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Oxygenation of Benzyldimethylamine by Singlet Oxygen. Products and Mechanism

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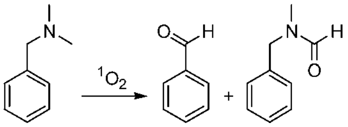
ABSTRACT



A product study of the reaction of benzyldimethylamine (1) with thermally and photochemically generated $^1O_2$ in MeCN was carried out. Benzaldehyde and *N*-benzyl-*N*-methylformamide are the reaction products, oxygenation representing ca. 9% of the overall quenching of $^1O_2$ by 1. The temperature effect and the intermolecular and intramolecular kinetic deuterium isotope effects were also determined. It is suggested that the products derive from an intracomplex hydrogen atom transfer in a reversibly formed charge-transfer complex.

The ability of tertiary amines to quench O_2 ($^1\Delta_g$), henceforth indicated as $^1O_2$, in a very efficient way is well recognized.[1] The quenching is predominantly of a physical nature, particularly with aromatic amines, but there are several reports indicating that chemical quenching is also possible.[2]

However, despite the large number of papers dealing with this subject, very little information is presently available concerning the reaction products as well as their mechanism of formation. An electron-transfer mechanism has been proposed in several cases,[2f,h,i] which has been experimentally substantiated only with NADH[2c] and aromatic amines of very low oxidation potential (<0.5 V vs SCE, in water).[2d,g] On the other hand, it is doubtful that such a mechanism may be general, given the low reduction potential of $^1O_2$ (about 0.1 V vs SCE, in MeCN),[3] which makes a full-fledged electron transfer process highly endergonic, especially with aliphatic amines. Another important point is that in most studies $^1O_2$ is produced by a sensitized photooxygenation with the consequent possibility of a competition between the oxidation of the substrate by $^1O_2$ (type II mechanism) and that by the excited sensitizer (type I mechanism). Thus, so far, product studies under rigorously controlled conditions are lacking.

In view of the continuous interest in $^1O_2$ reactivity with organic compounds, we now report on a detailed product study of the reaction of benzyldimethylamine (**1**) with $^1O_2$ in MeCN where $^1O_2$ has been generated both thermally and photochemically. The photoxygenation of **1** sensitized by methylene blue or rose bengal has already been studied by Inoue and co-workers.[4] Competition between type I and type II oxygenation mechanisms was suggested.

Reactions with Thermally Generated $^1O_2$. $^1O_2$ was generated by heating the endoperoxide of 1,4-dimethylnaph-

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[1] Schweitzer, C.; Schmidt, R. *Chem. Rev.* **2003**, *103*, 1685.

[2] (a) Smith, W. F., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 186. (b) Bellus, D.; Lind, H. *Chem. Commun.* **1972**, 1199. (c) Peters, G.; Rodgers, M. A. J. *Biochim. Biophys. Acta* **1981**, *637*, 43. (d) Manring, L. E.; Foote, C. S. *J. Phys. Chem.* **1982**, *86*, 1257. (e) Saito, I.; Matsuura, T.; Inoue, K. *J. Am. Chem. Soc.* **1983**, *105*, 3200. (f) Haugen, C. M.; Bergmark, W. R.; Whitten, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 10293. (g) Darmanyan A. P.; Jenks, W. S.; Jardon, P. *J. Phys. Chem. A* **1998**, *102*, 7420. (h) Bernstein, R.; Foote, C. S. *J. Phys. Chem. A* **1999**, *103*, 7244. (i) Cocquet, G.; Rool, P.; Ferroud, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, *14*, 2277.

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[4] Inoue, K.; Saito, I.; Matsuura, T. *Chem. Lett.* **1977**, 607.

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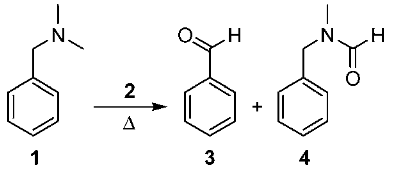
Scheme 1



thalene (**2**).[5] A 10:1 excess of **2** was added to 1 mL of a 0.01 M solution of **1** in MeCN and the resulting solution left at 40 °C in the dark for 4 h. The reaction mixture was examined by GC and GC-MS. All **2** was converted to 1,4-dimethylnaphthalene, and two reaction products were observed (comparison with authentic specimens), namely, benzaldehyde (**3**) and *N*-benzyl-*N*-methylformamide (**4**). The **3**/**4** molar ratio was 1.4 ± 0.2, and the overall yield of products was around 22%, with respect to the starting amine (Scheme 1, Table 1A, entry 1). The mass balance was excellent (95 ± 5%).

