Interaction between Molecular Oxygen and Nitroxide Radicals: A Search for a Reversible Complex

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Dedicated to the memory of Professor *Hanns Fischer*

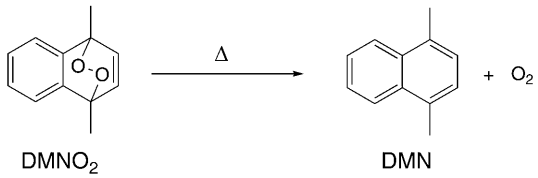
At high concentrations of oxygen, the EPR spectrum of the nitroxide radical 4-oxo-TEMPO (=4-oxo-2,2,6,6-tetramethylpiperidin-1-yloxy) is found to broaden significantly. In addition to the expected broadening, double integration of the EPR signals indicates that a significant fraction of the nitroxide spins has 'disappeared'. In perfluoro(2-butyltetrahydrofuran) at 273 K, the extent of diminution of the EPR signal intensity is *ca.* 20%. The results are analyzed in terms of collision and supramolecular complexes between oxygen and 4-oxo-TEMPO. It is concluded that a supramolecular complex is responsible for the observed phenomenon.

Introduction. – Molecular oxygen exists as a ground-state triplet and possesses a low-lying singlet state [1]. The interaction of triplet O_2 as well as singlet O_2 in solution with nitroxide radicals, a well-studied class of persistent paramagnetic species [2][3], has been investigated in great detail in recent years. For example, the EPR spectroscopy of the interaction of triplet O_2 with nitroxide radicals has been extensively studied, and constitutes the basis of a widely applied method for quantitatively determining triplet O_2 in solution (termed oximetry) [4]. Oximetry is based on the line broadening of the nitroxide EPR signal, which is directly related to the concentration of triplet O_2. Moreover, nitroxide radicals are also efficient quenchers of singlet O_2, in which the quenching step involves most likely a combination of charge-transfer and spin–spin interactions [5][6]. The spin–spin interactions with singlet O_2 may be monitored by EPR spectroscopy, since during this interaction of singlet O_2 and a nitroxide, the nitroxide radicals become absorptively polarized, a feature that is readily detected by time-resolved electron paramagnetic resonance (TR-EPR) [7–10].

We have initiated investigations of the interaction of O_2 with nitroxides by EPR by employing the thermal decomposition of endoperoxides as a source of O_2 (*Scheme*) [11]. Decomposition of endoperoxides in the presence of nitroxide in organic solvents produces an unusual EPR phenomenon: After most of the *endo*-peroxide had decom-

posed, the EPR spectrum of the nitroxide is severely broadened, but after a period of time, the nitroxide spectrum sharpens and eventually reaches a level of broadening identical to that for an air-saturated solution. These results were interpreted [11] to mean that the thermolysis had produced a supersaturated solution of triplet O_2 (the cause of the severe broadening), which then returned to its equilibrium concentration, thus regenerating the corresponding nitroxide spectrum.

Scheme



During the course of these studies, we became aware of a report that the EPR spectrum of nitroxides 'disappeared' upon addition of triplet O_2 at low (77 K) temperatures in polymer films [12]. The disappearance was found to be reversible, and the EPR signal reappeared upon removal of the triplet O_2. The disappearance and regeneration of the nitroxide EPR signal in the presence of triplet O_2 was rationalized in terms of the reversible formation of a *diamagnetic* complex of unknown stoichiometry between the triplet O_2 and nitroxide. Given the rather extensive EPR-spectral investigations of nitroxides and triplet O_2, it was rather surprising that such a phenomenon had not been reported previously for *solutions* of nitroxides and triplet O_2; however, if the complex has a low stability, and thus possesses a small equilibrium constant, it is plausible that the complex may not have been detectable in solution at room temperature.

