PAPER

Cite this: Org. Biomol. Chem., 2013, 11, 7738

Received 29th July 2013, Accepted 11th September 2013 DOI: 10.1039/c3ob41549j

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Introduction

The discovery^{1,2} 3 decades ago of nitroxide mediated polymerization (NMP) has generated a large number of investigations into the synthesis of initiators/mediators (alkoxyamines), kinetic investigations, and preparation and application of new materials.^{3–7} As discussed in several reviews and articles, the initiation stage plays a significant role in the quality of the polymer prepared by NMP.^{5,8–11} Hence, it has been shown that the faster the C–ON bond homolysis, the better the control of the NMP.¹¹ Another interesting aspect of the preparation of such activated molecules is related to the safety of their use.¹² Indeed, fast decomposing compounds have drastic shipping and storing rules.¹³ Then, two antagonist properties for the initiator must be combined: fast homolysis for NMP and high stability for shipping and storage. Consequently, the

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Chemically triggered C–ON bond homolysis in alkoxyamines: regioselectivity and chemoselectivity^{†‡}

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Recently, we examplified the activation of the C–ON bond homolysis by protonation, alkylation, benzylation, acylation, oxidation and complexation with a Lewis acid of the nitrogen atom of the 1-(pyridin-4-yl)ethyl fragment (*Chem. Commun.*, 2011, 4291 and *Org. Lett.*, 2012, 358) and of the 1-(pyridin-2-yl)ethyl fragment (*J. Org. Chem.* ASAP Doi:10.1021/jo401674v) of (*N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*N*-oxyl) SG1-based alkoxyamines. The quaternization of the 1-(pyridin-3-yl)ethyl fragment by the aforementioned reactions was investigated for the corresponding SG1-based alkoxyamines. In sharp contrast to the quaternization at *ortho* and *para* positions of the pyridyl moiety, the effect of the quaternization at the *meta* position was weak. The effects of quaternization at *ortho*, *meta* and *para* positions were investigated through natural bond orbital and Mulliken charges, HOMO–LUMO interactions in the starting materials and the radical stabilization energy of the released 1-puridylmethyl radicals using DFT calculations with the B3LYP/6-31G(d) and UBMK/6-311+G(3df,2p)//R(O)B3LYP/6-31G(d) methods, respectively.

development of alkoxyamines (initiators) which are rather stable and suitable for selective chemical activation is one way to fulfil the aforementioned requirements. Recently, we showed that the C-ON bond homolysis in $1a^{14}$ and $3a^{15,16}$ (Fig. 1) was chemically activated by protonation, oxidation, alkylation (for 3a), acylation (for 3a), benzylation (for 3a), and complexation with a Lewis acid (for 3a). The activation was an interplay of several effects: stabilization of the released alkyl radical, charge distribution (polar effect) in the starting materials,^{14,16} steric effect, and solvent¹⁵⁻¹⁸ effect. These investigations on 1a and 3a and their derivatives revealed very strong similarities (charge distribution) and clear differences (unsuccessful activation, and stabilization of the released radical).15,16 Thus, this prompted us to investigate the effect of the activation on the meta position in 2a (Fig. 1). Again similarities and differences of 2a with 1a and 3a were observed; that is, as for 3a all positions of 2a were available for the activation, while charge distribution in starting materials and stabilization of the released alkyl radical were different compared with 1a, 3a and their derivatives. To get deeper insight into the various effects involved in the activation of the C-ON bond homolysis in 1a-3a, DFT calculations were performed to determine the natural bond orbital (NBO) and the Mulliken charge distribution, the HOMO-LUMO energy gap in the starting materials and the NBO interactions, as well as the radical stabilization energy (RSE) and the shape of the SOMO for benzylic models of the released alkyl radicals.

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 $[\]dagger$ Part 8: G. Audran, L. Bosco, P. Brémond, S. R. A. Marque, V. Roubaud, and D. Siri, J. Org. Chem., accepted.

[‡]Electronic supplementary information (ESI) available: Optimization of geometry structures of **1a**, **2a**, **3a** and their derivatives as well as their NBO charges by DFT, radical stabilization energy estimated using DFT, preparation of **2a–g**, and **4**. See DOI: 10.1039/c3ob41549j

Paper



Fig. 1 Alkoxyamines 1a-3a and their derivatives.

Experimental section

Synthesis

All reactants and solvents were purchased and used as received. Alkoxyamine **2a** was prepared from 4-(1-bromoethyl)pyridine and **SG1** nitroxide (*N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*N*-oxyl) as previously described (Scheme 1 and ESI‡). Alkoxyamines **2b–g** were then prepared from **2a** as displayed in Scheme 1 (see ESI‡). Alkoxyamines **2b** and **2d** were prepared *in situ*, and **2c**, **2e**, and **2g** were prepared in



Scheme 1 Preparation of 2a-g

quantitative yields and purified by precipitation or solvent removal *in vacuo*. Each alkoxyamine was obtained as a mixture of two diastereoisomers.

