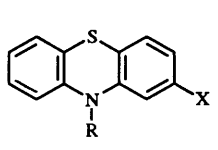
Catalytic oxidation of chlorpromazine and related phenothiazines. Cation radicals as the reactive intermediates in sulfoxide formation

Eric Bosch and Jay K. Kochi *
Chemistry Department, University of Houston, Houston, TX 77204-5641, USA

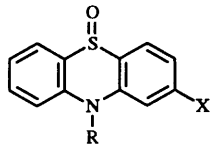
The aerial oxidation of various phenothiazines to the corresponding sulfoxides is catalysed by nitric oxide and related nitrogen oxides. The reactive intermediate in the catalytic autoxidation is the phenothiazine cation radical which is subsequently transformed to the sulfoxide by nitrate present in the reaction medium. These results are pertinent to any further discussion of the activity and/or metabolism of phenothiazine-based drugs.

1. Introduction

Phenothiazine drugs are potent antihistamines and widely used as neuroleptics.[1] Thus chlorpromazine, **1a**, has been applied over the past 40 years for its sedative and antipsychotic activity.[1b] In general, the pharmacologically active phenothiazines such as **1a–c** contain an alkylamino side chain at position 10 (N) and a functional group (chlorine, methoxy or trifluoromethyl) at position 2.



1



2

a R = $(CH_2)_3NMe_2$, X = Cl
b R = $CH_2CH(Me)NMe_2$, X = H
c R = $(CH_2)_3N(CH_2CH_2)_2NMe$, X = CF_3

d R = Me, X = H
e R = Ph, X = H

The major metabolite in the biotransformation of the phenothiazine-based drugs is the corresponding sulfoxide **2**[2] which is presumably formed *via* the cation radical.[3] Indeed, several authors have proposed that the cation radical itself is the pharmacologically active form.[4] Numerous studies have thus focussed on the generation of phenothiazine cation radicals, by chemical,[5] electrochemical[6] and enzymatic[7] means, and their subsequent transformation to the corresponding sulfoxide.[8] Although the sulfoxides generally lack antipsychotic activity, they may be responsible for side effects (*e.g.* cardiotoxic activity[9]) associated with drug use.

Recently, nitric oxide (NO) has been identified[10] as an important biological messenger in a wide range of physiological processes including neurotransmission. In this context, it is important to address the question of how nitric oxide and related nitrogen oxides can interact with pharamacologically active phenothiazines and their congeners. Accordingly, we now report the novel autoxidation of various phenothiazines to their sulfoxides catalysed by nitric oxide, and demonstrate that phenothiazine cation radicals are the reactive intermediates.

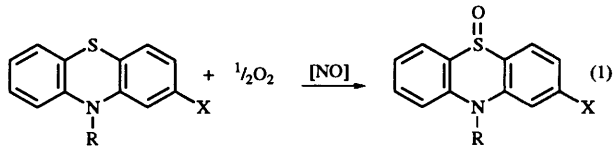
Results

I. Nitrogen oxide catalysis in the aerial oxidation of phenothiazines

A solution of chlorpromazine hydrochloride **1a** (2.03 mmol) in an aqueous citrate buffer (pH 3; 50 cm^3) remained intact in air even after prolonged stirring in the dark at room temperature. However, the colourless solution immediately turned red upon the addition of a catalytic amount of nitric oxide (NO; 0.1 mmol), but after 2 h the colour was bleached. The pale yellow solution was made basic and extracted with dichloromethane. Removal of the CH_2Cl_2 under reduced pressure afforded a quantitative yield of the sulfoxide **2a** as a pale yellow crystalline solid, which upon spectral analysis (NMR, IR and GC-MS) was found to be singularly free of organic impurities (< 3%). The same series of colour changes and overall reactivity were observed in phosphate buffer at pH 7. The catalytic autoxidation of chlorpromazine hydrochloride could also be carried out in organic solvents such as dichloromethane and acetonitrile. (It is noteworthy that the solution of the chlorpromazine **1a** in a deoxygenated citrate buffer saturated with nitric oxide was indefinitely stable when protected from air.)

The catalytic auxtoxidation could also be performed with other nitrogen oxides such as nitrogen dioxide (NO_2), nitrosonium tetrafluoroborate ($NO^+BF_4^-$), nitrous acid (HNO_2) and nitric acid (HNO_3). This simple procedure was applied to the autoxidation of the various *N*-alkylated and arylated phenothiazines, thianthrene and phenoxathiin listed in Table 1.

In order to quantify the oxygen requirement, a solution of *N*-methylphenothiazine **1d** (434 mg, 2.04 mmol) in acetonitrile (60 cm^3) cooled to −20 °C, was treated with NO (2.2 cm^3, 0.1 mmol) and the oxygen uptake measured volumetrically with the aid of a gas burette. Cessation occurred when 22.6 cm^3 (1.01 mmol) of dioxygen had been consumed (25 min). Subsequent removal of the solvent under reduced pressure led to crystalline sulfoxide **2d** in excellent yield according to the 2:1 stoichiometry in eqn. (1).

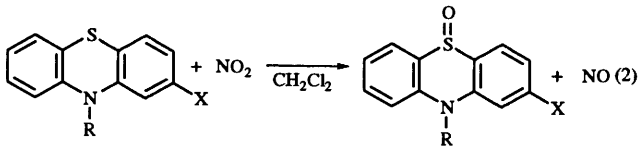


(1)

The known rapid autoxidation of nitric oxide to nitrogen dioxide[11] led us to investigate the direct oxidation of various phenothiazines with *stoichiometric* amounts of NO_2 in organic solvents under anaerobic conditions.† Thus, the addition of an equimolar amount of chlorpromazine hydrochloride **1a** to a dichloromethane solution of nitrogen dioxide under an atmosphere of argon led to a transient red solution which

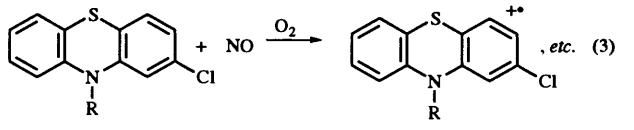
† The use of anhydrous dichloromethane circumvented the extraneous equilibria of NO_2 in water to generate nitrous acid (nitrite) and nitric acid (nitrate). Under anaerobic conditions the formation and reactivity of NO could be monitored.

quickly (< 1 min) faded to pale yellow. Spectral analysis (UV and IR) of the head gas revealed the characteristic absorption bands of nitric oxide at λ 204, 214 and 226 nm [12] and ν_{NO} 1904, 1876 and 1851 cm^{-1}.[13] The solvent and nitric oxide were removed under reduced pressure, and the sulfoxide **2a** was isolated in quantitative yield [see eqn. (2)].

