JOC The Journal of Organic Chemistry

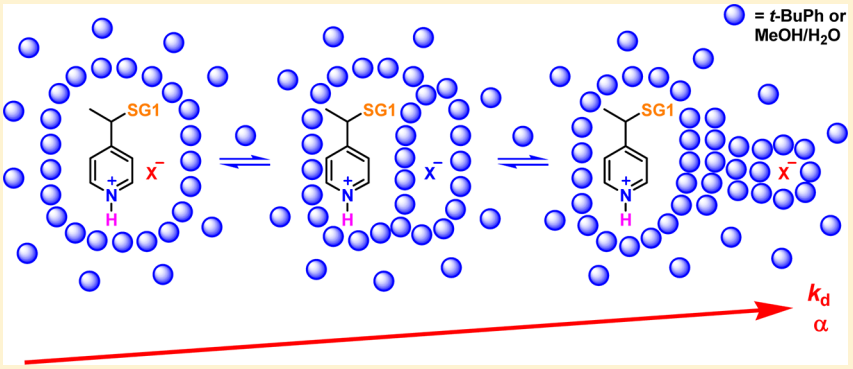
Note

pubs.acs.org/joc

# Chemically Triggered C–ON Bond Homolysis in Alkoxyamines. 6. Effect of the Counteranion

Gérard Audran, Paul Brémond, Sylvain R. A. Marque,* and Germain Obame

Aix-Marseille Université, CNRS, ICR UMR-7273, case 551, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France




**ABSTRACT:** We showed (*J. Org. Chem.* 2012, 77, 9634) that the activation by methylation of pyridyl-based alkoxyamine **1** increased with the hydrogen bond donor properties of solvents. In this paper, activation of **1** by protonation with acids, $CF_3COOH$ and CSA, in *tert*-butylbenzene (*t*-BuPh) and in $H_2O$/MeOH afforded, with $CF_3COOH$, $k_d$ 28-fold larger in $H_2O$/MeOH than in *t*-BuPh, whereas it was only 4-fold larger when CSA was used. This puzzling observation was ascribed to the dissociation of the intimate ion pair.

Since its discovery,[1−3] nitroxide-mediated polymerization (NMP) has generated a tremendous amount of work on designing new alkoxyamines (initiator/controller agents),[4−7] unveiling kinetics,[8−11] and devising new materials.[12−15] However, until recently,[16−18] the investigation of the solvent effect on the rate constant $k_d$ of the C–ON bond homolysis in alkoxyamines did not arouse much interest.[19−26] In general, a very weak solvent effect was commonly accepted.[14,15,17,19] However, it has been shown that changing the solvent can significantly affect the fate of NMP experiments; for example, for isoprene a poor quality bulk NMP has been reported whereas a successful one has been reported in 1,4-dioxane or pyridine as solvent.[27,28] Moreover, with the simple alkoxyamine models **1** and **3** (**1** activated by methylation, Figure 1), we showed that the hydrogen bond donor (HBD) property of solvents increased $k_d$ (C–ON bond homolysis) although no extra lone pair was available in **3** compared to **1** (the formation of an ammonium salt in **3** suppressed the nitrogen lone pair available on the pyridyl moiety of **1**).

This puzzling solvent effect was assumed to be due to the separation of the intimate ion pair, which is expected to depend both on the HBD property of the solvent and on the type of counteranion (Figure 2). Unfortunately, only a few methylating agents with different counteranions are available. To circumvent this limitation and to support our claim concerning the effect of the counteranion, we investigated the effect of the dissociation of the intimate ion pair for salts of **2a–g** on $k_d$. These salts were prepared with various acids, HCl, HBr, $H_2SO_4$, $HClO_4$, $CF_3COOH$, *p*-toluenesulfonic acid (PTSA), and camphorsulfonic acid (CSA), in *tert*-butylbenzene (*t*-BuPh) as apolar solvent and in a water/methanol (1:1 v/v) mixture as polar solvent. As expected, the high dissociative property of water implies a smaller effect of the counteranion (~2-fold difference from HCl to $CF_3COOH$) than in *tert*-butylbenzene (~4-fold difference from HCl to CSA). This nicely confirms the role of the counteranion and the ability of the solvent to dissociate the intimate ion pair through its HBD property.

