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Thermodynamic and kinetic considerations for the reaction of semiquinone radicals to form superoxide and hydrogen peroxide

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Abstract

The quinone/semiquinone/hydroquinone triad ($Q/SQ^{\bullet -}/H_2Q$) represents a class of compounds that has great importance in a wide range of biological processes. The half-cell reduction potentials of these redox couples in aqueous solutions at neutral pH, $E^{\circ\prime}$, provide a window to understanding the thermodynamic and kinetic characteristics of this triad and their associated chemistry and biochemistry *in vivo*. Substituents on the quinone ring can significantly influence the electron density "on the ring" and thus modify $E^{\circ\prime}$ dramatically. $E^{\circ\prime}$ of the quinone governs the reaction of semiquinone with dioxygen to form superoxide. At near-neutral pH the pK_a's of the hydroquinone are outstanding indicators of the electron density in the aromatic ring of the members of these triads (electrophilicity) and thus are excellent tools to predict half-cell reduction potentials for both the one-electron and two-electron couples, which in turn allow estimates of rate constants for the reactions of these triads. For example, the higher the pK_a's of H_2Q, the lower the reduction potentials and the higher the rate constants for the reaction of $SQ^{\bullet -}$ with dioxygen to form superoxide. However, hydroquinone autoxidation is controlled by the concentration of di-ionized hydroquinone; thus, the lower the pK_a's the less stable H_2Q to autoxidation. Catalysts, e.g., metals and quinone, can accelerate oxidation processes; by removing superoxide and increasing the rate of formation of quinone, superoxide dismutase can accelerate oxidation of hydroquinones and thereby increase the flux of hydrogen peroxide. The principal reactions of quinones are with nucleophiles via Michael addition, for example, with thiols and amines. The rate constants for these addition reactions are also related to $E^{\circ\prime}$. Thus, pK_a's of a hydroquinone and $E^{\circ\prime}$ are central to the chemistry of these triads.

Keywords

Semiquinone; Free radical; Reduction potentials; Thermodynamics

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Introduction

Mass spectrometry of interstellar dust observed onboard the NASA spacecraft STARDUST has found quinones to be the principal class of compounds in the dust, indicating they are among the oldest organic molecules in the universe [1]. The quinone/semiquinone/hydroquinone ($Q/SQ^{\bullet -}/H_2Q$) triad is an important component of many redox systems in biology (Fig. 1). This moiety is a common constituent of many biologically relevant molecules, serving as a vital link in the movement of electrons through cells and tissues; the moiety can also be at the root of pathology, as in the case of many xenobiotics (Fig. 2). Coenzyme Q (ubiquinone) serves as a key agent for electron and proton transfer in mitochondria [2,3], while plastoquinone serves a similar function in photosynthesis [4]. The quinone moiety is also a key functional group in vitamin K. Quinones/hydroquinones are moieties central in the mechanisms of action of many xenobiotics, ranging from drugs such as adriamycin [5–7], to phytochemicals that have health benefits, such as *epi*gallocatechin gallate [8–10].

The unique redox characteristics of the $Q/SQ^{\bullet -}/H_2Q$ triad allow it to serve as a one-electron as well as a two-electron acceptor/donor. An important chemical feature of quinones is the ability to undergo a reversible oxidation-reduction without a change in structure; i.e., the quinone/quinol ring remains intact thereby allowing redox cycling. In the context of the $Q/SQ^{\bullet -}/H_2Q$ triad, redox cycling would be enzymatic reduction of Q to $SQ^{\bullet -}$ or H_2Q and the subsequent oxidation to form superoxide and hydrogen peroxide. This futile cycle results in an apparent nonending shunting of electrons from cellular reducing equivalents to dioxygen, forming potentially damaging reactive oxygen species.

The goal of this paper is to provide information on the fundamental thermodynamics and kinetics of the reaction of semiquinone radical with dioxygen to form superoxide. We have collected in Table A1 the half-cell reduction potentials of many $Q/SQ^{\bullet -}/H_2Q$ triads. In Table A2 the second-order rate constants for the reaction of various semiquinones with dioxygen to form superoxide are tabulated. The thermodynamics of $Q/SQ^{\bullet -}/H_2Q$ triads at near-neutral pH also provide insight into other reactions of the members of these triads, such as the Michael addition of nucleophiles, e.g., thiols. Insights into these chemistries are available when the relative electrophilicities of these species are taken into account; the pK_as of hydroquinones serve as excellent reporters of the relative electrophilicities of members of these triads.

Half-cell reduction potentials, E°′, for $Q/SQ^{\bullet -}/H_2Q$ triads

Quinones are used as oxidizing agents in organic synthesis, e.g., 2, 3-dichloro-5, 6-dicyano -1, 4-benzoquinone [15], whereas hydroquinones are used as reducing agents, e.g., in photographic developers. However, the oxidizing and reducing abilities of these compounds vary greatly, depending on the nature of substituents on the ring, R_2, R_3, R_5, and R_6 of Fig. 1. Their relative oxidizing or reducing capacity can be assessed by half-cell reduction potentials.

The reduction of a quinone can occur in two sequential one-electron transfer reactions (Eqs. (1) and (2)) [16]. The complete reduction of a quinone to a hydroquinone requires two electrons and two protons (Eq. (3)) [17]. The intermediate semiquinone ($SQ^{\bullet -}$) is a relatively stable free radical, compared to highly reactive free radicals such as the hydroxyl radical; however, semiquinone radicals are relatively unstable species compared to quinones and hydroquinones. Semiquinones and hydroquinones readily undergo the reverse of Eqs. (1)–(3) in the presence of appropriate electron acceptors (oxidants, e.g., dioxygen).

$$Q+e^- \rightleftharpoons SQ^{\bullet-} \quad (1)$$

$$SQ^{\bullet-}+e^-+2H^+ \rightleftharpoons H_2Q \quad (2)$$

$$\textbf{Net} \quad Q+2e^-+2H^+ \rightleftharpoons H_2Q \quad (3)$$

The ease of reduction of a quinone or semiquinone is quantified by the half-cell reduction potential ($E^{\circ\prime}$), when expressed in volts (V) or millivolts (mV) [18,19].1

The more positive the reduction potential, the more easily the quinone or semiquinone is reduced. Conversely, the more negative this potential the more difficult it is to reduce the species. For example, 1,4-benzoquinone has a standard one-electron half-cell reduction potential of +99 mV to form benzosemiquinone; duroquinone (D-$SQ^{\bullet-}$), which has four methyl substituents on the quinone ring, has $E^{\circ\prime} = -240$ mV. Thus, 1,4-benzoquinone is much easier to reduce than duroquinone, i.e., it is a better oxidizing agent; however, durosemiquinone will be a stronger reducing agent than benzosemiquinone.

The chemistry of cells and tissues is clearly not occurring under standard conditions. Given the standard potential of the half-cell, the reduction potential for a redox couple at nonstandard concentrations (E) can be calculated using the Nernst equation (Eq. (4). Here, Q_r is the reaction quotient for the half-reaction, simply the ratio of the [reduced species]/[oxidized species],

$$E=E^{\circ\prime}-\frac{RT}{nF}\ln Q_r \quad (4)$$

R is the gas constant in appropriate units, 8.314 J K^{-1} mol^{-1}, T is the temperature in Kelvin, **F** is the Faraday constant 9.6485 × 10^4 C mol^{-1}, and n is the number of electrons in the reduction reaction. If in the Nernst equation we use $\log_{10}$ rather than natural logarithm, then, at 25 °C (298.15 K), 2.3RT/n**F** = 59.1/n (mV); at 37 °C, 2.3RT/n**F** = 61.5/n (mV). Then, Eq. (4) will have the form:

$$E=E^{\circ\prime}-\frac{59.1}{n}\log Q_r(mV) \text{ at } 25^{\circ}C \quad (5)$$

With this form of the Nernst equation, real-world estimates are easily made from the quantitative information under standard conditions. Cells and tissues have a relatively reduced redox environment compared to that of the biosphere; these potentials have a limited range to be compatible with life [20,21].

[1]A standard half-cell reduction potential (E°) indicates that it was measured under standard conditions: 25 °C, 1.0 M concentration for each species participating in the reaction, pH 0.0 when in aqueous solution; a partial pressure of 100 kPa (0.986 atm) for each gas that is part of the reaction, and metals in their pure state. The superscript ° on the E implies these standard conditions. Standard reduction potentials are relative to the standard hydrogen electrode (SHE), a reference electrode that is given a value of 0.00 V at all temperatures. Historically, some countries including the United States and Canada used standard oxidation potentials rather than reduction potentials in their calculations. These are simply the negative of standard reduction potentials. However, the term "redox potential" is widely used; this results in much confusion because it is not clear if a reduction or oxidation potential is being referred to. In modern chemistry texts all potentials quoted are reduction potentials. In the field of redox biology we suggest that this convention be adopted to eliminate possible confusion. $E^{\circ\prime}$ is widely used to indicate that the pH is 7.0, rather than 0.0.

Quinones can undergo two sequential one-electron oxidations, $Q/SQ^{\bullet -}$ and then $SQ^{\bullet -},2H^+/H_2Q$.2 Each step will have a distinct reduction potential. For example, for the first electron for duroquinone, $E^{\circ\prime}(Q/SQ^{\bullet -}) = -240$ mV, while for the second electron $E^{\circ\prime}(SQ^{\bullet -},2H^+/H_2Q) = +350$ mV. These potentials indicate that the durosemiquinone is relatively3 reducing and at the same time it could also oxidize an appropriate electron donor by one electron to form H_2Q.

Since $SQ^{\bullet -}$ can be both oxidizing and reducing, it will readily disproportionate to its corresponding hydroquinone and quinone (Eq. (6) and Fig. 3). This reaction requires two protons:

$$2SQ^{\bullet -}+2H^+ \rightleftharpoons Q+H_2Q \qquad K_6=\frac{[Q][H_2Q]}{[SQ^{\bullet -}]^2[H^+]^2} \tag{6}$$

The rate for the forward reaction of Eq. (6) will slow as the pH is increased [22,23]. Thus, as the pH of a solution is raised semiquinone radical will become more persistent, allowing for a greater steady-state concentration and ease of detection, for example, by EPR spectroscopy (assuming no other chemistry is introduced) [24].

However, the reversible nature of these oxidations and reductions is shown by the comproportionation reaction of a quinone and hydroquinone yielding two $SQ^{\bullet -}$, reverse of Eq. (6). Because the reaction of Eq. (6) is reversible, the mixing of Q and H_2Q will result in $SQ^{\bullet -}$ being formed via comproportionation. Thus, when both Q and H_2Q are present, there will always be some $SQ^{\bullet -}$ in the system. How much will depend on the thermodynamics (equilibrium constant, *K*) for the reaction of Eq. (6), the pH, and the presence or absence of oxygen.

In Fig. 3 we present the thermodynamics of three different $Q/SQ^{\bullet -}/H_2Q$ triads graphically. Here we see that durosemiquinone is energetically "uphill" with respect to both D-Q and D-H_2Q. Thus, the equilibrium constant for the reaction of Eq. (6) is large; i.e., the concentration of D-$SQ^{\bullet -}$ will be very low at equilibrium. For both B-$SQ^{\bullet -}$ and Cl_2-$SQ^{\bullet -}$ it is energetically "uphill" to the quinone; however, to get to the hydroquinone is energetically downhill. The overall energetics yields smaller equilibrium constants. With these smaller equilibrium constants for the dismutation reaction we would predict that semiquinone radicals would be present at relatively higher concentrations. They would appear as more persistent (and detectable) radicals when $Q/SQ^{\bullet -}/H_2Q$ triads are examined by EPR [25].

The substituents on a quinone ring can have a significant influence on the reduction potentials of the triad. For example, alkyl groups donate electrons into aromatic systems. As methyl groups are added to a benzoquinone ring, we would expect the resulting quinone to be less electrophilic; it should be "harder" to put an electron into Q to form $SQ^{\bullet -}$; we would expect the one-electron reduction potentials to become more negative with increasing numbers of alkyl substituents. Indeed, as one, two, three, and then four alkyl groups are added to the benzoquinone ring, we see a linear decrease in the one-electron reduction potential of Q (Fig. 4 line a). As might be expected, this pattern holds for 1,4-naphthoquinones as well (Fig. 4 line b).

[2]The notations $Q/SQ^{\bullet -}$ and $SQ^{\bullet -},2H^+/H_2Q$ represent the reactions of Eqs. (1) and (2). If in an electrochemical cell, then the slash (/) would represent the electrode of the cell.

[3]The word "relatively" is used here because the reference is the standard hydrogen electrode, $E^{\circ\prime} = 0$ mV.

If electron-withdrawing substituents (relatively electronegative, e.g., chlorine and bromine) are added to a benzoquinone ring, we would anticipate that the resulting quinone will be more electrophilic. Thus, it should be "easier" to put an electron into Q to form $SQ^{\bullet -}$. Indeed, the one-electron reduction potentials of chlorine-substituted quinones become more positive with increasing numbers of chlorines ($E^{\circ\prime}$ = +99 mV for (benzoquinone), +470 mV for dichloroquinone, and +650 mV for tetrachloroquinone (Fig. 4 line c).

This principle also holds for two-electron reduction potentials of quinones. A plot of $E^{\circ\prime}$(Q/H_2Q) vs number of methyl substituents on benzoquinone demonstrates a linear decrease in the two-electron reduction potential (Fig. 4 line d). These trends allow estimates of $E^{\circ\prime}$ for triads for which experimental data are not yet available. In addition, these potentials provide information for the understanding of the reactions of $Q/SQ^{\bullet -}/H_2Q$ triads with nucleophiles and dioxygen.

Superoxide and superoxide dismutase

A potentially important reaction for semiquinones is their reaction with dioxygen to form superoxide (Eq. (7)). As indicated, this is an equilibrium reaction; the product quinone can be

$$SQ^{\bullet -} + O_2 \rightleftharpoons Q + O_2^{\bullet -} \tag{7}$$

reduced by superoxide; reverse Eq. (7). The equilibrium position of Eq. (7) is determined by $E^{\circ\prime}(Q/SQ^{\bullet -})$ and $E^{\circ\prime}(O_2/O_2^{\bullet -})$. Using the potentials of the quinones listed in Table A1, the equilibrium constant (K) for the reaction of Eq. (7) can be determined. The reduction potential for the $O_2/O_2^{\bullet -}$ couple was initially determined to be −155 mV(1.0 M O_2) [26,27]. However, a careful reexamination of this couple indicates that a better value is −180 mV[28,29]. Using $E^{\circ\prime}(O_2/O_2^{\bullet -}) = -180$ mV and $E^{\circ\prime}(Q/SQ^{\bullet -})$ = +99 mV for benzoquinone, in conjunction with Eq. (8), the equilibrium constant for reaction (7), where $SQ^{\bullet -}$ is benzosemiquinone, is estimated as 2×10^{-5}; for durosemiquinone the equilibrium constant at pH 7.0 is estimated to be 26.

$$E^{\circ\prime}(O_2/O_2^{\bullet -}) - E^{\circ\prime}(Q/SQ^{\bullet -}) = (RT/F) \ln K \tag{8}$$

If a quinone has $E^{\circ\prime}(Q/SQ^{\bullet -})$ lower than the one-electron reduction potential of oxygen (<− 180 mV), e.g., mitomycin C, adriamycin, and menadione, the equilibrium position for the reaction of Eq. (7) will lie to the right, favoring formation of superoxide. For those quinones that have $E^{\circ\prime}(Q/SQ^{\bullet -})$ greater than −180 mV, the equilibrium of Eq. (7) will lie to the left, and the generation of superoxide will not be thermodynamically favorable. However, it must be kept in mind that "not thermodynamically favorable" does not mean that superoxide will not be formed. Because $K = k_{forward}/k_{reverse}$, not thermodynamically favorable means that the reverse rate constant is greater than the forward rate constant. Thus, superoxide can be formed; however, the consequences of its formation in biological systems will be a function of the rate of formation of the semiquinone and the presence of reaction targets other than quinone.