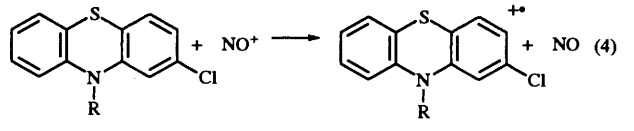


II. Spectral observation of phenothiazine cation radicals as the reactive intermediates

The catalytic autoxidations of the various phenothiazines listed in Table 1 shared in common the appearance of a fleeting red colour, the intensity and duration of which were roughly proportional to the speed of the oxidation. Since these changes are the earmarks of a reactive intermediate,[14] the coloured species were carefully monitored by UV–VIS spectroscopy as follows. Purified nitric oxide was bubbled through a solution of chlorpromazine hydrochloride (0.01 mol dm^{-3}; 5 cm^3) in an oxygenated citrate buffer (pH 3) at 25 °C. Fig. 1 shows that the transient red solution characterized by UV–VIS spectral monitoring consisted of chlorpromazine cation radical with a pair of diagnostic absorption bands with λ_{max} 526 and 770 nm.[15] The sulfoxide **2a** was isolated in quantitative yield from



the bleached solution. The same red colour was observed in a citrate buffer at pH 5 and in a phosphate buffer at pH 7. The cation radicals of each of the phenothiazines listed in Table 1 were similarly characterized by UV–VIS spectral analysis of the reaction mixture (see Table 2). Furthermore, the same intermediates were observed when nitric oxide was replaced with either nitrous acid, nitrogen dioxide or nitrosonium tetrafluoroborate [see eqn. (4)].

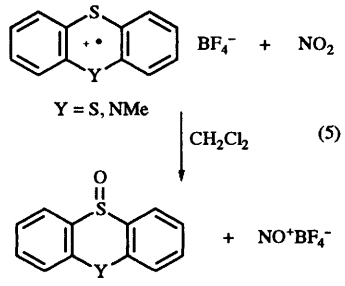


III. Further reactions of phenothiazine cation radicals with various nitrogen oxides

Crystalline cation radical salts of *N*-methylphenothiazine and thianthrene were allowed to react under anaerobic conditions with each of the purified nitrogen oxides as either the uncharged radicals NO$^{\bullet}$ and $NO_2^{\bullet}$ or the diamagnetic anions NO_2^- and NO_3^- as follows.†

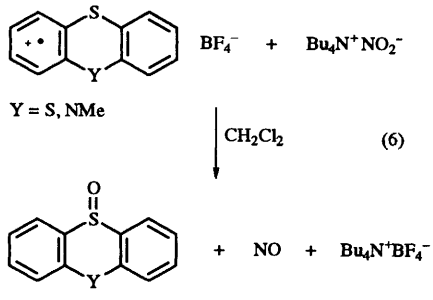
Nitric oxide. *N*-Methylphenothiazine cation radical did not react with a saturated solution of nitric oxide in dichloromethane in the absence of oxygen. Thus, a deep red solution of the phenothiazine cation radical persisted indefinitely at 25 °C when protected from air.

Nitrogen dioxide. The addition of nitrogen dioxide (1 equiv.) to a cold (−50 °C) solution of *N*-methylphenothiazine tetrafluoroborate in dichloromethane resulted in the immediate bleaching of the red colour with the concomitant formation of a white suspension that was identified as $NO^+BF_4^-$ by IR absorption spectroscopy ν(NO) 2341 cm^{-1} and $\nu(BF_4^-)$ 1050 cm^{-1}.[16] The sulfoxide **2d** was isolated in 94% as a crystalline solid [see eqn. (5)]. [The addition of an excess of



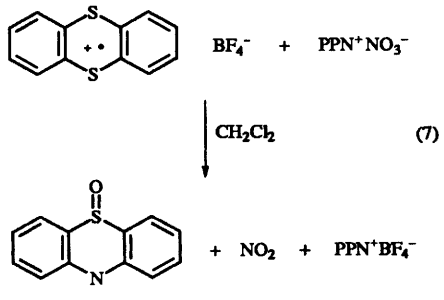
nitrogen dioxide to a solution of *N*-methylphenothiazine cation radical tetrafluoroborate in dichloromethane resulted in the further transformation of the sulfoxide to a mixture of ring nitrated products (see Experimental section).] Similarly, thianthrene cation radical (as the tetrafluoroborate salt) reacted with nitrogen dioxide (1 equiv.) to afford quantitative yields of thianthrene sulfoxide and $NO^+BF_4^-$. In the presence of an excess of nitrogen dioxide, however, there was no evidence for the further nitration of thianthrene sulfoxide.

Nitrite. The addition of nitrite (as the tetrabutylammonium salt) to a dichloromethane solution of *N*-methylphenothazine cation radical tetrafluoroborate at 0 °C led to an immediate bleaching of the red colour. Spectral analysis (UV–VIS, IR) of the head gas revealed the characteristic absorptions of nitric oxide, which was the only gaseous nitrogen oxide formed. The nitric oxide was removed under reduced pressure and the sulfoxide **2d** isolated in quantiative yield after aqueous work-up [see eqn. (6)]. Thianthrene radical cation reacted with



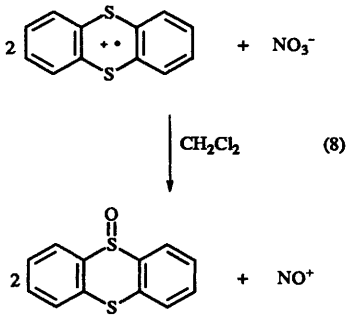
nitrite in a similar manner to afford quanitative yields of thianthrene sulfoxide and nitric oxide [17] in accord with eqn. (6).

Nitrate. The addition of nitrate (1 equiv. as the PPN salt [18]) to a deep-purple dichloromethane solution of thianthrene cation radical tetrafluoroborate resulted in the immediate bleaching of the colour with the concomitant formation of a yellow–brown head gas, the spectral analysis of which revealed the characteristic IR absorption bands of NO_2 with ν_{NO} 1629 and 1601 cm^{-1}.[19] Thianthrene sulfoxide was isolated in quantitative yield [see eqn. (7)].



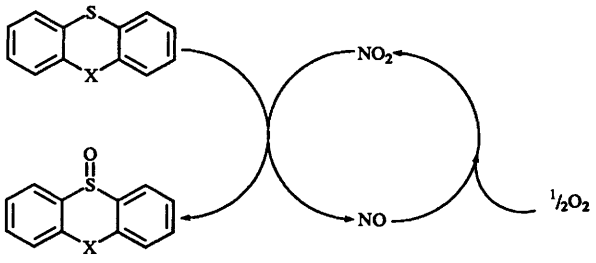
† See footnote on p. 1057.

In a separate experiment, thianthrene cation radical was treated with 0.5 equiv. of nitrate salt. The deep purple solution was rapidly bleached, but no nitrogen oxide was detected by spectral analysis of the head gas. The addition of pentane to the solution led to a white precipitate which was identified as the nitrosonium salt, $NO^+BF_4^-$. A quantitative yield of thianthrene sulfoxide was isolated from the reaction mixture[20] according to the 2:1 stoichiometry in eqn. (8).



Discussion

The efficient catalytic autoxidation of phenothiazines with nitric oxide as represented in eqn. (1) provides a simple and practical procedure for the preparation of various phenothiazine sulfoxides. Since nitric oxide is incapable of the direct oxidation of the phenothiazines, the catalytic oxidation clearly relies on the ready conversion of NO by air (O_2) into NO_2.[11] The effective oxidant would thus appear to be NO_2. Indeed the stoichiometric oxidation of phenothiazines by NO_2 to the sulfoxide and NO as described in eqn. (2) can be coupled with the reoxidation of the NO to NO_2. Such a redox cycle for the catalytic oxidation of phenothiazines is depicted in Scheme 1.



