ORGANIC LETTERS

2012
Vol. 14, No. 1
358–361

Chemically Triggered C–ON Bond Homolysis of Alkoxyamines. Quaternization of the Alkyl Fragment

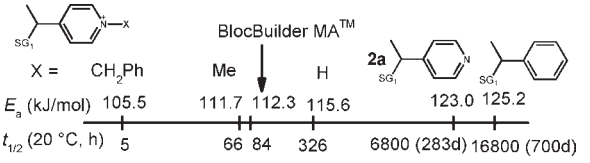
Paul Brémond,* Abdoulaye Koïta, Sylvain R. A. Marque,* Vincent Pesce, Valérie Roubaud, and Didier Siri

Laboratoire Chimie Provence UMR 6264 – CNRS, Université de Provence, case 521, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

sylvain.marque@univ-provence.fr; paul.bremond@univ-provence.fr

Received November 20, 2011

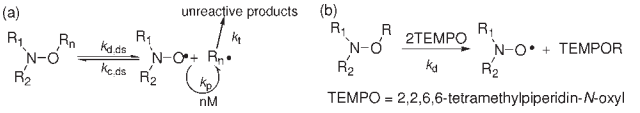
ABSTRACT



The C–ON bond homolysis in alkoxyamine 2a can be chemically triggered by the protonation of the 4-pyridylalkyl fragment. The resulting 15-fold increase in k_d (*Chem. Commun.* 2011, *47*, 4291–4293) was investigated experimentally and theoretically by quaternization of the pyridyl moiety using methylating (MeOTs), acylating (AcCl), and benzylating ($PhCH_2Br$) agents as well as by oxidation of the pyridyl moiety into *N*-oxide and by the formation of a dative bond with BH_3 as a Lewis acid.

For 25 years, much effort has been devoted to the development of Nitroxide Mediated Polymerization (NMP) and the controller (nitroxide)/initiator (alkoxyamine) couple.[1−5] Initiator/controller preparation, kinetics, polymerizations, and applications to the preparation of new materials are the topics of several reviews.[1−5] NMP, like the conventional radical polymerization, is described by a three-stage polymerization process. For the sake of simplicity, NMP is often displayed as in Scheme 1a, $k_{d,ds}$ being the rate constant for the homolysis of the C–ON bond of the dormant species ds into nitroxyl and macro-alkyl radicals and $k_{c,ds}$ its reformation rate constant, k_p the propagation rate constant, and k_t the termination rate constant. The main feature of NMP is the quasi-absence of termination reactions which are maintained at a very low level due to the equilibrium between dormant and active species. It appears that the fate of the NMP as well as its wide use both rely on the very fine-tuning of the homolysis rate constants k_d and the reformation rate constant k_c of the initiating alkoxyamine as well as the $k_{d,ds}$ and $k_{c,ds}$ of the dormant species.[4,5] Furthermore, this tuning can be antagonistic depending on the monomer undergoing the polymerization.[4,5] It led to developing alkoxyamines suitable only for a few monomers, as exemplified by **1** (Figure 1): very efficient to promote the NMP of monosubstituted monomers and unsuccessful for 1,1-disubstituted monomers under general conditions.[1−5] Moreover, new stringent requirements have arisen concerning the shipping of materials decomposing at low temperature.[6] Thus, the development of the chemically triggered C–ON bond homolysis is a new direction for NMP research.

Scheme 1. (a) Simplified Scheme for NMP; (b) Conditions To Investigate the C–ON Bond Homolysis of **2a**–**2g**



(1) Ananchenko, G.; Beaudoin, E.; Bertin, D.; Gigmes, D.; Lagarde, P.; Marque, S. R. A.; Revalor, E.; Tordo, P. *J. Phys. Org. Chem.* **2006**, *19*, 269–275. Fischer, H. *Chem. Rev.* **2001**, *101*, 3581–3610.

(2) Goto, A.; Fukuda, T. *Prog. Polym. Sci.* **2004**, *29*, 329–385.

(3) Braunecker, W. A.; Matyjaszewski, K. *Prog. Polym. Sci.* **2007**, *32*, 93–146.

(4) Bertin, D.; Gigmes, D.; Marque, S. R. A.; Tordo, P. *Chem. Soc. Rev.* **2011**, *40*, 2189–2198.

