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The Singlet Oxygen Oxidation of Chlorpromazine and Some Phenothiazine Derivatives. Products and Reaction Mechanisms

Enrico Baciocchi,*,§ Tiziana Del Giacco,‡ Osvaldo Lanzalunga,†,§ Andrea Lapi,*,†,§ and Daniele Raponi†

Dipartimento di Chimica and Istituto CNR di Metodologie Chimiche-IMC, Sezione Meccanismi di Reazione c/o Dipartimento di Chimica, Sapienza Università di Roma, P.le A. Moro 5, 00185 Rome, Italy, and Dipartimento di Chimica and Centro di Eccellenza Materiali Innovativi Nanostrutturati, Università di Perugia, via Elce di sotto 8, 06123 Perugia, Italy

enrico.baciocchi@uniroma1.it; andrea.lapi@uniroma1.it

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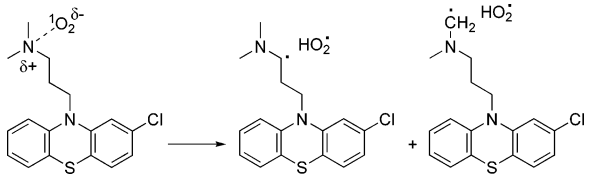
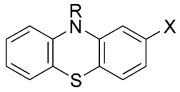


A kinetic and product study of the reactions of chlorpromazine **1**, *N*-methylphenothiazine **2**, and *N*-ethylphenothiazine **3** with singlet oxygen was carried out in MeOH and MeCN. **1** undergoes exclusive side-chain cleavage, whereas the reactions of **2** and **3**, in MeOH, afforded only the corresponding sulfoxides. A mechanism for the reaction of **1** is proposed where the first step involves an interaction between singlet oxygen and the side-chain dimethylamino nitrogen. This explains why no side-chain cleavage is observed for **2** and **3**.

Phenothiazine derivatives have found a large variety of applications as dyes, antioxidants, and drugs. Accordingly, the antihistaminic and neuroleptic properties of some phenothiazine derivatives are well-known,[1] and chlorpromazine (**1**) has been intensively used over the past 50 years as a potent sedative and antipsychotic drug.[1] Moreover, given the phototoxicity of these drugs,[2] a large number of investigations on the photochemical properties of these substances have been carried out.[3] Several reports also indicate that irradiation of phenothiazines can produce singlet oxygen (indicated as $^1O_2$),[4] but, surprisingly, very few studies have dealt with the chemical reactivity of $^1O_2$ with the phenothiazines themselves. In this regard, however, a very interesting result is that chlorpromazine **1** reacts with $^1O_2$, in MeOH, to give complete side-chain cleavage affording 2-chlorophenothiazine as the only product.[5] This result has attracted our attention as it contrasts with that of the reaction between *N*-methylphenothiazine (**2**) and $^1O_2$ in the same solvent that produces only the corresponding sulfoxide with no formation of side-chain cleavage products.[5a,6]

The absence of N-demethylation products in the reaction of **2** can be rationalized since it is known that aromatic amines generally exhibit exclusive physical quenching of $^1O_2$.[7] Conversely, at present, there is no adequate explanation for the behaviors of **1**. It was suggested that $^1O_2$ can attack the CH_2 group α to the ring nitrogen of **1** forming an α-amino hydroperoxide whose fragmentation might lead to 2-chlorophenothiazine.[5a] More recently, Braun et al. hypothesized the initial formation of a charge transfer (CT) complex mainly involving the ring nitrogen and $^1O_2$ and invoked an unclear anchimeric effect of the dimethylamino group in a side-chain Grob-like fragmentation.[8] However, neither of the hypotheses was substantiated by a mechanistic investigation.

In the light of our interest for the reactivity of tertiary amines with singlet oxygen[9] and in view of the great biological importance of phenothiazine derivatives, we felt it worthwhile to reinvestigate the reaction of **1** with $^1O_2$ by carrying out a kinetic and product study in MeOH and MeCN. The aim was to acquire information on the mechanism of the side-chain cleavage and on the factors determining the different behaviors of **1** and **2**. To get a better insight, the reactions of chlorpromazine hydrochloride (**1·HCl**), *N*-ethylphenothiazine (**3**), *N*-[3-(1-piperidyl)propyl]phenothiazine (**4**), and promazine (**5**) with $^1O_2$ were also investigated.



