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Stereoelectronic effects in radical processes†

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ABSTRACT: A kinetic study of the H-abstraction reaction from cyclic and acyclic alkylarene substrates by the nitroxyl radical (dubbed BTNO) of 1-hydroxy-benzotriazole (HBT) has been carried out in MeCN solution at 25 °C. BTNO was generated from one-electron oxidation of HBT by cerium(IV) ammonium nitrate. The H-abstraction reactivity measured with the cyclic alkylarenes is invariably higher than that with the acyclic counterparts. This is explained as the contribution of hyperconjugation between the aromatic π-system and the scissile benzylic C—H bond of the substrate, which weakens the C—H bond in the transition state and promotes its cleavage. Stereoelectronic considerations enable to appreciate why the weakening effect is more pronounced in the cyclic system than in the acyclic counterpart, thereby justifying the higher reactivity of the former. Evidence for the intervention of stereoelectronic effects is embodied by the dissociation energies of the C—H bonds, having always lower values for the cyclic substrates investigated. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: nitroxyl radicals; HBT; mechanisms; kinetic study; bond dissociation energies; activation parameters

INTRODUCTION

Hydroxylamines (>N—OH) as precursors of nitroxyl radicals (>N—O·) have recently gained considerable attention. For example *N*-hydroxy-phthalimide (HPI), in combination with O_2 and co-catalysts like $Co(OAc)_2$ or $Co(acac)_2$, provides a remarkable catalytic system for the oxidation of appropriate organic compounds.[1,2] The key reactive intermediate is the phthalimide-*N*-oxyl radical (PINO), formed in the preliminary interaction of HPI with O_2 and the Co(II) salt.[1–3] PINO removes H-atom from C—H bonds endowed with suitable bond energy, in substrates like alcohols, alkylarenes, amides and even alkanes, oxidizing them under mild conditions. The synthetic value of the procedure has prompted studies on the reactivity features of PINO, as well as of other nitroxyl radicals.[3–6]

We have recently reported on the generation of the >N—O· species originating from 1-hydroxybenzotriazole (HBT) through monoelectronic oxidation with cerium(IV) ammonium nitrate (i.e., CAN) in MeCN solution (Scheme 1),[7] and dubbed it BTNO (i.e., benzotriazole nitroxyl radical). Characterization of BTNO by EPR, laser flash photolysis and cyclic voltammetry has been described,[7a] and rate constants of H-abstraction by BTNO from a number of H-donor substrates (RH) determined at 25°C in MeCN solution by a spectroscopic survey.[7b]

We report here kinetic data for the reaction of BTNO with H-donors having cyclic structure, and compare them with the corresponding data of the open-chain counterparts. Relevant enthalpic data and stereoelectronic considerations will enable to comment on peculiar structure-reactivity findings.

RESULTS

The kinetic system has already been described.[7] Briefly, the nitroxyl radical BTNO is generated in a spectrophotometric cuvette by adding a solution (0.5 mM) of the one-electron oxidant CAN to a solution (0.5 mM) of precursor HBT, both being dissolved in MeCN. The broad absorption band of the nitroxyl radical develops almost immediately (15 ms) in the 400–600 nm region, having λ_{max} at 474 nm and ϵ 1840 M^{-1} cm^{-1}.[7] Fast addition by syringe of a solution of the C—H bearing substrate (RH), enough to make an initial concentration 10–50 times higher than that of BTNO, marks the beginning of the kinetic experiment. The progress of the radical H-abstraction process is monitored at 474 nm and 25°C by stopped-flow or conventional spectrophotometers, half-lives ranging from 30 ms to tenths of seconds. The pseudo first-order rate constants k', determined at three-to-four initial concentrations of RH, are converted into second-order rate constants k_H, and normalized for the number of equivalent hydrogen atoms (Table 1). Uncertainty of the kinetic determinations, from at least duplicated experiments, is typically 3% but it may reach 10% for the

