Hydrogen atom abstraction from C–H bonds of benzylamides by the aminoxyl radical BTNO: A kinetic study

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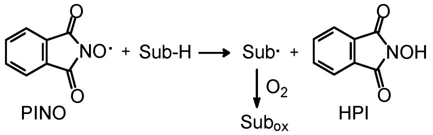
The aminoxyl radical BTNO (benzotriazole-*N*-oxyl; >N–O$^\bullet$) is generated from HBT (1-hydroxybenzotriazole; >N–OH) by oxidation with a Ce^{IV} salt. BTNO presents a broad absorption band with λ_{max} 474 nm that lends itself to investigate the kinetics of H-abstraction from H-donor substrates by spectrophotometry. Thus, rate constants (k_H) of H-abstraction by BTNO from CH_2-groups α to the nitrogen atom in X-substituted-(*N*-acetyl)benzylamines ($X-C_6H_4CH_2NHCOCH_3$) have been determined in MeCN solution at 25 °C. Correlation of the k_H^X data with the Hammett σ^+ parameters gives a small value for ρ (–0.65) that is compatible with a radical H-abstraction step. The sizeable value ($k_H/k_D = 8.8$) of the kinetic isotope effect from a suitably deuteriated amide substrate further confirms H-abstraction as rate-determining. Evidence is acquired for the relevance of stereoelectronic effects that speed up the H-abstraction whenever the scissile C–H bond is co-linear with either the nitrogen lone-pair of the amide moiety or an adjacent aromatic group. An assessment of the dissociation energy value of the benzylic C–H bond in Ar*CH*$_2$NHCOMe is accordingly reported.

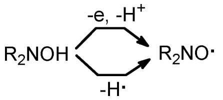
Introduction

The aminoxyl radicals ($R_2NO^\bullet$) are valuable and versatile reactive intermediates in numerous applications.[1] In particular, the synthetic importance of aminoxyl radicals is highlighted by their use as catalysts in oxidation reactions endowed with low environmental impact.[1–4] Among these radicals PINO (phthalimide *N*-oxyl), derived from HPI (*N*-hydroxyphthalimide), offers a prominent case.[5] PINO removes a hydrogen atom from a substrate (by hydrogen atom transfer, HAT), enabling subsequent interaction with O_2 and therefore an oxidation outcome (Scheme 1).



Scheme 1 Oxidation of an H-donor substrate (Sub-H) by radical PINO in the presence of dioxygen.

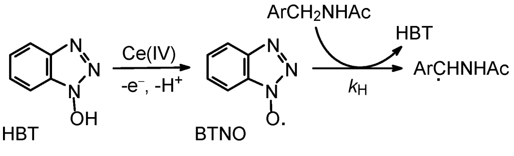
In principle, aminoxyl radicals can be obtained from the parent hydroxylamines by either H-abstraction or electron-abstraction followed by deprotonation (Scheme 2).[1]



Scheme 2 Possible pathways of generation of aminoxyl radicals.

For example, PINO is generated from HPI by the action of O_2 and $Co(OAc)_2$,[4,5] or else by oxidation with $Pb(OAc)_4$;[6] PINO has alternatively been generated electrochemically.[7] Kinetic studies of the H-abstraction reaction from substrates having C–H or O–H bonds of appropriate energy have provided information upon the reactivity of PINO towards alkylarenes or phenols.[6a,8] The synthetic value of the oxidation reactions induced by PINO has stimulated us to assess the reactivity features of this, as well of other aminoxyl radicals more closely.