Scheme 1

However, this simple scheme does not account for the appearance of the strong red colour of the phenothiazine cation radical (see Fig. 1) throughout the catalytic process. The intermediate formation of the cation radical implies that the catalytic cycle involves the 1-electron oxidation of phenothiazines[21] such as that presented in eqn. (4) and Table 1. [Note that NO^+ is a strong 1-electron oxidant[23] with a rather high reduction potential of $E^{\circ}_{red} = 1.50$ V *vs.* SCE.[23]] In this regard, we have demonstrated that the nitrosonium cation is generated in solutions of NO_2 when electron-rich donors are present.[24,‡] For example, the addition of aromatic donors (ArH) to dichloromethane solutions of NO_2 results in an immediate dark-red

‡ NO_2 is known to exist in dynamic equilibrium with the nitro-nitro dimer (O_2NNO_2) and the nitrito-nitro dimer ($ONONO_2$). However, there is no evidence for the formation of the disproportionated dimer $NO^+NO_3^-$ in dichloromethane solutions containing only NO_2. There are several reports of the low-temperature matrix identification of $NO^+NO_3^-$ which is formed from the nitrito-nitro dimer.[25]

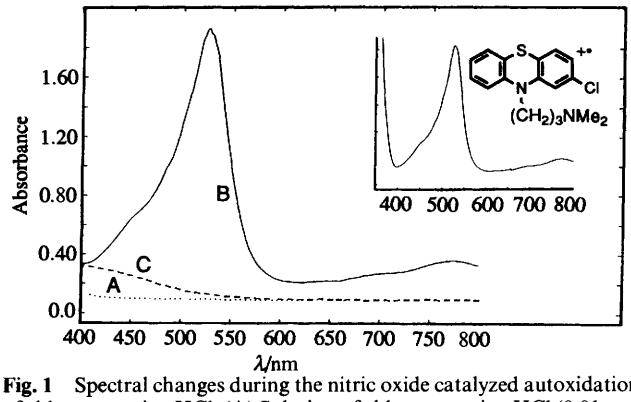


Fig. 1 Spectral changes during the nitric oxide catalyzed autoxidation of chlorpromazine·HCl. (A) Solution of chlorpromazine·HCl (0.01 mol dm^{-3} in oxygenated citrate buffer at pH 3 (.....). (B) Immediately after bubbling nitric oxide through the solution (——). (C) After 15 min immediately before work-up (– – – –). Inset: Chlorpromazine cation radical in sulfuric acid.

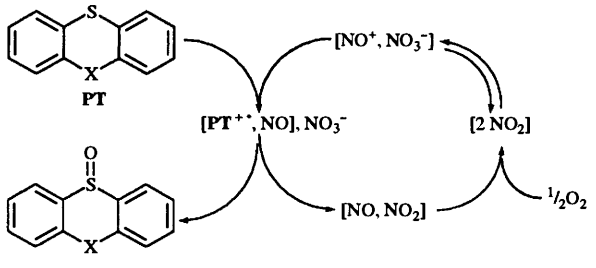
colouration due to the charge-transfer complexes [ArH, NO^+]-NO_3^-.§ Such an induced disproportionation of NO_2 by an added aromatic donor is described in eqn. (9).

$$2NO_2 \rightleftharpoons ONONO_2 \xrightleftharpoons{ArH} [ArH, NO^+]\,NO_3^- \quad (9)$$

Since the phenothiazines (PT) in Table 2 are excellent electron donors (all with $E_{1/2} < 1.22$ V *vs.* SCE) they are also expected to induce the disproportionation of NO_2 according to eqn. (9). As such, we believe the charge-transfer complex [PT, NO^+]NO_3^- is the intermediate which is readily converted into the cation radical by an internal electron transfer in eqn. (10).¶

$$PT + 2NO_2 \rightleftharpoons [PT,NO^+]\,NO_3^- \longrightarrow PT^{+\cdot} + NO + NO_3^- \quad (10)$$

The subsequent conversion of phenothiazine cation radicals by nitrate [see eqn. (7)] is included in Scheme 2 to more accurately represent the catalytic cycle.



Scheme 2

When nitrite ‖ is the added nitrogen oxide in Table 1, the acidic medium converts it into the active nitrosonium oxidant

§ The extent of the ionization in eqn. (9) (to produce the charge-transfer complex), is correlated to the ionization potential of the arene. For example, hexamethylbenzene (IP = 7.85 eV) leads to 80% ionization of N_2O_4 whereas durene (IP = 8.05 eV) results in less than 25% complex formation.[24]

¶ It should be noted that NO_2 is a weak oxidant with $E^{\circ}_{red} = +0.25$ V *vs.* SCE [L.Eberson and F. Radner, *Acta Chem. Scand., Sect. B*, 1985, **39**, 343]. Thus the alternative formation of phenothiazoine cation radicals by direct electron transfer to NO_2 is unlikely since the driving force for electron transfer from the phenothiazines in Table 1 (with $E^{\circ}_{ox} > +0.6$ V *vs.* SCE) to NO_2 is endergonic by *ca.* 9 kcal mol^{-1}.

‖ The stoichiometric oxidation of phenothiazines with nitrite has been reported in acid solution. However, no report of the intense colouration (of cation radicals) or of the catalytic nature of the oxidation was made.[26]

Table 1 Air oxidation of phenothiazines and related arenes catalysed by nitrogen oxides[a]

Substrate	(mmol)	Catalyst	(mmol)	Product	Yield (%)
Chlorpromazine·HCl	(2.03)[b]	NO	(0.10)	Chlorpromazine sulfoxide	99
Chlorpromazine·HCl	(2.03)[b]	NO_2^-	(0.17)	Chlorpromazine sulfoxide	100
Promethazine·HCl	(2.43)[c]	NO^+	(0.17)	Promethazine sulfoxide	96
Promethazine·HCl	(2.27)[b]	NO_2^-	(0.13)	Promethazine sulfoxide	100
Trifluorperazine·2HCl	(1.94)[d]	NO_2^-	(0.17)	Trifluorperazine sulfoxide	100
N-Phenylphenothiazine	(3.18)[c]	NO^+	(0.10)	*N*-Phenylphenothiazine sulfoxide	100
N-Methylphenothiazine	(2.04)[c]	NO	(0.10)	*N*-Methylphenothiazine sulfoxide	97
N-Methylphenothiazine	(2.00)[e]	NO^+	(0.10)	*N*-Methylphenothiazine sulfoxide	98
N-Methylphenothiazine	(1.90)[d]	NO_2^-	(0.14)	*N*-Methylphenothiazine sulfoxide	93
N-Methylphenothiazine	(1.25)[e]	NO_2	(0.05)	*N*-Methylphenothiazine sulfoxide	100
Phenoxathiin	(1.61)[c]	NO^+	(0.02)	Phenoxathiin sulfoxide	93
Phenoxathiin	(5.00)[e]	NO_2	(0.18)	Phenoxathiin sulfoxide	100
Thianthrene	(7.87)[e]	NO^+	(0.08)	Thianthrene sulfoxide	99
Thianthrene	(4.30)[e]	NO_2	(0.18)	Thianthrene sulfoxide	100

[a] All reactions performed under an atmosphere of oxygen in the solvent system specified. Typical procedure: the substrate was dissolved in the solvent (30 cm^3 $mmol^{-1}$), the catalyst added, and the mixture stirred for 3 h. [b] In citrate buffer pH 3. [c] In acetonitrile. [d] In acetonitrile–water (1 : 1) with 1 cm^3 of conc. HCl added. [e] In dichloromethane.

