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Reactivity of Ubiquinones and Ubiquinols with Free Radicals

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The reactivity of quinones **1–4** and of the corresponding quinols **5–8** towards carbon- and oxygen-centred radicals were studied. All quinones bearing at least one nuclear position free, readily react with alkyl and phenyl radicals to afford the alkylated quinones **12–24**; however, quinones **1** and **3** reacted with 2-cyano-2-propyl radical to yield products (the mono- and di-ethers **9–11**) derived from the attack on the carbonylic oxygen. The reactions carried out on quinones with the benzoyloxy radical led to no reaction products and in the case of Q_{10}, the isoprenic chain also remained unchanged. Quinols **5–8** reacted only with oxygen-centred radicals (benzoyloxy and 2-cyano-2-propylperoxy radicals) to give the corresponding quinones. The isoprenic chain of Q_{10} did not undergo attack even with peroxy radicals. Carbon-centred radicals resulted unable to abstract hydrogen from the studied quinols.

Keywords: Quinones, quinols, free radicals, antioxidants

INTRODUCTION

Free radicals are known to play an important role in many areas of biology and are therefore being actively investigated in connection with various human health diseases.[1] They are reactive species that can exert a physiological role in an organism, e.g. the radicals produced during phagocytosis,[2] but can also be harmful, e.g. in producing DNA damage[3] or lipid peroxidation.[4]

A hierarchy of free radical reactions exists, which can be deployed by organisms that generate these radicals during normal metabolic processes. Organisms are protected against radical-induced damage by various antioxidant defence strategies which are committed to counteract the oxidative attack in its early moments, i.e. formation of the priming radicals, as well as during the initiation and chain propagation processes. Furthermore, part of the antioxidant defence is the capability of removing damaged structures and repairing them. Finally, adaptation can also be included into the antioxidant mechanism.[5] Many of the preventive

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antioxidant mechanisms rely on some enzymatic reactions; among the chain-breaking low molecular weight antioxidants exerting their action in a lipophylic environment, ubiquinones and Vitamin E play a well recognised role.[6]

Coenzyme Q, or ubiquinone, is an integral redox and proton translocating component of the mitochondrial electron transport chain.[7,8] It is also widely distributed in other membranes and even in plasma lipoproteins, where its antioxidant role is well recognised.[9] Coenzyme Q exists in three oxidation states, i.e. the fully reduced form (QH_2, ubiquinol), the fully oxidized one (Q, ubiquinone) and the intermediate state ($Q^{\bullet -}$, ubisemiquinone radical). The antioxidant action of coenzyme Q is usually ascribed to the fully reduced form, which acts as a phenolic antioxidant, leading to termination of radical chain reactions. This fact is of major significance in as much as coenzyme Q is the only lipophylic antioxidant which humans can synthesise and for which cells possess enzymatic mechanisms which regenerate the ubiquinolic form from ubiquinone.[10] Another well recognised antioxidant property of coenzyme Q relies on its capability of regenerating the active form of Vitamin E from the tocopheryl radical;[6] coenzyme Q and Vitamin E are therefore integrated into a regenerative cycle.

In order to better understand this antioxidant behaviour, kinetic studies on the reaction between active free radicals, such as peroxyl, aryloxyl, tocopheroxyl and singlet oxygen, and biological hydroquinones have been performed and structure–activity-relationships for the above reactions have been clarified.[11–14]

In the light of these considerations, the reactions between 1,4-benzoquinone (BQ), duroquinone (DQ), coenzymes Q_0 and Q_{10} (all these substrates either in the oxidized or in the reduced form) and various C- and O-centred radicals were studied from a chemical point of view.

MATERIALS AND METHODS

Melting points were uncorrected and were measured with an electrothermal apparatus. IR solid state spectra were measured on a Perkin Elmer Spectrum MGX1 spectrophotometer equipped with a Spectra Tech. "Collector" for DRIFT measurements. ^1H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ solution on a Varian Gemini 200 spectrometer (TMS was the reference peak). Mass spectra were performed on a Carlo Erba QMD 1000 mass spectrometer, equipped with a Fisons GC 8060 gaschromatograph.

