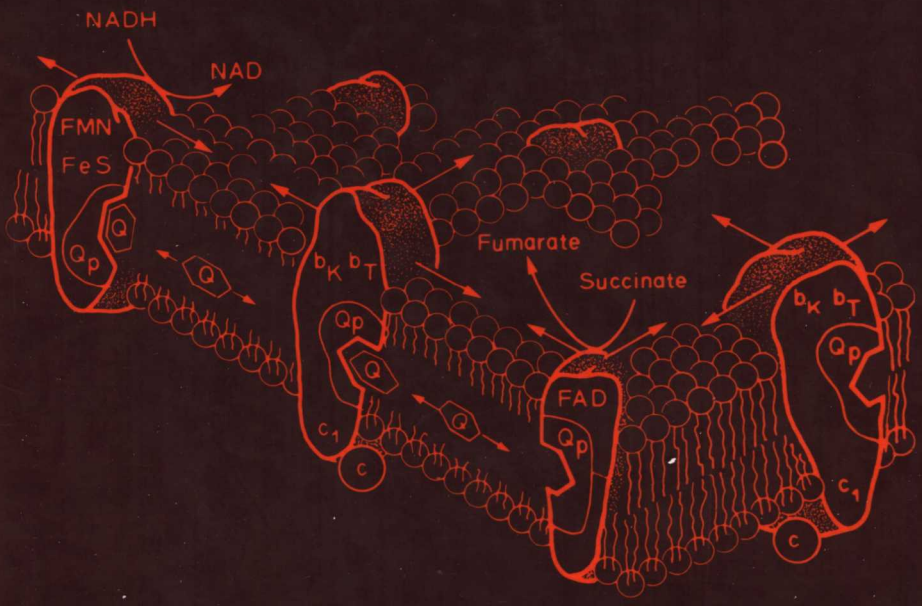
Coenzyme Q

BIOCHEMISTRY, BIOENERGETICS and CLINICAL APPLICATIONS of UBIQUINONE

edited by

G. LENAZ



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Biochemistry, Bioenergetics and Clinical Applications of Ubiquinone

Edited by
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Bologna, Italy

A Wiley Interscience Publication

JOHN WILEY & SONS
Chichester · New York · Brisbane · Toronto · Singapore

Library of Congress Cataloging in Publication Data:
Main entry under title:

Coenzyme Q

'A Wiley–Interscience publication.'
Includes index.
1. Ubiquinones. 2. Ubiquinones—Therapeutic use.
I. Lenaz, Giorgio. [DNLM: 1. Ubiquinone. QU 135 C672]
QP801.U2C464 1985 615'.35 84-15355
ISBN 0 471 10286 5

British Library Cataloguing in Publication Data:

Coenzyme Q.
1. Quinone
I. Lenaz G.
574.19'121 QP801.Q5

ISBN 0 471 10286 5

Typeset by Spire Print Services, Salisbury, Wiltshire
Printed in Great Britain by
St Edmundsbury Press, Bury St Edmunds, Suffolk

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Edited by G. Lenaz

CHAPTER I

Chemical Structure and Properties of Coenzyme Q and Related Compounds

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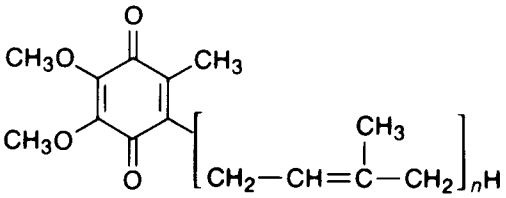
Abbreviations: CNQ, 3-ω-cyclohexyloctyl-2-hydroxy-1,4-naphthoquinone; CQQ, 7-ω-cyclohexyloctyl-2-hydroxy-5,8-quinolinequinone; DB, 2,3-dimethoxy-5-methyl-6-decyl-1,4-benzoquinone; DBMIB, 2,5-dibromo-3-methyl-6-isopropylbenzoquinone; DMPC, dimyristoylphosphatidylcholine; DPPC, dipalmitoylphosphatidylcholine; EPR/ESR, electron paramagnetic/spin resonance; H–10, dihydrocoenzyme Q_{10}; HFB, 2,3-dimethoxy-5-hydroxy-6- farnesyl-1,4-benzoquinone; HiPIP, high potential iron protein; HMHQQ, 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_3; Q_0C_{10}NAPA, 2,3-dimethoxy-5-methyl-6-[10-[-(4-azido-2-nitroanilino)propionoxy]decyl]-1,4-benzoquinone; Q_0C_{10}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_1 complex; QP-S, Q-binding protein of succinate dehydrogenase; UHDBT,5-*n*-undecyl-6-hydroxy-4,7-dioxobenzothiazole.

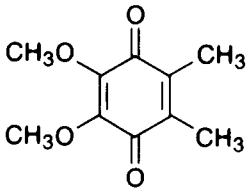
INTRODUCTION

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

Aurantiogliocladin (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.[8]



I. Coenzyme Q (n = 1–12)



II. Aurantioglíocladin

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[9] and rhodoquinone[10] occur in nature.