1: R = $(CH_2)_3NMe_2$, X = Cl
2: R = Me, X = H
3: R = Et, X = H
4: R = $(CH_2)_3$-N⟨⟩, X = Cl
5: R = $(CH_2)_3NMe_2$, X = H
6: R = H, X = Cl
7: R = CHO, X = Cl
8: R = $(CH_2)_3NHCH_3$, X = Cl
12: R = CH_2CHO, X = Cl

Kinetic Study. The rate constants (k_Q) for the total quenching (physical and chemical) of $^1O_2$ by **1**, **2**, and **1·HCl** were measured in CD_3OD[10] and MeCN by laser flash photolysis experiments following the decay rate of the singlet oxygen luminescence at 1270 nm. The results are reported in Table 1.

† Dipartimento di Chimica, Università La Sapienza.
§ IMC-CNR.
‡ Università di Perugia.

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(10) In MeOH, the $^1O_2$ lifetime is too short for the quenching rate measurements.[11]

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TABLE 1. Rate Constants (k_Q) for the Total Quenching of Singlet Oxygen by Chlorpromazine (1), *N*-Methylphenothiazine (2), and Chlorpromazine Hydrochloride (1·HCl)

compound	k_Q (M^{-1} s^{-1}) CD_3OD	k_Q (M^{-1} s^{-1}) MeCN
1	7.28×10^7 [a]	1.36×10^8
2	3.79×10^7 [b]	3.68×10^7
1·HCl	1.63×10^7	2.56×10^7

[a] A value of 3.5×10^7 M^{-1} s^{-1} is reported in bromobenzene/MeOH 2:1.[5a] [b] Much lower values, ca. 10^6 M^{-1} s^{-1}, have been reported[5a,12] that, however, were obtained in competitive experiments (Monroe method).[13]

The relatively high quenching rate of the phenothiazines investigated (all above 10^7 M^{-1} s^{-1}) is mainly due to the presence of the nitrogen atom, with the sulfur playing an almost negligible role. Accordingly, it is well-known that aromatic amines quench $^1O_2$ much more efficiently than aromatic sulfides.[11] Pertinent to the case in point is that the quenching rate of diphenylamine[14] is almost 2 orders of magnitude higher than that of diphenyl sulfide.[15] Both in CD_3OD and MeCN, **1** is a 2−3 times faster quencher than **2**, an effect suggesting a favorable role of the side-chain nitrogen atom with respect to the interaction with singlet oxygen. This suggestion is supported by the observation that **1·HCl**, where the lone pair of the dimethylamino nitrogen is no longer available for the formation of a CT complex with $^1O_2$,[16] exhibits a quenching rate lower than those of **1** and **2**. Thus, the kinetic data cast serious doubts on the hypothesis that the ring nitrogen is the actual reactive center of **1** in the chemical quenching of $^1O_2$.

Product Study. The irradiations (400−600 nm) were carried out in a photoreactor using rose bengal (10^{-4} M) as the sensitizer, at 25°C. Substrate concentrations in oxygen-saturated solvents were 10^{-2} M, and irradiation times ranged from 10 min to 3 h (maximum conversion 12%). Product analysis was carried out by GC and GC−MS by comparison with authentic specimens. In a number of experiments, a 5% $K_2Cr_2O_7$ filter (1 cm width) was used to be certain to ensure a wavelength cutting <400 nm. In all cases, no products were observed when irradiations were performed in the absence of rose bengal or O_2. The mass balance was always greater than 95%.