Kinetic measurements

Rate constants were measured as previously described^{15–19} using 2 equivalents of TEMPO as an alkyl radical scavenger in *tert*-butylbenzene (*t*-BuPh) as a solvent (Scheme 2) and using ³¹P NMR on Bruker 300 and 400 Advance spectrometers. A few examples of the plots for the first-order decay (eqn (1)) of the major and minor diastereoisomers of alkoxyamines **2a–g** are displayed in Fig. 2. The activation energy E_a of each reaction (Table 1) was estimated using the averaged frequency factor $A = 2.4 \times 10^{14} \text{ s}^{-1}$ and eqn (2).²⁰

$$\ln \frac{[\text{alkoxyamine}]_t}{[\text{alkoxyamine}]_0} = -k_{\rm d}t \tag{1}$$

$$k_{\rm d} = A {\rm e}^{-E_{\rm a}/RT} \tag{2}$$

$$\begin{array}{c} R_1 & R \\ N-O' & \xrightarrow{2 \text{ TEMPO}} & R_1 \\ R_2' & k_d & R_2' \end{array} \xrightarrow{R_1} N-O \cdot + \text{ TEMPO-R} \\ \end{array}$$

TEMPO = 2,2,6,6-tetramethylpiperidin-N-oxyl

Scheme 2 Scavenging experiment to determine k_{d} .



Fig. 2 Plot of $\ln([alkoxyamine]_t/[alkoxyamine]_{t=0})$ vs. t for major (left) and minor (right) diastereoisomers of **2a** (\blacksquare , \square) and **2g** (\bigstar , \Leftrightarrow) at 85 °C and **2d** (\bullet , \bigcirc) and **2e** (\bigstar , \bigtriangleup) at 61 °C.

Table 1 Experimental temperature T (°C) and C–ON bond homolysis rate constant k_{d} , activation energies E_a and the relative rate constants $k_{rel,2}$ ($k_{rel} = k_{d,2b-g}/k_{d,2a}$) at 120 °C for the minor and the major diastereoisomers of alkoxyamines **2a–g** as well as $k_{rel,1}$ and $k_{rel,3}$ for the diastereoisomers of **1a–c** and **3a–g** in *tert*-butylben-zene as a solvent unless otherwise mentioned

2	T (°C)	$k_{\rm d}$ ^{<i>a,b</i>}	$k_{\rm d}$ ^{b,c}	$E_{a}{}^{a,d}$	$E_{a}^{c,d}$	$k_{\mathrm{rel},1}{}^{a,e}$	$k_{\mathrm{rel},1}$ ^{c,e}	$k_{\rm rel,2}{}^a$	$k_{\rm rel,2}$ ^c	$k_{\rm rel,3}{}^{a,f}$	$k_{\rm rel,3}$ ^{c,f}
a	85	2.1	2.6	123.8	123.2	1	1	1	1	1	1
b	80	5.3	6.9	119.4	118.6	10.2	11.8	3.9	4.1	9.3	9.5
с	80	2.8	2.6	121.2	121.5	19.2	11.8	2.2	1.7	17.1	16.1
d	61^g	0.5	1.2	119.5	117.1	h	h	3.7^{g}	6.4^g	10.2	12.2
е	61	0.4	0.9	120.1	117.9	h	h	3.1	5.0	20.0	31.5
f	61^g	0.5	2.7	119.5	114.8	h	h	3.7^{g}	13.0^{g}	65.5^{g}	209.6^{g}
g	81	4.3	5.0	120.3	119.9	h	h	2.9	2.7	10.2	9.5

^{*a*} Major diastereoisomer. ^{*b*} Given in 10⁻⁴ s⁻¹. ^{*c*} Minor diastereoisomer. ^{*d*} Given in kJ mol⁻¹. ^{*e*} Given in ref. 14. ^{*f*} Given in ref. 16. ^{*g*} In *t*-BuPh–CH₂Cl₂ (v/v 1:1). ^{*h*} Not determined.

pK_a determination

Experiments were performed in the D_2O -MeOH- d_4 mixture as **2a** is not soluble in water, and ¹H NMR signals of the aromatic region were recorded to determine pK_a values. Each diastereoisomer was measured independently. pH was adjusted by adding the corresponding acid and controlled using an HI2211 pH/ORP meter from Hanna Instruments and a 4 mm micro-titration electrode from Bioblock.