Experiments were performed in the $H_2O$/MeOH (1:1 v/v) mixture (or $D_2O$/MeOH-$d_4$ when $^1H$ NMR signal was recorded), **1** being insoluble in water. From the pH dependence of the $^1H$ NMR signal recorded at room temperature in $D_2O$/MeOH-$d_4$ (1:1 v:v), a significant shift was observed for the aromatic protons from pH 7 to 2.5 (Figure 3). The titration curve for **1** (Figure 3) affords a p$K_a$ value of 4.67 for the major diastereoisomer *RR*/*SS* of **1**, in nice agreement with the reported value of 4.70 for the minor diastereoisomer *RS*/*SR*[29] and in sharp contrast with the value given for the *para*-ethyl pyridine (p$K_a$ = 6.02).[30,31] $k_d$ values (Table 1) were measured at pH ranging between 2.9 ($H_2SO_4$) and 1.7 (CSA), meaning that roughly 99% to 99.9%, respectively, of **1** was protonated. $HClO_4$, $H_2SO_4$, and HBr are not soluble in *t*-BuPh, and the corresponding alkoxyamines were not prepared, while gaseous[32] HCl was bubbled through the solution to afford **2g**. In both solvents $H_2O$/MeOH (1:1 v:v) mixture and in *t*-BuPh, $k_d'$ for the minor diastereoisomer is

**Received:** June 7, 2013
**Published:** July 15, 2013

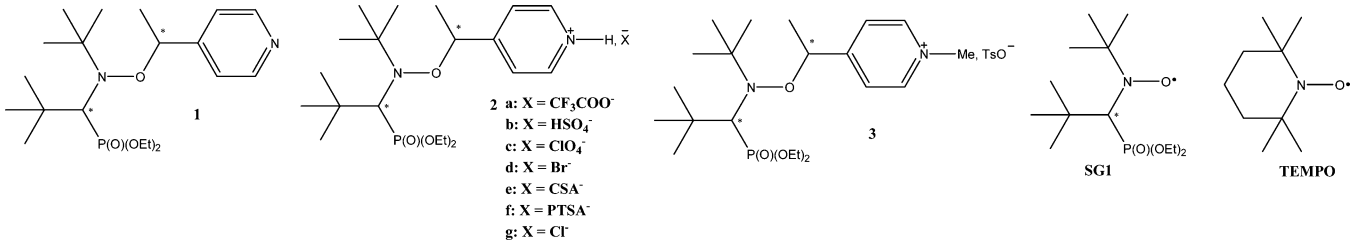



**Figure 1.** Alkoxyamines investigated.

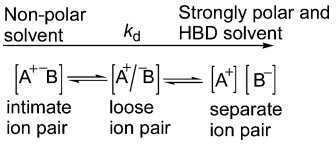



**Figure 2.** Evolution of $k_d$ with the type of ion pairs.

roughly 1.5-fold larger than for the major diastereoisomer, except for CSA and PTSA (1.9- and 1.8-fold, respectively, in *t*-BuPh, see Tables 1 and 2), $HClO_4$, and $CF_3COOH$ (no difference between the diastereoisomers in Tables 1 and 2, respectively). Nevertheless, the difference between the two diastereoisomers is in the range reported for other types of activation and solvent and does not deserve more comments.[16,18,33]