Reactions in MeOH. The reaction of **2** with $^1O_2$ (1 h irradiation) in MeOH confirmed previous results,[5a] affording exclusively the corresponding sulfoxide. No side-chain cleavage products were observed. In **2**, however, the nitrogen is bonded to a methyl group and not to a methylene group as the ring nitrogen in **1**. Thus, *N*-ethylphenothiazine (**3**) was also investigated, but the result was the same as for **2**. The reaction product was the sulfoxide, and no side-chain cleavage products were observed. These results are described in Figure S1 of the Supporting Information.

Several differences with respect to the previous study[5a] were instead observed when the reaction of **1** was investigated. Exclusive side-chain cleavage was observed, but besides 2-chlorophenothiazine (**6**), the only product according to the previous report, *N*,*N*-dimethylformamide (DMF), *N*-formyl-2-chlorophenothiazine (**7**), *N*-(3-methylaminopropyl)-2-chlorophenothiazine (**8**), and formaldehyde were also detected. No sulfoxidation products were formed. When the irradiation time was extended (from 10 min to 1 h), the product distribution remained unchanged, as shown in Table 2.

TABLE 2. Conversion and Product Distribution in the Reaction of 1 with Singlet Oxygen in MeOH

		Product Distribution[a]			
reaction time	conversion	**6**	**7**	**8**	DMF
10 min	1%	49%	7%	5%	40%
1 h	5%	49%	7%	5%	40%

[a] Errors are ca. 5% on the molar amount for all of the products with the exception of DMF, for which the error is ca. 20%. CH_2O (not quantitated) was also detected in the reaction mixture.

Almost identical results were obtained when promazine (**5**) was irradiated in the place of **1** (Figure S4). Clearly, as expected, the chloro substituent plays no role in the reaction of **1** with $^1O_2$.

From the results in Table 2, it can be noted that DMF is formed in amounts approximately comparable (the quantitative analysis of small amounts of DMF was subject to considerable error) with those of **6** and **7**. This observation and the formation of the N-demethylated product **8** suggest, in agreement with kinetic results, that the reaction center is the *N*-dimethylamino nitrogen and not the ring nitrogen as previously hypothesized. It follows that the side-chain reactivity of chlorpromazine **1** is determined by the dimethylamino functionality in the side chain.[17] In other words, **1** substantially behaves as an aliphatic tertiary amine that exhibits also chemical quenching of $^1O_2$[7,9] and not as an aromatic amine (like **2** and **3**) that exhibits only physical quenching.

Thus, a reasonable mechanism is that a CT complex is formed involving the *N*-dimethylamino nitrogen of **1** and $^1O_2$. This complex, in addition to intersystem crossing (the main process, vide infra), undergoes α-hydrogen abstraction to form two transient α-amino carbon radicals, **9** and **10** (Scheme 1, paths a and b). From **9**, the formation of **8** can follow the pathway proposed for N-demethylation of trialkylamines[7,9] (Scheme 1, path c). Very likely, **6** and **7** as well as DMF should derive from **10** (path d). The formation of DMF clearly indicates a bond cleavage between the carbon atoms α and β to the side-chain nitrogen, but at this stage, no further hypothesis on the cleavage mechanism is possible.

It was therefore decided to study a chlorpromazine analogue, such as **4**, with a side-chain alkylamino group heavier than the dimethylamino group of **1**. **4** should behave as **1**, but product identification and quantitative analysis should be easier also because the ring hydrogens in *N*-alkylpiperidines are not reactive toward $^1O_2$.[9a] The decision turned out to be rewarding because the rose bengal sensitized irradiation of **4**, in addition to the expected **6**, **7**, and *N*-formylpiperidine **11**, gave another product: the *N*-(formylmethyl)-2-chlorophenothiazine **12** (Table 3). **12**, however, practically disappears at longer reaction times (3 h), presumably producing **6** and **7** (vide infra).

These results clearly indicate that, also with **4**, the interaction with $^1O_2$ concerns the side-chain nitrogen almost exclusively.