1,4-Benzoquinone **1**, 2,3,5,6-tetramethyl-1, 4-benzoquinone (duroquinone) **2**, 2-methyl-5, 6-dimethoxy-1,4-benzoquinone (Q_0) **3**, hydroquinone **5**, α,α'-azo*iso*butyronitrile (AIBN), dibenzoylperoxide (DBP), alkyl iodides (RX: a, R = Me; b, R = Et; c, R = Pr^i; d, R = Bu^t; e, R = Allyl), *p*-methoxybenzendiazonium tetrafluoroborate were purchased from Aldrich. Coenzyme Q_{10} was purchased from Kaneka. Hydroquinones **6**,[15] **7**[15] and **8**[16] were prepared according to literature reports and were stored under Argon at low temperature. All the other reagents and solvents were Carlo Erba or Aldrich RP-ACS grade and were purified according to the literature.[17]

Reaction of Quinones 1–4 with α,α'Azo*iso*butyronitrile (AIBN)

General procedure A solution of α,α'-azo*iso*butyronitrile (6 mmol) in toluene (25 ml) was added dropwise under a stream of Argon to a solution of quinone (2 mmol). The reaction mixture was refluxed for 9 h (only 30 min for quinone **1**). The solvent was then evaporated to dryness and the residue chromatographed on a SiO_2 column using cyclohexane as an eluant, to which ethyl acetate was progressively added until a 8/2 ratio was obtained. All the isolated compounds were identified by their spectroscopic data, which are reported below also for compounds **9** and

10 even already known.[18,19] Conversion factors are set out in Table I together with the yields of the isolated products.

O-(2-Cyano-2-propyl)-1,4-hydroquinone (**9**). Oil; IR (DRIFT) ν_{OH} 3433 cm^{-1}, ν_{CN} 2239 cm^{-1}; ^{1}H-NMR (200 MHz, $CDC1_3$) δ 1.67 (s, 6H, 2-CH_3), 5.66 (s-br, 1H, -OH), 6.77 (dd, 2H, arom, J = 8.5, J = 2.4 Hz), 7.04 (dd, 2H, arom, J = 8.5, J = 2.4 Hz); MS (EI^+) *m/z* 177 (M+, 78), 149 (63), 109 (100), 81 (75).

O,O-Di-(2-cyano-2-propyl)-1,4-hydroquinone (**10**). M.p.: 123–125 °C; IR (DRIFT) ν_{CN} 2239 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.71 (s, 12H, 4-CH_3), 7.15 (s, 4H, arom); MS (EI^+) *m/z* 244 (M+, 15), 218 (25), 177 (100), 151 (26), 121 (87), 109 (43).

2,3-Dimethoxy-5-methyl-O,O-di-(2-cyano-2-propyl)-1,4-hydroquinone (**11**). M.p.: uncrystallizable material; IR (DRIFT) ν_{CN} 2239 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.71 (s, 12H, 4-CH_3), 2.24 (d, 3H, -CH_3, J = 0.7 Hz), 3.85 (s, 3H, -OCH_3), 3.87 (s, 3H, -OCH_3), 6.91 (q, 1H, arom, J = 0.7 Hz); MS (EI^+) *m/z* 318 (M+, 17), 292 (100), 250 (37), 224 (24), 182 (68).

Reaction of Quinones 1–4 with Dibenzoylperoxide (DBP)

General procedure A solution of quinone (2 mmol) and dibenzoylperoxide (DBP) (4 mmol) in toluene (25 ml) was heated to 90 °C under a stream of Argon and under stirring for 10 h (only 4 h for quinone **1**). The reaction mixture was then evaporated to dryness and the residue chromatographed on a SiO_2 column using cyclohexane as an eluant, to which ethyl acetate was progressively added until a 8/2 ratio was obtained. Compound **12** is commercially available and was identified by comparison with an authentic sample. All the other isolated compounds were identified by their spectroscopic data, which are reported below also for compound **13** even already known.[20] Conversion factors are set out in Table I together with the yields of the isolated products.