(5) Gigmes, D.; Marque, S. R. A. *Handbook of Radical Chemistry*; Studer, A., Chatgilialoglu, C., Eds.; Wiley-VCH: 2012, in press.

(6) MSDS and FDS sheets from Arkema.

10.1021/ol2031075
Published on Web 12/16/2011

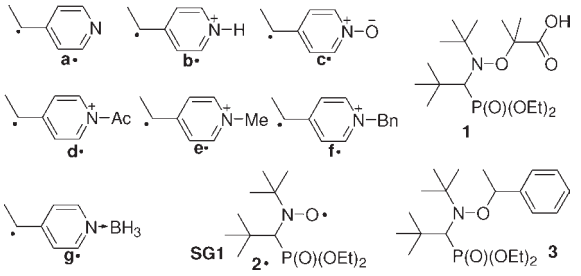
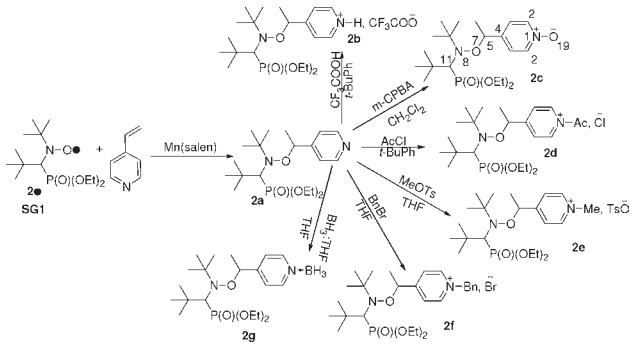


Figure 1. Activated alkoxyamines and their released radicals.

Very recently, Bagryanskaya et al.[7] showed that the protonation of the nitroxide fragment led to a decrease of k_d while our group showed that the protonation of the pyridyl group of **2a** affording **2b** (Scheme 2) led to a 15-fold increase in k_d.[8] Then, we turned our interest to other activations (Scheme 2) such as the oxidation of the pyridyl fragment (**2c**), its quaternization by acetylation (**2d**), by methylation (**2e**), and by benzylation (**2f**), and its complexation with a Lewis acid (**2g**). The reactivity was also investigated by DFT calculations.

Scheme 2. Preparation of **2a**−**g**



Alkoxyamines **2b**−**g** were prepared using trifluoroacetic acid,[8] *m*-chloroperbenzoic acid, acetyl chloride, methyl tosylate, benzyl bromide, and a borane−THF complex, respectively (Scheme 2 and Supporting Information). Except for **2b** and **2d** that were prepared *in situ*, other alkoxyamines **2c**, **2e**−**g** were prepared at rt in quantitative yields and purified by either precipitation or solvent removal under vacuum. Based on the X-ray data reported for **2a**,[8] the *RR*/*SS* configuration is ascribed to the minor diastereoisomer. Rate constants were measured as previously described using 2 equiv of TEMPO as alkyl radical scavengers in *tert*-butylbenzene (*t*-BuPh) as solvent (Scheme 1b).[8,9] Except for **2b** and **2d** generated *in situ*, all other k_d values were measured on pure compounds (Table 1). Figure 2 displays the plots for the first-order decay of the activated major and minor diastereoisomers of alkoxyamines. The activation energies E_a of each reaction (Table 1) were estimated using the averaged frequency factor $A = 2.4 \times 10^{14}$ s^{-1}.[10]

Table 1. Experimental Temperature T (°C) and C−ON Bond Homolysis Rate Constant k_d, Activation Energies E_a, and Relative Rate Constants $k_{d,rel}$ for the Minor and the Major Diastereoisomers of Alkoxyamines **2a**−**2g** in *tert*-Butylbenzene As Solvent unless Otherwise Mentioned

		k_d (10^{-3} s^{-1})[a]		E_a (kJ/mol)[b]		$k_{d,rel}$ (120 °C)[c]	
	T	minor	major	minor	major	minor	major
2a[d]	80	0.15	0.15	123.0	123.0	1	1
2a['e]	80	0.31	0.27	120.9	121.3	1.9	1.6
2b	80[f]	1.7	2.4	–	–	–	–
2b	61	0.22	0.14	115.6[g]	115.7[g]	9.5	9.3
2c	61	0.37	0.41	113.9	113.7	16.1	17.1
2d	60	0.24	0.19	114.8	115.4	12.2	10.2
2e	61	0.83	0.49	111.7	113.2	31.5	20.0
2e[''e]	50	1.38	0.81	106.7	108.1	145.2	94.6
2e[''h]	41	0.55	0.29	106.1	107.8	174.5	103.7
2f[e]	50[f]	2.14	0.51	105.5	109.3	209.6	65.5
2g	60	0.18	0.19	115.6	115.4	9.5	10.2