As expected, $k_d'$ is larger in $H_2O$/MeOH (Table 1) than in *t*-BuPH (Table 2). Amazingly, although the measured species are expected to be the same, i.e, the protonated forms of **1**, $k_d'$ values span the range from 4- to 28-fold for **2e** (camphorsulfonate anion, $\Delta E_a$ = 4 kJ/mol)[34,35] and **2a** (trifluoroacetate anion, $\Delta E_a$ = 9 kJ/mol),[34,35] respectively, from *t*-BuPh to $H_2O$/MeOH, confirming that $k_d'$ depends significantly on the counteranion, as previously claimed.[18] Taking into account that the values of the Abraham's parameters[36−38] $\alpha$ are 0 and 1.17 for *t*-BuPh and water,[39] respectively, a better solvation of the counteranion is expected in $H_2O$/MeOH than in *t*-BuPh, and thus, the counteranion effect is expected weaker in $H_2O$/MeOH than in *t*-BuPh, as the nearly separated ion pair predominates in the former. This is nicely highlighted by the weaker salt effect observed in $H_2O$/MeOH ($k_d'$($CF_3COOH$)/$k_d'$(acid) spans from 1 for $H_2SO_4$ to 2 for HCl in $H_2O$/MeOH) compared to *t*-BuPh ($k_d'$(CSA)/$k_d'$(acid) spans from 3 for PTSA to 4.2 for $CF_3COOH$) as expected from the $\alpha$ values, i.e., the higher the $\alpha$ value, the smaller the difference between the counteranions. On the other hand, $k_d'$ exhibits its lowest values with HCl and $CF_3COOH$ meaning that they are involved in a strong ion pair whereas the largest $k_d'$ is found with CSA, for which the alkyl part is the most apolar and thus the ion pair is the weakest. It is well-known that entropic[40] and enthalpic[37] are solvent dependent. The increase of $k_d$ by going from *t*-BuPh to water/MeOH mixture and by changing the counteranion is likely related to the activation entropy as the dissociation of salt increases the freedom of motion and to the activation enthalpy as the dissociation increase the positive charge on the alkyl fragment, and, hence the effect of the polarity.[41]

In conclusion, the strength of the ion pair, which is related both to the dissociation/solvation properties of the solvent (partly highlighted by the solvent descriptor $\alpha$) and to the solubility of the alkyl moiety, plays a significant role. For example, at 37 °C in *t*-BuPh, a 20-fold increase in $k_d$ was reported from **1** ($t_{1/2}$ = 18 d) to **2a** ($t_{1/2}$ = 22 h) whereas an 80-fold increase was observed for **2e** ($t_{1/2}$ = 5 h). On the other hand, at 37 °C in $H_2O$/MeOH, a 38-fold increase in $k_d$ was observed from **1** ($t_{1/2}$ = 4 d) to **2g** ($t_{1/2}$ = 150 min) whereas a 130-fold increased was observed for **2a** ($t_{1/2}$ = 44 min). Consequently, by changing the solvent and the counteranion, one shifts from the nonapplicable alkoxyamine **1** to the alkoxyamine **2a** suitable for biological applications. Moreover, at 37 °C, a 1067-fold increase[42] in $k_d$ was predicted upon protonation of **1**, and disappointment was felt when a 20-fold increase in $k_d$ was observed when $CF_3COOH$ was used in *t*-BuPh as solvent.[42] Nevertheless, a 577-fold increase in $k_d$ was observed for **2a** in $H_2O$/MeOH, only two times lower than predicted. Consequently, these results showed that the