2,3-Diphenyl-1,4-benzoquinone (**13**). M.p.: 121–122 °C; IR (DRIFT) $\nu_{C=O}$ 1657 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.96 (s, 2H, arom), 7.02 (m, 4H, arom), 7.24 (m, 6H, arom); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 128.2, 128.9, 131.0, 132.9, 136.9, 143.9, 187.6; MS (EI^+) *m/z* 260 (M+, 100), 231 (25), 215 (10), 202 (12), 178 (32), 152 (10).

2,3-Dimethoxy-5-methyl-6-phenyl-1,4-benzoquinone (**14**). M.p.: uncrystallizable material; IR (DRIFT) $\nu_{C=O}$ 1657 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.95 (s, 3H, -CH_3), 4.02 (s, 3H, -OCH_3), 4.07 (s, 3H, -OCH_3), 7.15 (m, 2H, arom), 7.42 (m, 3H, arom); MS (EI^+) *m/z* 258 (M+, 48), 213 (54), 115 (100), 105 (78), 77 (58).

2,3-Dimethoxy-5-methyl-6-benzyl-1,4-benzoquinone (**15**). M.p.: uncrystallizable material; IR (DRIFT) $\nu_{C=O}$ 1658 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.09 (s, 3H, -CH_3), 3.85 (s, 2H, -CH_2-), 3.99 (s, 3H, -OCH_3), 4.00 (s, 3H, -OCH_3), 7.21 (m, 5H, arom); MS (EI^+) *m/z* 272 (M+, 53), 257 (100), 242 (38), 197 (54), 128 (63), 77 (71).

Reaction of Quinones 1–4 with Alkyl iodides RX (R: a = Me; b = Et; c = Pr^i; d = Bu^t; e = Allyl)

General procedure A solution of *p*-methoxybenzendiazonium tetrafluoroborate (0.5 mmol) in DMSO (10 ml) was added dropwise, at 40 °C, under a stream of Argon during 15 min to a stirred solution of quinone (2.5 mmol), alkyl iodide (5 mmol) and $FeSO_4 \cdot 7H_2O$ (0.5 mmol) in DMSO (15 ml). Only when methyl iodide was used, the temperature was kept at 25 °C. The reaction mixture was left to react for other 15 min, then diluted with water and extracted with $CHCl_3$. The $CHCl_3$ layer was dried with Na_2SO_4 and evaporated to dryness; the residue was chromatographed on a SiO_2 column using cyclohexane as an eluant, to which ethyl acetate was progressively added until a 8/2 ratio was obtained. Compounds **2**, **16a** and **18** are commercially available and were identified by comparison with authentic samples, while all the other isolated compounds were identified by their spectroscopic data, which are reported below

also for compounds **16b**, **16c**, **16e**, **17**, **19**, **20**, **23a** and **23e** even already known (see Experimental). Conversion factors are set out in Table I together with the yields of the isolated products.

2-Ethyl-1,4-benzoquinone (**16b**).[21] M.p.: 34–36 °C; IR (DRIFT) $\nu_{C=O}$ 1653 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.14 (t, 3H, -CH_3, J = 7.4 Hz), 2.47 (qd, 2H, -CH_2-, J = 7.4, J = 1.7 Hz), 6.57 (m, 1H, arom), 6.74 (m, 2H, arom); MS (EI^+) *m/z* 136 (M+, 65), 107 (100), 79 (38).

2-Isopropyl-1,4-benzoquinone (**16c**).[22] M.p.: 33–35 °C; IR (DRIFT) $\nu_{C=O}$ 1655 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.13 (d, 6H, 2-CH_3, J = 6.9 Hz), 3.03 (heptd, 1H, -CH-, J = 6.9, J = 1.0 Hz), 6.54 (m, 1H, arom), 6.72 (m, 2H, arom); MS (EI^+) *m/z* 150 (M+, 45), 135 (22), 122 (87), 107 (78), 79 (100).

2-Allyl-1,4-benzoquinone (**16e**).[23] Oil; IR (DRIFT) $\nu_{C=O}$ 1654 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.19 (d-br, 2H, -CH_2-, J = 6.8 Hz), 5.19 (m, 2H, =CH_2), 5.81 (ddt, 1H, -CH=, J = 17.2, J = 10.4, J = 6.8 Hz), 6.59 (m, 1H, arom), 6.75 (m, 2H, arom); MS (EI^+) *m/z* 148 (M+, 100), 133 (31), 121 (48), 107 (21), 77 (48).