[a] Measured at the experimental temperature. The reported values are the averaged of two runs for each compound. Statistical error less than 2%. For all reported values, the error is lower than 5% and is mainly due to discrepancies in the temperature measurements. [b] Activation energy E_a estimated applying the averaged frequency factor $A = 2.4 \times 10^{14}$ s^{-1} (see ref 10). Error was given as 2 kJ/mol. [c] Relative $k_{d,rel}$ values estimated at 120 °C using the E_a values given in the 5th and 6th columns, and $A = 2.4 \times 10^{14}$ s^{-1}. [d] Given in ref 8. [e] In CH_2Cl_2/*t*-BuPh (v/v 1:1). [f] One run. [g] Averaged values from k_d values measured at 80 and 61 °C. [h] In MeOH/H_2O (v/v 1:1).

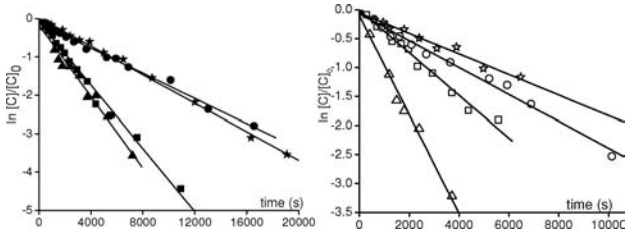


Figure 2. Plot ln([alkoxyamine]$_t$/[alkoxyamine]$_{t=0}$) vs t for major (left) and minor (right) diastereoisomers of **2c** (■,□), **2d** (●,○), **2e** (▲,△), and **2g** (★,☆) at 60 °C.

Except for **2c** and **2g**, other activation procedures involve the quaternization of the nitrogen atom of the pyridyl ring. Thus, one would expect rather close k_d values in sharp contrast to the values reported in Table 1, e.g., $k_{d,2f} = 5 \cdot k_{d,2b}$[11] and $k_{d,2e} = 3.3 \cdot k_{d,2b}$. Amazingly, the effect

(7) Edeleva, M. V.; Kirilyuk, I. A.; Zhurko, I. F.; Parkhomenko, D. A.; Tsentalovich, Y. P.; Bagryanskaya, E. G. *J. Org. Chem.* **2011**, *76*, 5558–5573.

(8) Brémond, P.; Marque, S. R. A. *Chem. Commun.* **2011**, *47* (14), 4291–4293.

(9) Bertin, D.; Gigmes, D.; Marque, S.; Tordo, P. *e-Polym.* **2003**, *2*, 1–9.

(10) Bertin, D.; Gigmes, D.; Marque, S. R. A. *Recent Res. Devel. Org. Chem.* **2006**, *10*, 63–121.

(11) As **2f** is not soluble in *t*-BuPh as solvent, its reactivity in this solvent was estimated from the k_d values given in *t*-BuPh/CH_2Cl_2 and *t*-BuPh for **2e**.

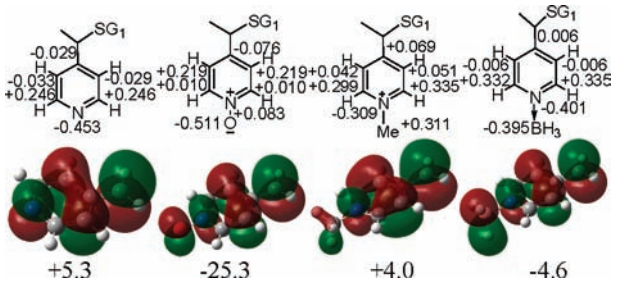
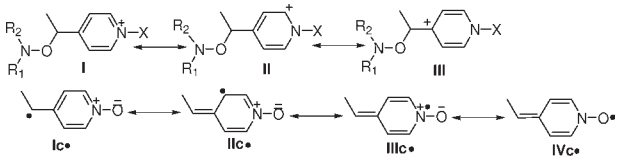


