EPR studies of the copper-catalysed oxidation of thiols with peroxides

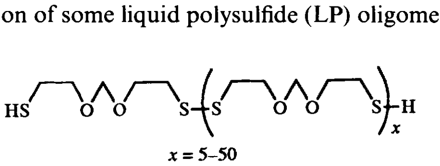
Garry Scrivens,[a] Bruce C. Gilbert *,[a] and Timothy C. P. Lee[b]
[a] *Department of Chemistry, University of York, Heslington, York, UK YO1 5DD*
[b] *Morton International Ltd., University of Warwick Science Park, Sir William Lyons Road, Coventry, UK CV4 7EZ*

EPR spectroscopy has been employed to monitor the reactions of Cu^{II} and the formation of organic radicals in the copper-catalysed oxidation of thiols to disulfides in the presence of oxygen and peroxides. Reaction of Cu^{II} with RSH gives Cu^{I} and disulfide (a process whose stoichiometry is 1 : 1 in certain solvents), which is followed by electron transfer to the peroxide to give Cu^{II} and, for example, $HO^{\bullet}$ (from H_2O_2) and $Bu^tO^{\bullet}$ (from Bu^tO_2H) which convert more thiol into disulfide. EPR and UV–VIS spectroscopy allow the kinetic parameters of these reactions to be determined in *N*,*N*-dimethylformamide (DMF).

Introduction

The oxidation of thiols to disulfides can be achieved in a variety of ways, including the use of transition-metal ions [*e.g.* iron(III),[1-3] copper(II)[3] and manganese(III)[4]], metal oxides,[5-8] halogens,[9] peroxides (including hydrogen peroxide[9,10] and perborates[11]) and oxygen itself[12-14] (especially in basic solution). The mechanisms proposed are diverse and not always clearly established: for example in reactions of peroxides the rates are affected by the presence of trace amounts of certain transition-metal ions[9,10] and a radical-chain mechanism may be involved. Complications which can arise from the variety of radical reactions undergone by thiyl (sulfenyl) radicals ($RS^{\bullet}$) are recognized,[15] and the ease of peroxidation of intermediates and products is an important factor to be borne in mind when conditions for oxidation are chosen.[16]

We have previously reported a mechanistic investigation of the oxidation of some liquid polysulfide (LP) oligomers (*e.g.* **1**)



1

to high-molecular-weight polymers *via* the formation of new –SS– links by reaction with stoichiometric amounts of MnO_2.[7] Spin-trapping techniques were employed in conjunction with EPR spectroscopy to establish that the reaction involves the formation of thiyl radicals, followed, depending upon conditions, either by direct dimerization to disulfide or reaction with thiolate anions to give the appropriate radical anion $RSSR^{\bullet -}$, which may then activate oxygen or added peroxides for subsequent oxidation.

The initial aim of the work described here was to explore the possibility that other high-valent transition metals, in catalytic quantities, could be used to effect this transformation in homogeneous solution, oxygen or peroxides being employed to regenerate the oxidant. It is known that Cu^{II} can be employed as a stoichiometric oxidant to convert thiols to disulfides and monosulfides[3] though a simple electron-transfer step to give $RS^{\bullet}$ is not necessarily involved and the mechanism is believed to be complex; for example it has been proposed that reaction between Cu^{II} and RSH (*e.g.* cysteine) proceeds *via* a copper(II)–cysteine complex[17] as well as a copper(I)–thiyl radical complex,[18] and examples of copper(I) thiolate clusters have been isolated following reaction of, for example, copper(II) nitrate with an excess of BuSH in basic conditions[19] (see also ref. 20). It is likely that such reactions are critically dependent on the conditions—typically the solvent, the structure of the thiol, and the nature of the copper(II) complex employed. Possible complications may be caused by the ability of both Cu^{II} and Cu^{I} to bring about the decomposition of disulfides (see *e.g.* refs. 21, 22 and 23, respectively).

We report here observations which establish that copper(I) is formed in the oxidation of the LP polymer (**1**, $x = 5$) and some model thiols by copper(II), and that reaction with peroxides then regenerates copper(II) with the appropriate disulfide, in a reaction which involves free radicals.

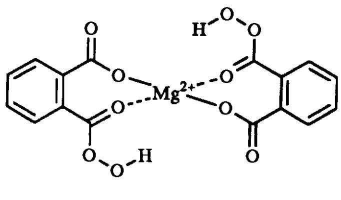
Results and discussion

Oxidation of thiols with Cu^{II} and with Cu^{II}–peroxide mixtures

In an initial set of experiments we explored the nature of the reactions between LP-3 (**1**, $x = 5$) and hydrogen peroxide (100 vol; 8.8 mol dm^{-3}) in the presence of a relatively low concentration of Cu^{II} in a system with no added solvent. The procedure typically involved addition of $CuCl_2$ to LP-3, followed by the addition of the peroxide; the ratio of $[RSH]:[H_2O_2]$ was normally taken as 1 : 1, with $[RSH]:[CuCl_2]$ varied between > 300 : 1 and *ca.* 2 : 1. In each case the formation of a rubber occurred rapidly following the addition of peroxide (the 'curing' took typically 5–30 min): the rate of reaction increased with increases in $[Cu^{II}]$ and $[H_2O_2]$. In parallel experiments with LP-2C (**1**, $x = 23$), rheological measurements (in which the viscosity and elasticity of the substance is determined[24]) were used to study the progress of polymerization (see also ref. 7). These experiments showed that as the reactions proceed the mixture becomes more viscous until the 'gel point' is reached (typically between 5 and 30 min after mixing). After the gel-point, the mixtures become increasingly rigid until the end point is reached (typically after several hours).

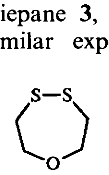
In order to carry out the experiment under more readily controlled conditions, we studied the oxidation of LP-3 (0.01 mol in 100 cm^3 methylbenzene) by H_2O_2 (0.02 mol in 12 cm^3 water) in the presence of a low concentration of $CuCl_2$ (0.0002 mol in *ca.* 12 cm^3 water) in a two-phase system. As $CuCl_2$ solution was added at room temperature, with stirring, to the solution of LP-3, a white precipitate (presumably a copper salt) was formed; then H_2O_2 solution was added. Samples were withdrawn from the methylbenzene layer at various time intervals, the solvent was removed by evaporation and the residue (increasingly viscous with time after mixing) redissolved in $CDCl_3$. Study of the product by ^1H NMR spectroscopy showed the progressive disappearance of the resonances associated with the thiol proton [δ *ca.* 1.60 (t, *J* 8.3 Hz)] and with the neighbouring methylene protons [δ *ca.* 2.72 (tt, *J* 8.3 Hz, *J'* 6.3 Hz) and 3.70 (t, *J* 6.3 Hz)] and the increase in the appropriate disulfide resonances [at δ *ca.* 2.91 (t, J 6.3 Hz) and 3.81 (t, J 6.3 Hz)];[7] the resonance due to the $-OCH_2O-$ group [at δ *ca.* 4.72 (s)] is not affected by oxidation of the thiol to disulfide. These results are consistent with the complete conversion of thiol to disulfide (and hence formation of a rubber).

The oxidation of LP-3 to disulfide could also be very effectively achieved with *tert*-butyl hydroperoxide, for example in experiments involving the addition of a 70% aqueous solution of Bu^tO_2H to a mixture of LP-3 and $CuCl_2$, so that a 1:1 molar ratio of Bu^tO_2H:RSH was obtained; the $CuCl_2$:RSH molar ratio was varied between 0.1:1 and 0.003:1. Magnesium monoperoxyphthalate (MMPP, **2**) was also found to bring about the oxidation of LP-3 in the presence of $CuCl_2$ as catalyst. For example in similar experiments to those with H_2O_2 and Bu^tO_2H, MMPP was added to an LP-3–$CuCl_2$ solvent-free mixture so that the MMPP:RSH molar ratio was *ca.* 1:1 and the RSH:$CuCl_2$ molar ratio was varied between 1:0.1 and 1:0.003; in all cases the formation of a rubber was observed. Polymerization was not observed with di-*tert*-butyl peroxide or potassium peroxydisulphate under similar conditions; in the case of the latter this is presumably due to its insolubility in LP3.