We have recently reported on the H-abstraction reactivity of another aminoxyl radical, that is, BTNO (benzotriazole *N*-oxyl).[9] This radical has been generated from oxidation of HBT (1-hydroxybenzotriazole) with a Ce^{IV} salt (Scheme 3) and characterized by UV-Vis and EPR spectra, laser flash photolysis and cyclic voltammetry.[9a] Rate constants of H-abstraction (k_H) from C–H bonds of H-donor substrates, including benzyl alcohols and alkylarenes, have been determined spectroscopically and found to be in the 10^{-3} to 10^2 M^{-1} s^{-1} range at 25 °C in MeCN solution.[9b] With selected substrates, activation parameters for the H-abstraction step have been measured, and the activation energy successfully correlated to the dissociation energy of the C–H bond undergoing cleavage.[9b] Whenever comparing BTNO *vs* PINO, the radical reactivity of PINO has always been found higher than that of BTNO towards similar substrates. The explanation provided is that PINO gives rise to a stronger NO–H bond (in HPI) upon H-abstraction from a substrate, as compared to the weaker NO–H bond in HBT (88 *vs. ca.* 85 kcal/mol, respectively), this representing a crucial factor for a radical process where bond cleavage and formation dominate the reactivity.[1,9b]



Scheme 3 Kinetic study of the H-abstraction from the C–H bond α to an amide-nitrogen by BTNO.

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The present paper deepens our understanding of the reactivity of aminoxyl radicals in the H-abstraction reaction, a topic recently reviewed.[1] It also extends this knowledge to the oxidation of amides, a class of substrates never explored kinetically so far. In fact, we report on a kinetic study of the H-abstraction by BTNO from the C–H bond α to the nitrogen atom of amides (Scheme 3), a reaction investigated for synthetic purposes by the use of PINO.[10]

During our kinetic study, evidence for the important contribution from stereoelectronic effects upon the H-abstraction reactivity has appeared. More specifically, the co-linearity between the α-C–H bond undergoing cleavage and the nitrogen lone-pair of the amide comes out as a key structural requirement.[11] Likewise, for substrates similarly bearing a lone-pair, such as alcohols or ethers or amines, the H-abstraction by *t*-BuO. (or other radicals as well) had been described to be more rapid than H-abstraction from simple hydrocarbons as a result of the specific contribution from stereoelectronic effects.[11,12] We report here on our attempt to give quantitative support to these issues. Activation parameters for H-abstraction from the α-C–H bond in two amide substrates have been determined, and enable to assess the contribution from stereoelectronic effects in decreasing the energy value of the scissile C–H bond.

Results and discussion

H-abstraction reactivity

Addition of a stoichiometric amount of the monoelectronic oxidant cerium(IV) ammonium nitrate $(NH_4)_2Ce(NO_3)_6$ (*i.e.*, CAN; E° 1.3 V *vs* the normal hydrogen electrode, NHE)[13] to HBT (E° 1.08 V *vs* NHE)[14] in MeCN solution at 25 °C, both compounds being at 0.5 mM initial concentration, gives rise to a broad absorption band in the 350–600 nm range (Fig. 1)[9] having λ_{max} at 474 nm and ε 1840 M^{-1} cm^{-1}.

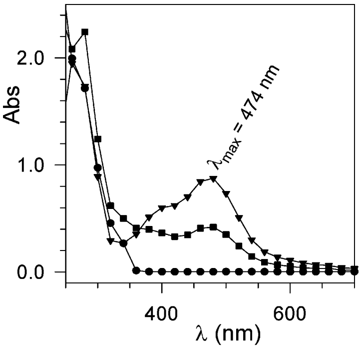
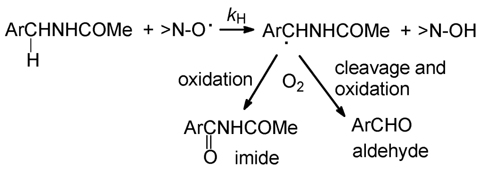


Fig. 1 UV-Vis spectrum of a 0.5 mM solution of HBT in MeCN: (●) before the addition of CAN; after the addition of CAN (0.5 mM): (▼) 15 ms after the addition, (■) 110 s after the addition.

