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Hydrogen abstraction from H-donor substrates by the 6-CF₃-benzotriazol-*N*-oxyl radical (TFNO)

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The aminoxyl radical 6-trifluoromethyl-benzotriazol-*N*-oxyl (TFNO) has been generated from the parent hydroxylamine 6-CF₃-1-hydroxy-benzotriazole (TFBT) by one-electron oxidation with a Ce^{IV} salt and characterized by spectrophotometry and cyclic voltammetry (CV). Rate constants of H-abstraction (k_H) by TFNO from a number of H-donor benzylic substrates have been determined spectrophotometrically in MeCN solution at 25 °C. A radical H-atom transfer (HAT) route of oxidation is substantiated for TFNO by several pieces of evidence. The kinetic data also testify the relevance of stereoelectronic effects upon the HAT reactivity of TFNO. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: aminoxyl radicals; bond energy; hydrogen atom transfer; kinetics; oxidation reactions; stereoelectronic effects

INTRODUCTION

Removal of hydrogen atom from a substrate is a fundamental event that allows the subsequent interaction with dioxygen and therefore leads to an oxidation outcome.^[1] Transfer of hydrogen atom from C-H bonds to free-radical species, and to oxygencentred radicals in particular, takes place in many instances,^[2] including not only the degradation of chemicals in the troposphere,^[3] biochemical reactions,^[4] synthetic organic transformations,^[5] but also the pathogenesis of some diseases.^[6] Oxygencentred radicals, such as the aminoxyl radicals (R_2NO_2) from appropriate hydroxylamine (R₂NO—H) precursors, participate in many industrial procedures,^[5,7,8] and promote the environmental benign aerobic oxidation of a number of substrates by H-abstraction.^[9-11] Phthalimide N-oxyl radical (PINO) provides a prominent case (Fig. 1), and the synthetic value of PINO-induced oxidations is recognized and has prompted studies upon the reactivity features of the aminoxyl radical intermediates.^[9,10,12,13]

Kinetic surveys have been already performed with PINO or else with its X-aryl-substituted cognates, [13-17] and have been recently complemented by a kinetic investigation with another aminoxyl radical, that is benzotriazole N-oxyl (BTNO),^[18] originating from precursor 1-hydroxy-benzotriazole (HBT).^[19] Another kinetic study had been reported with bis(trifluoromethyl)aminoxyl radical,^[20] (CF₃)₂N—O· (dubbed here BTFN). We now compare the previous kinetic data with newly acquired data concerning the H-abstraction reactivity of 6-trifluoromethyl-benzotriazol-N-oxyl radical (dubbed TFNO) (Fig. 1) towards H-donors. Mechanistic evidence has been collected with this particular aminoxyl radical, and a deeper insight into the H-abstraction reactivity of this class of compounds now becomes possible. In addition, and by resorting to suitable substrates, we gain a quantitative appreciation of the stereoelectronic effects that drive the H-abstraction step by the aminoxyl radicals.

RESULTS AND DISCUSSION

Characterization of the radical TFNO

The generation of an aminoxyl radical from the parent hydroxylamine (>NO-H) is in principle possible by either H-atom abstraction or else by one-electron abstraction followed by deprotonation.^[9,10] The resulting >N-O species can be either persistent or short-living depending on the structure, and characterized by appropriate spectroscopic methods.^[9] For example, PINO was generated from precursor N-hydroxyphthalimide (HPI) by oxidation with Pb(OAc)₄ in AcOH solution, and showed an electronic spectrum with maximum of absorbance at 380 nm.^[14] It underwent spontaneous decay with a half-life of 7900 s. Analogously, BTNO was generated from precursor HBT by oxidation with cerium(IV) ammonium nitrate (CAN) in MeCN solution; it showed $\lambda_{\rm max}$ at 474 nm and a spontaneous decay with half-life of 110 s. $^{[19]}$ Additional characterization of these aminoxyl radicals was possible by means of laser flash photolysis, cyclic voltammetry (CV) and electron paramagnetic resonance (EPR) spectroscopy.^[9,10] The latter technique was the one formerly employed in the kinetic investigation with BTFN (Fig. 1) in Freon.^[20]

We report here on the first generation of TFNO from the commercially available $6-CF_3-1$ -hydroxy-benzotriazole (TFBT) precursor. Following the addition of a stoichiometric amount

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Figure 1. Aminoxyl radicals (>N—O·) of interest in this study (full names are given in the text)

of the monoelectronic oxidant CAN (E° 1.3 V vs. NHE)^[18] to a 0.8 mM solution of TFBT (curve •) in MeCN at 25 °C, a new and broad absorption band develops in the range of 350–600 nm (curve $\mathbf{\nabla}$), with $\lambda_{\rm max}$ at 450 nm and ε 1516 M⁻¹ cm⁻¹ (Fig. 2). The generated species is not stable but decays according to an exponential curve having half-life of 70 s.