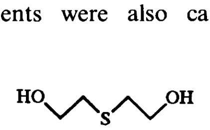


2

Related experiments were carried out on the oxidation of propanethiol and 2-mercaptoethanol (2-sulfenylethanol) with the aqueous copper(II) chloride–hydrogen peroxide system. The experiments typically involved a RSH:H_2O_2:$CuCl_2$ molar ratio of 1:1:0.1 (with [RSH] typically *ca.* 0.1 mol dm^{-3}). For example, addition of *ca.* 1 g of neat propanethiol to *ca.* 15 cm^3 of aqueous $CuCl_2$ solution (0.05 mol dm^{-3}), so that the [RSH]:[Cu] ratio was 10:1, gave a pale yellow precipitate. Addition of 0.8 cm^3 of H_2O_2 (8.8 mol dm^{-3}) in a single aliquot brought about a slow change in colour (over *ca.* 3 h) to give a green–brown precipitate and finally dissolution of this to leave a blue solution [typical of aquo copper(II)]. Extraction of the organic products into $CHCl_3$ followed by analysis by GC–MS (see Experimental) gave a single large peak due to the disulfide (PrSSPr); only traces of other products (in too low concentrations to be characterized by GC–MS) were detected. A similar experiment with 2-mercaptoethanol in aqueous solution in which the products were extracted into ethyl ethanoate and then identified by GC–MS, gave the corresponding disulfide (this assignment was verified by comparison with an authentic sample), along with very small amounts of 1,4,5-oxadithiepane **3**, the monosulfide **4** and other minor products. Similar experiments were also carried out in *N*,*N*-dimethylformamide (DMF): 2-mercaptoethanol was oxidized by H_2O_2 in the presence of $CuCl_2$ as catalyst (with similar concentrations to the experiments in water). The colour of the solution changed from colourless (or very pale yellow) to green (typical of $CuCl_2$ in DMF); analysis of the organic products by GC showed that the disulfide was again the major product (this assignment was verified by comparison with an authentic sample).



3



4

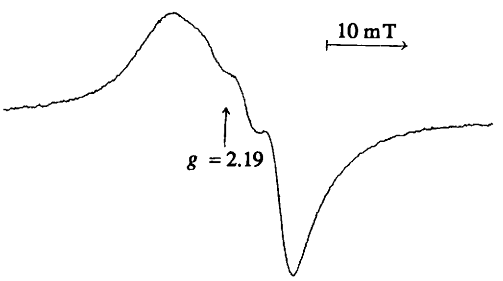


Fig. 1 EPR spectrum of $CuCl_2$ (0.025 mol dm^{-3}) in DMF at room temperature

Oxidation could also be brought about by molecular oxygen. For example, when an aqueous solution containing 2-mercaptoethanol (0.5 mol dm^{-3}) and copper(II) chloride (0.05 mol dm^{-3}) was stirred for five days in an unstoppered flask, complete conversion of disulfide was observed (as monitored by GC–MS after extraction into ethyl ethanoate); the reaction was much slower under nitrogen.

Finally we studied the products and stoichiometry of the reaction between copper(II) and thiol in the absence of oxygen and peroxides. ^{1}H NMR spectroscopy showed that addition of $CuCl_2$ to 2-mercaptoethanol in deuteriated acetone led to the conversion of thiol to disulfide. Integration of the disulfide resonances showed, to within experimental error, that two moles of Cu^{II} convert two moles of thiol into one mole of disulfide [reaction (1)]. The resonances associated with any

$$2Cu^{II} + 2RSH \longrightarrow 2Cu^{I} + 2H^+ + RS_2R \qquad (1)$$

excess thiol (*i.e.* which has not been oxidized to disulfide) are identical to those obtained from 2-mercaptoethanol in deuteriated acetone under acidic conditions. We conclude that under appropriate conditions there is a stoichiometric reaction between copper(II) and thiol, presumably followed, in the presence of peroxides, by regeneration of copper(II) (which would account for its effect in catalytic quantities). The nature of the reoxidation was next explored.

EPR and UV–VIS studies of the copper complexes present during reaction

Initial experiments were carried out by the addition of either LP-3 or 2-mercaptoethanol to solutions of copper(II) chloride in DMF at room temperature. On addition of thiol to $CuCl_2$ the intensity of the copper(II) EPR signal (see Fig. 1) decreased, with no changes in shape. The spectrum was completely removed when an equivalent amount (or excess) of thiol was added (N.B. 0.5 mol equiv. of the dithiol LP-3). We also noted that the green colour of the $CuCl_2$–DMF solution faded as thiol was added to give a colourless solution (at which point the solution was also EPR-silent). These experiments establish that a 1:1 (RSH:$CuCl_2$) stoichiometry is required to remove the EPR signal of copper(II) in DMF (see above). No EPR signal from copper(II) could be obtained from frozen glasses (down to 77 K) of the RSH–$CuCl_2$ solution (with molar ratios > 1:1), and no absorptions characteristic of copper(II) could be seen in UV–VIS spectra under similar conditions. Absence of paramagnetic Cu^{II} is also indicated by the well resolved ^{1}H NMR spectrum obtained above. These observations also lead to the conclusion that copper(I) is formed (further evidence is presented later).

When hydrogen peroxide was then added to solutions containing the copper(I)–thiol complex the EPR signal from Cu(II) was re-formed in a manner which depended critically upon the relative concentrations of thiol, copper and hydrogen peroxide originally present: the reaction showed an induction period when [RSH] $\gg$ [Cu^{II}], and a rate of regeneration of Cu^{II},

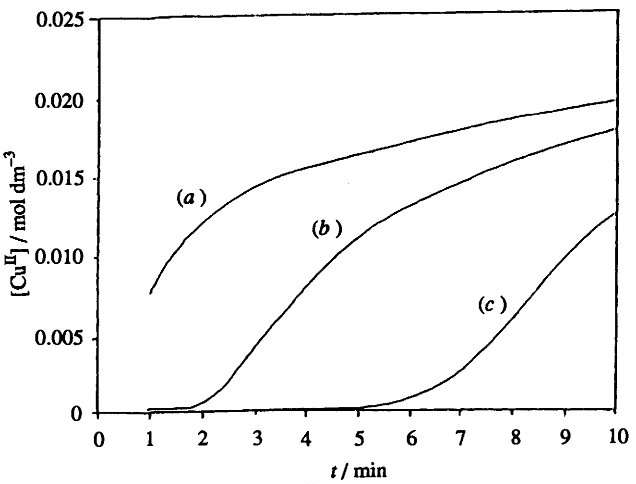


Fig. 2 Growth with time of $[Cu^{II}]$, monitored by EPR spectroscopy (see Fig. 1) in DMF when H_2O_2 (0.0625 mol dm^{-3}) was added to Cu^I (0.025 mol dm^{-3}), the latter being generated by the reaction between Cu^{II} (initial concentration 0.025 mol dm^{-3}) and the dithiol LP-3 which is present in variable concentrations: (*a*) 0.0125, (*b*) 0.0250 and (*c*) 0.0375 mol dm^{-3}. All concentrations given refer to those after mixing.