The band pertains to the formation of the BTNO species: electron transfer from HBT to CAN is in fact exoergonic and occurs quantitatively (cf. Scheme 3).[9] The spectrum of BTNO is not stable but decays according to an almost first-order exponential curve (k_{decay} = 5.1 × 10^{-3} s^{-1} in MeCN at 25 °C), with a half life of 140 s at 0.5 mM.[9b] The spontaneous decay of BTNO is strongly accelerated in the presence of purposely added H-donor substrates. By following the progress of the reaction at 474 nm through stopped-flow or conventional spectrophotometry, the reactivity of BTNO in the H-abstraction from the CH_2-group in α to nitrogen is investigated here for a series of amides (Ar*CH*$_2$NHCOMe, cf. Schemes 3 and 4). Previous synthetic investigations had shown that the radical oxidation performed by either PINO or BTNO in the presence of O_2 gives rise to carbonyl end-products (imide + aldehyde) from a common α-amido carbon radical intermediate originating from cleavage of the α-C–H bond of the amide substrate (Scheme 4).[10,15]



Scheme 4 Pathways of products formation in the HAT route of oxidation of amides by an aminoxyl radical.

For kinetic purposes, the solution of the C-H bearing substrate is employed here at initial concentrations higher than the concentration of BTNO, in order to fulfil the pseudo first-order kinetic conditions, and the drop of absorbance at 474 nm is followed. The pseudo-first-order rate constants *k′*, determined at 25 °C at three-to-four initial concentrations of amide from at least duplicated experiments, are converted into second-order H-abstraction rate constants (k_H) by determining the slope of a *k′ vs.* [SubH]° plot, as shown in Fig. 2 for the case of 4-chloro-*N*-benzylacetamide. Typical uncertainty of the kinetic data ranges from 3 to 6%.

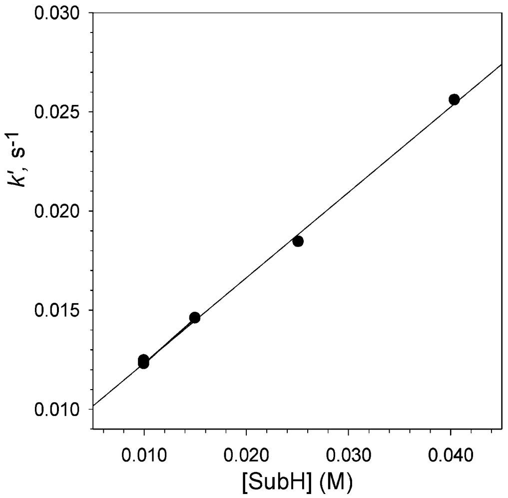
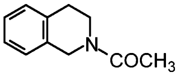


Fig. 2 Determination of the second order rate constant k_H for reaction of BTNO with 4-chloro-*N*-benzylacetamide in MeCN at 25 °C, from the plot of the pseudo-first-order rate constants *k′* at various initial concentration of the substrate.

The *k′* constants are faster than the spontaneous decay of BTNO in all cases investigated, as the linearity of the plot and the minor *y*-intercept in Fig. 2 demonstrates, and exhibit first-order dependence on the excess substrate concentration. The second-order rate constants (k_H) are given in Table 1 for the substrates of this study, which includes the α,α-bisdeuterio-*N*-benzylacetamide purposely synthesized (*vide infra*).

Table 1 Summary of the rate constants k_H (M^{-1} s^{-1}) obtained spectrophotometrically at 25 °C in MeCN solution from reaction of BTNO with amide substrates[a]

Substrate	k_H (M^{-1} s^{-1})
$PhCH_2NHCOMe$	0.49
$PhCD_2NHCOMe$	0.056
4-MeO-$C_6H_4CH_2NHCOMe$	2.54
4-Me-$C_6H_4CH_2NHCOMe$	1.17
4-Cl-$C_6H_4CH_2NHCOMe$	0.43
4-CF_3-$C_6H_4CH_2NHCOMe$	0.26
4-NO_2-$C_6H_4CH_2NHCOMe$	0.33
PhCH(Me)NHCOMe	0.11
 *N*-Acetyl-tetrahydroisoquinoline	26

[a] Initial conditions: [BTNO] 0.5 mM, [SubH] 5–40 mM. Determinations in triplicate; typical errors 3–6%.