The disappearance of the nitroxide EPR signal in O_2-saturated solutions may have serious implications on the quantitative reliability of oximetry. It therefore seemed advisable to check the results quantitatively by spectroscopic methods other than EPR, if possible. However, such experiments may be difficult if the putative complex is only formed in very low equilibrium concentrations. The concentration of the complex could be enhanced by the following: by employing a higher nitroxide concentration, by increasing the concentration of O_2 in the solution, or by decreasing the temperature. Of these three options, increasing the nitroxide concentration was considered to be the least attractive, since it would be difficult to measure accurately a small decrease of a very large initial nitroxide EPR signal. A more straightforward option is to increase the concentration of triplet O_2 in the solution at a fixed and relatively low nitroxide concentration. For example, a solvent may be employed in which the O_2 has a high solubility; alternatively, a lower temperature could be used since gases such as O_2 are expected to be more soluble under such conditions.

Perfluorinated solvents are well-known to dissolve relatively high concentrations of O_2 gas compared to typical organic solvents. As a test solvent, perfluoro (2-butyltetrahydrofuran) (=2,3,3,4,4,5,5-heptafluoro-tetrahydro-2-(1,1,2,2,3,3,4,4,4-nonafluorobutyl)furan; PFTF) appears to be attractive, in view of the fact that it both possesses a high solubility of O_2 gas and may also be cooled to relatively low temperatures. It was anticipated that a temperature could be reached where the amount of dissolved

O_2 in the nitroxide solutions would be sufficient to quench a significant fraction of the EPR signal of the nitroxide radical. Presumably, under the same conditions, the concentration of the complex between O_2 and nitroxide might be sufficiently high for to be detected by an independent spectroscopic method, such as UV/VIS absorption.

Results. – *Fig. 1* shows the time profile of the doubly integrated intensity of the EPR spectrum of 4-oxo-TEMPO (=4-oxo-2,2,6,6-tetramethylpiperidin-1-yloxy; 4oT) during the thermal decomposition of 1,4-dimethylnaphthalene endoperoxide ($DMNO_2$) at 330 K, along with the EPR spectra obtained at 0, 2, 7, 26, and 63 min after initiating the thermolysis. The initial EPR signal (*Fig. 1*, left) in air-saturated solutions corresponds to the well-known relatively sharp three-line nitroxide spectrum of 4oT. After 6–8 min (*ca.* 90% of the endoperoxide had decomposed), the spectrum appeared severely broadened. After *ca.* 20 min, the EPR signal began to sharpen up, and after *ca.* 60 min, the characteristic sharp three-line spectrum (*Fig. 1*, right) was regenerated. As reported previously [11], the evolution of the *Lorentzian* component of the linewidth for the nitroxide spectrum (ΔH^L) correlates with the O_2 concentration in the solution, even when the three hyperfine lines are not resolved. For instance, the broadest signal, which also corresponds to the minimum of the curve in *Fig. 1* (*t* 6.3 min), has ΔH^L =20.3 G, corresponding to an O_2 concentration of 93 mM. The *loss* of signal intensity reaches a maximum value of 33% at *t* 6.3 min. For comparison, the loss of signal in an O_2-saturated solution (*ca.* 9 mM) [13] of benzene at room temperature is *ca.* 10% and does not change with time.

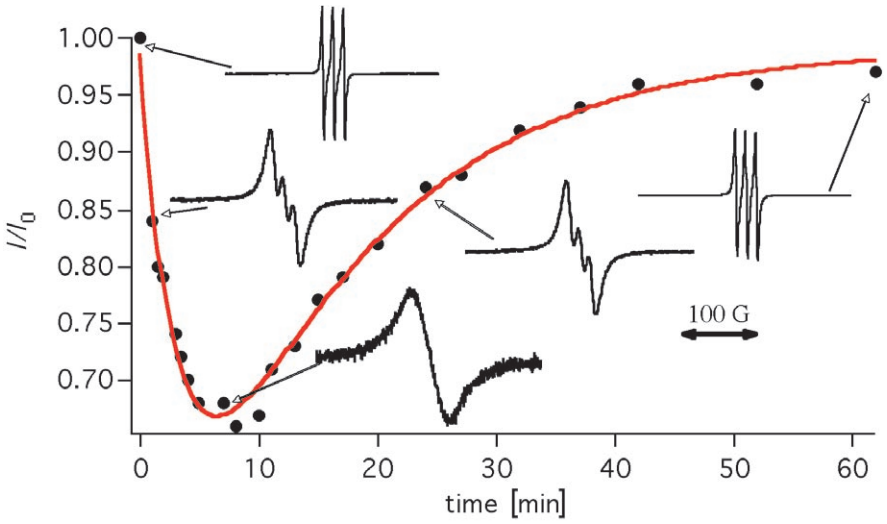


Fig. 1. *Time profile of the doubly integrated intensity of the EPR signal of 4-oxo-TEMPO* (0.6 mM) *during the thermal decomposition of 1,4-dimethylnaphthalene endoperoxide in benzene at 300 K.* Spectra after 0, 2, 7, 26, and 63 min.

