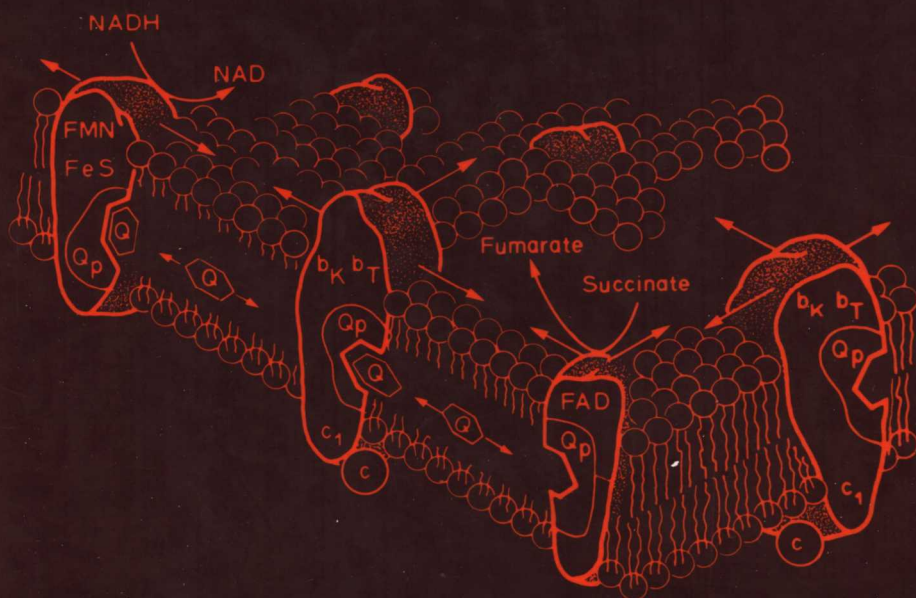


# Coenzyme Q

## BIOCHEMISTRY, BIOENERGETICS and CLINICAL APPLICATIONS of UBIQUINONE

*edited by*  
**G.LENAZ**



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## Biochemistry, Bioenergetics and Clinical Applications of Ubiquinone

*Edited by*

**G. Lenaz**

*Istituto ed Orto Botanico,  
University of Bologna,  
Bologna, Italy*

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## CHAPTER I

# Chemical Structure and Properties of Coenzyme Q and Related Compounds

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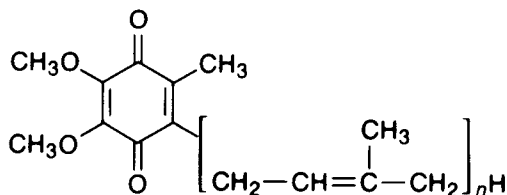
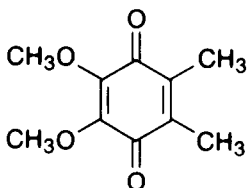
**Abbreviations:** CNQ, 3- $\omega$ -cyclohexyloctyl-2-hydroxy-1,4-naphthoquinone; CQQ, 7- $\omega$ -cyclohexyloctyl-2-hydroxy-5,8-quinolinequinone; DB, 2,3-dimethoxy-5-methyl-6-decyl-1,4-benzoquinone; DBMIB, 2,5-dibromo-3-methyl-6-isopropylbenzoquinone; DMPC, dimyristoylphosphatidylcholine; DPPC, dipalmitoylphosphatidylcholine; EPR/ESR, electron paramagnetic/spin resonance; H-10, dihydrocoenzyme Q<sub>10</sub>; HFB, 2,3-dimethoxy-5-hydroxy-6-farnesyl-1,4-benzoquinone; HiPIP, high potential iron protein; HMQQ, 7-(*n*-heptadecyl)mercapto-6-hydroxy-5,8-quinolinequinone; HPB, 2,3-dimethoxy-5-hydroxy-6-phytyl-1,4-benzoquinone; NMR, nuclear magnetic resonance; PB, 2,3-dimethoxy-5-methyl-6-pentyl-1,4-benzoquinone; PDB, 6-pentadecyl Q<sub>3</sub>; Q<sub>0</sub>C<sub>10</sub>NAPA, 2,3-dimethoxy-5-methyl-6-[10-[(4-azido-2-nitroanilino)propionyloxy]decyl]-1,4-benzoquinone; Q<sub>0</sub>C<sub>10</sub>TMOPOC, 2, 3-dimethoxy-5-methyl-6-[10-(2, 2, 5, 5-tetramethyl-3-pyrrolin-1-oxyl-3-carboxy)decyl]-1,4-benzoquinone; QP-C, Q-binding protein of *bc*<sub>1</sub> complex; QP-S, Q-binding protein of succinate dehydrogenase; UHDBT, 5-*n*-undecyl-6-hydroxy-4,7-dioxobenzothiazole.