One of these potential reaction targets is the enzyme superoxide dismutase (SOD). SOD is an important antioxidant enzyme involved in removing superoxide and thereby protecting cells against oxidative damage; it reacts rapidly with superoxide radical ($k = 2.4 \times 10^9$ M^{-1} s^{-1} [30]), facilitating its dismutation, thereby keeping a low steady-state level (Eq. (9)). In

cells and tissues it will compete favorably with quinone for superoxide, thereby pulling reaction (7) to the right, even if reaction (7) is not “thermodynamically favorable” [24,31].

$$2O_2^{\bullet-} + 2H^+ \xrightarrow{SOD} O_2 + H_2O_2 \quad (9)$$

Because O_2 has no charge, the Marcus theory of electron transfer predicts that the rate constants for the reaction of $SQ^{\bullet-}$ with O_2 (Eq. (7)) (Table A2) will be a function of the change in the Gibbs free energy for this reaction. A plot of log $k_{forward}$ vs $E^{\circ\prime}(Q/SQ^{\bullet-})$ for a subset of the $Q/SQ^{\bullet-}$ couples of Table A1 shows two distinct groups, each having an approximate linear relationship (within the noise of the available data) (Fig. 5A). Detailed analyses by Meisel [32] and Wardman [23] show a gentle parabolic shape, mostly in accord with the Marcus theory. In Fig. 5A the data fall into two categories: (i) for $E^{\circ\prime} < -150$ mV the rate constants appear to be influenced by diffusion, i.e., $k > 10^8\ M^{-1}\ s^{-1}$; and (ii) when $E^{\circ\prime} > -150$ mV the rate constants follow well the Marcus theory for electron transfer, here approximated by a linear relationship.

On fitting the data of these two groups to separate linear functions, we can estimate $k_{forward}$ of Eq. (7) for different $SQ^{\bullet-}$ if we know $E^{\circ\prime}(Q/SQ^{\bullet-})$. For example, for 2,5-dichloro-1,4-benzoquinone $E^{\circ\prime}(Q/SQ^{\bullet-})$ = +470 mV, log $k_{forward}$ is estimated as −0.15 or $k_{forward} = 10^{(-0.15)} = 0.7$; for 2,3,5,6-tetrachloro-1,4-benzoquinone, $k_{forward} = 10^{(-2.57)} = 0.003$. Thus, the rate constants for formation of superoxide by semiquinone radicals can vary over at least 11 orders of magnitude: for anthraquinone $E^{\circ\prime}(Q/SQ^{\bullet-}) = -445$ mV, $k = 5 \times 10^8\ M^{-1}\ s^{-1}$, while for tetrachloro-1,4-benzoquinone, $E^{\circ\prime}(Q/SQ^{\bullet-})$ = +650 mV, $k = 3 \times 10^{-3}\ M^{-1}\ s^{-1}$ (estimated).

Making a similar plot for $k_{reverse}$, i.e., log($k_{reverse}$) vs $E^{\circ\prime}(Q/SQ^{\bullet-})$, we again see an approximate linear relationship (Fig. 5B). As might be expected, the larger the forward rate constant for Eq. (7), the smaller the rate constant for the reverse reaction. A plot of log(experimentally determined equilibrium constants) vs $E^{\circ\prime}(Q/SQ^{\bullet-})$ yields a straight line as expected (Fig. 6).

To understand how the presence of SOD will affect the reverse of Eq. (7), one needs to compare pseudo-first-order rate constants for the competing reactions of superoxide with SOD or quinone. Each reaction is second-order. The rate constant for the reaction of superoxide with SOD is $2 \times 10^9\ M^{-1}\ s^{-1}$ [33]. If we assume a typical concentration for CuZnSOD to be 20 μM in tissues [34,35], then the pseudo-first-order rate constant for the reaction of superoxide with SOD in cells is $\approx 4 \times 10^4\ s^{-1}$ ($k'_{SOD} = k[20 \times 10^{-6}\ M]$). When the pseudo-first-order rate constant for the reaction of superoxide with Q (k'_Q) is equal to $4 \times 10^4\ s^{-1}$, then one-half of the superoxide will with react with SOD and one-half will react with Q, assuming no other significant “sinks” for superoxide. If $k'_Q < k'_{SOD}$, i.e, $k'_{SOD} : k'_Q > 1$, then the major fraction of superoxide will react with SOD; if this ratio is < 1, then the major fraction will react with quinone.

As an example, if for Eq. (7) $k_{reverse} = 10^6\ M^{-1}\ s^{-1}$, then [Q] must be 40 mM just to compete on an equal basis with SOD; if $k_{reverse} = 10^9\ M^{-1}\ s^{-1}$ then [Q] must be 40 μM to compete on an equal basis with SOD. A concentration of 40 mM Q inside a cell is quite unrealistic for most xenobiotics, even 40 μM seems challenging. Thus, we suggest that in nearly all circumstances, SOD will pull Eq. (7) to the right by competing against the reverse reaction [36–38]. SOD will lower the steady-state concentration of $O_2^{\bullet-}$. However, if $SQ^{\bullet-}$ is readily regenerated from Q and/or H_2Q, then SOD will increase the flux of $O_2^{\bullet-}$, which will

then lead to an increased flux of H_2O_2 [38]. Thus, the rate of the forward reaction of Eq. (7) is a key factor in determining the flux of $O_2^{\bullet-}$ and H_2O_2 in cells and tissues.

pK_a's

The pK_a of a proton reflects the electron density on the atom with which it forms a hydrogen bond. In general the higher the electron density, the greater the negative charge, the higher the pK_a, and vice versa. Because the core structure of $Q/SQ^{\bullet-}/H_2Q$ triads is nearly the same, the pK_a's of a hydroquinone will also reflect the relative electron density not only on the oxygens of the hydroquinone but also the relative electron density in the aromatic core of each member of a triad. Thus, the pK_a's of hydroquinones will reflect the relative electron density in the aromatic core (electrophilicity) of a series of quinones and semiquinones, as well as the parent hydroquinone.

Hydroquinones are very weak diacids with first pK_a's typically in the range of 9 – 11. The second pK_a is uniformly 2.0 units higher (Fig. 7). From the trends seen in Figs. 4 and 7, we see, as expected, that electron-donating groups on the hydroquinone ring lead to higher pK_a's, while electron-withdrawing groups lead to lower pK_a's. Protonated semiquinones ($SQH^{\bullet}$) will also have an associated pK_a; this pK_a is typically in the range of 4 – 5 [13]. Thus, in near-neutral aqueous solution semiquinone radicals will exist primarily in their anionic, i.e., nonprotonated form ($SQ^{\bullet-}$), while hydroquinones will in general exist as H_2Q with smaller amounts of HQ^- (in general <1%); the concentration of Q^{2-} will be about 1% of that of HQ^-.

From Fig. 7 it is clear that the pK_a's of a hydroquinone are outstanding indicators of the one-electron reduction potential of the corresponding quinone; $E^{\circ\prime}(Q/SQ^{\bullet-})$ is determined by the nature of the “R groups” on the quinone/hydroquinone ring, which is reflected in the pK_a's. In Fig. 5 we see that the rate constants for the reactions of Eq. (7) are a function of $E^{\circ\prime}(Q/SQ^{\bullet-})$; thus, it would appear that the pK_a's of H_2Q are outstanding indicators of relative electron densities, providing a window to understanding the production of $O_2^{\bullet-}$ by $SQ^{\bullet-}$ at near-neutral pH. In fact, a plot of the log(forward rate constant) or log(reverse rate constant) for Eq. (7) vs pK_{a1} of the corresponding hydroquinone shows a linear relationship (Fig. 8).

Essentially we see that electron-withdrawing groups on the semiquinone ring will lead to a less reactive (less reducing), more persistent free radical that reacts relatively slowly with dioxygen to produce superoxide. Conversely, electron-donating groups result in a more reducing semiquinone radical that is less persistent and will readily react with dioxygen to produce superoxide. These properties at near-neutral pH are related to the electron densities in the aromatic moiety of the semiquinone and are reflected in the pK_a's of the hydroquinone (Figs. 5 and 7. There must be a near linear offset in the overall electron density in the aromatic moiety of a triad as we go from Q to $SQ^{\bullet-}$ to QH_2, so it all works.

That there is indeed a linear offset in the electron density, i.e., relative electrophilicity, in the members of a $Q/SQ^{\bullet-}/H_2Q$ triad is seen when the first pK_a's of hydroquinones are compared to the pK_a's of corresponding protonated semiquinones (Fig. 9). This linear relationship supports the use of pK_a's to understand the chemistry of these triads.

There are now many computational tools to estimate the pK_a's of a broad range of organic compounds, including hydroquinones. With these pK_a's it would be possible to estimate $E^{\circ\prime}(Q/SQ^{\bullet-})$ and the other reduction potentials of a triad and even rate constants for Eq. (7) based on the data from a series of triads that have similar structures and properties.

A broader approach to understanding the reactivity and mechanisms of toxicity of $Q/SQ^{\bullet -}/H_2Q$ triads would be to use the electrophilicity index or similar approaches [41–43]. However, this is beyond the scope of this paper.

Hydroquinone autoxidation

The autoxidation of hydroquinones has been studied for over a century [44,45] (autoxidation is oxidation in the absence of metal catalysts [46].) In general, autoxidation of hydroquinones to corresponding quinones results in the stoichiometic production of H_2O_2. The oxidation is pH dependent; the rate increases as the pH increases [47]. In homogeneous aqueous solution, the rate law for the autoxidation of a family of 1,4-hydroquinones has been observed to be first-order with respect to $[H_2Q]$ and $[O_2]$; however, it is second order in $[OH^-]$ [48–50]. This oxidation can be inhibited by reducing agents [51–53]; the rate law can change in the presence of catalysts [16,54].

Because kinetic studies at near-neutral pH have found that the initial rate of oxidation of 1,4-hydroquiones is second order in $[OH^-]$, the key species in the autoxidation of hydroquinones is Q^{2-}; i.e., Q^{2-} is the species that actually undergoes autoxidation, Eqs. (10)–(13).

$$H_2Q \overset{pk_{a1}}{\rightleftharpoons} HQ^- + H^+ \tag{10}$$

$$HQ^- \overset{pk_{a2}}{\rightleftharpoons} Q^{2-} + H^+ \tag{11}$$

$$Q^{2-} + O_2 + 2H^+ \overset{k}{\rightarrow} Q + H_2O_2 \tag{12}$$

$$\textbf{Net} \quad H_2Q + O_2 \rightarrow Q + H_2O_2 \tag{13}$$

The reaction of Eq. (12) is spin-restricted and thus expected to be quite slow [46]. Here we indicate H_2O_2 as the product of Eq. (12) and of the overall reaction Eq. (13), as observed by researchers over the decades. However, the reaction of Eq. (12) will most likely occur as two sequential steps with superoxide and semiquinone as intermediates. The actual mechanism can be quite complex and Eqs. (10)–(13) as written are not intended to convey the detailed mechanism of every oxidation. The mechanism will change if metals are present or if superoxide is a chain-carrying radical in the oxidation process; see below (Catalysts for oxidation of H_2Q). As an example of Eqs. (10)–(13), the ascorbate dianion undergoes true autoxidation, a reaction parallel to Eq. (12), with a rate constant of about 200 M^{-1} s^{-1} [55]. Thus, the initial rate of autoxidation of a hydroquinone at near-neutral pH will actually be a function of $[Q^{2-}]$. The lower the pK_a's of a hydroquinone, the greater the concentration of Q^{2-} at near-neutral pH. Thus, electron density in the aromatic moiety of hydroquinones, as reflected in its pK_a's, is central to its rate of autoxidation.

A clear example of this is seen in the autoxidation of a series of chlorinated 1,4-hydroquinones (Fig. 10). The rate of autoxidation of this family of hydroquinones, as measured by the rate of oxygen consumption, increases with increased chlorination of the hydroquinone ring. The initial rates for the autoxidation of this set of chlorinated hydroquinones at pH 7.4 increases by a factor of 10 as the number of chlorines on the

oxygenated ring increases from 0 to 3 (Fig. 11) [56]. The factor of 10 increase in the rate of autoxidation follows closely the lowering of the pK_a's of the hydroquinone by one pK_a unit on the addition of each chlorine to the hydroquinone ring, except for the trichlorinated hydroquinone (Fig. 11). If the rate constants for the reaction of Eq. (12) are similar for each Q^{2-}, then the rate of autoxidation will be proportional to the concentration of Q^{2-}. Indeed, when log(rate) is plotted against the fraction of hydroquinone present in the di-ionized form (Q^{2-}), we see a slope of exactly 1.0, consistent with the reaction of Eq. (12) being central in the autoxidation hydroquinones in near-neutral solution. This is seen in the slope of the lines being exactly 1.0. These data suggest that for the rate law $-d[O_2]/dt = -k[Q^{2-}][O_2]$, $k = 2 \times 10^2\ M^{-1}\ s^{-1}$. This rate constant appears to hold across all Q^{2-} in this series; interestingly this is also consistent with that observed for the ascorbate dianion [55].

The experimental observation that electron-withdrawing groups on a semiquinone ring result in semiquinones that are more persistent compared to when there are electron-donating groups on the ring appears [25] to be at odds with the observation that electron-withdrawing groups make the hydroquinone more susceptible to autoxidation. As discussed above, both observations can be related to the pK_a's of the parent hydroquinone. Thus, you cannot win—a $Q/SQ^{\bullet -}/H_2Q$ triad that readily produces superoxide via $SQ^{\bullet -}$ will have a relatively stable hydroquinone, with respect to autoxidation; however, a $Q/SQ^{\bullet -}/H_2Q$ triad that has a semiquinone that reacts very slowly with dioxygen to produce superoxide will have a hydroquinone that readily undergoes autoxidation to produce hydrogen peroxide.