2,3-Dimethyl-1,4-benzoquinone (**17**).[24] M.p.: 55–57 °C; IR (DRIFT) $\nu_{C=O}$ 1655 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.97 (s, 6H, 2-CH_3), 6.66 (s, 2H, arom); MS (EI^+) *m/z* 136 (M+, 65), 107 (15), 79 (54), 68 (100).

2,3,5-Trimethyl-1,4-benzoquinone (**19**).[24] M.p.: 32–33 °C; IR (DRIFT) $\nu_{C=O}$ 1654 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.89 (s, 3H, -CH_3), 1.90 (s, 3H, -CH_3), 1.93 (d, 3H, -CH_3, J = 1.6 Hz), 6.45 (q-br, 1H, arom, J = 1.6 Hz); MS (EI^+) *m/z* 150 (M+, 100), 122 (52), 107 (83), 79 (76), 68 (63).

2-(*p*-Methoxyphenyl)-1,4-benzoquinone (**20**).[25] M.p.: 116–117 °C; IR (DRIFT) $\nu_{C=O}$ 1647 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.86 (s, 3H, -OCH_3), 6.83 (m, 3H, arom), 6.98 (dd, 2H, arom, J = 6.8, J = 2.2 Hz), 7.49 (dd, 2H, arom, J = 6.8, J = 2.2 Hz); MS (EI^+) *m/z* 214 (M+, 100), 186 (45), 132 (85), 89 (74).

2,3,6-Trimethyl-5-(*p*-methoxyphenyl)-1,4-benzoquinone (**21**). M.p.: uncrystallizable material; IR (DRIFT) $\nu_{C=O}$ 1650 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.97 (s, 3H, -CH_3), 1.99 (s, 3H, -CH_3), 2.02 (s, 3H, -CH_3), 3.85 (s, 3H, -OCH_3), 7.09 (d, 2H, arom, J = 8.8 Hz), 7.57 (d, 2H, arom, J = 8.8 Hz); MS (EI^+) *m/z* 256 (M+, 100), 241 (82), 225 (35), 213 (51), 103 (41), 77 (50).

2-*Iso*propyl-3-(*p*-methoxyphenyl)-1,4-benzoquinone (**22**). M.p.: uncrystallizable material; IR (DRIFT) $\nu_{C=O}$ 1655 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.22 (d, 6H, 2-CH_3, J = 7.0 Hz), 2.83 (hept, 1H, -CH-, J = 7.0 Hz), 3.85 (s, 3H, -OCH_3), 6.75 (m, 2H, arom), 6.97 (d, 2H, arom, J = 9.1 Hz), 7.01 (d, 2H, arom, J = 9.1 Hz); MS (EI^+) *m/z* 256 (M+, 78), 241 (100), 227 (28), 77 (24).

2,3-Dimethoxy-5,6-dimethyl-1,4-benzoquinone (**23a**).[26] M.p.: 61–62 °C; IR (DRIFT) $\nu_{C=O}$ 1647 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.00 (s, 6H, 2-CH_3), 3.99 (s, 6H, 2-OCH_3); MS (EI^+) *m/z* 196 (M+, 64), 181 (52), 151 (81), 97 (100), 54 (65).

2,3-Dimethoxy-5-ethyl-6-methyl-1,4-benzoquinone (**23b**). M.p.: uncrystallizable material; IR (DRIFT) $\nu_{C=O}$ 1649 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.03 (t, 3H, -CH_3, J = 7.6 Hz), 2.00 (s, 3H, -CH_3), 2.47 (q, 2H, -CH_2-, J = 7.6 Hz), 3.97 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3); MS (EI^+) *m/z* 210 (M+, 100), 195 (82), 181 (18), 165 (90), 111 (85), 79 (34), 53 (82).