Figure 3. UB3LYP/6-31G(d,p) NBO charges (top) for **2a**,**c**,**e**, and **g** (left to right). UBMK/6-311+G(3df,2p)//RB3LYP/6-31G(d) SOMO (middle) and RSE (kJ/mol, bottom) of the corresponding benzylic radical models.

of the chemical activation of the alkyl fragment depends on both the type of activation and the diastereoisomer, that is, $k_{d,\mathbf{2c}} \approx k_{d,\mathbf{2d}} \approx k_{d,\mathbf{2g}} \approx k_{d,\mathbf{2b}} < k_{d,\mathbf{2e}} < k_{d,\mathbf{2f}}$[11] and $k_{d,\mathbf{2e}} = 31.5 \cdot k_{d,\mathbf{2a}}$ for the minor diastereoisomer, and $k_{d,\mathbf{2d}} \approx k_{d,\mathbf{2g}} \approx k_{d,\mathbf{2b}} < k_{d,\mathbf{2c}} \approx k_{d,\mathbf{2e}} \approx k_{d,\mathbf{2f}}$[11] for the major diastereoisomer. Furthermore, for the major diastereoisomer k_d values span a 2-fold range whereas a roughly 6-fold range is observed for the minor diastereoisomer. This difference in reactivity between diastereoisomers has already been reported[12−15] and ascribed to either a hyperconjugation effect[16] or a remote steric effect.[17] It is noteworthy to mention that **2f** is not soluble in *t*-BuPh in sharp contrast to the others salts. It prompted us to investigate the solvent effect on **2a**, **2e**, and **2f**. The solvent effect has been little investigated, and only a weak 2-fold effect has been reported, in good agreement with the increase observed (**2a′** in Table 1) for **2a** from *t*-BuPh to *t*-BuPh/CH_2Cl_2 (v/v 1:1).[18] On the other hand, a clear 5-fold increase in k_d was observed for **2e** in *t*-BuPh to *t*-BuPh/CH_2Cl_2 and a slightly larger increase to MeOH/H_2O (v/v 1:1). Indeed, in *t*-BuPh as solvent, intimate ion pairs are expected,[19] and hence, a part of the positive charge is used to neutralize the negative charge maintained in close vicinity, weakening the polar effect,[19] whereas in a more polar solvent (*t*-BuPh/CH_2Cl_2) the charge dissociation is more effective, involving a stronger effect of the positive charge on the increase in the electronegativity χ at C5 (*vide infra*) and consequently an increase in k_d.

Scheme 3. Mesomeric Forms for **2b,e,f** (top) and **c•** (bottom)



As suspected, this solvent effect depends dramatically on the type of alkoxyamine and is currently under investigation. In a recent work, we showed that the increase of k_d under protonation was due to the increase in the electronegativity χ on the carbon atom of the C−ON bond,[20] that is, a weakening of the bond strength of the C−ON bond, as given by eq 1, which links the bond dissociation energy BDE to the square of the difference in electronegativity χ for the atoms forming the bond, i.e., the smaller the difference, the weaker the bond.

$$\mathrm{BDE(A-B)} = \frac{1}{2}(\mathrm{BDE(A-A)} + \mathrm{BDE(B-B)}) + 23(\chi_A - \chi_B)^2 \quad (1)$$

Due to the small changes in ^{31}P NMR shifts (Table 1SI), no correlation was observed.

In general, ^{13}C NMR shifts are good probes for changes in electronegativity χ and also for changes in the charge on atoms. The charge changes imply that, from the mesomeric forms of the charged pyridyl moiety (Scheme 3), unshielding at C4 is expected. Unshielding ($\Delta\delta$ = 9−12 ppm, Table 1SI) was observed for **2b**, **2d**−**f**, pointing to a positive charge at C4, hence, supporting an increase in χ at C5, leading to the observed increase in k_d. On the other hand, the shielding ($\Delta\delta$ = −8 ppm) observed for **2c** suggested a decrease in χ and thus a lower k_d than the case for **2a**, in sharp contrast to the reported value ($k_{d,\mathbf{2c}} = 16.1 \cdot k_{d,\mathbf{2a}}$). In fact, the mesomeric forms of **c•** (Scheme 3) show the possibility of a nitroxide as a mesomeric form (**IVc•**), which would involve extra stabilization of the released radical, which in turn would overmatch the polar effect (decrease in χ) and would lead to the observed increase in k_d. Amazingly, shifts at C4 for **2g** and **2a** were very similar, suggesting very close k_d values, whereas a 10-fold higher k_d was observed for **2g**. To gain deeper insight into the various effects involved in the chemical triggering of the C−ON bond homolysis in alkoxyamines, calculations were performed using the B3LYP/6-31G(d,p) method, to optimize the geometries and to determine the NBO charges, and the UBMK/6-311+G(3df,2p)//RB3LYP/6-31G(d) method to estimate the Radical Stabilization Energies (RSE) of the benzyl alkyl radical models. For the sake of simplicity, calculations were performed only on the minor diastereoisomer