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## INTRODUCTION

The natural coenzyme Q series<sup>1</sup> with its monounsaturated isoprenoid homologs from 1 to 12 isoprene units<sup>2-5</sup> are based on the 2,3-dimethoxy-5-methylbenzoquinone nucleus (I). The chemical structure of coenzyme Q was first reported by Folkers' group.<sup>6</sup> The whole series of coenzyme Q homologs was synthesized by Mayer and Isler<sup>7</sup> (Fig. 1).

Aurantioagliocladin (II) is the only other naturally occurring compound that belongs to the coenzyme Q series. It is an antibiotic isolated from *Gliocladium* species by Vischer.<sup>8</sup>

I. Coenzyme Q ( $n = 1-12$ )

II. Aurantiogliocladin

FIGURE 1

The most important aspects of coenzyme Q chemistry in relation to function are the redox properties of the quinone group and the physical properties of the isoprenoid sidechains. All aspects of the coenzyme Q structure have been modified by synthesis, while some modified coenzyme Q analogs such as the epoxyubiquinone series<sup>9</sup> and rhodoquinone<sup>10</sup> occur in nature.

The chemistry and synthesis of coenzyme Q homologs have been reviewed by Mayer and Isler,<sup>7</sup> biosynthesis in bacteria by Gibson and Young,<sup>11</sup> in animals by Winrow and Rudney.<sup>12</sup> The synthesis of some modified coenzyme Q analogs has been described by Wan and Folkers,<sup>13</sup> the synthesis of photoaffinity and spin labels by Yu and Yu.<sup>14</sup>

## I. THE CHEMISTRY OF COENZYME Q HOMOLOGS

### A. Coenzyme Q<sub>0</sub> to Q<sub>12</sub>

As shown in I, the coenzyme Q series encompasses the 2,3-dimethoxy-5-methyl-6-polyprenylbenzoquinone nucleus with sidechains containing 1-12 isoprenoid units. For isolation of various coenzyme Q homologs from natural sources see refs. 15-19 and also Chapter II of this volume.

The synthesis of various ubiquinones is reported by Mayer and Isler,<sup>7</sup> and biosynthesis by Threlfall<sup>15</sup> and Bentley and Campbell.<sup>16</sup>

Coenzyme Q homologs 1-12 are soluble in most organic solvents but not in water due to their long isoprenoid sidechains. Only homologs 6-12 can be obtained in crystalline form at room temperature (Table 1).

TABLE 1 The Melting Points of Coenzyme Q and Related Compounds.

Compound	Melting point (°C)	Reference
Coenzyme Q <sub>5</sub>	20	Ramasarma <sup>19</sup>
Coenzyme Q <sub>6</sub>	19–20	Ramasarma <sup>19</sup>
Coenzyme Q <sub>7</sub>	31–32	Ramasarma <sup>19</sup>
Coenzyme Q <sub>8</sub>	37–38	Ramasarma <sup>19</sup>
Coenzyme Q <sub>9</sub>	44–45	Ramasarma <sup>19</sup>
Coenzyme Q <sub>10</sub>	49	Ramasarma <sup>19</sup>
Demethylubiquinone <sub>7</sub>	38	Imada <i>et al.</i> <sup>152</sup>
Ethoxycoenzyme Q <sub>10</sub>	43–43.5	Linn <i>et al.</i> <sup>48</sup>
Diethoxycoenzyme Q <sub>10</sub>	34.5–35.5	Linn <i>et al.</i> <sup>48</sup>
Dihydrocoenzyme Q <sub>10</sub> (H–10)	28.5–29.5	Gale <i>et al.</i> <sup>79</sup>
Dihydrocoenzyme Q <sub>10</sub> (H–10)	29	Lavate <i>et al.</i> <sup>81</sup>
Ubichromenol	18	Laidman <i>et al.</i> <sup>57</sup>
Rhodoquinone <sub>10</sub> (natural)	69–70	Glover and Threlfall <sup>10</sup>
Rhodoquinone <sub>10</sub> (synthetic)	39–45	Moore and Folkers <sup>38</sup>
Rhodoquinone <sub>10</sub>	69–70	Parson and Rudney <sup>152</sup>
Rhodoquinone <sub>10</sub>	66.5–67	Powls and Hemming <sup>41</sup>
Rhodoquinone <sub>9</sub>	66.5–67	Ozawa <i>et al.</i> <sup>43</sup>