DFT calculations

All calculations were performed using the Gaussian package 09, revision A02.²¹ The geometries of the alkoxyamines were optimized at the B3LYP/6-31G(d) level of theory. Vibrational frequencies were calculated at the RB3LYP/6-31G(d) level of theory to ensure that the obtained geometries are minima (no imaginary frequency). The vibrational frequencies were scaled by a usual factor of 0.9608 to provide zero point vibrational energy. The corresponding thermal corrections were included to obtain the enthalpy and Gibbs free energy values under the standard conditions (p = 1 atm and T = 298.15 K). The energies were calculated using the UBMK/

6-311+G(3df,2p) method. NBO and Mulliken charges as well as NBO interactions were estimated using NBO 5.0 software.²² For RSE calculations on benzyl radicals, the geometry optimizations were performed using R(O)B3LYP/6-31G(d) and vibrational frequencies were calculated at the R(O)B3LYP/ 6-31G(d) level using a scale factor of 0.9806 to provide zero point vibrational energy. In order to obtain accurate energies, single point calculations were performed at the UBMK/ 6-311+G(3df,2p) level of theory on the R(O)B3LYP/6-31G(d)geometries.²³

Results

Chemical modes of activation

Alkoxyamine 2a was prepared from 4-(1-bromoethyl)pyridine and SG1 nitroxide (*N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*N*-oxyl) with copper salts as a catalyst,^{15,16} (Scheme 1 and ESI‡). Alkoxyamines 2b-g were then prepared from 2a using trifluoroacetic acid (2b), *m*-chloroperbenzoic acid (2c), methyl tosylate (2e), benzyl bromide (2f), acetyl chloride (2d) and borane–THF complex (2g). The



Fig. 3 (a) ¹H NMR signal in the aromatic zone for the major (left, pH = 2.36, 4.14, and 6.00 from top to bottom) and the minor (right, pH = 2.20, 4.16, and 6.09 from top to bottom) diastereoisomers of **2a/2b** (0.02 M), at room temperature in D_2O-CD_3OD (v/v 1 : 1). (b) Titration curves (\blacksquare and \blacktriangle for major and minor diastereoisomers, respectively) obtained using the signal displayed in (a). pH was set with DCl and NaOD.¶

configurations were tentatively ascribed as RS/SR and SS/RR for the major and minor diastereoisomers, respectively, using ³¹P NMR.§

Table 2 Mulliken and NBO charges at the *ipso* carbon of the pyridyl moiety for **1a–c,g**, **2a–c,g** and **3a–c,g**, the HOMO and LUMO energies, and HOMO–LUMO energy gaps $\Delta E_{\rm HL}$ calculated using the B3LYP/6-31G(d,p) method for the *RR/ SS* diastereoisomer, and SOMO energies for **a''–b''** calculated at UBMK/6-311+G-(3df,2p)//R(O)B3LYP/6-31G(d) level

Determination of pK_a

From the pH dependence of the ¹H NMR signal recorded at room temperature in D₂O–MeOH- d_4 (1 : 1 v : v), a significant shift was observed for the aromatic protons from pH 7 to 2.5 (Fig. 3a).¶²⁴ Using the Henderson–Hasselbach equation (eqn (3)),²⁵ the titration curve for **2a** (Fig. 3) afforded p K_a values of 4.27 and 4.13 for the major and minor diastereoisomers of **3a**, in sharp contrast with the value given for the *meta*-ethyl pyridine (p $K_a = 5.68$).||^{26–31} These low p K_a values for the diastereoisomers of **2b** can be ascribed to the electron withdrawing properties of the nitroxyl fragment. Such a lowering of p K_a has also been reported for **1b**¹⁴ and **3b**.^{18,32}

$$\delta_{\rm pH} = \delta_{\rm 2a} + \frac{\delta_{\rm 2b} - \delta_{\rm 2a}}{1 + 10^{pK_{\rm a} - p\rm{H}}} \tag{3}$$

Kinetic measurements

Rate constants were measured as previously described using two equivalents of TEMPO as an alkyl radical scavenger in *tert*butylbenzene (*t*-BuPh) as a solvent (Scheme 2).¹⁹ Except for **2b** and **2d** generated *in situ*, all k_d values were measured on pure compounds (Fig. 2 and Table 1). Interestingly, a 2–3-fold weaker effect was observed for **2a–g** than for **3a–c**. Almost no difference in k_{rel} or k_d was observed for the diastereoisomers of **2a–c,g** whereas a 2-fold difference was observed for **2d** and **2e** and a 5-fold difference was observed for **2f**. Such differences were also observed for the diastereoisomers of **3a–g**. Such a

	Charges		Energy					
	Mulliken	NBO	HOMO ^a	LUMO ^a	$\Delta E_{ m HL}{}^a$	SOMO ^{<i>a,c</i>}		
la	0.26	0.20^{d}	-577	-63	-514	-611		
۱b	0.35	0.26^{d}	-946	-544	-402	-1131		
lc	0.31	0.15^{d}	-581	-107	-474	-63		
lg	0.33	0.26^{e}	-694	-160	-534	-681		
2a	0.11	-0.10	-590	-69	-521	-603		
2b	0.09	-0.05	-868	-596	-272	-1079		
2c	0.07	-0.07	-602^{b}	-105	-497	-647		
2g	0.08	-0.08	-616	-171	-445	-672		
Ba	0.14	-0.03^{f}	-595	-66	-529	-645		
3b	0.16	$0.08^{g,h}$	-846	-600	-246	-1132		
Bc	0.14	-0.08^{f}	-603^{b}	-102	-501	-605		
ßg	0.15	0.01^{f}	-622	-164	-458	-692		

