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DYE-SENSITIZED PHOTOOXIDATION OF PHENOTHIAZINE

AN ESR STUDY

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Abstract—The dye-sensitized or direct-light induced photooxidation of phenothiazine yielded phenothiazine nitroxide (1) and phenothiazanyl (2) radical depending on the reaction conditions. A singlet oxygen mechanism is suggested.

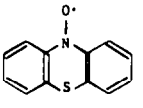
During the past few years the chemistry of phenothiazine has been enjoying an intense interest mainly because of the neuroleptic action of its substituted derivatives.[1] The observation that patients treated with high doses of phenothiazine drugs often show hyperpigmentation of the skin[2] promoted our interest in the light-induced reactions of these compounds.

The study to be described here was undertaken with the aim of identifying paramagnetic species generated from phenothiazine under different light-irradiation conditions. Thus phenothiazine can be photooxidized[3] at room temperature to yield free radicals which can be detected and characterized by ESR. The reaction could be sensitized by dyes such as methylene blue, rose bengal and substituted porphines, using light which is exclusively absorbed by the sensitizer in the visible range of the spectrum close to the red limit, or alternatively could be induced by direct excitation of phenothiazine. Two different radicals which could be discriminated only by the difference in the nitrogen and some of the protons hyperfine splittings were obtained. The results are summarized in Table 1.

Since the radicals were generated in oxygenated solutions, the spectra recorded with the start of irradiation were poorly resolved. The resolution was markedly improved with the irradiation time due to the consumption of oxygen by the chemical reaction or by controlling the initial amount of oxygen in the solution.

The unresolved radicals 1 and 2 appear as a triplet and a very broad line, respectively, so that they can be roughly differentiated even before the final resolution is obtained.

The elucidation of the structure of phenothiazine radicals has long been an area of concern.[3-5] Despite their relative simplicity, there was not a concensus of opinion as to the structures assigned, primarily because of difficulty of assigning the ESR data specifically to phenothiazine nitroxide (1) or to the neutral radical (phenothizinyl) (2).



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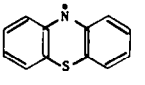


2

While the isotopically normal phenothiazine nitroxide cannot be differentiated from phenothiazinyl by hyperfine interactions in the ESR spectra, the ^{17}O-labeled nitroxide is expected to show additional splitting due to the ^{17}O nucleus. (I = 5/2 therefore, each ESR resonance line will be split into six components). Consequently a mixture of oxygen enriched in ^{17}O (89·33% ^{17}O, the Heavy Oxygen Separation Plant, The Weizmann Institute of Science) was leaked into a very carefully degassed solution of phenothiazine and methylene blue in methanol.

The irradiation of this solution ($\lambda > 590\,m\mu$) yields a spectrum which displays additional lines due to ^{17}O splitting (Fig. 1). This result clearly show that the radical obtained in these conditions is the nitroxide (1). Computer simulated spectrum to fit the experimental one was plotted using the measured parameters of radical 1, $|a^{^{17}O}| = 12{\cdot}5$ G and ^{17}O content of 80%. Employing this splitting constant, the spin density at the O atom could be calculated from the relationship $a_0 = Q^0_{00}\rho_0{}^6$, where $Q^0_{00} = -41 \pm 3$G, to be $0{\cdot}305 \pm 0{\cdot}024$.

Our value for the spin density on O atom falls in the range of 0·233–0·321 as determined by Chiu *et al.*[4] for the spin density on N atom. This is consistent with the finding

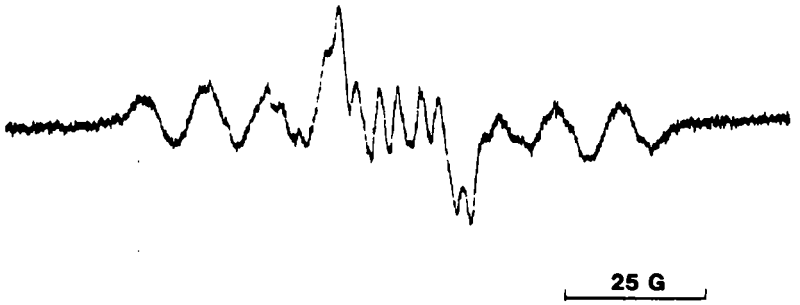


Fig. 1. X-Band ESR spectrum of ^{17}O-labeled phenothiazine nitroxide in methanol, at ambient temperature.

Table 1.

Sensitizer	Solvent	Radical generated	Hyperfine splitting (G)
Methylene blue[a]	Methanol	1	9·6 (triplet) 2·25 (quintet) 0·6 (quintet)
Rose bengal[b]	Methanol	1	9·6 (triplet) 2·25 (quintet) 0·6 (quintet)
Zn-mesotetraphenyl[b] porphine	Methanol	1	9·6 (triplet) 2·25 (quintet) 0·6 (quintet)
—	Methanol[b]	—	
Zn-mesotetraphenyl[b] porphine	Benzene	2	7·1 (triplet) 3·65 (triplet) 2·86 (triplet) 0·95 (quintet)
—	Benzene[b]	—	
—	Benzene[c]	2	7·1 (triplet) 3·65 (triplet) 2·86 (triplet) 0·95 (quintet)
—	Methanol[c]	1 + 2	7·1 (triplet) 3·6 (triplet) 2·6 (triplet) 1·0 (triplet) 0·75 (triplet)[d]
—	Ethanol[c]	1 + 2	7·1 (triplet) 3·6 (triplet) 2·6 (triplet) 1·0 (triplet) 0·75 (triplet)[d]
—	Acetonitrile[c]	2	7·1 (triplet) 3.65 (triplet) 2·80 (triplet) 0·9 (quintet)
—	Acetone[c]	2	7·1 (triplet) 3·65 (triplet) 2·80 (triplet) 0·95 (quintet)

