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ELECTROCHEMICAL STUDIES OF THE REDOX BEHAVIOR OF UBIQUINONE-1

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SUMMARY

The electrochemical reduction of ubiquinone has been studied in acetonitrile in the presence of acids of widely varying proton donor strength. The final product of two-electron reduction is the hydroquinone. No evidence could be found to suggest that the corresponding chromanol, the product expected from reductive cyclization, is formed in the electroreduction of ubiquinone-1.

The extensive substitution of the biologically active quinones suggests that the quinones and their reduction products may function *in vivo* in an environment where the availabilities of water and protons are low. Since the redox behavior of *p*-benzoquinone in aprotic, non-aqueous solvents differs significantly from its behavior in aqueous systems[1], alternate reduction pathways may arise in the reduction of the more complicated biologically active quinones in non-aqueous solvent systems. Previous reports[2–5] have shown that α-tocopherylquinone, a quinone which has no unsaturation in its long side-chain substituent, can undergo reductive cyclization to yield α-tocopherol in the presence of certain proton donors. Since chromanol formation has been postulated also for the other biologically active quinones[6], we have studied the reduction pathways of ubiquinone-1 in presence of several proton donors of varying acid strength in acetonitrile. The experimental procedures used here have been described previously[5].

Since plausible cyclization mechanisms can be written for the several protonated forms of the radical ion and dianion, the electrochemical reduction of ubiquinone-1 was studied in the presence of several different acids. By careful selection of the proton donor strength and the proper choice of reduction potentials, the following semiquinone and hydroquinone species were prepared electrochemically *in situ*: $QH^+{}_2\cdot$, $QH\cdot$, $Q^-\cdot$, QH_2, QH^-, and Q^{2-}. Transient semiquinone species have been reported recently to be the initial products in the flash photolysis studies of vitamin K_1[7]. The final reaction product, the corresponding chromanol, was thought to arise by a reaction pathway involving the radical anion and the quinone methide.

The search for chromanol formation was made indirectly by double potential step chronoamperometry and directly by cyclic voltammetry[5]. Previous reports from this laboratory[3–5] have shown that a chromanol is oxidized to the corresponding carbonium in a two-electron process at 0.7 V *vs.* saturated calomel electrode. In the absence of nucleophiles, such as water, the carbonium ion is relatively stable and can be reduced back to the original chromanol near 0.6 V on the reverse, cathodic sweep

of a cyclic voltammetry experiment. The absence of a reversible redox process in this potential region (0.6–0.7 V) is therefore considered as negative evidence for chromanol formation.

The cyclic voltammetric (Table I) and chronoamperometric (Table II) data for the reduction of ubiquinone-1 in the absence of a proton donor show that reduction occurs in discrete, one-electron steps with each step being chemically reversible. The data also show that reductive cyclization is not occurring at a sufficient rate during the course of these experiments (appoximately 10 sec in duration) to allow the detection of the chromanol. A sequence of reactions consistent with these results is shown in Eqn. 1.

$$Q \underset{-e}{\overset{e}{\rightleftarrows}} Q^{-\cdot} \underset{-e}{\overset{e}{\rightleftarrows}} Q^{2-} \tag{1}$$

The addition of the weak acid, diethyl malonate, results in the protonation of the dianion, Q^{2-}, and a concomitant disappearance of the anodic wave for the oxidation of the dianion back to the radical anion (Table I). Since the addition of the acid alters neither the peak location nor the peak height for the first cathodic wave, and since the only anodic wave corresponds to the reoxidation of the radical anion, $Q^{-\cdot}$, these data suggest a solution redox reaction involving ubiquinone-1 and the monoprotonated dianion (Eqns. 2–4). Again no cyclic voltammetric evidence could be found to suggest formation of the chromanol.

$$Q \underset{-e}{\overset{e}{\rightleftarrows}} Q^{-\cdot} \underset{e}{\overset{e}{\rightleftarrows}} Q^{2-} \tag{2}$$

$$Q^{2-} + HA \rightleftarrows QH^{-} + A^{-} \tag{3}$$

$$QH^{-} + Q \xrightarrow{\text{fast}} 2Q^{-\cdot} + H^{+} \tag{4}$$

Stronger proton donors, such as benzenethiol, cause protonation of the radical anion. As shown by the cyclic voltammetric data (Table I), the wave for the reduction of the quinone to the radical anion is shifted anodically, which indicates a rapid protonation of the radical anion, and doubles in height, which indicates that the product

TABLE I

CYCLIC VOLTAMMETRY DATA FOR THE REDUCTION OF UBIQUINONE-1 *

Acid	[*Acid*] / [*Ubiquinone-1*]	*Cathodic*			*Anodic*	
		$E_{p,c(1)}$	$i_p/v^{1/2}C$ **	$E_{p,c(2)}$	$E_{p,a(2)}$	$E_{p,a(1)}$
None	0	−0.87	224	−1.74	−1.43	−0.81
Diethylmalonate	2	−0.87	229	−1.29	None	−0.81
Benzenethiol	10	−0.75	450	None	None	−0.08
H_2SO_4 ***	2	−0.18	330	−0.82 (small)	−0.73	0.72
$HClO_4$ ***	2	−0.10	290	−0.82 (small)	−0.73	0.82

* Volts *vs.* saturated calomel electrode.
** Units are $\mu A \cdot sec^{1/2} \cdot mM^{-1} \cdot V^{-1/2}$.
*** See text.