The molecular weights of various coenzyme Q homologs and related compounds are shown in Table 2, their spectral properties and extinction coefficients are described in Chapter II and IV of this volume (also refs. 17–19).

## B. Oxidation–reduction potentials

The oxidation–reduction potentials of the various coenzyme Q homologs are discussed by Ramasarma.<sup>19</sup>

Since redox potentials can be determined by polarography or by reductive titration, there is variation in the values reported from pure compounds and for quinones in various organelles, as shown in Table 3. The most frequently quoted midpoint potential value for isolated coenzyme Q is +104 mV to +112 mV,<sup>10</sup> for beef heart submitochondrial particles it is +65 mV,<sup>20</sup> for plant mitochondria +70 mV,<sup>21</sup> and for the ubiquinone/ubiquinol couple in *Rhodopseudomonas* it is +92 mV.<sup>22</sup> The semiquinone forms of many substituted benzoquinones give high redox potentials,<sup>23,24</sup> especially if they are short-lived. In the case of coenzyme Q semiquinones, the redox potentials of the radical forms may be lowered to a more normal level by stabilization through binding to a corresponding apoprotein.<sup>25</sup> Practical methods for measuring the redox states of coenzyme Q in tissues are given by Kröger.<sup>26</sup>

TABLE 2 The Molecular Weights of Coenzyme Q and Related Compounds.