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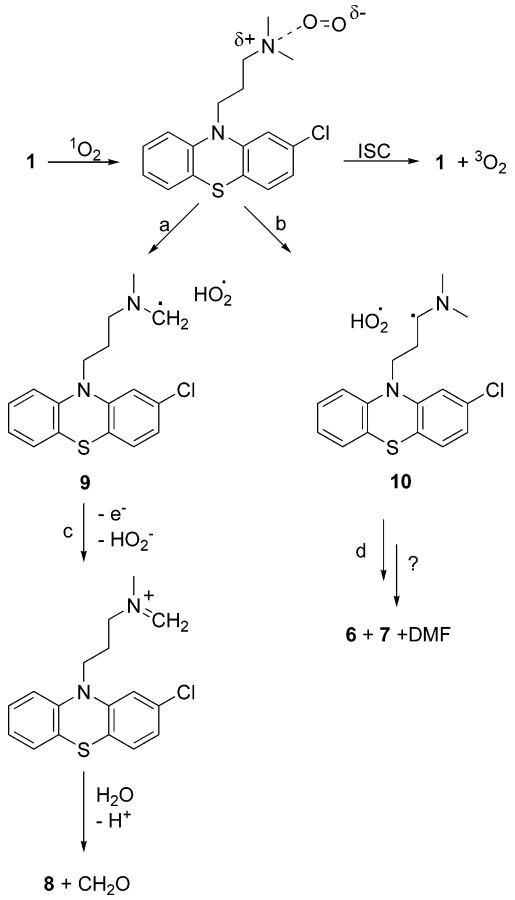
(16) (a) There is wide consensus that amines quench $^1O_2$ via the preliminary formation of a charge transfer complex (exciplex) involving the nitrogen atom lone pair.[16b,c] (b) Gorman, A. A. *Adv. Photochem.* **1992**, *17*, 217. (c) Schweitzer, C.; Schmidt, R. *Chem. Rev.* **2003**, *103*, 1685.

(17) When **1·HCl** is used as the substrate, the side-chain cleavage becomes a minor reaction, with sulfoxidation being the main process (see Supporting Information).

SCHEME 1



All products should derive from the carbon radical **13**, and this conclusion is nicely supported by the finding that the amount of formed *N*-formylpiperidine (that can be quantitated much better than DMF) now satisfactorily corresponds to the total amount of all phenothiazine products. More importantly, the identification of the aldehyde **12** as a reaction intermediate en route from **13** to **6** and **7** allows us to suggest the mechanism reported in Scheme 2.

Via oxidation and proton loss, the carbon radical **13** formed from **4** can be converted to the enamine **14** (path a).[18] Since enamines are known to react very rapidly with $^1O_2$ (rates in the order of 10^8 M^{-1} s^{-1})[19] to form carbonyl fragments,[20] it is therefore conceivable that **14**, as soon as it is formed, is converted to *N*-formylpiperidine and the aldehyde **12** by reaction with $^1O_2$. Finally, **12** is converted to 2-chlorophenothiazine and *N*-formyl-2-chlorophenothiazine under the reaction conditions (vide infra).

There is little doubt that also, for the chlorpromazine case, the conversion of **10** into **6** and **7** takes place as described for **13** in Scheme 2. The lack of evidence in the reaction of **1** for the intermediacy of **12** is probably due to the fact that this aldehyde is less stable under the conditions of photooxygenation of **1** than in those of **4**. Accordingly, when **12** was subject to rose bengal sensitized irradiation in the presence of **1** (1:100 molar ratio),[21] it was found that no **12** was present in the reaction mixture after 10 min irradiation. Moreover, when **12** was irradiated in the presence of promazine **5** (**5** behaves exactly as chlorpromazine, but this experiment allows us to distinguish the products coming from **12**, containing chlorine, from those coming from **5**, not containing chlorine),[22] **12** was completely consumed after 10 min of irradiation, and **6** and **7** were formed in a ratio similar to that observed in the reactions of **1** and **4** (Supporting Information).

TABLE 3. Conversion and Product Distribution in the Reaction of 4 with Singlet Oxygen in MeOH

		Product Distribution[a]			
reaction time	conversion	**6**	**7**	**12**	*N*-formylpiperidine
1 h	8%	26%	4%	20%	50%
3 h	12%	44%	8%	0.4%	48%

[a] Errors are ca. 5% on the molar amount for all of the products.

