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Short Communication

A radical route in the biomimetic oxidation of a tertiary amine

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ABSTRACT: Whereas the biomimetic oxidative *N*-dealkylation of tertiary amines with *t*-BuOOH and an iron(III) tetraphenylporphyrin typically proceeds by an electron transfer (ET) route, a radical H-atom transfer (HAT) route has been found to operate with *N*-benzylaziridine (1), an amine that is fairly resistant towards one-electron oxidation for steric reasons. New mechanistic information is presented in favour of this radical route, and the exclusive formation of the dimeric product *N*,*N*′-dibenzylpiperazine (2) is explained in the light of the Baldwin's rules. Flash photolysis data provide a rate constant of 1.7×10^5 s^{-1} for the ring opening of the aziridine radical ($1^{\cdot}$) to the imine radical ($4^{\cdot}$) in the early stages of the process leading to 2. Semiempirical calculations indicate the ring-opened radical $4^{\cdot}$ to be more stable than $1^{\cdot}$. Copyright © 2002 John Wiley & Sons, Ltd.

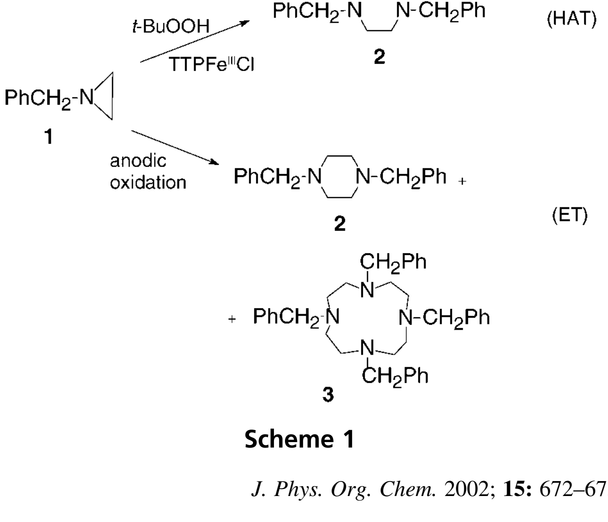
KEYWORDS: oxidation: hydrogen abstraction; aziridines; ring closure; flash photolysis

INTRODUCTION

Among the reactions catalysed by monoxygenase enzymes, such as cytochrome P450, the oxidative *N*-dealkylation of tertiary amines is receiving continuous interest.[1] Metalloporphyrins, as model compounds of cytochrome P450, also catalyse this important process.[2] Consensus has been reached for an electron transfer (ET) character of the mechanism of this *N*-dealkylation,[1,3] as shown by recent evidence presented also by our group.[4] In contrast, in the case of the biomimetic reaction of tertiary amine *N*-benzylaziridine (**1**) with the system *t*-BuOOH–TPPFe^{III}Cl [where TPPFe^{III}Cl stands for iron(III) tetraphenylporphyrin chloride] as the oxidant, a radical hydrogen atom transfer (HAT) mechanism appears to be responsible for the formation of a dimeric compound, *N*,*N*′-dibenzylpiperazine **2** (Scheme 1),[5] in yields ranging from 5 to 60% depending on the conditions, but in all cases performed with a defect of the oxidant.

It was possible to suggest the operation of the HAT route on the basis of the observation that an independent reaction of **1** under *bona fide* HAT conditions gave only dimer **2**, whereas reaction of **1** under *bona fide* ET conditions (e.g. anodic oxidation) gave both dimer **2** and tetramer **3**.[5] This distinction has been commented upon,[5] and the lack of tetramer **3** is accordingly considered as the key evidence in favour of the radical route of Scheme 2 for the biomimetic reaction of **1**.[5,6]