Table 2 Donor properties of phenothiazines and related arenes: UV–VIS spectral characterization of the phenothiazine cation radicals

Substrate	IP (eV)	$E_{1/2}$ (V *vs.* SCE)[c]	λ_{max}/nm
Chlorpromazine	7.16[a]	0.60[d]	526, 770[f]
Promethazine	7.20[a]	0.66[d]	518, 710, 785, 444[f]
Trifluorperazine	7.31[a]	0.66[d]	500, 626, 692, 772[f]
N-Methylphenothiazine	7.15[a]	0.70[e]	514, 764, 442[g,h]
N-Phenylphenothiazine		0.66[e]	514, 446, 694, 778[g,h]
Phenoxathiin	7.75[b]	1.19[e]	584[i]
Thianthrene	7.94[b]	1.21[e]	540[j]

[a] Data from L. N. Domelsmith, L. L. Munchausen and K. N. Houk, *J. Am. Chem. Soc.*, 1977, **99**, 6506. [b] Data from O. G. Rodin, V. F. Traven, V. V. Redchenko, M. Y. Eismont and B. I. Stepanov, *Zh. Obshch. Khim.*, 1983, **53**, 2537. [c] Reversible oxidation potential at v = 0.1 V s^{-1}. [d] Recorded in 0.1 mol dm^{-3} HCl. [e] Recorded in acetonitrile solution with TBAP (0.1 mol dm^{-3}) as electrolyte. [f] Data from ref. 15. [g] Data from R. E. Hester and K. P. J. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1981, 852. [h] Data from E. Wagner, S. Filipek and M. K. Kalinowski, *Monatsh. Chem.*, 1988, 929. [i] Data from ref. 45. [j] Data from (*a*) O. Hammerich and V. D. Parker, *Acta Chem. Scand., Sect. B*, 1982, **36**, 421; (*b*) G. Jones, II, B. Huang and S. F. Griffin, *J. Org. Chem.*, 1993, **58**, 2035; see also ref. 15.

according to the stoichiometry:[27] $NO_2^- + 2H^+ \longrightarrow NO^+ + H_2O$. As such, the different systems employed in Table 1 are all accommodated by the catalytic mechanism in Scheme 2 in which NO^+ is the common component.** Critical to the catalytic autoxidation of phenothiazines is the facile interconversion of the various nitrogen oxides. Thus oxygen (air) is initially responsible for the rapid conversion of nitric oxide into nitrogen dioxide which thence leads to the production of phenothiazine cation radicals ($PT^{\bullet+}$) according to eqns. (9) and (10). The versatility of nitrogen oxides in phenothiazine oxidation is further underscored in the subsequent transformation of the cation radical intermediate. Thus, nitrate, nitrogen dioxide and nitrite are capable of effecting a rapid oxygen-atom transfer to the phenothiazine cation radical to afford quantitative yields of the sulfoxide together with the (1-electron) reduced species *viz.*, nitrogen dioxide, nitrosonium cation, and nitric oxide according to eqns. (7), (5) and (6) respectively.††

Finally, we point out the relevance of these studies to the burgeoning field of nitric oxide biochemistry since the relatively inert nature of nitric oxide[29] is in stark contrast to the rich electron-transfer[30] and nitrosative chemistry[31] of its redox partner nitrosonium cation. Therefore, any description of the activity/reactivity of NO in biological systems must take account of the ready formation of NO^+ from NO in the presence of air (O_2). Indeed, this formulation (*i.e.* the formation of NO^+ as the reactive species) adequately describes the *S*-nitrosation of thiols[32] and the *N*-nitrosation[33] of amides which have been shown to occur with NO only under aerobic conditions (or with NO_2).

Experimental

Materials

Nitric oxide (>99%, Matheson) was purified by passage through a column of NaOH and over a cold finger cooled at −78 °C in a solid CO_2–acetone bath. Nitrosonium tetrafluoroborate (Strem) was stored in a vacuum atmospheres HE-493 dry box free from traces of oxygen, moisture and solvent vapours. Nitrogen dioxide was purified by published procedures.[34] Sodium nitrite (Aldrich) was used without further

** The autoxidation of sulfides catalysed by ceric ammonium nitrate reported by Riley *et al.*,[28] may also proceed *via* the same (nitrogen oxide) cycle. The chain carrier may be trace quantities of nitrogen oxides formed after the initial oxidation by CAN.

†† The particular nitrogen oxide that actually quenches the cation radical during the catalytic autoxidation will depend on the reaction conditions, the concentrations, and the rates of the individual reactions. (The kinetics of the reaction of cation radicals with the various nitrogen oxides, NO_2^-, NO_2 and NO_3^- is currently under study.) For example, the termolecular rate constant for the reaction of thianthrene cation radical salts with nitrate [eqn. (8)] has been determined by Blount:[20] $k_2 = 1.3 \times 10^{11}$ dm^6 mol^{-2} s^{-1} (CH_2Cl_2); $k_2 = 1.4 \times 10^{10}$ dm^6 mol^{-2} s^{-1} (MeCN); see also: I. Jelinek, I. Nemcova and P. Rychlovsky, *Talanta*, 1991, **38**, 1309.

purification. Tetrabutylammonium nitrite (Fluka) was dried by azeotropic distillation with benzene and then dried *in vacuo* for 16 h. PPN nitrate was pepared according to the literature procedure.[35] Citrate buffer solution, pH 3 and pH 5 (EM Science) and phosphate buffer solution (Fisher) were used as received. Preparative-scale oxidations were performed with reagent grade acetonitrile (Fisher) and dichloromethane (EM Science). The reactions of phenothiazine cation radicals were performed in dichloromethane† purified as previously described.[36] Chlorpromazine hydrochloride (ICN), promethazine, thianthrene (Aldrich), trifluoperazine (Fluka) and phenothiazine (Eastman) were used as received. *N*-Phenylphenothiazine[37] and *N*-methylphenothiazine[38] were prepared by published procedures. Phenoxathiin was a gift from R. Rathore. Thianthrene cation radical tetrafluoroborate was prepared according to the literature procedure.[39] *N*-Methylphenothiazine cation radical tetrafluoroborate was prepared by a modification of the literature procedure[22a] [dichloromethane was used as solvent in place of acetonitrile]. The salts of both cation radicals were analysed by iodometric titration (96–98%).

Instrumentation

^1H and ^{13}C NMR spectra were recorded in [^2H]chloroform on a General Electric QE-300 NMR spectrometer and the chemical shifts are reported in ppm units downfield from tetramethylsilane. UV–VIS absorption spectra were recorded on a Hewlett-Packard 8450A diode-array spectrometer. IR spectra were recorded on a Nicolet 10DX FT spectrometer. Gas chromatography was performed on a Hewlett-Packard 5890A series gas chromatograph equipped with a 3392 integrator. GC-MS analyses were carried out on a Hewlett-Packard 5890 chromatograph interfaced to a HP 5970 mass spectrometer (EI, 70 eV). Melting points were measured with a Mel-Temp (Laboratory Devices) apparatus and are uncorrected. Cyclic voltammetry (CV) was performed on a BAS-100A Electrochemical Analyser. The CV cell was of an airtight design with high vacuum Teflon valves and Viton O-ring seals to allow an inert atmosphere to be maintained without contamination by grease. The working electrode consisted of an adjustable plantinum disc embedded in a glass seal to allow periodic polishing (with a fine emery cloth) without changing the surface area (~ 1 mm^2) significantly. The SCE reference electrode and its salt bridge was separated from the catholyte by a sintered glass frit. The counter electrode consisted of a platinum gauze that was separated from the working electrode by ~ 3 mm.