[a] $\lambda > 590$ mμ (Corning CS 2-62 cut-off filter).
[b] $\lambda > 480$ mμ (Schott GG 498 cut-off filter).
[c] $\lambda > 300$ mμ (Pyrex filter).
[d] *Coupling constants for radical II.*

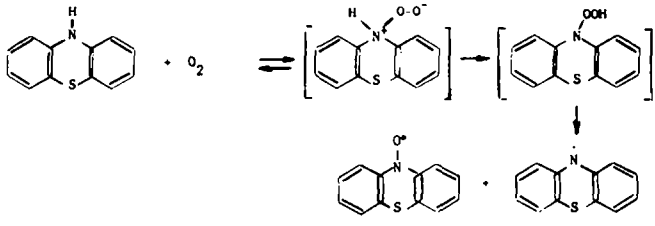
that the $p\pi$ spin densities on the N and O atoms in nitroxide radicals are essentially equal.[7]

A ^{17}O-spectrum similar to that obtained in the methylene blue-sensitized reaction resulted when phenothiazine was directly irradiated in a methanol solution. However in this case ^{17}O-splitting disappeared with the irradiation (*vide infra*). Nevertheless, even the described data cannot discriminate between the neutral and nitroxyl radical of the phenothiazine and the same radicals derived from its corresponding 5-sulfoxide. The latter compound was isolated from the photooxidation of phenothiazine on a preparative scale[8] and might well be the precursor of the radicals observed. However, under similar photochemical reaction conditions as employed for phenothiazine, in sensitized or direct light-induced reactions, no detectable amount of paramagnetic species are formed from the phenothiazine-5-oxide.

The direct irradiation of phenothiazine in alcohol solutions yields initially both radicals 1 and 2. Under continuous irradiation, however, the phenothiazine nitroxide disappears and leaves the pure phenothiazinyl radical. The rate of disappearance increases with the intensity of the irradiation light. We suggest that the disappearance of nitroxyl radical is due to a photochemical reaction with the excess of phenothiazine present. Since the nitroxyl radical 1 could not be isolated in pure form, this suggestion was proved indirectly. Thus a solution of 2,2,6,6-tetramethyl-4-piperidone-1-oxyl (Frinton Lab.) in methanol was irradiated in the ESR cavity at room temperature with light of $\lambda > 300$ nm (Pyrex filter). While under these conditions the radical was stable, the addition of phenothiazine to such a solution before irradiation provoked a marked and continuous disappearance of the radical with the irradiation time. It was noted that no complementary radical such as phenothiazinyl could be detected. This suggests that in the photooxidation of phenothiazine, radical 2 is not a "second generation" derived from 1.

Scheme 1 depicts the suggested mechanism for radical formation.

The low ionization potential of phenothiazine[9] (6·7 eV) makes this compound an ideal substrate for singlet $^1\Delta_g$ oxygen attack. The excitation of oxygen in the reaction mixture, can be achieved by energy transfer from the excited sensitizer or excited phenothiazine itself. Thus the first step in the oxidation is an electrophilic attack by $O_2(^1\Delta_g)$, on the unshared electron pair of nitrogen to yield a nitrogen hydroperoxide.[10,11] Subsequently depending upon reaction conditions the N–O or O–O bonds are cleaved to yield the observed radicals. The main support for the involvement of singlet molecular oxygen is provided by the methylene blue-sensitized reaction. Thus,



Scheme 1.

in this case, any alternative mechanism should involve the interaction between the excited sensitizer and phenothizine, which competes with the energy transfer to the ground state oxygen. Such an interaction (Type 1 photooxidation)[12] must lead to the formation of dye-free radicals. Although detectable at room temperature under our experimental conditions,[13] no such species were observed in the reaction mixture. In the same context, it was also noted that in carefully degassed solutions of phenothiazine and methylene blue no radicals were generated at all by irradiation. Furthermore, the DABCO a well known physical quencher of singlet-oxygen[14] efficiently, inhibited the radical formation in the dye sensitized reaction (5×10^{-3} M DABCO, 1×10^{-4} M phenothiazine). In control experiments, several commercially available nitroxides were unaffected by the presence of DABCO, when irradiated by light of $\lambda > 590$ mμ. Finally the photooxidation of phenothiazine was attempted in benzene solution using rubrene (5,6,11,12-tetraphenylnaphthacene) as sensitizer. Rubrene is known to selfsensitize its oxidation by a singlet oxygen mechanism.[15] In this case, although a well resolved spectrum could not be obtained to enable a definite identification, the broad envelope of the signal initially recorded indicates the formation of phenothiazanyl radical.

It is to be pointed out that the above arguments do not exclude a different mechanism operating in the direct-light induced reactions. We are at present attempting to determine the short-lived species involved in this process.

EXPERIMENTAL

Phenothiazine (Fluka A. G.) was recrystallized from MeOH (m.p. 181–183°) after treatment of the solution with activated charcoal. A sample sublimed under reduced pressure had the same m.p. and ESR spectrum as the freshly recrystallized sample. The irradiations were performed in the cavity of a Varian E-12 ESR spectrometer with an Osram HBO 200 W lamp housed in a Wild projector. All measurements were performed at room temperature. Typical concentrations were phenothiazine 10^{-3} M and 5×10^{-4} M for direct-light induced and photosensitized reaction, respectively, and 5×10^{-5} M sensitizer.

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