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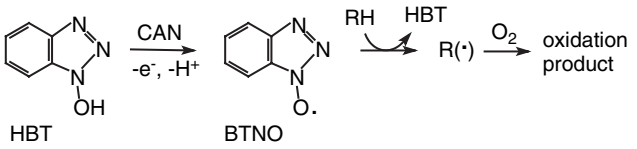
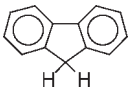
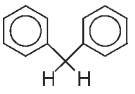
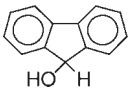
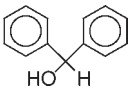
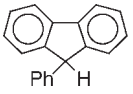
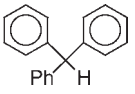
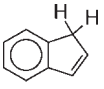
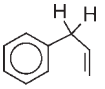
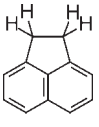
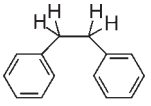


Scheme 1

slower compounds. In addition to the cyclic substrates, the open-chain structural counterparts are also studied, and the *Cyclic*/*Open* reactivity ratio is reckoned.

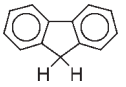
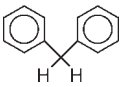
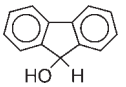
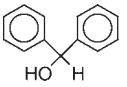
In the previous kinetic study, the activation parameters for H-abstraction by BTNO from some RH substrates have been determined.[7b] Consequently, the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ data for a few of the *Cyclic versus Open* substrate pairs of Table 1 are available, and reported in Table 2. Unfortunately, activation parameters for the remaining pairs of Table 1 could not be measured, because the reaction rates are too fast above 25°C, or else too slow to enable a clear-cut investigation with respect to the competing spontaneous decay of the BTNO reactive intermediate.[7]

Table 1. Normalized second-order rate constant k_H (in $M^{-1}\,s^{-1}$) of H-abstraction from H-donor substrates by BTNO at 25°C in MeCN. Literature BDE(C–H) data of the substrates (from Ref. 8) are given in kcal/mol

Cyclic	Open-chain	*Cyclic*/*Open* relative reactivity[a]
		
$k_H = 1.9$ BDE(C–H) = 82	$k_H = 0.36$ BDE(C–H) = 85	5.3
		
$k_H = 10$ BDE(C–H) = 73	$k_H = 3.2$ BDE(C–H) = 76	3.1
		
$k_H = 18$ BDE(C–H) = 74	$k_H = 2.3$ BDE(C–H) = 81	7.8
		
$k_H = 45$ BDE(C–H) = 82	$k_H = 2.3$ BDE(C–H) = 84	20
		
$k_H = 1.3$ BDE(C–H) = 84	$k_H = 0.04$ BDE(C–H) = 87	35

[a] The rate constants have a ± 3% experimental error, and the *Cyclic*/*Open* ratios must be taken with a 10% confidence limit.

Table 2. Activation parameters for two of the substrate pairs of Table 1 (from Ref. 7b)

Substrate (RH)	$\Delta H^{\neq}$ (kcal/mol) (±0.15)	$\Delta S^{\neq}$ (eu) (±1)
	8.3	−29
	10	−26
	4.5	−38
	6.0	−36

DISCUSSION

The data of Table 1 show a uniformly higher reactivity of the cyclic substrates in reaction with BTNO, when compared with their open-chain counterparts. The *Cyclic*/*Open* relative reactivity ranges from 3 to 35 folds, by taking into account the experimental uncertainty. In a radical process, such as the present H-abstraction reaction, the reactivity of a series of substrates is expected to reflect the trend of energy of the C—H bonds undergoing cleavage in the rate determining step.[3,4a,7b] Previous evidence enables to confirm the C—H cleavage as rate determining in reaction of BTNO, and a linear Evans–Polanyi correlation of E_a *versus* BDE(C—H) has been obtained for a series of H-donors, with slope $\alpha = 0.44$.[7] Therefore, a substantial extent of H-abstraction takes place in the transition state and, consistently, the *Cyclic*/*Open* relative reactivity does reflect BDE(C—H) data of the substrates (in Table 1)[8] significantly. Although this correlation between reactivity and thermochemical data is reasonable and expected, less predictable is the finding that the experimental BDE(C—H) values differ considerably between the cyclic and acyclic partner in each pair of substrates, in spite of the otherwise very comparable structure, all being in fact benzylic derivatives. Where does this difference in the enthalpic BDE(C—H) data come from? Is it due to stereoelectronic effects?