2,3-Dimethoxy-5-*iso*propyl-6-methyl-1,4-benzoquinone (**23c**). M.p.: uncrystallizable material; IR (DRIFT) $\nu_{C=O}$ 1649 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.23 (d, 6H, 2-CH_3, J = 7.0 Hz), 2.01 (s, 3H, -CH_3), 3.07 (hept, 1H, -CH-, J = 7.0 Hz), 3.93 (s, 3H, -OCH_3), 3.96 (s, 3H, -OCH_3); MS (EI^+) *m/z* 224 (M+, 100), 209 (35), 196 (32), 181 (87), 177 (71), 79 (28).

2,3-Dimethoxy-5-allyl-6-methyl-1,4-benzoquinone (**23e**).[26] Oil; IR (DRIFT) $\nu_{C=O}$ 1657 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.02 (s, 3H, -CH_3), 3.24 (d-br, 2H, -CH_2-, J = 6.2 Hz), 3.99 (s, 3H, -OCH_3), 4.00 (s, 3H, -OCH_3), 5.05 (m, 2H, =CH_2), 5.75 (ddt, 1H, -CH=, J = 16.0, J = 9.8, J = 6.2 Hz); MS (EI^+) *m/z* 222 (M+, 100), 207 (91), 192 (24), 189 (24), 179 (51), 108 (47), 79 (64).

2,3-Dimethoxy-5-(*p*-methoxyphenyl)-6-methyl-1,4-benzoquinone (**24**). M.p.: uncrystallizable material; IR (DRIFT) $\nu_{C=O}$ 1655 cm^{-1}; ^{1}H-NMR

(200 MHz, $CDCl_3$) δ 1.99 (s, 3H, $-CH_3$), 3.85 (s, 3H, $-OCH_3$), 4.01 (s, 3H, $-OCH_3$), 4.05 (s, 3H, $-OCH_3$), 6.96 (d-br, 2H, arom, J = 6.7 Hz), 7.10 (d-br, 2H, arom, J = 6.7 Hz); MS (EI^+) *m/z* 288 (M+, 54), 273 (25), 257 (64), 243 (81), 181 (100), 77 (55).

Reaction of Quinols 5–8 with α,α′-azo*iso*butyronitrile (AIBN)

General procedure A solution of α,α′-azo*iso*butyronitrile (6 mmol) in toluene (25 ml) was added dropwise under a stream of Argon to a solution of hydroquinone (2 mmol). The reaction mixture was refluxed for 10 h. The solvent was then evaporated to dryness and the residue chromatographed on a SiO_2 column using cyclohexane as an eluant, to which ethyl acetate was progressively added until a 8/2 ratio was obtained. The starting hydroquinone was recovered in quantitative yield. When the same reaction was carried out in the presence of oxygen, after 1 h the corresponding quinone was quantitatively isolated.

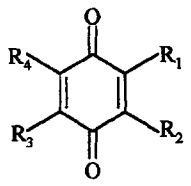
Reaction of Quinols 5–8 with Dibenzoylperoxide (DBP)

General procedure A solution of hydroquinone (2 mmol) and dibenzoylperoxide (DBP) (4 mmol) in toluene (25 ml) was heated to 70–80 °C under a stream of Argon and under stirring for 2 h. The reaction mixture was then evaporated to dryness and the residue chromatographed on a SiO_2 column using cyclohexane as an eluant, to which ethyl acetate was progressively added until a 8/2 ratio was obtained. The corresponding quinone was isolated in quantitative yield.

RESULTS

The studied compounds are quinones and ubiquinones **1–4** and the corresponding quinols and ubiquinols **5–8**. Quinones and ubiquinones **1–4** were reacted with 2-cyano-2-propyl radicals generated by thermal decomposition of α,α′-azo*iso*butyronitrile (AIBN): only compounds **1** and **3** afforded to products **9**, **10** and **11**, whereas compounds **2** and **4** resulted unreactive. Compounds **9**, **10**, already known,[18,19] and **11** were identified by their spectroscopic data, here reported for the first time. For all compounds, the IR spectra showed the absence of $\nu_{C=O}$ absorptions, whereas for compound **9** only, the ν_{OH} absorption at 3432 cm^{-1} was observed. These findings together with those obtained by ^1H NMR and mass spectra, clearly demonstrated that the radical addition occurred at the oxygen atoms.