Hammett correlation

The effect of the substituents upon reactivity is reckoned by correlating the k_H^X data for reaction of the 4-X-*N*-benzylacetamides with BTNO (in Table 1) *vs* the σ constants of the X-substituents according to the Hammett equation ($\log k_X/k_H = \rho\sigma$). A slightly better linearity is obtained in the plot (Fig. 3) when using the σ^+ parameters, which take into account the resonance contribution from electron-donor substituents more effectively.[16] The correlation parameter ρ, obtained from the slope of the plot, is –0.65. This is a small value, as expected for a radical process, and its negative sign besides the better fit to the σ^+ parameters confirms the polar character of the aminoxyl radical.[8b,9,10] The present ρ value compares very well with the one previously determined (*i.e.*, –0.55 *vs* σ^+) for reaction of BTNO with another series of benzylic substrates, that is, the 4-X-substituted benzyl alcohols (4-X-$C_6H_4CH_2OH$).[9a] A common selectivity trend for H-abstraction by BTNO from benzylic C–H bonds in the two series of substrates emerges.[1] This is likely to be due to the analogous stabilization offered by the X-substituents of the aromatic ring to an incipient benzylic radical in the transition state: electron-donor groups make the H-abstraction faster whereas electron-withdrawing ones slow it down.[17] This is tantamount to saying that the C–H bond undergoing cleavage in the two series of substrates is made weaker or stronger by the X-substituents, causing a faster or slower H-abstraction, respectively. Earlier and strictly related studies of the reactivity of the radical PINO with benzylic substrates such as 4-X-$C_6H_4CH_2OH$ had provided ρ values of –0.68 in MeCN and of –0.41 in AcOH, once again giving better correlation with σ^+.[1,6a,8b] The consistency of these ρ values stresses the uniform pattern of selectivity of the electrophilic >N–O• species (either PINO or BTNO) in the HAT reaction. Finally, the relative reactivity from competitive oxidations for a series of X-*N*-benzylacetamides in reaction with alkylperoxy-λ^3-iodane, *i.e.*, a radical HAT agent, had been reported in the literature,[18] and a ρ value (*i.e.*, –0.56) very close to our finding given. This supports the same extent of stabilization/destabilization offered by X-substituents to an incipient benzyl radical α to nitrogen in the rate-determining H-abstraction step.

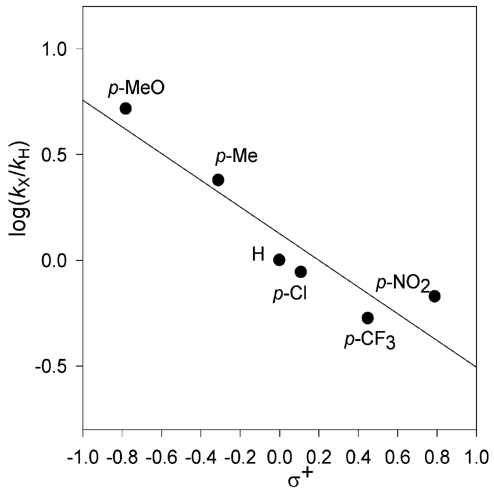
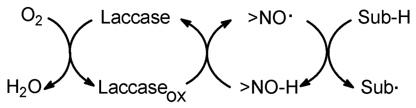


Fig. 3 Hammett plot for the reaction of 4-X-substituted *N*-benzylacetamides with BTNO in MeCN at 25 °C.

Kinetic isotope effect

The ratio of the rate constants for reaction of BTNO with $PhCH_2NHCOMe$ and $PhCD_2NHCOMe$ (in Table 1) gives k_H/k_D = 8.8. This sizeable value is consistent with a rate-determining H-abstraction step, and supports the contribution from tunnelling already commented on for reaction of either PINO or BTNO with various H-donors (k_H/k_D values in the 11–27 range).[6a,8b,9]

Both the ρ and k_H/k_D data (–0.65 and 8.8) obtained here with the CAN/HBT oxidizing system compare favourably with the corresponding ones (*i.e.*, –0.64 and 6.4, respectively) obtained in the oxidation of X-substituted benzyl alcohols by the copper enzyme laccase as the oxidant in the presence of HBT.[19] The close agreement provides clear-cut support to the involvement of the very >N–O• radical BTNO as the reactive intermediate in that kind of chemo-enzymatic oxidation, in keeping with the necessary monoelectronic oxidation of mediator HBT by laccase as outlined in Scheme 5.[14]



Scheme 5 The aerobic chemo-enzymatic oxidation of an H-donor substrate (Sub-H) by laccase with a >NO-H mediator.

