter regression (eq 10) was performed including alkoxyamines based on linear nitroxyl fragments.

$$\log(k_d/s^{-1}) = -2.85(\pm 0.16)\sigma_{I,n} - 0.83(\pm 0.04)E_{s,n} - 5.72(\pm 0.11) \quad (8)$$

$$R^2 = 0.96; \quad s = 0.13; \quad N = 31; \quad F_{30,0.01\%} = 340$$

$$\log(k_d/s^{-1}) = -2.81(\pm 0.15)\sigma_{I,n} - 0.83(\pm 0.03)E_{s,n} - 5.73(\pm 0.11) \quad (9)$$

$$R^2 = 0.95; \quad s = 0.15; \quad N = 43; \quad F_{42,0.01\%} = 383$$

$$\log(k_d/s^{-1}) = -2.91(\pm 0.13)\sigma_{I,n} - 0.85(\pm 0.03)E_{s,n} - 5.81(\pm 0.09) \quad (10)$$

$$R^2 = 0.96; \quad s = 0.14; \quad N = 53; \quad F_{52,0.01\%} = 591$$

Discussion

General Comments on the Arrhenius Parameters and the Taft—Ingold Equation. From the literature,[79] A values around 10^{13} to 5×10^{13} s^{-1} are expected for the bond homolysis of small molecules i.e., no activation entropy effect, whereas larger A values ($10^{17}-10^{18}$ s^{-1}) are expected for the fission of molecules in two large groups. These high A values are due to an increase of activation entropy because the number of freedom for rotation increases.[79] However, the homolysis of alkoxyamine into two large groups i.e., the alkyl and nitroxyl radicals, requires the passage from sp^3-hybridized nitrogen atom in the initial state to sp^2-hybrized nitrogen atom in the transition state (from the Hammond postulate, for endothermic reaction the structure of the transition state resembles to the structures of the products i.e., nitroxyl and alkyl radicals). Such rehybridization is energetically expensive in hindered molecules such as α,α′-tetrasubstituted alkoxyamines, and this should decrease the activation entropy. Consequently, the A values are expected in the range $10^{13}-10^{15}$ s^{-1} as observed (Table 1). Furthermore, rings can adopt many conformations, and the entropic cost increases with the number of conformation "*to freeze*" in the transition state, and the A values decrease. Up to now, no logical variations of A values have been observed, thus for the sake of simplicity, it is assumed that the averaged frequency factor ($A = 2.4 \times 10^{14}$ s^{-1}) holds for all alkoxyamines. The bond strength (enthalpic term), the steric hindrance and the polarity of the bond are all included in the activation energy E_a. In general, eq 1 is valid only for a family of compounds.[80] For practical reasons (vide supra), one seeks a general relationship for all cyclic alkoxyamines, and the development of constants for the cyclic strain makes it possible to take into account the entropic effect due to the number of possible ring conformations. Hence, a relationship taking into account all rings whatever the size is possible, and this makes it possible to detect the entropic changes due to the substituents (vide infra).

Five-Membered Ring Nitroxyl Fragments. The steric effects of various groups—Me,[46] Et,[46] Ph, cyclohexyl, and CMe_2CN—are well accounted for by eqs 3−8 (pentagons in Figure 1). For five-membered ring nitroxyl fragment based alkoxyamines **4′** and **6′** close to the line, r(C5″) has to be used instead of r(C5),[73] which means the cyclic strain or the number of conformations (vide infra) is modified by the substitution or hybridization sp^2 or sp^3 in positions 3 and/or 4, as observed for six-membered ring nitroxyl fragment based alkoxyamines (see below). It is probable that the buttressing effect mentioned by Aldabbagh et al. does not occur.[75]