TABLE II

CHRONOAMPEROMETRIC AND DOUBLE POTENTIAL STEP CHRONOAMPEROMETRIC RESULTS FOR THE REDUCTION OF UBIQUINONE-I

Applied potentials (*E vs.* saturated calomel electrode)		$it^{1/2}/CA$ ($A \cdot sec^{1/2} \cdot mole^{-1} \cdot cm$)	t_r(*sec*)	$\theta = t_r/t_f$	i_r/i_f	
					*Calc.**	*Exptl.*
E_c	E_a					
		(A) $Q + e \rightleftharpoons Q^{-\cdot}$, no acid added				
−1.0	0	195	0.5	1.00	0.29	0.25
			0.05	0.10	2.20	2.23
			0.005	0.01	9.00	9.30
		(B) $Q + 2e \rightleftharpoons Q^{2-}$, no acid added				
−1.8	0	415	0.5	1.00	0.29	0.23
			0.05	0.10	2.20	2.10
			0.005	0.01	9.00	9.50
		(C) $Q + HA + 2e \rightleftharpoons QH^- + A^-$, [diethylmalonate]/[quinone] = 2				
−1.4	0	400	0.5	1.00	0.29	0.25
			0.05	0.10	2.20	1.90
			0.005	0.01	9.00	8.70
		(D) $Q + 2e + 2HA \rightleftharpoons H_2Q + 2A^{-\cdot}$, [benzenethiol]/[quinone] = 10				
−1.1	0.2	390	0.5	1.00	0.29	0.27
			0.05	0.10	2.20	2.18
			0.005	0.01	9.00	10.0

* Calculated values for diffusion-controlled, reversible processes. $i_r/i_f = [(1 + \theta^{1/2}) - \theta^{1/2}]/[\theta^{1/2}\ (1 + \theta^{1/2}]$. For a discusssion of double potential step chronoamperometry theory, see W. M. SMIT AND M. D. WIJNEN, *Rec. Trav. Chim. Pays-Bas*, 79 (1960) 5.

of the protonation reaction, $QH\cdot$, is reduced at this potential. In addition, the cathodic wave for the reduction of the radical anion disappears, as does the anodic wave for the oxidation of the radical anion back to the quinone. A sequence of reactions consistent with these processes is given by Eqns. 5–8. Double potential step chronoamperometric data (Table II) are consistent with this interpretation and indicate that the chromanol is not formed under these reaction conditions.

$$Q + e \rightleftarrows Q^{-\cdot} \tag{5}$$

$$Q^{-\cdot} + HA \rightleftarrows QH\cdot + A^- \tag{6}$$

$$QH\cdot + e \rightleftarrows QH^- \tag{7}$$

$$Q^{-\cdot} + QH\cdot \rightleftarrows Q + QH^- \tag{8}$$

When a very strong proton donor is added, such as H_2SO_4 or $HClO_4$ two partially merged cathodic processes appear in the potential range 0.2 to −0.2 V. The more negative of the two cathodic processes was shown from separate studies to arise from proton reduction. In addition to these processes, a third, cathodic wave is seen near −0.8 V. This process, which has been attributed above to the reduction of unproto-

nated quinone, decrease in magnitude with an increase in the concentration of the proton donor. Since the protonated quinone also would be expected to be reduced near 0.6 V if it were the predominate quinone species in solution[5], the combination of results indicates that the several quinone reduction processes are kinetically controlled. A scheme (Eqns. 9 and 10) consistent with these observations involves reduction of the protonated quinone which is formed by protonation of ubiquinone-1 in the vicinity of the electrode surface immediately prior to the electron transfer.

$$Q + H^+ \xrightarrow{\text{slow}} QH^+ \underset{-e}{\overset{e}{\rightleftarrows}} QH\cdot \tag{9}$$

$$QH\cdot + H^+ \rightleftarrows QH_2^{+}\cdot \underset{-e}{\overset{e}{\rightleftarrows}} \tag{10}$$

The product of the none-electron transfer, $QH\cdot$, is assumed to be rapidly protonated and immediately reduced at the applied potential to the corresponding hydroquinone. Reoxidation of the hydroquinone to the quinone is seen near 0.7 V on the reverse, anodic sweep. The absence of a cathodic peak near 0.6 V on the second cathodic sweep is evidence that the chromanol is not formed during the electroreduction of the protonated ubiquinone-1.

The results of this study indicate that chromanol formation is unlikely to occur by either anion or radical attack of quinone oxygen on the double bond of the unsaturated side chain in the reduction of biologically active quinones. While this conclusion would appear to negate the possibility of a chromanol being a form of "stabilized hydroquinone"[6], the result is consistent with the inability of numerous researchers[6,8,9] to detect significant amounts of the corresponding quinones with a hydroxyl group in the three position of the terpenoid side chain. This latter type of quinone would be expected if the chromanol were oxidized, either chemically or electrochemically, in aqueous containing media[3,5,10,11].

Thus, the electrochemical behavior of ubiquinone-1 differs little from the behavior reported previously for the quinone moiety of α-tocopherylquinone[5]. The main difference which is observed between the two quinones arises because of the presence of the 3-hydroxy group in the saturated side chain of α-tocopherylquinone. This modification permits hemiketal formation in α-tocopherylquinone with subsequent dehydration of the hemiketal and reduction of the resulting carbonium ion to give the chromanol.

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