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Chemical Evidence for Peroxy Radicals Intermediacy in Copper(II) Reaction with Hydroperoxides.

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Abstract : Two unprecedented decompositions of tertiary hydroperoxides by Cu(II) in CH_3CN have been encountered : deoxygenation of 4- hydroperoxy cyclohexa 2,5- dienones **1** and **2** brings chemical support to the existence of intermediate peroxy radicals R-OO˙ **1'** and **2'**.

Decomposition of hydroperoxides in presence of transition metal ions has been extensively investigated[1,2]; these studies have been prompted by both synthetic and biological interests. Alkyl hydroperoxides are classically reduced by Cu(I) salts or other low-valence transition metal salts [M(n) = Fe(II), Mn(II), Ag(I), Co(II), Cr(II), Ti(III),...] to alkoxy radicals [equation (1)] which either are subsequently reduced to alcohols or fragment to provide ketones and alkyl radicals.

$$\text{R-OOH} + \text{Cu(I)} \rightarrow \text{R-O}^{\cdot} + \text{Cu(II) (OH)} \qquad (1)$$

Several authors[3-6] have proposed that hydroperoxides could be oxidized by Cu(II) salts [like by many M(n + 1) species] to peroxy radicals [equation (2)] :

$$\text{R-OOH} + \text{Cu(II)} \rightarrow \text{R-OO}^{\cdot} + \text{Cu(I)} + \text{H}^{+} \qquad (2)$$

Alkyl hydroperoxides are inert to Cu(II) carboxylates[5] at room temperature, in chlorobenzene, but the decomposition is reactivated by addition of diamino ligands[7].

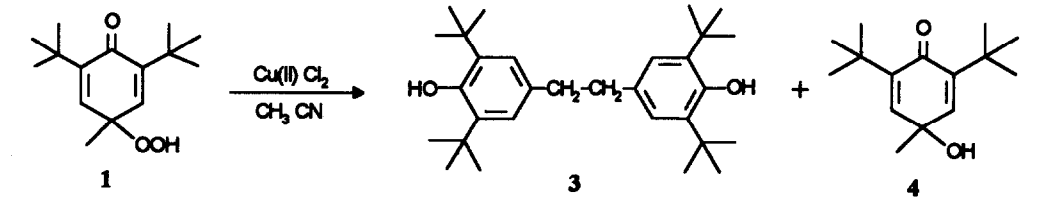
The involvement of equation 2 is difficult to prove since peroxy radicals, generally in thermal chain decompositions, mainly decompose to alkoxy radicals via tetroxides[8-12] [equation (3)], so reaction products of equations (1) and (2) are undistinguishable.

$$2\ \text{R-OO}^{\cdot} \rightarrow [\text{R-O-O-O-O-R}] \rightarrow 2\ \text{R-O}^{\cdot} + \text{O}_2 \qquad (3)$$

Here are described two unprecedented homolytic evolutions in the reaction of Cu(II) with peculiar tertiary alkyl hydroperoxides that give support to the existence of peroxy radicals ROO˙ as intermediates [equation (2)].

RESULTS

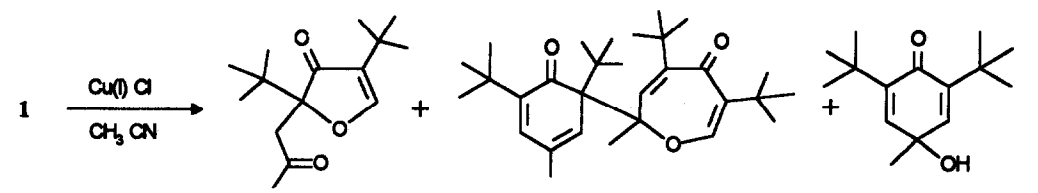
Two new transformations are observed when hydroperoxides **1** and **2**, characterized by 4-hydroperoxy cyclohexa 2,5- dienone structures, react at room temperature, in dry acetonitrile, under a nitrogen atmosphere, with cupric chloride [Cu(II)Cl_2] in excess (4 molar equivalents), to provide chiefly **deoxygenation** products. So, 2,6- di -*tert*-butyl 4- hydroperoxy 4- methyl cyclohexa 2,5-dienone **1** is reduced into the dehydrodimeric compound, bis 1,2- (3,5- di- *tert*-butyl 4- hydroxy phenyl)- ethane **3** (70% yield), and quinol **4** (28% yield); the related steroid tertiary hydroperoxide **2** provides two deoxygenation products: estrone **5** (28%) and 10β- chloro estradien dione **6** (25%) besides corresponding quinol **7** (27%).



