THE PHOTO-DEOXYGENATION OF HETEROCYCLIC *N*-OXIDES

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Abstract - 2-Methoxy and 2-nitrophenazine 10-oxide are deoxygenated by irradiation in the presence of triethylamine, 2,3-dimethyl-2-butene and triethylphosphite *via* electron transfer to the singlet excited state, as shown by the comparison of reaction quantum yield and fluorescence quenching. 1,4-Dimethoxybenzene quenches the singlet, but causes no deoxygenation. The same mechanism operates in the photoreduction of benzo[*c*]cinnoline 5-oxide, but it is too slow to compete efficiently with the rearrangement in the case of quinoline 1-oxide. The photo-deoxygenation of the boron trifluoride ground state complexes of these substrate is in every case unefficient.

The *N*-oxides of heteroaromatic derivatives differ from the parent compounds in many chemical properties: [1,2] one of the most characteristic is their photoreactivity, which extends to almost all known terms.[1-4] Usually the main photoprocess observed is a rearrangement. Several types of such rearrangements are known, and are useful for the synthesis of various heterocycles. Deoxygenation usually occurs as a side process, accounting for at most a few percent of the converted *N*-oxide, although some cases are known where this is the main process (usually, this is the case for the *N*-oxides of very electron-poor heterocycles) and furthermore deoxygenation predominates in the presence of some additives such as boron trifluoride[5] and triphenylphosphine.[6] The interest of deoxygenation mainly lies in the possibility of using *N*-oxides as mild photochemical (as well as thermal) oxidants, through a reaction which may mimic some biological oxidations.[7-10]

Although the general pattern of the photoreactions of *N*-oxides has been recognized and is generally possible to predict which kind of photochemistry can be expected from a particular derivative, the detailed mechanism of these processes is not known. Rearrangements are singlet state process apparently occurring in a very short time. Although the deep-seated rearrangements occurring under these conditions often can conveniently be rationalized as involving several steps, e.g. a series of pericylic reactions, there is practically no firm evidence or any intermediate. As far as the photo-deoxygenation is concerned, various models have been proposed. These include: direct oxygen transfer from an excited state of the *N*-oxide, presumably *via* previous electron-transfer (path a, Scheme 1).[8,11,12] Hydrogen abstraction by an excited state (path b).[13,14] Photoisomerization of the *N*-oxide to yield an unstable intermediate, presumably in common with the rearrangement path, which has

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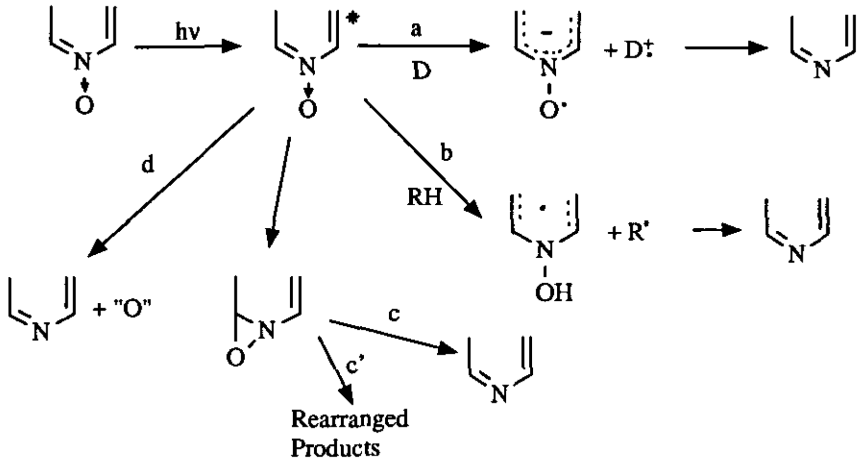
This paper is dedicated to Professor Alan R. Katritzky on occasion of his 65th birthday