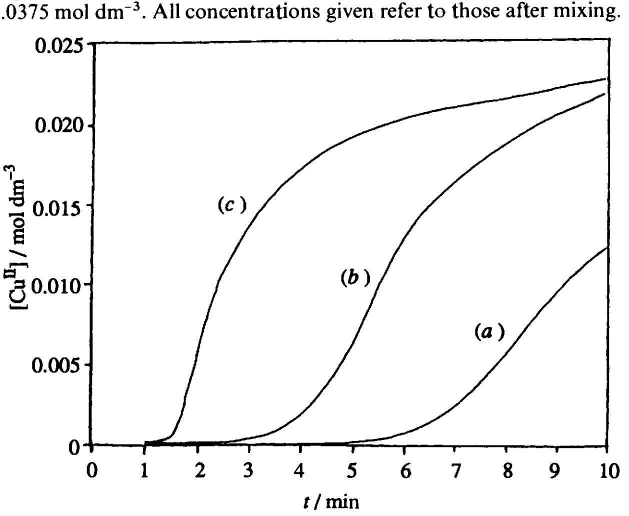


Fig. 3 Growth with time of $[Cu^{II}]$, monitored by EPR spectroscopy (see Fig. 1) in DMF when different concentrations of H_2O_2 were added to Cu^I (0.025 mol dm^{-3}), the latter being generated from the reaction of Cu^{II} (0.025 mol dm^{-3}) and the dithiol LP-3 (0.025 mol dm^{-3}): (*a*) $[H_2O_2]$ 0.063, (b) $[H_2O_2]$ 0.125 and (*c*) $[H_2O_2]$ 0.187 mol dm^{-3}. All concentrations given refer to those after mixing.

after the induction period, which depended upon $[H_2O_2]$, as illustrated in Figs. 2 and 3. We interpret these observations in terms of the very rapid reaction of RSH with Cu^{II}, as noted above, to give Cu^I, and the re-oxidation of Cu^I to Cu^{II} with H_2O_2 [reactions (1) and (2)] when the excess of thiol has been

$$Cu^I + H_2O_2 \longrightarrow Cu^{II} + HO^\bullet + HO^- \qquad (2)$$

consumed: more detailed evidence for the mechanism is presented later, but we note at this stage that it resembles that which is believed to explain the catalytic role of Cu^{II} in the oxidation of thiols to disulfides with the binuclear superoxo cobalt(III) complex $[Co_2(O_2)(CN)_{10}]^{5-}$.[25] Similar behaviour was observed with other peroxides including Bu^tO_2H and MMPP, but not $Bu^tO_2Bu^t$ and $K_2S_2O_8$ (the latter is relatively insoluble in DMF). The rate of regeneration of copper(II) proved to be relatively insensitive to the structure of the thiol, for those studied (see below). To give further evidence that a discrete copper(I) species is formed and re-oxidized, we studied the addition of 2-mercaptoethanol to a mixture of Cu^ICl and HCl (1 : 1 molar proportions) in DMF. This produces a colourless solution, which on reaction with H_2O_2 or Bu^tO_2H generates Cu^{II} (as detected by EPR and UV–VIS spectroscopy), exactly as noted above and with identical rate (see below). This further confirms that a copper(I) intermediate is indeed formed in the reaction between $Cu^{II}Cl_2$ and RSH in DMF.

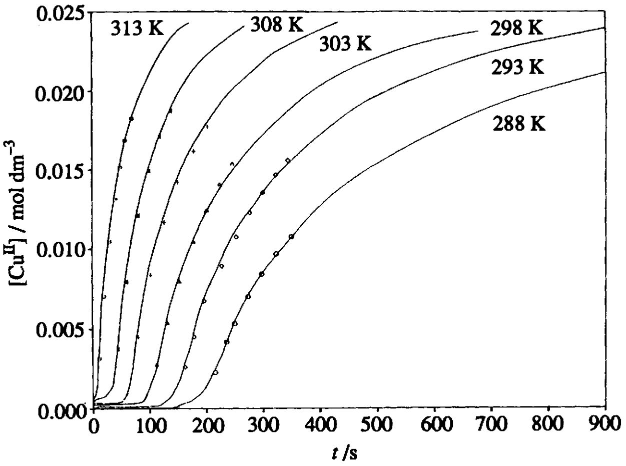


Fig. 4 The solid lines show the growth with time of $[Cu^{II}]$, and its absorbance (at λ = 800 nm), at different temperatures, when H_2O_2 (0.0625 mol dm^{-3}) was added to Cu^I (0.025 mol dm^{-3}) in DMF, the latter being generated from the reaction of Cu^{II} (0.025 mol dm^{-3}) and the dithiol LP-3 (0.025 mol dm^{-3}). The symbols show the results of kinetic simulations based on eqn. (i) and using the rate constants obtained from linear regression (see Fig. 6). All concentrations given refer to those after mixing.

Similar results were obtained using UV–VIS spectroscopy to study the disappearance and subsequent reappearance of copper(II) in related experiments with $CuCl_2$ in DMF. Addition of deoxygenated solutions of RSH (LP-3) to deoxygenated solutions of $CuCl_2$ in DMF (final concentrations typically 0.05 mol dm^{-3} and 0.025 mol dm^{-3}, respectively) led to the immediate removal of the characteristic UV–VIS spectrum from copper(II) (in most of our experiments we monitored the complete disappearance of the absorption at λ = 800 nm). Additions of solutions of either H_2O_2 or Bu^tO_2H led to the reappearance of copper(II) (as judged by the increase in the absorbance at λ = 800 nm and to the generation of a spectrum identical to that recorded initially for $CuCl_2$); the trends in the rate of build-up, and occurrence of an induction period (for $[RSH]_0 > [Cu^{II}]_0$) match exactly those monitored by EPR spectroscopy. Fig. 4 shows the results for specific experiments in which $CuCl_2$, RSH (LP-3) and H_2O_2 were mixed (giving concentrations of 0.025, 0.050 and 0.0625 mol dm^{-3}, respectively) over a range of temperatures. Fig. 5 shows the analogous results with Bu^tO_2H used as oxidant.

Kinetic analysis

The UV–VIS and EPR results were analysed to provide detailed kinetic information for the reaction of $CuCl_2$ with RSH (R = LP-3) and both H_2O_2 and Bu^tO_2H in DMF as solvent. If we assume that a copper(I) complex is generated in the initial reaction, that (as indicated by spin-trapping results presented later) reaction with H_2O_2 (or Bu^tO_2H) regenerates copper(II) and $HO^\bullet$ [which itself reacts with copper(I): reaction (3)[26]], and

$$Cu^I + HO^\bullet \longrightarrow Cu^{II} + HO^- \qquad (3)$$

the excess thiol is consumed during the induction period [*via* reaction (1), to give overall reaction (4)], then we can calculate

$$H_2O_2 + 2RSH \xrightarrow{Cu^{II}} 2H_2O + RS_2R \qquad (4)$$

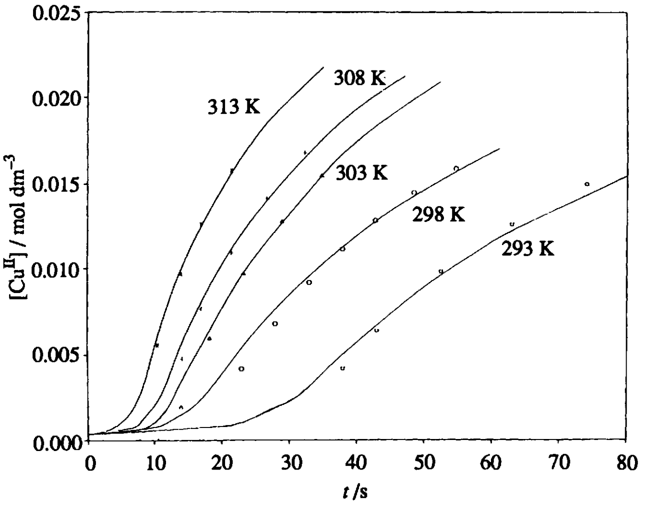


Fig. 5 The solid lines show the growth with time of $[Cu^{II}]$, and its absorbance (at $\lambda = 800$ nm), at different temperatures, when Bu^tO_2H (0.0625 mol dm^{-3}) was added to Cu^I (0.025 mol dm^{-3}) in DMF, the latter being generated from the reaction of Cu^{II} (0.025 mol dm^{-3}) and the dithiol LP-3 (0.025 mol dm^{-3}). The symbols show the results of kinetic simulations based on eqn. (i) and using the rate constants obtained from linear regression (see Fig. 7). All concentrations given refer to those after mixing.