1 **3** **4**

2 **5** **6** **7**

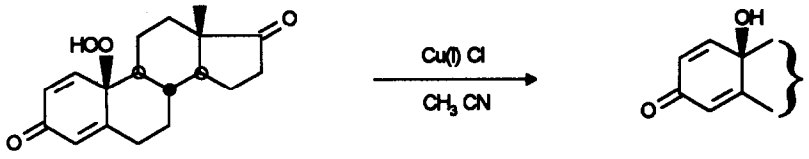
It was also important to state the part of Cu(I) in these Cu(II) mediated decompositions since Cu(I) should be produced in the reaction of hydroperoxides with Cu(II) [equation (2)]. The interactions of these tertiary hydroperoxides **1**, **2** with Cu(I)Cl have been studied in the same experimental conditions. Deoxygenation reactions (from **1** and **2**) are no more observed but only products that may be explained from intermediate alkoxy radicals. Dihydrofuranone **8** (47% yield), "dehydrodimer" diketone **9** (20% yield) and quinol **4** (33%) are isolated from hydroperoxide **1**.



8 **9** **4**

Dihydrofuranone **8** has been previously prepared[13] through performic acid oxidation of quinol **4** and diketone **9** obtained[14] by Co(II) salen-catalyzed oxidation of 4- methyl 2,6- di- *tert*- butyl phenol by dioxygen.

In contrast, 10β- quinol **7** is the sole product (85%) obtained from 10β- hydroperoxide **2**.



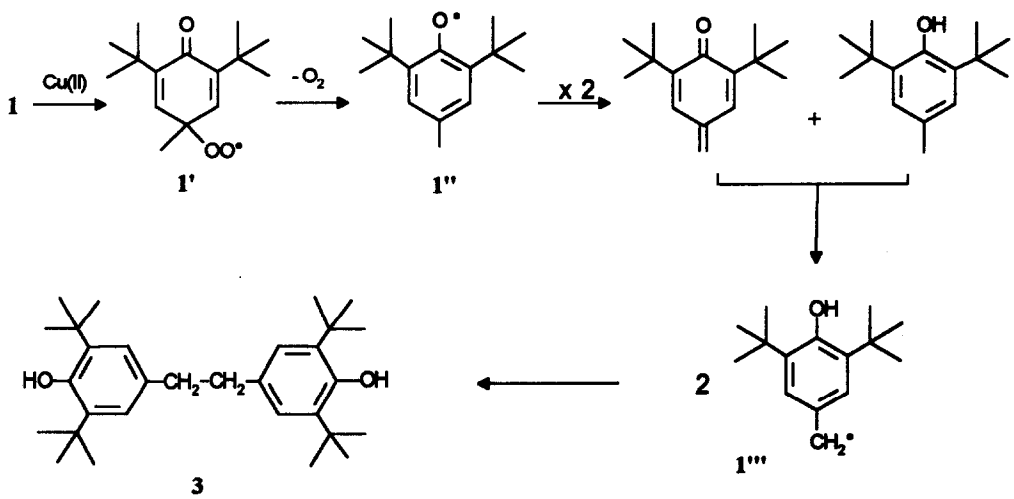
2 **7**

DISCUSSION

Oxidation of hydroperoxides into peroxy radicals by Cu(II) [equation (2)] is not unexpected, since we have measured a high value for the potential of 10^{-1} M $Cu(II)Cl_2$ solution in acetonitrile: E_0 = 1.12 V *vs* SCE (0.1 M tetraethylammonium perchlorate, Pt electrodes).