Nitrogen oxide-catalysed oxidation of phenothiazines

General procedure

Nitric Oxide.—A solution of chlorpromazine hydrochloride **1a** (720 mg, 2.03 mmol) in acetonitrile (50 cm^3) was prepared in a 100 cm^3 flask fitted with a side arm. The flask was purged with O_2, stoppered with a rubber septum, and an O_2-filled balloon was attached to the side arm of the flask in order to maintain the oxygen atmosphere. The colourless solution was cooled to −20 °C in a solid CO_2–acetone bath, and nitric oxide (2.2 cm^3, 0.10 mmol) was bubbled into the stirred solution with the aid of a gas-tight syringe. The reaction mixture (which immediately turned red), was stirred and warmed to room temperature over the course of 2 h. The resultant pale yellow solution was diluted with dichloromethane (50 cm^3) and washed with aqueous KOH (2 × 25 cm^3). The organic layer was separated, dried and evaporated under reduced pressure to afford the sulfoxide **2a** as a pale yellow crystalline solid (680 mg, 100%) which upon GC-MS and NMR analysis was found to be free of organic impurities (< 3%).

Measurement of oxygen uptake. A solution of *N*-methylphenothiazine **1d** (435 mg, 2.04 mmol) in acetonitrile (60 cm^3) was prepared in a 100 cm^3 flask fitted with a side arm. The flask was purged with O_2, stoppered with a rubber septum and the side arm of the flask was connected to a pressure-equalized gas burette filled with oxygen. The colourless solution was cooled to −20 °C in a constant temperature solid CO_2–acetone bath and allowed to equilibrate over 15 min. Nitric oxide (2.2 cm^3, 0.10 mmol) was bubbled into the stirred solution with the aid of a gas-tight syringe, whereupon the solution immediately turned red. The temperature was carefully maintained at −20 °C and the solution stirred while the oxygen uptake was monitored. After 6 min, 22.6 cm^3 of oxygen (1.01 mmol) was consumed and the uptake of oxygen ceased. The solution was diluted with dichloromethane and washed with aqueous KOH. The organic layer was separated, dried and the solvent evaporated under reduced pressure to afford the sulfoxide **2d** as a pale yellow crystalline solid (451 mg, 97%) which upon GC-MS and NMR analysis was found to be free of organic impurities (< 3%). The same general procedure was used with each of the other catalyst/solvent systems described in Table 1. Traces of coloured impurities were removed by passage of the crude reaction mixture through a short column of silica. The characteristic spectral data of the products reported in Table 1 were as follows. Chlorpromazine sulfoxide **2a**: mp 111–113 °C (lit.,[40] 110–112 °C); δ_H 2.03 (m, *J* 7.8, 2 H), 2.33 (s, 3 H), 2.44 (m, 2 H), 4.30 (t, *J* 7.5, 2 H), 7.20 (dd, *J* 8.4, 1.2, 1 H), 7.29 (t, *J* 7.4, 1 H), 7.54 (d, *J* 8.4, 1 H), 7.61–7.66 (m, 2 H), 7.84 (d, *J* 8.4, 1 H) and 7.95 (dd, *J* 1.2, 7.5, 1 H); δ_C 23.78, 45.09, 45.17, 55.68, 115.42, 121.12, 121.58, 123.44, 130.93, 132.14, 132.45, 137.06, 138.17 and 138.56; ν_{max}(KBr)/cm^{-1} 750, 922, 1026, 1047, 1249, 1418, 1456, 1581, 2773, 2817 and 2944; GC-MS 334 (M^+).

Promethazine sulfoxide **2b**: mp 117–118 °C (lit.,[40] 120 °C); δ_H 0.81 (d, *J* 6.3, 3 H), 2.22 (s, 6 H), 2.99 (m, 1 H), 4.1 (m, 1 H), 4.29 (m, 1 H), 7.10 (m, 2 H), 7.36–7.43 (m, 6 H) and 7.76 (m, 2 H); δ_C 11.07, 40.70, 50.07, 56.54, 116.28, 121.64, 121.50, 125.27, 125.70, 130.32, 132.01, 132.22, 138.08, 139.66; ν_{max}(KBr)/cm^{-1} 756, 946, 975, 1249, 1365, 1460, 1571, 1585, 2790, 2831, 2969 and 3059; GC-MS 300 (M^+).

Trifluoperazine sulfoxide **2c**: mp 144–146 °C;[41] δ_H 0.81 (d, *J* 6.3, 3 H), 2.22 (s, 6 H), 2.99 (m, 1 H), 4.1 (m, 1 H), 4.29 (m, 1 H), 7.10 (m, 2 H), 7.36–7.43 (m, 6 H) and 7.76 (m, 2 H); δ_C 11.07, 40.70, 50.07, 56.54, 116.28, 121.64, 121.50, 125.27, 125.70, 130.32, 132.01, 132.22, 138.08 and 139.66; ν_{max}(KBr)/cm^{-1} 764, 928, 1026, 1133, 1168, 1250, 1280, 1290, 1311, 1336, 1364, 1432, 1455, 1578, 2766 and 2944; GC-MS 423 (M^+).

N-Methylphenothiazine sulfoxide **2d**: mp 185 (lit.,[42] 172 °C); δ_H 3.69 (s, 3), 7.27 (t, *J* 7.5, 2 H), 7.39 (d, *J* 8.7, 2 H), 7.64 (dd, *J* 1.2, 8.4, 2 H) and 7.90 (dd, *J* 1.2, 8.4, 2 H); δ_C 34.99, 115.45, 121.54, 122.82, 130.53, 132.81 and 139.45; ν_{max}(KBr)/cm^{-1} 763, 1018, 1048, 1260, 1357, 1460, 1478, 1581, 3010 and 3059; GC-MS 229 (M^+).

N-Phenylphenothiazine sulfoxide **2e**: mp 170–171 °C (lit.,[43] 172 °C); δ_H 6.74 (d, *J* 8.7, 2 H), 7.23–7.30 (m, 2 H), 7.39–7.45 (m, 4 H), 7.62–7.75 (m, 3 H) and 8.03 (d, 7.5, 2 H); δ_C 11.07, 40.07, 50.07, 56.54, 116.28, 121.64, 121.50, 125.27, 125.70, 130.32, 132.01, 132.22, 138.08 and 139.66; ν_{max}(KBr)/cm^{-1} 709, 753, 1029, 1260, 1300, 1340, 1443, 1459, 1491, 1575, 1585 and 3034; GC-MS 291 (M^+).

Thianthrene sulfoxide: mp 142 °C (lit.,[44] 143 °C); δ_H 7.41 (dt, *J* 0.9, 7.5, 2 H), 7.54 (t, *J* 6.9, 2 H), 7.61 (d, *J* 7.5, 2 H), and 7.91 (dd, *J* 0.9, 8.4, 2 H); GC-MS 232 (M^+).