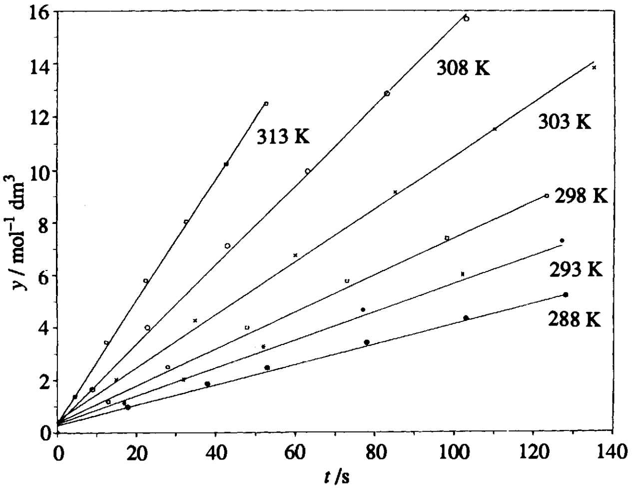


Fig. 6 Variation of $\ln\{[B_0(A_0 - x/2)/A_0(B_0 - x)]\}/(2A_0 - B_0)$, y, with time [see eqn. (i)], for the reaction between H_2O_2 and Cu^I over a range of temperatures; the gradient gives the rate constant for the reaction at a given temperature

the values of $[Cu^I]_0$, $[RSH]_0$ and $[H_2O_2]_0$ at the end of the induction period for a given experiment [*i.e.* the 'initial' concentrations of Cu^I, RSH and H_2O_2 appropriate to the commencement of subsequent reactions (2) and (3)].

Writing $[H_2O_2]$ as A_0 and $[Cu^I]$ as B_0 at the beginning of the reaction (after the induction period), we can derive eqn. (i),

$$\ln\{[B_0(A_0 - x/2)]/[A_0(B_0 - x)]\}/(2A_0 - B_0) = kt \quad \text{(i)}$$

in which x refers to the concentration of copper(I) reacted after time t (as measured from the concentration of $[Cu^{II}]$ determined by UV–VIS or EPR spectroscopy).

Fig. 6 shows the expected straight line plots of $\ln\{[B_0(A_0 - x/2)/A_0(B_0 - x)]\}/(2A_0 - B_0)$ *vs.* t for the reaction of H_2O_2 with Cu^I ($A_0 = 0.05$, $B_0 = 0.025$ mol dm^{-3}) over the temperature range 288–313 K; Fig. 7 shows the analogous plots for the reaction of Bu^tO_2H with Cu^I. The rate constants, k, for the reaction of Cu^I with peroxides, can be derived from the gradient of the plots over the temperature range studied (see Table 1).

Table 1 Rate constants for the reactions between copper(I) (from $CuCl_2$ and LP-3) and both H_2O_2 and Bu^tO_2H in DMF[a]

	k/dm^3 mol^{-1} s^{-1}	
T/K	H_2O_2	Bu^tO_2H
288	0.03 ± 0.01	0.15 ± 0.04
293	0.04 ± 0.01	0.20 ± 0.04
298	0.06 ± 0.02	0.26 ± 0.05
303	0.08 ± 0.02	0.41 ± 0.06
308	0.12 ± 0.03	0.51 ± 0.07
313	0.18 ± 0.04	0.67 ± 0.08

[a] For the conditions and method of analysis, see text. [b] Errors are obtained from linear regression analysis.

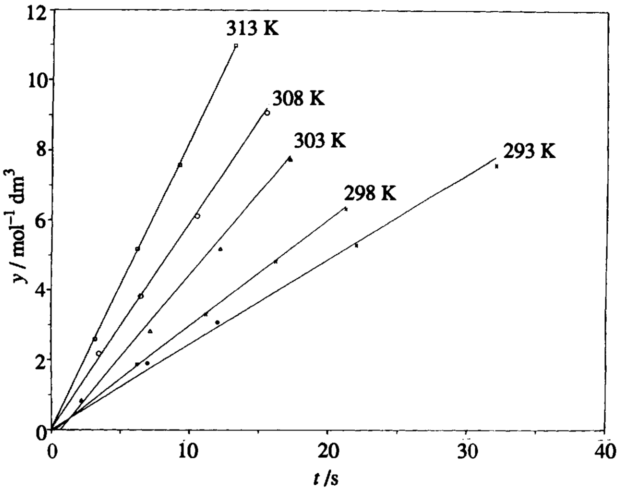


Fig. 7 Variation of $\ln\{[B_0(A_0 - x/2)/A_0(B_0 - x)]\}/(2A_0 - B_0)$, y, with time [see eqn. (i)], for the reaction between Bu^tO_2H and Cu^I over a range of temperatures

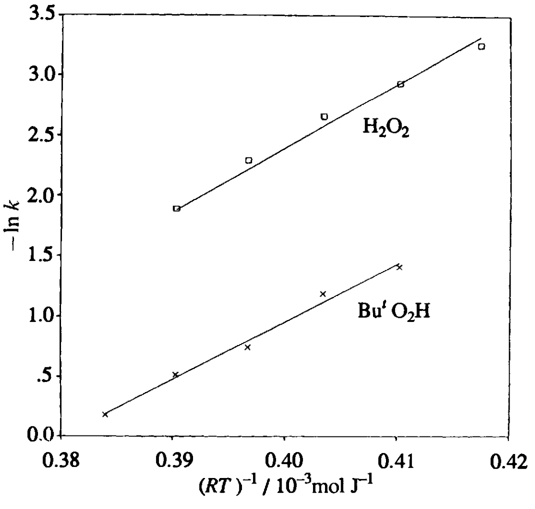


Fig. 8 Arrhenius plot of the variation of $-\ln k$ with $1/RT$ for the reaction of Cu^I with H_2O_2 and Bu^tO_2H. Values of k used and the resultant E_a values are shown in Table 1.

The activation energies and pre-exponential factors for the reaction of Cu^I with H_2O_2 and Bu^tO_2H were found by (Arrhenius) analysis of the rate constants (see Fig. 8), giving an activation energy and pre-exponential factor of *ca.* 53 kJ mol^{-1} and *ca.* 1.2×10^8 dm^3 mol^{-1} s^{-1} respectively for the H_2O_2 reaction and *ca.* 48 kJ mol^{-1} and *ca.* 6.5×10^7 dm^3 mol^{-1} s^{-1} respectively for Bu^tO_2H. The kinetic plots were also satisfactorily simulated using the rate constants from Table 1: simulations of the rate of re-formation of copper(II) are compared