Catalysts for oxidation of H_2Q

The above discussion focuses on the autoxidation of hydroquinones. However, catalysts can accelerate the oxidation of hydroquinones. For example, redox-active transition metals, e.g., manganese, iron, and copper, will serve as catalysts for the oxidation of hydroquinones [16,54,57–60]. These metals assist in overcoming the spin restriction by forming complexes with the monoanion (HQ^-) as they facilitate the electron transfer to dioxygen. In autoxidation, the kinetic rate law is second-order in [OH^-]. However, in metal-catalyzed oxidations, the rate law is often first-order in [OH^-], consistent with the monoanion being the important species in this route of oxidation. Redox-active metals are ubiquitous; adventitious metals are present on glassware and in all buffer solutions unless measures are taken to remove them [61]. Redox-active metals with appropriate coordination environments accelerate the oxidation of hydroquinones compared to autoxidation, principally by changing the mechanism.

Another, often overlooked, catalyst for the oxidation of H_2Q is the quinone formed as a product. This has been demonstrated by the observation of an apparent “self-acceleration” during the autoxidation of many hydroquinones. The reaction kinetics show a significant induction (lag) period that can be eliminated by addition of very small amounts of Q [24,62]. When Q is present, the reverse of Eq. (6) will occur, i.e., H_2Q and Q will comproportionate to form $2SQ^{\bullet -}$; $SQ^{\bullet -}$ will then react with dioxygen to produce $O_2^{\bullet -}$, Eq. (7); $O_2^{\bullet -}$ will dismute, either spontaneously or as catalyzed by SOD to form H_2O_2 in biological systems. Thus H_2Q is oxidized, Eq. (13), albeit by a different mechanism than autoxidation.

Quinone will only be an efficient catalyst if the corresponding semiquinone radical reacts readily with dioxygen to form superoxide. When a semiquinone has electron-withdrawing groups on the ring, the rate constant for the reaction of $SQ^{\bullet -}$ with dioxygen to form $O_2^{\bullet -}$ (Eq. (7)) will be small; electron-donating groups result in higher values for the rate constant for superoxide production. Thus, the efficiency of $Q/SQ^{\bullet -}$ in the catalysis of the oxidation of H_2Q is really a function of how efficiently $SQ^{\bullet -}$ forms superoxide.

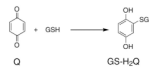
SOD can accelerate the rate of oxidation of some hydroquinones [24,62]. SOD removes superoxide, Eq. (9), forming H_2O_2. By removing $O_2^{\bullet -}$, SOD increases the rate of formation of both H_2O_2 and of quinone, the two end products of oxidation of H_2Q. Thus, SOD accelerates the overall rate of oxidation of certain hydroquinones by minimizing the reverse of Eq. (7) as well as providing Q, which can serve as an apparent catalyst. SOD will have the greatest effect on the rate of oxidation of hydroquinones that have electron-donating substituents on the ring because it will increase the rate of formation of Q, a catalyst.

SOD can also slow the rate of autoxidation of some substances, e.g., when the superoxide produced is also a chain-propagating species. For example, the oxidation of epinephrine (adrenaline), a catechol, has been the subject of many studies [63]. It readily autoxidizes at higher pH and trace catalytic metals can accelerate its air oxidation. On the discovery of SOD, it was then found that autoxidation of epinephrine produces superoxide and this superoxide can serve as a chain-carrying radical [64]. Removing this chain-carrying radical by SOD will slow its oxidation. These reactions form the basis of an activity assay for SOD [64].

The oxidation of hydroxylated aromatics can be quite complex [65]. For example, the air oxidation of dialuric acid (2,4,5,6-tetrahydroxypyrimidine) can be accelerated by catalytic metals [66], as well as the presence of its two-electron oxidation product, alloxan. Dialuric acid and alloxan will undergo a comproportionation reaction, parallel to the reverse of Eq. (6), forming a reducing radical parallel to $SQ^{\bullet -}$, which will in turn react with dioxygen to form superoxide [65]. Superoxide is a chain-carrying radical in this system; thus, the presence of SOD will change the rate as well as the form of the kinetic rate law of this oxidation. The kinetic rate law that describes the oxidation can change considerably, depending on the environment and the mechanism that dominates the oxidation [65].

Thiols/GSH, addition of nucleophiles to quinone compounds

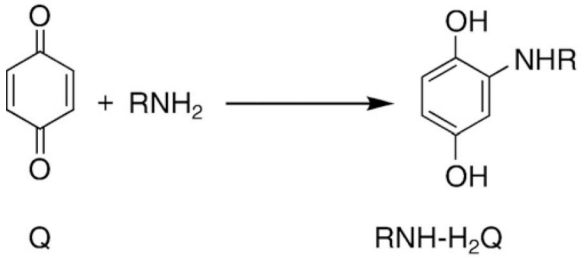
Above we have focussed on the oxidation reactions of the $Q/SQ^{\bullet -}/H_2Q$ triad and the associated production of $O_2^{\bullet -}$ and H_2O_2. However, because quinones are electrophilic, they have another chemistry that can be the principal mechanism for their toxicity, i.e., the reductive addition (Michael reaction) of nucleophiles such as amines and thiols [67–69]. Eq. (14) is representative of this type of reaction with quinones; showing the reductive addition of glutathione to B-Q to form a monothiol ether of benzohydroquinone, $GS\text{-}H_2Q$. On oxidation of $GS\text{-}H_2Q$ to GS-Q, another reductive addition can occur to yield $(GS)_2\text{-}H_2Q$; this cycle of oxidation and reductive addition can occur until all four “open” sites on benzoquinone are glutathionylated [56,68]. The rate constant for the addition reaction of the first thiol to benzoquinone is on the order of 10^5 M^{-1} s^{-1} in pH 6.0 buffer [70]. Because the kinetics of nucleophilic addition of a thiol to a quinone ring is controlled by the concentration of the ionized form of the thiol, the rate constant for thiol addition to benzoquinone at pH 7 will be about 10 times faster, i.e., *k* is on the order of 10^6 M^{-1} s^{-1} [23,71,72].



(14)

In addition to thiols, amine compounds can also serve as nucleophiles, undergoing reductive addition to Q, Eq. (15). Naturally, all free amino acids contain an RNH_2 moiety, but in proteins the amine groups, such as on lysine and arginine, or the amine groups of DNA bases can also serve as appropriate nucleophiles for Eq. (15). Parallel with thiols, it is the

unprotonated amine (R-NH_2) rather than the protonated form ($R-NH_3^+$) that is the effective nucleophile. As amines are much weaker nucleophiles than thiolates (RS^-), they react with benzoquinones much more slowly; rate constants for reductive addition of amino acids to Q are on the order of 10^{-2} M^{-1} s^{-1} in pH 7.4 buffer [73]. This difference of 10^8 in rate constants and the fact that the concentration of reactive thiols in cells and tissues is high indicate that the dominant reaction of quinones will be with thiolates rather than amines.



(15)

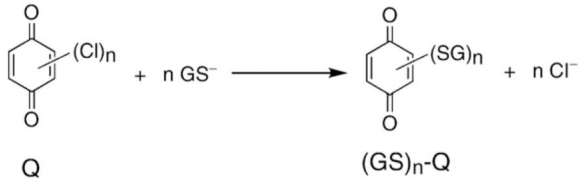
The actual rate constants for the reductive addition of nucleophiles to quinone rings will not only be a function of the nucleophilicity of the nucleophile, but also the electrophilicity of the quinone ring. As manifest in their wide range of half-cell reduction potentials, quinones have a wide range of electrophilicity. We would expect that quinones with very positive half-cell reduction potentials will react rapidly with nucleophiles, while quinones with lower reduction potentials will react more slowly [74]. Indeed, when log(rate constant) values for the reaction of glutathione with a series of benzoquinones are plotted against either the one-electron or two-electron reduction potential of the quinones, we see remarkable linear relationships (Fig. 12). Thus, the half-cell reduction potentials of quinones can be used to estimate rate constants for the reductive addition of nucleophiles (Eqs. (14) and (15)).

Because pK_a is a measure of electrophilicity for members of $Q/SQ^{\bullet -}/H_2Q$ triads, we would anticipate that rate constants for the reductive addition of nucleophiles, such as GSH, might also correlate well with rate constants for the addition reaction (Fig. 13). Thus, pK_a's in combination with other information can be used to predict this aspect of the chemistry and even aspects of potential mechanisms of the toxicology of these types of compounds.

Coenzyme Q_{10} is an important redox species in the mitochondrial electron transport chain. The location of CoQ_{10} in membranes in not understood, but with a very large octanol/water partition coefficient (log(*P*) ≈ 20 [75]) it is clearly very lipophilic, residing in the lipid bilayer [3,76,77]. When in a lipid phase, the thermodynamics will be somewhat different, similar to the thermodynamics in an organic solvent. In general E^os of $Q/SQ^{\bullet -}/H_2Q$ triads in organic solvents have similar relative values to the corresponding E^os in aqueous solution, but with an offset [23,78]. It is interesting to note that coenzyme Q has all four positions on the quinone ring occupied by alkyl and alkoxyl groups. Thus, Michael addition to the quinone ring is blocked, protecting CoQ from this type of chemistry.

Plastoquinone has a role in the electron transport chain of photosynthesis. It has one open site that could participate in a Michael addition reaction by appropriate nucleophiles (Fig. 2). However, the substituents on the plastoquinone ring have a net electron-donating effect, $E_1^{\circ\prime} \approx -165$ mV (estimated from Fig. 4 and Ref. [79]). Thus, a reductive addition reaction will be relatively slow, approximately ≈ 10^1 M^{-1} s^{-1} for a thiol (Fig. 12).

In addition to reductive addition (Michael reaction) strong nucleophiles can also displace weaker nucleophiles on a quinone ring. For example, thiolates, e.g., ionized glutathione (GS^-), are strong nucleophiles that can displace chlorine on a quinone ring, Eq. (16). This



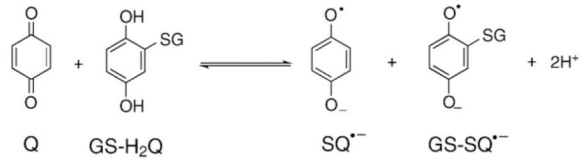
(16)

type of reaction is typically facilitated by glutathione transferases [80,81]. However, it can also occur in the absence of enzymes, such as with halogen-substituted diaziridinylbenzoquinones [82], dioxygenated PCBs with chlorine on the quinone ring [56], as well as chlorinated naphthoquinones [83]. Because the product after the nucleophilic substitution reaction is still a quinone, more than one chlorine on a quinone ring can be displaced. In fact all four chlorines of tetrachloro-1,4-benzoquinone can be displaced by glutathione yielding *tetra*-glutathiyl-1,4-benzoquinone [56]. These substitution reactions are rapid and will be of significance in a biological milieu.

The autoxidation of hydroquinone generates hydrogen peroxide and quinone. Hydrogen peroxide is a nucleophile and has been shown to react with benzoquinone [24,49,84,85] as well as chlorinated benzoquinone [86]. Reductive addition can occur at higher pH environments because peroxide anion (HOO^-) is a powerful nucleophile, much more reactive than hydroxide anion (pK_{a1} for H_2O_2 is 11.7 [87]). However, this reaction is most likely insignificant *in vivo*, as the amount of HOO^- present will be infinitesimally small due to the neutral environment.

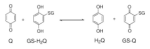
Cross-oxidation

The dismutation reaction of Eq. (6) is indeed an equilibrium reaction. If a quinone and hydroquinone are introduced into a solution, they will comproportionate to form two semiquinone radicals. The quinone and hydroquinone can be “different” resulting in two different semiquinone radicals; Eq. (17) is an example. The behavior of each of these radicals



(17)

will be governed by their individual thermodynamics. The system will come to equilibrium with a ratio of two different quinones, two different hydroquinones (Eq. (18)), and smaller amounts of two different semiquinones [24];



(18)

the ratio will all depend on the thermodynamics of each $Q/SQ^{\bullet-}/H_2Q$ triad. This is often referred to as a cross-oxidation; the rate can be relatively fast [71]. Naturally, if oxygen is present, then oxidation of the hydroquinones and semiquinones can occur, Eqs. (7) and (13).

Quinones are oxidants; thus, as noted above, they can oxidize species other than hydroquinones. For example, the more oxidizing quinones are capable of oxidizing NADPH [88]. For example, benzoquinone ($E_2^{\circ\prime}$ =+286 mV) will oxidize NADPH ($E_2^{\circ\prime}$ =+320 mV) with a rate constant on the order of 1 M^{-1} s^{-1} [88]. The rate constant will be smaller for quinones with more negative potentials, and conversely, larger with more positive potentials. Thus, half-cell reduction potentials can give insight into the wide range of reactions of members of $Q/SQ^{\bullet-}/H_2Q$ triads.

Summary

In this treatise we provide a comprehensive overview of how the fundamental thermodynamic and kinetic properties of $Q/SQ^{\bullet-}/H_2Q$ triads are intertwined. At near-neutral pH, the pK_a's of the hydroquinone are outstanding indicators of these properties; i.e., they can be used to understand $E^{\circ\prime}$ as well as the reaction kinetics for a range of reactions, including reactions with dioxygen to make $O_2^{\bullet-}$ and H_2O_2. However, $E^{\circ\prime}$ can also guide our understanding of nucleophilic addition reactions to quinone rings.

Here we have presented and discussed details of:

1. Molecules containing a quinone/semiquinone/hydroquinone moiety can serve as either one- or two-electron acceptors/donors. The reduction of a quinone typically occurs in two sequential one-electron transfer reactions to generate hydroquinone via semiquinone.
2. The ability of the $Q/SQ^{\bullet-}/H_2Q$ triad to facilitate electron-transfer is dependent on the reduction potentials of the members of the triad. The more positive the reduction potential, the more easily the quinone or semiquinone is reduced. Conversely, the more negative this potential the more difficult it is to reduce the species.
3. The substituents on a quinone ring greatly influence the reduction potentials of the triad at neutral pH. Electron-withdrawing groups lead to higher reduction potentials (more positive); electron-donating substituents lead to lower reduction potentials (more negative).
4. Semiquinones can react with dioxygen to form superoxide. The more negative the reduction potential of a $Q/SQ^{\bullet-}$ redox couple, the greater the rate constant for production of superoxide by $SQ^{\bullet-}$; at the same time, the rate constant for the back reaction will be smaller, Eq. (7). These rate constants can vary over at least 11 orders of magnitude.
5. SOD can remove superoxide produced by $SQ^{\bullet-}$, thereby pulling the reaction of Eq. (7) to the right. This will result in an increase in the rate of formation of quinone, which can serve as a catalyst to increase the rate of autoxidation of hydroquinones. SOD can also increase the rate of hydrogen peroxide production from $Q/SQ^{\bullet-}/H_2Q$ triads in some settings [38]. If superoxide is a chain-carrying radical in an oxidation process, then SOD will slow the rate of oxidation of a hydroquinone.
6. The pK_a's of a hydroquinone can serve as a barometer for the relative electron density in the aromatic moieties of $Q/SQ^{\bullet-}/H_2Q$ triads (electrophilicity). Electron-donating groups on the hydroquinone ring lead to higher pK_a's (lower

electrophilicity), while electron-withdrawing groups lead to lower pK_a's (higher electrophilicity).