In agreement with the quantitative oxidation of TFBT by the one-electron oxidant CAN, investigation by CV shows a reversible scan for a 2 mM solution of TFBT in MeCN in the presence of pyridine (4 mM) and 0.1 M LiClO₄ (Fig. 3), from which the redox potential (E°) of the $>NO\cdot/>NO^-$ couple is obtained as 1.06 V *versus* normal hydrogen electrode (NHE). In buffered (pH 6.9) water solution, the E° is 1.16 V *versus* NHE. These data are in keeping with a reversible one-electron oxidation of the conjugate base of TFBT to TFNO (Scheme 1).^[21,22]

Because of the limited stability of TFNO, we have not been able to carry out the determination of the energy value of the NO—H



Figure 2. UV–Vis spectrum of TFBT (0.8 mM) in MeCN in the absence of CAN (\bullet); in the presence of CAN (0.8 mM) (\mathbf{V}) 15 ms after mixing



Figure 3. Cyclic voltammetry in MeCN solution (V vs. Ag/AgCl): [TFBT] = 2 mM, [Py] = 4 mM

bond of TFBT by EPR equilibration methods,^[23] but nevertheless have attained an evaluation of that BDE_{NO—H} as 86 ± 1 kcal/mol from resorting to a thermochemical cycle.^[24,25] By and large, all the evidence collected on TFNO is in keeping with the formerly reported characterization of the parent BTNO species from HBT (Table 1).^[18] In particular, the BDE_{NO—H} values are almost equal within the errors (refer to Experimental section).

Hydrogen-abstraction reactivity by TFNO

The spontaneous decay of TFNO is strongly accelerated in the presence of H-donor substrates bearing C—H bonds of suitable energy. Accordingly, it becomes possible to investigate the H-atom transfer (HAT) reactivity ($k_{\rm H}$) of TFNO from substrates, such as benzyl alcohols, alkylarenes or allylalkanes (Eqn (1)), by using UV–Vis spectroscopy, and monitoring the disappearance of the OD₄₅₀ of TFNO under the above described conditions in MeCN solution at 25 °C.

$$\begin{array}{l} \text{TFNO} + \text{ArCH}_2\text{OH} \xrightarrow[-\text{TFBT}]{k_{\text{H}}} \text{ArCH}(\cdot)\text{OH} \\ \xrightarrow[O_2]{O_2} \text{ product}(e.g. \text{ArCHO}) \end{array} \tag{1}$$

TFNO is generated in the spectrophotometric cuvette by quickly mixing a 0.5 mM CAN solution with a 1 mM TFBT solution, both in MeCN at 25 °C. The reading of the initial absorption at 450 nm confirms quantitative generation of TFNO. Fast addition of a solution of the C—H bearing substrate marks the beginning of the kinetic experiment; 3–5 initial concentrations of the substrate are typically investigated in concentration exceeding



Scheme 1. Electrochemical generation of TFNO

Table 1. Comparison of the properties of the >NO—H and >NO. species in the benzotriazole family				
	N N OH	F ₃ C N OH		
	НВТ	TFBT		
$pK_a (NO-H)^a$ E° , V vs. NHE, in MeCN ^b E° , V vs. NHE, in buffered water (pH 6.9) BDE_{NO-H} , in kcal/mol ^c λ_{max} of >NO. (in MeCN) Half-life of >NO·(in MeCN) ^d	4.6 0.967 1.06 85 ^c 474 nm 110 s	4.0 1.06 1.16 86 ^c 450 nm 70 s		
^a From Ref. ^[21,22] . ^b In the presence of pyridine; refer also Ref. ^[23] . ^c Calculated from a thermochemical cycle (±1 kcal/mol), refer Experimental section and Ref. ^[23] . ^d Spontaneous decay, k _(decay) .				

that of TFNO by 10–100 fold. The time-dependent depletion of TFNO at OD₄₅₀ is monitored by stopped-flow spectrophotometry because the reaction times are in general in the few seconds range. Under these pseudo first-order conditions, the H-abstraction rate from the substrate is higher than the spontaneous decay of TFNO in all cases reported in Table 2. The pseudo first-order rate constants k', determined from at least duplicated experiments,