Scheme 1

strong oxidizing properties; a fused oxaziridine has been proposed for this role (path c).[12,15,16] Photocleavage of the N-O bond to give some reactive form of oxygen (atomic oxygen)(path d).[17]

Direct involvement of the excited state of the *N*-oxides has been discussed in several cases,[8,11-14] and some evidence has been obtained both for the singlet (path a)[8,11] and for the triplet (path b)[13] paths. The attribution is facilitated when the molecules involved emit fluorescence or, respectively, phosphorescence. However, this is not the general case, and many *N*-oxides do not emit detectably, nor show absorbing transients by flash-photolysis, and in most cases indications about the mechanism have been obtained from indirect means, e.g. the structure of the oxygenation products[16] or the detection of radicals during photolysis.[18]

Clearly, further studies are required in order to clarify the mechanism of deoxygenation and its relation to the rearrangement. In the following, we offer a contribution towards this aim by comparing the photo-deoxygenation under various conditions of some *N*-oxides chosen as representative of the different known photochemical behaviours. These are: quinoline 1-oxide (**1**) (this rearranges efficiently, but does not fluoresce), benzo[*c*]cinnoline 5-oxide (**2**) (it neither fluoresces nor reacts photochemically), 2-nitrophenazine 10-oxide (**3**) (it fluoresces but does not react photochemically) and 2-methoxyphenazine 10-oxide (**4**) (it both rearranges and fluoresces).

The photodeoxygenation of these *N*-oxides was monitored in the presence of the following additives: triethylamine (TEA), 2,3-dimethyl-2-butene (DMB), 1,4-dimethoxybenzene (DMOB), triethylphosphite (TEP), boron trifluoride etherate (BTF). The irradiations were carried out in dichloromethane, since strong polar or protic solvents have an effect of their own on the photochemistry of these substrates. An important difference was noted between these additives: while the first four compound do not affect the absorption spectrum of any of the *N*-oxides used, in the case of BTF (0.1 M) the absorption spectrum was completely changed and further spectroscopic properties (nmr) likewise indicated complete complexation of all the substrates under this condition.

Representative results are reported in Table 1 and the trends observed are summarized in the following. Quinoline 1-oxide (**1**) is known to rearrange efficiently to yield, in aprotic solvents, benzo-3,1-oxazepine.[19] We noticed that this photoreaction was only weakly quenched by TEA, TEP, and DMB, and almost not at all by

Table 1. Rearrangement (ϕ_r) and deoxygenation (ϕ_d) quantum yield (x10^2) for the *N*-oxides (**1-4**) in dichloromethane in the presence of additives (0.1 M).

Substrate		No Additive	TEA	DMB	TEP	DMOB	BTF
1	ϕ_r	20	17	18	17	18	<0.1
	ϕ_d	0.3	0.7	0.4	0.7	0.4	2
2	ϕ_d	<0.1	1.2	0.8	2	<0.1	<0.1
3	ϕ_d	<0.1	2.1	2.1	7.6	<0.1	<0.1
4	ϕ_r	2.3	1.1	1.1	1.5	0.4	<0.1
	ϕ_d	<0.1	0.8	1.6	2.9	<0.1	0.3

Table 2. Fluorescence quenching constants (K_{sv}, M^{-1}) for compounds (**3**) and (**4**) in dichloromethane.

