Steric Effects of Ring Substituents on the Decay and Reformation Kinetics of Piperazinone-Based Alkoxyamines

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Received October 21, 2002
Revised Manuscript Received March 6, 2003

Introduction

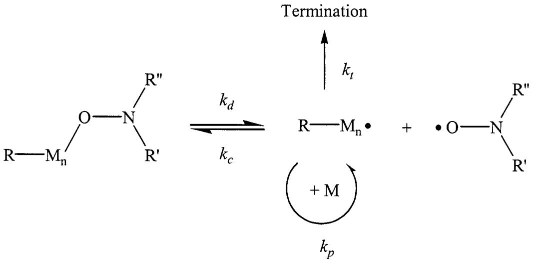
Since the seminal work of Rizzardo[1] and Georges,[2] nitroxide mediated free radical polymerizations (NMP)[3] are often used for the synthesis of living polymers and copolymers with small polydispersities, controlled molecular weights, and architectures. They compete in this field with atom transfer radical polymerizations (ATRP)[4] and reversible addition−fragmentation transfer (RAFT) processes.[5]

The mechanism is outlined in Scheme 1.[3,6] Nitroxide-capped chain molecules, the dormant polymer species, cleave into propagating and persistent nitroxide radicals. The propagating radicals grow by monomer addition and reform longer dormant chains by cross-coupling with the nitroxides. Simultaneously, the usual self-termination of the propagating radicals to unreactive polymer products takes place. This removes propagating radicals and increases of the nitroxide concentration in time; the cross-coupling reaction therefore dominates over self-termination. For an extended time range, a quasi-equilibrium of the reversible cleavage exists which is characterized by weakly time-dependent radical concentrations and a large excess of the persistent over the propagating radicals.

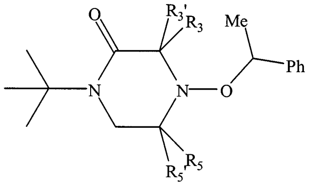
For a well controlled and living radical polymerization of a given monomer with propagation and termination constants k_p and k_t, the rate constants of the reversible cleavage k_d and k_c must fall into proper ranges.[3,6] In general, one aims at relatively large equilibrium constants $K = k_d/k_c$ because they yield large propagating radical concentrations, and, hence, comparatively fast monomer conversions. Furthermore, at a given time the polydispersity index is smaller for a larger k_d.[6−8] Consequently, the determination of K, k_d, and k_c has recently found considerable attention both for polymeric[8,9] and low molecular weight model systems.[10]

Among other factors, the steric effects of substituents of both the leaving and the nitroxide radicals affect the rate constants,[10] although systematic studies are scarce. Here, we present rate constants and their temperature dependence for a series of piperazinone derived alkoxyamines (1-*tert*-butyl-3,3,5,5-tetraalkyl-4-(1-phenylethoxy)piperazin-2-ones, alkyl = methyl, ethyl) of the general structure shown in Scheme 2. Within the series, methyl substituents at the 3 and 5 ring positions are successively replaced by ethyl groups. The effects of this replacement on the cleavage and recoupling constants are found to be inversely related, which we rationalize in terms of a known additive scheme of steric substituent parameters. The effects also explain trends in the performance of the piperazinone-derived alkoxyamines as initiators for living and controlled styrene polymerizations.

Scheme 1



Scheme 2



Experimental Section

The synthesis and the properties of all piperazinone derived nitroxides and alkoxyamines used in this study have recently been described.[11] They were analytically pure. α,α′-Dimethyldibenzyl ketone (purity >98%) was synthesized according to a published procedure.[12] The solvent *tert*-butylbenzene (Fluka, >99%) was distilled once before use.

Rate constants for the decay of the alkoxyamines k_d were obtained from the appearance of the nitroxide radical ESR signals as described before[13] in sealed but not deoxygenated solutions where dissolved oxygen scavenges the released phenethyl radicals. The nitroxide growth obeyed the expected first-order kinetics and ended at the expected concentration for full alkoxyamine conversion. Measurements at different temperatures yielded the frequency factors and activation energies by Arrhenius analysis.