Six-Membered Ring Nitroxyl Fragments. In a previous work,[46] it was mentioned that the sp^2 or sp^3 hybridization of the C atom in position 3 modifies the values of the cyclic strain constant r(C6). Assuming that r(C6′) should be applied for a ring containing a sp^2 hybridized C atom,[46] alkoxyamines **7**, **27**, and **42** (triangles in Figure 1) should lie close to the regression line, like **26**, whereas they lie close to the regression line when r(C6) is applied (filled hexagons in Figure 1). Reciprocally, assuming that r(C6) should be applied for a ring with all sp^3 hybridized atoms,[46] alkoxyamines **32**, **33**, and **36** (triangles in Figure 1) should lie close to the regression line, like for example **11**, **34**, and **43**, whereas they lie close to the regression line when r(C6′) is applied (open hexagons in Figure 1). Consequently, for

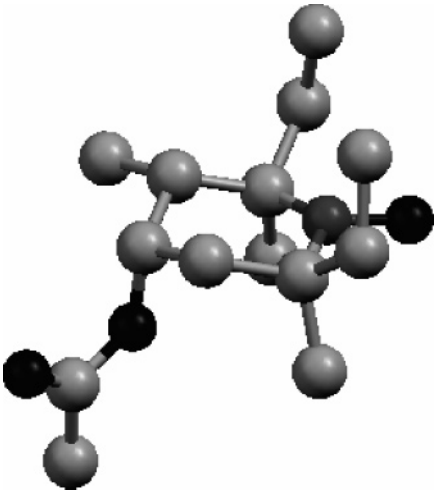
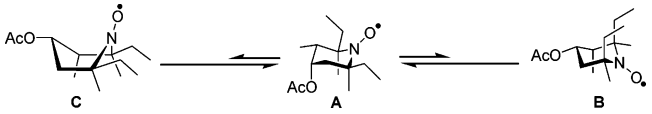


Figure 2. X-ray structure of 3a.

Scheme 5



a six-membered ring, the hybridization of the ring atoms has no effect on k_d but the effect of the substituent position is striking; that is, a substituent in position 4 has no significant steric effect whereas a substituent in position 3 increases k_d. This is highlighted by the marked increase of k_d for **46** (Scheme 2); e.g., $k_{d,\mathbf{46}}$ ($k_d = 1.6 \times 10^{-3}$ s^{-1})[81] is roughly 5 times higher than $k_{d,\mathbf{11}}$ ($k_d = 3.1 \times 10^{-4}$ s^{-1} in Table 2). It is well-known that stereomutations in alkoxyamines based on cyclic nitroxyl fragments are many and are very complicated processes.[82−87] Thus, it can be assumed that the ring adopts several conformations which have to be "*frozen*" in TS, which is costly in terms of activation entropy; i.e., $\Delta S^{\ddagger}$ is small and thus k_d decreases. On the grounds of the endothermic C−ON bond homolysis and the Hammond postulate, one can assume a late TS and a structure and a conformation for the nitroxyl fragment close to that of the nitroxyl radical. Assuming that the nitroxyl fragment in the alkoxyamine adopts the same conformations as those of the nitroxyl radicals, the X-ray structure of the nitroxyl radical **3a** (Figure 2 and Scheme 5), i.e., the most stable conformation in the crystal state and the one assumed in solution, reveals the two ethyl groups in pseudoequatorial position, as expected for bulky groups, the methyl group in position 3 in equatorial position (trans relationship with the ethyl groups), and the acetoxy group in position 4 in axial position (trans relationship with the ethyl groups). A chair ⇄ chair chemical exchange (form **A** ⇄ form **B**, Scheme 5) in **3a** leads to the disfavored form **B** because of four strong 1,3-syn interactions (Et ↔ Et, 2Et ↔ H, and Me ↔ H interactions). In the absence of substituent in position 3, a chair ⇄ boat chemical exchange is possible whereas such chemical exchange (form **C**, Scheme 5) is forbidden by the presence of the methyl group in position 3, that is, form **C** exhibits strong Me ↔ Me 1,2- and 1,3-syn interactions. Therefore, if conformers such as forms **B** and **C** do not exist in TS because of too high steric strain, then fewer conformations need to be "*frozen*" in TS, and thus $\Delta S^{\ddagger}$ is less small.