	TEA	DMB	TEP	DMOB
3	104	69	20	100
4	13	13	6	37

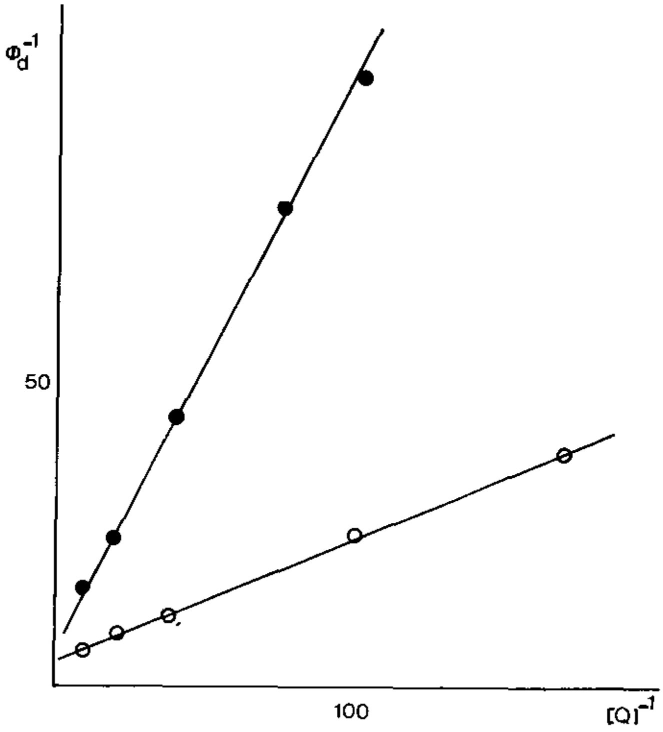
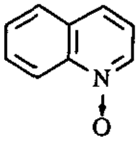


Figure 1. Double reciprocal plot of the deoxygenation quantum yield of substrates (3) (open circles) and (4) (filled circles vs the quencher concentration.



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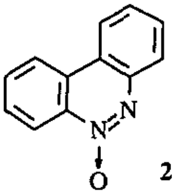

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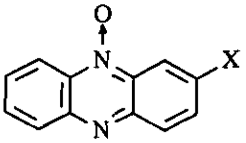


3 (X=NO_2)
4 (X=OMe)

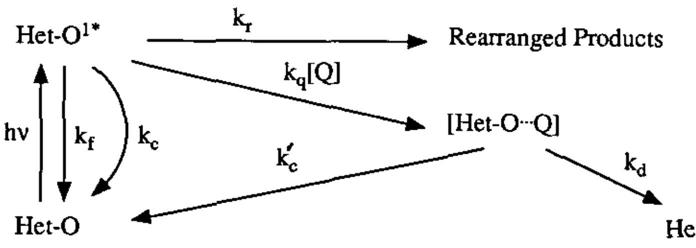
DMOB. In the first two cases a slight increase of the photodeoxygenation was noticed, although rearrangement remained the main path. With BTF deoxygenation was the only photoreaction, but it took place quite sluggishly. Benzo[*c*]cinnoline 5-oxide (**2**) was found to be almost unreactive upon irradiation in both protic and aprotic media, with only a slow deoxygenation. In the presence of TEA, DMB and TEP, but not of DMOB, a reasonably efficient photodeoxygenation set in. The BTF complex was weakly photoreactive, the main process being also here deoxygenation.

Similarly to compound (**2**), 2-nitrophenazine 10-oxide (**3**) was quite photostable both in aprotic and protic solvents. However, in the presence of TEA, DMB and TEP deoxygenation was much faster, while again no such effect was observed with DMOB. Since the molecule is emitting, the fluorescence quenching in the presence of the same additives was likewise measured. The complex with BTF was virtually unreactive.

Finally, 2-methoxyphenazine 10-oxide (**4**) is known to rearrange photochemically.[20] In the presence of TEA, DMB and TEP deoxygenation accompanies the rearrangement. Again no such effect is observed with DMOB. The fluorescence quenching was measured also in this case. The complex with BTF reacts, and yields 2-methoxyphenazine.

The dependence of the reaction quantum yield on the additive concentration was measured in most cases, With *N*-oxides (**2**) and (**3**) the only reaction was deoxygenation and it increased with the additive concentration in the case of TEP and also, though to a lesser degree, particularly with **3**, also with TEA and DMB. With **4** as the substrate the extent of deoxygenation increased at the expenses of that of rearrangement with TEP, TEA and DMB, while the rearrangement was quenched without introducing deoxygenation with DMOB. With quinoline 1-oxide (**1**) the total quantum yield was in every case only slightly decreased (with a limited increase of deoxygenation) upon increasing the additive concentration.