Table 2. Second-order rate constants of H-abstraction $(k_{\rm H})$

from H-donors (RH) by TFNO at 25 °C in MeCN. Available bond

dissociation energy values (BDE_{C-H}) of RH are given.				
Substrate, RH	k _H (M ⁻¹ s ⁻¹) ^a	BDE _{C—H} (kcal/mol) ^b		
4-MeO-C ₆ H₄CH₂OH	54	78–82		
3-MeO-C ₆ H ₄ CH ₂ OH	26	78-82		
4-Me-C ₆ H ₄ CH ₂ OH	40	78-82		
PhCH₂OH	23	80		
4-CI-C ₆ H ₄ CH ₂ OH	15	83–85		
4-CF ₃ -C ₆ H ₄ CH ₂ OH	7.6	83–85		
4-NO ₂ -C ₆ H ₄ CH ₂ OH	7.2	83–85		
(PhCH ₂) ₂ O	22	n.a. ^c		
4-MeO-C ₆ H ₄ CH ₃	1.8	89–90		
4-MeO-C ₆ H ₄ CH ₂ CH ₃	6.2	85–87		
4-MeO-C ₆ H ₄ CHMe ₂	27	83–85		
PhCH(Me)OH	23	n.a. ^c		
cyclohexene	27	82		
Ph ₂ CH ₂	5.4	84		
Ph₂CHOH	25	78		
fluorene	24	82		
PhCH ₂ CN	0.4	n.a. ^c		
a				

^a Experimental conditions: [TFNO] 0.5 mM, [RH] 5–25 mM in MeCN solution. Determinations in triplicate; typical error \pm 3%. ^b From Refs ^[18] and ^[26]. ^c Not available.

are converted into second-order H-abstraction rate constants ($k_{\rm H}$) by determining the slope of a k' versus [subst]° linear plot (Fig. 4).^[18] No investigation is possible with either H-donor substrates, too reactive for our experimental equipment, or slower-reacting substrates whose 'apparent' first-order rate constant matches the $k_{\rm (decay)}$ of TFNO. Typical uncertainty in the kinetic determinations ranges from 2 to 5%.

It is appropriate to state that, although the $k_{\rm H}$ data in Table 2 cover a range exceeding two powers of ten, the corresponding range of bond dissociation energy (BDE) values is unfortunately not wide enough, nor the latter data are known with sufficient precision, to warrant a significant correlation of reactivity with bond energy, as we were able to do in the previous investigation with BTNO.^[18] Nevertheless, the $k_{\rm H}$ values of Ph₂CH₂ and Ph₂CHOH (5.4 and 25 M⁻¹s⁻¹) obtained here with TFNO do scale with the available BDE_{C—H} values (84 and 78 kcal/mol,



Figure 4. Pseudo first-order (k') rate constants for H-abstraction from 4-Cl-benzyl alcohol by TFNO (0.5 mM) in MeCN at 25 °C. The slope of the linear plot gives the second-order rate constant k_{H} ; the ratio of the initial concentrations of TFNO and substrate is indicated

respectively).^[26] Likewise, the rate constants of abstraction of a primary *versus* secondary *versus* tertiary benzylic hydrogen atom from, respectively, MeO-C₆H₄CH₃ *versus* MeO-C₆H₄CH₂CH₃ *versus* MeO-C₆H₄CH₂CH₃ *versus* MeO-C₆H₄CHMe₂ are compatible with the corresponding values of BDE_{C—H} (*ca.* 89, 86 and 84 kcal/mol, respectively).^[26] Therefore, a higher HAT reactivity for weaker bonds can be inferred, a result consistent with analogous findings for PINO and BTNO.^[14,16,17]

Summing it up, the reactivity features of TFNO in the HAT process (Table 2) are akin to those of other aminoxyl radicals,^[10] including the finding of an accelerating effect from electron-donor and the retarding effect from electron-withdrawing substituents on the benzylic substrate. Significant figures for this comparison of reactivity among aminoxyl radicals are selected and given in Table 3, proper allowance being made to the different solvents employed (no major effects upon the rates are however expected in these radical processes^[14,15,27]).

It is worth to point out that the reactivity of abstraction of benzylic hydrogens by the present aminoxyl radicals is substantially lower than that documented for other oxygen-centred radicals,^[10,20,28] such as HO· or t-BuO·, the second-order rate constants of which being in the range of 10⁶-10⁹ for similar substrates under similar conditions. Because HO· and t-BuO· form much stronger O—H bonds upon HAT (119 and 109 kcal/mol, respectively)^[26] than the aminoxyl radicals (>NO-H ca. 80-89 kcal/mol),^[9,17] a fair convergence of thermodynamic and reactivity features emerges: the stronger the O-H bond formed by the abstracting oxygen-radical (RO-) the higher the H-abstraction reactivity. More on this point, and although the difference in BDE_{NO-H} values among the hydroxylamine precursors of the aminoxyl radicals of Table 3 is admittedly quite small, some comments about their different reactivity are anyhow possible. In fact, there is no doubt that PINO is more reactive than BTFN, in keeping with the higher energy of the NO-H bond it forms on H-abstraction (88 vs. 84 kcal/mol).^[10] The BDE_{NO-H} of TFBT and HBT are instead intermediate in value between the two above