^{*a*} In kJ mol⁻¹. ^{*b*} HOMO-1, see text. ^{*c*} SOMO are given for the benzylic radical models **a**^{*r*}, **b**^{*r*}, **c**^{*r*}, and **g**^{*r*} at positions *ortho* (alkoxyamine family 1), *meta* (alkoxyamine family 2), and *para* (alkoxyamine family 3), see Fig. 8. ^{*d*} Given in toluene in ref. 14. ^{*e*} Not calculated in ref. 14. ^{*f*} Given in ref. 16. ^{*g*} In ref 32. ^{*h*} It was given for 3**e** as 0.069 in ref. 16.

difference of *ca.* 2–3-fold in k_d between diastereoisomers has already been reported^{33–36} and ascribed either to a hyperconjugation effect³⁷ or to a remote steric effect.^{36,38} It does not deserve more comments. For **2f** and **3f**, a 5-fold difference between the diastereoisomers might be ascribed to a remote strain.**

DFT calculations

For the sake of simplicity, calculations were performed using the B3LYP/6-31G(d) method only for the *RR/SS* diastereoisomer. For comparison, Mulliken and NBO charges at the *ipso*

 $[\]$ The same approach was applied for 1a. See ref. 14.

[¶]All pH measured in D₂O–MeOH- d_4 were re-estimated using pH = 0.929pH* + 0.42. pH* is the pH measured in D₂O–MeOH- d_4 solutions using a pH-meter calibrated with non-deuterated water solutions. See ref. 24.

 $[\]parallel \mathrm{p}K_\mathrm{a} = 5.58$ is also given in ref. 30 and 31. Non-corrected value.

^{**}No calculations were performed because of a small energy gap and the presence of many conformers.



2a

2b











3b

3a



positions were calculated for **1a–c,g**, **2a–c,g**, and **3a–c,g** (Table 2). To perform a frontier molecular orbital analysis, the HOMO (Fig. 4) and LUMO (Fig. 5) orbitals, as well as the HOMO–LUMO energy gap $\Delta E_{\rm HL}$, were calculated for **1a–c,g**, **2a–c,g**, and **3a–c,g** (Table 2). Taking into account that reformation and homolysis cross at the same TS, involving an interaction between the nitroxide π^* SOMO and the alkyl radical SOMO (Fig. 6b), which resembles the TS of the C–ON bond homolysis (Fig. 6a) leading to the formation of the $\sigma_{\rm C-ON}$ bond, one would expect, in the alkoxyamine, an interaction between the π -type LUMO and a σ -type HOMO (Fig. 6a) exhibiting a high electron density on both the nitrogen atom, due to its lone pair, and the C–ON bond. As expected, all HOMOs (Fig. 4) – except for **2c** and **3c**, for which the HOMOs do not display the expected shape which is observed for their HOMO $-1\uparrow\uparrow$ – and all LUMOs (Fig. 5) exhibit the expected shape whatever the type of alkoxyamine – *ortho*, *meta*, or *para* – and the activation mode – protonation or oxidation. This is expected to hold for the other modes of activation, *i.e.*, acylation, methylation, benzylation, and complexation with a Lewis acid.

Although HOMO and LUMO exhibit the right shape, neither their own values nor the values of their energy gap $\Delta E_{\text{H-L}}$ (Table 2) describe qualitatively and quantitatively the trends experimentally observed, except for family 2 for which the expected trend is observed.

^{††}For **2c** and **3c**, their HOMOs are mainly centered on the aromatic ring.





Fig. 6 Interaction expected at TS (a) for the C–ON homolysis and (b) for the re-formation of the C–ON bond.

Using the isodesmic reaction displayed in Scheme 3, RSE for all positions – *ortho* (1), *meta* (2), and *para* (3) – were calculated for the benzylic radical models $\mathbf{a'-c',g'}$ (Fig. 7) of the released alkyl radicals $\mathbf{a-c,g}$ (Fig. 1). The SOMOs of the



Scheme 3 Isodesmic reaction used to determine RSE.

benzylic radical models were also calculated using the UBMK/ 6-311+G(3df,2p)//R(O)B3LYP/6-31G(d) method (Fig. 8‡‡ and Table 2). They agree with the RSE values and the mesomeric forms (Fig. 7) as they confirm the delocalization of the odd electron on the oxygen atom at the *ortho* and *para* positions in **c**'' leading to the nitroxide mesomeric forms **V** and **IV**, respectively (Fig. 7), whereas such a delocalization is not observed for the *meta* position in **c**''. However, the SOMO of \mathbf{a}_{o} '' is lower than that of \mathbf{c}_{o} '' although less stabilized, while the SOMOs of \mathbf{a}_{p} '' and \mathbf{c}_{p} '' exhibit close energies. Moreover, the least stabilized \mathbf{c}_{m} '' radical exhibits the lowest SOMO. Furthermore, the same mesomeric forms are expected for \mathbf{g}_{o} '', \mathbf{g}_{m} '', \mathbf{g}_{p} '' as for

 $[\]ddagger$ As seen in Fig. 8, the absence of odd electron density on the nitrogen atom in g_m ' forbids any SOMO $\rightarrow \sigma_{B-H}$ interaction. Thus, the stabilizing two-electron-two orbital interactions are the same in 2g and g_m , in sharp contrast with 3g and g_p .