7. The pK_a's of a hydroquinone can be used to estimate the reduction potential of the members of a Q/$SQ^{\bullet -}$/H_2Q triad as well as the kinetic rate constants for their reactions.
8. In general, autoxidation of hydroquinones to corresponding quinones results in the stoichiometic production of H_2O_2. The rate of oxidation is pH dependent; the rate increases as the pH increases. By changing the mechanism, catalysts, such as quinone and redox-active metals, can accelerate the oxidation of hydroquinones.
9. The reactions of hydroquinones are the result of formation of ionic species, QH^- and Q^{2-}.
10. Nucleophiles, e.g., amines and thiols, can react with quinones via the Michael reaction (reductive addition) yielding corresponding hydroquinone conjugates.
11. Thiolates, e.g., GS^-, can displace chlorine on quinone rings via nucleophilic substitution.

The biochemistry and toxicology of Q/$SQ^{\bullet -}$/H_2Q triads are modulated by the presence of substituents on the aromatic ring that effectively determine their electrophilic properties. These properties dictate their reactions with both electrophiles and nucleophiles; they govern the kinetics of Eq. (7), both the forward and the reverse reactions.

Abbreviations

AZQ	2,5-diaziridinyl-3,6-bis(carbethoxyamino)-1,4-benzoquinone
B-H_2Q	benzohydroquinone
B-Q	benzoquinone
B-$SQ^{\bullet -}$	benzosemiquinone
BZQ	5-diaziridinyl-3,6-*bis*(2-hydroxyethylamino)-1,4-benzoquinone
Cl_2-H_2Q	2,5-dichlorobenzohydroquinone
Cl_2-Q	2,5-dichlorobenzoquinone
Cl_2-$SQ^{\bullet -}$	2,5-dichlorobenzosemiquinone
D-H_2Q	durohydroquinone
D-Q	duroquinone
D-$SQ^{\bullet -}$	durosemiquinone
DETAPAC	diethylenetriaminepentaacetic acid
E	nonstandard concentrations half-cell reduction potential
***E*°**	standard half-cell reduction potential
***E*°′**	standard half-cell reduction potential at pH 7.0
EDTA	ethylenediaminetetraacetic acid
EPR	electron paramagnetic resonance
F	Faraday constant
G	Gibbs free energy

GSH	glutathione
GS-H_2Q	glutathionylated hydroquinone
$(GS)_2$-H_2Q	diglutathionylated hydroquinone
GS-$SQ^{\bullet-}$	glutathionylated semiquinone
GS-Q	glutathionylated quinone
RNH-H_2Q	amino hydroquinone
H_2Q	a generic hydroquinone
$HO^{\bullet}$	hydroxyl radical
HQ^-	a generic monoanionic hydroquinone
$O_2^{\bullet-}$	superoxide
PCB	polychlorinated biphenyl
Q	a generic quinone
Q_r	reaction quotient or mass action expression
Q^{2-}	a generic dianionic hydroquinone
ROS	reactive oxygen species
SHE	standard hydrogen electrode
SOD	superoxide dismutase
$SQ^{\bullet-}$	a generic semiquinone
$SQH^{\bullet}$	a generic protonated semiquinone radical.

Acknowledgments

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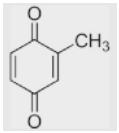
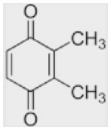
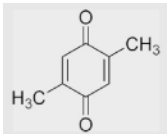
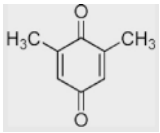
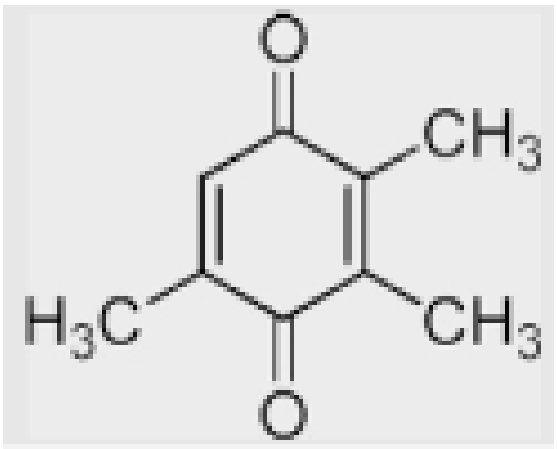
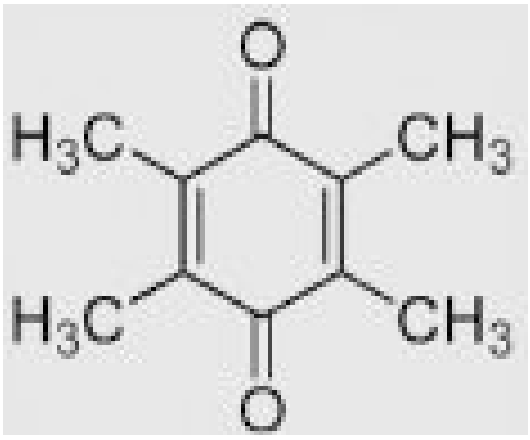
Appendix

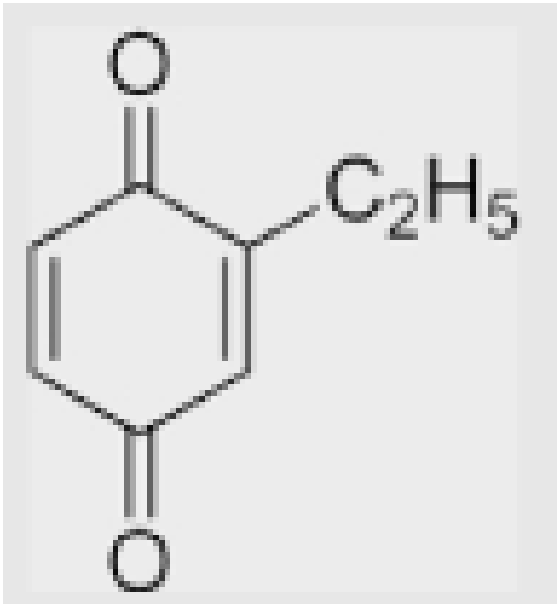
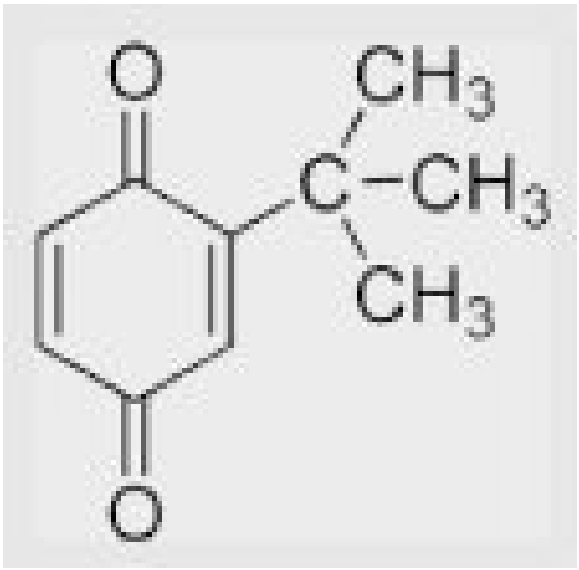
Table A1 has collected information on the reduction potentials for members of $Q/SQ^{\bullet-}/H_2Q$ triads at pH 7. Table A2 presents kinetic information on Eq. (7), the formation of superoxide by various semiquinones. We have worked to minimize errors; we hope none remain

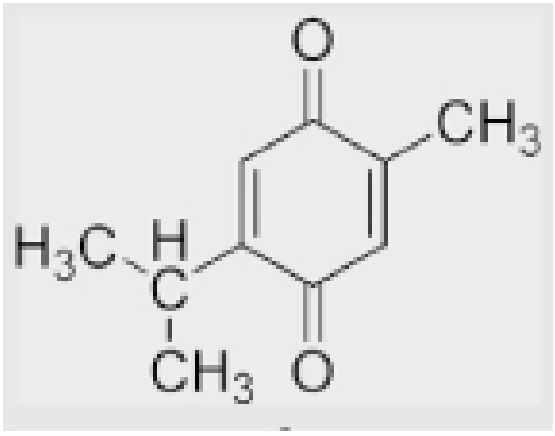
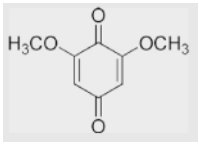
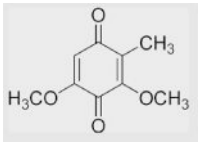
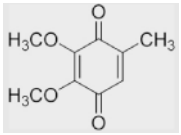
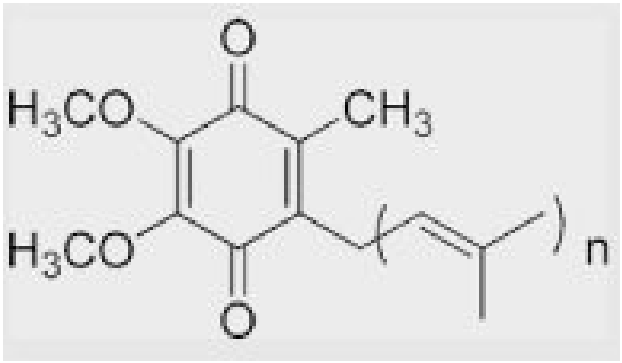
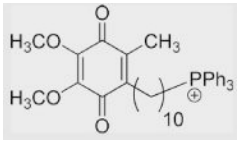
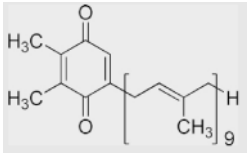
Table A1

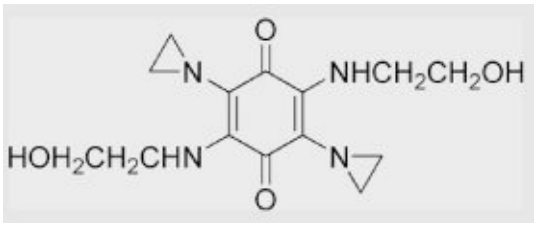
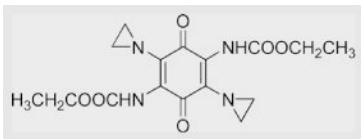
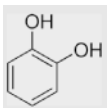
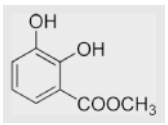
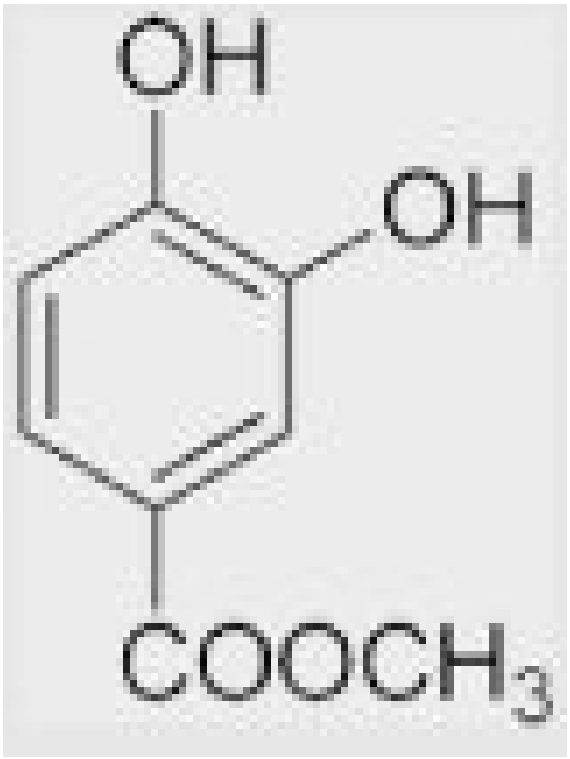
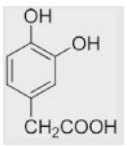
Reduction potentials ($Q/SQ^{\bullet-}$; $SQ^{\bullet-},2H^+/H_2Q$; $Q,2H^+/H_2Q$) for $Q/SQ^{\bullet-}/H_2Q$ triads at pH 7[a,b]

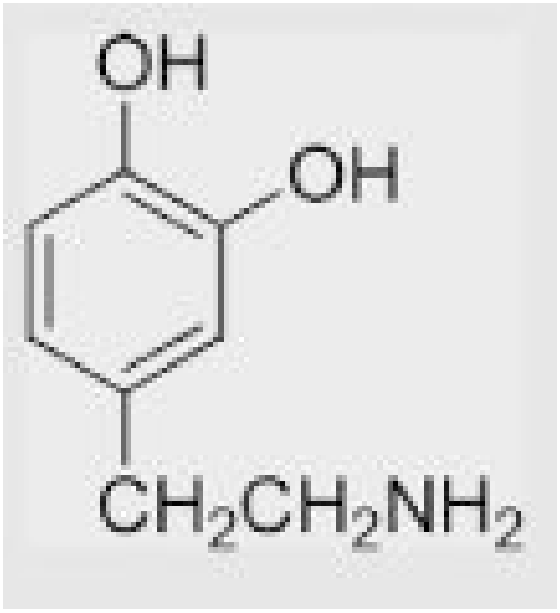
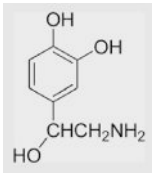
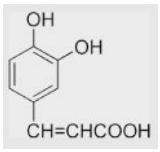
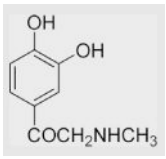
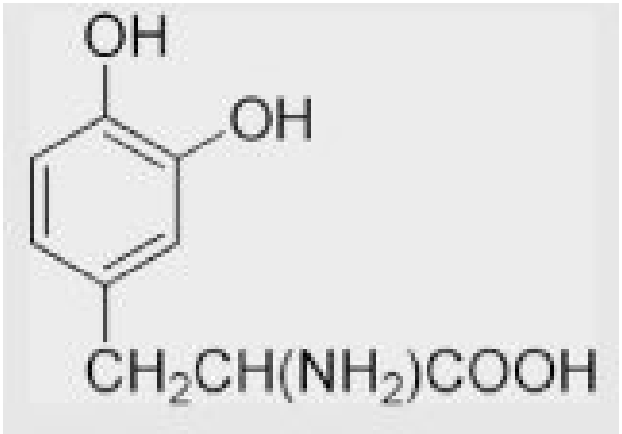
No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H2Q$) /mV	$E^{o\prime}$ ($Q/H2Q$) /mV	R
1	Benzoquinone					
1.1	1,4-Benzoquinone		78 99	448 459 473 23 57 1041	286	[7 [1 [8 [3 [3 [8