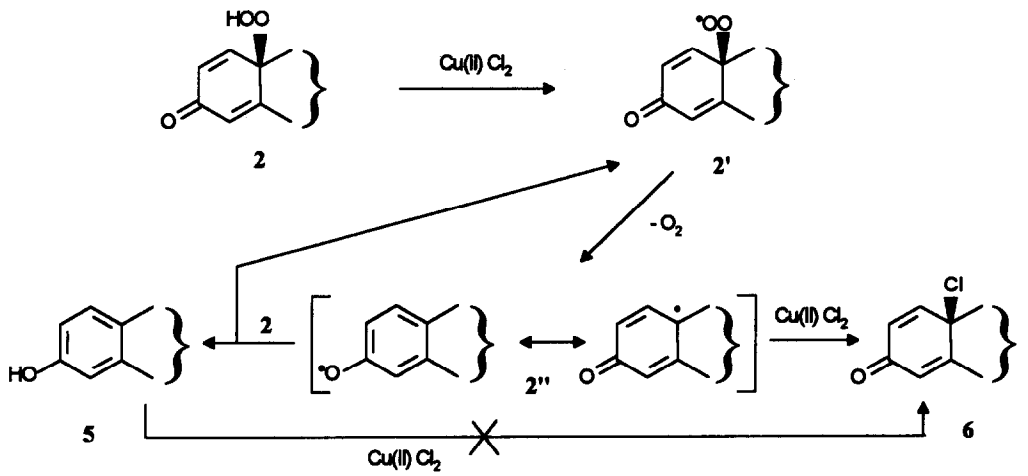
With the exception of quinols **4** and **7**, minor products which are very likely issued from alkoxy radicals RO˙ [equations (1) and / or (3)], the major products of the reaction of cyclohexadienone peroxides **1** and **2** with excess cupric chloride may be explained by an homolytic deoxygenation of peroxy radicals [equation (4)] which is original (to our knowledge) but not surprising since R˙ radicals are highly stabilized by their aromatic phenoxy forms **1''** and **2''**, and thus resonance energy recovery may be the driving force of such deoxygenation reactions.

$$R\text{-}OO^{\cdot} \rightarrow R^{\cdot} + O_2 \qquad (4)$$



Peroxy radical **1'** is assumed to loose dioxygen and thus provide a phenoxy radical **1''**, well known to disproportionate and rearrange into benzyl radical **1'''** and finally dimerize[15] into diphenol **3**.

The corresponding phenoxy radical **2''** issued from peroxy radical **2'** do not present such a behaviour since dimerizations are never observed from steroid radicals, probably due to important steric hindrance. It achieves hydrogen abstraction, likely with the most labile hydrogen ROO-H of **2**, to provide estrone **5** and another **2'** radical (chain reaction).