In the investigated cyclic substrates, the scissile benzylic C—H bond is almost collinear with the

p-orbitals of the aromatic system, due to the planarity of the strainless five-membered ring. This is likely to weaken the C—H bond as a consequence of the favorable interaction with the π-cloud (hyperconjugation); moreover, the benzylic radical in formation will enjoy optimal mesomeric stabilization with the aromatic system. Both these features are bound to make the H-abstraction easier. In the acyclic counterparts, in contrast, free rotation between the aromatic ring(s) and the benzylic CH_2 (or CH) group prevents an equally significant contribution from hyperconjugation. As a consequence, normal BDE(C—H) values ensue, and no special acceleration to the H-abstraction results.

The *Cyclic*/*Open* kinetic difference reported in Table 1 and the explanation we provide for it, is supported by the activation parameters of two specific substrate pairs given in Table 2. The $\Delta H^{\neq}$ for the reaction of the acyclic diphenylmethane with BTNO is 1.7 kcal/mol *higher* than that of its cyclic counterpart fluorene, and a similar $\Delta\Delta H^{\neq}$ of 1.5 kcal/mol is found between the open 1,1-diphenylmethanol and the cyclic 9-fluorenol. Since there is a ΔBDE(C—H) of 3 kcal/mol between diphenylmethane and fluorene, and a ΔBDE(C—H) of 2 kcal/mol between 1,1-diphenylmethanol and 9-fluorenol, it follows that a sizeable fraction of these ΔBDE(C—H) is reflected as $\Delta\Delta H^{\neq}$ for the two pairs, in keeping with the sizeable Evans–Polanyi's α value for H-abstraction by BTNO.[7b] Hence, the *Cyclic*/*Open* kinetic difference is basically an enthalpy-dependent feature, and stems from a hyperconjugative effect that weakens the scissile benzylic C—H bond of the cyclic substrate with respect to the acyclic counterpart. No difference in $\Delta S^{\neq}$ values, in fact, emerges between the cyclic and acyclic substrate in each pair, within the experimental errors.

In conclusion, in acyclic compounds the conformation where the scissile benzylic C—H bond is aligned with the π-system (Fig. 1, left), and thus suitably weakened for H-abstraction, is disfavored by the unfavorable enthalpic interactions of any *a* substituent with the aromatic ring. The bulkier *a*, the more this conformation will be disfavored with respect to the other (Fig. 1, right), where the encumbered substituent is hosted above the ring plane, but H-abstraction is not assisted by hyperconjugation.

Stereoelectronic considerations similar to those described here have been previously proposed in order to rationalize reactivity findings in the deprotonation of radical cations of alkylarenes generated by monoelectronic oxidation. Loss of H^+ from aromatic radical cations requires eclipsing of a benzylic C—H bond with the ring π orbitals (see Fig. 1) so that electron shift from the C—H bond to the π-system and concurrent benzylic deprotonation takes place with regain of aromaticity. Because bulky *a* substituents are more conveniently hosted as indicated in the right part of Fig. 1, this conformation prevents deprotonation. Arnold,[9] Baciocchi,[10] and Tolbert[11] have brought several examples on this point. The most recent one is a kinetic (pulse radiolysis) and product study by Bietti *et al.*[12] on the side-chain fragmentation of the radical cation of a cyclic compound. This occurs through cleavage of the benzylic C—H bond, whereas in the open-chain counterpart exclusive C—C bond cleavage takes place. This is a remarkable example of the relevance of stereoelectronic effects on gearing the competition between product-determining routes in an electron-transfer process. Stereoelectronic effects were surely considered of relevance upon the reactivity features of electron-deficient species, such as the radical ions. Our present study shows that even in the case of simple covalent precursors stereoelectronic effects can influence the reactive behavior appreciably.

Figure 1. Left: conformation more suitable to H-removal. **Right**: conformation less sterically hindered. The plane of the aromatic ring is represented as a rectangle

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