Phenoxathiin sulfoxide: mp 150 °C (lit.,[45] 153 °C); ν_{max}-(Nujol)/cm^{-1} 758, 775, 882, 1040, 1136, 1223, 1271, 1316, 1436, 1453, 1476 and 1586; δ_H 7.36 (t, *J* 7.2, 2 H), 7.44 (d, *J* 8.1, 2 H), 7.61 (dt, *J* 1.2, 9, 2 H) and 7.91 (dd, *J* 1.2, 7.5, 2 H); δ_C 11.07,

† See footnote on p. 1057.

40.70, 50.07, 56.54, 116.28, 121.64, 121.50, 125.27, 125.70, 130.32, 132.01, 132.22, 138.08 and 139.66; GC-MS 300 (M^+).

Stoichiometric oxidation of phenothiazines with nitrogen dioxide

A dichloromethane solution of chlorpromazine hydrochloride **1a** (18 mg, 0.05 mmol, 4.5 cm^3) was prepared under an argon atmosphere in a 25 cm^3 flask fitted with a Schlenk adaptor. A dichloromethane solution of nitrogen dioxide (0.5 cm^3, 0.05 mmol) was added to the mixture with the aid of an all-glass syringe. The resulting red solution quickly (< 1 min) faded to pale yellow. The head gases were transferred to an evacuated gas-IR cell (5 cm path length). The IR spectrum showed the characteristic stretching frequencies at 1904, 1876 and 1851 cm^{-1} of nitric oxide[13] as the only nitrogen oxide. The head gases were transferred to an evacuated 1 cm quartz cuvette fitted with a Teflon stopcock and the UV–VIS absorption spectrum was found to be the same as that of an authentic sample of nitric oxide with λ 204, 214 and 222 nm.[12] Removal of the solvent and nitric oxide under reduced pressure led to the sulfoxide **2a** (16 mg, 94%). The oxidation of *N*-methylphenothiazine, phenoxathiin and thianthrene with nitrogen dioxide had the same stoichiometry.

UV–VIS spectral observation of phenothiazine cation radicals

Nitric oxide/oxygen. A solution (5 cm^3) of chlorpromazine hydrochloride **1a** (17.8 mg, 0.05 mmol) in oxygenated aqueous citrate buffer (pH 3) was prepared in a quartz cuvette fitted with a side arm and a Teflon stopcock. When dry nitric oxide (0.02 mmol) was bubbled through the solution, a transient red colour resulted immediately. The UV–VIS absorption spectrum of the red solution revealed the characteristic absorption bands of chlorpromazine cation radical at λ 526 and 770 nm.[15] After 2 min, the pink colour faded to pale yellow, and work-up yielded the sulfoxide **2a** as a pale yellow crystalline solid (16.5 mg, 98%).

Nitrite. A solution of promethazine hydrochloride **1b** (16 mg, 0.05 mmol) in citrate buffer (5 cm^3) at pH 3 was prepared under an oxygen atmosphere in a quartz cuvette fitted with a gas-tight rubber septum. A solution of sodium nitrite (1 mg, 0.01 mmol) in citrate buffer (1 cm^3) was added to the solution with the aid of a hypodermic syringe. The solution immediately turned red, and the UV–VIS absorption specrum was the same as that of an authentic sample of promethazine cation radical (λ_{max} 518 nm).[15] The red solution faded to pale yellow over the course of 5 min, and work-up afforded the sulfoxide **2b** in high yield (14 mg, 94%).

Nitrogen dioxide. The oxidation of chlorpromazine with NO_2 (0.2 equiv.) under an oxygen atmosphere was performed at −78 °C in dichloromethane solution. The transient red colour was quite persistent, and UV–VIS spectral analysis confirmed the presence of chlorpromazine cation radical (λ_{max} 526 and 770 nm).[15]

Reaction of phenothiazine cation radicals with various nitrogen oxides

Nitrogen dioxide. A cold (0 °C) dichloromethane solution of nitrogen dioxide (1.0 mol dm^{-3}; 0.25 cm^3) was added dropwise to a dark red solution of *N*-methylphenothiazine cation radical tetrafluoroborate (78 mg, 0.26 mmol) in dichloromethane (30 cm^3) cooled at −50 °C in a solid CO_2–acetone bath under an argon atmosphere. The dark red solution was bleached within a minute to a pale yellow solution containing a fine white suspension. The supernatant liquid −50 °C was carefully removed with the aid of a Teflon cannula, and the white solid washed once with cold dichloromethane. The solid was dried *in vacuo* and transferred to a dry box. The IR spectrum in the region 4000 to 650 cm^{-1} was the same as that of an authentic sample of $NO^+BF_4^-$ with $\nu(NO^+)$ = 2341 cm^{-1} and $\nu(BF_4^-)$ = 1050 cm^{-1}.[16] The dichloromethane solutions were combined, washed with water, dried, and evaporated under reduced pressure to afford the crystalline sulfoxide **2d** in excellent yield (56 mg, 94%).

In a separate experiment, an excess of nitrogen dioxide (1.0 cm^3; 1.0 mol dm^{-3}) was added dropwise to a cold (0 °C) dark red solution of *N*-methylphenothiazine cation radical tetrafluoroborate (114 mg, 0.38 mmol) in dichloromethane (30 cm^3) under an argon atmosphere. Although the dark red solution was immediately bleached to a yellow colour, upon continued stirring a dark brown colour formed. After 25 min, the solvent and excess of nitrogen oxides were removed under reduced pressure. The oily residue was diluted with dichloromethane (50 cm^3), washed with water, dried, and evaporated under reduced pressure. The nitro-*N*-methylphenothiazine sulfoxide§§ was purified by flash chromatography with methanol–ether (1:4) as eluent; δ_H 3.84 (s, 3 H), 7.40 (t, *J* 7.5, 1), 7.47 (d, *J* 9.3, 1 H), 7.50 (d, *J* 8.4, 1 H), 7.72 (dt, *J* 1.2, 8.4, 1 H), 7.97 (dd, *J* 1.2, 7.5, 1 H), 8.41 (dd, *J* 2.4, 9.3, 1 H), 8.80 (d, *J* 2.7, 1 H); δ_C 36.08, 115.94, 116.33, 123.78, 124.10, 124.60, 127.42, 127.46, 130.81, 133.49, 138.41, 140.95 and 143.57; IR ν_{max}(film)/cm^{-1} 3090, 3061, 2926, 1586, 1512, 1465, 1327, 1283, 1263, 1123, 1048, 1029, 904, 760, 750 and 730; GC–MS 274 (M^+). A minor isomer was detected by ^1H NMR analysis: δ_H(partial) 3.94 (s, 3 H), 7.61 (d, *J* 9.3, 1 H), 8.49 (dd, *J* 2.7, 9.3, 1 H), 8.85 (d, *J* 2.7, 1 H).

Thianthrene cation radical tetrafluoroborate (114 mg, 0.38 mmol) was treated with NO_2 (1 equiv.) in dichloromethane (75 cm^3) under an argon atmosphere at 25 °C. The deep purple colour was immediately bleached, concomitant with the formation of a white suspension. The products were thianthrene sulfoxide (120 mg, 98%) and $NO^+BF_4^-$ (39 mg, 88%). In a separate experiment, thianthrene cation radical tetrafluoroborate (133 mg, 0.44 mmol) and an excess of nitrogen dioxide (1.0 mmol) were mixed in dichloromethane at 25 °C under an argon atmosphere. The deep purple colour of the solution was bleached within 1 min. It yielded a white suspension in a pale yellow solution together with a yellow–brown head gas. This mixture was stirred at 25 °C for an additional 2 h with no apparent change. After removal of the excess of NO_2 *in vacuo* nitrosonium tetrafluoroborate (36 mg, 71%) and thianthrene sulfoxide (97 mg, 95%) were isolated.