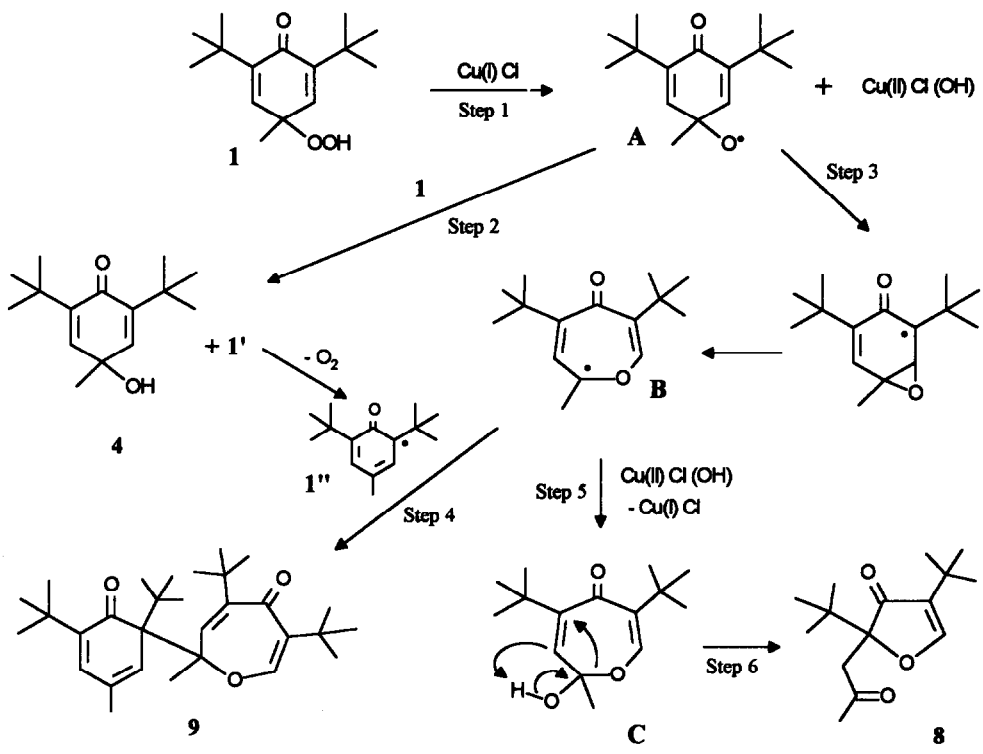


The other deoxygenation product 10β-chloro compound **6** is not issued from further $Cu(II)Cl_2$ reaction with estrone **5** since we have checked that estrone does not react with cupric chloride in these experimental conditions (20°C in acetonitrile). It may rather be proposed that radical **2''** interacts in its 10β site with $Cu(II)Cl_2$ according to Kochi' s ligand transfer oxidation[16-18] on carbon-centered radicals [equation (5)] :

$$R^{\cdot} + Cu(II)Cl_2 \rightarrow R\text{-}Cl + Cu(I)Cl \qquad (5)$$

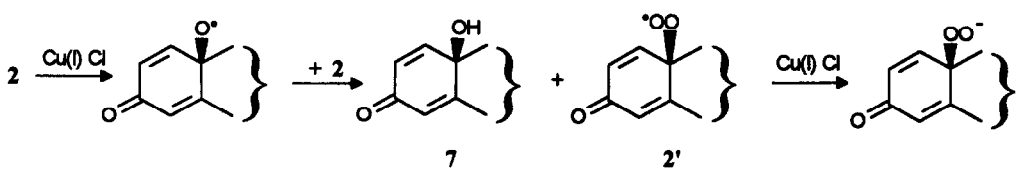
The nature of dioxygen produced in equation (4) (excited singlet state or fundamental triplet state) has not been elucidated yet.

All products issued from reaction of hydroperoxides **1**, **2** with excess (4 molar equivalents) cuprous chloride may be relevant to an intermediate alkoxy radical RO˙ (equation 1). Cu(I)-mediated decomposition of hydroperoxide **1** affords corresponding quinol **4** directly issued from hydrogen abstraction of peroxydic hydrogen of **1** by the alkoxy **A** radical (next scheme, step 2). The same **A** radical leads to products **8** and **9** *via* the common intermediacy of the radical rearrangement **A** (oxy radical) → **B** (oxepinone radical) (step 3). This rearrangement has been previously postulated in literature[19].



Dehydrodimer diketone **9** formation (step 4) may be explained by combination of radical **B** and substituted phenoxy radical **1''** (issued from deoxygenation of radical **1'** produced in step 2). To account for dihydrofuranone **8**, the oxydation of radical **B** (step 5) by Cu(II)Cl(OH) formed in the redox reaction (step 1) into intermediate **C** may be considered since this cupric compound is known to be a powerful oxidizing species able to transfer hydroxyl group to radicals[20]. Rearrangement of **C** intermediate into a 5- membered heterocycle **8** (step 6) may be easily rationalized and compared to closely related classical cyclizations.

In contrast, Cu(I) mediated decomposition of hydroperoxide **2** gives only rise to quinol **7**. The absence of deoxygenation or rearrangement products implies that peroxy radical **2'**, eventually produced by alkoxy radical transfer on hydroperoxide **2**, is rapidly reduced into **2** hydroperoxy anion by Cu(I)Cl in large excess (4 molar equiv.) and high concentration (0.1 M). Measured potential of such a solution is 0.47 V *vs* SCE, to be compared with the very higher 1.12 V of the reverse $[Cu(II)Cl_2]$ oxidant system.