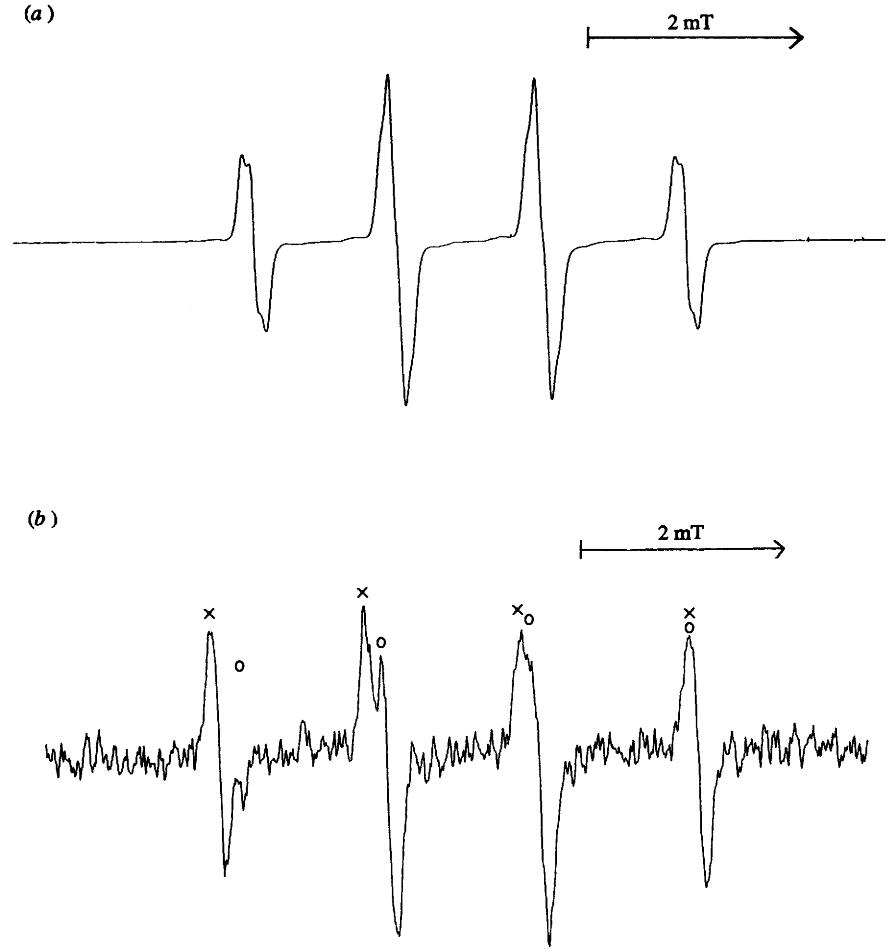
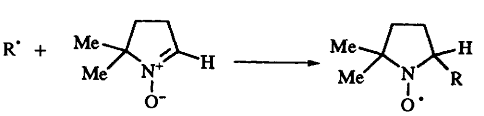


Fig. 9 (*a*) EPR spectrum of the thiyl radical adduct from LP-3 and DMPO in DMF, formed by UV irradiation of LP-3 (for parameters see Table 2). (*b*) EPR spectrum of the thiyl radical adduct (x) and the hydroxyl radical adduct (○) of DMPO obtained from the reaction between Cu^{I} (8 x 10^{-4} mol dm^{-3}) and H_2O_2 (0.031 mol dm^{-3}) in presence of 2-mercaptoethanol (0.024 mol dm^{-3}) and DMPO (0.0125 mol dm^{-3}) in aqueous solution. All concentrations given refer to those after mixing.

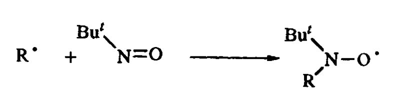
with the results of EPR and UV–VIS experiments in Figs. 4 and 5. The rates of reaction of the Cu^{I} complex with peroxide are much lower than those reported for the reaction of Cu$^{I}_{aq}$ with H_2O_2 (*ca.* 4 x 10^3 dm^3 mol^{-1} s^{-1})[27] and Bu^{t}O$_2$H (*ca.* 5 x 10^3 dm^3 mol^{-1} s^{-1})[27] as well as $S_2O_8{}^{2-}$ (10^6–10^7 dm^3 mol^{-1} s^{-1});[27,28] this presumably reflects stabilization of Cu^{I} by Cl$^-$ and the solvent DMF. It is notable that, as indicated by the spin-trapping results (below), the reaction does indeed produce hydroxyl radicals [it has been suggested[27] that aquated copper(I) reacts with H_2O_2 to produce initially Cu$^+$·O$_2$H$^-$, rather than HO$^•$]. Since closely similar results were obtained with both LP-3 and 2-mercaptoethanol, this provides further evidence that a discrete solvated copper(I) species [rather than *e.g.* a copper(I)-thiol complex] is involved.

EPR spin-trapping studies of radical formation in the Cu^{II}–RSH–peroxide reactions

For the majority of our experiments 5,5-dimethylpyrroline *N*-oxide (DMPO, **5**) was employed to trap radicals generated in the reaction so that the EPR spectra of relatively long-lived aminoxyls generated by addition to the double bond would reveal the nature of the short-lived intermediates [reaction (5)]. 2-Methyl-2-nitrosopropane (MNP, **6**) was also employed [reaction (6)]. Experiments were mostly carried out using water and DMF as solvents.


(5)

DMPO **5**


(6)

MNP **6**

In initial experiments with DMPO we set out to ascertain the precise hyperfine splittings associated with various radical adducts under the conditions employed. Photolysis of hydrogen peroxide itself was used to generate $^•$OH (and hence its adduct), and photolysis of LP-3 and 2-hydroxyethyl disulfide (HOCH$_2$-CH$_2$S$_2$CH$_3$CH$_2$OH) and Bu^{t}O$_2$Bu^t was employed to generate RS$^•$ and Bu^{t}O respectively (in water the latter route also gives Me$^•$ *via* fragmentation[29]); an example is shown in Fig. 9. The hydroxyl radical was also generated by the Fenton reaction between Fe^{II} and H_2O_2 (using 8 x 10^{-4} mol dm^{-3} FeCl$_2$ and 0.0016 mol dm^{-3} H_2O_2) and the adduct of HO$_2$$^•$ was generated by addition of superoxide to DMPO. Data on these adducts are tabulated together in Table 2 (see also refs. 30–32 for comparable sets of splitting constants).

The reactions of copper(II) chloride (typically 0.05 mol dm^{-3}) with thiols LP-3 and 2-mercaptoethanol (typically > 0.05 mol dm^{-3}) in DMF were first studied in experiments involving DMPO (typically 0.0125 mol dm^{-3}). We believe that it is

Table 2 EPR parameters for aminoxyls formed as spin adducts of 5,5-dimethylpyrroline *N*-oxide (DMPO) and 2-methyl-2-nitrosopropane (MNP) in photolytic reactions of peroxides and disulfides and by reaction of copper(I) complexes with peroxides[a]

Trap	Addend	Solvent	Hyperfine splittings[b]/mT			Method of generation
			a(N)	*a*(β-H)	*a*(other)	
DMPO	LP-S•	DMF	1.36	1.30	0.06 (2) (δ-H)	Photolysis of LP-3 LP-3 + $Ar_3N^{•+}$ Cu^I + H_2O_2 + LP-3 Cu^I + Bu^tO_2H + LP-3 Cu^I + MMPP + LP-3
MNP	LP-S•	DMF	1.82			Cu^I + Bu^tO_2H + LP-3
DMPO	$HO[CH_2]_2S^•$	DMF	1.37	1.34	0.06 (2) (δ-H)	Photolysis of $HO[CH_2]_2S_2[CH_2]_2OH$ $HO[CH_2]_2SH + Ar_3N^{•+}$ $Cu^I + HO[CH_2]_2SH + Bu^tO_2H$ $Cu^I + HO[CH_2]_2SH + H_2O_2$
MNP	$HO[CH_2]_2S^•$	DMF	1.81			$Cu^I + HO[CH_2]_2SH + H_2O_2$
DMPO	$HO[CH_2]_2S^•$	H_2O	1.53	1.68	0.06 (2) (δ-H)	Photolysis of $HO[CH_2]_2S_2[CH_2]_2OH$ $Cu^I + HO[CH_2]_2SH + H_2O_2$ $Cu^I + HO[CH_2]_2SH + Bu^tO_2H$
DMPO	HO•	DMF	1.36	1.14	0.07 (γ-H)	Photolysis of H_2O_2 $FeCl_2 + H_2O_2$ $Cu^I + H_2O_2$ + RSH $Cu^I + Bu^tO_2H$ + RSH Cu^I + MMPP + RSH
DMPO	HO•	H_2O	1.49	1.49		Photolysis of H_2O_2 $Cu^I + H_2O_2$ + RSH
DMPO	$Bu^tO^•$	DMF	1.34	0.99	0.15 (γ-H)	Photolysis of $Bu^tO_2Bu^t$ $Cu^I + Bu^tO_2H$ + RSH
MNP	$Bu^tO^•$	DMF	2.69			$Cu^I + Bu^tO_2H$ + RSH
DMPO	$HO_2^•$	DMF	1.28	0.99	0.13 (γ-H)	KO_2 $CuCl_2 + H_2O_2$ $Cu^I + H_2O_2$ + RSH
DMPO	$Me_2N\dot{C}(O)$	DMF	1.44	1.76		Photolysis of H_2O_2 Photolysis of $Bu^tO_2Bu^t$ $Cu^I + H_2O_2$ + RSH $Cu^I + Bu^tO_2H$ + RSH
MNP	$Me_2N\dot{C}(O)$	DMF	1.19		0.07 (β-N)	$Cu^I + Bu^tO_2H$ + RSH
DMPO	$HC(O)NMeCH_2^•$	DMF	1.42	2.00		Photolysis of H_2O_2 Photolysis of $Bu^tO_2Bu^t$ $Cu^I + H_2O_2$ + RSH $Cu^I + Bu^tO_2H$ + RSH
MNP	$HC(O)NMeCH_2^•$	DMF	1.48		0.88 (2) (β-H); 0.23 (β-N)	$Cu^I + H_2O_2$ + RSH $Cu^I + Bu^tO_2H$ + RSH
DMPO	Me•	H_2O	1.64	2.36		$Cu^I + Bu^tO_2H$ + RSH