(12) Marque, S.; Le Mercier, C.; Tordo, P.; Fischer, H. *Macromolecules* **2000**, *33*, 4403–4410.
(13) Bertin, D.; Gigmes, D.; Marque, S.; Maurin, R.; Tordo, P. *J. Polym. Sci.: Polym. Chem.* **2004**, *42*, 3504–3515.
(14) Bertin, D.; Gigmes, D.; Marque, S. R. A.; Milardo, S.; Peri, J.; Tordo, P. *Collect. Czech. Chem. Commun.* **2004**, *69*, 2223–2238.
(15) Li, L. C.; Hamer, G. K.; Georges, M. K. *Macromolecules* **2006**, *39*, 9201–9207.
(16) Beaudoin, E.; Bertin, D.; Gigmes, D.; Marque, S. R. A.; Siri, D.; Tordo, P. *Eur. J. Org. Chem.* **2006**, *7*, 1755–1768.
(17) Blachon, A.; Marque, S. R. A.; Roubaud, V.; Siri, D. *Polymers* **2010**, *2*, 353–363.
(18) Dielectric constant ε is 2.37, 8.92, 32.66, and 78.54 for *t*-BuPh, CH_2Cl_2, MeOH, and H_2O, respectively. Dipole moment μ is 0.36, 1.14, 2.87, and 1.87 D for *t*-BuPh, CH_2Cl_2, MeOH, and H_2O, respectively. Herrenschmidt, Y.-L.; Guetté, J.-P. *Solvants Organiques in Technique de l'Ingénieur* **1988**, *6*, K310−1–K310−17. *Handbook of Chemistry and Physics*, 6th ed.; Weast, R. C., Astle, M. J., Eds.; CRC Press: Boca Raton, FL, 1981−1982; pp E-52 and E-63.
(19) Bertin, D.; Gigmes, D.; Marque, S. R. A.; Siri, D.; Tordo, P.; Trappo, G. *ChemPhysChem* **2008**, *9*, 272–281.
(20) Bagryanskaya, E.; Brémond, P.; Edeleva, M.; Marque, S. R. A.; Parkhomenko, D.; Roubaud, V.; Siri, D. *Macromol. Rapid Commun.* **2011**, ASAP (DOI: 10.1002/marc.201100590).

and show that, whatever the activation, alkoxyamines **2b**, **2c**, and **2e**−**g** display the same conformation as **2a** (Figure 1SI and Table 2SI), meaning that the substitution at N1 did not give rise to any significant steric effect. As already reported,[16,19] no correlation was found between the geometric parameters of the reactive center ($l_{C5—O7}$, $l_{N8—O7}$, $d_{C5—N8}$, and α_{N8O7C5} in Table 2SI) and the k_d of the alkoxyamine.

Calculated Gibbs energies of homolysis are in good agreement with the reactivity observed; i.e., ΔG_r decreased from **2a** to **2b,e**−**g** ($\Delta\Delta G_r = -6.2$ to -5.5 kJ/mol) as k_d increased, except for **2c** which has the lowest value of ΔG_r ($\Delta\Delta G_r = -22.4$ kJ/mol) and lower k_d than **2e**. It has to be mentioned that the calculations did not take into account the counteranion which is different for each molecule and which might play a role during the homolysis.