Therefore, such activation entropy effect should be observed through changes in the values of the frequency factor A. Assuming that the small polar effect due to the hydroxyl group in position 4 on the ring of the nitroxyl fragment of **46** is contained in the activation energy $E_{a,\mathbf{11}}$—that is, in the polar term[88] of the BDE(C−O)—and assuming that the substituent in position 4 has no steric effect (see Table 3), the frequency factor A (not estimated) for the C−ON bond homolysis of **11** should be close to the frequency factor observed for the homolysis of TEMPO−PhEt; that is, $A_{\mathbf{11}} = 2.5 \times 10^{14}$ s^{-1}. Assuming the methyl group in position 3 on the ring of the nitroxyl fragment in **46** has an influence only on the activation entropy in TS, that is, $E_{a,\mathbf{46}} = E_{a,\mathbf{11}} =$ 134.6 kJ/mol and with $k_{d,\mathbf{46}} = 1.6 \times 10^{-3}$ s^{-1} (see above),[81] one should expect a value of 1.2×10^{15} s^{-1} for $A_{\mathbf{46}}$. This is a reasonable value for bond homolysis and is 5 times higher than that of **11**. However, despite a given error of a factor two for the values of A, it would have been difficult to observe this 5-fold increase because of the error compensation effect of the activation parameters,[89] that is the same rate constants can be estimated from different (E_a, A) couples. It has to be mentioned that several authors have observed frequency factors A above 10^{15} s^{-1} but with an increase of E_a that undermines any unambiguous interpretation of the results.[90] The steric influence of the monocyclic substituents in molecules **10**, **23**, and **24** is well accounted for by the cyclic steric constants (Table 3) of Fujita.[53] The upward deviation observed for **37** might be due to the presence of two cyclohexyl groups generating some deformations of the nitroxyl ring and making the cyclohexyl groups bulkier than expected (r(C6″)) but smaller than the ethyl group. Molecules **5**, **8**, **9**, **13**, **16**, **21**, **40**, **41**, and **45** (crossed hexagons in Figure 1) were plotted separately because of the polar effect due to the presence of the COOMe, CH_2OMe, CH_2OCH_2Ph, and CH_2OSiMe_2t-Bu groups. The closeness of molecules **16**, **21**, **40**, **41,** and **45** to the regression line shows that the steric and polar effects of the CH_2OMe, CH_2OCH_2Ph, and CH_2OSiMe_2t-Bu groups are well accounted for by eqs 2−8. Furthermore, it also shows that the configuration cis-trans around the nitroxyl moiety has no significant influence on k_d. For molecules **5**, **8**, **9**, and **13**, the analysis is made more difficult because the ester group can adopt many conformations, which generate different steric strains (Janus group), and hence r(COOMe) can have different values. Assuming the bulky ester groups prefer pseudoequatorial positions to pseudoaxial positions, molecule **9** with the cis relationship for the ester groups should provide the "*normal*" value for r(COOMe); that is, r(COOMe) = −1.55. However, using this value to estimate $E_{s,n}$ for **5**, **8** and **13** makes these molecules outliers. The downward deviation of **5** is probably due to a larger number of conformations to be *frozen* in TS (see above) because of the *trans* relationship of the ester group in **5** always involving an ester group in pseudoaxial position, whereas it cannot occur for **9**. The downward deviations of **8** and **13** are discussed in the leveled steric effect section. Molecules **19**, **22**, **29**, and **31** (stars in Figure 1) are discussed in the intramolecular hydrogen bonding section.