Table 1. Benzyldimethylamine Oxygenation by Thermally and Photochemically Generated Singlet Oxygen in MeCN

entry	reaction conditions[a]	products (μmol)[b] 3	products (μmol)[b] 4	3/4
	(A) oxygenation by thermally generated $^1O_2$			
1		1.3 (0.1)	0.93 (0.04)	1.4 (0.2)
2	**1** (2×10^{-2} M)	1.2 (0.1)	0.89 (0.05)	1.3 (0.2)
3	**1** (5×10^{-2} M)	1.4 (0.1)	1.07 (0.07)	1.3 (0.2)
4	BQ (2.5 mM)	1.2 (0.1)	0.94 (0.04)	1.3 (0.1)
5	TBP (5 mM)	1.4 (0.1)	1.1 (0.1)	1.3 (0.2)
	(B) oxygenation by photochemically generated $^1O_2$			
6		5.6 (0.4)	3.8 (0.2)	1.5 (0.2)
7	25 °C[c]	54 (4)	43 (3)	1.3 (0.2)
8	−48 °C[c]	35 (4)	28 (3)	1.3 (0.2)

[a] If not specified, the inital concentrations are: **1** (10^{-2} M), **2** (0.1 M), TPP (10^{-4} M). Reactions with **2** were carried out at 40 °C for 4 h. With TPP, at 25 °C for 30 min if not specified. [b] Calculated by GC analysis. Average of at least three determinations. The error (standard deviation) in the last significant digit is given in parentheses. [c] Volume: 50 mL. Reaction time: 10 min.

As control experiments showed that no reaction occurs between $^3O_2$ and **1** under the reaction conditions, it is clear that some chemical quenching actually occurs in the reaction of **1** with $^1O_2$ in MeCN and that **3** and **4** are the products formed in this process. It was also found that the extent of chemical quenching is unaffected by the presence of 2,4,6-tri-*tert*-butylphenol (TBP), entry 5 in Table 1A, as well as by the presence of benzoquinone (BQ), entry 4 in Table 1A. An additional and important observation was that the number of micromoles of products formed is almost independent of the substrate concentration (Table 1A, entries 1−3). This indicates that substantially all $^1O_2$ formed reacts with **1**. Thus, by considering the molar ratio between the endoperoxide used and **1** (10) and the fact that the yield in $^1O_2$ from the endoperoxide is 25%,[6] we can estimate that the contribution of chemical quenching to the overall quenching (chemical + physical quenching) of $^1O_2$ by **1** in MeCN is about 9%. By time-resolved luminescence at 1270 nm, it was determined that for **1** the overall quenching occurs with a rate constant (k_q) of 9.7×10^7 M^{-1} s^{-1};[7] hence, the rate constant for product formation is ca. 1×10^7 M^{-1} s^{-1}.

The kinetic deuterium isotope effect (KDIE) of the oxygenation reaction was measured by using (benzyl-d_2)-dimethylamine (**1-d$_2$**), which, by reaction with $^1O_2$, forms benzaldehyde-α-d_1 (**3-d$_1$**) and *N*-methyl-*N*-(benzyl-d_2)-formamide (**4-d$_2$**). The intramolecular KDIE, [$(k_H/k_D)_{intra}$ = 3.5 ± 0.6] was obtained by comparing the **3-d$_1$**/**4-d$_2$** molar ratio obtained from **1-d$_2$** with the **3**/**4** molar ratio observed for the reaction of **1**, of course assuming that the reactivity of the *N*-methyl group is the same in **1** and **1-d$_2$**. For the intermolecular KDIE [$(k_H/k_D)_{inter}$ = 2.93 ± 0.02], an equimolar mixture of **1** and **1-d$_2$** was reacted with $^1O_2$ and the molar ratio between **3** and **3-d$_1$** was measured. To the best of our knowledge, these are the first values of KDIE determined in the oxygenation of amines by $^1O_2$. The results are summarized in Table 2A.[8]

Reactions with Photochemically Generated $^1O_2$. Having unequivocally established the properties of the chemical quenching of $^1O_2$ by **1** in MeCN, we considered it worthwhile to check if the same results would be obtained by using photosensisitized generation of $^1O_2$. Tetraphenylporphyrin (TPP) was used as the sensitizer, since its singlet excited state is a weaker oxidant (E_{red} = 0.81 V vs SCE)[9] than the excited states of methylene blue and rose bengal used by Inoue. This was expected to give us more chances to obtain an exclusive type II mechanism of photooxygenation.