To probe the polar effect, NBO atomic charges on the aromatic moiety (Figures 3 and 1SI) were calculated by summing the partial charges of the hydrogen and carbon atoms. As expected from the mesomeric forms **I-III** (Scheme 3), strong positive partial charges are located on C2 (+0.299 to +0.352) and on C4 (+0.063 to +0.080) for **2b**,**e**, and **f** (Figures 3 and 1SI) whereas negative (−0.029 and −0.076) or slightly positive (+0.006) charges are observed on C4 for **2a**,**c**, and **g**, respectively (Figures 3 and 1SI), meaning that χ_{C5} increased for **2b**,**e**, and **f** and that χ_{C5} decreased for **2c** or increased slightly for **2g**.

These charge distributions are in good agreement with the expectations from the ^{13}C NMR chemical shifts (vide supra). Moreover, the positive RSE (Figures 3 and 1SI) of a benzylic radical model for **a•**, **b•**, **e•**, and **f•** show that the presence of either a heteroatom in the aromatic ring or a charge implies a destabilization of the released radical.

Consequently, the NBO partial charges well describe the expected increase in χ for **2b**,**f**, and **e** and the decrease in BDE as predicted by eq 1, confirming the polar effect previously claimed by the authors.[14,16,21,22] However, the polar effect is not sufficient enough to describe the experimental results observed for **2c**, **2e**−**g**. Interestingly, the benzylic radical model of **c•** exhibits a large negative RSE value, meaning a highly stabilized radical. Indeed, the odd electron is delocalized over the aromatic ring and on O19, implying the presence of the highly stabilized mesomeric nitroxide forms (**IVc•** in Scheme 3 and Figure 3). This extra

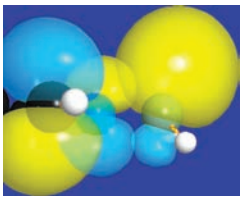


Figure 4. NBO view of the $\sigma_{B-H}\rightarrow\pi^*$ for the model of **g•**.

stabilization overmatches the detrimental polar effect and leads to $k_{d,2c} \approx 2k_{d,2d}$ by chance. The slightly negative RSE value for the benzylic radical model of **g•** points again at a stabilized alkyl radical. In fact, the N→B dative bond induces a hyperconjugation effect by the back-donation of the B−H bonding orbital σ_{B-H} into the antibonding orbital π^* of the aromatic ring ($E_{\sigma\rightarrow\pi^*} = 13.0$ kJ/mol, Figures 3 and 4). This stabilization combined with the slight increase in χ leads to $k_{d,2g} = k_{d,2b}$.

However, the trends given by the polar ($k_{d,2c} < k_{d,2a} < k_{d,2g} < k_{d,2e} \approx k_{d,2f} < k_{d,2b}$) and stabilization ($k_{d,2a} \approx k_{d,2b} \approx k_{d,2e} \approx k_{d,2f} < k_{d,2g} < k_{d,2c}$) effects do not account for the whole reactivity reported, i.e., $k_{d,2a} < k_{d,2b} \approx k_{d,2c} \approx k_{d,2g} < k_{d,2e} < k_{d,2f}$. This might be due to the strength of the intimate ion pair, which is expected to depend on the type of counteranion, the latter being different for each alkoxyamine. This effect is currently under investigation.

The results reported above highlight the importance of the polar effect and how k_d values can be increased by activation of the pyridine moiety. Although the change in E_a looks small, e.g., 20 kJ/mol from **3** ($E_a = 125.2$ kJ/mol) to **2f**, it generates dramatic changes in half-live times, such as, for example, going from 700 days for **3** at rt to 5 h for **2f**. Such opportunities open new aspects for applications in NMP and radical chemistry at low temperature.

Acknowledgment. CNRS and University of Provence are acknowledged for their support and an ANR SonRadIs grant (ANR-11-JS07-002-01). The authors are grateful for the time allocation for calculations from the Centre Régional de Compétence en Modélisation Moléculaire.

Supporting Information Available. Preparation of alkoxyamines **2a**−**g**, characterization data, kinetics procedures and measurements, calculation details. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Bertin, D.; Gigmes, D.; Marque, S. R. A.; Tordo, P. *Macromolecules* **2005**, *38* (7), 2638–2650.

(22) Ananchenko, G.; Beaudoin, E.; Bertin, D.; Gigmes, D.; Lagarde, P.; Marque, S. R. A.; Revalor, E.; Tordo, P. *J. Phys. Org. Chem.* **2006**, *19*, 269–275.