A mechanism accounting for the above data is shown in Scheme 2, where the decay paths from the singlet excited state of a *N*-oxide (Het-O) are shown, viz fluorescence (k_f), internal conversion to the ground state (k_c) and rearrangement (k_r). In the presence of a quencher (Q) the singlet state is intercepted (bimolecular rate k_q) and a complex is formed. In turn, this decays to the ground state (k_c) or leads to deoxygenation (k_d).



Scheme 2

Deoxygenation directly from the singlet is much slower than the other unimolecular processes, as shown by the almost negligible quantum yield of deoxygenation in neat CH_2Cl_2 from all the present *N*-oxides, and is not considered in the scheme. Furthermore, the involvement of a triplet state is disregarded as this stage (see below). The discussion can be conveniently started from the two phenazine derivatives, since in this case the effects of the quencher both on the photoreaction and on the fluorescence can be measured.

With these compounds, the exclusive involvement of the singlet excited state is apparent already from a qualitative examination. In the presence of the quenchers, deoxygenation competes with fluorescence with the nitro derivative (**3**), and with both fluorescence and rearrangement with the methoxy derivative (**4**) (see Tables 1 and 2).

From a quantitative point of view, from Scheme 2 one derives the well known Stern-Volmer equation for fluorescence quenching (eq. 1). The corresponding K_{SV} values are reported in Table 2, and the trend observed shows that the quenching involves charge transfer to the excited *N*-oxide.

$$\frac{I^o}{I} = 1 + \frac{k_q}{k_c+k_f}[Q] = 1 + K_{SV}[Q] \qquad (1)$$

$$\Phi_d = \frac{k_d}{k_d+k_c'} \cdot \frac{k_q[Q]}{k_c+k_f+k_q[Q]} \qquad (2)$$

$$\Phi_d^{-1} = \frac{k_d+k_c'}{k_d}\left(1 + \frac{k_c+k_f}{k_q[Q]}\right) = \frac{k_d+k_c'}{k_d}\left(1 + \frac{1}{K_{SV}[Q]}\right) \qquad (3)$$

$$\frac{\Phi_r^o}{\Phi_r} = 1 + K_{sv}[Q] \qquad (4)$$

Likewise, for the deoxygenation quantum yield one obtains eq. 2. Eq. 3 predicts a linear dependence of the reciprocal of the deoxygenation quantum yield on the reciprocal of the quencher concentration, and furthermore the intercept/slope ratio in this plot is identical with the K_{SV} value from the fluorescence data. This is verified for the photoreaction of both **3** and **4** with TEP (see Figure1). The plot gives a K_{SV} value of 27 M^{-1} for **3** (20 M^{-1} from fluorescence quenching) and 5 M^{-1} for **4** (6 M^{-1} from fluorescence). Since the lifetime of fluorescence is in both cases in the order of nanoseconds, k_q is *ca* 10^8 $M^{-1}s^{-1}$. The $(k_d+k_c)/k_d$ value is 10 in the first case and 9 in the latter one. Thus the complex has a *ca* 90% probability to decay to the ground state without reaction and a 10% probability of decay with transfer of the oxygen atom to the quencher.

For the case where k_d is negligible, viz Q quenches the excited state but causes no deoxygenation, the dependence of the rearrangement quantum yield on the quencher concentration is expressed by eq. 4. This behaviour is verified for the photoreaction of compound (**4**) in the presence of DMOB (Figure2, K_{SV} 40 M^{-1}, compare with 37 from fluorescence measurements).