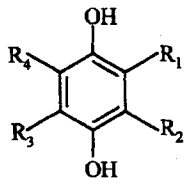
The reactions of **1–4** with dibenzoylperoxide (DBP) carried out in toluene at 90 °C afforded to compounds **12–15**. In this case too, compounds **2** and **4** resulted unreactive. The thermal decomposition of dibenzoylperoxide gives rise to the benzoyloxyl radical, which, at reaction temperature decarboxylates to the phenyl radical or abstracts a benzylic hydrogen from toluene generating a benzyl radical.[27] This behaviour justifies the formation of the isolated



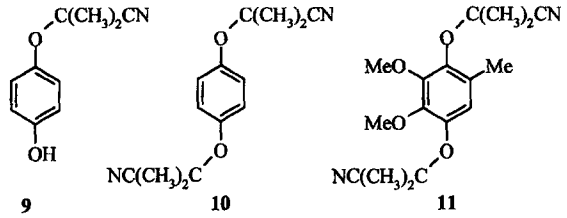
1-4

Compound	R_1	R_2	R_3	R_4	Compound
Q, 1	H	H	H	H	QH_2, 5
DQ, 2	CH_3	CH_3	CH_3	CH_3	DQH_2, 6
Q_0, 3	CH_3	H	OCH_3	OCH_3	Q_0H_2, 7
Q_{10}, 4	CH_3	*	OCH_3	OCH_3	$Q_{10}H_2$, 8

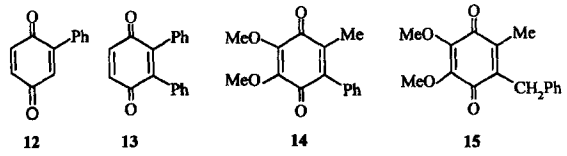
* $(CH_2CH{=}C(CH_3)CH_2)_{10}H$



5-8



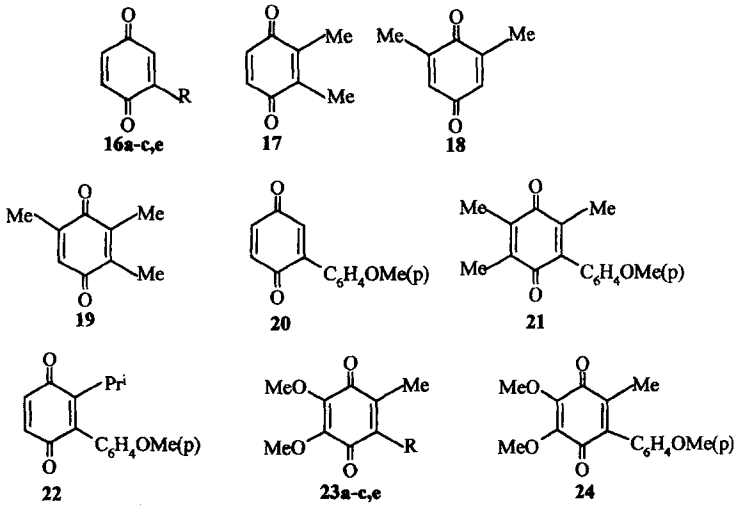
9 **10** **11**



12 **13** **14** **15**

products **12–14** and **15**; however we are unable to understand why no benzyl substituted product was isolated in the case of compound **1**. Compound **12**, commercially available, was identified by comparison with an authentic sample, while compounds **13–15** by their spectroscopic data. The quinonoid structure was confirmed by the IR spectra: in fact for all of these compounds typical bands for the $\nu_{C=O}$ absorption were present at around 1650–1660 cm^{-1}. The assignment of the 2,3-diphenyl structure for quinone **13** was attained by comparing the ^{1}H and ^{13}C NMR spectra with those reported in the literature for this compound[20] and for 2,5-[28] and 2,6-diphenyl-1,4-benzoquinone.[29,30]