Therefore, the present kinetic study corroborates our trust in the mechanism of the chemo-enzymatic oxidation by laccase and mediator compounds having the >NO-H functionality.[14]

Evaluation of the BDE(C-H) for the benzylic CH_2-group in $ArCH_2NHCOMe$

In the radical HAT route investigated here, the dissociation energy of the C–H bond undergoing cleavage, *i.e.* BDE(C-H), embodies a crucial reactivity feature.[1] Accordingly, the weaker the C–H bond the faster is expected the HAT route, either with BTNO or other radical species. We had corroborated this expectation by correlating the energies of activation of the BTNO-induced HAT route with an homologous series of benzylic substrates (alkylarenes and benzyl alcohols) *vs* the corresponding BDE(C-H) data according to the Evans-Polanyi equation ($E_a = \alpha$ BDE(C-H) + const).[9b] Unfortunately, not always are thermochemical data available in order to attempt a similar correlation and the ensuing rationalization of the reactivity trend. This in part is the case of the present study because BDE(C-H) data for amide substrates are scarce.[20]

What energy value could the benzylic C–H bond of Ph*CH₂*NHCOMe have? The k_H rate constant determined here (Table 1) for reaction of BTNO with $PhCH_2NHCOMe$ is 0.49 M^{-1} s^{-1}; the k_H determined under the same conditions for reaction of BTNO with $PhCH_2OH$ is very close in value (*i.e.*, 0.94 M^{-1} s^{-1}).[9b] Because we extrapolated a BDE(C-H) of 79 kcal/mol for $PhCH_2OH$,[9b] the corresponding BDE(C-H) of $PhCH_2NHCOMe$ ought to be pretty close in value. Strangely enough, the reactivity of BTNO with the benzylic C–H bond of the *amine* $PhCH_2NEt_2$, despite a reported BDE(C-H) of 89 kcal/mol,[20] was *too fast* to measure (> 100 M^{-1} s^{-1}) with our kinetic device.[9b] The BDE(C-H) of the latter compound is 10 kcal/mol *larger* than the extrapolated BDE(C–H) of $PhCH_2OH$, the k_H of which was slow enough to measure.[9b] Either our extrapolated BDE(C-H) of $PhCH_2OH$ is *too low*, or the literature value of BDE(C-H) for $PhCH_2NEt_2$ is *too high*!

In the attempt to settle this point, we have determined the activation parameters for reaction of BTNO with $PhCH_2NHCOMe$. The rate constants, measured in the temperature range of 12.5 to 49.8 °C according to the experimental procedure described above, are given in Table 2. From use of the Arrhenius equation ($\ln k_H = \ln A - E_a/RT$),[16] an E_a of 4.1 ± 0.2 kcal/mol is obtained. An analogous determination yields an E_a value of 3.1 ± 0.3 kcal/mol for reaction of BTNO with 4-MeO-$C_6H_4CH_2NHCOMe$ (Table 2).

By entering the newly acquired E_a value (*i.e.*, 4.1 kcal/mol) of Ph*CH₂*NHCOMe in the Evans-Polanyi plot already obtained for reaction of BTNO with a few benzylic substrates (Fig. 4),[9b] a BDE(C-H) of 71 kcal/mol can be extrapolated; analogously, for 4-MeO-C_6H_4*CH₂*NHCOMe (E_a of 3.1 kcal/mol) a BDE(C–H) of 68 kcal/mol is extrapolated. On *averaging* these two numbers, one gets 70 (±2) kcal/mol for the dissociation energy of these particular C–H bonds: this certainly represents a small BDE value, particularly when compared to the archetypal benzylic BDE(C-H) of 88.5 kcal/mol of toluene.[20] Such a conspicuous drop of C–H bond energy on going from $PhCH_3$ to $ArCH_2NHCOMe$, whatever the precision of our determinations is, is likely to be ascribed to the operation of stereoelectronic effects upon the amide substrate, as we comment on in the next section.