Compound	Formula	Molecular weight	Reference
Coenzyme Q <sub>0</sub>	C <sub>9</sub> H <sub>10</sub> O <sub>4</sub>	182	Crane <sup>153</sup>
Coenzyme Q <sub>1</sub>	C <sub>14</sub> H <sub>13</sub> O <sub>4</sub>	245	Muraca <i>et al.</i> <sup>154</sup>
Coenzyme Q <sub>2</sub>	C <sub>19</sub> H <sub>22</sub> O <sub>4</sub>	314	Muraca <i>et al.</i> <sup>154</sup>
Coenzyme Q <sub>3</sub>	C <sub>24</sub> H <sub>31</sub> O <sub>4</sub>	383	Muraca <i>et al.</i> <sup>154</sup>
Coenzyme Q <sub>4</sub>	C <sub>29</sub> H <sub>40</sub> O <sub>4</sub>	452	Daves <i>et al.</i> <sup>3</sup>
Coenzyme Q <sub>5</sub>	C <sub>34</sub> H <sub>49</sub> O <sub>4</sub>	521	Friis <i>et al.</i> <sup>4</sup>
Coenzyme Q <sub>6</sub>	C <sub>39</sub> H <sub>58</sub> O <sub>4</sub>	590	Muraca <i>et al.</i> <sup>154</sup>
Coenzyme Q <sub>7</sub>	C <sub>44</sub> H <sub>67</sub> O <sub>4</sub>	659	Muraca <i>et al.</i> <sup>154</sup>
Coenzyme Q <sub>8</sub>	C <sub>49</sub> H <sub>76</sub> O <sub>4</sub>	728	Muraca <i>et al.</i> <sup>154</sup>
Coenzyme Q <sub>9</sub>	C <sub>54</sub> H <sub>82</sub> O <sub>4</sub>	794	Olson and Dialameh <sup>155</sup>
Coenzyme Q <sub>10</sub>	C <sub>59</sub> H <sub>90</sub> O <sub>4</sub>	862	Muraca <i>et al.</i> <sup>154</sup>
Epoxycoenzyme Q (product D)		878	Friis <i>et al.</i> <sup>9</sup>
6',7'-Epoxyubiquinone <sub>3</sub>	—	402	Friis <i>et al.</i> <sup>9</sup>
10',11'-Epoxyubiquinone <sub>3</sub>	—	402	Friis <i>et al.</i> <sup>9</sup>
α-Epoxycoenzyme Q <sub>8</sub>	C <sub>49</sub> H <sub>74</sub> O <sub>5</sub>	742	Morimoto <i>et al.</i> <sup>175</sup>
α-Epoxycoenzyme Q <sub>9</sub>	C <sub>54</sub> H <sub>82</sub> O <sub>5</sub>	810	Morimoto <i>et al.</i> <sup>175</sup>
β-Epoxycoenzyme Q <sub>8</sub>	C <sub>49</sub> H <sub>74</sub> O <sub>5</sub>	742	Morimoto <i>et al.</i> <sup>175</sup>
β-Epoxycoenzyme Q <sub>9</sub>	C <sub>54</sub> H <sub>82</sub> O <sub>5</sub>	810	Morimoto <i>et al.</i> <sup>175</sup>
α-Epoxycoenzyme Q <sub>10</sub>	C <sub>59</sub> H <sub>90</sub> O <sub>5</sub>	878	Morimoto <i>et al.</i> <sup>175</sup>
β-Epoxycoenzyme Q <sub>10</sub>	C <sub>59</sub> H <sub>90</sub> O <sub>5</sub>	878	Morimoto <i>et al.</i> <sup>175</sup>
Epoxyubiquinone <sub>10</sub>	C <sub>59</sub> H <sub>90</sub> O <sub>5</sub>	878	Farley <i>et al.</i> <sup>76</sup>
Isoubiquinone <sub>7</sub>	C <sub>44</sub> H <sub>66</sub> O <sub>4</sub>	658	Imada and Morimoto <sup>89</sup>
α-Hydroxyisoubiquinone <sub>7</sub>	C <sub>44</sub> H <sub>66</sub> O <sub>5</sub>	674	Imada and Morimoto <sup>89</sup>
cis-Coenzyme Q <sub>7</sub>		659	Morimoto <i>et al.</i> <sup>156</sup>
cis-Monoethoxycoenzyme Q <sub>7</sub>		673	Morimoto <i>et al.</i> <sup>156</sup>
cis-Diethoxycoenzyme Q <sub>7</sub>		687	Morimoto <i>et al.</i> <sup>156</sup>
cis-Isocoenzyme Q <sub>7</sub>		659	Morimoto <i>et al.</i> <sup>156</sup>
cis-Monoethoxyisocoenzyme Q <sub>7</sub>		673	Morimoto <i>et al.</i> <sup>156</sup>
cis-Diethoxyisocoenzyme Q <sub>7</sub>		687	Morimoto <i>et al.</i> <sup>156</sup>
Demethoxycoenzyme Q <sub>8</sub>	C <sub>48</sub> H <sub>72</sub> O <sub>3</sub>	696	Morimoto <i>et al.</i> <sup>175</sup>
Demethoxycoenzyme Q <sub>9</sub>	C <sub>53</sub> H <sub>80</sub> O <sub>3</sub>	764	Morimoto <i>et al.</i> <sup>175</sup>
Ethoxycoenzyme Q <sub>10</sub>	C <sub>60</sub> H <sub>92</sub> O <sub>4</sub>	876	Linn <i>et al.</i> <sup>48</sup>
Diethoxycoenzyme Q <sub>10</sub>	C <sub>59</sub> H <sub>90</sub> O <sub>4</sub>	890	Linn <i>et al.</i> <sup>48</sup>
Ubichromenol <sub>10</sub>	C <sub>59</sub> H <sub>90</sub> O <sub>4</sub>	862	Links and Tol <sup>58</sup>
Ubichromanol <sub>10</sub> (calculated) (obtained for 1 ubichromanol + 2CH <sub>3</sub> OH)	C <sub>59</sub> H <sub>92</sub> O <sub>4</sub>	864	Links and Tol <sup>58</sup>
	C <sub>61</sub> H <sub>100</sub> O <sub>6</sub>	928	Links and Tol <sup>58</sup>
Rhodoquinone <sub>10</sub>	C <sub>58</sub> H <sub>89</sub> NO <sub>3</sub>	847	Thomson <sup>157</sup>
Rhodoquinone <sub>9</sub>	C <sub>53</sub> H <sub>81</sub> NO <sub>3</sub>	779	Thomson <sup>157</sup>