In independent experiments, the concentration of triplet O_2 was computed from the line-broadening of the nitroxide EPR signal in benzene. The results are shown in *Table 1*. From the data, it may be seen that the O_2 concentration increases from its initial equi-

Table 1. *Loss of Nitroxide EPR Signal of 4oT* (0.6 mM) *as a Function of Oxygen Concentration after the Thermal Decomposition of $DMNO_2$ for Different Times in Benzene*

Time [min]	Loss of signal[a])	Oxygen concentration[b]) [mM]
0.0	0.0	1.9
2.1	0.20	50
4.2	0.26	69
6.3	0.32	72
10.6	0.31	62
17.0	0.23	39
27.6	0.12	16
41.4	0.04	5.5
62.5	0.02	2.4

[a]) Calculated by double integration. [b]) Calculated by oximetry as reported in [11].

librium value (under air-saturated condition) of 1.9 mM [13] to a maximum of *ca.* 72 mM and finally back to its equilibrium value of 1.9 mM.

Since the O_2 solubility in fluorinated solvents is 3 to 10 times greater than in benzene [14], the loss of the nitroxide EPR signal was investigated in an O_2-saturated fluorinated solvent. For this purpose, perfluoro(2-butyltetrahydrofuran) (PFTF) was chosen because it can dissolve O_2 gas up to a concentration of 21.3 mM at 295 K [15]. *Fig. 2* shows that an O_2-saturated solution of 4oT in PFTF causes a loss of $21 \pm 5\%$ for the nitroxide signal (by double integration) at 295 K.

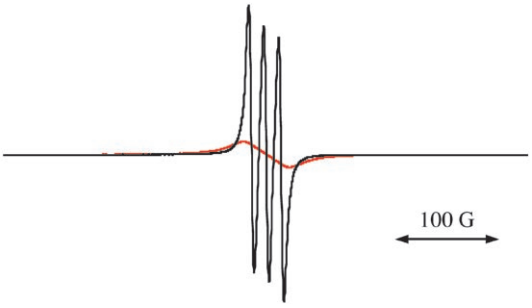


Fig. 2. *Loss of intensity of the EPR signal of 4-oxo-TEMPO* (0.6 mM) *in an O_2-saturated solution of PFTF at 295 K* (red trace), *as compared to an air-saturated solution* (black trace)

To investigate the possible temperature dependence of the amount of lost nitroxide signal in O_2-saturated solutions, equivalent experiments were performed as described in *Fig. 2*, but at a lower temperature (273 K). The EPR experiments at 273 K showed a loss of *ca.* 20% of nitroxide signal in O_2-saturated PFTF solutions compared to air-saturated solutions. This indicates that there is no temperature dependence within our investigated temperature range.

The latter conditions appeared to be advantageous for detecting directly the putative oxygen–nitroxide complex by means of UV/VIS spectroscopy. For the UV/VIS absorption studies, we used TEMPO (T) instead of 4-oxo-TEMPO to eliminate the car-