[a] For the conditions and methods of experiments, see text. [b] Splitting constants are quoted to an accuracy of ± 0.01 mT.

particularly significant that no evidence could be obtained for the formation of free thiyl radicals at this stage in the reaction. Related background experiments on the reaction between copper(II) chloride (typically 0.0042 mol dm^{-3}) and hydrogen peroxide (0.01 mol dm^{-3}) only showed the development of weak signals from $HO_2^•$ adducts presumably formed by reaction of H_2O_2 with copper(II). In marked contrast, strong signals of radical-adducts from DMPO (sometimes in complex mixtures) were observed in experiments in which peroxides were added to solutions containing DMPO (typically 0.0125 mol dm^{-3}) and copper(II)/thiol mixtures [which we believe immediately react to give copper(I) and disulfide, see earlier]. The results may be summarized as follows (see also Table 2 and Figs. 9–11).

(*i*) Experiments in aqueous solution involving 2-mercaptoethanol (0.025 mol dm^{-3}), copper(II) chloride (8×10^{-4} mol dm^{-3}) and DMPO (0.0125 mol dm^{-3}), in which H_2O_2 was then added (final concentration 0.031 mol dm^{-3}) gave clear signals from both •OH and thiyl adducts, confirming that both are formed in the reaction (see Fig. 9). As the trap concentration was increased, the concentration of the hydroxyl radical adduct grew at the expense of the thiyl radical-adduct. In experiments with increased concentrations of Cu^I, the hydroxyl radical also dominates. These observations suggest that the HO• formed in

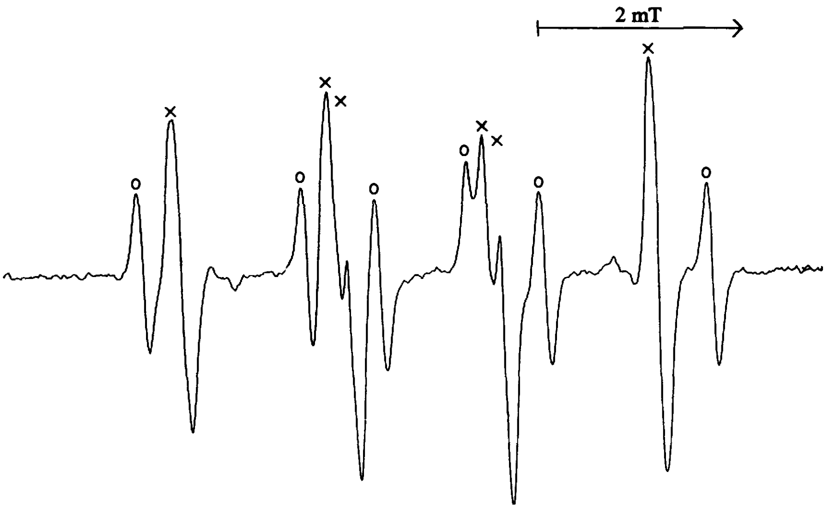


Fig. 10 EPR spectrum of the thiyl radical adduct (×) and the methyl radical adduct (O) of DMPO obtained from the reaction between Cu$^{\mathrm{I}}$ (8×10^{-4} mol dm^{-3}) and Bu^{t}O$_2$H (0.031 mol dm^{-3}) in the presence of 2-mercaptoethanol (0.024 mol dm^{-3}) and DMPO (0.0125 mol dm^{-3}) in aqueous solution. All concentrations given refer to those after mixing.

the reaction between Cu$^{\mathrm{I}}$ and H_2O_2, reacts not only with Cu$^{\mathrm{I}}$ to give Cu$^{\mathrm{II}}$ and HO$^-$ [reaction (3)] but also reacts (competitively) with both the trap and with excess of thiol to give RS$^\bullet$ [reaction (7)] (which presumably forms RSSR).

$$\mathrm{HO^\bullet + RSH \longrightarrow H_2O + RS^\bullet} \qquad (7)$$

(*ii*) Parallel experiments in aqueous solution involving preformed Cu$^{\mathrm{I}}$ and Bu^{t}O$_2$H again provided conclusive evidence for the formation of thiyl radicals (presumably from reaction of Bu^{t}O$^\bullet$ with RSH) and for the trapping of the methyl radical (evidently *via* fragmentation of Bu^{t}O$^\bullet$) (see Fig. 10). The signal from the latter built up with time; we believe that this reflects the initial removal of Bu^{t}O$^\bullet$ by excess thiol, after which fragmentation and addition can be discerned [reactions (8)–(10)].

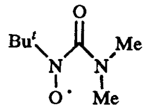
$$\mathrm{Cu^{I} + Bu^tO_2H \longrightarrow Cu^{II} + Bu^tO^\bullet + HO^-} \qquad (8)$$

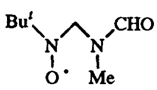
$$\mathrm{Bu^tO^\bullet + RSH \longrightarrow Bu^tOH + RS^\bullet} \qquad (9)$$

$$\mathrm{Bu^tO^\bullet \xrightarrow{H_2O} Me_2C{=}O + Me^\bullet} \qquad (10)$$

(*iii*) In experiments with DMF as solvent, the EPR spectra were particularly strong and complex, and critically dependent upon the precise conditions employed. For example, at low concentrations of Cu$^{\mathrm{I}}$ [with significant excess of thiol (LP-3 or 2-mercaptoethanol)], addition of H_2O_2 led to the production of strong EPR signals from RS$^\bullet$ adducts from both DMPO and MNP. DMPO-thiyl adduct spectra were observed when H_2O_2 (0.031 mol dm^{-3}) was reacted with copper(I) (1.8×10^{-4} mol dm^{-3}) in the presence of DMPO (0.0125 mol dm^{-3}) and excess thiol (0.025 mol dm^{-3}) in DMF. With time, signals from hydroxyl adducts grow stronger, presumably as excess thiol is consumed [reactions (1) and (5)].

When the experiment was repeated with higher concentrations of Cu$^{\mathrm{I}}$ (and therefore with a smaller excess of thiol), strong signals were obtained from the hydroxyl adduct. When the concentration of Cu$^{\mathrm{I}}$ was raised still further, these were accompanied by signals from adducts whose parameters are typical of carbon-centred radical adducts (see Fig. 11 and Table 2). We believe that these are due to the formation (evidently *via* reaction of $^\bullet$OH) of solvent-derived radicals $^\bullet$C(O)NMe$_2$ and $^\bullet$CH$_2$NMeCHO [reaction (11)]: crucial supporting evidence derives from parallel experiments with MNP in which corresponding adducts were detected [with characteristic splittings, involving a low a(N) for **7** and second nitrogen splitting for **8**, see Fig. 11]. The ultimate appearance of the HO$_2^\bullet$ adduct of DMPO (at the end of the reaction) is believed to characterize the formation of relatively high concentrations of copper(II) and its reaction with H_2O_2.