Quinones and ubiquinones **1–4** were also reacted with a series of alkyl radicals namely, methyl, ethyl, *iso*-propyl, *tert*-butyl and allyl radicals, formed by iodine abstraction from the appropriate alkyl iodides by *p*-methoxyphenyl radicals generated in turn from the *p*-methoxybenzendiazonium salt reduced by Fe(II).[31] In all cases the generated radicals, *p*-methoxyphenyl included, were trapped by compounds **1** and **3** at their nuclear positions affording to compounds **2**, **16–24**. Also in this case no reaction was observed for the tetrasubstituted quinones **2** and **4**. All compounds were identified by their spectroscopic data: in particular compounds **2**, **16a** and **18** are commercially available, while compounds **16b**, **16c**, **16e**, **17**, **19**, **20**, **23a** and **23e** were already known (see Experimental). All the isolated compounds showed the correct molecular ion peaks and IR absorptions in agree-



16a-c,e **17** **18**

19 **20** **21**

22 **23a-c,e** **24**

a: R = Me; b: R = Et; c: R = Pr^{i}; d: R = Bu^{t}; e: R = Allyl

TABLE I Conversion factors, time of reaction and yields of products isolated in the reactions of **1,3** with AIBN, DBP and alkyl radicals

Reagents	Conv. Factor (%)	Time in h	Isolated products (% yields)
1 + AIBN[a]	47	30′	**9** (61); **10** (39)
3 + AIBN[a]	32	9	**11** (100)
1 + DBP[b]	41	4	**12** (57); **13** (43)
3 + DBP[b]	56	10	**14** (51); **15** (49)
1 + $Me^{\bullet}$[c]	75	30′	**2** (16); **16a** (11); **17** (13); **18** (7); **19** (20); **20** (24); **21** (9)
1 + $Et^{\bullet}$[c]	80	30′	**16b** (60); **20** (40)
1 + $Pr^{i\bullet}$[c]	82	30′	**16c** (48); **20** (42); **22** (10)
1 + $Bu^{t\bullet}$[c]	54	30′	**20** (100)
1 + Allyl$^{\bullet}$[c]	50	30′	**16e** (61); **20** (39)
3 + $Me^{\bullet}$[c]	20	30′	**23a** (67); **24** (33)
3 + $Et^{\bullet}$[c]	22	30′	**23b** (65); **24** (35)
3 + $Pr^{i\bullet}$[c]	25	30′	**23c** (63); **24** (37)
3 + $Bu^{t\bullet}$[c]	10	30′	**24** (100)
3 + Allyl$^{\bullet}$[c]	15	30′	**23e** (70); **24** (30)

[a] In toluene under reflux; [b] In toluene at 90 °C; [c] Alkyl radicals were generated according to ref. 31.

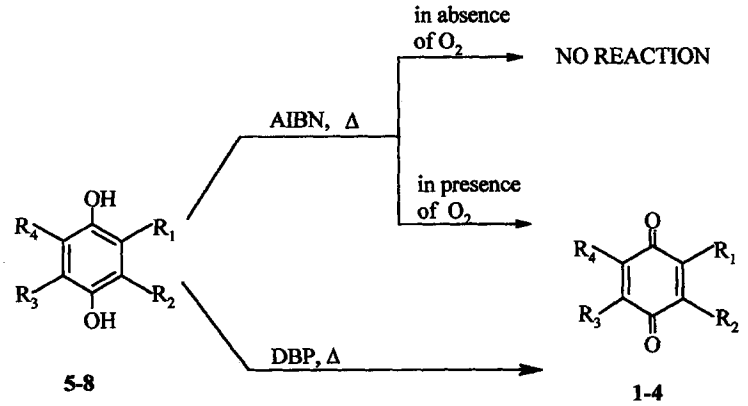
ment with the quinonoid structure. On the other hand ^{1}H NMR spectra confirm the monosubstituted structures for **16** and **20**, the disubstituted for **17**, **18**, **22**, the trisubstituted for **19** and the tetrasubstituted one for derivatives **21**, **23** and **24**.

Table I collects the conversion factors and the yields of the isolated products for each reaction.

Also the quinols and ubiquinols **5–8** were reacted with AIBN (in the presence and absence of oxygen) and DBP: they afforded to the corresponding quinones and ubiquinones in quantitative yields only with AIBN in toluene at 70–80 °C in the presence of oxygen and with benzoyloxyl radical, generated by decomposition of dibenzoylperoxide in toluene at 90 °C, while with AIBN in the absence of oxygen, only the starting materials were recovered (Scheme 1).