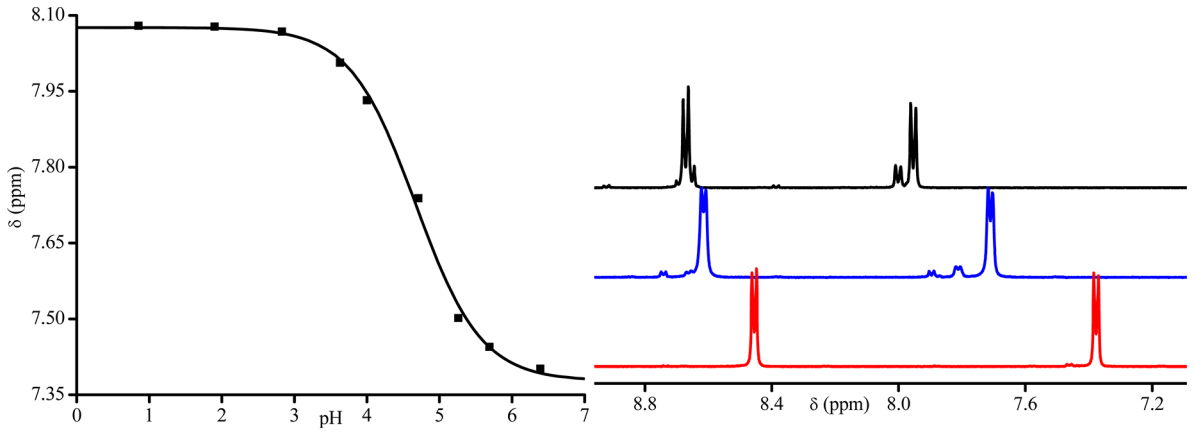



**Figure 3.** Titration curve (left) for **1** (0.02 M) obtained using the $^1$H NMR signal (right, pH = 0.85, 4.7, and 6.4 from top to bottom) in the aromatic zone, at room temperature in $D_2O$/$CD_3OD$ (v/v 1:1). pH was set with DCl and NaOD. The small peaks are ascribed to the minor diastereoisomer of **1**.


dx.doi.org/10.1021/jo401227a | J. Org. Chem. 2013, 78, 7754−7757

**Table 1. $k_d$ Values and Activation Energies $E_a$ Measured for Various Acids in the $H_2O$/MeOH (1:1 v/v) Mixture for pH between 1.7 and 2.9 at the Experimental Temperature $T$ and the Re-estimated $k_d'$ Values at 50 °C for the Minor and Major Diastereoisomers of 2a−g**

| | | | | major isomer (*RS*/*SR*)[a] | | | minor isomer (*RR*/*SS*)[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| **2** | acid | pH[b] | $T$ (°C) | $k_d$[c,d] | $E_a$ (kJ/mol)[e,f] | $k_d'$ (50 °C)[c,g] | $k_d$[c,d] | $E_a$ (kJ/mol)[e,f] | $k_d'$ (50 °C)[c,g] |
| **a** | $CF_3COOH$ | 2.7 | 50 | 9.5 | 107.7 | 9.5 | 14.2 | 106.6 | 14.2 |
| **b** | $H_2SO_4$ | 2.9 | 50 | 9.2 | 107.7 | 9.2 | 12.5 | 106.9 | 12.5 |
| **c** | $HClO_4$ | 2.7 | 50 | 4.5 | 109.7 | 4.5 | 8.1 | 108.1 | 8.1 |
| **d** | HBr | 2.7 | 50 | 6.8 | 108.6 | 6.8 | 11.0 | 107.3 | 11.0 |
| **e** | CSA | 1.7 | 50 | 6.4 | 108.7 | 6.4 | 9.4 | 107.7 | 9.4 |
| **f** | PTSA | 2.0 | 55 | 10.2 | 109.1 | 5.6 | 14.3 | 108.2 | 7.8 |
| **g** | HCl | 2.0 | 55 | 8.2 | 109.7 | 4.4 | 11.0 | 108.3[h,i] | 7.5 |

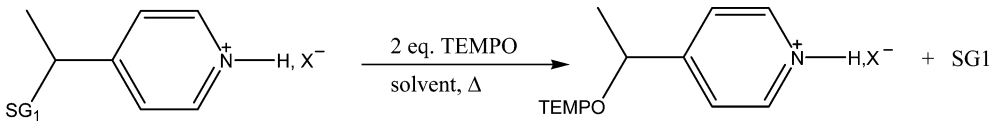
[a]As given in ref 42. [b]Measured at room temperature. [c]Given in $10^{-4}$ $s^{-1}$. [d]Statistical errors are less than 2%. [e]Estimated using the average value of $A = 2.4 \times 10^{14}$ $s^{-1}$. See refs 34 and 35. [f]Commonly accepted errors are given as ±1 kJ/mol. [g]Estimated using the frequency factor given in footnote *e* combined to the data in the sixth column for the major isomer and to those in the ninth column for the minor isomer. [h]$E_a$ = 107.8 kJ/mol in ref 29. [i]Averaged value with the value reported in footnote *h*.