Actually, when **1** (0.01 M) was irradiated (external irradiation) for 30 min at 450−600 nm in the presence of TPP (1×10^{-4} M) in O_2-saturated MeCN, **3** and **4** were obtained in a ratio of 1.5 ± 0.2 (mass balance = 98%) which is the same, within experimental error, as that found in the reaction with the endoperoxide (Table 1B, entry 6).[10] Still more significantly, when the reaction of **1-d$_2$** was investigated, the values of KDIE were very close to those obtained with thermally generated $^1O_2$ (Table 2B). While these results are already strong evidence in favor of a predominant

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[5] (a) Turro, N. J.; Chow, M. F. *J. Am. Chem. Soc.* **1981**, *103*, 7218. (b) Adam, W.; Prein, M. *Acc. Chem. Res.* **1996**, *29*, 275. (c) Greer, A.; Vassilikogiannakis, G.; Lee, K.-C.; Koffas, T. S.; Nahm, K.; Foote, C. S. *J. Org. Chem.* **2000**, *65*, 6876. (d) Ben-Shabat, S.; Itagaki, Y.; Jockusch, S.; Sparrow, J. R.; Turro, N. J.; Nakanishi, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 814. (e) Poon, T.; Turro, N. J.; Chapman, J.; Lakshminarasimhan, P.; Lei, X.; Jockusch, S.; Franz, R.; Washington, I.; Adam, W.; Bosio, S. G. *Org. Lett.* **2003**, *5*, 4951.

[6] Günther, G. S.; Lemp, E. M.; Zanocco, A. L. *J. Photochem. Photobiol. A* **2002**, *151*, 1. However, Turro et al. report a 76% yield of $^1O_2$ in dioxane.[5a]

[7] Determined by laser flash photolysis experiments (see Supporting Information).

[8] In view of the largely predominant physical quenching, k_q for **1-d$_2$** (9.9×10^7 M^{-1} s^{-1}) is the same as that for **1**, within the experimental error.

[9] Darwent, J. R.; Douglas, P.; Harriman, A.; Porter, G.; Richoux, M.-C. *Coord. Chem. Rev.* **1982**, *44*, 83.

[10] With longer reaction times, higher conversions can be reached but significant overoxidation takes place. Thus, after 90 min of irradiation with 5% TPP, the conversion of **1** is 90% complete, but the yield of **3** + **4** is only 50%.

Table 2. Benzyldimethylamine and (Benzyl-d_2)dimethylamine Oxygenation by Thermally and Photochemically Generated Singlet Oxygen in MeCN

amine	products (μmol)[a,b] **3-d$_1$**	**4-d$_2$**	**3**	**4**	k_H/k_D [b]
(A) oxygenation by thermally generated $^1O_2$					
1-d$_2$	0.51 (0.01)	1.28 (0.01)			3.5 (0.6)[c]
1-d$_2$ + **1**	0.27 (0.01)	0.64 (0.02)	0.77 (0.01)	0.61 (0.02)	2.93 (0.02)[d]
(B) oxygenation by photochemically generated $^1O_2$					
1-d$_2$	1.7 (0.2)	4.0 (0.1)			3.5 (0.8)[c]
1-d$_2$ + **1**	0.76 (0.05)	1.80 (0.03)	2.34 (0.05)	1.83 (0.03)	3.06 (0.06)[d]

[a] Calculated by GC and GC-MS analysis. In competitive oxygenations of **1** + **1-d$_2$**, the **3**/**3-d$_1$** and **4**/**4-d$_2$** ratios were determined by GC-MS analysis. [b] Average of at least three independent determinations. The error (standard deviation) in the last significant digit is given in parentheses. [c] Determined from the **3**/**4** and **3-d$_1$**/**4-d$_2$** ratios obtained in independent oxygenations of **1** and **1-d$_2$**. [d] Determined by GC-MS analysis of benzaldehyde by the ratio of the intensity of the molecular peaks *m/z* = 106 and 107, corrected for the ^{13}C contribution.