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

I. THE CHEMISTRY OF COENZYME Q HOMOLOGS

A. Coenzyme Q_0 to Q_{12}

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,[7] and biosynthesis by Threlfall[15] and Bentley and Campbell.[16]

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_5	20	Ramasarma[19]
Coenzyme Q_6	19–20	Ramasarma[19]
Coenzyme Q_7	31–32	Ramasarma[19]
Coenzyme Q_8	37–38	Ramasarma[19]
Coenzyme Q_9	44–45	Ramasarma[19]
Coenzyme Q_{10}	49	Ramasarma[19]
Demethylubiquinone$_7$	38	Imada *et al.*[152]
Ethoxycoenzyme Q_{10}	43–43.5	Linn *et al.*[48]
Diethoxycoenzyme Q_{10}	34.5–35.5	Linn *et al.*[48]
Dihydrocoenzyme Q_{10} (H–10)	28.5–29.5	Gale *et al.*[79]
Dihydrocoenzyme Q_{10} (H–10)	29	Lavate *et al.*[81]
Ubichromenol	18	Laidman *et al.*[57]
Rhodoquinone$_{10}$ (natural)	69–70	Glover and Threlfall[10]
Rhodoquinone$_{10}$ (synthetic)	39–45	Moore and Folkers[38]
Rhodoquinone$_{10}$	69–70	Parson and Rudney[152]
Rhodoquinone$_{10}$	66.5–67	Powls and Hemming[41]
Rhodoquinone$_9$	66.5–67	Ozawa *et al.*[43]

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.[19]

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,[10] for beef heart submitochondrial particles it is +65 mV,[20] for plant mitochondria +70 mV,[21] and for the ubiquinone/ubiquinol couple in *Rhodopseudomonas* it is +92 mV.[22] The semiquinone forms of many substituted benzoquinones give high redox potentials,[23,24] 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.[25] Practical methods for measuring the redox states of coenzyme Q in tissues are given by Kröger.[26]

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

Compound	Formula	Molecular weight	Reference
Coenzyme Q_0	$C_9H_{10}O_4$	182	Crane[153]
Coenzyme Q_1	$C_{14}H_{13}O_4$	245	Muraca *et al.*[154]
Coenzyme Q_2	$C_{19}H_{22}O_4$	314	Muraca *et al.*[154]
Coenzyme Q_3	$C_{24}H_{31}O_4$	383	Muraca *et al.*[154]
Coenzyme Q_4	$C_{29}H_{40}O_4$	452	Daves *et al.*[3]
Coenzyme Q_5	$C_{34}H_{49}O_4$	521	Friis *et al.*[4]
Coenzyme Q_6	$C_{39}H_{58}O_4$	590	Muraca *et al.*[154]
Coenzyme Q_7	$C_{44}H_{67}O_4$	659	Muraca *et al.*[154]
Coenzyme Q_8	$C_{49}H_{76}O_4$	728	Muraca *et al.*[154]
Coenzyme Q_9	$C_{54}H_{82}O_4$	794	Olson and Dialameh[155]
Coenzyme Q_{10}	$C_{59}H_{90}O_4$	862	Muraca *et al.*[154]
Epoxycoenzyme Q (product D)		878	Friis *et al.*[9]
6′,7′-Epoxyubiquinone$_3$	–	402	Friis *et al.*[9]
10′,11′-Epoxyubiquinone$_3$	–	402	Friis *et al.*[9]
α-Epoxycoenzyme Q_8	$C_{49}H_{74}O_5$	742	Morimoto *et al.*[175]
α-Epoxycoenzyme Q_9	$C_{54}H_{82}O_5$	810	Morimoto *et al.*[175]
β-Epoxycoenzyme Q_8	$C_{49}H_{74}O_5$	742	Morimoto *et al.*[175]
β-Epoxycoenzyme Q_9	$C_{54}H_{82}O_5$	810	Morimoto *et al.*[175]
α-Epoxycoenzyme Q_{10}	$C_{59}H_{90}O_5$	878	Morimoto *et al.*[175]
β-Epoxycoenzyme Q_{10}	$C_{59}H_{90}O_5$	878	Morimoto *et al.*[175]
Epoxyubiquinone$_{10}$	$C_{59}H_{90}O_5$	878	Farley *et al.*[76]
Isoubiquinone$_7$	$C_{44}H_{66}O_4$	658	Imada and Morimoto[89]
α-Hydroxyisoubiquinone$_7$	$C_{44}H_{66}O_5$	674	Imada and Morimoto[89]
cis-Coenzyme Q_7		659	Morimoto *et al.*[156]
cis-Monoethoxycoenzyme Q_7		673	Morimoto *et al.*[156]
cis-Diethoxycoenzyme Q_7		687	Morimoto *et al.*[156]
cis-Isocoenzyme Q_7		659	Morimoto *et al.*[156]
cis-Monoethoxyisocoenzyme Q_7		673	Morimoto *et al.*[156]
cis-Diethoxyisocoenzyme Q_7		687	Morimoto *et al.*[156]
Demethoxycoenzyme Q_8	$C_{48}H_{72}O_3$	696	Morimoto *et al.*[175]
Demethoxycoenzyme Q_9	$C_{53}H_{80}O_3$	764	Morimoto *et al.*[175]
Ethoxycoenzyme Q_{10}	$C_{60}H_{92}O_4$	876	Linn *et al.*[48]
Diethoxycoenzyme Q_{10}	$C_{59}H_{90}O_4$	890	Linn *et al.*[48]
Ubichromenol$_{10}$	$C_{59}H_{90}O_4$	862	Links and Tol[58]
Ubichromanol$_{10}$ (calculated)	$C_{59}H_{92}O_4$	864	Links and Tol[58]
(obtained for 1 ubichromanol + $2CH_3OH$)	$C_{61}H_{100}O_6$	928	Links and Tol[58]
Rhodoquinone$_{10}$	$C_{58}H_{89}NO_3$	847	Thomson[157]
Rhodoquinone$_9$	$C_{53}H_{81}NO_3$	779	Thomson[157]

