Quenching of Singlet Oxygen by Tertiary Aliphatic Amines. Structural Effects on Rates and Products

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In memoriam Professor *Hanns Fischer*

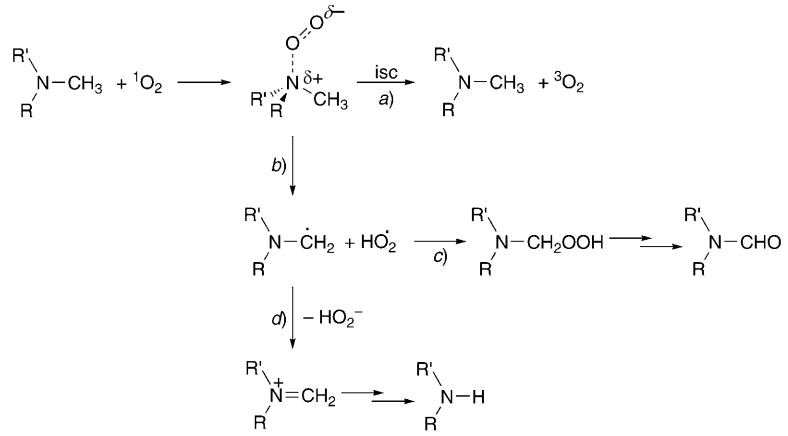
A kinetic and product study of the reaction of a series of α-methyl-substituted *N*-methylpiperidines with thermally generated $^1O_2$ in MeCN was carried out. It was found that as the number of α-methyl groups (Me in α-position relative to the N-atom) increases, the rate of $^1O_2$ quenching (physical plus chemical) slightly decreases. This finding shows that, with respect to the reaction rate, steric effects are much more important than electronic effects as the latter should have produced the opposite result. The opposite outcome was instead found for the chemical quenching that leads to the *N*-demethylation products and *N*-formyl derivatives. The same trend was observed for the ratio between *N*-demethylation and formation of the *N*-formyl derivatives (NH/NCHO ratio). All these results are consistent with the mechanism reported in *Scheme 1* where an exciplex is first formed that by a H-atom transfer process produces an α-amino-substituted C-radical. The latter forms the product of *N*-demethylation by one electron oxidation, or affords the *N*-formyl derivative by radical coupling (*Scheme 1*). Similar results were obtained with *N,N*-dimethylcyclohexanamine. However, this 'acyclic' amine exhibited behaviors quite distinct from those of the *N*-methylpiperidines series, with respect to reaction rate, extent of chemical quenching, and NH/NCHO ratio.

Introduction. – The ability of tertiary aliphatic amines to efficiently quench O_2 ($^1\Delta_g$), henceforth indicated as $^1O_2$, is well recognized [1]. There is substantial agreement that this reaction involves the reversible formation of an exciplex with partial charge-transfer character that can proceed to the starting amine and the ground triplet state $O_2(^3\Sigma_g^-)$, henceforth indicated as O_2 (physical quenching), or to products (chemical quenching) [1a,c]. In some cases, an electron-transfer mechanism has been proposed [2], but this seems unlikely in view of its high endergonicity.

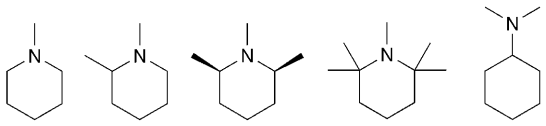
While the kinetic aspects of the reactions of amines with $^1O_2$ have been investigated in some detail [1], much less information is presently available concerning the products formation, although it is well established that chemical quenching accompanies physical quenching in a substantial number of amines [2][3]. Few pioneering studies are available [3a,b,d], but information is almost completely lacking with respect to the role of structural effects on the extent of chemical quenching and, most particularly, with respect to the mechanistic aspects of the process by which the exciplex is converted into the reaction products.