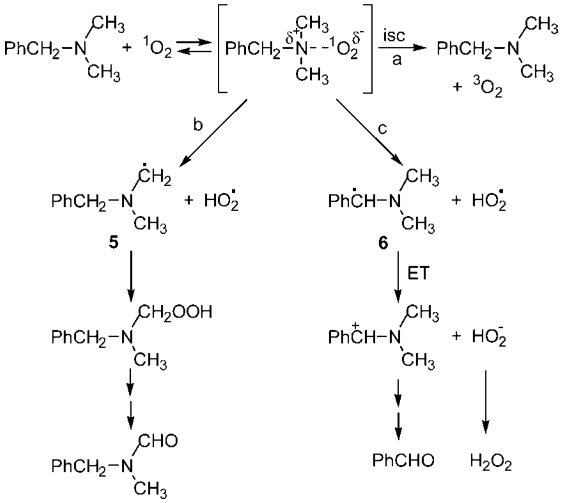
operation of the type II mechanism, further support in this respect was found in experiments in the presence of DABCO (an efficient, exclusively physical, quencher of $^1O_2$).[11] Accordingly, a progressive decrease in the product yields was observed by increasing the concentration of DABCO. Moreover, the ratio between the product yields (**3** + **4**) in the absence and in the presence of DABCO was linearly correlated to the DABCO concentration. From this correlation it was possible to calculate a value of 3.0×10^8 M^{-1} s^{-1} as the rate constant for quenching of $^1O_2$ by DABCO in MeCN, which resulted in agreement with literature values (For details, see Supporting Information).[12]

Having obtained overwhelming evidence that the type II mechanism is operating in the photoxygenation of **1** in the presence of TPP, it was possible to study the temperature effect on this reaction. To this purpose, irradiation of a **1**/TPP/O_2 solution was carried out at 25 and −48 °C for 10 min. The total amount of product (**3** + **4**) formed was 97 μmol at 25 °C and 63 μmol at −48 °C (Table 1B, entries 7 and 8). No appreciable effect of the temperature upon k_q was observed when rate measurements of $^1O_2$ quenching by **1** were carried out at 20 °C and −15 °C.[13]

Reaction Mechanism. The experiments described above clearly showed that **3** and **4** are the products formed by the reaction of **1** with $^1O_2$. Concerning their mechanism of formation, the possibility of an autoxidation process promoted by $^1O_2$ is excluded by the observation that there is no inhibition of the reaction by TBP (Table 1A, entry 5). An electron transfer process involving the formation of a radical cation, which then undergoes proton loss, is also highly unlikely being largely endergonic (the difference in the reduction potential between $1^{+\bullet}$ and $^1O_2$ is about 0.7 V). Also inconsistent with this mechanism is the observation that benzoquinone, a trap for $O_2^{-\bullet}$ that should form in the electron-transfer process,[14] does not exert any appreciable effect on the reaction yield (Table 1A, entry 4).[15]

There is a general agreement on the hypothesis that physical quenching of $^1O_2$ by amines involves the formation of an exciplex with partial charge transfer (CT) character as the reaction intermediate, and it has been suggested that such an exciplex can also be the intermediate in the chemical quenching.[1,2e,g,16] That is, once formed, the exciplex can undergo intersystem crossing (isc) to give the amine and $^3O_2$ (physical quenching) or be converted into products (chemical quenching). In view of the almost negligible effect of the temperature observed with respect to the rate of formation of **3** and **4**, it is very likely that this mechanism also operates in the reaction of **1** with $^1O_2$ in MeCN (Scheme 2, paths a and b + c).[16c]

Scheme 2



It has been pointed out that a close analogy exists between the properties of $^1O_2$ (an electronically excited state) and those of ketone triplets.[13b] It therefore seems reasonable to suggest that **3** and **4** derive from an exciplex formed by **1** and $^1O_2$ via an intracomplex hydrogen atom transfer similar

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[11] Silverman, S. K.; Foote, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 7672.

[12] Wilkinson, F.; Helman, W. P.; Ross, A. B. *J. Phys. Chem. Ref. Data* **1995**, *24*, 663.

[13] (a) These measurements were carried out by laser flash photolysis experiments in the presence of 1,3-diphenylisobenzofuran according to the procedure described by Gorman et al.[13b] The values of k_q are 1.3×10^8 M^{-1} s^{-1} and 1.4×10^8 M^{-1} s^{-1} at 20 and −15 °C, respectively. (b) Gorman, A. A.; Gould, I. R.; Hamblett, I.; Standen, M. C. *J. Am. Chem. Soc.* **1984**, *106*, 6956.

to that proposed for the reactions of triplet ketones with amines and alkylaromatics.[17] In our case, the hydrogen is transferred from the α-carbon to $^1O_2$, leading to the carbon radicals **5** and **6** and $HO_2^•$ (Scheme 2, paths b and c). A significant extent of charge transfer can take place in the exciplex to give the transfer of hydrogen a partial character of proton transfer.

