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Singlet Oxygen Mediated Alkaloid Tertiary Amines Oxidation by Single Electron Transfer

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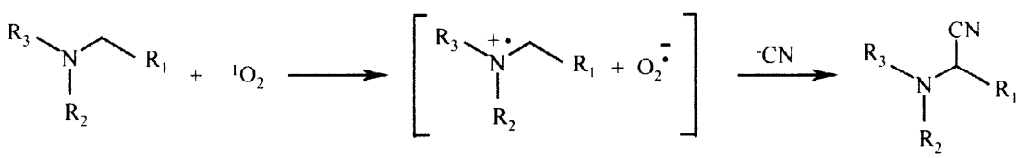
Abstract : A chemical study of the oxidation of tertiary amines and alkaloids through monoelectronic transfer is presented and allows us to assign to singlet oxygen a new behavior as electron acceptor during the oxidation process. © 1998 Elsevier Science Ltd. All rights reserved.

Singlet oxygen and electron-transfer-initiated photoxygenations have gained considerable attention in recent years[1,2]. This interest is all the more increasing that it is now well established that singlet oxygen is responsible for photodynamic destruction of both commercially and biologically important molecules.

More particularly, singlet oxygen has been shown to be able to induce DNA[3] damage and to be mutagenic. But nevertheless, singlet oxygen is also used for the treatment of certain tumors by photodynamic therapy[4]. As a consequence, it is of some practical importance to search for and to investigate oxidation mechanisms initiated by singlet oxygen.

In the early seventies, Mazur[5] and Foote[6] first suggested the possibility of direct electron transfer from substrate to singlet oxygen yielding substrate radical cation and superoxide. Those substrates include phenols[7], sulfides[8], amines[9,10], enamines[6], azines[11] and azide anions[12]. It has also been suggested that mitochondorial components such as NADH and cytochrome *c* are able to transfer one electron to singlet oxygen giving rise to $O_2^{\cdot-}$[13]. However, direct evidence for the formation of superoxide anion ($O_2^{\cdot-}$) has not been obtained for either the reaction or the quenching process. The radical cation $O_2^{\cdot-}$ pair would be short-lived because of the rapid reverse electron-transfer and chemical reaction within the cage.

We now report a non-ambiguous singlet oxygen oxidation of some alkaloid tertiary amines (Figure 1) by single electron transfer (Scheme 1).



Scheme 1

In our attempts to determine the intervention of $O_2^{\cdot-}$ formed in such reactions, we used a chemical $^1O_2$ source. Actually, the use of a photochemical $^1O_2$ source produces many reacting intermediates able to generate

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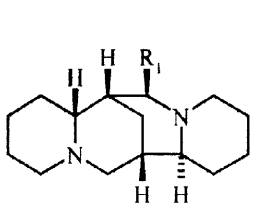
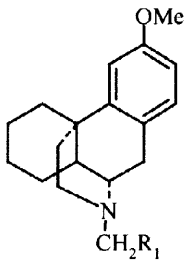
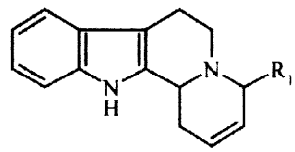
superoxide anion. But then, it is difficult to assign the formation of superoxide anion to only the reaction of singlet oxygen with the amine.



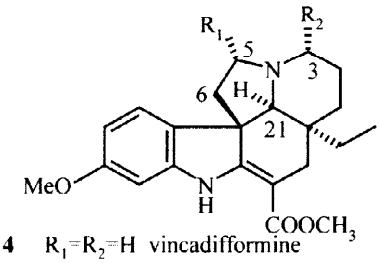
1 R_1=H sparteïne
1a R_1=CN 17b-cyanosparteïne



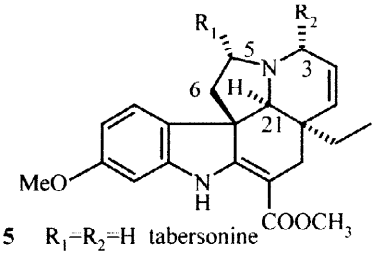
2 R_1=H dextromethorphan
2a R_1=CN *N*-cyanomethyl-dextromethorphan