TABLE 3 The Redox Potential of Coenzyme Q Homologs and Related Compounds.

Source of Quinone	Redox couple or conditions	Redox potential	Reference
Beef heart mitochondria Synthetic ubiquinones	Ubiquinone/ubiquinol	$E_{m(7.0)} = +104 \text{ mV}$	Morton <sup>158</sup> Clark <sup>23</sup>
	Polarography	$E_{m(7.4)} = +98 \text{ mV}$	Moret <i>et al.</i> <sup>159</sup>
	Reductive titration	$E_{m(7.0)} = +112 \text{ mV}$	Schnarf <sup>160</sup>
Submitochondrial particles from beef heart mitochondria	Ubiquinone/ubiquinol	$E_{m(7.0)} = +65 \text{ mV}$	Urban and Klingenberg <sup>20</sup>
	Ubiquinol/ubiquinone	$E_m = +30 \text{ mV}$	
	Ubiquinol/semiquinone	$E_m = +300 \text{ mV}$ (estimated)	
Complex III of beef heart mitochondria	Ubisemiquinone/ubiquinone	$E_m = -300 \text{ mV}$ (estimated)	Nelson <i>et al.</i> <sup>161</sup>
	$Q/QH_2$	$E_{m(7.0)} = +84 \text{ mV}$	Nelson <i>et al.</i> <sup>161</sup>
	$Q^{\cdot}/QH_2$	$E_{m(7.0)} = +204 \text{ mV}$	De Vries <i>et al.</i> <sup>162</sup>
	$Q_{60}/Q_1^{\cdot}$	$E_{m(7.0)} = +36 \text{ mV}$	
	$Q^{\cdot}/QH_2$	$E_{m(7.0)} = +233 \text{ mV}$	
	$Q_{60}/Q_1^{\cdot}$	$E_{m(7.0)} = -65 \text{ mV}$	
Succinate-cytochrome c reductase <sup>*</sup> complex from beef heart mitochondria Synthetic ubiquinol-1	$Q/\text{semiquinone}$	$E_{m(7.4)} = +140 \text{ mV}$	Salerno and Ohnishi <sup>25</sup>
	$QH_2/Q$	$E_0 = +490 \text{ mV}$	Rich and Bendall <sup>24</sup>
	$QH^{\cdot}/QH^{\cdot}$	$E_0 = +191 \text{ mV}$	Rich <sup>163</sup>
	$Q/Q$	$E_0 = -240 \text{ mV}$	Rich <sup>163</sup>
	$Q/\text{semiquinone}$	$E_{m(8.0)} = +67 \text{ mV}$	Rutherford and Evans <sup>164</sup>
<i>Rhodopsseudomonas viridis</i> chromatophores	Semiquinone/quinol	$E_{m(8.0)} = -155 \text{ mV}$	Rutherford and Evans <sup>165</sup>
	$Q_2/Q_1^{\cdot}$	$E_{m(7.0)} = +130 \text{ mV}$	
	(possibly an iron complex)		
<i>Rhodopsseudomonas sphaeroides</i> chromatophores	$Q_2/Q_2H^{\cdot}$	$E_{m(7.0)} = +100 \text{ mV}$	Rutherford and Evans <sup>166</sup>
	$Q_2H/Q_2H^{\cdot}$	$E_{m(7.0)} = +20 \text{ mV}$	
	Ubiquinone/ubiquinol	$E_{m(7.0)} = +92 \text{ mV}$	
Mung bean mitochondria	Ubiquinone/Ubiquinol	$E_{m(7.0)} = +0.114 \text{ mV}$	Takamiya and Dutton <sup>22</sup>
		$E_{m(7.2)} = +70 \text{ mV}$	Shelhorn <i>et al.</i> <sup>167</sup> Storey <sup>21</sup>