EXPERIMENTAL

General. M.p.s were determined on a Kofler (Reichert) apparatus; i.r. and u.v. spectra were respectively obtained on Perkin-Elmer 298 and Cary 15 spectrophotometers; mass spectra (m.s.) were recorded on a MS 30 AET instrument (70 eV); preparative thin layer chromatography (t.l.c.) were carried out on homemade plates (Merck GF 254 silica gel, 200 x 200 x 1.5 mm); ^1H n.m.r. spectra were obtained in $CDCl_3$ (internal standard $SiMe_4$) on a Varian EM 390 (90 Mhz) and ^{13}C NMR spectra on a Varian FT 80, *J* values (coupling constants) are given in Hz.

Materials. Most reagents are commercialy available. CH_3CN was dried over $CaCl_2$, distilled from P_4O_{10} and kept over molecular sieves (3 Å).

2,6- di- tert- butyl 4- hydroperoxy 4- methyl cyclohexa 2,5- dienone **1** was synthesized[21] by autoxidation of 2,6- di- *tert*- butyl 4- methyl phenol with dioxygen, in ethanol, in presence of potassium hydroxide and purified by preparative t.l.c. chromatography; m.p. 115-116°C; u.v.(methanol), λ(nm) (ε) 234 (10,500); i.r.(KBr) (ν cm^{-1}) : 3,390, 1,670, 1,645, 1,625 cm^{-1}; ^1H n.m.r., δ = 1.22 (s, 18 H, 2 *t*Bu), 1.32 (s, 3 H, CH_3), 6.6 (s, 2 H, 3 and 5- H), 8.35 (s,1 H, OOH).

10β-hydroperoxy estra 1(2), 4(5)- dien 3, 17- dione **2** : previously unknown, has been prepared by eosin-sensitized photooxidation of estrone in methanol. This method was adapted from previous papers[22-23] (oxidation of *p*-unsubstituted phenols into *p*-quinones). A solution of 1 mmol. estrone **5** and 0.1 mmol eosin disodium salt in 60 ml methanol is irradiated with a Philips 500 W mercury lamp, through an orange filter (λ > 530 nm), with dioxygen bubbling, during 7 h, at 20°C. The solvent is evaporated and the crude material is eluted on a silica gel (Merck 60 H) column with cyclohexane-ethyl acetate (50-50, v/v). After unreacted estrone (less polar), hydroperoxide **2** is isolated (67% yield) as colorless crystals, m.p. 208 °C; (Found C, 71.4; H, 7.4; O, 21.2. Calc. for $C_{18}H_{22}O_4$: C, 71.5; H, 7.33; O, 21.17 %); u.v.(EtOH) λ (nm) (ε) : 237 (15,800); i.r. (KBr) (ν cm^{-1}) 3,190, 1,735, 1,605, 1,620; ^1H n.m.r., (δ) 0.87 (s, 18-CH_3), 6.1 (m, 4-H), 6.23 (dd, $J_{1\text{-}2}$ 11, $J_{2\text{-}4}$ 2, 2-H), 7.18 (d, $J_{1\text{-}2}$ 11, 1-H); this hydroperoxide is quantitatively reduced by an excess (1.2 equivalent) of triphenyl phosphine in ethyl acetate (1.5 h at 20°C) into 10-β hydroxy estra 1(2), 4(5)-dien 3,17-dione **7** (m.p. 214-215°C), identified with an authentic[24] sample.

Note : 10β- hydroperoxy 17β- hydroxy estra 1(2), 4(5)- dien 3- one (m.p. 211 °C) has been also prepared from estradiol by the same photooxidation procedure in comparable yield.

Reaction of hydroperoxides **1, 2** *with Cu(II)Cl_2 in acetonitrile.* As a typical experiment, anhydrous cupric chloride [Cu(II)Cl_2], 4 mmol, in 35 ml dry CH_3CN is stirred under a nitrogen atmosphere at room temperature (20°C) and 1 mmol hydroperoxide **1, 2** in 5 ml CH_3CN is added dropwise in 5 mn; the reaction mixture is stirred for 1 h. The solvent is evaporated in vacuum and the crude product extracted twice (2 x 30 ml) with ethyl acetate, washed with saturated brine and dried

with $MgSO_4$. Reaction products are immediately separated by preparative t.l.c. using cyclohexane / ethyl acetate mixtures as eluent : 90 / 10 (v/v) to isolate the products from **1** and 50 / 50 the steroids from **2**.