Nitrite. A dichloromethane solution of tetrabutylammonium nitrite (173 mg, 0.60 mmol, 5 cm^3) was added with the aid of a Teflon cannula to a dark red solution of *N*-methylphenothiazine cation radical tetrafluoroborate (182 mg, 0.60 mmol) in dichloromethane (90 cm^3) under an argon atmosphere at 25 °C. The colour was immediately bleached and UV–VIS and IR spectral analysis of the head gases showed that nitric oxide was formed. Nitric oxide was removed *in vacuo*, and the dichloromethane solution washed with water (3 × 25 cm^3), dried, and evaporated under reduced pressure. The sulfoxide **2d** was isolated as a colourless crystalline solid (120 mg, 98%). Similarly, the treatment of thianthrene cation radical tetrafluoroborate (92 mg, 0.31 mmol) with tetrabutylammonium nitrite (95 mg, 0.33 mmol) afforded thianthrene sulfoxide and nitric oxide.

Nitrate. A dichloromethane solution of PPN nitrate (330 mg,

§§ The *N*-alkylphenothiazine sulfoxides with oxidation potentials in the range 1.5 V are subject to further oxidation by nitrosonium cation. However, thianthrene sulfoxide (with E_p = 1.85 V *vs.* SCE) is not susceptible to further oxidation due to the higher oxidation potential. The reaction of *N*-phenylphenothiazine radical cation perchlorate with an excess of nitrite in an oxygen atmosphere has been reported to give nitroaromatics.[46]

0.55 mmol, 10 cm^3) was added with the aid of a cannula to a deep purple solution of thianthrene cation radical tetrafluoroborate (166 mg, 0.55 mmol) in dichloromethane (90 cm^3) under an argon atmosphere at 25 °C. The deep purple solution was immediately bleached. The solution was stirred for a further 10 min, and the brown head gas transferred to an evacuated gas-phase IR cell (5 cm path length). The IR spectrum showed the characteristic stretching frequencies at 1629 and 1600 cm^{-1} of NO_2. Nitrogen dioxide was removed *in vacuo* and the dichloromethane solution was washed with water (3 × 25 cm^3) to yield thianthrene sulfoxide in quantitative yield. In a separate experiment, a dichloromethane solution of PPN nitrate (195 mg, 0.33 mmol, 10 cm^3) was added with the aid of a cannula into a vigorously stirred deep purple of thianthrene cation radical tetrafluoroborate (195 mg, 0.64 mmol) in dichloromethane (60 cm^3) under an argon atmosphere at 25 °C. The deep purple colour was immediately bleached but the head gas remained colourless. The solution was stirred for a further 10 min, and the head gases transferred to an evacuated gas-phase IR cell (5 cm path length). Neither NO nor NO_2 were observed in the IR spectrum. The solution was concentrated under reduced pressure to 25 cm^3 and diluted with pentane (40 cm^3) to precipitate a white solid. The supernatant solution was removed with the aid of a cannula, and the solid dried *in vacuo* and transferred to a dry box. IR analysis of the solid revealed the characteristic absorption band of nitrosonium at $\nu = 2340$ cm^{-1} in addition to the diagnostic IR bands of $PPN^+BF_4^-$. The pentane solution and the solid were combined and yielded thianthrene oxide in excellent yield (117 mg, 92%).

Acknowledgements

We thank the National Science Foundation, R. A. Welch Foundation, and the Texas Advanced Research Project for financial assistance.

