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The Avarol-Avarone Redox Behaviour in Acetonitrile*

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The oxidation of avarol and the reduction of avarone were studied at a Pt electrode in acetonitrile-tetraethyl-ammonium perchlorate media. The oxidation of avarol in acetonitrile takes place by formation of a two electron oxidation product, presumably the »protonated avarone«. The reduction of avarone takes place in two steps by formation of the stable radical anion which is reduced to the dianion at a more negative potential.

INTRODUCTION

Terpenoids containing the 1,4-benzoquinone ring system are frequently present in plants and animals of both terrestrial and marine origin. Although a fair amount of evidence indicating the importance of some of these lipid soluble compounds in electron transfer processes in biological systems has accumulated, the mechanism of their action is not well understood. Attempts to clarify the biological function by examining redox reactions of quinones and hydroquinones by electrochemical methods in different media have shown these reactions to be extremely complex; the results of such studies, including those on biologically important quinone derivatives, have been extensively reviewed.[1-3]

As already mentioned, terpene quinones and hydroquinones have been also isolated from marine organisms, primarily algae and sponges. In our search for biologically active marine natural products, we found that the lipid extract of the relatively abundant Mediterranean sponge *Dysidea avara* shows a strong activity against gram positive bacteria. Purification of the lipid extract yielded avarol, a sesquiterpene hydroquinone with a rearranged drimane skeleton, earlier isolated by Minale *et al.*[4] Our recently published finding that both avarol (QH$_2$) and the corresponding quinone avarone (Q) not only show exceptionally strong antibacterial effects, but also cytostatic activity,[5] initiated our investigation of their redox reactions. In this work, the results of the investigation of oxidation of avarol and reduction of avarone at a Pt

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* Dedicated to Professor M. Lj. Mihailović, on the occasion of his 60th birthday.

electrode in an acetonitrile-tetraethyl ammonium perchlorate medium are presented.

Avarol (QH₂)   Avarone (Q)
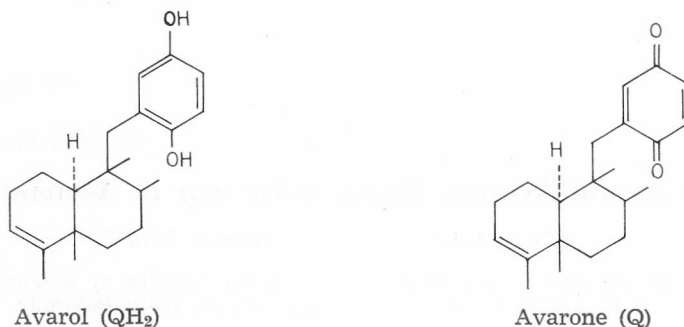
RESULTS AND DISCUSSION

Cyclic voltammograms were run at a series of potential scan rates using a platinum electrode in carefully purified acetonitrile. The cyclic voltammogram of avarol exhibits an irreversible oxidation peak at $+ 1.07$ V *vs.* SCE. When the direction of the potential scan is reversed to the cathodic counterpart, after the initial anodic peak, a reduction peak around $+ 0.20$ V *vs.* SCE is observed (Figure 1a). The shape of the avarol oxidation voltammogram is similar to that of hydroquinone.[6] The cathodic peak at $+ 0.20$ V *vs.* SCE can be attributed to the reduction of the protonated avarone following the essentially same arguments given for hydroquinone.[6,7] Namely, addition of a base, such as 2,6-lutidine, gives rise to a new oxidation peak about 0.40 V negative to the QH₂ oxidation peak (Figure 1b). As the concentration of 2,6-lutidine is increased, the height of the new cathodic peak at $- 0.30$ V *vs.* SCE increases at the expense of the peak at $+ 0.20$ V, corresponding to the reduction of the protonated species Q formed during the oxidation wave. In the presence of
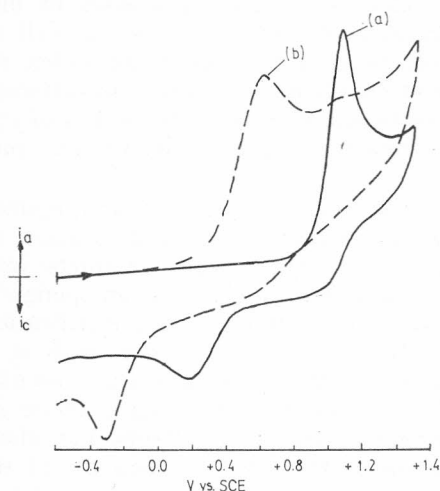