DISCUSSION

As stated in the introduction, ubiquinones and ubiquinols exert a very complex activity in biological systems. Besides its important role in the mitochondrial respiratory chain,[10,32] coenzyme



SCHEME 1

Q_{10} shows, especially in its reduced form, an antioxidant activity[33–35] and on the basis of a recent study, it could also mimic SOD.[36] At this regard, considering that the most important radicals involved in oxidative stress are carbon- and oxygen- (mainly peroxy) centred radicals, we reacted quinones **1–4** and quinols **5–8** with alkyl, aryl, alkoxyl and aroyloxyl radicals. The results reported in Table I reveal some important features.

When carbon-centred radicals, generated in different ways, were used, only quinones and ubiquinones bearing at least one free nuclear position, such as quinones **1** (BQ) and **3** (Q_0) reacted by behaving as a spin trap towards these radicals; on the other hand quinones fully substituted on the ring, such as compounds **2** (DQ) and **4** (Q_{10}), resulted totally unreactive. This behaviour is the same either with alkyl and aryl radicals, which always attack nuclear positions, or with 2-cyano-2-propyl radical, generated by thermal decomposition of AIBN, which prefers the oxygen of the carbonyl group. In order to explain these findings, some steric hindrance shown by fully substituted quinones may be invoked,[19] but also this hypothesis is unlikely on the basis of the formation of compound **11** from Q_0, which in part shows steric hindrance quite similar to that shown by duroquinone and Q_{10}. In particular it has been hypothesised that in a first moment the attack occurs on the ring and then subsequently there is (or not) a transposition on the oxygen: in this way, only substrates with a free nuclear position can react.[37] Another important question is why some free radicals attack the C=C bond and others the oxygen atoms of the C=O bond.[38] The behaviour of alkyl radicals could be likely explained on the basis of their nucleophilic character (polar effects)[39,40] and by the fact that a carbon-carbon bond is formed (enthalpic factors).[31] As a matter of fact, the behaviour of phenyl and 2-cyano-2-propyl radicals should be the same: in fact, since these two radicals have very close ionization potential values (8.20[41] and 8.32[42] eV, respectively), they show a similar nucleophilic–electrophilic character. In practice, the phenyl radical directly attacks the nuclear positions, affording to compounds **12–14**, whereas the 2-cyano-2-propyl radical prefers the oxygen atoms, giving the mono and diether derivatives **9–11**. Thus, in these cases, enthalpic effects and some not well defined steric hindrance could play a more important role. The lack of trapping of Bu^t radical by all quinones could be likely due to steric hindrance factors, together with the fact that this radical rapidly decomposes to 2-methylpropene.

Oxygen-centred radicals, generated by thermal decomposition of DBP in toluene, resulted unreactive towards all the studied quinones: in fact in these conditions the benzoyloxyl radical, rather than attack the substrate, quickly decarboxylates to give the phenyl radical (see the formation of compounds **12–14**) or abstracts an hydrogen from toluene to give the benzyl radical which is readily trapped to form compound **15**. These findings can be justified considering that an hypothetical attack of the benzoyloxyl radical on nuclear carbons or on carbonyl oxygen would however be unfavourable: in the first case due to the strong electrophilic character of this radical, while in the latter for enthalpic factors.

The results obtained with quinols and ubiquinols confirm that these compounds are endowed with relevant antioxidant activity towards oxygen-centred radicals. In fact, the reaction of quinols with the 2-cyano-2-propyl radical was possible only in the presence of oxygen, since this allowed the formation of the corresponding peroxyl radicals. This result is confirmed by the reaction of quinols with dibenzoylperoxide decomposed at 70–80 °C. In these conditions the dibenzoylperoxide generates the benzoyloxyl radical which promptly oxidises quinol to the corresponding quinone.

On the basis of the obtained results, the antioxidant character of quinones and quinols is better understood. Quinones, which are able to trap C-centred radicals, work as chain-breaking

acceptors, whereas quinols, which are easily oxidized to the corresponding quinones by releasing two hydrogens to O-centred radicals, may be considered as chain-breaking donors. In conclusion, even if quinones are oxidized species, they could be regarded as antioxidants, which are notoriously compounds in their reduced form.

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