Recently, we have reported a detailed kinetic and products study of the reaction of *N*,*N*-dimethylbenzylamine with $^1O_2$ [4]. The mechanism depicted in *Scheme 1* has been suggested where the key step is a H-atom transfer (HAT) process, within the exciplex, from the CH_3–N group to oxygen (*Path b*). The formed C-radical and $HO_2^{\bullet}$ can then undergo radical coupling, to eventually give a formamide derivative (*Path c*)[1]), or electron transfer to produce an iminium cation leading to the *N*-dealkylation product (*Path d*).

Scheme 1



To have more detailed information concerning this mechanism and the structural factors at the basis of the competition between physical and chemical quenching as well as between the paths leading to *N*-demethylation and formamide formation, we carried out a kinetic and product study of the reaction of a series of α-methyl substituted *N*-methylpiperidines (*i.e.*, of **1**–**4**) with $^1O_2$ in MeCN. For the purpose of comparison, an 'acyclic' amine, *N*,*N*-dimethylcyclohexanamine (**5**), was also investigated. As in our previous study [4], $^1O_2$ was generated by thermal decomposition of 1,4-dimethylnaphthalene endoperoxide [5].



1 **2** **3** **4** **5**

Results and Discussion. – The reactions of the amines **1**–**5** with thermally generated $^1O_2$ were carried out with 0.01M substrate and 0.01M–0.1M 1,4-dimethylnaphthalene endoperoxide (depending on the extent of chemical quenching), at 40° for 4 h.

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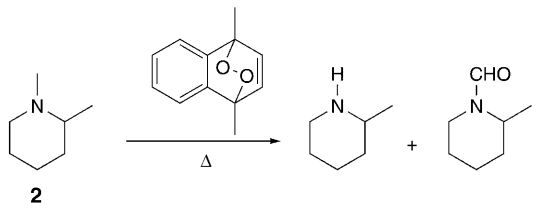
[1]) It is, however, possible that some formamide also derives from reaction of the C-radical with O_2.

Under these conditions, all the 1,4-dimethylnaphthalene endoperoxide decomposes to give 1,4-dimethylnaphthalene and $^1O_2$ in 70% yield, referred to the initial amount of endoperoxide [6]. Products were characterized (comparison with authentic compounds) and quantified by GC and GC/MS. With piperidines **2**–**4**, the reaction products were the secondary amine (*N*-demethylation product) and the *N*-formyl derivative (*i.e.*, the piperidine-1-carboxaldehyde as shown in *Scheme 2* for the specific case of piperidine **2**) that formed in substantial yields. With **1**, however, practically only the *N*-formyl derivative was formed. The 'acyclic' amine **5** exhibited the same behavior as **2**–**4**, affording the *N*-demethylated product (*N*-methylcyclohexanamine) and the *N*-formyl derivative (*N*-methyl-*N*-cyclohexylformamide).

Scheme 2



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Under the above conditions, all $^1O_2$ generated by the endoperoxide is quenched by the 0.01M substrate, since the latter quenches $^1O_2$ at a rate in the order of 10^8 M^{-1} s^{-1} (*vide infra*) that is much higher than the decay rate of $^1O_2$ in MeCN (10^4 s^{-1} [1b]). Thus, the fraction of chemical quenching (Q_c), that is the fraction of exciplex that undergoes product formation with respect to the total quenching (chemical plus physical), can easily be calculated as the total product yield *vs.* the amount of singlet oxygen that has been generated. Products, yields, and fractions of chemical quenching (Q_c) are reported in the *Table*. In the same table are also displayed the rates of total quenching, k_Q, measured by time-resolved luminescence at 1270 nm, together with the peak-potential (E_p) values of the amines that were measured in MeCN by cyclic voltammetry.