The initiation of this process has been ascribed to the formation *t*-BuO$^{\cdot}$ from the *t*-BuOOH–TPPFe^{III}Cl system; *t*-BuO$^{\cdot}$ then removes a benzylic hydrogen from the substrate. Indeed, *N*-benzylaziridine **1** is a more difficult substrate to oxidize ($E^{P} = 1.7$ V vs SCE)[5,7] in one-electron processes with respect to normal tertiary amines (0.7–0.9 V vs SCE), owing to the steric constraint of the three-membered ring, and in agreement with the IP^{v} data determined by photoelectron spectroscopy.[8] On this basis, the occurrence of a radical HAT route appears reasonable. This proposition is also consistent with the



Scheme 1

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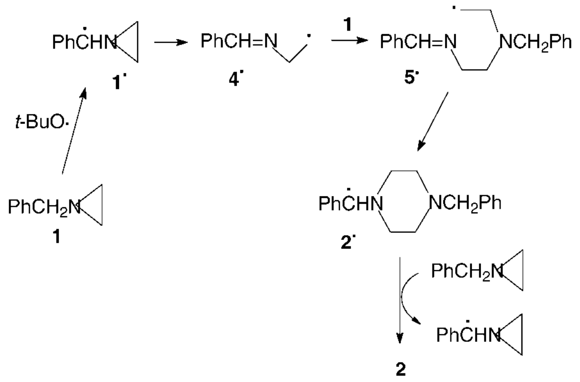


Scheme 2

operation of a HAT route with substrates that are more difficult to oxidize than simple tertiary amines, such as the alkanes in *C*-hydroxylation reactions or the ethers in *O*-dealkylation reactions, catalysed by cytochrome P450 or metalloporphyrins.[1a,9]

In order to offer further support for the HAT mechanism outlined in Scheme 2, we have studied the kinetics of some of the reactive steps leading from **1** to the formation of dimer **2** by using the laser flash photolysis technique.

RESULTS

Flash photolysis experiments

The radical HAT mechanism (Scheme 2) should be triggered by H-abstraction from **1** to give the benzylic radical $\mathbf{1}^{\cdot}$.[5] It therefore appeared crucial to generate $\mathbf{1}^{\cdot}$ unambiguously, and to follow its dynamic evolution. To this end, t-BuO$^{\cdot}$ was generated by means of laser flash photolysis by the photoinduced cleavage of (t-BuO)$_2$ (Scheme 3).[10]

$$(t\text{-BuO})_2 \xrightarrow{h\nu} 2\ t\text{-BuO}\cdot$$

$$t\text{-BuO}\cdot + \mathbf{1} \rightarrow t\text{-BuOH} + \mathbf{1}\cdot$$

Scheme 3

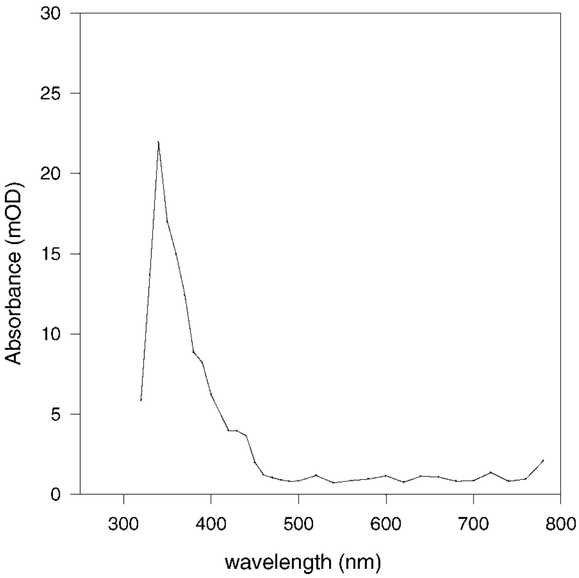
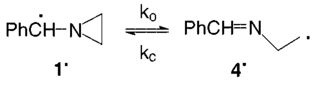


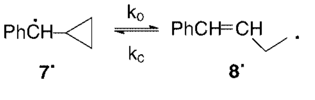
Figure 1. Absorption spectrum of the $1^{\cdot}$ species, following photolysis in neat (t-BuO)$_2$