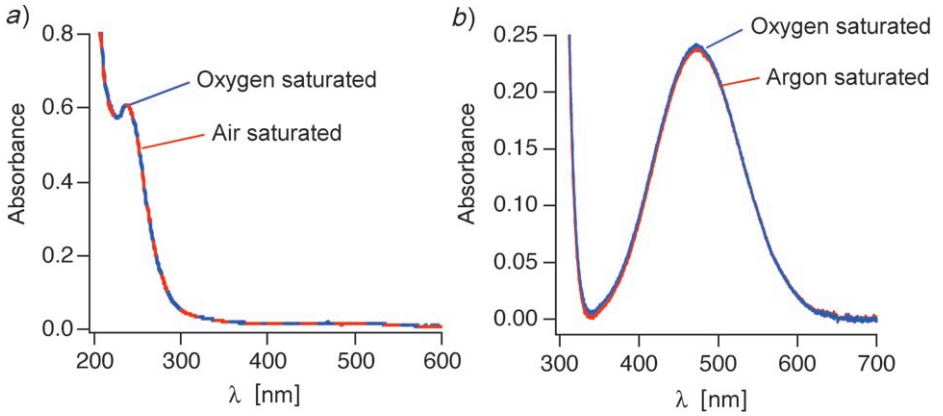


Fig. 3. *UV/VIS Spectra of TEMPO* (T) (0.6 mM) a) *in PFTF at 295 K* (path length 1 cm) *and* b) *in hexane at 295 K* (path length 1 m)

bonyl absorption from 4oT. *Fig. 3,a* shows the UV/VIS spectrum of T in PFTF. The spectrum of T consists of a relatively strong π–π^* transition ($\varepsilon = 3000$) which maximizes at 240 nm and a very weak n–π^* transition ($\varepsilon = 5$) which maximizes at 470 nm [2][3]. Although *ca.* 20% of the nitroxide EPR signal had disappeared in PFTF at 295 K, *Fig. 3,a* reveals that the π–π^* transition is not affected by Ar or O_2 bubbling.

To investigate if the weak n–π^* transition at 470 nm is affected by the presence of O_2, a capillary waveguide spectrometer was employed to increase the sensitivity by extending the optical path length to 1 m. For these experiments, hexane was used as solvent instead of the preferred PFTF, because the low refractive index of PFTF causes a total loss of light in the *Teflon*-coated waveguide. As shown in *Fig. 3,b*, no change of the n–π^* transition of T at 470 nm was observed in the presence or absence of O_2. Under the same conditions, a loss of signal of *ca.* 10% in the EPR signal of T is observed in O_2-saturated solution.

The possibility that the loss of the EPR signal intensity of the nitroxide radical at high O_2 concentrations results from an artifact of the double-integration method needs to be considered, although we are unaware of any such artifact. To test for such an artifact, the double integration was performed by increasing the nitroxide concentration and assessing whether the EPR signal intensity increases proportionally. In *Table 2* are reported the double-integrated signal intensities of benzene solution with nitroxide concentrations that range from 0.5 to 100 mM. Within the experimental error, no loss of the EPR signal intensity was observed. Moreover, increasing the field sweep from 300 to 500 G results in no change on the amount of signal loss. Thus, an artifact in the double-integration method is unlikely. The loss in the EPR signal intensity is specific for the nitroxide–oxygen system.

Discussion. – *Complexes of Molecular Oxygen with Organic Molecules.* Triplet O_2 is well-known to form weak complexes with closed-shell organic molecules. An example is the reversible formation of complexes which lead to enhancement of the $S_0 \rightarrow T$ absorption bands of organic molecules [16]. The complexes are believed to result

Table 2. *Normalized Double-Integration Intensity Varying the Concentration of 4oT in Benzene.* The experimental error is estimated to be ±5%.

Nitroxide concentration [mM]	0.5	1.0	5.0	10	50	100
Normalized double-integration intensity	0.53	1.0	4.8	10	53	104

from weak but stabilizing charge-transfer (donor–acceptor) interactions [17]. The binding energies of these complexes are of the order of kT, which implies very small concentrations of the complexes at room temperatures, but the possibility of higher concentrations at low temperatures. Although triplet O_2 is a paramagnetic molecule with a spin of 1, an EPR spectrum is not detected in liquids at room temperature because of extreme signal broadening. This results from the very fast (*ca.* 7–8 ps) electron-spin relaxation time, a consequence of the strong contact and dipole–dipole interactions [18][19]. NMR Spectroscopy has provided evidence for complexes between triplet O_2 and organic molecules [20] through the observation of paramagnetic shifts of the NMR signals and their temperature and concentration dependence. While these studies reveal an interaction between O_2 and organic molecules, the detailed structure of the complexes remains obscure.