7


8

$$\mathrm{HO^\bullet + M_2NCHO \longrightarrow H_2O + Me_2NC(O)^\bullet + {}^\bullet CH_2NMeCHO} \qquad (11)$$

(*iv*) In parallel experiments involving Cu$^{\mathrm{I}}$ and Bu^{t}O$_2$H in DMF, clear evidence for thiyl-radical formation was obtained with both DMPO and MNP especially in experiments with low concentrations of Cu$^{\mathrm{I}}$ and Bu^{t}O$_2$H (8×10^{-4} mol dm^{-3} Cu$^{\mathrm{I}}$ and 0.025 mol dm^{-3} Bu^{t}O$_2$H). Other signals developed with time and were also more pronounced in experiments with higher concentrations of Cu$^{\mathrm{I}}$: these are attributed to adducts of Bu^{t}O$^\bullet$ and also adducts of solvent derived species (see Table 2).

(*v*) A limited number of experiments were also carried out with MMPP (**2**). For example, when Cu$^{\mathrm{I}}$ (7.8×10^{-4} mol dm^{-3}) was reacted with MMPP (0.025 mol dm^{-3}) in the presence of DMPO (0.0125 mol dm^{-3}) and excess thiol (0.05 mol dm^{-3}), the thiyl adduct of DMPO was initially detected; this signal quickly decayed as the excess thiol was consumed, and a signal due to the hydroxyl adduct of DMPO emerged. We conclude that the one-electron transfer occurs from Cu$^{\mathrm{I}}$ to the peroxide and that this gives RCO$_2^-$ and HO$^\bullet$ [reaction (12)] rather than RCO$_2^\bullet$ and HO$^-$; this behaviour parallels the results from earlier work with Cu$^{\mathrm{I}}$ and MMPP (N.B. Ti$^{\mathrm{III}}$ and Fe$^{\mathrm{II}}$ react to give RCO$_2^\bullet$ and HO$^-$).[33]

$$\mathrm{Cu^{I} + RCO_3H \longrightarrow Cu^{II} + RCO_2^- + HO^\bullet} \qquad (12)$$

Reaction of the copper(I)–thiol complex with one-electron oxidants

If our assertion is correct that copper(II) reacts with appropriate thiols to give copper(I) and that this reacts with peroxides by single-electron transfer to give copper(II), HO$^\bullet$ from H_2O_2 and

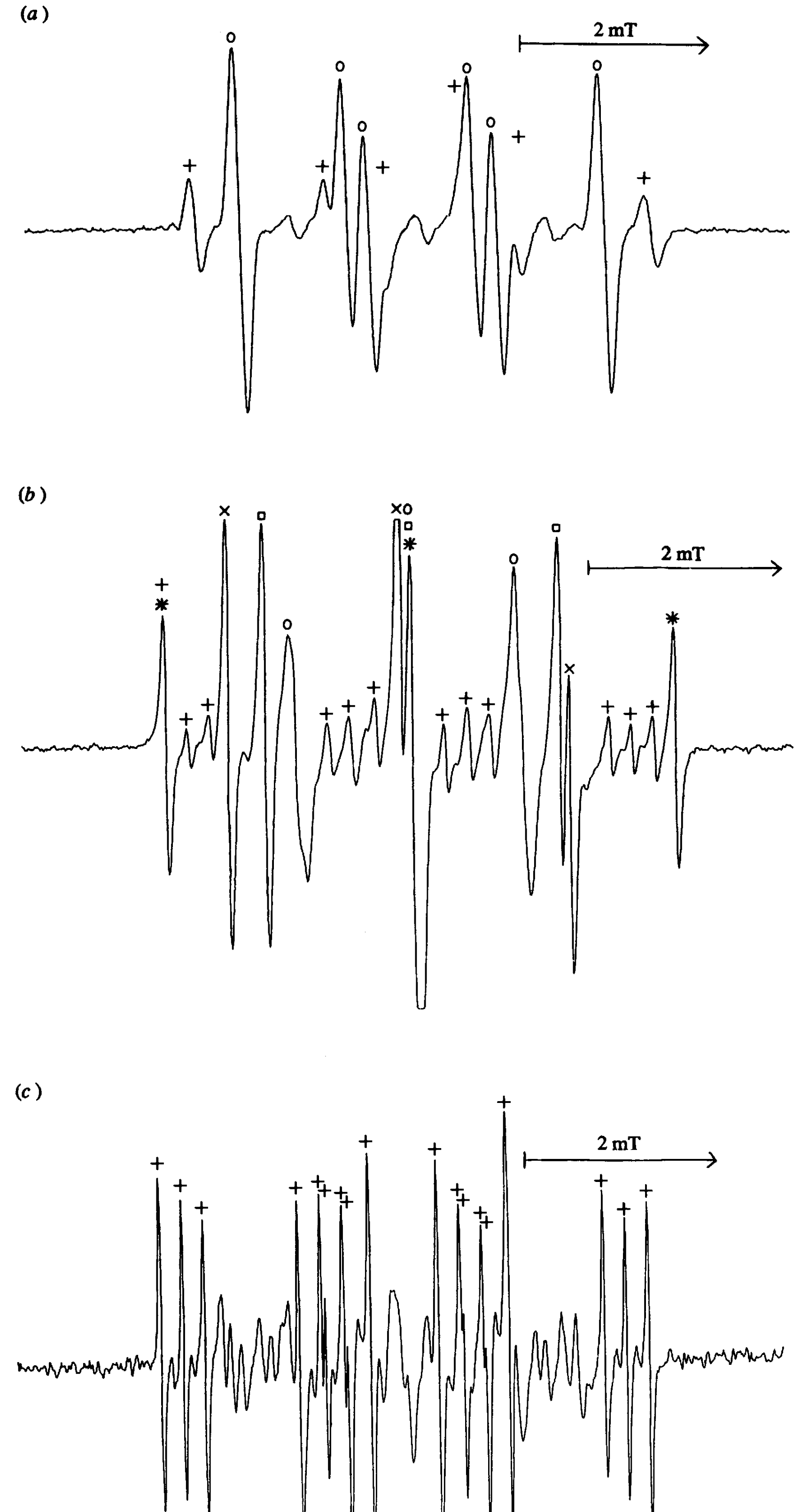


Fig. 11 (*a*) EPR spectrum of the hydroxyl radical adduct (○) and the $^{\bullet}CH_2NMeCHO$ radical adduct (+) of DMPO obtained from the reaction between Cu^I (3 × 10^{-3} mol dm^{-3}) and H_2O_2 (0.25 mol dm^{-3}) in the presence of LP-3 (0.025 mol dm^{-3}) and DMPO (0.0125 mol dm^{-3}) in DMF. All concentrations given refer to those after mixing. (*b*) EPR spectrum of the thiyl radical adduct (×), the $Me_2NC(O)^{\bullet}$ radical adduct (○), the $^{\bullet}CH_2NMeCHO$ radical adduct (+) and the $Bu^tO^{\bullet}$ radical adduct (✱) of MNP obtained from the reaction between Cu^I (3 × 10^{-3} mol dm^{-3}) and Bu^tO_2H (0.25 mol dm^{-3}) in the presence of LP-3 (0.025 mol dm^{-3}) and MNP (0.0125 mol dm^{-3}) in DMF. (□) is the signal from di-*tert*-butylaminoxyl (DBNO) formed by self-reaction of MNP. All concentrations given refer to those after mixing. (*c*) EPR spectrum of the $^{\bullet}CH_2NMeCHO$ radical adduct of MNP obtained from the reaction between Cu^I (3 × 10^{-3} mol dm^{-3}) and H_2O_2 (0.25 mol dm^{-3}) in presence of 2-mercaptoethanol (0.025 mol dm^{-3}) and MNP (0.0125 mol dm^{-3}). The lines marked '+' are the outer lines of the β-proton splitting pattern (the inner lines are broadened). The spectrum was recorded *ca.* 8 min after mixing: the DMF-derived radicals increase in intensity with time while other adducts decay. All concentrations given refer to those after mixing.

further RS_2R, then we would expect to bring about the same reaction with other one-electron oxidants. Our approach involved the use of the aminium radical cation $NAr_3^{\bullet +}$ $SbCl_6^-$ (Ar = 4-bromophenyl) in experiments with LP-3 and $CuCl_2$ in molar ratios $RSH:Ar_3N^{\bullet +}:CuCl_2$ of 1:*ca.* 2:0.1. Additions of solutions of $Ar_3N^{\bullet +}$ to those containing copper(I) led to the formation and build up of copper(II) (as described earlier); the formation of disulfide was indicated by the formation of a rubber in a solvent-free system.