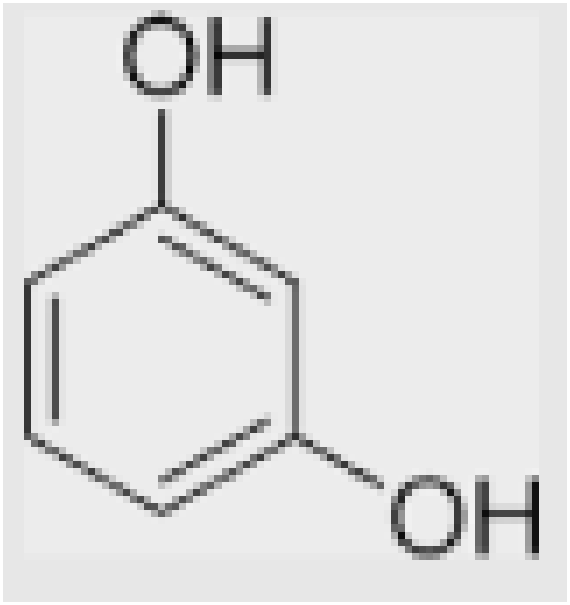
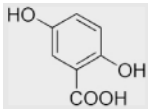
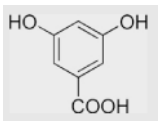
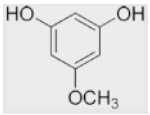
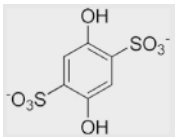
No.	Compounds	Structure	$E^{o\prime}$ (Q/SQ$^{\bullet-}$) /mV	$E^{o\prime}$ (SQ$^{\bullet-}$/H2Q) /mV	$E^{o\prime}$ (Q/H2Q) /mV	R
1.2	Methyl-1,4-benzoquinone		23 23	460 437 414	230	[8 [7 [7
1.3	2,3-Dimethyl-1,4-benzoquinone		−74	430 424	175	[8 [7
1.4	2,5-Dimethyl-1,4-benzoquinone		−66	420 426	176 180	[8 [1 [7
1.5	2,6-Dimethyl-1,4-benzoquinone		−80 −80	363	142	[7 [7
1.6	2,3,5-Trimethyl-1,4-benzoquinone		−165	385 393	114	[8 [7
1.7	2,3,5,6-Tetramethyl-1, 4-benzoquinone (Duroquinone)		−264 −240	350 354 −54±5	68	[2 [7 [3

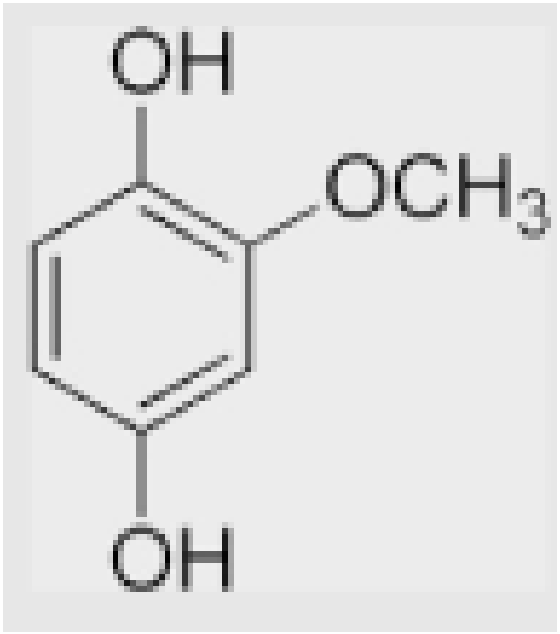
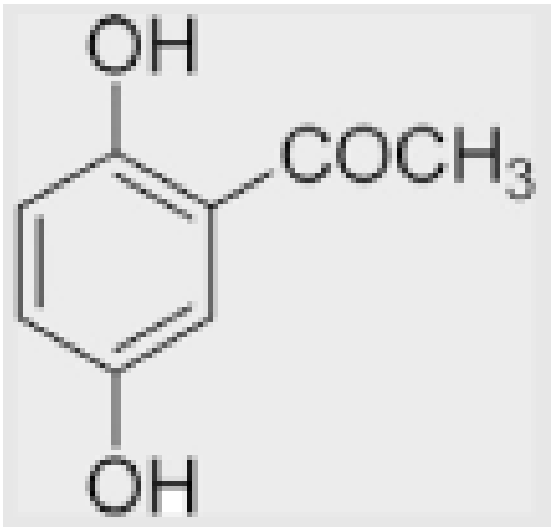
No.	Compounds	Structure	$E^{o\prime}$ (Q/SQ$^{\bullet-}$) /mV	$E^{o\prime}$ (SQ$^{\bullet-}$/H2Q) /mV	$E^{o\prime}$ (Q/H2Q) /mV	R
1.8	Ethyl-1,4-benzoquinone		0	395	−395	[4
1.9	*t*-Butyl-1,4-benzoquinone		219±14 −25±6 −23±6 −32	1061±14 489±6 −75±15 453		[5 [5 [5 [7

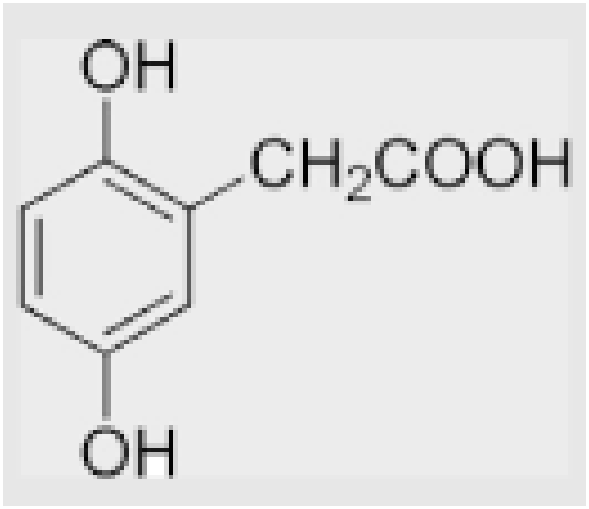
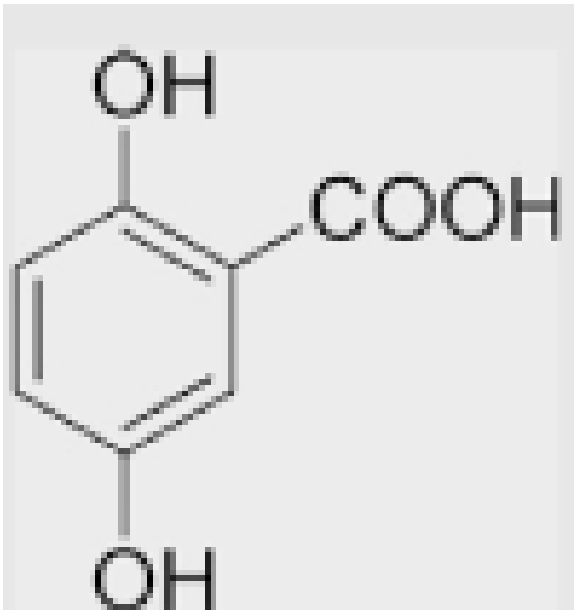
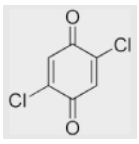
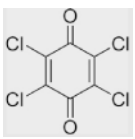
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
1.10	2-Methyl-5-*iso*-propyl-1, 4-benzoquinone		−70	358	−428	[4
1.11	2,6-Methoxyl-1,4-benzoquinone		−150	187	−337	[7
1.12	2,6-Methoxyl-3-methyl-1, 4-benzoquinone		−110	~290	~399	[7
1.13	2,3-Methoxyl-5-methyl-1, 4-benzoquinone (Ubiquinone-0)		−130			[9
1.14	Coenzyme Q (Ubiquinone)		−230	≈ 190	70	[1
1.15	Mitoquinone		−105			[9
1.16	Plastoquinone		−165	55	110	[7

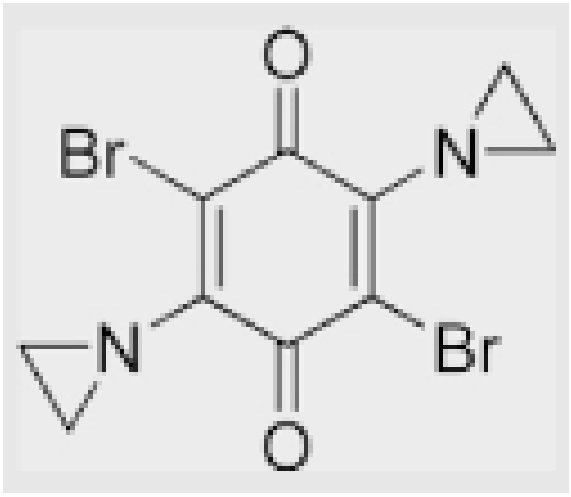
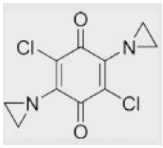
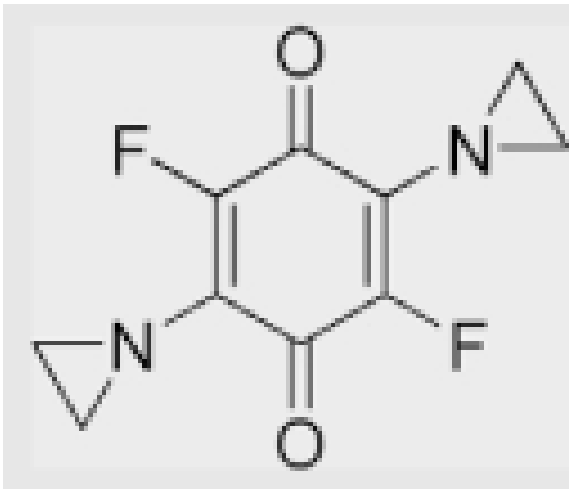
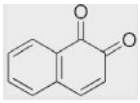
No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H_2Q$) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
1.17	2,5-Diaziridinyl-3,6-bis (2-hydroxyethylamino)-1, 4-benzoquinone (BZQ)		−383±10			[9
1.18	2,5-Diaziridinyl-3,6-bis (carbethoxyamino)-1, 4-benzoquinone (AZQ)		−228±10 −168			[9 [9
2	1,2-Dihydroxybenzene					
2.1	1,2-Dihydroxybenzene (catechol)		210	530 43±5 139±20 98 850 1060	370	[3 [3 [3 [9 [3 [3
2.2	2,3-Dihydroxybenzoate			118±5		[3
2.3	3,4-Dihydroxybenzoate			119±5		[3
2.4	3,4-Dihydroxyphenylacetate			21		[9

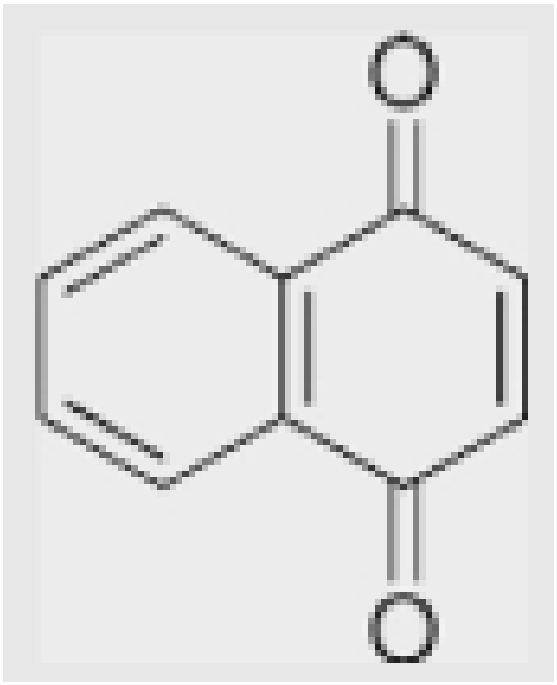
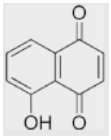
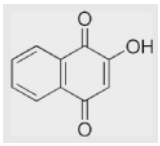
No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H_2Q$) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
2.5	3-Hydroxytyramine			18		[3
2.6	DL-Norepinephrine			44		[3
2.7	3,4-Dihydroxycinnamate			84 540 880 1090		[3 [5 [5 [5
2.8	Adrenalone			~180		[5
2.9	DL-β-3,4-Dihydroxyphenylalanine (DL-DOPA)			14		[5

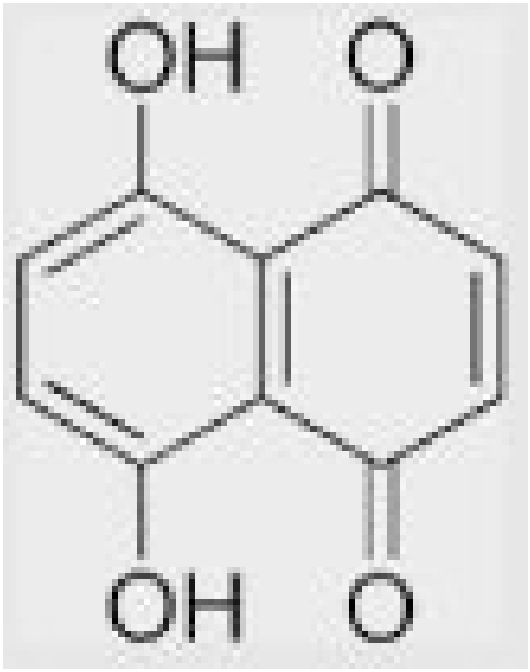
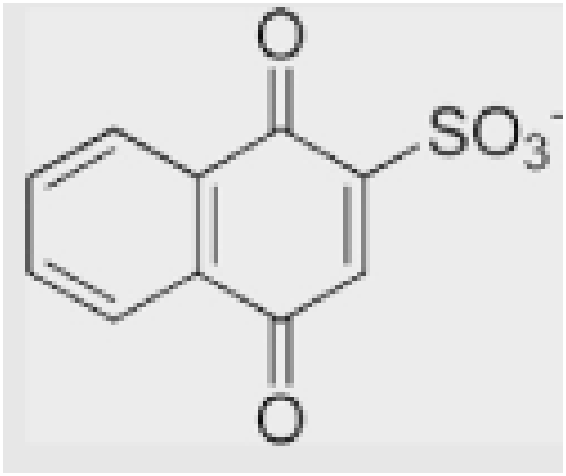
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
3	1,3-Dihydroxybenzene					
3.1	1,3-Dihydroxybenzene (Resorcinol)			385 810 300±8 304±5 310 720 1130		[9 [9 [3 [3 [3 [3
3.2	2,5-Dihydroxybenzoic acid			33		[9
3.3	3,5-Dihydroxybenzoic acid			280		[9
3.4	3,5-Dihydroxyanisole			840 530 850 1060		[9 [9 [9
4	1,4-Dihydroxybenzene					
4.1	1,4-Dihydroxybenzene-2, 5-disulfonate ion			116		[1