An additional finding (Supporting Information) was that the irradiation of **12** forms **6** and **7** only in the presence of rose bengal, which indicates that this conversion also requires $^1O_2$. Moreover, it was observed that the presence of an amine (e.g., benzyldimethylamine or *N*-ethylpiperidine) significantly speeds up the reaction, but the entity of the effect appears to depend on the nature of the amine. Thus, **12** was almost completely converted into **6** and **7** in the presence of benzyldimethylamine after 10 min of irradiation, whereas in the presence of *N*-ethylpiperidine, only 45% of **12** was consumed (Supporting Information). This can satisfactorily explain why **12** is detected in the reaction of **4** (a *N*-alkylpiperidine) and not in the reaction of **1** (a *N*,*N*-dimethyl tertiary amine).

The $^1O_2$-promoted conversion of **12** into **6** and **7** is unprecedented and represents an interesting case of an aromatic amine which exhibits a very high reactivity toward $^1O_2$. However, at present, no firm hypothesis can be formulated on the reaction mechanism of this product since it has not been possible to detect any intermediate (probably because they are very labile species) en route from **12** to **6** and **7**.

We also measured the rate constants (k_R) of product formation (chemical quenching) for the reactions of **1** (side-chain cleavage) and **2** (sulfoxide formation) with $^1O_2$ in MeOH by competitive experiments with 2-methyl-2-pentene,[23] a substrate that exhibits exclusive chemical quenching of $^1O_2$ at a known rate.[24] The rate constant for **1**, k_R(**1**), is 1.2×10^5 M^{-1} s^{-1}, a value that when compared with the rate constant for the total quenching of $^1O_2$, k_Q(**1**) = 7.28×10^7 M^{-1} s^{-1} (Table 1), tells us that the chemical quenching of $^1O_2$ by chlorpromazine accounts for only 0.16% of the total quenching. This value is very low, particularly when compared with that of other aliphatic tertiary amines. For example, in the case of benzyldimethylamine, chemical quenching of $^1O_2$ is around 9% of the total quenching.[9b]

The rate constant for the sulfoxidation of **2**, k_R(**2**), turned out to be 2.2×10^5 M^{-1} s^{-1}. This value is about 2-fold higher than

(18) (a) The formation of enamines has already been observed in the reaction of lidocaine (a tertiary *N*,*N*-diethylamine) with $^1O_2$.[18b] (b) Zanocco, A. L.; Lemp, E.; Pizarro, N.; de la Fuente, J. R.; Günther, G. *J. Photochem. Photobiol. A: Chem.* **2001**, *140*, 109.

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(21) Corresponding to the 2-chlorophenothiazine formed from **1** under the same conditions.

(22) To reproduce the reaction conditions, **5** was 10^{-4} M and **12** was 10^{-2} M. These experiments were carried out using a potassium dichromate filter to exclude any direct excitation of the substrate.

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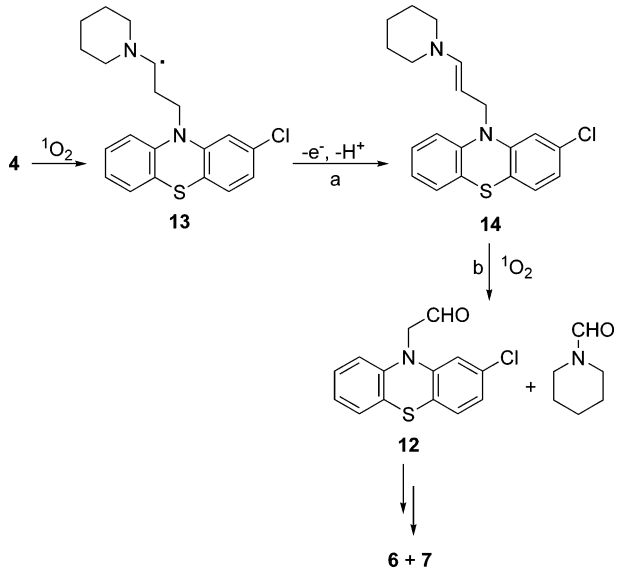
SCHEME 2