Considering first the kinetic results for the *N*-methylpiperidines, the data in the *Table* show that the progressive addition of α-methyl groups in the piperidine ring

Table. *Amine Oxygenations by $^1O_2$*

Amine	E_p[b]) [V]	k_Q [M^{-1} s^{-1}]	Products yields [%][a])		Q_c [%][c])	NH/NCHO[d])
			Secondary amine	*N*-Formyl derivative		
1[e])	1.04	$1.7\cdot10^8$	traces	12 (±1)	2	0
2[f])	0.98	$9.3\cdot10^7$	15 (±1)	8.0 (±0.4)	7	1.9
3[f])	0.94	$8.8\cdot10^7$	28 (±2)	2.5 (±0.1)	9	11
4[g])	0.76	$8.9\cdot10^7$	23 (±1)	1.2 (±0.1)	35	19
5[h])	0.90	$2.7\cdot10^8$	9.2 (±0.5)	4.2 (±0.2)	10	2.2

[a]) Referred to the initial amount of the starting amine and determined by GC analysis. [b]) E_p *vs.* Ag/AgCl in MeCN at 25°. [c]) Total product yield *vs.* the amount of $^1O_2$ generated. [d]) Molar ratio between the secondary amine and the *N*-formyl derivatives, see text. [e]) Amine/endoperoxide 10 : 1. [f]) Amine/endoperoxide 5 : 1. [g]) Amine/endoperoxide 1 : 1. [h]) Amine/endoperoxide 2 : 1.

(Me in α-position to the N-atom) lowers the rate of total quenching k_Q. The effect, however, is rather small since k_Q goes from $1.7 \cdot 10^8$ M^{-1} s^{-1} for **1** (no α-methyl groups) to $8.9 \cdot 10^7$ M^{-1} s^{-1} for **4** (4 α-methyl groups). A possible explanation is that, as previously proposed by *Monroe* [7], the α-methyl groups reduce the rate by a steric effect since the formation of the exciplex requires a close approach of $^1O_2$ to the N-atom of the amine. The entity of the steric effect is probably much larger than that appearing from the rate data. Accordingly, the oxidation potential values reported in the *Table* show that the progressive addition of α-methyl groups has also the effect of decreasing the oxidation potential of the piperidine. This effect should determine an *increase* in the quenching rate [8], which is a result opposite to what found. Clearly, steric effects must be very significant as they have overcome electronic effects to a large extent.

It can also be noted that *N*,*N*-dimethylcyclohexanamine (**5**) exhibits a k_Q value higher than that of **4**, even though the oxidation potential of the former is significantly higher than that of the second (0.90 *vs.* 0.76 V). Model inspections clearly indicate that steric hindrance around the N-atom is much less in **5** than in **4**[2]). Thus, again, steric effects appear to outweigh electronic effects with respect to the rate of $^1O_2$ quenching.

In contrast to what was observed for the k_Q value, the presence of the α-methyl groups in *N*-methylpiperidines has a very positive effect upon the extent of chemical quenching that significantly increases on passing from **1** to **4** (from 2 to 35%). Thus, the α-methyl groups favor more the path leading to products than that leading to physical quenching. Interestingly, a plot of Q_c values for **1**–**4** against the oxidation potentials is roughly linear (*Fig. 1*) indicating that the competition between physical quenching and chemical quenching (a HAT process according to *Scheme 1*) is influenced by the same (electronic) effects that influence the oxidation potential. Namely, the extent of the chemical quenching increases as the oxidation potential of the amine becomes lower. Since the exciplex is suggested to be a charge-transfer complex, the present results would indicate that its tendency to undergo a HAT transfer increases as the extent of charge transfer increases (the oxidation potential of the amine becomes lower). This is in agreement with our previous hypothesis [4] that the H-atom transfer in the exciplex has substantial character of proton transfer[3]).

Even though the correlation between Q_c and E_p for piperidines is very rough, it is quite clear that the Q_c value for the 'acyclic' amine **5** (statistically corrected) falls quite significantly below the Q_c *vs.* E_p line of the piperidines (*Fig. 1*). At present, it is not possible to provide a reasonable explanation.

Coming to the product nature, the first notation is that with both *N*-methylpiperidines **1**–**3** and *N*,*N*-dimethylcyclohexanamine (**5**), the chemical quenching concerns only the C–H bonds of the *N*-methyl groups. The ring C–H bonds in α-position to

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[2]) A greater steric demand for **4** than for **5** has recently been suggested to explain the different catalytic effect of the two amines in ketone enolization [9].