3 R_1=H indoloquinolizidine
3a R_1=CN 17-cyanoindolo-quinolizidine



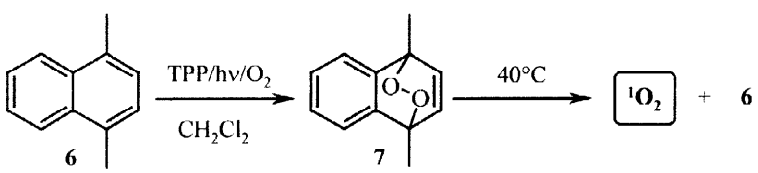
4 R_1=R_2=H vincadifformine
4a R_1=CN; R_2=H 5a-cyanovincadifformine
4b R_1=H; R_2=CN 3a-cyanovincadifformine



5 R_1=R_2=H tabersonine
5a R_1=CN; R_2=H 5a-cyanotabersonine
5b R_1=H; R_2=CN 3a-cyanotabersonine

Figure 1: various alkaloid tertiary amines oxidized by singlet oxygen

Various types of chemical $^1O_2$ sources have thus far been reported. Among them 1,4-dimethylnaphtalene endoperoxide is known to release $^1O_2$ under very mild conditions[1] (Scheme 2).



Scheme 2

5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) sensitized photooxygenation of **6** in dichloromethane at room temperature gave the corresponding 1,4-dimethylnaphtalene endoperoxide **7** in quantitative yield. Under dichloromethane reflux, the endoperoxide **7** produced the parent 1,4-dimethylnaphtalene **6** with liberation of $^1O_2$, in approximately 50% yield.

In a typical procedure, a previously degassed solution of tertiary amine **1-5** (0.8 mmol) with trimethylsilyl cyanide (TMSCN) (2 mmol, 2.5 eq.) as cyanide ion source, in 20 mL of dichloromethane, was refluxed gently under a nitrogen atmosphere in the presence of 1,4-dimethylnaphtalene endoperoxide **7** (8 mmol, 10 eq.). The organic layer was washed three times with a 10% sodium carbonate solution (20 mL). The combined organic layers were dried over anhydrous ammonium sulfate. After solvent removal under vacuum, the crude product **1a-5a, 4b, 5b** was purified by filtration on aluminium oxide using hexane and then toluene as the eluants. The results are summarized in Table 1.

Table 1

Substrate	Product	Yield (%)
1 R_1=H sparteïne	**1a** R_1=CN 17β-cyanosparteïne[14]	92
2 R_1=H dextromethorphan	**2a** R_1=CN *N*-cyanomethyldextromethorphan[14]	77
3 R_1=H indoloquinolizidine	**3a** R_1=CN 17-cyanoindoloquinolizidine	50*
4 R_1=R_2=H vincadifformine	**4a** R_1=CN; R_2=H 5α-vincadifformine[14-16]	75
	4b R_1=H; R_2=CN 3α-vincadifformine[16]	**4a:4b** 7:3
5 R_1=R_2=H tabersonine	**5a** R_1=CN; R_2=H 5α- tabersonine[17]	77
	5b R_1=H; R_2=CN 3α- tabersonine[15,16]	**5a:5b** 1:1

* : Similar yield was obtained when the reaction was performed in acetonitrile.

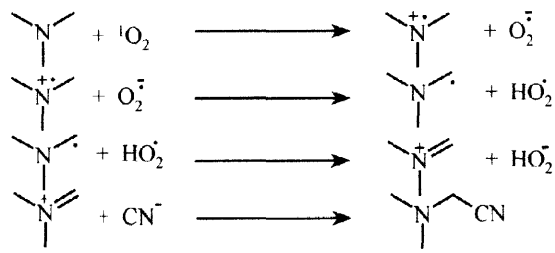
The structures of the products were fully ascertained by complete spectroscopic determination (MS, IR, UV, NMR spectra, ^1H, ^{13}C, homonuclear and heteronuclear correlation, and NOE difference experiments). All products, except 5α-cyanotabersonine **5a**, were also identified by comparison with authentic samples previously synthesized in our laboratory by a photooxidation process[14-16]. The structure of the new product **5a** was unambiguously established considering for example the following arguments:

- As the H_β-5 signal is a doublet at 4.13 ppm for **4a**, a similar signal is observed for **5a**. Selective irradiation of this signal showed disappearance of coupling constant of H-6 signal at 2.19 ppm.
- Carbon atoms C_5 and C_6 in **5a** are less shielded than in **4**, due to α,β inductive effects.
- Carbon atoms C_3 and C_{21} in **5a** are significantly more shielded than in **4**, due to steric effects.

These experimental results indicate that both excited singlet oxygen and superoxide anion are sequentially involved as critical intermediates in tertiary amine clean oxidation. Effectively, the regio- and stereoselectivity of these reactions are identical to those specifically obtained by photooxidation, known to proceed by a single electron transfer mechanism.