**Table 2. $k_d$ Values and Activation Energies $E_a$ Measured for Various Acids in *t*-BuPh at the Experimental Temperature $T$ and the Re-estimated $k_d'$ Values at 50 °C for the Minor and Major Diastereoisomers of 2a−g**

| | | | major isomer (*RS*/*SR*)[a] | | | minor isomer (*RR*/*SS*)[a] | | |
|---|---|---|---|---|---|---|---|---|
| **2** | acid | $T$ (°C) | $k_d$[b,c] | $E_a$ (kJ/mol)[d,e] | $k_d'$ (50 °C)[b,f] | $k_d$[b,c] | $E_a$ (kJ/mol)[d,e] | $k_d'$ (50 °C)[b,f] |
| **a** | $CF_3COOH$ | *g* | *g* | 115.6[h] | 0.5 | | 115.4[h] | **0.5** |
| **b** | $H_2SO_4$ | *g* | *g* | *i* | *i* | *g* | *i* | *i* |
| **c** | $HClO_4$ | *g* | *g* | *i* | *i* | *g* | *i* | *i* |
| **d** | HBr | *g* | *g* | *i* | *i* | *g* | *i* | *i* |
| **e** | CSA | 60 | 4.1 | 113.3 | 1.2 | 7.3 | 111.7 | 2.1 |
| **f** | PTSA | 60 | 2.5 | 114.7 | 0.7 | 3.5 | 113.8 | 1.0 |
| **g** | HCl | 60 | 1.6 | 115.9 | 0.4 | 2.0 | 115.6 | 0.5 |

[a]As given in ref 42. [b]Given in $10^{-4}$ $s^{-1}$. [c]Statistical errors are less than 2%. [d]Estimated using the average value of $A = 2.4 \times 10^{14}$ $s^{-1}$. See ref 34 and 35. [e]Commonly accepted errors are given as ±1 kJ/mol. [f]Estimated using the frequency factor given in footnote *d* combined to the data in the fifth column for the major isomer, and to those in the eighth column for the minor isomer. [g]Not measured. See text. [h]Given in ref 33. [i]Not estimated.

**Scheme 1. Scavenging Experiment Applied to Measure $k_d$**




predictive equations developed in the past years[43−45] are still robust but difficult of use with protonated or activated alkoxyamines, as the effects of the solvent and the counteranion need to be taken into account. This observation opens new opportunities to tune the initiation stage of NMP experiments, increasing its potential for new applications.

## EXPERIMENTAL SECTION

Alkoxyamine **1** was prepared as previously reported (*RS*/*SR* and *RR*/*SS* diastereomeric ratio 2:1, respectively).[42] Solvents, organics, and mineral acids were used as received.[46] A water/methanol (1:1 v:v) mixture was used to solve **1**, and the pH was adjusted by adding the corresponding acid and controlled with a HI2211 pH/ORP Meter from Hanna Instruments and a 4 mm microtitration electrode from Bioblock. The $^1H$ and $^{31}P$ NMR data for **2a−g** were in good agreement with those reported for **2a**.[16,18,29] The diastereosiomers were identified as previously reported.[42] Rate constants $k_d$ were measured, in general, in a single run at the temperature reported in Table 1, using $^{31}P$ NMR as previously described with 2 equiv of TEMPO as alkyl radical scavengers and 2 equiv of acid in *t*-BuPh (Scheme 1).[47] Temperature of the oil bath was maintained to within ±1 °C.