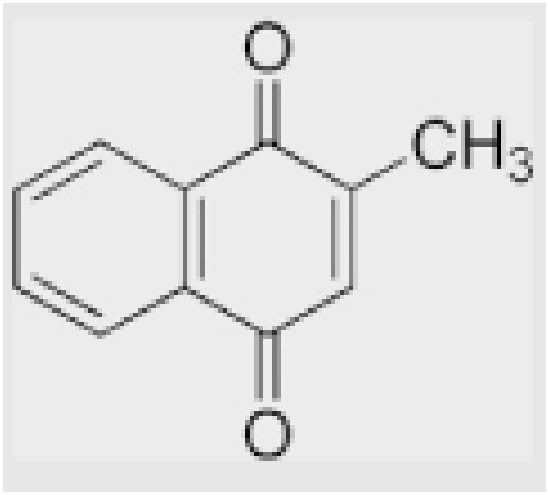
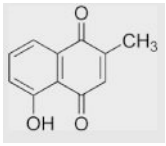
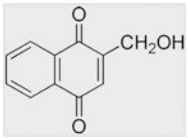
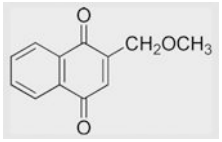
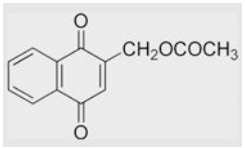
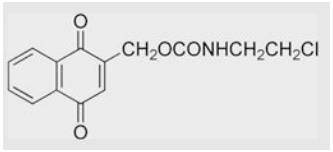
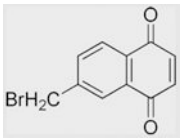
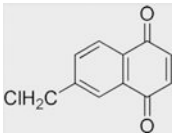
No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H_2Q$) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
4.2	Methoxyhydroquinone			−85		[5
4.3	2,5-Dihydroxyacetophenone			118±10		[3

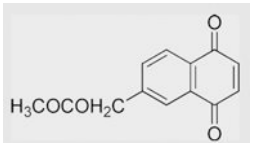
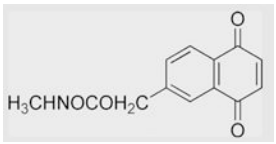
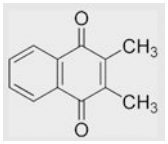
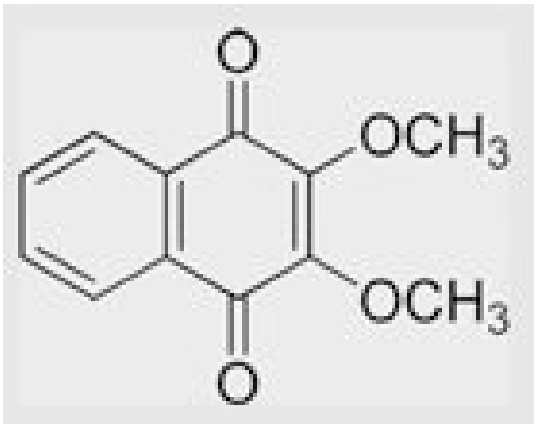
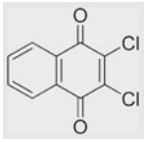
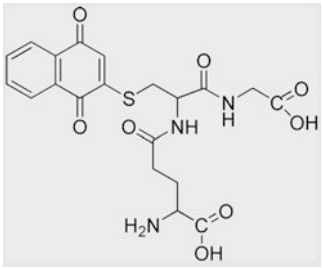
No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H_2Q$) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
4.4	2,5-Dihydroxyphenylacetate (Homogentisic acid)			−50		[5
4.5	2,5-Dihydroxybenzoate			33±10		[3
5	Halogenated quinones					
5.1	2,5-Dichloro-1, 4-benzoquinone		470	617	544	[7
5.2	2,3,5,6-Tetrachloro-1, 4-benzoquinone		650	>650		[7

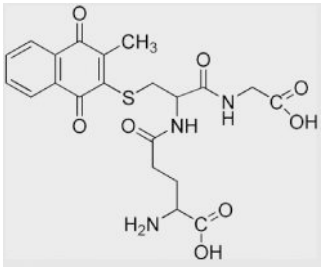
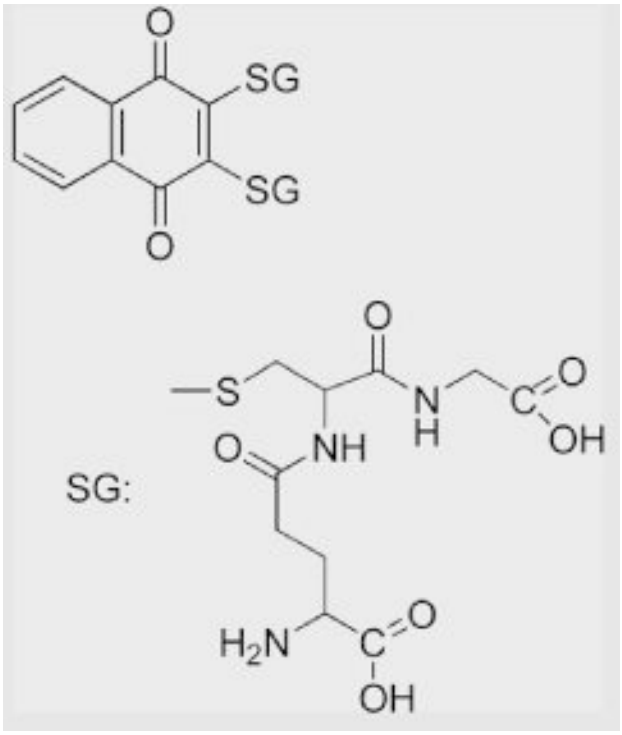
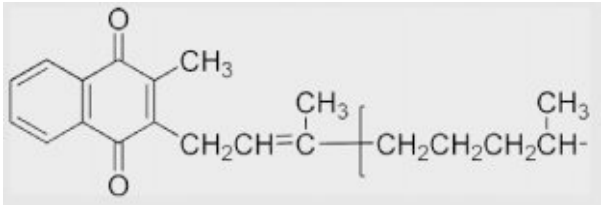
No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H_2Q$) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
5.3	2,5-Diaziridinyl-3,6-bromo-1, 4-benzoquinone		32±9			[8
5.4	2,5-Diaziridinyl-3,6-chloro-1, 4-benzoquinone		51±11			[8
5.5	2,5-Diaziridinyl-3,6-iodo-1, 4-benzoquinone		90±15			[8
6	Naphthoquinones					
6.1	1,2-Naphthoquinone		68 −89			[1 [8

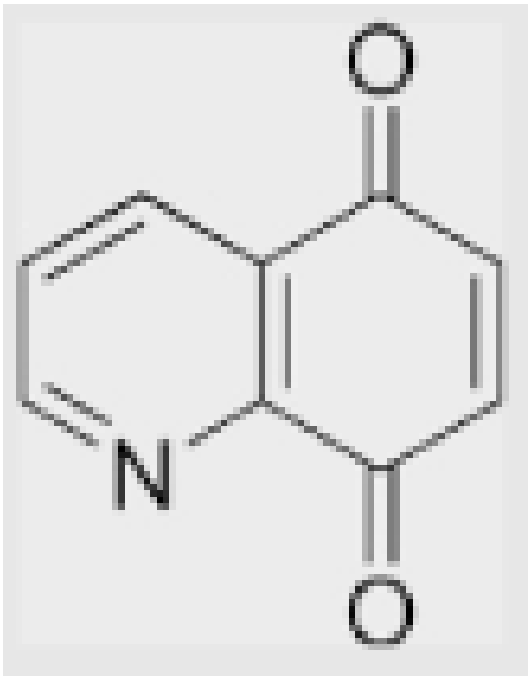
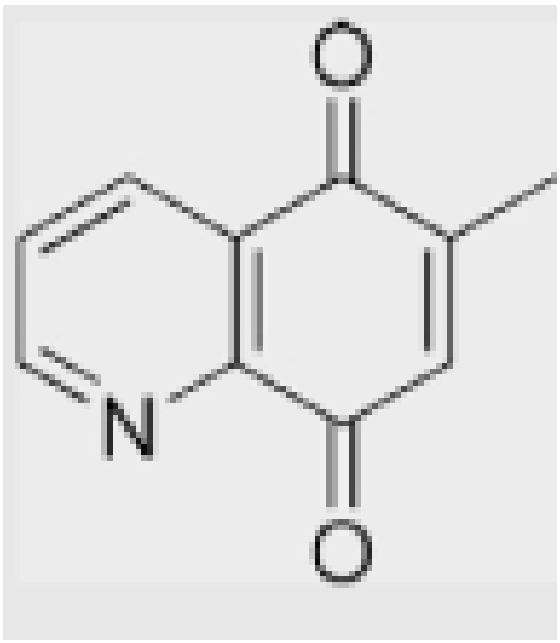
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
6.2	1,4-Naphthoquinone		50 −140			[1 [8
6.3	5-Hydroxy-1, 4-naphthoquinone (juglone)		−93 −95			[1 [1
6.4	2-Hydroxy-1, 4-naphthoquinone (lawsone)		−139 −415			[1 [1

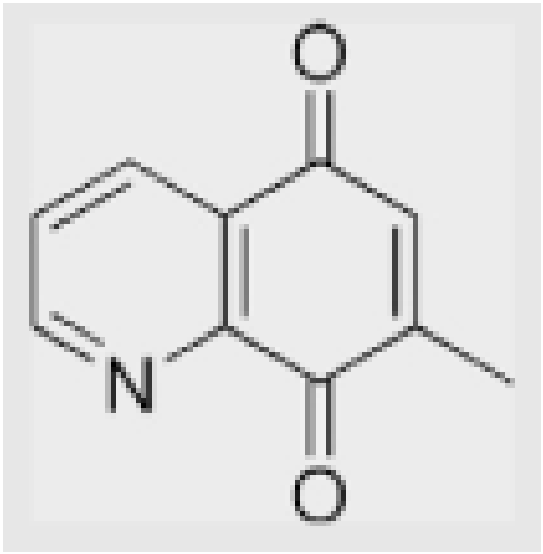
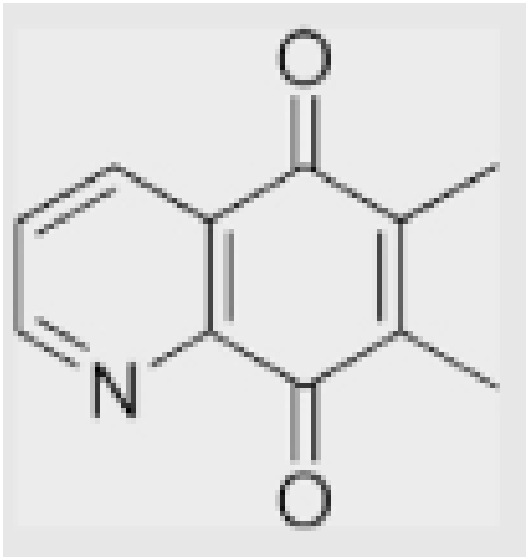
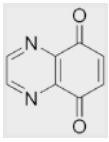
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
6.5	5,8-Dihydroxy-1,4-naphthoquinone		−110			[1
6.6	1,4-Naphthoquinone-2-sulfonate ion		−60	300	120	[7

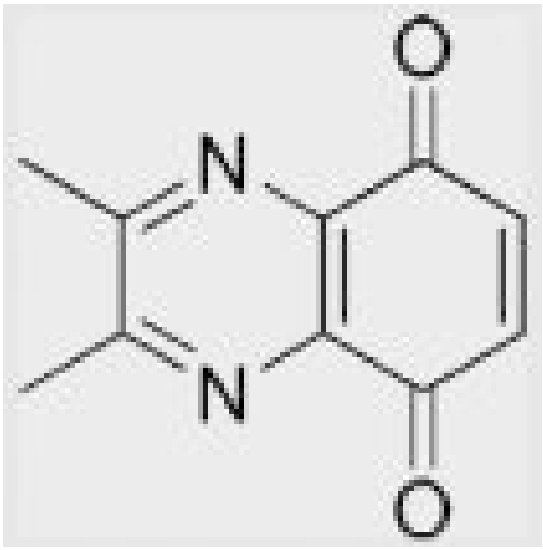
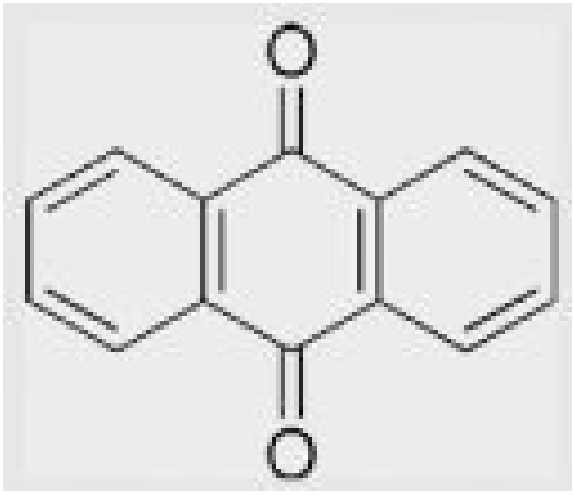
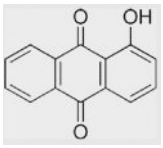
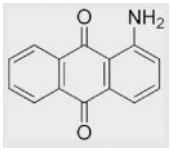
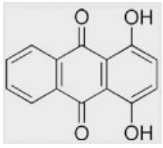
No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H_2Q$) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
6.7	2-Methyl-1,4-naphthoquinone (Menadione)		−203 −335	193	−5	[7 [1
6.8	5-Hydroxy-2-methyl-1, 4-naphthoquinone (Plumbagin)		−156			[1
6.9	2-Hydroxymethyl-1,4-naphthoquinone		−152			[1
6.10	2-(Methoxymethyl)-1,4-naphthoquinone		−129			[1
6.11	2-[(Acetyloxy)methyl]-1, 4-naphthoquinone		−106			[1
6.12	2-[[[(2-Chloroethyl)amino] carbonyl]oxy]methyl-1, 4-naphthoquinone		−122			[1
6.13	6-(Bromomethyl)-1,4-naphthoquinone		−92			[1
6.14	6-(Chloromethyl)-1,4-naphthoquinone		−94			[1