For the determination of the cross-reaction rate constants, phenethyl radicals were produced by laser flash photolysis (308 nm) of α,α′-dimethyldibenzyl ketone in solutions containing the nitroxides, and their decay was followed in time at $\lambda = 321$ nm. All details of the technique were described earlier.[14]

Prior to polymerization, styrene (for synthesis, stabilized with 4-*tert*-butylpyrocatechol, Merck-Schuchhard) was freshly distilled at 40 °C under reduced pressure to remove the inhibitor. Polymerizations were carried out in 100 mL Schlenk tubes equipped with a magnetic stirrer and an argon inlet. The Schlenk tubes were charged with 50 mL of styrene (45.45 g, 0.436 mol) and calculated amounts of alkoxyamine. Oxygen was removed from the monomer solution by three consecutive freeze−thaw cycles with argon purge. The Schlenk tubes were then immersed into preheated oil baths and left to polymerize at 100, 110, 120, and 130 °C for 6 h. After polymerization, the residual monomer was removed by drying under vacuum at 70 °C until constant weight was achieved.

Molecular weights were determined by gel permeation chromatography on a HP 1090 liquid chromatograph equipped with an internal DAAD detector ($\lambda = 254$ nm) and an RI

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10.1021/ma021605d CCC: $25.00

Table 1. Rate Constants for the Cleavage and the Reformation of Piperazinone Derived Alkoxyamines, Where Statistical Errors of the Rate Constants are Below 10%

substituents	$k_{d,393}$, s^{-1}	A_d, 10^{14} s^{-1}	E_{ad}, kJ/mol	$k_{c,296}$, M^{-1} s^{-1}	$k_{c,323}$, M^{-1} s^{-1}	$k_{c,373}$, M^{-1} s^{-1}	K_{393}, M
3,3,5,5-tetramethyl	1.3×10^{-4}		138[a]	2.6×10^{8}	2.9×10^{8}	3.0×10^{8}	4.2×10^{-13}
3-ethyl-3,5,5-trimethyl	2.4×10^{-4}	1.0	133	1.9×10^{8}	2.1×10^{8}	2.2×10^{8}	1.0×10^{-13}
3,5-diethyl-3,5-dimethyl	4.9×10^{-4}	1.0	130	1.2×10^{8}	1.4×10^{8}	1.5×10^{8}	3.3×10^{-12}
5,5-diethyl-3,3-dimethyl[b]				1.0×10^{8}	1.1×10^{8}	1.1×10^{8}	
3,3-diethyl-5,5-dimethyl	1.6×10^{-3}	0.9	126	1.0×10^{8}	1.1×10^{8}	1.1×10^{8}	1.5×10^{-11}
3,3,5-triethyl-5-methyl[c]	3.6×10^{-3}	2.4	127				
3,5,5-triethyl-3-methyl	1.5×10^{-3}	0.9	126	6.8×10^{7}	7.8×10^{7}	8.6×10^{7}	4.2×10^{-11}
3,3,5,5-tetraethyl	8.1×10^{-3}	0.9	121	4.0×10^{7}	4.5×10^{7}	5.6×10^{7}	1.4×10^{-10}

[a] Calculated with an assumed frequency factor $A_d = 2.4 \times 10^{14}$s^{-1}. [b] Alkoxyamine not available. [c] Nitroxide radical not available.

detector (ERC, model 7510). Tetrahydrofuran (HPLC analyzed grade, J. T. Baker) was used as solvent and as eluent with a flow rate of 1 mL/min at room temperature. Toluene (ACS grade, Merck-Schuchhard) was used as an internal standard. Columns were obtained from PSS GmbH (PSS SDV-Gel (5 μ) 10^5, 10^3, 100 Å) and were calibrated against narrowly distributed polystyrene standards (Polymer Laboratories and PSS GmbH)

Results and Discussion

Table 1 summarizes the results of the kinetic measurements. With increasing ethyl substitution the rate constant k_d of the alkoxyamine decay increases and the activation energy decreases. The frequency factors do not vary systematically. Most of them are smaller than the average value $A_d = 2.4 \times 10^{14}$s^{-1}, which was obtained earlier for a large series of various alkoxyamines,[13] but the difference is considered insignificant. Since the cleavage reaction is endothermic, the activation energy should be close to the dissociation energy of the breaking O−C bond so that the substituent effect is very likely caused by a strain on this bond due to increasing steric congestion.