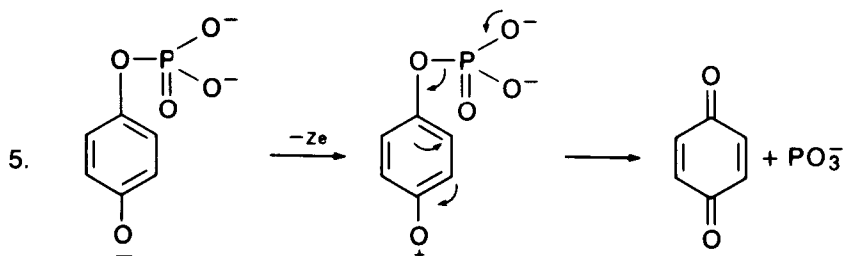
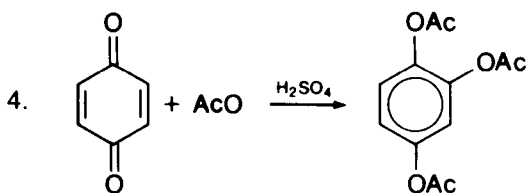
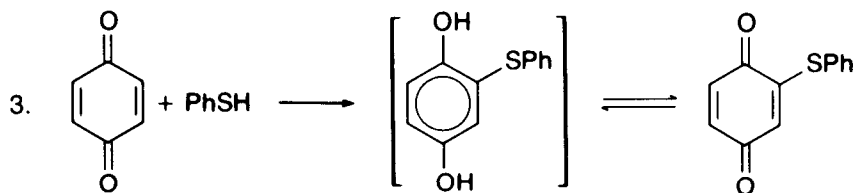
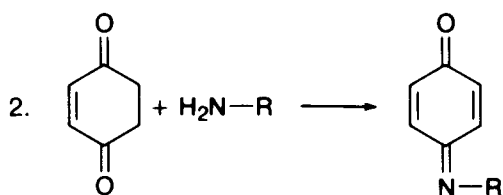
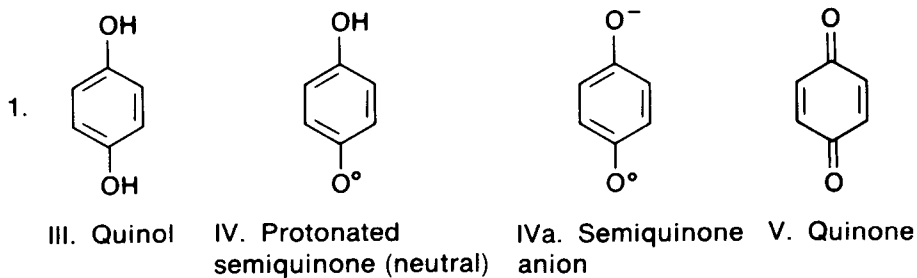
**TABLE 4**  $pK_a$  Values for Various Benzoquinones and Benzoquinols, Including Coenzyme  $Q_{10}$ .

	$pK_a$ in $H_2O$	$^{\circ}C$	Reference
Hydroquinone			
Coenzyme $Q_{10}$ , neutral	13.3	23	Morrison <i>et al.</i> <sup>168</sup>
Tetramethylbenzohydroquinone, neutral	11.2	25	
Tetramethylbenzohydroquinone, anion	12.7	25	
Benzohydroquinone, neutral	9.9	25	
Benzohydroquinone, anion	11.4	26	
Methylbenzohydroquinone, neutral	10.0	25	
Methylbenzohydroquinone, anion	11.6	26	
2,6-Dichlorobenzohydroquinone, neutral	7.3	26	
2,6-Dichlorobenzohydroquinone, anion	10.0	26	
Semiquinone			
Benzoquinone	4.00	—	Swallow <sup>169</sup>
Methylbenzoquinone	4.45	—	
2,6-Dimethylbenzoquinone	4.75	—	
2,5-Dimethylbenzoquinone	4.60	—	
2,3-Dimethylbenzoquinone	4.65	—	
Trimethylbenzoquinone	4.95	—	
Duroquinone	5.10	—	
4- <i>t</i> -Butyl-1,2-benzoquinone	5.20	—	
4-Methyl-1,2-benzoquinone	4.50	—	
3-Methoxy-1,2-benzoquinone	5.00	—	
1,2-Benzoquinone	5.00	—	