A solution of **1** in neat (t-BuO)$_2$ was argon purged and irradiated at 308 nm, and spectra were recorded. A transient species was characterized by a maximum of absorbance at $\lambda = 340$ nm (Fig. 1); it disappeared with a rate constant of $1.7 \times 10^5\ \mathrm{s}^{-1}$ at 25 °C. The lifetime of this transient species was shorter in the presence of dissolved molecular oxygen, which is known to act as a radical scavenger.[11] Based on the similarity with the reported absorbances of benzylic radicals,[12] and on the sensitivity of this transient species to molecular oxygen, we assign it to the benzylic radical $\mathbf{1}^{\cdot}$. In fact, a selective H-abstraction from the benzylic bond of **1** is expected, the *tert*-butoxide radical (t-BuO$^{\cdot}$) being known to undergo efficient H-atom abstraction reaction with benzylic hydrogens; see, for example, Ref. 13), if one compares the bond dissociation energy, *BDE*(C—H), of 89 kcal mol^{-1} for this benzylic bond with those of other C—H bonds in the molecule of **1** (ca 110–113 kcal mol^{-1}) (1 kcal = 4.184 kJ) (for related *BDE* data, see Ref. 14). In order to confirm this conclusion, we synthesized *N*-phenylaziridine **6**, which does not contain benzylic bonds but only strong aromatic or vinyl-like C—H bonds,[8] and subjected it to the same flash photolysis experiment. At variance with **1**, **6** did not show any UV absorption band, nor did it react.

We suggest that the observed unimolecular decay ($k = 1.7 \times 10^5\ \mathrm{s}^{-1}$) of radical $\mathbf{1}^{\cdot}$ is associated with the ring-opening process of the aziridine to the imine radical $\mathbf{4}^{\cdot}$, with the consequent loss of the benzylic chromophore ($\lambda_{\max} = 340$ nm), in analogy with the reported benzyl radical ⇌ homoallyl radical rearrangement of benzylcyclopropane ($7^{\cdot}$ and $8^{\cdot}$, respectively) [Eqns (1) and (2)].[15]



(1)



(2)

The ring-opening rate constant (k_0) of $7^{\cdot}$ had previously been evaluated to be less than $2 \times 10^5\ \mathrm{s}^{-1}$ at 42 °C, and equilibrium (2) was reported to be shifted to the left, owing to a k_c of $1.2 \times 10^7\ \mathrm{s}^{-1}$.[15]

As further support for our interpretation, the formation of radical $\mathbf{2}^{\cdot}$ was obtained under the same flash photolysis conditions reported above for **1**$^{\cdot}$. Once again, a transient species with an absorbance maximum at $\lambda = 340$ nm was recorded, the lifetime of which was shortened by molecular oxygen, both evidence pointing to the generation of a benzylic radical. In this case, however, the rate of disappearance of the transient species was more than 20 times *slower* than that of **1**$^{\cdot}$, and equal to 5.4×10^3 s^{-1} at 25 °C. We had previously generated **2**$^{\cdot}$ from **2**, and verified that **2**$^{\cdot}$ does not undergo ring opening to **5**$^{\cdot}$ but gives rise to PhCHO and *N*-benzylpiperidine (see footnote 22 in Ref. 5). We conclude that the recorded unimolecular decay pertains to this fragmentation of intermediate **2**$^{\cdot}$, which is slower than that of **1**$^{\cdot}$ because it lacks the driving force due to the cleavage of a strained three-membered ring.