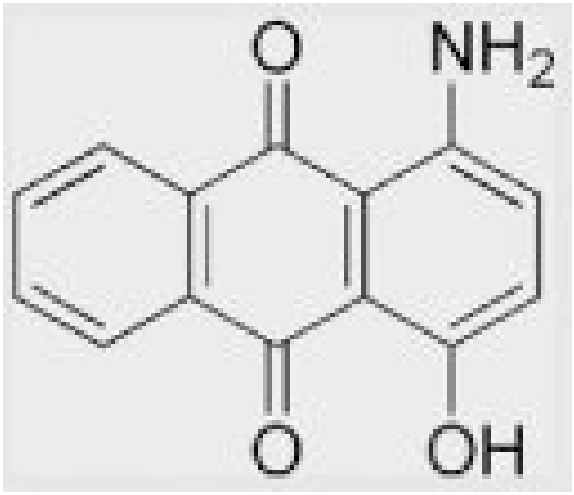
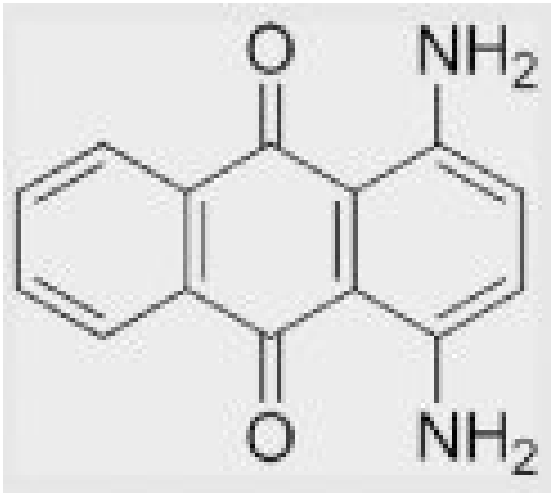
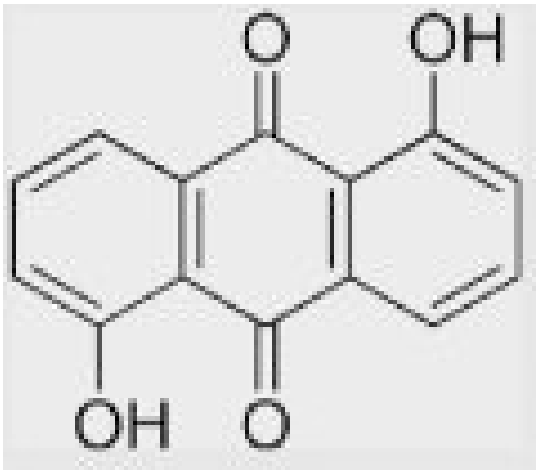
No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H_2Q$) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
6.15	6-[(Acetyloxy)methyl]-1, 4-naphthoquinone		−94			[1
6.16	6-[[(Methylamino)carbonyl] oxy]methyl-1,4-naphthoquinone		−99			[1
6.17	2,3-Dimethyl-1,4-naphthoquinone		−240			[8
6.18	2,3-Dimethoxy-1,4-naphthoquinone (DMNQ)		−240 −183			[1 [1
6.19	2,3-Dichloro-1,4-naphthoquinone		−36			[1
6.20	3-Glutathionyl-l,4-naphthoquinone		−132			[1

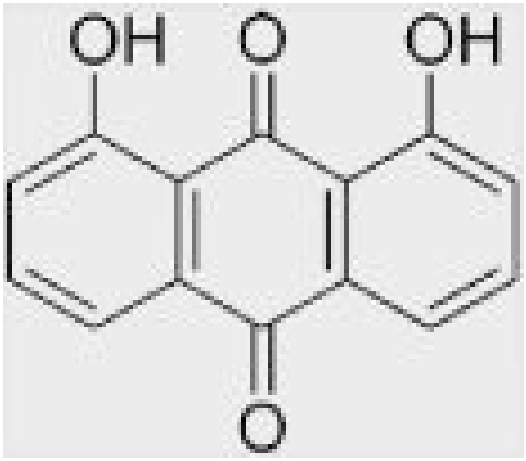
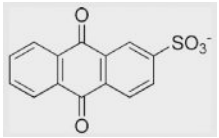
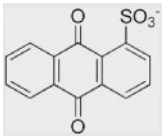
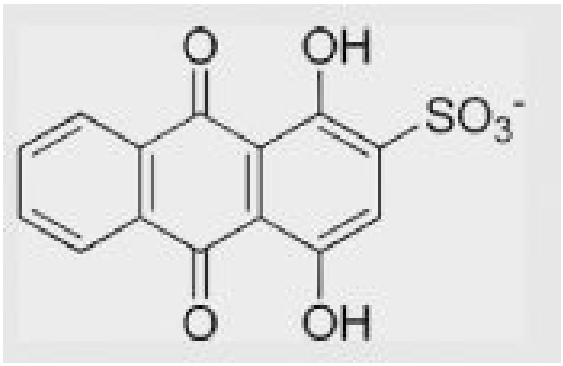
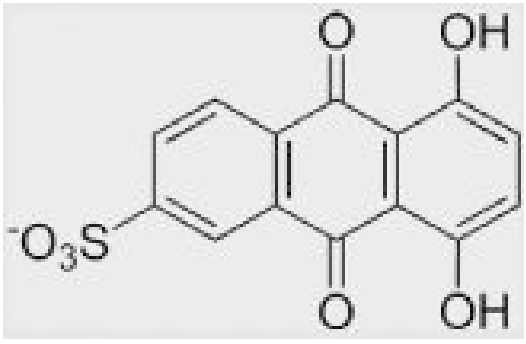
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
6.21	3-Glutathionyl-2-methyl-1, 4-naphthoquinone		−192 −195			[1 [1
6.22	2,3-Diglutathionyl-1,4-naphthoquinone		−150			[1
6.23	2-Methyl-3-phytyl-1,4-naphthoquinone		−170	220	−60	[7

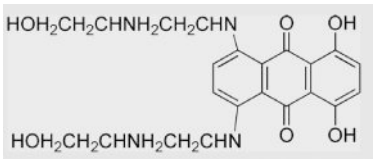
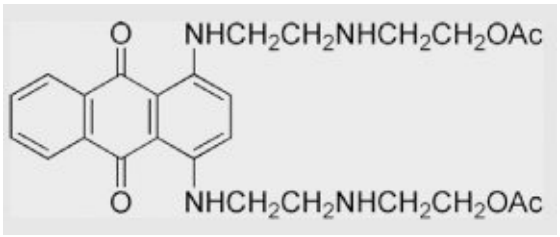
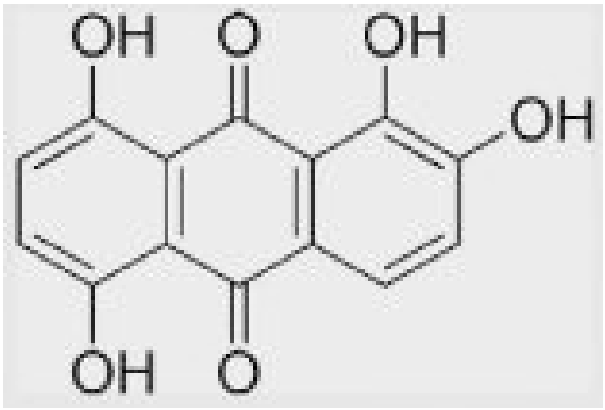
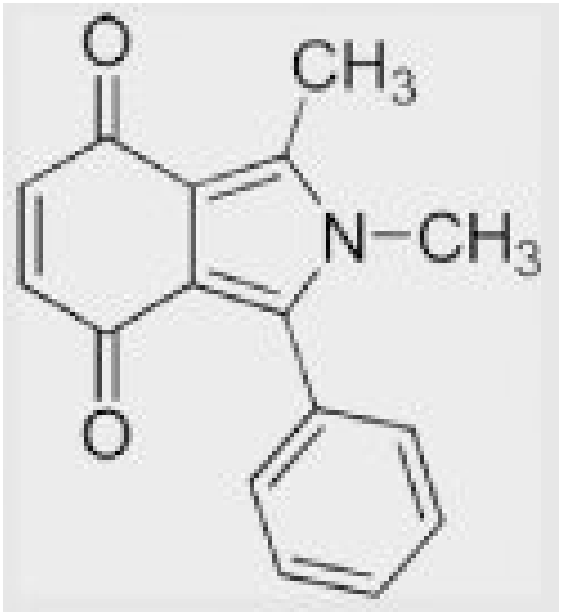
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
6.24	Quinoline-5,8-dione				−218	[1
6.25	6-Methylquinoline-5,8-dione				−279	[1

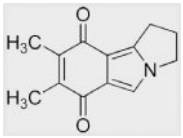
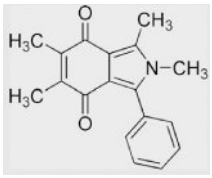
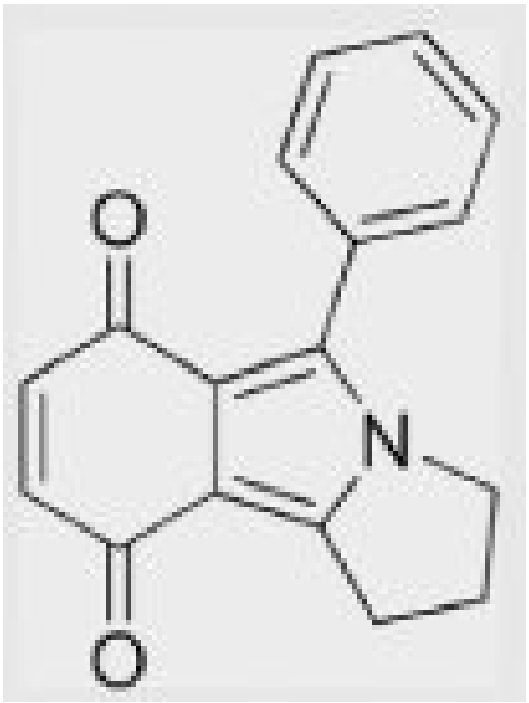
No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H_2Q$) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
6.26	7-Methylquinoline-5,8-dione				−282	[1
6.27	6,7-Dimethylquinoline-5,8-dione				−317	[1
6.28	Quinoxaline-5,8-dione				−163	[1

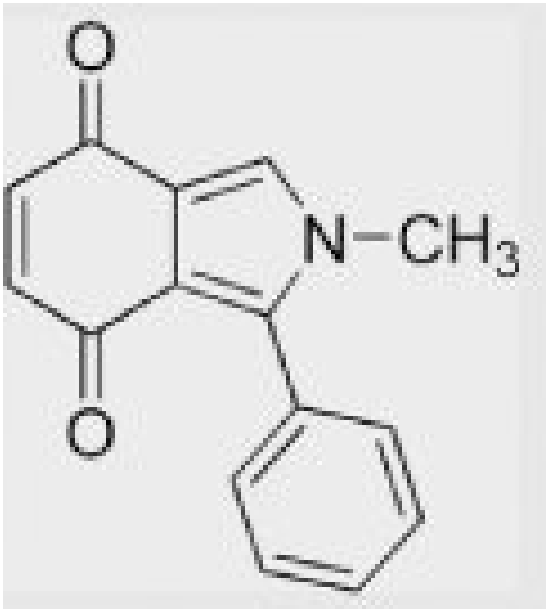
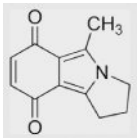
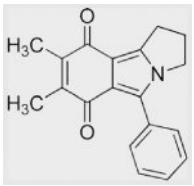
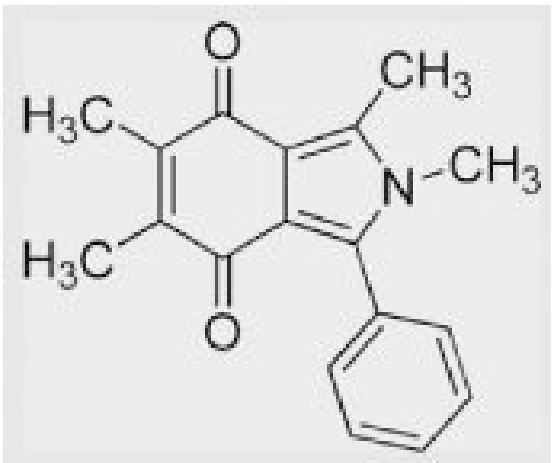
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
6.29	2,3-Dimethylquinoxaline-5,8-dione				−211	[1
7	Anthraquinones					
7.1	9,10-Anthraquinone		−445 −445			[1 [1
7.2	1-Hydroxyl-9,10-anthraquinone		−385 −415			[1 [1
7.3	1-Amino-9,10-anthraquinone		−435 −480			[1 [1
7.4	1,4-Dihydroxy-9,10-anthraquinone		−249 −304			[1 [1

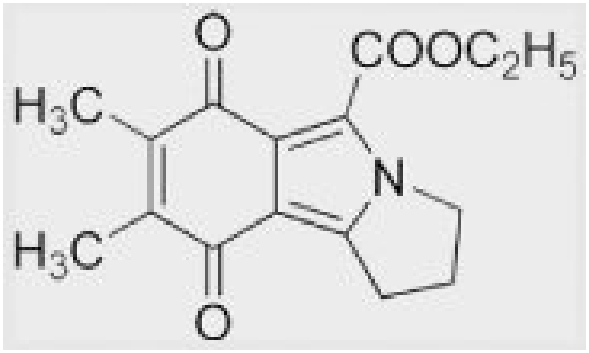
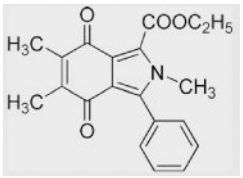
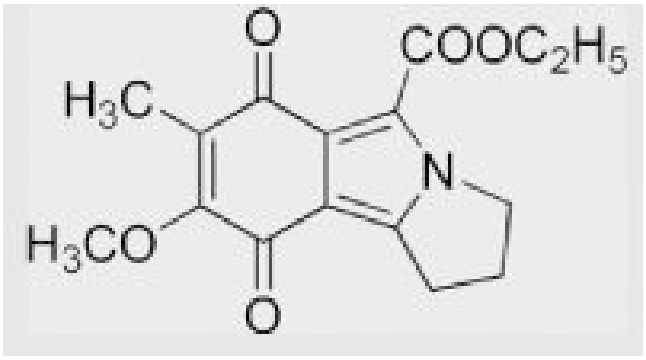
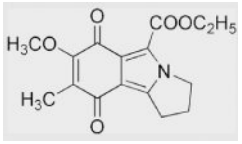
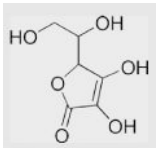
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
7.5	1-Amino-4-hydroxy-9,10-anthraquinone		−408 −414			[1 [1
7.6	1,4-Diamino-9,10-anthraquinone		−410 −424			[1 [1
7.7	1,5-Dihydroxy-9,10-anthraquinone		−306 −340			[1 [1