Scheme 2. Polar effects upon the transition state of a radical HAT process by an electrophilic aminoxyl radical

Table 3. Comparison of kinetic data ($k_{\rm H}$, M ⁻	1 s ⁻¹ , at 25 °C) of H-abstraction among aminoxyl radicals (structures and names in Fig. 1;
n.d. stands for not determined)	

Substrate, RH (BDE _{C—H} , in kcal/mol) ^a	PINO, ^b in AcOH BDE _{NO—H} = 88.3 kcal/mol ^e	BTFN, ^c in Freon BDE _{NO—H} = 84.0 kcal/mol ^e	BTNO, ^d in MeCN BDE _{NO—H} = 85 kcal/mol ^f	TFNO in MeCN BDE _{NO—H} = 86 kcal/mol ^f
PhCH ₂ OH (80)	11	n.d.	1.8	23
<i>p</i> -MeO-C ₆ H ₄ CH ₂ OH (<i>ca</i> . 79)	45	n.d.	7.8	54
PhCH ₃ (89)	0.62	8.9 10 ⁻³	0.26 ^g	1.8 ^g
$PhCH_2CH_3$ (85)	5.4	0.3	0.70 ^g	6.2 ^g
PhCHMe ₂ (84)	27	0.3	0.55 ^g	54 ^g
Ph ₂ CHOH (78)	58	n.d.	3.2	25
Ph ₂ CH ₂ (84)	13	0.48	0.72	5.4
Ph ₃ CH (81)	59	8.8	2.3	n.d.
Fluorene (82)	40	n.d.	3.8	24
- [27]				

^a From Ref ^[26].

^b From oxidation of HPI with Pb(OAc)₄ at 25 °C, Refs ^[14,27].

^c From Ref. ^[20], at 25 °C.

 $^{\rm d}$ From oxidation of HBT with CAN at 25 $^{\circ}\text{C},$ Ref. $^{[18]}$

 e Experimental value (±0.5 kcal/mol), Refs $^{[9]}$ and $^{[10]}$

 $^{
m f}$ A reasonable confidence limit for our calculated BDE $_{
m NO-H}$ values is ± 1 kcal/mol, Ref. $^{[23]}$.

^g As *p*-MeO-derivatives.



Scheme 3. Competition of ET versus HAT routes with an aminoxyl radical

cases and indeed very close together,^[10,23] so that it is a little puzzling that TFNO comes out 3–10 fold more reactive than BTNO. However, because the >N-O radicals are known to be electrophilic,^[9,10,17,29] the presence of the electron-withdrawing CF₃-substituent in TFNO may confer additional polar stabilization to the transition state of the HAT (*cf.* Scheme 2). It will assist the development of a partial negative charge on the abstracting aminoxyl radical, as mirrored by the favourable effect from the electron-donor substituents (X) on the benzylic alcohol counterpart, where a partial positive charge develops (*vide also infra*).

Therefore, the H-abstraction reactivity of the aminoxyl radicals appears to be not only dominated by the enthalpic requirements of the NO—H bond energy in formation, but also by the polar effects sketched in Scheme 2 that may provide electrostatic stabilization to the transition state of the radical HAT route.

Mechanistic insight

Recent studies have supported the capability of the aminoxyl radicals to remove electrons from electron-rich substrates, giving an electron-transfer (ET) route as opposed to the expected HAT pathway (Scheme 3).^[10,30,31] Inspired by the finding that polar effects (Scheme 2) are relevant for TFNO and make it somewhat more reactive than BTNO, i.e. the parent aminoxyl radical for which a clean HAT route had been substantiated,^[18,19] we have deemed that a full mechanistic characterization of the reaction of TFNO towards H-donors was required in the event that the competing ET route could take over.



Figure 5. Hammett correlation for reaction of TFNO with X-substituted benzyl alcohols in MeCN solution at 25 $^\circ\text{C}$

Table 4.	Kinetic da	a of either	H- or D-a	abstraction b	y TFNO
from a se	eries of ber	zylic alcoh	ols, in Me	CN at 25 °C	

Substrate	$k_{\rm H}$ or $k_{\rm D}$ (M ⁻¹ s ⁻¹)	k _H /k _D
4-MeOC ₆ H ₄ CH ₂ OH	54	6.3
4-MeOC ₆ H ₄ CD ₂ OH	8.6	
PhCH₂OH	23	16
PhCD₂OH	1.4	
4-CF ₃ C ₆ H ₄ CH ₂ OH	7.6	17
4-CF ₃ C ₆ H ₄ CD ₂ OH	0.44	
4-CF ₃ C ₆ H ₄ CD ₂ OH	0.44	