Actually, the issue could be even more complex than this, as a referee has correctly pointed out. First, we neglet the effect of the solvent when comparing kinetic data *vs.* BDE data. Hydrogen bonding between our solvent (MeCN) and substrates such as $PhCH_2NHCOMe$ or $PhCH_2OH$ can certainly affect the rate constants. However, the Evans-Polanyi plot of Fig. 4 shows good linearity for five substrates encompassing alkylarenes and benzylic alcohols, regardless their apolar or polar nature. Therefore, the hydrogen bonding issue provides only a partial explanation for the discrepancy between rate constants and BDE values stressed above. Secondly, we can not exclude that the high rate constant obtained[9b] for reaction of BTNO with $PhCH_2NEt_2$ is rather due to the incursion of a mechanism different from the HAT one. For example, the abstraction of electron (ET) by BTNO from the electron-rich $PhCH_2NEt_2$ could be alternatively envisioned. A similar ET route is documented for reaction of the aminoxyl radical PINO (0.92 V/NHE for the PINO/PINO- redox couple) with 4-X-substituted-*N*,*N*-dimethylanilines (redox potentials in the 0.5–1.1 V/NHE range), as reported recently.[1,21] Benzyl amines are however more difficult to remove an electron from (redox potentials > 1 V/NHE)[22] than anilines, and an ET route between BTNO and $PhCH_2NEt_2$ could be thought as less favoured. For sure, an ET route between BTNO and the present series of amides can be disregarded in view of redox potential considerations, as the one-electron oxidation of $PhNHCOCH_3$ has a redox potential >1.8 V/NHE.[23] Anyhow, we take the ET point as a sound suggestion, and work has already been planned in order to better investigate the boundaries of the ET/HAT dichotomy for reaction of aminoxyl radicals with benzylamines.

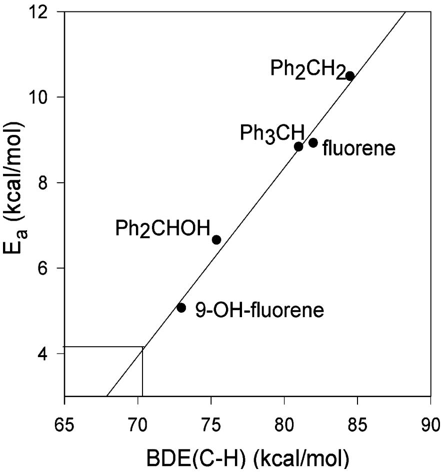


Fig. 4 Evans-Polanyi plot for reaction of BTNO with benzylic substrates (from ref. 9b), and extrapolation of the BDE(C-H) of Ph*CH₂*NHCOMe from the E_a value obtained (see text).

Table 2 Rate constants of H-abstraction for reaction of BTNO with two amides at various temperatures in MeCN solution. Typical errors are in the 3–5% range

$PhCH_2NHCOMe$		4-MeO-C_6H_4-$CH_2NHCOMe$	
k_H (M^{-1} s^{-1})	T (°C)	k_H (M^{-1} s^{-1})	T (°C)
0.364	12.5	0.72	12.7
0.393	18.1	—	—
0.490	25.0	0.80	25.5
0.680	41.3	1.13	38.5
0.832	49.8	—	—

Stereoelectronic effects

Griller *et al.*[11] have convincingly demonstrated that hyperconjugation from the lone-pair of a heteroatom weakens an adjacent C–H bond, and stabilizes an intervening C-radical generated by H-abstraction. The contribution from this weakening effect on the energy of an adjacent C–H bond is the greater the more co-linear are the C–H bond and the lone-pair,[11] as shown in Fig. 5 for the case of an amine.

This interaction reportedly accounts for a 7–9 kcal/mol weakening of the C–H bond.[12] For torsion angles (θ) wider than

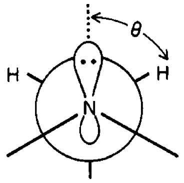


Fig. 5 Stereoelectronic interaction between the lone-pair of an amine and a C–H bond. Reprinted with permission from Griller *et al.* (ref. 11). Copyright (1981) American Chemical Society.