References

1 (*a*) M. Gordon, P. N. Craig and C. L. Zirkle in *Molecular Modification in Drug Design. Adv. Chem. Ser.*, vol. 45, ACS, Washington, D.C., 1964, pp. 140–147; (*b*) P. Mitchell, *Austral. New Zealand J. Psych.*, 1993, **27**, 370.
2 I. S. Forrest and E. Usdin, in *Psychotherapeutic Drugs*, eds. E. Usdin, I. S. Forrest, Marcel Dekker, New York, 1977; pp. 709–713, 756–759; P. Turano, W. J. Turner and A. A. Manian, *J. Chromatogr.*, 1973, **75**, 277.
3 I. S. Forrest and D. E. Green, *J. Forensic Sci.*, 1972, **17**, 592–617.
4 T. Akera and T. M. Brody, *Mol. Pharmacol.*, 1968, **4**, 600; T. Akera and T. M. Brody, *Biochem. Pharmacol.*, 1972, **21**, 1403; C. M. Gooley, H. Keyzer and F. Setchell, *Nature*, 1969, **223**, 81; T. Akera and T. M. Brody, *Mol. Pharmacol.*, 1969, **5**, 605; G. Testylier, D. Daveloose, F. Leterrier, O. Buchmann and M. Shimoni, *Photochem. Photobiol.*, 1984, **39**, 273; L. H. Piette, G. Bulow and I. Yamazaki, *Biochim. Biophys. Acta*, 1964, **88**, 120; S. Ohnishi and H. M. McConnell, *J. Am. Chem. Soc.*, 1965, **87**, 2293.
5 D. C. Borg and G. C. Cotzias, *Proc. Natl. Acad. Sci. USA*, 1962, **48**, 623; L. Levy, T. N. Tozer, L. D. Tuck and D. B. Loveland, *J. Med. Chem.*, 1972, **15**, 898.
6 P. H. Sackett, J. S. Mayausky, T. Smith, S. Kalus and R. L. McCreery, *J. Med. Chem.*, 1981, **24**, 1342.
7 P. P. Kelder, N. J. de Mol and L. H. M. Janssen, *Biochem. Pharmacol.*, 1991, **42**, 1551; P. P. Kelder, M. J. E. Fischer, N. J. de Mol and L. H. M. Janssen, *Archives Biochem. Biophys.*, 1991, **284**, 313; A. Vasquez, J. Tudela, R. Varon and F. A. Garcia-Canovas, *Biochem. Pharmacol.*, 1992, **44**, 889; R. A. Lovstad, *Biochem. Pharmacol.*, 1974, **23**, 1045; 1975, **24**, 475; *Biochem. Pharmacol.*, 1975, **24**, 475. See also; R. P. Mason in *Free Radicals in Biology*, vol. 5, ed. W. A. Pryor, Academic, New York, 1982, ch. 6, pp. 178–181.
8 H. Cheng, P. H. Sackett and R. L. McCreery, *J. Med. Chem.*, 1978, **21**, 948; P. H. Sackett and R. L. McCreery, *J. Med. Chem.*, 1979, **22**, 1448; H. Y. Cheng, P. H. Sackett and R. L. McCreery, *J. Am. Chem. Soc.*, 1978, **100**, 962, O. Hammerich and V. D. Parker, *Acta Chem. Scand., Sect. B*, 1982, **36**, 59; O. Hammerich and V. D. Parker, *Acta Chem. Scand., Sect. B*, 1983, **37**, 303.
9 (*a*) P. W. Hale, Jr. and A. Poklis, *Toxicol. Appl. Pharmacol.*, 1986, **86**, 44; (*b*) L. A. Gottschalk, E. Dinovo, R. Biener and B. R. Nandi, *J. Pharm. Sci.*, 1978, **67**, 155.
10 (*a*) P. L. Feldman, O. W. Griffith and D. J. Stuehr, *Chem. Eng. News*, 1993, Dec. 20, 26; (*b*) E. Culotta and D. E. Koshland, Jr., *Science*, 1992, **258**, 1862; (*c*) J. S. Stamler, D. J. Singel and J. Loscalzo, *Science*, 1992, **258**, 1898; (*d*) A. R. Butler and D. L. H. Williams, *Chem. Soc. Rev.*, 1993, 233.
11 (*a*) J. H. Smith, *J. Am. Chem. Soc.*, 1943, **65**, 74; (*b*) V. G. Kharitonov, A. R. Sundquist and V. S. Sharma, *J. Biol. Chem.*, 1994, **269**, 5881; (*c*) M. Kelm and J. Schrader, *Circ. Res.*, 1990, **66**, 1561.
12 F. F. Marmo, *J. Opt. Soc. Am.*, 1953, **43**, 1186.
13 W. G. Fateley, H. A. Bent and B. Crawford, Jr., *J. Chem. Phys.*, 1959, **31**, 204.
14 J. F. Bunnett, in *Investigation of Rates and Mechanisms of Reactions* Part I, C. F. Bernasconi, ed., Wiley, New York, 1986.
15 (*a*) A. Vasquez, J. Tudela, R. Varon and F. Garcia-Canovas, *Anal. Biochem.*, 1992, **202**, 245; (*b*) P. C. Dwivedi, K. Gurudath Rao, S. N. Bhat and C. N. R. Rao, *Spectrochim. Acta, Part A*, 1975, **31**, 129.
16 J. C. Evans, H. W. Rinn, S. J. Kuhn and G. A. Olah, *Inorg. Chem.*, 1964, **3**, 857.
17 H. S. Shine, J. J. Silber, R. J. Bussey and T. Okuyama, *J. Org. Chem.*, 1972, **37**, 2691.
18 Where PPN^+ is bis(triphenylphosphoranylidene)ammonium: J. K. Ruff and W. J. Schlienz, *Inorg. Synth.*, 1974, **15**, 83.
19 J. Laane and J. R. Ohlsen, *Prog. Inorg. Chem.*, 1980, **27**, 465.
20 This stoichiometry was proposed on the basis of kinetic data but was not established directly, J. E. Pemberton, G. L. McIntire, H. N. Blount and J. Evans, *J. Phys. Chem.*, 1979, **83**, 2697.
21 The electron-transfer mechanism has been proposed previously for the oxidation of phenothiazines to their cation radicals (as transient intermediates), (*a*) M. Matsui, Y. Miyamoto, K. Shibata and Y. Takase, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2526; (*b*) W. Adam, S. Huckmann and F. Vargas, *Tetrahedron Lett.*, 1989, **30**, 6315–6318; (*c*) see ref. 7.
22 (*a*) B. K. Bandlish and H. J. Shine, *J. Org. Chem.*, 1977, **42**, 561; (*b*) L. Eberson and F. Radner, *Acta Chem. Scand., Sect. B*, 1984, **38**, 861.
23 K. Y. Lee, D. J. Kuchynka and J. K. Kochi, *Inorg. Chem.*, 1990, **29**, 4196.
24 E. Bosch and J. K. Kochi, *Res. Chem. Intermed.*, 1993, **16**, 811.
25 (*a*) L. Parts and J. T. Miller, Jr., *J. Chem. Phys.*, 1965, **43**, 136; (*b*) A. Givan and A. Loewenschuss, *J. Chem. Phys.*, 1991, **94**, 7562.
26 See: M. L. Owens, E. C. Juenge and A. Poklis, *J. Pharm. Sci.*, 1989, **78**, 334.
27 D. L. H. Williams, *Nitrosation*, Cambridge University Press, New York, 1988, pp. 1–2.
28 D. P. Riley, M. R. Smith and P. E. Correa, *J. Am. Chem. Soc.*, 1988, **110**, 177 and references therein.
29 (*a*) E. G. Janzen, *Chem. Eng. News*, 1994, Mar. 14, 4; (*b*) E. G. Janzen, A. L. Wilcox and V. Manoharan, *J. Org. Chem.*, 1993, **58**, 3597; see also J. W. Wilt, in *Free Radicals*, J. K. Kochi, ed., Wiley, New York, 1973, vol. 1, pp. 382–384.
30 (*a*) A. S. Morkovnik, *J. Gen. Chem. (USSR) (Engl. Transl.)*, 1982, **52**, 1664; (*b*) W. Musker, T. L. Wolford and P. B. Roush, *J. Am. Chem. Soc.*, 1978, **100**, 6416; (*c*) E. K. Kim and J. K. Kochi, *J. Org. Chem.*, 1993, **58**, 789; (*d*) F. Radner, *J. Org. Chem.*, 1988, **53**, 702; see also Bandlish *et al.* in ref. 22*a* and Eberson *et al.* in ref. 22*b*.
31 D. L. H. Williams, ref. 18, pp. 19–21; see also E. Bosch and J. K. Kochi, *J. Org. Chem.*, 1994, **59**, 3314.
32 (*a*) W. A. Pryor, D. F. Church, C. K. Govindan and G. Crank, *J. Org. Chem.*, 1982, **47**, 156; (*b*) S. Oae, D. Fukushima and Y. H. Kim, *J. Chem. Soc., Chem. Commun.*, 1977, 407; (*c*) S. Oae, Y. H. Kim and D. Fukushima, *J. Chem. Soc., Perkin Trans. 1*, 1978, 913.
33 E. H. White, *J. Am. Chem. Soc.*, 1955, **77**, 6008.
34 C. C. Addison, *Chemistry in Liquid Dinitrogen Tetraoxide*, Vieweg, Braunschweig, 1967.
35 See Ruff *et al.* in ref. 18.
36 R. Rathore, E. Bosch and J. K. Kochi, *Tetrahedron*, 1994, **50**, 6727.
37 H. Gilman, P. R. Van Ess and D. A. Shirley, *J. Am. Chem. Soc.*, 1944, **66**, 1214.
38 M. H. Litt and J. Radovic, *J. Phys. Chem.*, 1974, **78**, 1750.
39 B. Boduszek and H. J. Shine, *J. Org. Chem.*, 1988, **53**, 5142.
40 See Owens *et al.* in ref. 26.

41 C. L. Huang and K. G. Bhansal, *J. Pharm. Sci.*, 1968, **57**, 1511.
42 C. D. M. Ten Berge and C. H. P. Bruins, *Pharm. Weekbl.*, 1969, **104**, 1433.
43 H. Gilman and R. O. Ranck, *J. Org. Chem.*, 1958, **23**, 1903.
44 H. J. Shine and L. Piette, *J. Am. Chem. Soc.*, 1962, **84**, 4798.
45 H. J. Shine and R. J. Small, *J. Org. Chem.*, 1965, **30**, 2140.
46 B. K. Bandlish, K. Kim and H. J. Shine, *J. Heterocycl. Chem.*, 1977, **14**, 209.

Paper 4/06333C
Received 14*th October* 1994
Accepted 20*th December* 1994