Formation of Singlet Oxygen in the Deoxygenation of Heteroarene *N*-Oxides by Dimethyldioxirane

Waldemar Adam,[a] Karlis Briviba,[b] Frank Duschek,[c] Dieter Golsch,*[a] Wolfgang Kiefer[c] and Helmut Sies[b]

[a] *Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany*
[b] *Institute of Physiological Chemistry I, Heinrich-Heine-Universität Düsseldorf, PO Box 101007, D-40001 Düsseldorf, Germany*
[c] *Institute of Physical Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany*

4-Dimethylaminopyridine-*N*-oxide **2** and 2′,3′,5′-triacetyladenosine-N^1-oxide **4** are partially deoxygenated by dimethyldioxirane (DMD) to the corresponding amines **1** and **3**; the formation of singlet oxygen suggests a polar rather than a radical mechanism, in which we propose S_N2 attack of the *N*-oxide on the dioxirane peroxide bond.

The mechanism of *N*-oxidation of heteroarenes of the pyridine type has been recently established[1] to be an S_N2 attack of the nitrogen lone pair on the peroxide bond, to afford usually high yields of *N*-oxides. However, here we provide cogent experimental evidence that at least in some cases the resulting *N*-oxide efficiently decomposes the dioxirane with liberation of oxygen gas and regeneration of the heteroarene.

An optimal case concerns the DMD oxidation of 4-dimethylaminopyridine **1** to its *N*-1-oxide **2**. While 1.0 equiv. of DMD led to 57% conversion, 3.0 or 5.0 equiv. reached maximally 84% *N*-oxide. Nevertheless, the DMD was consumed within a few minutes at 0 °C with gas evolution. By means of a gas burette, the expected amount (*ca.* 4.3 equiv.) of oxygen gas evolution was established. The suspicion that the *N*-oxide **2** decomposed the dioxirane was confirmed by the reaction of the authentic *N*-oxide with DMD; thus, the use of 1, 2 and 5 equiv. of DMD led to the same mixture of 84 : 16 (*N*-oxide–amine) under oxygen gas liberation. These experiments are summarized in Fig. 1.

If the deoxygenation of *N*-oxides by dioxirane proceeds also by an S_N2 attack of the nucleophilic *N*-oxide oxygen atom on the dioxirane peroxide bond, the mechanism in Scheme 1 should apply. The proposed dipolar intermediate should lead to singlet oxygen in this novel deoxygenation, as is observed in other heterolytic dioxygen-producing processes, most prominently the chemiluminescent decomposition of hydrogen peroxide by hypochlorite ion[2] and triphenyl phosphite ozonide.[3] Thus, as a crucial test for the postulated singlet oxygen generation (Scheme 1), we searched and, indeed, observed the expected dimol visible [eqn. (1)] and monomol IR [eqn. (2)] chemiluminescence[4] in the *N*-oxide-promoted decomposition of dimethyldioxirane.

$$O_2(^1\Delta_g) + O_2(^1\Delta_g) \rightarrow 2\ O_2\ (^3\Sigma_g^-) + h\nu\ (634 \text{ and } 703\ \text{nm}) \quad (1)$$

$$O_2(^1\Delta_g) \rightarrow O_2\ (^3\Sigma_g^-) + h\nu\ (1268\ \text{nm}) \quad (2)$$

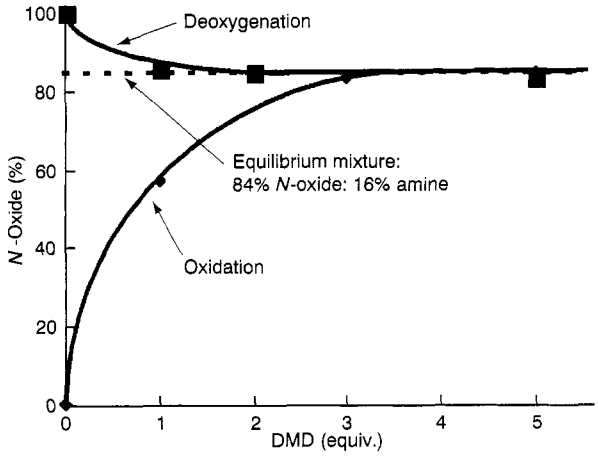
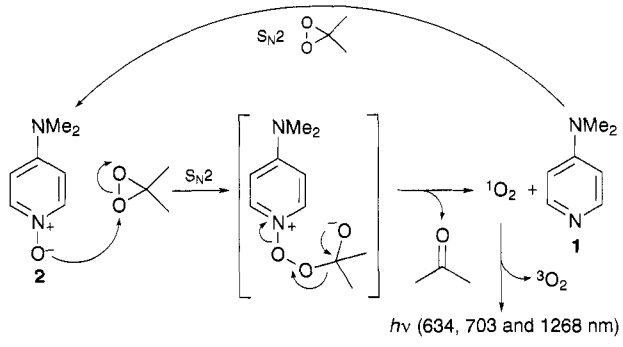