Because the complexes of triplet O_2 with organic molecules are weakly bound and their equilibrium concentrations are small, it is not a simple task to differentiate between a 'collision complex' and a 'supramolecular complex' of a nitroxide–oxygen complex. By a collision complex, we mean that there is no special binding between the triplet O_2 and nitroxide: the partners are in proximity simply as a consequence of the 'solvent cage' effect. The lifetime of a collision complex in solution is, therefore, equal to the time it takes two partners of the complex to exit the solvent cage (typically of the order of ps for nonviscous solvents). By a supramolecular complex, we imply that there is significant, but weak, binding of the partners which implies a longer lifetime, a definite stoichiometry, and a more or less definite structure than a collision complex. We codify the supramolecular complex by the symbol oxygen@nitroxide and the symbol oxygen/nitroxide to describe the collision complex.

Heisenberg exchange will broaden the nitroxide EPR spectra of both oxygen@nitroxide and oxygen/nitroxide complexes. For an oxygen@nitroxide complex, the broadening might be so severe that the nitroxide EPR signal will not be observable (such broadening is analogous to the situation for triplet O_2, whose EPR spectrum is not observable in liquids). In this event, the 'disappearance' of the nitroxide spectrum in the presence of triplet O_2 is not due to the formation of a supramolecular complex, but is simply the consequence of spreading of the EPR signal over such a wide range that no signal is registered on integration even over hundreds of Gauss.

Accepting this explanation requires the acceptance of the existence of two complexes, one complex that is responsible for the complete loss of EPR signal as determined by the double-integration method and one complex that possesses the broad, but measurable EPR signal shown in *Fig. 2*. An explanation consistent with this possibility is *i*) that the signal loss is due to the formation of a supramolecular oxygen@nitroxide complex for which there is enough of a mixing of the triplet O_2 spin with the nitroxide to cause extensive broadening, and *ii*) that the measured broad signal is due to the formation of collision oxygen/nitroxide complexes of the triplet O_2 and the nitroxide.

Possible Structures Suggested for the Putative Supramolecular Complex between Oxygen and Nitroxides. The simplest molecular structures for the oxygen@nitroxide complex are suggested in *Eqns. 1* and *2* (where R_2NO represents the nitroxide radical).

$$R_2NO + O_2 \rightarrow \underset{\mathbf{1}}{R_2NOOO} \quad (1)$$

$$R_2NOOO + ONR_2 \rightarrow \underset{\mathbf{2}}{R_2NOOOONR_2} \quad (2)$$

The 1:1 adduct **1** is a peroxy radical which would be expected to possess a very weak NO–OO bond, is paramagnetic, and exhibits an EPR signal. However, its stationary concentration may be too low for EPR detection. The 2:1 adduct **2** should also possess a weak NO–O bond, but in contrast to **1** could be diamagnetic and, thus, EPR silent. Unhindered nitroxides have been shown to dimerize through reversible formation of a weak NO–ON bond to form diamagnetic molecules [21], but such bond formation need not be considered here. Consequently, the two suggested structures **1** and **2** would explain the loss of the nitroxide radical EPR signal at high concentrations of triplet O_2. Furthermore, the possibility of an O_2-catalyzed formation of a nitroxide dimer could be considered, but is unlikely.

Should the structure of the complex be trioxy radical **1**, then the loss of EPR signal intensity at high O_2 concentrations could be due to extreme broadening of its EPR signal. To test for this possibility, the tails of the EPR signals in O_2- and air-saturated solutions in PFTF were subjected to double-integration with a very wide field sweep of 500 G. The same value of signal-intensity loss was observed as for a 300-G field sweep. Since the much larger field sweep did not reveal any enhanced intensity, we conjecture that the reversible loss of the EPR signal intensity during the decomposition of the endoperoxide is not due to formation of a paramagnetic trioxy radical **1**, unless the latter is exceptionally broadened. Peroxy radicals have an EPR signal width that typically ranges between *ca.* 5 to 30 G [22–24].