Hammett correlation

The H-abstraction reactivity of TFNO towards X-substituted benzyl alcohols (from $k_{\rm H}$ data in Table 2; *cf.* Eqn (1)) correlates with the σ^+ parameter of the X-substituents according to an Hammett-like equation (log $k_{\rm X}/k_{\rm H} = \rho\sigma^+$),^[32] and gives a linear plot with $\rho = -0.62 ~(\pm 0.06)$ (Fig. 5). This is indeed a small slope, as expected for a radical process,^[18] and compares well with a ρ value of -0.55 for the reaction of BTNO *versus* the same substrates in MeCN,^[19] as well as with a ρ of -0.41 for PINO whenever generated from HPI by Pb(OAc)₄ in AcOH solution.^[14]



Scheme 4. Products study for reaction of TFNO with probe substrate 1: $C\alpha - C\beta$ (above) *versus* $C\alpha - H$ (below) bond cleavage



Figure 6. Stereoelectronic interaction between the lone-pair of an amine and an adjacent C—H bond. Reprinted with permission from Griller *et al.*^[39]. Copyright (1981) American Chemical Society

Table 5. Rate constants of H-abstraction by TFNO in MeCN solution at 25 $^{\circ}C^{a}$				
Entry	Substrate _A	Substrate _B	$k_{\rm rel} ({\rm sub}_{\rm A}/{\rm sub}_{\rm B})^{\rm b}$	
1	Ph ₂ CHOH $k_{\rm H} = 25 {\rm M}^{-1} {\rm s}^{-1}$ BDFc $\mu = 78 {\rm kcal/mol}$	Ph_2CH_2 $k_H = 5.4 \text{ M}^{-1} \text{ s}^{-1}$ BDE c H = 84 kcal/mol	9	
2			16	
	H OH $k_{\rm H} = 190 {\rm M}^{-1} {\rm s}^{-1}$	H H H $k_{\rm H} = 24 {\rm M}^{-1} {\rm s}^{-1}$		
3	BDE _{C-H} = 73 kcal/mol (PhCH ₂) ₂ O $k_{\rm H} = 22 {\rm M}^{-1} {\rm s}^{-1}$	$BDE_{C-H} = 82 \text{ kcal/mol}$ $PhCH_2CH_2Ph$ $k_H = 0.88 \text{ M}^{-1} \text{ s}^{-1}$	25	
4	BDE _{C—H} = ca. 82 kcal/mol PhCH ₂ OH $k_{\rm H} = 23 {\rm M}^{-1} {\rm s}^{-1}$	BDE _{C—H} = 87 kcal/mol PhCH ₂ OC(O)Ph $k_{\rm H}$ = unreactive ^c	>80	
5	BDE _{C—H} = 80 kcal/mol	$BDE_{C-H} = n.a.$	>100	
	$k_{\rm H} = 62 {\rm M}^{-1} {\rm s}^{-1}$	$k_{\rm H} = {\rm unreactive}^{\rm c}$		
6	$BDE_{C-H} = n.a.^{\circ}$	BDE _{C-H} = n.a. ^o	>50	
7	$k_{\rm H} = 6.8 \text{M}^{-1} \text{s}^{-1}$ BDE _{C—H} (allylic) = ca. 82 kcal/mol PhCH ₂ NHC(O)Ph $k_{\rm H} = 2.2 \text{M}^{-1} \text{s}^{-1}$	$k_{\rm H} =$ unreactive ^c BDE _{C—H} (allylic) = ca. 90 kcal/mol PhCH ₂ OC(0)Ph $k_{\rm H} =$ unreactive ^c	>15	
8	BDE _{C-H} = n.a. ^o	$BDE_{C-H} = n.a.$ Ph_2CH_2	4.4	
9	$k_{\rm H} = 24 {\rm M}^{-1} {\rm s}^{-1}$ BDE _{C—H} = 82 kcal/mol	$k_{\rm H} = 5.4 {\rm M}^{-1} {\rm s}^{-1}$ BDE _{C—H} = 84 kcal/mol PhCH ₂ CH ₂ Ph	140	
	$k_{\rm H} = 124 {\rm M}^{-1} {\rm s}^{-1}$ BDE _{C—H} = 84 kcal/mol	$k_{\rm H} = 0.88 {\rm M}^{-1} {\rm s}^{-1}$ BDE _{C—H} = 87 kcal/mol		
			(Continues)	



^d Not available. A rate value too high for our spectrophotometric mixing device (8 ms of dead-time; i.e. $k_{\rm H} > 80 \,{\rm M}^{-1} \,{\rm s}^{-1}$).