30°, the effect drastically fades away.[11] Our above finding of a substantial reduction of BDE(C-H) when passing from $PhCH_3$ (88.5 kcal/mol) to $PhCH_2NHCOMe$ (71 kcal/mol) is likely due to the stereoelectronic interaction from the nitrogen lone-pair of the amide with the scissile C–H bond.

Additional data obtained from specific substrates enable us to further address the stereoelectronic issue. In a previous synthetic investigation,[15] the oxidation of *N*-acetyl-tetrahydroisoquinoline by BTNO gave evidence for *exclusive* functionalization at C1, *i.e.*, at the C–H bonds α to nitrogen, to produce an imide compound (cf. Scheme 4 and Fig. 6. Our present kinetic data (Table 1) point out that H-abstraction from *N*-acetyl-tetrahydroisoquinoline is indeed *much faster* (*ca.* 20–40 fold) than from the structurally comparable but *acyclic* $C_6H_5CH_2NHCOMe$ or 4-Me-$C_6H_4CH_2NHCOMe$. Simple modelling with Hyperchem shows that in *N*-acetyl-tetrahydroisoquinoline the benzylic C–H bond of C1 is almost co-linear with *both* the p-orbitals of the aromatic ring *and* with the nitrogen lone pair (Fig. 6), being kept in this profitable conformation by steric restrictions caused by the heterocyclic system. This *double* beneficial effect is likely to weaken that C–H bond, as well as to stabilize the intermediate benzyl radical at C1 (Fig. 6). In the *acyclic* counterparts, instead, free rotation of the chain partially disrupts a similarly profitable conformation of the corresponding C–H bond, and lessens the extent of stabilisation of the intermediate radical ArCH(•)NHCOMe.

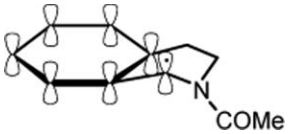


Fig. 6 Stabilising interaction from both the π-system and the nitrogen lone-pair to the C1 radical resulting from H-abstraction in *N*-acetyl-tetrahydroisoquinoline by BTNO.

As another example, the k_H rate constants of PhCH(Me)NHCOMe and $PhCH_2NHCOMe$ with BTNO (Table 1), when normalized for the number of equivalent H-atoms, are 0.11 and 0.24 M^{-1} s^{-1} respectively (or 0.46:1 in relative terms), thereby indicating an unfavourable contribution from the α-Me-substitution upon reactivity. In principle, H-abstraction from the secondary benzylic C–H bond of Ph*CH*(Me)NHCOMe ought to be easier and faster than for the primary C–H bond of PhCH_2NHCOMe. This is consistent with the relative reactivity of H-abstraction from $ArCH_2CH_3$ and $ArCH_3$ (normalised for the number of equivalent H-atoms)[9b] by BTNO, that is 4.2:1 (see also below), as well as with the BDE trend of a secondary *vs* primary benzylic C–H bond.[20] The specific unfavourable effect from α-Me substitution in PhCH(Me)NHCOMe offsets the expected easier cleavage of its secondary C–H bond, and accounts for an overall depression of the H-abstraction rate by *ca.* 9 fold (*i.e.*, 4.2/0.46). A plausible explanation for this unfavourable effect would be that PhCH(Me)NHCOMe is conformationally more stable (Fig. 7, left structure) whenever the larger groups in α, either Me- or–NHCOMe, are co-linear with the aromatic p-orbitals in order to lessen clash with the aromatic *ortho* C–H bonds.

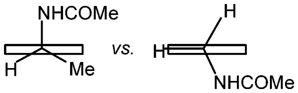
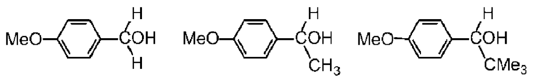


Fig. 7 Limiting conformations of PhCH(Me)NHCOMe and $PhCH_2$-NHCOMe. The section of the aromatic ring is represented as a rectangle.