Whatever the detailed mechanism, the observation of a clearly primary KDIE indicates that the hydrogen is transferred in the product-determining step. More significantly, the very close values of $(k_H/k_D)_{intra}$ and $(k_H/k_D)_{inter}$ [18] point to a conversion of the exciplex into carbon radicals in a single step, without the intervention of other intermediates.[19] Interestingly, the observed products suggest that the carbon radicals **5** and **6** follow different pathways. A possible hypothesis is that, as shown in Scheme 2, **5** reacts with $HO_2^•$ to form a hydroperoxide from which **4** can be formed, whereas **6** is oxidized by $HO_2^•$ to a carbocation that in several steps is converted into benzaldehyde. Consistent with this proposal is the observation that in the photooxygenation of **1**, H_2O_2 is formed in an amount equivalent to that of benzaldehyde.[20] The different behaviors of **5** and **6** may be due to the fact that **6** should be more easily oxidizable than **5**, due to the presence of the phenyl group, which, with respect to hydrogen, is expected to stabilize a carbocation more than a carbon radical. Alternatively (or in addition), steric effects that may make radical coupling more difficult in **6** than in **5** might come into play.

At any rate, the **3**/**4** product ratios observed (Table 1) indicate that transfer of hydrogen from the benzylic CH_2 is favored about 4 times (after statistical correction) with respect to hydrogen tranfer from the methyl groups, which is in line with the stronger bond dissociation energy of the methylic C−H bonds.[21]

However, it has to be noted that in the reaction of **1** with triplet benzophenone, a completely different regiochemistry is observed, as the hydrogen atom transfer concerns only the *N*-methyl group.[22] It should, however, be considered that the degree of charge transfer might be significantly higher in the benzophenone/amine CT complex, since triplet benzophenone has a much higher reduction potential than $^1O_2$. That in CT complexes the product distribution may depend on the degree of charge transfer is shown by the finding that only transfer of the benzylic hydrogen is found in the photoreduction of triplet azoalkanes (much weaker oxidants than benzophenone) by **1**.[23]

A final notation is that the significant chemical quenching observed with **1** ($E° = 0.82$ V vs SCE in MeCN)[24] contrasts with the behaviors of aromatic amines. These amines can have k_q values higher than that of **1** but exhibit partial chemical quenching only in H_2O and when an electron transfer is possible ($E° \leq 0.5$ V vs SCE).[2e,g] Thus, it would seem that with aromatic amines, hydrogen transfer in the CT complex cannot compete with isc. Only when the electron transfer is possible can conversion of the CT complex to a couple of radical ions compete with isc.

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Supporting Information Available: Experimental details and measurement of the quenching rate constant of $^1O_2$ by **1** and the effect of DABCO in the TPP-sensitized photooxygenation of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Manring, L. E.; Kramer, M. K.; Foote, C. S. *Tetrahedron Lett.* **1984**, *25*, 2523.

[15] (a) It has also been reported that no formation of $O_2^{-•}$ is observed in the reaction between **1** and $^1O_2$.[15b] In this study, however, the reaction products were not investigated. (b) Saito, I.; Matsuura, T.; Inoue, K. *J. Am. Chem. Soc.* **1981**, *103*, 188.

[16] (a) Young, R. H.; Martin, R. L.; Feriozi, D.; Brewer, D.; Kayser, R. *Photochem. Photobiol.* **1973**, *17*, 233. (b) Clennan, E. L.; Noe, L. J.; Wen, T.; Szneler, E. *J. Org. Chem.* **1989**, *54*, 3581. (c) Gorman, A. *Adv. Photochem.* **1992**, *17*, 217. (d) Martin, N. H.; Allen, N. W., III; Cottle, C. A.; Marschke, C. K., Jr. *J. Photochem. Photobiol. A* **1997**, *103*, 33.

[17] Wagner, P.; Park, B.-S *Org. Photochem.* **1991**, *11*, 227.

[18] Actually, the two values are within the experimental error. It should also be considered that $(k_H/k_D)_{intra}$ was obtained by product ratios measured in separate oxidations and is therefore less accurate than $(k_H/k_D)_{inter}$.

[19] Gollnick, K.; Lindner, J. K. E. *Tetrahedron Lett.* **1973**, *21*, 1903.

[20] Amount of H_2O_2 was quantitatively determined by titration with iodide ion (see Supporting Information).

[21] (a) Bond dissociation energy is 92.6 against 89.1 kcal mol^{-1} for the *N*-benzylic C−H bond.[21b] (b) Dombrowski, G. W.; Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R. *J. Org. Chem.* **1999**, *64*, 427.

[22] Cohen, S. G.; Stein, N. M. *J. Am. Chem. Soc.* **1971**, *93*, 6542.

[23] Adam, W.; Moorthy, J. N.; Nau, W. M.; Scaiano, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 6749.

[24] Hall, L. R.; Iwamoto, R. T.; Hanzlik, R. P. *J. Org. Chem.* **1989**, *54*, 2446.