Figure 1. Cyclic voltammograms of avarol (1 mM): (a) CH₃CN — 0.1 M Et₄NClO₄; (b) CH₃CN — 0.1 M Et₄NClO₄, 2,6-lutidine (10 mM). Scan rate 0.1 V s⁻¹.

excess of 2,6-lutidine, the peak at 0.20 V disappears. The process taking place at + 0.67 V *vs*. SCE is probably the oxidation of the avarol monoanion.[8]

The peak corresponding to the reduction of the 3,4-double bond in the terpene part of the molecule can be seen in the cyclic voltammogram at the potential of around − 1.95 *vs*. SCE (Figure 2), but this assumption requires confirmation by preparative experiments.
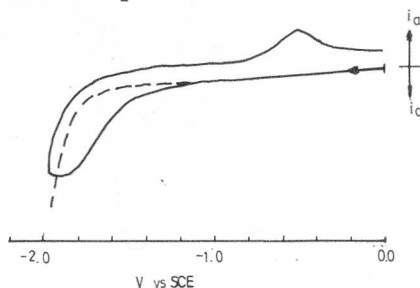

Figure 2. Cyclic voltammograms of avarol (1 mM): CH_3CN — 0.1 M Et_4NClO_4. Scan rate 0.1 V s^{-1}. Dotted line: solvent supporting electrolyte.

The cyclic voltammogram of a 1 mM solution of avarone (Q) in an aceto-nitrile-tetraethyl ammonium perchlorate medium using platinum as cathode shows two well defined peaks at − 0.55 V and − 1.18 V *vs*. SCE, respectively. Based on peak-potential separation (60 mV), peak-current ratio ($i_a/i_c = 1$) and peak-current dependence on the scan rate (0.1—1 V s^{-1}) the first wave was found to represent a reversible one electron reduction leading to the stable radical-anion (semiquinone) and the second, an irreversible reduction leading to the dianion. The irreversibility of the second wave is the result of the fast protonation of the dianion formed, following the second electron transfer (Figure 3a). In the presence of a weak acid, such as phenol, the second wave disappears, while the first wave increase (Figure 3b).

The current functions, $i_p/V^{1/2}$ C or $i_L/\omega^{1/2}$ C, obtained in the presence of phenol, indicate a two-electron behaviour. Our results, as well as related studies,[9,10] lead to the following mechanism which explains the single two-electron wave in the presence of a protone donor:

$$Q + e^- \rightleftharpoons Q^{.-}$$
$$Q^{.-} + HA \rightarrow QH^. + A^-$$
$$QH^. + e^- \rightleftharpoons QH^-$$
$$QH^- + HA \rightarrow QH_2 + A^-$$
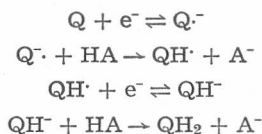
The protonated radical-anion (QH·) is a reducible species at the applied potential of the first wave, leading to the monoanion (QH$^-$) which is being protonated.