Seven-Membered Ring Nitroxyl Fragments. Molecules **30** and **38** are discussed in the leveled steric effect section. The difference of 6 kJ/mol between the global steric strain of $E'_{N,\mathbf{17}}$ and that of $E'_{N,\mathbf{39}}$ suggests that

the hybridization sp^2 or sp^3 of the ring carbon strongly modifies the homolysis of the C−ON bond. That is, the presence of a sp^2 carbon on the ring might either induce more strain in the ring or forbid the conformations required in TS for the cleavage to occur. It is worthwhile to mention that $E'_{N,\mathbf{39}}$ is the same as E'_N for the alkoxyamine based on the di-*tert*-butyl nitroxyl fragment,[46] which means no more cyclic strain for a seven-membered ring. For alkoxyamine **44**, when $E_{s,\mathbf{44}}$ is estimated with r(C7) the molecule deviates strongly (triangle in Figure 1 and italicized value in Table 2), whereas the molecule lies on the regression line (Figure 1) when r(C7‴) is applied; i.e., r(C7‴) is smaller than r(C7) by 0.11. This difference of 0.11 is the same difference as that observed between r(C6) and r(C6′), which would mean the same entropic effect observed with **26** is also observed with **44**. Hence, the presence of a methyl group probably limits the number of conformers to "*freeze*" in TS, and thus, $\Delta S^{\ddagger}$ is less small and k_d higher (vide supra). Note that the effects of the mono- or multisubstitution and sp^2 hybridization on positions 3, 5, and 6 are not yet fully understood.

Eight-Membered Ring Nitroxyl Fragments. The closeness of alkoxyamines **12**, **14**, **28**, and **35** to the regression line (circles in Figure 1) shows that the values of r(C8) and r(C8′) depend only slightly on positions 4 ($E'_{N,\mathbf{12}}$ and $E'_{N,\mathbf{28}}$) or 5 ($E'_{N,\mathbf{14}}$ and $E'_{N,\mathbf{35}}$) of the subtituents on the ring but depend more on the sp^2 ($E'_{N,\mathbf{12}}$ and $E'_{N,\mathbf{14}}$) or sp^3 ($E'_{N,\mathbf{28}}$ and $E'_{N,\mathbf{35}}$) hybridization of the carbons on these positions. The same explanation as the one given for alkoxyamines based on seven-membered ring nitroxyl fragments (vide supra) should account for the difference of 3.5 and 2.9 kJ/mol between $E'_{N,\mathbf{12}}$ and $E'_{N,\mathbf{28}}$ and between $E'_{N,\mathbf{14}}$ and $E'_{N,\mathbf{35}}$, respectively. Unlike what was expected, i.e., no cyclic strain for rings with more than seven atoms (vide supra), alkoxyamines **12**, **14**, **28**, and **35** exhibit larger $E'_{N,n}$ than their seven-membered ring homologues **17** and **39**; that is, $E_{a,\mathbf{12}\text{ or }\mathbf{14}}$ and $E_{a,\mathbf{28}\text{ or }\mathbf{35}}$ are smaller than $E_{a,\mathbf{17}}$ and $E_{a,\mathbf{39}}$, respectively. Such difference might be due either to increasing cyclic strain effects with the increase of the ring size or to more conformations to be *"frozen"* in TS because of a larger ring size, that is, the conformational effects overbalance the relief of the cyclic strain.

Leveled Steric Effect. The downward deviations observed ca. 9 kJ/mol for **8** and **13**, ca. 8 kJ/mol for **30**, and ca. 14.7 kJ/mol for **38** are too large to be ascribed to the experimental error (ca. 2 kJ/mol). Moreover, the estimated $E_{s,\mathbf{8}}$, $E_{s,\mathbf{13}}$, and $E_{s,\mathbf{38}}$ values are below −6, the value from which the leveled steric effect[26,91] may occur. Because ester groups can adopt many conformations, the replacement of the methyl groups of **9** by more sterically demanding ethyl groups in **13** may push the ester groups to adopt other conformations which induce relief strain, and for example, choosing[92] r(COOMe) at −0.42 shifts **8** and **13** toward the regression line. Both the deviating alkoxyamine **38** and the $E_{s,\mathbf{38}}$ smaller than −6 ($E_{s,\mathbf{38}} = -6.2$; see Table 2) point out the presence of the leveled steric effect. To move **38** closer to the regression line, the leveled steric effect—due to the replacement of four methyl groups in **39** by four more sterically demanding ethyl groups—might be balanced by either an increase of the cyclic steric strain (r(C8′) = 0.31, $E_s = -4.1$), or conformation changes which make the ethyl groups of **38** no more sterically demanding than the methyl groups of **39** ($E_s = -4.2$). Although $E_{s,\mathbf{30}}$ is above the threshold value but close to it, the leveled steric effect accounts for the observed reactivity. Assuming either a value of 0.31 for r(C8) or only two active ethyl groups either on each side ($E_s = -3.80$) or on the same side ($E_s = -4.2$) the leveled steric effect may be balanced.