The reactions of **3** and **4** in the presence of TEA and DMB follow a behaviour different from that observed with TEP, viz here the deoxygenation quantum yield grows with the quencher concentration much less than would be

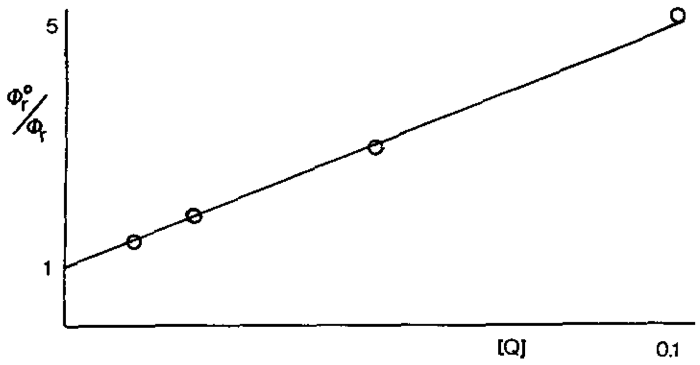
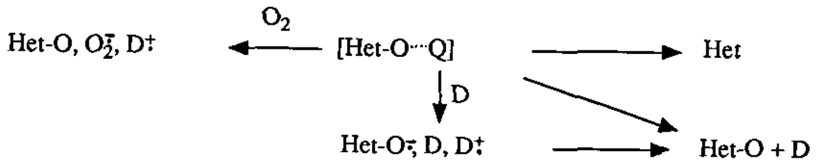


Figure 2. Quantum yield of rearrangement for substrate (4) in the absence and in the presence of DMOB.

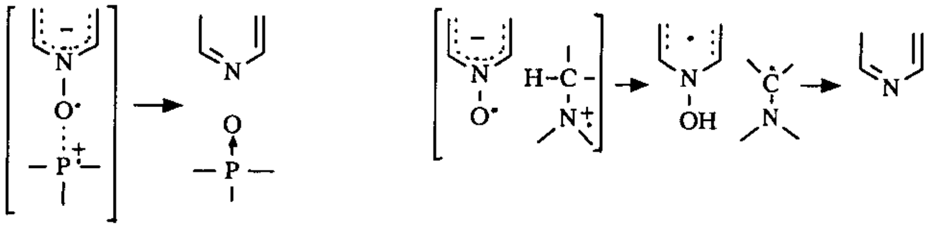
expected from eq.3, and actually in some cases it decreases at concentrations higher than 0.05 M. However, the deoxygenation remains always within the limits of the fraction of the singlet state quenched. By estrapolation at low quencher concentration one can see that the $(k_d+k_c)/k_d$ value is ca 10 also in these cases, thus also here only a fraction of the complex formed leads to deoxygenation.

A rationalization of the anomalous concentration dependence can be obtained by admitting that the complex can itself be quenched. The model seems appropriate, considering that, as shown by the trend in the K_{sv} values, complexation involves electron transfer. Then, electron donors such as TEA and DMB are expected to cause secondary electron transfer in competition with deoxygenation. Electron acceptors would also expected to act in the same way, and indeed the photodeoxygenation is strongly quenched in oxygen-saturated solution (it is reduced to 1/2 to 1/3 of the value in deoxygenated solutions), while fluorescence is only weakly affected. This is due to secondary electron transfer from the *N*-oxide radical anion to oxygen. Examples of similar electron transfer quenching of polarized exciplexes (or radical ion pairs) are known from the literature on the photochemistry of aromatics. This effect of oxygen and donors shows that the lifetime of the excited complex is somewhat longer than that of the *N*-oxide singlet, viz 10 to 100 ns.



The difference between the additives is also conveniently explained in this model. In the case of TEP, the complex evolves by oxygen transfer from the nitrogen to the phosphorus atom, and the N···O···P alignment is probably pre-existing. With TEA and DMB proton transfer from the donor radical cation to the *N*-oxide radical anion and subsequent transfer of the hydroxy group are required, therefore increasing the possibilities of deactivation before irreversible deoxygenation (see Scheme 3 for TEA). On the other hand, DMOB is a good hydrogen donor, but it lacks sufficiently acidic protons; therefore it quenches fluorescence and photorearrangement, but induces no photo-deoxygenation.