Additional ρ values (in the range of -0.5 to -0.7) are reported for X-substituted PINOs generated from X-substituted HPIs in MeCN solution.^[17] In all these cases better Hammett correlations are obtained *versus* the σ^+ parameter of the X-substituents than with the simple σ parameter, in line with the electrophilicity of the aminoxyl radicals.^[17,29] Thus, an uniform pattern of selectivity among these structurally similar >N—O· species does emerge. Small ρ values such as these are more compatible with a single-step HAT route rather than with the formal alternative of a concerted proton–electron transfer route (CPET; *cf.* last structure in Scheme 2).^[30,33] For example, in the recently reported oxidation of 4-X-substituted *N,N*-dimethylanilines by the very BTNO, a much larger ρ value of -3.8 has been obtained, and judged compatible with a two step electron transfer–proton transfer mechanism.^[34]

Kinetic isotope effect determination

The kinetic survey with TFNO has been extended towards a few deuteriated substrates, pertinent data being collected in Table 4.

The large values of the intermolecular $k_{\rm H}/k_{\rm D}$ ratio, ranging from 6 to 17, support a single-step rate-determining H-abstraction step, and confirm analogous results (in the range of 6–27) obtained for PINO and BTNO.^[9,14,15,17,18,27] The contribution from tunnelling is clear, as also documented elsewhere.^[14,17]

Products study for reaction of TFNO with a probe substrate

As described previously,^[35] the test substrate **1** presents the distinct advantage of giving rise to two different end-products depending on the operating mechanism of oxidation. In fact, under genuine ET conditions, **1** gives a transient **1**.+ intermediate that cleaves the $C\alpha$ — $C\beta$ bond of the side-chain, and affords the corresponding aldehyde (**2**) plus *tert*-butyl radical (Scheme 4).^[36]

The cleavage is driven by steric and stereoelectronic factors that make the loss of a tertiary radical easy.^[36] Conversely, under *bona fide* radical HAT conditions, **1** undergoes cleavage of the C α —H benzylic bond, and produces the corresponding ketone **3** exclusively.^[35,36] This clear-cut behaviour makes **1** a significant probe, capable of differentiating the mechanism of an oxidation reaction from product analysis.

Upon oxidation of **1** with TFNO in MeCN (*cf.* Experimental section), a 4% yield of ketone **3** is obtained with no traces of the aldehyde **2**; the rest of mass balance being the unreacted **1**. Under similar conditions, BTNO gave a strictly comparable result.^[19,35] Thus, the HAT pathway is utterly confirmed for both these aminoxyl radicals, and any competition by an ET route (*cf.* Scheme 3) can be discarded.

Stereoelectronic effects

In line with the concept of the anomeric effect,^[37,38] Griller *et al.*^[39] have convincingly demonstrated that conjugation from the lone-pair of a heteroatom weakens an adjacent C—H bond and stabilizes the intervening C-radical generated by H-abstraction. The contribution from this weakening effect upon the energy of the adjacent C—H bond is the greater the more co-linear are C—H bond and lone-pair.^[39,40] Figure 6 shows the case of an amine where the effect reportedly accounts for a 7–9 kcal/mol weakening of the adjacent C—H bond. A computational study similarly attains a 5 kcal/mol weakening of the α C—H bond for conjugation from an oxygen lone-pair.^[41]

For torsion angles (θ) wider than 30°, the relevance of the effect fades away drastically.^[39] Our finding of an appreciable rate increase when passing from Ph₂CH₂ to Ph₂CHOH (Table 2) is likely due to the profitable stereoelectronic interaction from the oxygen lone-pair of the alcohol with the scissile α C—H bond, an interaction that clearly lacks in the hydrocarbon counterpart, thereby confirming the analogous finding in the kinetic study with BTNO.^[18]

By exploiting the higher reactivity of TFNO than BTNO in HAT reactions, we have been able to extend the previous kinetic investigation on the stereoelectronic effects^[42,43] to additional and significant substrates. Table 5 gives the results for H-abstraction by TFNO, the investigated substrates being organized pairwise with their experimental $k_{\rm H}$ and $\rm BDE_{C--H}$ values (whenever available).^[26]

A few comments are in order:

 Abstraction of hydrogen from a C—H bond adjacent to an oxygen atom is always faster than from the parent hydrocarbon (entries 1-3),^[44] as mirrored by the corresponding BDE_{C—H} data,^[26] owing to the favourable stereoelectronic



Figure 7. Reduced availability of the oxygen lone-pair owing to conjugation with an adjacent group



Figure 8. Enforced co-linearity of a benzydrylic radical with the p-orbitals of the adjacent aromatic rings, as due to the planar 5-membered ring interconnecting the two π -systems (the case of entry 8 in Table 5 is shown)

interaction between oxygen lone-pair and C—H bond (*cf*. Fig. 6);

- (2) whenever the availability of the adjacent oxygen lone-pair is lessened by resonance with an electron withdrawing group, such as a carbonyl (Fig. 7), the stereoelectronic assistance in Fig. 6 is reduced (entries 4–6);^[45]
- (3) the stereoelectronic effect from the lone-pair of nitrogen is somewhat stronger than from oxygen (entry 7).^[39-41]
- (4) clearly, the stereoelectronic effect is particularly appreciable here because the >N—O· species is an electrophilic radical,^[9,10,12,13,17,29] and, therefore, susceptible to both bondpolarization effects (*cf.* Fig. 6) and polar effects (Scheme 2) upon reactivity.