k_R(**1**), which means that, in the reaction with $^1O_2$, the rate of sulfoxide formation for *N*-methylphenothiazine is larger than the rate of side-chain cleavage product formation for chlorpromazine. It is therefore quite surprising that with **1** sulfoxidation does not compete with side-chain cleavage. Moreover, in MeOH, the sulfoxidation rate of **2** by $^1O_2$ is significantly faster than the sulfoxidation rate of diphenyl sulfide, which can be estimated to be $\leq 10^4$ M^{-1} s^{-1}.[25] Thus, it would seem that in **2** there is some factor that makes the sulfoxidation rate significantly faster than expected. In fact, rate of sulfoxidation by direct interaction of $^1O_2$ with sulfur should be negligible as most of $^1O_2$ is physically quenched by the nitrogen.

In **2**, the interaction with $^1O_2$ predominantly involves the nitrogen atom, but as in a diarylamine, the formed CT complex should exclusively undergo intersystem crossing. However, sulfur is relatively close to nitrogen, and it may be tentatively suggested that the oxygen in the complex may also interact with sulfur, favoring the formation of a persulfoxide, the key intermediate in the sulfoxidation of sulfides by $^1O_2$.[26] This possibility may be lacking in **1** where the CT complex with $^1O_2$ should be mainly formed at the nitrogen of the alkylamine side chain. In this complex, the oxygen is too far from sulfur for an efficient interaction.

Reactions in MeCN. Chlorpromazine **1** and its piperidyl analogue **4** reacted with $^1O_2$ in MeCN to afford the same products observed in MeOH. In this case too, evidence for the intermediate **12** was obtained only with **4**. Thus, the mechanisms illustrated in Schemes 1 and 2 certainly hold also for the reactions in MeCN. The solvent change, instead, modified the result for the reactions of **2** and **3**. For both compounds, sulfoxide formation was not observed, and **2** and **3** were completely unreactive toward $^1O_2$. This result is quite expected since it is well-known that the sulfoxidation rate of sulfides by $^1O_2$ is much lower in MeCN than in MeOH since in the former solvent the intermediate persulfoxide is not stabilized by hydrogen bonding.[26] The details of the experiments carried out in MeCN are reported in Figures S2 and S3.

Experimental Section

Photooxidation General Procedure. Photooxidation reactions were carried out in a photoreactor equipped with 10 lamps (400−600 nm; 14 W each). A 4 mL solution containing the substrate (1×10^{-2} M) and rose bengal (1×10^{-4} M) in O_2-saturated CH_3OH (or CH_3CN) was irradiated for a time ranging from 10 min to 3 h in a rubber cap-sealed jacketed tube thermostated at 25 °C by a water-circulating apparatus. An internal standard (biphenyl) was added, and the mixture was analyzed by GC and GC−MS. The presence of formaldehyde was checked by treatment of the reaction mixture with dimedone followed by GC−MS analysis of the formaldehyde−dimedone derivative ($m/z = 292$).[27] In no case were products observed when the experiments were carried out in the absence of rose bengal or in a deoxygenated solution.

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Supporting Information Available: Experimental details, preparation and characterization of **4** and **7**, determination of k_R and k_Q rate constants, results for **1** and **4** in MeCN, results for **2**, **3**, **5**, and **1·HCl** in MeOH, and $^1O_2$-promoted oxidation of **12** in the presence of an amine. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) (a) The rate of chemical quenching of $^1O_2$ by diphenyl sulfide is unknown. However, it should be $< 1 \times 10^5$ M^{-1} s^{-1} that is the rate of total quenching for diphenyl sulfide.[15] Accordingly, di-*tert*-butyl sulfide and diphenyl sulfide exhibit similar rate of $^1O_2$ total quenching, whereas the chemical quenching of the former is about 10 times faster than that of the second.[25b] (b) Bonesi, S. M.; Fagnoni, M.; Monti, S.; Albini, A. *Photochem. Photobiol. Sci.* **2004**, *3*, 489.

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