The current-potential curves, obtained with rotating disc electrode, for the oxidation of avarol show one single wave. The dependence of the limiting current on the square root of the rotation speed (in the range of 100—3000 rev/min) was linear at 1.2 V *vs*. SCE, which corresponds to the plateau on the steady-state current-potential curves, indicating that the current is deter-mined by the rate of the mass transport of the electroactive species to the electrode surface (Figure 4a). The dependence of the limiting current on the square root of the rotation speed, for the reduction of avarone, was linear
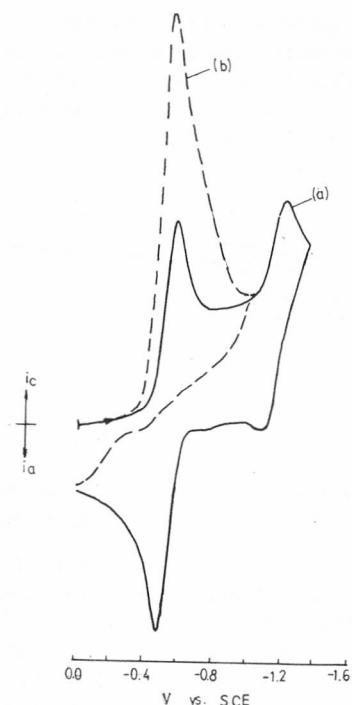
Figure 3. Cyclic voltammogram of avarone (1 mM): (a) CH_3CN — 0.1 M Et_4NClO_4; (b) CH_3CN — 0.1 M Et_4NClO_4, phenol (10 mM). Scan rate 0.1 V s^{-1}.
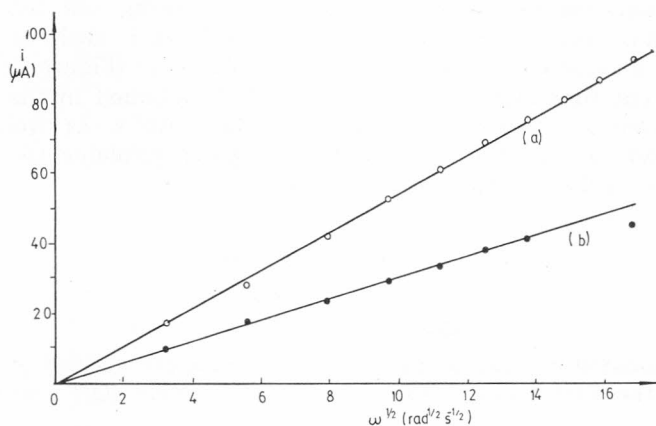

Figure 4. Plots of i_1 vs. $\omega^{1/2}$ for (a) avarol (1 mM) and (b) avarone (1 mM), Pt-disc electrode.

at the potential (— 0.7 V vs. SCE) which corresponds to the plateau of the first reduction wave in the acetonitrile — 0.1 M Et_4NClO_4 media (Figure 4b).

The diffusion coefficients were calculated by incorporating the values of various parameters in the Levich equation, assuming $n = 1$ for the first wave of avarone and $n = 2$ for the oxidation of avarol. The calculated values of

the diffusion coefficient for avarol $(0.85 \times 10^{-5}$ cm^2 s$^{-1})$ and for avarone $(0.89 \times 10^{-5}$ cm^2 s$^{-1})$ are similar, as one could expect.

Our results on the avarol-avarone redox behavior in acetonitrile are in accord with V. D. Parker's observation[6] that the oxidation of the QH$_2$ type compounds is a two electron process on the voltammetric time scale. On the other hand, the reduction of avarone in aprotic solvents is typical for the Q type compounds, taking place in two discrete one electron steps; however, in presence of weak acids, a single two electron process can be observed at the potential corresponding to the first reduction step taking place in aprotic medium. Further experiments on the avarol-avarone redox reactivity in aqueous ethanol solutions as well as solubilized in micelles are currently underway.

EXPERIMENTAL

Analytically pure samples of avarol and avarone, isolated and prepared as previously described,[5a,b] were used as 1 mM solutions.

Acetonitrile (Koch Light Ltd) was purified by a procedure similar to that of D. Clark et al.[11] The supporting electrolyte was tetraethyl ammonium perchlorate (C. Erba, polarographic grade) as a 0.1 M solution.

All electrochemical experiments were carried out with a Hi-Tek Instruments potentiostat, type DT 2101, a Chemical Electronics function generator, type RB 1, and Gould XY recorder. The cell, electrodes and apparatus for rotating disc voltametry were the same as described earlier.[12]

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IZVOD

Redoks ponašanje avarol-avarona u acetonitrilu

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Ispitivana je oksidacija biološki aktivnog seskviterpenskog hidrohinona ava-rola, izolovanog iz morskog sunđera *Dysidea avara*, i redukcija odgovarajućeg hinona, avarona, na platinskoj elektrodi, u rastvoru acetonitril-tetraetilamonijum--perhlorata. Utvrđeno je da se vrši dvoelektronska oksidacija avarola pri čemu verovatno nastaje protonovani avaron. Redukcija avarona vrši se u dva stupnja, nastajanjem stabilnog radikal-anjona koji se pri negativnijem pote˙ ijalu redukuje u dianjon.