Besides the stereoelectronic effect pertaining to the lone-pair of an adjacent heteroatom, H-abstraction from a benzylic (or allylic) C-H bond is faster whenever cyclic systems are considered, as opposed to open-chain counterparts.^[42] This is confirmed when comparing the values of BDE_{C-H} for the cyclic/ open pairs in entries 8–10, and supports previous kinetic findings in HAT processes by BTNO or PINO.^[10,42] Clearly, the homolytic cleavage of a benzylic (or allylic) C-H bond is assisted by π -conjugation with an aromatic (or vinylic) moiety that stabilizes the intervening carbon-radical. Such assistance is fostered in a cyclic compound where co-linearity between the C-H bond being cleaved and the adjacent π -system is enforced by steric restrictions from the ring system (Fig. 8), whereas in the corresponding open-chain compound the appropriate co-linearity would be somewhat disrupted owing to conformational freedom.^[42,43]

CONCLUSIONS

Rate constants of H-abstraction ($k_{\rm H}$) by TFNO from H-donor substrates have been determined spectroscopically. Hammett correlation of the reactivity of TFNO *versus* X-substituted benzyl

alcohols affords a small value for ρ (i.e. -0.62), compatible with a single-step radical H-atom abstraction from the benzylic position, rather than with a CPET route (*cf.* Scheme 3),^[31] that it is expected to provide larger ρ values (as -3.8,^[33,34] or even larger^[46]). A product study for reaction of TFNO with a probe substrate confirms a HAT route of oxidation. The primary kinetic isotope effect supports the H-abstraction as rate determining. The HAT reactivity has been compared within a series of four aminoxyl radicals and an uniform pattern of selectivity (Table 3) does emerge. In particular, the H-abstraction from H-donor substrates appears to be the faster the stronger the O-H bond (i.e. $\text{BDE}_{\text{NO}\text{--H}}$) that the $>\!\!N\text{---O}\!\cdot$ species gives rise to in the HAT step. In this respect, the slightly higher reactivity of TFNO than the parent BTNO species is at odds with the comparable values of their BDE_{NO-H} and ascribed to the electron-withdrawing CF₃-substituent in TFNO that confers additional polar stabilization to the transition state of the radical HAT (Scheme 2). Finally, and by exploiting the higher reactivity of TFNO than BTNO in HAT reactions, we have been able to substantiate a wider number of exemplary cases of stereoelectronic effects on the HAT reactivity. In the inspected cases, the conjugation of a C-H bond with either the lone-pair of an adjacent heteroatom or a π -system weakens the C—H bond and fosters its cleavage by the aminoxyl radical. The efficiency of the interaction is enhanced whenever a proper co-linear conformation is attained (Fig. 6), and this is particularly well met in rigid cyclic substrates (Fig. 8) where the loss of conformational freedom is not severe.

EXPERIMENTAL

General

Commercial TFBT (Aldrich) was used as received; all the substrates were purchases and used without further purification, if not already available in the laboratory.^[18] In particular, substrate **1** and products **2** and **3** were available from a previous study.^[35] Cerium(IV) ammonium nitrate (CAN; Erba RPE) was oven-dried before use.^[18] Reagent grade acetonitrile (Erba RPE) was used as the solvent. Bis α -deuteriated benzyl alcohols (*cf.* Table 4) were already available in the laboratory or synthesized as described previously^[35,47] by reduction of the corresponding carboxylic acids with LiAlD₄ in dry THF. Full ¹H-NMR (samples concentration: 65 mM) and MS characterization of the bis α -deuteriated benzyl alcohols were as follows.

- (1) [1,1-²H₁]-benzyl alcohol
 - (a) δ_H (200 MHz; CDCl₃) 1.9 (bs, 1*H*, O**H**), 7.3 (m, 5*H*, ArH);
 - (b) MS (m/z): 110 (M⁺), 93, 77, 51.
- (2) (b) M3 (H/2). The (H/2), 93, 77, 31. [1,1-²H₁]-4-(trifluoromethyl)benzyl alcohol
 - (a) δ_H (200 MHz; CDCl₃) 1.9 (bs, 1*H*, OH), 7.63–7.45 (AA'XX', 4*H*, ArH);
 - (b) MS (m/z): 178 (M⁺), 160, 109, 81, 77, 51.