The formation of either **1** or **2** might be expected to be accompanied by a measurable change in the UV/VIS spectrum of solutions of T. However, the UV/VIS spectra of solutions of T and O_2 (*Fig. 3*) fail to reveal any changes when 10% of the EPR spectrum has disappeared, even though a *ca.* 10% decrease in the intensity of the UV/VIS spectrum is easily observable. This result is consistent with either the lack of significant electronic interaction of O_2 and T or the absence of a complex such as **1** or **2**.

An alternative explanation for the loss of the EPR signal intensity is the formation of the diamagnetic 2:1 complex **2** between two 4oT radicals and one triplet O_2 molecule. This possibility is consistent with the failure to find spectral evidence for the broadening of the EPR signal expected for the trioxy radical **1**. However, the observed negligible change in the UV/VIS spectrum of solutions of the nitroxide and O_2 does raise some concern for this assignment.

On the other hand, the data in *Fig. 1* and *Table 1* is consistent with existence of structure **2**, *i.e.*, the formation of a complex between two nitroxide and a single O_2 molecule. Since the concentration of O_2 along the curve is known from oximetry and since the concentration of 4oT is fixed at 0.6 mM, the equilibrium constant may be computed

for the putative complex from *Fig. 1* or *Table 1*. The computed value of a 2 : 1 complex is $K \approx 2 \cdot 10^4$ M^{-2}. The value of K is constant for the values of *Fig. 1*, consistent with a 2 : 1 stoichiometry (and existence) of the complex.

Conclusions. – The decrease of the EPR signal intensity of nitroxide radicals, observed in the presence of high concentrations of triplet O_2 in benzene and PFTF solvents, is not an artifact of the double-integration method used in these EPR experiments. It is also unlikely that the loss of EPR signals is due to extreme line broadening resulting from a high density of a paramagnetic species. The observed loss of the EPR signal is tentatively assigned to the intervention of a diamagnetic complex **2** between triplet O_2 and two nitroxide radicals (*Eqn. 2*). The assignment is consistent with the stoichiometry deduced from the equilibrium constant extracted from the data in *Fig. 1* and *Table 1*. Although the structure has yet to be established unambiguously, we speculate that a reversible, diamagnetic complex between two nitroxide radicals and one O_2 molecule is involved. Further investigations will be necessary to clarify the structure of the putative complex.

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Experimental Part

General. The 4-oxo-TEMPO (=4-oxo-2,2,6,6-tetramethylpiperidin-1-yloxy; 4oT), TEMPO (=2,2,6,6-tetramethylpiperidin-1-yloxy; T), benzene, and hexane, spectrophotometric grade, were purchased from *Aldrich* and used without further purification; 1,4-dimethylnaphthalene endoperoxide ($DMNO_2$, *Scheme 1*) was synthesized according to the reported procedure [25]. The Ar and O_2 gases were purchased from *Airgas*; perfluoro(2-butyltetrahydrofuran) (PFTF) was obtained from *Oakwood Products, Inc.*

EPR Spectra: *Bruker-EMX* spectrometer operating at X-band (9.5 GHz). UV/VIS Spectra: *Agilent-8453* diode array UV/VIS spectrophotometer, quartz cuvettes of 1-cm optical path length; or *Ocean Optics* waveguide spectrophotometer consisting of a lamp *DT1000CE* (*Analytical Instruments System, Inc.*), a 1-m waveguide (*LWCC-2100*, *World Precision Instruments, Inc.*), and a CCD spectrometer (*USB2000 Ocean Optics, Inc.*).

Thermal Decomposition of 1,4-Dimethylnaphthalene Endoperoxide (=*1,4-Dihydro-1,4-dimethyl-1,4-etheno-2,3-benzodioxin*; $DMNO_2$). An air-saturated soln. of $DMNO_2$ (130 mM) that contained 0.6 mM 4oT at 330 K (±0.1 K) was allowed to decompose in the cavity of the EPR spectrometer. The acquisition parameters were optimized for a relatively fast acquisition time (40 s) and a good field resolution (500 G of sweep and 1024 points, see the Discussion section). The modulation amplitude was set to 1 G, and the microwave power to 0.2 mW to ensure the nonsaturation of the signal.

Oxygen Saturation Experiments. The nitroxide solution was purged gently with Ar and O_2 gas for 5 min. In these experiments, the evaporation of solvent was negligible.

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