Bis 1,2- (3,5- di- tert- butyl 4- hydroxy phenyl)- ethane **3** : colorless crystals; m.p. 170-171 °C (MeOH); lit.[25-27]; i.r. (KBr) (ν cm^{-1}) 3,520, 1,580; u.v.(ether) λ(nm) (ε) : 286 (4,200); this diphenol is highly sensitive to autoxidation in air and quantitatively provides tetra- *tert*- butyl-stilbenequinone (red crystals; m.p. 310-311°C, i.r. and n.m.r. spectra superimposable with those of an authentic sample[27]).

2,6- di- ter- butyl 4- hydroxy 4-methyl cyclohexa 2,5- dienone **4**: colorless crystals, m.p. 110-111°C; i.r. (KBr) (ν cm^{-1}) 3,350, 1,665, 1,645, 1,635, 1,620; u.v. (EtOH) λ (nm)(ε) : 234 (10,300); m.s. 236 (M^+); lit.[21].

10β-chloro estra 1(2), 4(5)- dien 3, 17- dione **6** : colorless crystals, m.p. 250°C (decomp.); i.r. (KBr) (ν cm^{-1}) 1,610, 1,635, 1,665, 1,640; u.v.(EtOH) λ(nm) (ε) : 243 (12,000); n.m.r. ^1H (δ) 0.85 (s, 3H, 18- CH_3), 6.05 (m, 1 H, 4-H), 6.2 (dd, 1 H, $J_{1\text{-}2}$ 11, $J_{2\text{-}4}$ 2, 2-H), 7.10 (d, 1 H, $J_{1\text{-}2}$ 11, 1-H); when heated in acetonitrile at 60° C, this chloro compound readily and unreversibly rearranges into 4-chloro estrone (m.p. 273-275 °C) and 2- chloro estrone (m.p. 223-224 °C) (isomers ratio 5 / 1) identified with authentic samples[28].

Reaction of hydroperoxides **1, 2** *with Cu(I)Cl in acetonitrile*. The same procedure and work up as above were used with Cu(I)Cl in excess (4 molar equivalent) instead of $Cu(II)Cl_2$ as only difference.

2,4- ditertiobutyl 2- (2-oxo propyl) 2,3- dihydro furan 3- one **8** : colorless crystals, m.p. 70°C (hexane); Lit.[13] m.p. 70°C; (Found C, 71.25; H, 9.6; Calc. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59 %); i.r. (KBr)(ν cm^{-1}) 3,080, 1,730, 1,690, 1,615; u.v.(MeOH) λ (nm) (ε) : 269 (5,200); n.m.r. ^1H (δ) 0.9 (s, 9H, *t*Bu), 1.18 (s, 9H, *t*Bu), 2.05 (s, 3H, CH_3-CO-), 2.97 (s, 2H, -CH_2-CO-), 7.85 (s, 1H, vinylic); ^{13}C (δ) 24.40, 28.19, 29.65, 31.36, 37.53, 45.15, 91.41, 129.36, 170.57, 203.91 and 205.19; m.s. 252 (M^+), 196, 153, 111, 57, 43.

Dehydrodimer diketone **9** : colorless crystals, m.p. 145°C; (Found C, 79.19; H, 10.21; Calc. for $C_{30}H_{46}O_3$: C, 79.20; H, 10.20 %); i.r. (KBr)(ν cm^{-1}) 1,660, 1,640, 1,630, 1,585; u.v. (MeOH) λ (nm)(ε) : 245 (7,730), 295 (400); n.m.r. ^1H (δ) 1.06 (s, 9H, *t*Bu), 1.23 (s, 9H , *t*Bu), 1.27 (s, 18H, 2 *t*Bu), 1.32 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 5.4 (s, 1H), 6.55 (d, 1H, J = 3.3 Hz), 6.8 (d, 1H, J = 3.3 Hz), 6.83 (s,1H). Lit.[14].

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