As was found for other cross-coupling reactions between carbon-centered and nitroxide radicals,[10,14] k_c is markedly below the diffusion-controlled limit of about 5×10^9 M^{-1} s^{-1}. It depends very little on temperature and has a very small positive activation energy. This indicates an entropy controlled reaction.[14] The replacement of methyl by ethyl groups decreases k_c markedly. This points to larger steric restrictions for the approach of the phenethyl radical to the nitroxyl oxygen atom for the ethyl than for the methyl substituted nitroxides, which lead to a more negative activation entropy. The substituent effects on k_d and k_c are inversely correlated. As k_d increases, k_c decreases. As a consequence, the equilibrium constants $K = k_d/k_c$ for the 3,3,5,5-tetramethyl- and the 3,3,5,5-tetraethyl-substituted nitroxides differ by more than 2 orders of magnitude.

The substituent effects on reaction rate constants are often rationalized in terms of the Taft−Ingold equation

$$\lg(k/k_0) = \rho\sigma + \delta E_s^{\,c} \tag{1}$$

where σ and $E_s^{\,c}$ are polar and (corrected Hancock[15]) steric substituent constants, k_0 refers to a reaction with standard substituents, and ρ and δ are parameters characterizing the reaction. Since ethyl and methyl groups have nearly equal polarity, only the last term of eq 1 must be considered here. According to Fujita et al.,[16] the total steric substituent constant of a tertiary carbon atom $R = CR_1R_2R_3$ such as C3 and C5 in the present alkoxyamines can be separated into additive components of the residues R_i. These authors analyzed the rate constants of the acid-catalyzed hydrolysis of esters $R_1R_2R_3CCOOEt$ and suggested the equation

$$E_s^{\,c}(CR_1R_2R_3) = -2.104 + 3.429E_s^{\,c}(R_1) + 1.978E_s^{\,c}(R_2) + 0.649E_s^{\,c}(R_3) \tag{2}$$

with $\delta = 1$ in (1). In applications of eq 2, the substituents must be ordered according to increasing size. More space-demanding substituents have more negative steric constants $E_s^{\,c}$ than less space-demanding ones because they congest the transition state of the hydrolysis more strongly, that is, the attack of the incoming water molecule on the ester carbon atom.[16]

In comparison to an ester hydrolysis, in the present reactions the alkyl substituted carbon atoms are one bond more remote from the reactive center, namely the nitroxyl oxygen. This should lead to $\delta < 1$ in eq 1. Furthermore, we assume additivity of the effects of the two groups of substituents at C3 and C5; that is, we set

$$E_s^{\,c} = E_s^{\,c}(C3R_1R_2R_3) + E_s^{\,c}(C5R_1R_2R_3). \tag{3}$$

To apply eqs 2 and 3, the proper order of the substituents at C3 and C5 has to be chosen. Whereas a methyl group has certainly to be placed before an ethyl group and $E_s^{\,c}(\mathrm{Me}) = 0$ and $E_s^{\,c}(\mathrm{Et}) = -0.38$ have been established,[16] the placement of the piperazinone ring carbonyl and methylene groups relative to methyl and ethyl is uncertain, so far.[17] However, the present analysis requires only the calculation of a relative change $\Delta E_s^{\,c}$ caused by the replacement of methyl by ethyl groups. Therefore, have arbitrarily taken the piperazinone ring groups as R_3 for both C3 and C5 and all compounds.