Fig. 1 Oxidation of 4-dimethylaminopyridine **1** and deoxygenation of its *N*-oxide **2** by DMD

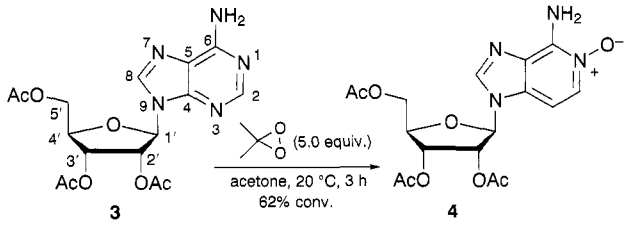
The monomol emission of $^1O_2$ in the DMD–*N*-oxide reaction was measured by means of a liquid nitrogen-cooled germanium photodiode detector[5] (800–1800 nm) with a bandpass filter for 1270 ± 10 nm.† The intensity of the IR chemiluminescence was solvent dependent, *i.e.* the relative intensities were 1.0 : 0.38 : 0.088 in acetone, acetone–methanol (33.8 : 66.2) and acetone–water (33.8 : 66.2), which is in agreement (r^2 = 0.967) with the singlet oxygen lifetimes in these solvent mixtures.[6] Since the *N*-oxide **2** concentration remains constant (it is also continuously reformed by oxidation of the amine until all DMD is consumed), pseudo-first-order kinetics of the infrared chemiluminescence emission applies, as manifested by a plot of log (I/I_0) against time (r^2 = 0.999).

2′,3′,5′-Triacetyladenosine **3** was oxidized at the *N*-1 position, which is known to be the most nucleophilic site in adenosine.[7a] However, analogously to 4-dimethylaminopyridine **1**, the *N*-oxide **4** was incompletely formed. Even with a five-fold excess of DMD only 62% conversion was observed, but the dioxirane was consumed with oxygen gas evolution (Scheme 2). Indeed, when the adenosine *N*-oxide **4** was treated with 5.0 equiv. of DMD at 20 °C in CH_2Cl_2, the same 62 : 38 *N*-oxide–adenosine mixture was observed as had been found in the oxidation of the adenosine **3** to the *N*-oxide **4** (Scheme 2). Presumably also in this case singlet oxygen is produced, a novel pathway for $^1O_2$ generation with interesting implications in biochemical systems.[7b]

In summary, we suspect that the deoxygenation of *N*-oxides by dimethyldioxirane with $^1O_2$ evolution may be a more general phenomenon that previously recognized. In this context,



Scheme 1



Scheme 2

Murray[8] already in 1989 and recently Messeguer and coworkers[9] brought attention to the fact that DMD is decomposed by *N*-oxides, but the formation of singlet oxygen was not demonstrated.

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Footnote

† The $^1O_2$ production was calibrated by the thermolysis of the disodium 3,3′-(1,4-naphthylidene)dipropionate endoperoxide ($NDPO_2$).[5] Thus, in the reaction of *N*-oxide **2** (0.24 mmol dm^{-3}) with DMD (7.0 mmol dm^{-3}) in methanol–acetone (11 : 1) at 37 °C, *ca.* 5% of the total oxygen gas evolved was produced as $^1O_2$ when compared with the $NDPO_2$ standard (7.5 mmol dm^{-3} produced 62 μmol dm^{-3} $^1O_2$ min^{-1}).

References

1 W. Adam and D. Golsch, *Angew. Chem.*, 1993, **105**, 771; *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 737.
2 C. S. Foote, S. Wexler and W. Ando, *Tetrahedron Lett.*, 1965, 4111.
3 R. W. Murray and H. L. Kaplan, *J. Am. Chem. Soc.*, 1969, **91**, 5358.
4 A. U. Khan and M. Kasha, *J. Am. Chem. Soc.*, 1970, **92**, 3293.
5 P. Di Mascio and H. Sies, *J. Am. Chem. Soc.*, 1989, **111**, 2909.
6 B. M. Monroe, in *Singlet* O_2, ed. A. A. Frimer, CRC Press, FL, 1985, vol. 1, ch. 5, *Singlet Oxygen in Solution: Lifetimes and Reaction Rate Constants*, p. 183.
7 (*a*) *Molecular Biology of Mutagens and Carcinogens*, ed. B. Singer and D. Grumberger, Plenum Press, New York, 1983, ch. IV; (*b*) R. J. H. Davies, D. R. Boyd, S. Kumar, N. D. Sharma and C. Stevenson, *Biochem. Biophys. Res. Commun.*, 1990, **169**, 87.
8 R. W. Murray, *Chem. Rev.*, 1989, **89**, 1187; the possibility of singlet oxygen formation was suggested, but not experimentally established.
9 M. Ferrer, F. Sánchez-Baeza, A. Messeguer, A. Diez and M. Rubiralta, *J. Chem. Soc., Chem. Commun.*, 1995, 293.