Consequently, the benzylic C–H bond is preferentially directed in the ring plane, where any incipient α-amido carbon radical resulting from H-abstraction would not experience π-stabilisation. This is going to slow down the oxidation with respect to $PhCH_2NHCOMe$ (Fig. 7, right structure), where co-linearity of one α-C–H bond with respect to the plane of the aromatic ring is always feasible.

In order to support this conformational issue, the hydrogen abstraction rate constants by BTNO from a series of benzyl alcohols have been determined in MeCN at 25 °C, and are reported in Scheme 6.



k_H (M^{-1} s^{-1})	3.1	5.9	2.3
k_{rel}	1.0	1.9	0.74

Scheme 6 Absolute (normalised) and relative rate constants of H-abstraction by BTNO.

Once again, whereas abstraction of a secondary H-atom is 1.9 fold faster than that of a primary one, in keeping with the corresponding BDE values,[20] co-linearity of the *t*-Bu-group with the aromatic p-orbitals in the tertiary alcohol is preferred because lessens steric hindrance (cf. Fig. 7, left structure), thereby pushing the scissile C–H bond in the ring-plane where no π-stabilization is experienced, and resulting in a depression of reactivity ($k_{rel} = 0.74$).

Conclusions

The reciprocal orientation between a C–H bond undergoing cleavage and the lone pair of an adjacent heteroatom, or else an adjacent aromatic ring, emerges as an important structural feature upon the reactivity of an homolytic C–H cleavage, and is responsible for substantial weakening of the C–H bond energy. We have attempted to highlight these structural features upon the HAT reactivity of the aminoxyl radical BTNO with a few examples of amide substrates.

Experimental

Reagents

HBT (Aldrich) was used as received; most of the substrates were obtained commercially and used without further purification. A few starting amides were synthesized from the parent amines by conventional acetylation with Ac_2O in pyridine,[24] and characterised by NMR and GC-MS.[15] Cerium(IV) ammonium nitrate (CAN; Erba RPE) was oven-dried before use. Reagent grade acetonitrile (Erba RPE) was used as the solvent. *N*-Acetyl-α,α-bisdeuteriated benzylamine was obtained from $LiAlD_4$ reduction of $PhCONH_2$ to $PhCD_2NH_2$ in a 1:2 THF:diethyl ether mixed solvent, followed by acetylation.[24] The purity was checked by GC-MS.

Instrumentation

The kinetic study was carried out with a Hi-Tech SFA-12 stopped flow instruments, interfaced to a HP 8453 diode array spectrophotometer, and having a thermostated cuvette holder. A conventional UV-Vis spectrophotometer (Perkin Elmer Lambda 18) was alternatively used. A thermocouple was employed for reading the temperature in the cuvette.

Kinetic Procedure

The BTNO species was generated in MeCN in a thermostated quartz cuvette, by adding a 0.5 mM solution of CAN to a 0.5 mM solution of HBT. A broad absorption band developed almost immediately (15 ms) in the 350–600 nm region (λ_{max} at 474 nm, ε 1840 M^{-1} cm^{-1}).[9] The A_{474} reading was not stable, but decayed with a half-life of *ca.* 140 s. The rate of decay was unaffected by the use of deareated MeCN. Rate constants of H-abstraction from H-donor substrates were determined at 25 °C in MeCN (Table 1), by following the decrease of the A_{474} band of BTNO. The initial concentration of the substrate was in the 0.5– to –4 × 10^{-2} M range, so to enable a pseudo-first-order treatment of the kinetic data. Plots of (A_t-A_∞) *vs* time were well fitted by a first-order exponential over more than three half-lives and pseudo-first-order rate constant (k') reckoned. From a plot of three-to five k' *vs* [subst]° data pairs, the second-order rate constant of H-abstraction (k_H) was obtained. Determination of H-abstraction rate constants was analogously carried out at different temperatures (in the 13–50 °C range) for $PhCH_2NHCOMe$ and 4-MeO-$C_6H_4CH_2NHCOMe$ (Table 2), for the calculation of the activation parameters from the Arrhenius plot.

Semiempirical calculations

The structure of a few substrates has been optimized by a semiempirical method (PM3 level) on using the Hyperchem program.

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