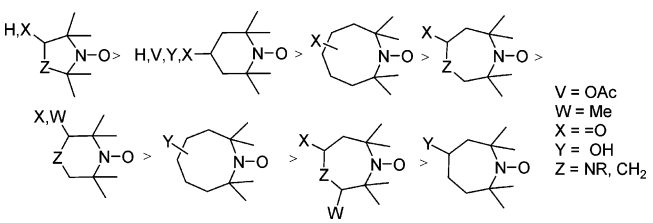
Intramolecular Hydrogen Bonding (IHB). A few years ago,[36] one of us showed the importance of IHB for the k_d of alkoxyamines containing nitroxyl fragments carrying groups capable of IHB. With polar and steric ($r(CH_2OH) = -0.06$)[77] effects accounted for by eq 1, the upward deviations (ca. 7 kJ/mol) observed for **19**, **22**, **29**, and **31** are too large to be ascribed to experimental errors (ca. 2 kJ/mol), and they are due to the potential IHB between the hydroxyl groups in positions 2 and 6 and the nitroxyl moiety. This IHB provokes a stabilization of the nitroxyl radical and thus of TS (Hammond's postulate) and hence increases k_d. It can be argued that $r(CH_2OH)$ is smaller than the estimated value, but values smaller than −0.5 given for $r(CH_2OMe)$ are unrealistic. Therefore, assuming the value of −0.5 for $r(CH_2OH)$, one would observe (not shown) upward deviations for **19** and **22** and downward deviations for **29** and **31**, which means the presence of IHB for **19** and **22** and some others effects that slow the homolysis for **29** and **31**. In contrast to previous observations,[36,46] alkoxyamines **19**, **22**, **29**, and **31** yielding nitroxyl radicals capable of IHB do not always exhibit higher k_d than alkoxyamines **16**, **21**, **40**, **41**, and **45** yielding nitroxyl radical carrying protected hydroxyl groups (Table 3); that is, $k_d(\mathbf{19}) \approx k_d(\mathbf{16})$ and $k_d(\mathbf{21})$,[93] $k_d(\mathbf{22}) > k_d(\mathbf{16})$ and $k_d(\mathbf{21})$, $k_d(\mathbf{29}) < k_d(\mathbf{41})$, and $k_d(\mathbf{31}) < k_d(\mathbf{40})$ and $k_d(\mathbf{45})$. Such differences are merely accounted for by the steric effect caused by the difference in bulkiness between the CH_2OH ($r = -0.06$) and CH_2OMe ($r = -0.50$), CH_2OCH_2Ph ($r = -0.50$), and CH_2OSiMe_2t-Bu ($r = -0.30$) groups (Table 3).

In a previous work, it was observed that nitroxyl radicals capable of IHB generally exhibit higher EPR nitrogen hyperfine coupling constants a_N than the corresponding nitroxyl radicals carrying protected hydroxyl groups, that is, nitroxyl radicals **19**•, **22**•, **29**•, and **31**• exhibit higher a_N than nitroxyl radicals **16**•, **40**•, **21**•, **41**•, and **45**• (Scheme 6) i.e., $a_{N,\mathbf{31}\bullet} = 1.523$ mT > $a_{N,\mathbf{40}\bullet} = 1.430$ mT and $a_{N,\mathbf{45}\bullet} = 1.437$ mT, $a_{N,\mathbf{29}\bullet} = 1.530$ mT > $a_{N,\mathbf{41}\bullet} = 1.380$ mT, and $a_{N,\mathbf{22}\bullet} = 1.520$ mT > $a_{N,\mathbf{16}\bullet} = 1.473$ mT and $a_{N,\mathbf{21}\bullet} = 1.516$ mT.[45,94] Hence, the higher a_N observed is in rather good agreement with a IHB stabilization of the TS of **19**, **22**, **29**, and **31**.