Instrumentation

The kinetic study was carried out with a Hi-Tech SFA-12 stopped flow instrument, interfaced to a HP 8453 diode array spectrophotometers, and having a thermostated cell holder. A thermocouple was employed for reading the temperature in the quartz cuvette. A VARIAN 3400/Star gas chromatograph, fitted with a $20\,m\times0.25\,mm\,$ methyl silicone gum capillary column, was employed in the GC analyses. GC-MS analyses were performed on a HP 5892 GC, equipped with a $12\,m\times0.2\,mm\,$ methyl silicone gum capillary column and coupled to a HP 5972 MSD instrument operating at 70 eV.

Kinetic procedure

The TFNO species was generated in the cuvette of the stoppedflow by adding a 0.5 mM solution of CAN to a 1.0 mM solution of TFBT, both in MeCN. A broad absorption band developed almost immediately (8 ms) in the 350–600 nm region (λ max at 450 nm, ε 1516 $dm^3 mol^{-1} cm^{-1}$). The OD₄₅₀ reading was not stable, but decayed with a half-life of 70 s. The rate of decay was unaffected by the use of de-aerated MeCN. Rate constants of H-abstraction from H-donor substrates were determined at 25 °C in MeCN, by following the decrease of OD₄₅₀ of TFNO. The initial concentration of the substrate was in excess with respect to the TFNO species, and in the range of 5-25 mM, so to enable a pseudo first-order treatment of the kinetic data. Plots of (OD_t-OD_{∞}) versus time were well fitted by a first-order exponential over more than three half-lives, and the rate constant (k') reckoned. From a plot of three-to five k' versus [subst] $^{\circ}$ data pairs, the second-order rate constant of H-abstraction $(k_{\rm H})$ was obtained. The intermolecular kinetic isotope effect for bis α -deuteriated-X-substituted benzyl alcohols (Table 4) was calculated from the ratio of the kH and kD rate constants with TFNO.

Products study with probe substrate (1)

As described previously,^[18,23,35] 60 mmol of substrate **1**, 20 mmol of TFBT and 20 mmol of CAN were let to react at room temperature in 3 ml MeCN. After a 5 h reaction time and conventional workup with ethyl acetate, GC-MS analysis enabled us to detect the formation of ketone **3** and the absence of aldehyde **2**; no other products besides unreacted **1** were detected. Quantitative determination of the yield of **3** (i.e. 4%) was carried out by GC with the internal standard method.

Electrochemical determinations

CV at the steady disc electrode (glassy-carbon disc, 1.5 mm in diameter)^[48] was carried out with TFBT (2 mM) at 25 °C in MeCN in the presence of pyridine (4 mM) and 0.1 M LiClO₄ (Fig. 3). A three-electrode circuit was used with a potentiostat with a positive feedback ohmic-drop compensation and a MPLI Hardware (Vernier Software & Technology) controlled by a program written in C++ language for Windows 95/98.^[49] A platinum wire (1 cm²) and a saturated calomel electrode (SCE) as reference were used; the E° value is obtained as the mean of the cathodic and anodic peak values of the reversible scan (Fig. 3),^[50] and referred to the normal hydrogen electrode (NHE), NHE = SCE + 0.241 V.^[51] Scan rates in the range of 10 mV/s to 10 V/s were investigated.

BDE determination

The BDE_{NO—H} of TFBT has been obtained from the following thermochemical cycle (pertinent data in Table 1, to be converted into kcal/mol), the value of E_2° being 54 kcal/mol.^[23–25]

$$\begin{array}{cccc} R_2 NO - H \xrightarrow{pK_a} & R_2 NO^- + & H^+ \\ & & \downarrow E_1^{\circ} & \downarrow E_2^{\circ} \\ R_2 NO - H \xrightarrow{BDE} & R_2 NO^- + & H^- \end{array}$$

and equation:^[9,24,24]

$$\mathsf{BDE}_{\mathsf{NO}-\mathsf{H}} = \mathsf{p}\mathcal{K}_{\mathsf{a}}(\mathsf{R}_{2}\mathsf{NO}\mathsf{H}) + \mathsf{E}_{1}^{\circ}\left(\frac{\mathsf{R}_{2}\mathsf{NO}^{\circ}}{\mathsf{R}_{2}\mathsf{NO}^{\circ}}\right) + \mathsf{E}_{2}^{\circ}\left(\frac{\mathsf{H}^{+}}{\mathsf{H}^{\circ}}\right) \tag{2}$$

This calculation has been calibrated in the case of HPI, obtaining a BDE_{NO—H} value of 88 kcal/mol *versus* the experimental value of 88.3 kcal/mol.^[9] This suggested us that a reasonable confidence limit for the calculated values is ± 1 kcal/mol (in Tables 1 and 3).

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