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

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

	pK_a in H_2O	°C	Reference
Hydroquinone			
Coenzyme Q_{10}, neutral	13.3	23	Morrison *et al.*[168]
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[169]
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-*t*-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[27] 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[28] used immobilized neutral coenzyme Q semiquinone and the semiquinone anion to study their ESR signals. Land and Swallow[29] 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*.[39,31] The UQ deficient mutant AN59 showed no $g = 2.003 \pm 0.001$ radical signal attributed to the semiquinone radical.

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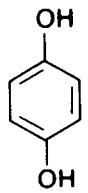
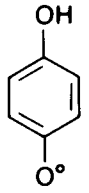
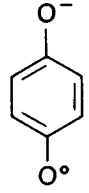


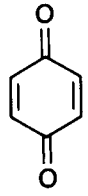
III. Quinol



IV. Protonated semiquinone (neutral)



IVa. Semiquinone anion



V. Quinone

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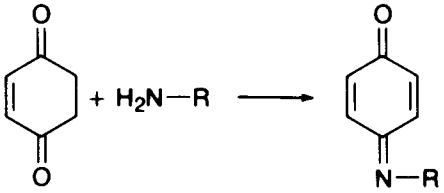

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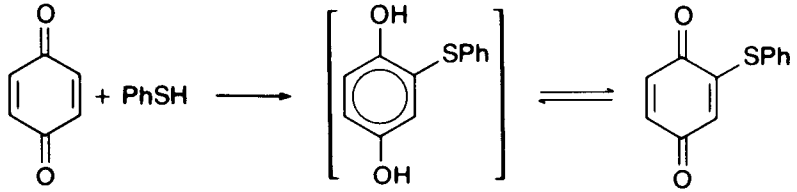

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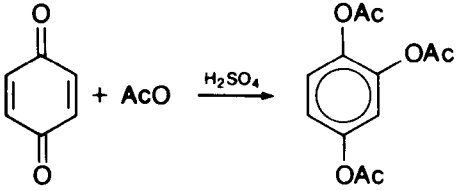

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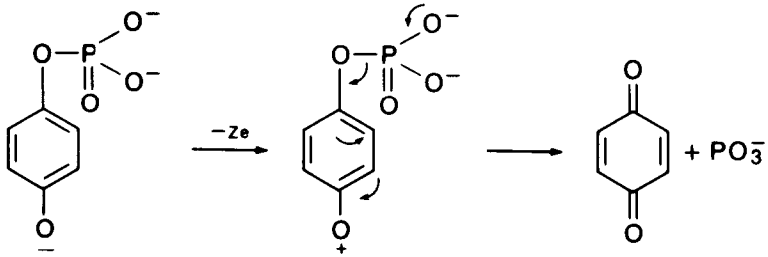

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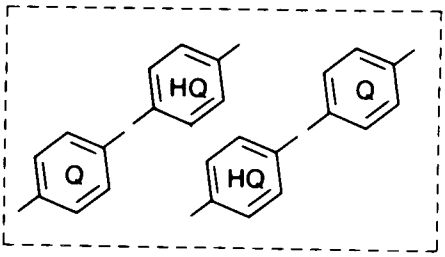

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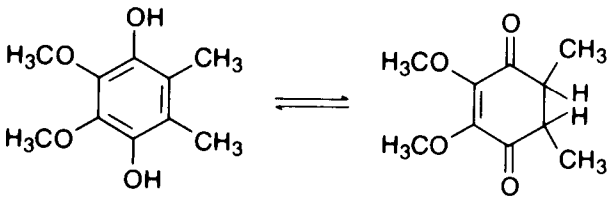

Aurantiogliocladin Gliorosein

FIGURE 2

Hamilton *et al.*[30] 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.[15]

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.[32]