Figure 1 shows logarithmic plots of the rate constants k_c at 373 K and k_d at 393 K vs $\Delta E_s^{\,c}$. As expected, k_c decreases as $\Delta E_s^{\,c}$ becomes more negative, that is, with increasing steric hindrance for the coupling reaction. k_d shows the opposite behavior, and this is also intuitively reasonable. The linear dependencies confirm eqs 2 and 3, and the slopes of the straight lines in Figure 1 are $\delta_c = 0.18$ and $\delta_d = -0.45$. As expected, the absolute values are smaller than one.[20] Interestingly, substitutions of methyl by ethyl at the 3- and 5-positions of the ring cause rather similar effects although these positions are chemically not equivalent.

Since they are not the main topic of this work, the results of styrene polymerizations initiated with the 3,3,5,5-tetramethyl-, 3,3-diethyl-5,5-dimethyl- and 3,3,5,5-tetraethyl-piperazinone-derived alkoxyamines will be published in detail elsewhere[21] and are mentioned here only briefly. With increasing conversion the number-average molecular weight of the polystyrenes increased linearly while the polydispersity index decreased. This

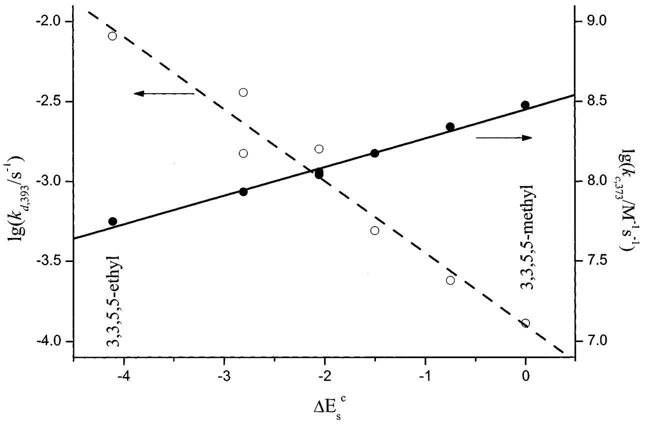

Figure 1. Rate parameters for the cleavage (k_d, 393 K, open symbols) and the reformation (k_c, 373 K, closed symbols) of various methyl and ethyl substituted piperazinone derived alkoxyamines in a semilogarithmic plot vs the steric substituent constant ΔE_s^c. Statistical errors of the rate constants are below 10%.

indicates living and controlled reactions. Moreover, after 6 h of polymerization at 120 °C the final monomer conversion increased and the polydispersity index decreased from 1.51 to 1.14 with increasing ethyl substitution. This agrees nicely with the increasing equilibrium and decay constants of Table 1 for the low molecular weight model compounds used in this study.

Acknowledgment. We thank the Swiss National Foundation for Scientific Research for financial support.