$k_d$ values were given by eq 1, with $C_0$ the initial concentration of alkoxyamine and $t$ the time. The activation energies $E_a$ were given by eq 2, with the frequency factor $A = 2.4 \times 10^{14}$ $s^{-1}$, the temperature $T$ and the constant $R$ = 8.314 J $K^1$ $mol^{-1}$:[34,35]

$$\ln \frac{C}{C_0} = -k_d t \quad (1)$$

$$k_d = A e^{-E_a/RT} \quad (2)$$

The plots drawn (not shown) from eq 1 were as good as those already reported.[16,18,29,33,42] To facilitate the discussion, all $k_d$ values were re-estimated at 50 °C using eq 2 and noted $k_d'$.

## AUTHOR INFORMATION

### Corresponding Author

*E-mail: sylvain.marque@univ-amu.fr.

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We are grateful to ANR SonRadIs (Grant No. 11-JS07-002-01) for financial support, to Aix-Marseille University, and to CNRS.

## REFERENCES


(1) Solomon, D. H.; Rizzardo, E.; Cacioli, P. Eur. Pat. Appl. 135280, 1985; US Patent 4,581,429,1986; *Chem. Abstr.* **1985**, *102*, 221335q.
(2) Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K. *Macromolecules* **1993**, *26*, 2987−2988.
(3) Moad, G.; Solomon, D. H. *The Chemistry of Radical Polymerization*, 2nd fully revised ed.; Elsevier: Amsterdam, 2006.
(4) Grubbs, R. B. *Polym. Rev.* **2011**, *51*, 104−137.
(5) Tebben, L.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5034−5068.
(6) Nesvadba, P. *Chimia* **2006**, *60*, 832−840.
(7) Bertin, D.; Gigmes, D.; Marque, S. R. A. *Recent Res. Dev. Org. Chem.* **2006**, *10*, 63−121.
(8) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581−3610 and references cited therein.
(9) Goto, A.; Fukuda, T. *Prog. Polym. Sci.* **2004**, *29*, 329−385 and references cited therein.
(10) Bertin, D.; Gigmes, D.; Marque, S. R. A.; Tordo, P. *Chem. Soc. Rev.* **2011**, *40*, 2189−2198 and references cited therein.
(11) Charleux, B.; Nicolas, J. *Polymer* **2007**, *48*, 5813−5833.
(12) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661−3688.
(13) Braunecker, W. A.; Matyjaszewski, K. *Prog. Polym. Sci.* **2007**, *32*, 93−146.
(14) Marque, S.; Gigmes, D. *Nitroxide-Mediated Polymerization and Its Applications in Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; John Wiley & Sons: Chichester, 2012; pp 1813−1850 and references cited therein.
(15) Nicolas, J.; Guillaneuf, Y.; Lefay, C.; Bertin, D.; Gigmes, D.; Charleux, B. *Prog. Polym. Sci.* **2013**, *38* (1), 63−235.
(16) Part 4: Audran, G.; Brémond, P.; Marque, S. R. A.; Obame, G. *Polymer Chem.* **2012**, *3*, 2901−2908.
(17) Zaremski, M.; Borisova, O.; Xin, C.; Golubev, V. B.; Billon, L. *J. Polym. Sci., Part A: Polym. Chem.* **2012**, *50*, 3437−3443.
(18) Part 5 Audran, G.; Brémond, P.; Marque, S. R. A.; Obame, G. *J. Org. Chem.* **2012**, *77* (21), 9634−9640.
(19) Guerret, O.; Couturier, J.-L.; Chauvin, F.; El-Bouazzy, H.; Bertin, D.; Gigmes, D.; Marque, S.; Fischer, H.; Tordo, P. *ACS Symp. Ser.* **2003**, *854*, 412−423.
(20) Moad, G.; Rizzardo, E. *Macromolecules* **1995**, *28*, 8722−8728.
(21) Marque, S.; Fischer, H.; Baier, E.; Studer, A. *J. Org. Chem.* **2001**, *66*, 1146−1156.