Concluding Remarks

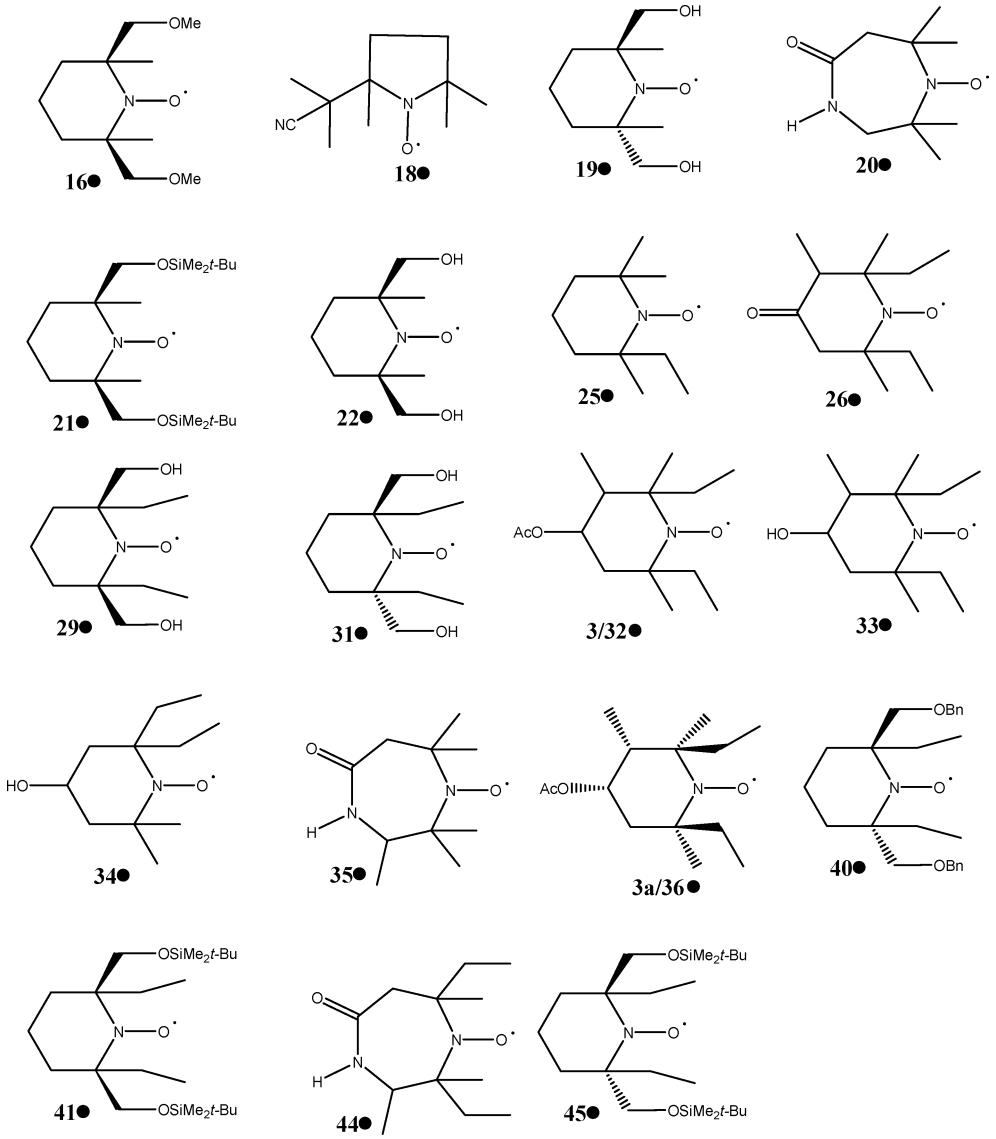
This study confirms many observations that have been done by us and others, such as the following.