References and Notes

(1) Solomon, D. H.; Rizzardo, E.; Cacioli, P. US Pat. 4581429; *Chem. Abstr.* **1985**, *102*, 221335q.
(2) Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K. *Macromolecules* **1993**, *26*, 2987.
(3) For a comprehensive review, see: Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661.
(4) For a comprehensive review, see: Kamigato, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689.
(5) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Lee, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559.
(6) For a comprehensive review, see: Fischer, H. *Chem. Rev.* **2001**, *101*, 3581.
(7) Fischer, H. *Macromolecules* **1997**, *30*, 5666. Fischer, H. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 1885. Souaille, M.; Fischer, H. *Macromolecules* **2000**, *33*, 7378.
(8) Goto, A.; Fukuda, T. *Macromolecules* **1997**, *30*, 4272. Fukuda, T.; Goto, A.; Ohno, K. *Macromol. Rapid Commun.* **2000**, *21*, 151. Fukuda, T.; Goto, A. *ACS Symposium Series* **2000**, *768*, 27. Goto, A.; Fukuda, T. *Macromol. Chem. Phys.* **2000**, *201*, 2138 and references therein.
(9) Greszta, D.; Matyjaszewski, K. *Macromolecules* **1996**, *29*, 5239. Greszta, D.; Matyjaszewski, K. *Macromolecules* **1996**, *29*, 7661. Bon, S. A. F.; Chambard, G.; German, A. L. *Macromolecules* **1999**, *32*, 8269. Benoit, D.; Grimaldi, S.; Robin, S.; Finet, J.-P.; Tordo, P.; Gnanou, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5929. Lutz, J.-F.; Lacroix-Desmazes, P.; Boutevin, B. *Macromol. Rapid Commun.* **2001**, *22*, 189. Bertin, D.; Chauvin, F.; Marque, S.; Tordo, P. *Macromolecules* **2002**, *35*, 3790. Ananchenko, G.; Fischer, H. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 3604. Ananchenko, G.; Souaille, M.; Fischer, H.; LeMercier, C.; Tordo, P. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 3264.
(10) Moad, G.; Rizzardo, E. *Macromolecules* **1995**, *28*, 8722. Baldovi, M. V.; Mohtat, N.; Scaiano, J. C. *Macromolecules* **1996**, *29*, 5497. Skene, W. G.; Belt, S. T.; Connolly, T. J.; Hahn, P.; Scaiano, J. C. *Macromolecules* **1998**, *31*, 9103. Ciriano, M. V.; Korth, H. G.; van Scheppeningen, W. B.; Mulder, P. *J. Am. Chem. Soc.* **1999**, *121*, 6375. Le Mercier, C.; Lutz, J.-F.; Marque, S.; Le Moigne, F.; Tordo, P.; Lacroix-Desmazes, P. Boutevin, B.; Couturier, J.-L.; Guerret, O.; Martschke, R.; Sobek, J.; Fischer, H. *ACS Symp. Ser.* **2000**, *768*, 108. Le Mercier, C.; Acerbis, A.; Chauvin, F.; Gigmes, D. Guewrret, O.; Lansalot, M.; Marque, S.; Le Moigne, F.; Fischer, H.; Tordo, P.; Lacroix-Desmazes, P. Boutevin, B.; Couturier, J.-L.; Guerret, O.; Martschke, R.; Sobek, J.; Fischer, H. *Macromol. Symp.* **2002**, *182*, 225. Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983. Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4992. Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 1629. Beckwith, A. L. J.; Bowry, V. W.; Moad, G. *J. Org. Chem.* **1988**, *53*, 1632. Goto, A.; Kwak, Y.; Yoshikawa, C.; Tsujii, Y.; Sugiura, Y.; *Macromolecules* **2002**, *35*, 3520.
(11) Nesvadba, P.; Kramer, A.; Zink, M. O. US Pat. 6479608 B1.
(12) Scaiano, J. C.; Tanner, M.; Weir, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 3496.
(13) Marque, S.; LeMercier, C.; Tordo, P.; Fischer, H. *Macromolecules* **2000**, *33*, 4403. Marque, S.; Fischer, H.; Baier, E.; Studer, A. *J. Org. Chem.* **2001**, *66*, 1146.
(14) Sobek, J.; Martschke, R.; Fischer, H. *J. Am. Chem. Soc.* **2001**, *123*, 2849.
(15) Hancock, K.; Meyers, E. A.; Nakajima, M. *J. Am. Chem. Soc.* **1961**, *83*, 4211.
(16) Fujita, K.; Takayama, C.; Nakajima, M. *J. Org. Chem.* **1973**, *38*, 1623.
(17) Relative rates of the methylation of tertiary piperidines and pyrrolidines differ only slightly from those of their linear homologues,[18] which indicates an equivalence of the ring substituents with an ethyl group. On the other hand, comparison of the dissociation constants k_d of a large number of cyclic and open chain alkoxyamines suggests that ring substituents should be placed in eq 2 even before methyl groups.[19]
(18) Takayama, C.; Fujita, K.; Nakajima, M. *J. Org. Chem.* **1979**, *44*, 2871.
(19) Marque, S. To be published.
(20) If the ring substituents are placed at positions 1 or 2, the slopes become $\delta_c = 0.36$ and $\delta_d = -0.91$, or $\delta_c = 0.22$ and $\delta_d = -0.57$, respectively.
(21) Nesvadba, P.; Bugnon, L.; Sift, R.; Wunderlich, W. To be published.

MA021605D