[3]) Clearly, dealing with a competition, it might also be suggested that the observed trend in the Q_c values is due to a physical quenching that becomes less efficient as the oxidation potential of the amine decreases. However, this possibility is highly unlikely as it is well known that the opposite holds in systems where only physical quenching is observed [8]. Steric effects could also be called into play, but it is very difficult to envisage that an increase in the steric hindrance from **1** to **4** can favor chemical quenching with respect to physical quenching.

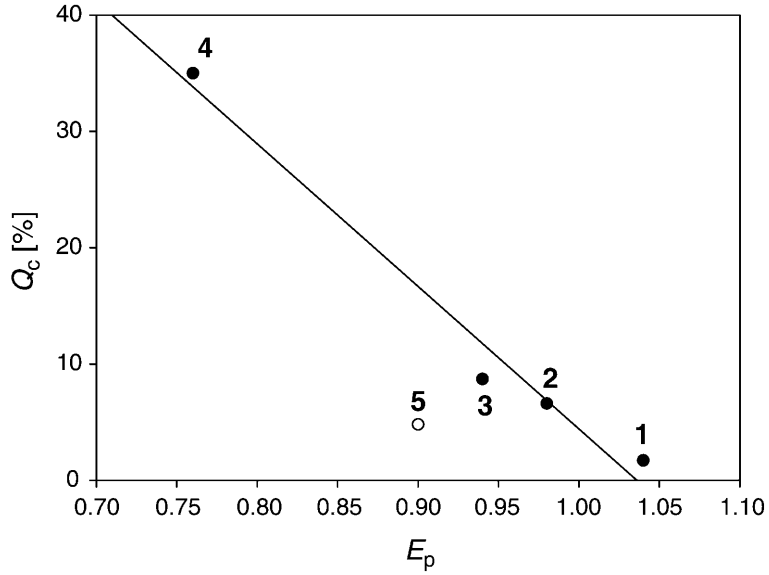

Fig. 1. *Chemical quenching* (Q_c) *of amines* **1**–**5** vs. *their oxidation potentials.* The Q_c value for **5** is statistically corrected on the basis of the number of *N*-methyl groups to be compared with that of the piperidine series.

the N-atom are practically unaffected. In general, a greater reactivity of exocyclic H–C(α) bonds (particularly of MeN groups) with respect to the endocyclic ones may be expected [1a], probably since only the former bonds can rotate around the N–C bond and assume the conformation most suitable for the cleavage (that with the H–C(α) bond *syn*-periplanar to the lone pair at the N-atom)[4]). For the case in point, it should be considered that the equatorial H–C(α) bonds of piperidine are not *syn*-periplanar with the lone pair at the N-atom and should have a low reactivity due to stereoelectronic effects[5]). On the other hand, no reactivity may be predicted for the axial H–C(α) bonds since they are *anti*-periplanar to the lone pair at the N-atom and, in the exciplex, reside on the face of the ring opposite to that where oxygen is located. This situation probably holds also for the ring H–C(α) bond of **5** since, in the most stable conformation of the amine (*ab initio* calculations), this bond too should be *anti*-periplanar with respect to the lone pair at the N-atom. Moreover, it should be added that in the case of **5**, there is also a high (6:1) statistical factor in favor of the MeN H-atoms.

Coming to the secondary amine/formamide (NH/NCHO) product ratio, it can be noted that it increases quite regularly in the order **1**<**2**<**3**<**4**, that is by increasing the number of α-methyl groups and decreasing the oxidation potential. As Q_c, also

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[4]) This conformation provides the maximum stabilization to the formed C-radical (stereoelectronic effect).

[5]) Dealing with competition reactions, also weak stereoelectronic effects (1 kcal mol^{-1} or less) can deeply influence the product distribution.