• k_d increases with the increasing ring size of the nitroxyl fragment up to seven members; i.e., the cyclic strain decreases along the series below:



The ring effects of the nitroxyl moiety can be summarized as follows: (i) five-membered rings exhibit

Scheme 6



strong cyclic strain that pulls back the substituents in α−positions and thus relief of the steric hindrance around the nitroxyl function is observed; (ii) the six-membered ring exhibits less cyclic strain than the five-membered one, and hence, the steric hindrance around the nitroxyl function is increased but sensitive to substitution on the 3-position of the ring; (iii) the seven-membered ring is large enough for its weak cyclic strain to match the steric hindrance of two *tert*-butyl groups bonded to the nitrogen atom, and the importance of the cyclic strain relief is sensitive to the hybridation of carbons 4 or 5 of the ring, and to the presence of substituents on positions 3 and 6. The steric strain would be smaller for rings composed of more than seven-members, as exemplified with the alkoxyamines based on eight-membered ring nitroxyl fragments.

•IHB increases markedly the values of k_d by stabilizing TS through stabilization of the nitroxyl radical.

•Electron-withdrawing groups attached to the ring of the nitroxyl fragment decrease markedly the values of k_d: the closer they are to the nitroxyl moiety, the smaller k_d is.

•The leveled steric effect also occurs for values of $E_{s,n}$ below −6 in alkoxyamines carrying cyclic nitroxyl fragments like those for alkoxyamines carrying linear nitroxyl fragments.

•Substitution on the carbon atom of the position 3 on the ring strikingly modifies the global steric strain $E'_{N,n}$, which can be ascribed to a limitation of the number of conformations to be "*frozen*" in the TS, i.e., a change in the activation entropy;

•The effect of the hybridization sp^2/sp^3 or the substitution on other positions than position 3 of the ring depends on the ring size; i.e., no effect of the substituent type or the hybridization in position 4 of a six-membered ring whereas the presence of sp^2 hybridized atom in the position 4 or 5 in a seven- or eight-membered ring, respectively, increases the steric constant r.

However, it is remarkable that eq 9 is sufficiently versatile and robust to account for the reactivity of 43 alkoxyamines out of 54 based on cyclic nitroxyl fragments. This versatility and robustness merely requires the generation of 8 new constants (Table 3) for five-, six-, seven- and eight-membered rings. Such an equation should play a pivotal role for designing more new efficient alkoxyamines.

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Supporting Information Available: Figure 1SI, showing a plot of log k_d vs eq 1 for alkoxyamines **4′**−**45**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(93) In the text, it was mentioned that the cis/trans configuration around the nitroxyl moiety has no significant influence for such alkoxyamines. However, such configurations might have an effect on the IHB occurrence in the nitroxyl radical.
(94) $a_{N,\mathbf{21}\bullet} \approx a_{N,\mathbf{22}\bullet}$ as expected for weakly electron-withdrawing groups such as CH_2OSiMe_2t-Bu (see Table 4), as shown in refs 46 and 65. Contrary to what was expected, $a_{N,\mathbf{41}\bullet}$ is very low. Consequently, the influence of the electron-withdrawing capacity of the CH_2OSiMe_2t-Bu groups seems to depend on the conformation around the nitroxyl moiety. It has to be mentioned that the values of a_N for **16•**, **22•**, and **41•** reported in ref 45 were different—1.530, 1.466, and 1.416 mT, respectively—from the ones reported in this paper. The new values were measured from samples kindly provided by Pr. Studer. The differences observed are due to misprints in ref 45.

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