Semiempirical calculations

Semiempirical calculations were performed for the structures involved in equilibria (1) and (2) by employing the MOPAC package,[4b] and the heats of formation of radicals **1**$^{\cdot}$, **4**$^{\cdot}$, **7**$^{\cdot}$ and **8**$^{\cdot}$ were obtained by MNDO. Rather than the absolute values of the heats of formation, the values of $\Delta\Delta H_f$ for equilibria (1) and (2) are given: ΔH_f (**1**$^{\cdot}$) $-$ ΔH_f (**4**$^{\cdot}$) = 2.89 kcal mol^{-1} and ΔH_f (**7**$^{\cdot}$) $-$ ΔH_f (**8**$^{\cdot}$) = -3.40 kcal mol^{-1}. Whereas for benzylcyclopropane the ring-opened homoallyl structure **8**$^{\cdot}$ is *less* stable than the cyclic structure **7**$^{\cdot}$, the opposite is true with aziridine **1**. The ring-opened structure **4**$^{\cdot}$ being more stable, equilibrium (1) results substantially shifted to the right (at least 100:1); conversely, and in agreement with the literature,[15] equilibrium (2) turns out to be shifted to the left.

DISCUSSION

The present results lend support to a reaction mechanism that has already been reported (Scheme 2),[5] and also offer new insight. Abstraction of an H-atom from the benzylic group of **1** leads to **1**$^{\cdot}$ and evidence for the formation of this reactive intermediate has now been obtained by flash photolysis experiments. This evidence supports our assumption that an H-atom abstraction process takes place from **1** with the system *t*-BuOOH–TPPFe$^{\text{III}}$Cl, following the formation of *t*-BuO$^{\cdot}$ according to Eqn. (3).[5]

$$t\text{-BuOOH} + \text{TPPFe}^{\text{III}} \rightarrow t\text{-BuO}\cdot + \text{TPPFe}^{\text{IV}}\text{-OH} \qquad (3)$$

The benzylic radical **1**$^{\cdot}$ then undergoes ring opening to the imine radical **4**$^{\cdot}$ [see Eqn. (1)]. A rate constant for this unimolecular process has been obtained, and calculations confirm that equilibrium (1) is shifted to the right. Addition of radical **4**$^{\cdot}$ to a molecule of **1** (present in large excess) gives rise to radical **5**$^{\cdot}$. A radical ring-closure addition to the imine moiety can then occur in a 6-*exo-trig* step, according to Baldwin's rules.[16] This is an intramolecular fast step, so that any bimolecular addition step of radical **5**$^{\cdot}$ to other molecules of **1**, that ought to lead to oligomerization and eventually to the cyclic tetramer **3** (Scheme 1), cannot reasonably compete, in agreement with the experimental findings.[5] This is the reason why the *exclusive* reaction pathway of **5**$^{\cdot}$ is cyclization to **2**$^{\cdot}$ (Scheme 1). The HAT process terminates with the formation of **2**, coupled with the generation of additional **1**$^{\cdot}$, thereby explaining yields of **2** that may exceed 100% with respect to the oxidant.[5]

EXPERIMENTAL

General. *tert*-Butyl peroxide was commercially available (Aldrich) and used as received. The synthesis of compounds **1** and **2** has been reported.[4b,5]

*Synthesis of N-phenylaziridine **6**.* This compound was obtained in a 35% yield according to a multistep reaction;[17] b.p. 47–49 °C at 2–3 Torr (lit.[17c] 60–61 °C at 9 Torr) (1 Torr = 133.3 Pa).

Laser flash photolysis. Nanosecond laser plash photolysis experiments were carried out using an excimer (Lambda Physik Lextra 50, XeCL, 308 nm) pumped dye laser (Lambda Phisyk LPD 3002, 7 ns pulse width) as the excitation source. Tuning of the excitation wavelength was possible through a dye laser chamber (Lambda Physik). Transient absorptions were monitored at right-angles to the excitation with a conventional xenon lamp, monochromator, photomultiplier tube arrangement. The excitation beam energy was typically attenuated to less than 2–3 mJ per pulse, and appropriate long-pass filters were placed on either side of the sample to prevent photolysis by the analysing light.[18]

Transient spectra of radicals. In a typical experiment, a quartz cuvette equipped with a Teflon stopcock was charged with 1.9 ml of a solution of the substrate (0.05–0.1 M) in neat *tert*-butyl peroxide. The solution was purged with the appropriate gas and excited at 308 nm and the spectrum collected.

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