	I	Ш	ш	IV	v	RSE (kJ/mol)
a' _{ortho} .	$H \longrightarrow H$ H H H H H H H H H	H N .	$\begin{array}{c} H \\ H \\ H \end{array} \xrightarrow{N = } \cdot \longleftrightarrow$	H H		6.6
a' _{meta} .	$H \longrightarrow N$ $H \longrightarrow N$	$H \rightarrow H$	$H = \bigvee_{H=N}^{H} \cdots \longrightarrow$	H = I = I = N		1.5
a' _{para}	$H \longrightarrow N \longrightarrow H$	H N	H → H →	H H		5.3
b' _{ortho} .	$\begin{array}{c} H \\ H \\ H \\ H \\ H \end{array} \xrightarrow{N=} \\ H \end{array} $	$\overset{H}{\underset{H}{}}\overset{N}{}\overset{N}{}}{}{}{}{}{}{}{}{}}{}$	$\begin{array}{c} \overset{H}{\longrightarrow} \overset{N}{\longrightarrow} \end{array} \end{array} \end{array} \end{array} \end{array} \end{array} \end{array} \end{array} \end{array}$	$\overset{H}{\underset{H}{\overset{N}{\longrightarrow}}}$		9.9
b' _{meta} .	$H \longrightarrow H$	H = I = I = I = I = I = I = I = I = I =	$H = \bigvee_{H}^{H} H$	$H \rightarrow H$		12.6
b' _{para} .	H H H	H H	$H = \left(\begin{array}{c} H \\ H \end{array} \right) H \left(\begin{array}{c} H \\ H \\ H \end{array} \right) H \left(\begin{array}{c} H \\ H \end{array} \right) H \left(\begin{array}{c} H \\ H \\ H \end{array} \right) H \left(\begin{array}{c} H \\ H \\ H \end{array} \right) H \left(\begin{array}{c} H \\ H \\ H \end{array} \right) H \left(\begin{array}{c} H \\ H \\ H \\ H \end{array} \right) H \left(\begin{array}{c} H \\ H \\ H \end{array} \right) H \left(\begin{array}{c} H \\ H \\ H \\ H \end{array} \right) H \left(\begin{array}{c} H \\ H \\ H \\ H \\ H \end{array} \right) H \left(\begin{array}{c} H \\ H $	H H		4.4
c' _{ortho} .	$\stackrel{O_{+}}{\longrightarrow} \stackrel{N=}{\longrightarrow} \stackrel{\bullet}{\longrightarrow}$		$\begin{array}{c} & & & \\ & & & & \\ & & & \\ & & & & \\ & & & \\ & & & & \\ & & & \\ & & & & \\$	H = H	$\rightarrow \overset{O}{H} = \overset{O}{}$	-9.2
C' _{meta} .	$H \longrightarrow N_{\Sigma}^{+}$		$H = \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\ \end{array} \right\rangle \left\langle \begin{array}{c} H \\ = \\ H \\$			5.4
C' _{para} .	$H \rightarrow H^{+} \overline{N} - \overline{0} \rightarrow H^{+} \overline{0}$	H H H	$H = \bigvee_{H=0}^{H} H = 0$	H H	→ H H H H -Ō	-25.3
g'ortho'	$H_{3}B$ H H H H	H_{3B}	$\begin{array}{c} H_{3}B\\ H\\ H\\ H\end{array} \xrightarrow{N} \end{array} \xrightarrow{N} $	H_{3B}		8.8
g' _{meta}	$H \longrightarrow N$ $H \longrightarrow N$ BH_2	$H \longrightarrow H$	$H = \bigvee_{H=1}^{H} H_{2}$	H = I = I = N		4.7
g'para	H H H H H H H H H H	- H → N+BH ₃ ←	$\rightarrow H^{H} \xrightarrow{N+BH_3} \xrightarrow{H} H^{H}$	H H H N+BH ₃		-4.6

Fig. 7 Mesomeric forms (I–V) of the non-activated (a'') and activated (b'', c'' and g'') benzylic models of the released alkyl radicals a'–c', and g' (Fig. 1) at the ortho (o), meta (m), and para (p) positions and their corresponding RSE values.