Such a selectivity during the oxidation process can be explained by the selectivity of the iminium radical cation deprotonation by superoxide anion. A stereoelectronic control, as proposed by Lewis[18], can explain the formation of 17β-cyanosparteïne **1a**. The oxidation of dextromethorphan **2** illustrates the selective deprotonation of the smaller substituant (CH_3>CH_3-CH_2>$CH(CH_3)_2$) leading to the formation of **2a**. Oxidation of the 1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine **3** shows the leaving of the more acidic proton (allylic proton). The low regioselectivity observed in the oxidation of the pyrrolidinic ring in vincadifformine **4** is due to the high basicity of superoxide anion and the weak stereoelectronic difference of the carbon atom positions C_3 and C_5. The well known easy oxidation of the pyrrolidinic ring[19], due to stereoelectronic and steric effects, and the easy deprotonation of the high acidic allylic protons explain the lack of regioselectivity in the tabersonine **5**.

Moreover in our current experimental conditions, the only oxidizing species is the excited singlet oxygen. We therefore propose the following reaction mechanism (Scheme 3).



Scheme 3

The first and key step is an electron transfer between the tertiary amine and the oxidizing singlet oxygen. Since superoxide is indicated to be quite basic, it can deprotonate the relative acidic proton of the methylide iminium radical cation. The α-aminated carbon radical generated is a strongly reducing species. Therefore, it is rapidly oxidized by a second electron transfer leading to an iminium cation. As previously shown in our studies, this cation is efficiently trapped under mild conditions to give the relatively stable α-aminonitrile[14,15].

These results contrast with those described in the literature by Foote[20] and Inoue[21,22]. They have reported that single electron transfer between electron donor and singlet oxygen only occured with rich electron donors such as tetramethylphenylenediamine (TMPD) or with substrates such as aromatic amines with oxidation potential less than 0.5 V. Furthermore, this electron transfer required very polar media and proceeded exclusively in aqueous media.

In summary, our results demonstrate the feasibility of an electron transfer mechanism in organic media of low polarity. Singlet oxygen, and subsequently superoxide anion, appear to be powerful, selective and efficient oxidizing reagents for tertiary amines and particularly for fragile alkaloids.

References and Notes

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17. **5a.** amorphous ; $C_{22}H_{23}N_3O_2$ M=361 ; IR film 3360, 2950, 2220, 1730, 1610 cm^{-1} ; MS 362 (MH^+, 100), 335 (100), 221 (24), 91 (26), 74 (18); ^1H NMR (200 MHz, $CDCl_3$, δ) 8.97 (s, 1H, N_aH), 7.32 (m, 1H, H-9), 7.18 (m, 1H, H-11), 6.91 (m, 1H, H-10), 6.84 (m, 1H, H-12), 5.95 (dd, 1H, $J_{15,14}$=9.7, $J_{15,3\beta}$=1.7, H-15), 5.78 (dd, 1H, $J_{14,15}$=9.7, $J_{14,3\beta}$=4.8, H-14), 4.45 (dd, 1H, $J_{3\beta,14}$=4.8, $J_{3\beta,15}$=1.7, H_β-3), 3.78 (s, 3H, OCH_3), 3.04 (d, 1H, $J_{21\alpha,17\alpha}$=1.8, H_α-21), 3.02 (m, 2H, H-5), 2.57 (dd, 1H, $J_{17\alpha,17\beta}$=15.1, $J_{17\alpha,21\alpha}$=1.8, H_α-17), 2.36 (d, 1H, $J_{17\beta,17\alpha}$=15.1, H_β-17), 2.07 (m, 1H, H-6), 1.85 (m, 1H, H-6), 1.00 (m, 2H, H-19), 0.66 (t, 3H, $J_{18,19}$=7.4, H-18); ^{13}C NMR ($CDCl_3$) 168.54 ($\underline{C}OOCH_3$), 165.91 (C_2), 142.82 (C_{13}), 137.73 (C_{15}), 136.85 (C_8), 127.98 (C_{11}), 121.69 (C_9), 120.97 (C_{10}), 119.74 (C_{14}), 115.60 (CN), 109.36 (C_{12}), 91.40 (C_{16}), 65.19 (C_{21}), 54.29 (C_7), 50.99 ($COO\underline{C}H_3$), 49.82 (C_3), 48.34 (C_5), 43.56 (C_6), 41.84 (C_{20}), 27.12 (C_{17}), 25.90 (C_{19}), 7.20 (C_{18}).
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