This mechanism is thus well established for the phenazine *N*-oxides (3) and (4). In the case of the benzocinnoline (2) the demonstration can not be complete, since the lack of fluorescence precludes obtaining direct evidence of



Scheme 3

the interaction between the quenchers and the excited state. However, the practically identical behaviour of the photoreduction in the presence of the same quenchers considered before strongly supports the proposal that the mechanism is the same also in this case.

The reaction of quinoline 1-oxide (**1**) differs from the previous examples in that the rearrangement remains the main process, with additive-induced deoxygenation. Nevertheless, the effect is again qualitatively the same, and this suggests that the the operation of the same mechanism as above, with the important difference that k_r is larger than in the previous cases (this is reflected in the lack of fluorescence and the relatively high quantum yield of rearrangement; all points to $k_r > 10^9\ M^{-1}s^{-1}$) and k_q is smaller (since this *N*-oxide is less reducible than the phenazine and benzocinnoline derivatives considered above).

The involvement of a triplet state is excluded in the case of compounds (3) and (4), and by analogy is unlikely also with the other derivatives. Therefore the triplet mechanism is probably limited to the special cases mentioned in the introduction.

Finally, the photoreaction in the presence of BTF is completely different. In this case, no excited state of the free *N*-oxide is involved. The reaction involves excitation of a preformed ground state complex. This does not rearrange (see the case of compound **1** and **4**), as one might expect since the rearrangement is attributed to a $\pi\pi^*$ excited state with strong intramolecular charge transfer character (from the oxygen atom to the ring), and this is obviously prohibited by complexation of the oxygen atom by BF_3 (the nmr spectra of these complexes are very similar to those of the unoxidized heterocycle). The only reaction remaining is deoxygenation, which however is rather inefficient. At least part of the explanation of this inefficiency lies in the fact that the ground-state complex absorbs at a lower wavelength, and a lower energy usually favours internal conversion to the ground state against chemical reaction from the excited state. In fact, the yield of deoxygenation drops in gowing from the quinoline to the phenazine derivatives, i.e. towards lower energy excited states.

In conclusion, this work shows that the electron transfer mechanism involving the singlet (path a in Scheme 1) is certainly an important path for the photo-deoxygenation of heterocycles *N*-oxides. A systematic examination has evidenced the requirements for making this path efficient, viz for making the quenching of the singlet state competitive with unimolecular decays. These are on one hand that the substrates are sufficiently easy to reduce (a condition met with polycyclic azine *N*-oxides and the *N*-oxides of aza or electron-withdrawing substituted azines), and on the other one that the rearrangement of the excited state is not too fast. Therefore, deoxygenation according to this mechanism is expected to be inefficient with quinoline or pyridine *N*-oxides and most of their simple derivatives. Different rationalizations have been reported in the literature (see Scheme 1) and it is entirely possible that some deoxygenations occur through (a) different mechanism(s), however, since a systematic study of the reaction quantum yield has not been made in those cases, the indirect evidence reported seem in most cases unsufficient for a firm conclusion.

EXPERIMENTAL

The *N*-oxides were prepared and purified according to literature methods. Irradiation was carried out using 3 ml samples in spectrometric cuvettes after deaeration by flushing with purified argon. The cuvettes were irradiated on a optical bench by means of a high-pressure mercury arc (Osram 150W), focalized and monochromatized through an interference filter (313 nm for **1** and **2**, 438 nm for **3** and **4**). The light flux was in the order of 10^{-7} Einstein/min. The *N*-oxide concentration was 10^{-3} M for **1** and **2** and 2×10^{-4} M for **3** and **4**. The extent of the photochemical reaction was determined by glc (for 1 and 2) and by hplc (for 3 and 4) by comparison with authentic samples. Conversion was in every case limited to ca 25%, and up to this point (and further) the reaction was linear with time. Fluorescence quenchings were measured on degassed samples by means of an Aminco-Bowman MPF spectrofluorimeter.

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