 $\mathbf{a}_{p'}$, $\mathbf{a}_{m'}$ and $\mathbf{a}_{p'}$, implying that the SOMO should vary by the same amount as observed when going from $\mathbf{a}_{o'}$ to $\mathbf{g}_{o'}$ and from $\mathbf{a}_{m'}$ to $\mathbf{g}_{m'}$ ($\Delta E = -70 \text{ kJ mol}^{-1}$) whereas the SOMO of $\mathbf{g}_{p'}$ is lowered by 47 kJ mol⁻¹ (Table 2). In fact, the stabilization of $\mathbf{c}_{o'}$ and $\mathbf{c}_{p'}$ involves the nitroxide mesomeric forms V and IV, respectively (Fig. 7). These forms are due to a three-electrontwo-orbital interaction between the SOMO and the lone pair on the oxygen atom of the N-oxide moiety. This SOMO $\rightarrow n_0$ interaction stabilizes the whole radical by stabilizing the lone pair and, in turn, raises the energy of the SOMO (Fig. 9). The energy for the SOMO of \mathbf{g}_p being higher than expected is also due to the three-electron-two orbital interaction involving the SOMO and a B-H bond. This SOMO $\rightarrow \sigma_{B-H}$ interaction (NBO interaction, $E_{(\sigma B-H \rightarrow SOMO)} = 19.0 \text{ kJ mol}^{-1}$ stabilizes the radical and raises the SOMO whereas the two-electron-two orbital interaction ($\sigma_{B-H \rightarrow \pi^*}$, NBO interaction $E = 21.5 \text{ kJ mol}^{-1}$) does not stabilize the radical (Fig. 9). The SOMO $\rightarrow \sigma_{B-H}$ interaction in \mathbf{g}_{o} ' is less efficient, which is likely due to the distribution of the odd electron density on the two ortho positions and a

slightly longer N \rightarrow B dative bond ($l_{N\rightarrow B} = 1.62$ Å) than in g_p ' ($l_{N\rightarrow B} = 1.60$ Å).

Multiparameter correlations

The rate constant k_d of the C–ON bond homolysis can be correlated to several parameters: σ_{RS} , for the radical stabilization effect, σ_I , for the polar effect, and ν , for the steric effect. It can be assumed that the pyridinyl moiety activated at the *para* position as well as at the *meta* position is not more sterically demanding than a phenyl ring. It can be assumed that the pyridyl moiety activated by protonation or oxidation at the *ortho* position is sterically not more demanding than a phenyl ring. A change in polarity due to the activation can be estimated for protonation and methylation although the original fragments are not available and need to be estimated using a set of equations and several assumptions affording only rough values of σ_I . In the seminal article of this series, it was assumed that the stabilization for the pyridinyl-based released radical was very close to that reported for the styryl radical.

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Fig. 8 SOMOs of radicals a''-c'', g'' (from left to right) for the ortho (o), meta (m), and para (p) positions, from top to bottom. Italicized values are for SOMOs energies (kJ mol⁻¹).

However, recent calculations on a model showed that the stabilization energy is different depending on the activation and the position (Fig. 7). Unfortunately, the needed α and β hydrogen hyperfine coupling constants of the activated methyl (or alkyl methyl) pyridyl radical are not available in the literature to determine $\sigma_{\rm RS}$ values.^{20,39} Due to drastic assumptions to estimate $\sigma_{\rm I}$ and $\sigma_{\rm RS}$, the multiparameter correlation cannot be applied to discuss quantitatively the results reported in Table 1.

Discussion

Recently, alkoxyamine activation was applied to families **1** and **3** and proved to be dependent both on the alkoxyamine family and on the activation modes. Interestingly, alkoxyamine **2a** is

activated by the same modes as for **3a**, in sharp contrast with **1a** for which only protonation and oxidation are effective due to the steric strain at the *ortho* position. However, the activation observed for **2a** does not depend too much on the mode of activation, *i.e.*, 2–4-fold and 3–6-fold for the major and the minor diastereoisomer,§§ respectively, in sharp contrast with the 10–30-fold observed for **3a** (Table 1).¶¶ Indeed, the effects involved in the activation of **2a** are not so clear-cut (*vide infra*) as for **3a**; that is, all released radicals are not stabilized (positive RSE values in Fig. 7) and the NBO charges|||| at the *ipso* position do not change too much depending on the activation

^{§§} Solvent effects were included.

^{¶¶}Solvent effects were not included.

 $^{\|\|}$ NBO charges are used to describe the effect of the activation on the electronegativity χ of the carbon atom of the C–ON bond. See ref. 16.



LUMO ------

Fig. 9 Orbital interactions involved in the stabilization of c_0'' and c_p'' (left side) and in the position (right side) of the SOMOs for g_p'' (blue) and g_m'' (red).



Fig. 10 Expected position of reactants, products, and TS states depending on (a) the polar effect, (b) no effect, and (c) the stabilization effect. Double head arrows are for the activation energy *E*_a of the C–ON bond homolysis.

mode (Table 2), implying balanced effects affording only a low activation at the *meta* position.