(22) Grattan, D. W.; Carlsson, D. J.; Howard, J. A. *Can. J. Chem.* **1979**, *57*, 2834.
(23) Kuo, K. H.; Chiu, W. Y.; Cheng, K. C. *Polym. Int.* **2008**, *57*, 730.
(24) Chenal, M.; Mura, S.; Marchal, C.; Gigmes, D.; Charleux, B.; Fattal, E.; Couvreur, P.; Nicolas, J. *Macromolecules* **2010**, *43*, 9291.
(25) Ding, X. Z.; Fischer, A.; Yang, S. W.; Wu, P.; Brembilla, A.; Lochon, P. *Eur. Polym. J.* **2001**, *37*, 1561−1569.
(26) Ding, X. Z.; Fischer, A.; Brembilla, A.; Lochon, P. *J. Polym. Sci.: Pol. Chem.* **2000**, *38*, 3067−3073.
(27) Harisson, S.; Couvreur, P.; Nicolas, J. *Macromolecules* **2011**, *44*, 9230−9238.
(28) Harisson, S.; Couvreur, P.; Nicolas, J. *Macromol. Rapid Commun.* **2012**, *33*, 805−810.
(29) Part 2: Bagryanskaya, E.; Brémond, P.; Edeleva, M.; Marque, S. R. A.; Parkhomenko, D.; Roubaud, V.; Siri, D. *Macromol. Rapid Commun.* **2012**, *33*, 152−157.
(30) Gramstad, T. *Acta Chem. Scand.* **1993**, *47*, 985.
(31) Wilson, J. W.; Worrall, J. *Chem. Eng. Data* **1968**, *13*, 537.
(32) HCl gas was generated by adding dropwise $H_2SO_4$ onto NaCl (conventional procedure). See: Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemichals*, 5th ed.; Butterworth Heinemann: Amsterdam, 2003.
(33) Part 3: Brémond, P.; Koïta, A.; Marque, S. R. A.; Pesce, V.; Roubaud, V.; Siri, D. *Org. Lett.* **2012**, *14*, 358−361.
(34) Bertin, D.; Gigmes, D.; Marque, S. R. A.; Tordo, P. *Macromolecules* **2005**, *38* (7), 2638−2650.
(35) For the sake of simplicity, the average value of *A* (see ref 34) was used. However, one must keep in minds for the discussion (see text) *A* is also dependent on the solvent.
(36) Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Duce, P. P.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 699−711.
(37) Reichardt, C.; Welton, T. *Solvent and Solvent Effect in Organic Chemistry*, 4th ed.; Wiley-VCH: New York, 2011.
(38) Abraham's parameters are parameters developed to estimate the hydrogen bond acceptor (HBA, parameter $\alpha$) and hydrogen bond donor (HBD, $\alpha$ parameter) properties of solvent. See refs 36 and 37.
(39) The $\alpha$ value for the mixture $H_2O$/MeOH has not been reported. For MeOH, $\alpha$ = 0.98. See ref 37.
(40) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; John Wiley and Sons: New York, 1963.
(41) The authors thank the reviewers to point to this possibility.
(42) Part 1: Brémond, P.; Marque, S. R. A. *Chem. Commun.* **2011**, *47*, 4291−4293.
(43) Bertin, D.; Gigmes, D.; Marque, S. R. A.; Tordo, P. *Macromolecules* **2005**, *38* (7), 2638−2650.
(44) Ananchenko, G.; Beaudoin, E.; Bertin, D.; Gigmes, D.; Lagarde, P.; Marque, S. R. A.; Revalor, E.; Tordo, P. *J. Phys. Org. Chem.* **2006**, *19* (4), 269−275.
(45) Bertin, D.; Dufils, P.-E.; Durand, I.; Gigmes, D.; Giovanetti, B.; Guillaneuf, Y.; Marque, S. R. A.; Phan, T.; Tordo, P. *Macromol. Chem. Phys.* **2008**, *209*, 220−224.
(46) Solvents for kinetics were EPR or HPLC grades. Solvents for synthesis were of lower grades and alkoxyamine **1** was carefully purified.
(47) Bertin, D.; Gigmes, D.; Marque, S.; Tordo, P. *e-Polym.* **2003**, *2*, 1−9.