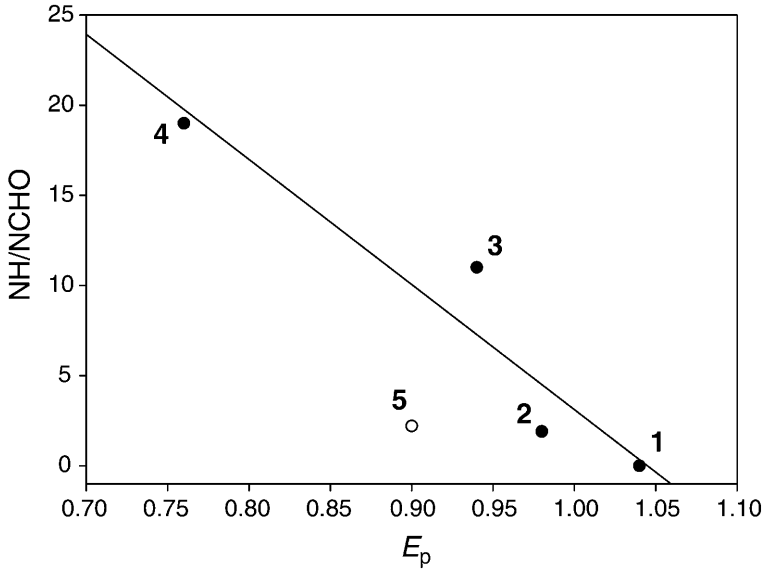

Fig. 2. *Secondary amine*/N-*formyl derivative* (NH/NCHO) *molar ratio* vs. *amine oxidation potentials*

the NH/NCHO ratio exhibits a roughly linear correlation when plotted against the E_p values of the amines (*Fig. 2*). One possibility is that the factors that lower the oxidation potential of the amine also lower the oxidation potential of the C-radical formed in *Path b* of *Scheme 1*. Therefore, the electron-transfer path leading to *N*-demethylation (*Path d*) may be favored with respect to *Path c*. Steric effects, however, should also be considered given that they increase as well in the order **1** < **2** < **3** < **4**. Thus, an additional suggestion might be that steric effects indirectly favor the secondary-amine formation by making more difficult the radical coupling pathway (*Path c* in *Scheme 1*). It is reasonable to think that very likely both electronic and steric effects can play a role in determining the NH/NCHO ratio. Even though we are unable to establish the relative importance of the two effects, there is no doubt that the observed trend in the NH/NCHO ratio is consistent with the mechanism described in *Scheme 1*.

The 'acyclic' amine **5** behaves differently than *N*-methylpiperidines also with respect to the NH/NCHO ratio that, accordingly, is significantly lower than that expected for an *N*-methylpiperidine with similar E_p value (see *Fig. 2*). A possibility is that with the 'acyclic' amine, the radical coupling of *Path c* is favored by the same steric factors suggested to operate with respect to the rate of quenching.

In conclusion, the results observed in the $^1O_2$-promoted oxidation of the *N*-methylpiperidine series indicate that electronic and steric effects may be differently felt in the various steps of the mechanism that leads to products (*Scheme 1*). Thus, the overall reaction rate appears to be affected much more by steric effects than by electronic effects. Conversely, electronic effects appear to be the dominant ones in the conversion of the exciplex into products. Accordingly, the extent of chemical quenching quite regularly increases as the amine oxidation potential becomes lower. This indicates that the HAT inside the exciplex is facilitated by enhancing the charge-transfer character of the

exciplex itself. Both electronic and steric effects are suggested to operate with respect to the competition between the two pathways that convert the intermediate α-positioned C-radical into the secondary amine and the *N*-formyl derivative, respectively (*Scheme 1*). At present, however, it is not possible to establish their relative weight. Finally, the 'acyclic' amine **5** was found to present behaviors clearly distinct from those of piperidines. Accordingly, with respect to the latter, the rate of exciplex formation is higher, while the extent of chemical quenching and the ratio between *N*-demethylation and formamide formation are significantly lower. A minor role of steric effects in the reaction of the 'acyclic' tertiary amine than in that of piperidines might, at least in part, explain the observed effects.