Recently, we showed that the reactivity generated by the various modes of activation of the pyridinyl moiety of alkoxyamines belonging to families 1 and 3, as well as 2 (*vide supra*), was mainly controlled by the stabilization of the released alkyl radical (stabilization of the product and hence of the TS, as predicted by Hammond's postulate, see Fig. 10c) and by the difference in electronegativity χ between the oxygen and carbon atoms of the C–ON bond (eqn (4b)), as given by eqn (4a) describing the strength of the bond as the sum of enthalpic (difference in bond dissociation energy (BDE)) and

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Fig. 11 (a) Radical stabilization energy (RSE) for alkyl radicals a"-c" and g" (from left to right) activated at *ortho* (o), *meta* (m), and *para* (p) positions and (b) NBO charges at the *ipso* position for alkoxyamines 1–3 (*ortho*, *meta*, and *para*, respectively) for various modes of activation (from left to right, non-activated, protonated (H⁺), oxidized (O⁻), and complexed (BH₃)).

polar terms (difference in electronegativity χ) as proposed by Pauling:

$$BDE(A - B) = \frac{1}{2}(BDE(A - A) + BDE(B - B)) + 96.23(\chi_A - \chi_B)^2$$
(4a)

$$BDE(R^{1}R^{2}NO - CR^{3}R^{4}R^{5}) = \frac{1}{2} (BDE(R^{1}R^{2}NO - ONR^{1}R^{2})) + \frac{1}{2} (BDE(R^{3}R^{4}R^{5}C - CR^{3}R^{4}R^{5})) + 96.23(\chi_{O} - \chi_{C})^{2}$$
(4b)

Consequently, any increase^{***} in $\chi_{\rm C}$ would lead to a decrease in the square of the difference between $\chi_{\rm C}$ and $\chi_{\rm O}$ affording a decrease in BDE compared to a reference (Fig. 10b). In general, this polar effect is ascribed to the destabilization of the reactant state (Fig. 10a). Changes in $\chi_{\rm C}$ are due to the strength of the electron withdrawing group attached to the carbon atom of the C-ON bond, and are taken into account by the NBO charges, in our case, at the ipso position of the pyridyl moiety (Table 2). The enthalpic term in eqn (4a) and (4b) is more closely related to the stabilization of the released radicals. As given by Hammond's postulate, an endothermic reaction, such as the C-ON bond homolysis in alkoxyamines, exhibits a late TS, i.e., a product-like TS. Consequently, any stabilization of the products stabilizes TS (Fig. 10c) implying a decrease in BDE. This enthalpic effect is nicely accounted for by the RSE values for the released alkyl radical.

Thus, to get a deeper and clearer insight into the effect of various modes of activation at the *ortho*, *meta*, and *para* positions, calculations were performed to determine NBO charges in alkoxyamines **1a–c,g**, **2a–c,g**, and **3a–c,g** (Table 2) as well as the RSE of the benzylic models of the corresponding released radicals (Fig. 7).

The RSE calculated for all positions possible for the pyridylmethyl radical are all positive, meaning that these radicals are all less stabilized than the corresponding benzylic radical (Fig. 7 and Scheme 3). However, the *meta* position is a little bit less destabilized than the *ortho* and *para* positions (Fig. 11) because the odd electron is never localized on the nitrogen atom, as highlighted by its SOMO (Fig. 8) avoiding any electrostatic repelling effect between the nitrogen lone pair and the odd electron. On the other hand, the NBO charge is more important in the *ortho* position as the nitrogen atom is nearer to the C–ON bond than the *meta* and *para* positions (Fig. 11b). Consequently, polar and stabilization effects balanced each other, leading to very similar k_d values for **1a–3a** and the styryl homologue ($E_a = 124.5$ kJ mol⁻¹ in ref. 20 and 33).

As for the non-activated pyridinylmethyl radical, all RSE for the protonated homologues are positive, meaning that the radicals are destabilized upon protonation. In contrast with the non-activated **a**'' radical, the *meta* position for radical **b**'' is less stabilized (Fig. 11a). On the other hand, **1b** and **3b** exhibit the highest positive NBO charges (Fig. 11b) whereas this value is negative for **2b** because the protonation at positions *ortho* (**1b**) and *para* (**3b**) generates a positive charge at the *ipso* position (mesomeric forms **III** and **IV** for **3b** and **1b**, respectively, Fig. 12). Thus the increase in k_d for **1b** and **3b** is ascribed to the polar effect as all released radicals are destabilized.

In sharp contrast with the non-activated and the protonated released benzylic-type radicals, RSEs for $\mathbf{c}_{o'}$ and $\mathbf{c}_{p'}$ are largely negative (Table 2 and Fig. 11b) although still positive for $\mathbf{c}_{m'}$, meaning that the activation at the *ortho* and *meta* positions stabilizes the radical more than the activation at the *meta* position. This stabilization is nicely accounted for by an extra stabilization mesomeric form (4 for $\mathbf{c}_{m'}$ against 5 for $\mathbf{c}_{o'}$ and $\mathbf{c}_{p''}$, Fig. 7), *i.e.* the nitroxide mesomeric forms **V** and **IV** (Fig. 7) for $\mathbf{c}_{o'}$ and $\mathbf{c}_{p''}$, respectively. The *ortho* position in $\mathbf{c}_{o'}$ is less stabilized than the *para* position in $\mathbf{c}_{p''}$ (Table 2) because the odd electron density is distributed at two *ortho* positions in $\mathbf{c}_{o''}$ as displayed in their respective SOMOs

^{***} Assuming $\chi_{\rm C} < \chi_{\rm O}$.