Conclusions

Spectroscopic studies, involving EPR spectra of copper(II) and trapped free-radicals, as well as UV-VIS results for copper, provide strong evidence for an initial reaction between certain substituted thiols and copper(II) in which copper(I) and disulfide, but not free radicals, are formed. Copper(I) reacts readily with oxygen and with several peroxides, although not $Bu^tO_2Bu^t$, *via* a one-electron transfer step, the kinetics of which have been explored for H_2O_2 and Bu^tO_2H; oxygen-centred radicals result, which subsequently give rise to the formation of thiyl radicals in the presence of excess thiol. Thus, under appropriate conditions copper salts can serve as catalytic oxidants for thiols (to give RS_2R) in the presence of peroxides, *e.g.* hydrogen peroxide. It will be of interest to study the structure and rate of formation of the copper(I) intermediates formed in similar systems [*e.g.* on varying the solvent, the copper(II) salt, the structure of the thiol] and to investigate their reactivity with oxidants such as H_2O_2 and Bu^tO_2H. The relevance of these observations to the oxidation of a range of thiols, including biologically important examples such as cysteine and glutathione will also be studied.

Experimental

EPR spectra were measured on a JEOL JES RE1X spectrometer equipped with X-band klystron and 100 kHz modulation. Splitting constants were determined to within ± 0.01 mT using the spectrometer field scan and *g*-values (for the copper species) were determined to within ± 0.001. UV-VIS spectra were measured on a Shimadzu UV 160A spectrometer equipped with a variable temperature unit. NMR spectra were recorded in deuteriated chloroform and deuteriated acetone solutions on either a Bruker FX90 or a JEOL JNM-EX270 spectrometer. GC analyses were performed on a Phillips Pye Unicam PU 4500 chromatograph fitted with a flame-ionization detector, coupled to a Shimadzu Chromatopac C-R3A integrator. A Carbowax capillary column (30 m × 0.32 mm, 0.25 μm film thickness) was used with helium as the carrier gas. GC-MS spectra were obtained by coupling the GC to a VG Autospec Mass Spectrometer. Detector response and retention times were calibrated by comparison with known concentrations of authentic material. Rheological measurements were performed on a Carri-Med CSL-500 rheometer, using parallel-plate geometry, operating in a constant strain mode at 40 °C.

All compounds were obtained from either Morton International Ltd. or Aldrich, and used as supplied and peroxide concentrations were determined by iodometric titration.

Acknowledgements

We thank the EPSRC and Morton International Ltd. for their support for this research *via* a CASE award for G. S., and Dr P. H. Walton, Dr J. E. Bennett and Mr R. J. Coates for helpful discussions.

References

1 B. Pispisa, G. Paradossi, A. Palleschi and A. Desideri, *J. Phys. Chem.*, 1988, **92**, 3422.
2 A. A. Neyaglov, N. G. Digurov, T. V. Bukharkina, A. M. Mazgurov and A. M. Fakhriev, *Kinet. Catal.*, 1991, **32**, 479.
3 T. J. Wallace, *J. Org. Chem.*, 1966, **31**, 3071.
4 T. Nakaya, H. Arabori and M. Imoto, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 1888.
5 T. J. Wallace, *J. Org. Chem.*, 1966, **31**, 1217.
6 E. P. Papadopulos, A. Jarrar and C. H. Issidorides, *J. Org. Chem.*, 1966, **31**, 615.
7 R. J. Coates, B. C. Gilbert and T. C. P. Lee, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1387.
8 T. Mukaiyama and T. Endo, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 2388.
9 G. Capozzi and G. Modena, *Oxidation of Thiols*, in *Chemistry of the Thiol Group*, Part 2, ed. S. Patai, Wiley, 1974, ch. 17, p. 785.
10 E. I. Kalinina, E. M. Lukina and V. P. Masleunikov, *Trudy Khim. i Khim. Tekhnol.*, 1967, 190.
11 A. McKillop, D. Koyunçu, A. Krief, W. Dumont, P. Renier and M. Trabelsi, *Tetrahedron Lett.*, 1990, **31**, 5007.
12 T. J. Wallace and A. Schriesheim, *J. Org. Chem.*, 1962, **27**, 1514.
13 T. J. Wallace and A. Schriesheim, *Tetrahedron*, 1965, **21**, 2271.
14 T. J. Wallace, A. Schriesheim and W. Bartok, *J. Org. Chem.*, 1963, **23**, 1311.
15 B. C. Gilbert, *Structure and Reaction Mechanisms in Sulphur-Radical Chemistry Revealed by E.S.R. Spectroscopy*, in *Sulphur-Centred Reactive Intermediates in Chemistry and Biology*, ed. C. Chatgilialoglu and K.-D. Asmus, Plenum Press, 1990, p. 135.
16 W. E. Savige and J. A. Maclaren, *Oxidation of Disulphides, with Special Reference to Cystine*, in *The Chemistry of Organic Sulphur Compounds*, Part 2, ed. N. Kharasch and C. Y. Meyers, Pergamon Press, 1966, ch. 15, p. 367.
17 F. J. Davis, B. C. Gilbert, R. O. C. Norman and M. C. R. Symons, *J. Chem. Soc. Perkin Trans. 2*, 1983, 1763.
18 W. E. Blumberg and J. Peisach, *J. Chem. Phys.*, 1968, **49**, 1793.
19 I. G. Dance, *J. Chem. Soc., Chem. Commun.*, 1976, 68.
20 R. Chadha, R. Kumar and D. G. Tuck, *J. Chem. Soc., Chem. Commun.*, 1986, 188.
21 O. Yamauchi and H. Seki, *Chem. Lett.*, 1982, 1241.
22 L. S. Higashi, M. Lundeen, E. Hilti and K. Seff, *Inorg. Chem.*, 1977, **16**, 310.
23 T. Ottersen, L. G. Warner and K. Seff, *Inorg. Chem.*, 1974, **13**, 1904.
24 H. A. Barnes, J. F. Hutton and K. Walters, *An Introduction to Rheology*, Elsevier, 1989.
25 S. K. Ghosh, S. K. Saha, M. C. Ghosh, R. N. Bose, J. W. Reed and E. S. Gould, *Inorg. Chem.*, 1992, **31**, 3358.
26 N. L. Sukhov, M. A. Akinshin and B. G. Ershov, *High Energy Chem.*, 1986, **20**, 303.
27 M. Masarwa, H. Cohen, D. Meyerstein, D. L. Hickman, A. Bakac and J. H. Espenson, *J. Am. Chem. Soc.*, 1988, **110**, 4293.
28 B. C. Gilbert and J. K. Stell, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1867.
29 B. C. Gilbert, P. D. R. Marshall, R. O. C. Norman, N. Pineda and P. S. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1392.
30 G. R. Buettner, *Free Radical Biol. Med.*, 1987, **3**, 259.
31 E. G. Janzen, G. A. Coulter, U. M. Oehler and J. P. Bergsma, *Can. J. Chem.*, 1982, **60**, 2725.
32 J. R. Harbour and M. L. Hair, *J. Phys. Chem.*, 1978, **82**, 1397.
33 B. C. Gilbert, J. K. Stell, A. C. Whitwood, C. Halliwell and W. R. Sanderson, *J. Chem. Soc., Perkin Trans. 2*, 1991, 629.

Paper 4/07625G
Received 14*th December* 1994
Accepted 23*rd January* 1995