MIUR, University 'La Sapienza' of Rome, and University of Perugia are thanked for the financial support.

Experimental Part

General. Reagents: 1-methylpiperidine (**1**), 1,2,2,6,6-pentamethylpiperidine (**4**) and *N*,*N*-dimethylcyclohexanamine (**5**) were commercially available (*Aldrich*) and passed through alumina before use. The 1,2-dimethylpiperidine (**2**) and *cis*-1,2,6-trimethylpiperidine (**3**) were prepared by *N*-methylation of 2-methylpiperidine (*Aldrich*) and *cis*-2,6-dimethylpiperidine (*Aldrich*), resp., with methyl iodide (*Fluka*). The 1,4-dimethylnaphthalene endoperoxide was prepared according to [5a]. Products: all the secondary amines as well as piperidine-1-carboxaldehyde (*Aldrich*) were commercially available. *N*-Cyclohexyl-*N*-methylformamide was prepared by reaction of *N*-methylcyclohexanamine with formic acid. The 2-methylpiperidine-1-carboxaldehyde, *cis*-2,6-dimethylpiperidine-1-carboxaldehyde and 2,2,6,6-tetramethylpiperidine-1-carboxaldehyde were prepared according to [10]. Acetonitrile (*Carlo Erba, HPLC-plus* grade) was used without further purification. GC: *Varian CP 3800.* GC/MS: *Agilent 6800N* equipped with an *Agilent-5973Network* mass selective detector.

Oxidation by Thermally Generated Singlet Oxygen. A 2-ml soln. of amine (10^{-2} M) and 1,4-dimethylnaphthalene endoperoxide (0.1M for **1**, $5\cdot10^{-2}$ M for **2** and **3**, 10^{-2} M for **4** and $2\cdot10^{-2}$ M for **5**) in MeCN was heated at 40° (water bath) in the dark for 4 h. An internal standard (4-methylbenzophenone) was added, and the mixture was analyzed by GC and GC/MS. No reaction was observed when oxygen-saturated amine solns. were kept at 40° for 4 h in the absence of 1,4-dimethylnaphthalene endoperoxide.

Amine Oxidation Potentials. Cyclic voltammetry was carried out in an N_2-purged soln. of the amine (2 mM) and tetrabutylammonium tetrafluoroborate (0.1M) in MeCN at 25°. The cell contained an 1.5-mm disc glassy carbon electrode, a Pt auxiliary electrode and an Ag/AgCl (in 3M KCl) reference electrode. For each amine, at least four determinations were carried out.

Determination of $^1O_2$ Quenching Rate Constants (k_q). $^1O_2$ was produced in MeCN by energy transfer to O_2 from the triplet state of phenalenone ($5.0\cdot10^{-5}$ M), generated by excitation at 355 nm from a Nd : YAG laser (*Continuum*, *Surelite II*, pulse width *ca.* 7 ns and energy < 3 mJ per pulse). The phosphorescence emission of $^1O_2$ emerging from the cuvette passed through a cut-off filter at 1050 nm (*Oriel, 51362*) and three pieces of gelatin cut-off filter at 870 nm (*Kodak Wratten, 87C*) and was detected by a germanium diode detector (*Judson, J16 SP*, 5-mm diameter) [11]. After amplification with a two-stage home-made amplifer (*ca.* 100 MHz bandwidth, 14 dB), the output of the diode was fed into a digital signal analyzer (*Tektronik DSA602*) and computer stored and analyzed (*Tektronik PEP301*). Rate constants for the quenching of $^1O_2$ (k_q) were determined from the decrease of $^1O_2$ emission lifetime in O_2-saturated MeCN, in the presence of various amounts of amine ($0.15-4.0\cdot10^{-3}$ M). All measurements were carried out at $22\pm2°$.

Ab initio *Calculations on* **5**. The minimum energy geometry for **5** was determined by *ab initio* calculations at the HF/6-31G* level on a *Silicon-Graphics-O_2* platform using a Spartan 5.0.1 program.

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Received April 21, 2006