### C. Coenzyme Q semiquinones

Coenzyme  $Q_{10}$  and its homologs (V) can be partially reduced to semiquinone form.  $QH^0$  generally designates the neutral or protonated ubisemiquinone (IV),  $Q^{\bullet}$  the ubisemiquinone anion (IVa) and  $QWH_2$  the fully reduced ubiquinol (III). The  $pK_a$  values of ubisemiquinone and ubiquinol are reported in Table 4. Marcus and Hawley<sup>27</sup> carried out electrochemical reduction of ubiquinone-1 in acetonitrile in the presence of acids of varying proton donor strength. They found only the hydroquinone forms, but no corresponding chromanol forms expected from reductive cyclization. In other model systems Hales and Case<sup>28</sup> used immobilized neutral coenzyme Q semiquinone and the semiquinone anion to study their ESR signals. Land and Swallow<sup>29</sup> have studied the optical absorption spectra of anionic and neutral ubisemiquinone free radicals produced by pulse radiolysis.

Coenzyme Q semiquinone signals have also been detected by ESR in the membranes of *Escherichia coli*.<sup>39,31</sup> The UQ deficient mutant AN59 showed no  $g = 2.003 \pm 0.001$  radical signal attributed to the semiquinone radical.





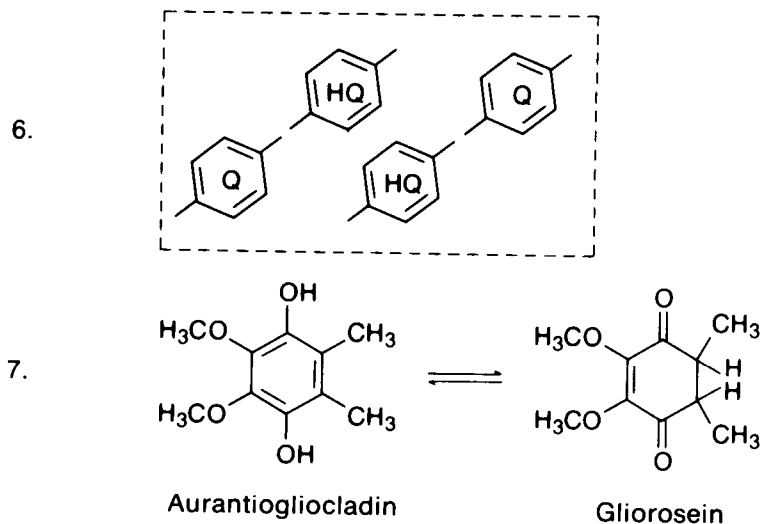


FIGURE 2

Hamilton *et al.*<sup>30</sup> point out that a chromanoxyl radical cannot be excluded as a source for this signal.

A shift from quinol to ene-diol structure has been reported during the reduction of aurantiogliocladin. Similar changes have not been reported for isoprenoid coenzyme Q homologs.<sup>15</sup>

## D. Chemical reactions of quinones (Fig. 2)

### 1. Oxidation-reduction

Oxidation-reduction reactions are the simplest and most frequently observed biological reactions of quinones, including coenzyme Q and its analogs. Isolated quinones can easily be reduced to colorless leuco compounds with alkaline sodium dithionite, alkaline borohydride, zinc, catalytic hydrogen or other reducing agents. These leuco forms of quinones can be reoxidized by exposure to air or oxygen.

### 2. Reactions with amines

Quinones, including coenzyme Q, can react with certain amines by a normal condensation reaction to yield quinone imines. This reaction has been utilized in the detection of coenzyme Q precursors.<sup>32</sup>