(Fig. 8). The non-delocalization of the odd electron on the *N*-oxide moiety in $\mathbf{c}_{m'}$ is nicely confirmed by the shape of its SOMO (Fig. 8) which shows the absence of spin density on the nitrogen atom. In alkoxyamine 3c, the oxidation at the para positions for 3a generates a negative partial NBO charge (Fig. 11 and Table 2) at the *ipso* position, as highlighted by its mesomeric form III (Fig. 12). In sharp contrast, the oxidation at the ortho position in 1a generates a positive partial NBO charge (Table 2 and Fig. 10b) whereas a negative partial NBO charge is expected from its mesomeric form IV (Fig. 11). This implies that the electron withdrawing effect of the N-oxide moiety overmatches its resonance effect affording an increase in the electronegativity χ at the carbon atom of the C-ON bond.^{†††} The oxidation at the meta position of 2a affords negative NBO partial charges at the ortho and para positions as highlighted by the mesomeric forms of 2c (Fig. 12). Consequently, the *ipso* position in 2c is not deactivated by the presence of a negative charge, except that the remote meta position for the N-oxide moiety decreases its electron withdrawing effect which cannot balance the effect of the negative partial charges at the two ortho positions (mesomeric forms III and IV in Fig. 12).

The benzylic-type radical g_p ' carrying the BH₃ group on the nitrogen atom exhibits a negative value of RSE (Fig. 11a and Table 2), meaning that this radical is stabilized whereas

positive RSEs are observed when the BH₃ group is carried by the nitrogen atom at the *meta* and *ortho* positions for g_m " and g_o ", respectively, denoting non-stabilized radicals. The same mesomeric forms are expected for g" as for a" (Fig. 7). As discussed above, the stabilization of g_p " is due to the 3 electron-2 orbital $\sigma_{B-H} \rightarrow$ SOMO interaction between one bonding B-H orbital and the SOMO (Fig. 9), in sharp contrast with g_m ". This extra stabilization of g_p " combined with the positive NBO charge at the *ipso* position in 3g affords an activation as large as that for 3b.

Only a few general trends can emerge from the above thorough analysis: (i) the polar effect is always weak when the activation is performed at the *meta* position (negative NBO charges at the *ipso* position, Fig. 11b); (ii) the polar effect is the strongest when the activation is performed at the *ortho* position (positive NBO charges at the *ipso* position, Fig. 11b); (iii) the released alkyl radical is always destabilized (positive RSE values, Fig. 11a) when the activation is performed at the *meta* position.

Conclusion

DFT calculations showed that the effects triggered by the mode of activation depend both on the mode of activation and on the position targeted. This leads to a subtle interplay of polar and stabilization effects which can be either additive/synergetic or antagonistic. The main consequence is the occurrence of similar reactivities (the same k_d or $k_{d,rel}$) stemming from

 $[\]uparrow\uparrow\uparrow\uparrow$ It is known that the electron withdrawing effect of the *N*-oxide moiety is as large as the one of the NO₂ group. See ref. 40.

different effects. Furthermore, cybotactic and salt effects also play significant roles depending on the mode and likely the site of activation. Consequently, this entanglement of effects forbids the use of DFT calculations and of multiparameter correlations to discuss quantitatively the effects investigated.

This paper highlights very well the versatility of the mode of activation, that is, the occurrence of the activation depends on the regioisomer (6 modes of activation for the meta and para regioisomers against two for the ortho regioisomer) as does the efficiency (strong activation for the ortho and para regioisomers against weak activation for the meta regioisomer). This clear difference in activation depending on the position opens up interesting opportunities with heteroaromatic rings such as 1,2-, 1,3-, and 1,4-pyrazine, triazine, pyrimidine, etc. For example, with 1,4-pyrazine-based alkoxyamines, selective alkylation of the nitrogen at the *meta* position by an activated polymer chain might be envisioned, affording only a weak activation of the alkoxyamine C-ON bond, and then, using the nitrogen atom at the ortho position for late activation by either protonation or oxidation. In such a case, it would be possible to enhance the versatility of the NMP method and its combination with other methods.

Acknowledgements

The authors are grateful to the ANR (grant ANR-11-JS07-002-01), to Aix-Marseille University, and to CNRS for financial support. MBBI thanks the government of Gabon for his grant and L. Bosco for the pH measurements. This work was supported by the computing facilities of the CRCMM, 'Centre Régional de Compétences en Modélisation Moléculaire de Marseille'.

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