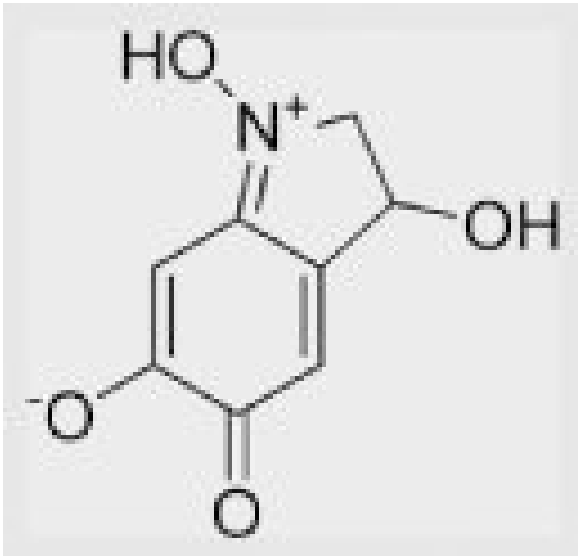
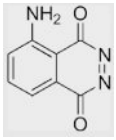
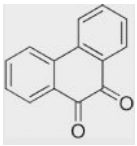
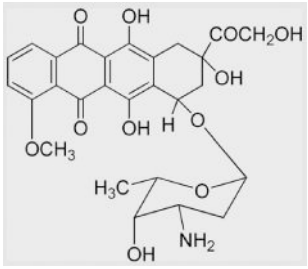
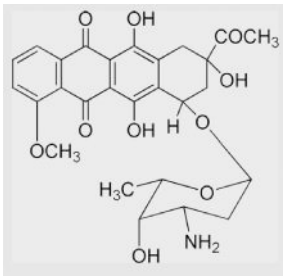
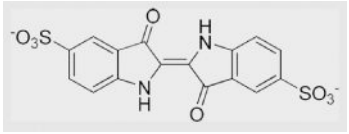
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
7.8	1,8-Dihydroxy-9,10-anthraquinone		−325 −405			[1 [1
7.9	9,10-Anthraquinone-2-sulfonate ion		−266 −390 −380	−76	−228	[1 [1 [7
7.10	Anthraquinone-1-sulfonate ion		−218			[1
7.11	1,4-Dihydroxy-9,10-anthraquinone-2-sulfonate ion		−270			[1
7.12	1,4-Dihydroxy-9,10-anthraquinone-6-sulfonate ion		−249			[1

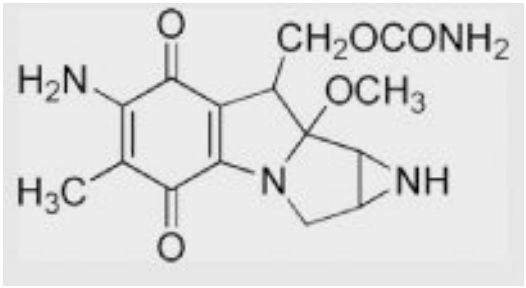
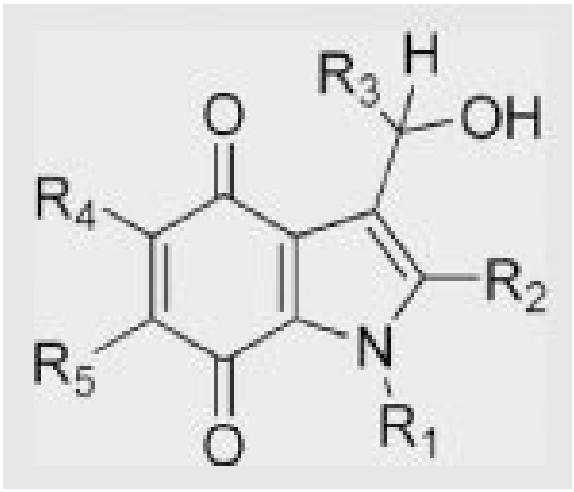
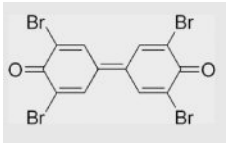
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
7.13	1,4-Dihydroxy-5,8-bis [(2-hydroxyethylamino) ethyl]amino-9,10-anthraquinone		−527			[1
7.14	1,4-bis[(2-hydroxyethylamino) ethyl]amino-9,10-anthraquinone diacetate		−348			[9
7.15	1,2,5,8-tetrahydroxyanthracene-9, 10-dione (quinalizarin)			73		[9
8	Isoindole-4,7-diones					
8.1	1,2-Dimethyl-3-phenylisoindole-4,7-dione		−440			[1

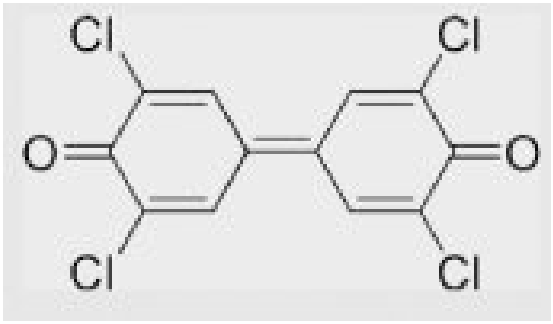
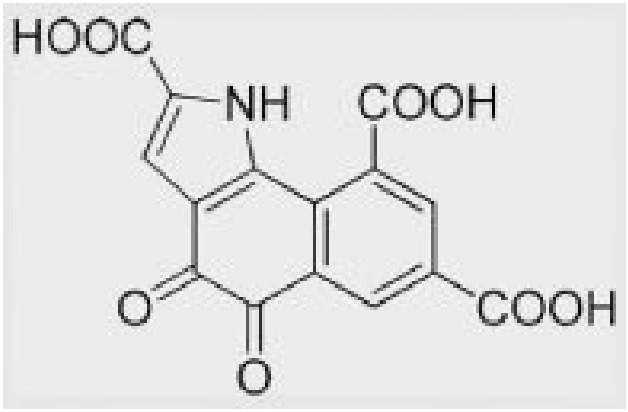
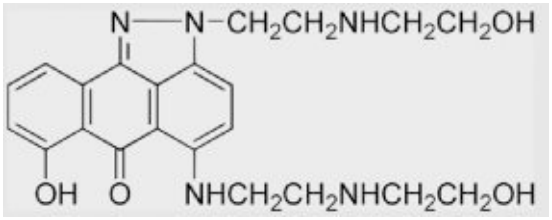
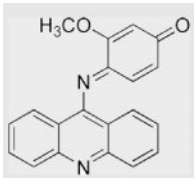
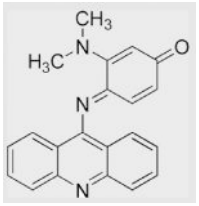
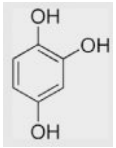
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
8.2	5-Methyl-1, 2-trimethyleneisoindole-4,7-dione		−420			[1
8.3	1,2,5-Trimethyl-3-phenylisoindole-4, 7-dione		−423			[1
8.4	1-Phenyl-2, 3-trimethyleneisoindole-4,7-dione		−427			[1

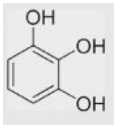
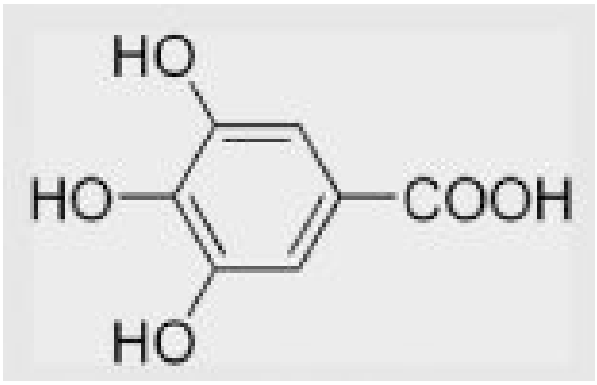
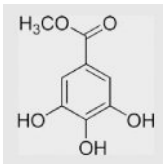
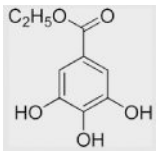
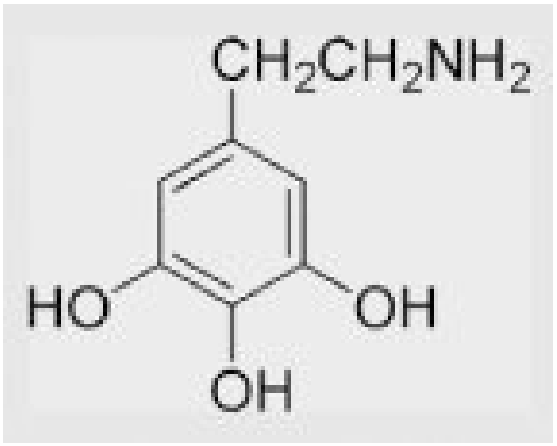
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
8.5	2-Methyl-3-phenylisoindole-4, 7-dione		−419			[1
8.6	1-Methyl-2, 3-trimethyleneisoindole-4,7-dione		−438			[1
8.7	5,6-Dimethyl-3-phenyl-1, 2-trimethyleneisoindole-4,7-dione		−435			[1
8.8	1,2,5,6-Tetramethyl-3-phenylisoindole-4,7-dione		−452			[1

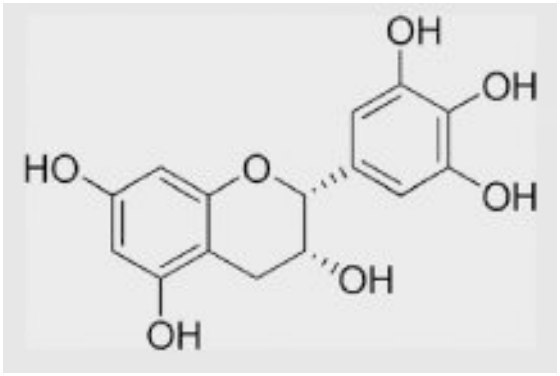
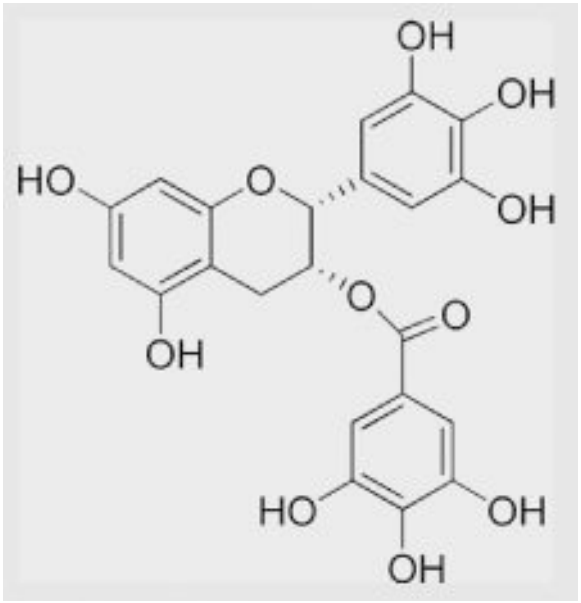
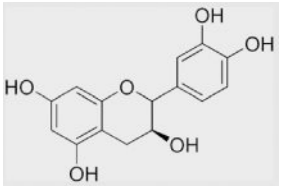
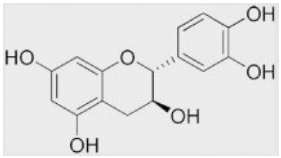
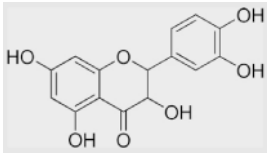
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
8.9	1-Ethoxycarbonyl-5-methyl-2, 3-trimethyleneisoindole-4,7-dione		−368			[1
8.10	1-Ethoxycarbonyl-2,5-dimethyl-3-phenylisoindole-4,7-dione		−366			[1
8.11	1-Ethoxycarbonyl-6-methoxy-5-methyl-2, 3-trimethyleneisoindole-4,7-dione		−383			[1
8.12	1-Ethoxycarbonyl-5-methoxy-6-methyl-2, 3-trimethyleneisoindole-4, 7-dione		−378			[1
9	Miscellaneous					
9.1	Ascorbic acid		−175 ≈ −180	282 ≈ 300	54 ≈ 60	[5

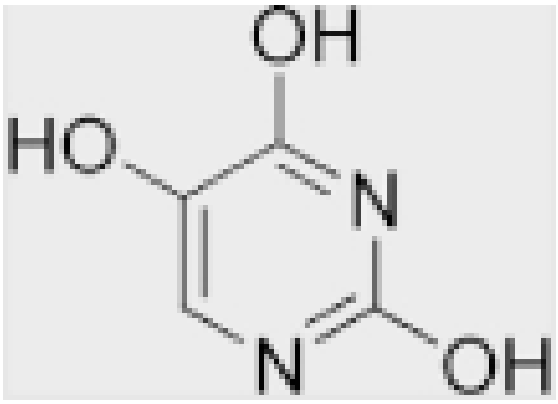
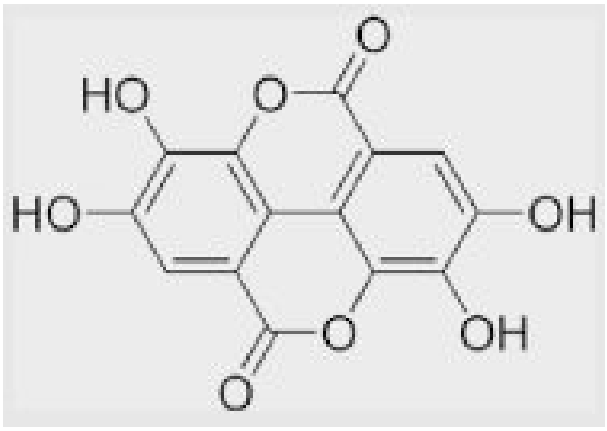
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
9.2	Adrenochrome		−253			[9
9.3	5-Aminophthalazine-1,4-dione		240			[1
9.4	9,10-Phenanthrenequinone		−124			[1
9.5	Adriamycin		−292 −328 −341			[9 [1 [1
9.6	Daunomycin		−305 −341			[9 [1
9.7	Indigodisulfonate ion		−247			[1

No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
9.8	Mitomycin C		−310	55	−368	[1
9.9	Indolequinones					[1
		R_1 = CH_3, R_2 = R_3 = R_5 = H, R4 = OCH_3	−332±9			
		R_1 = R_2 = CH_3, R_3 = R_5 = H, R4 = OCH_3	−376±9			
		R_1 = R_2 = R_5 = CH_3, R_3 = H, R4 = OCH_3	−317±8			
		R_1 = R_2 = CH_3, R_3 = R_5 = H, R4 = Morpholino	−365±8			
		R_1 = CH_3, R_2 = Ph, R_3 = R_5 = H, R4 = OCH_3	−315±8			
		R_1 = c-Pr, R_2 = CH_3, R_3 = R_5 = H, R4 = OCH_3	−336±5			
		R_1 = CH_2Ph, R_2 = C_2H_5, R_3 = R_5 = H, R4 = OCH_3	−326±3			
		R_1 = Ph, R_2 = CH_3, R_3 = R_5 = H, R4 = OCH_3	−336±5			
		R_1 = Ph, R_2 = R_5 = CH_3, R_3 = H, R4 = OCH_3	−346±5			
		R_1 = p-F-C6H4, R_2 = CH_3, R_3 = R_5 = H, R4 = OCH_3	−310±4			
		R_1 = n-Pr, R_2 = CH_3, R_3 = R_5 = H, R4 = OCH_3	−318±4			
		R_1 = n-Pr, R_2 = R_5 = CH_3, R_3 = H, R4 = OCH_3	−324±4			
		R_1 = R_2 = R_3 = CH_3, R_5 = H, R4 = OCH_3	−302±9			
		R_1 = R_2 = R_3 = CH_3, R_5 = H, R4 = 4-Methylpiperazin-1-yl	−285±5			
		R_1 = R_2 = CH_3, R_3 = Ph, R_5 = H, R4 = OCH_3	−332±9			
		R_1 = R_2 = CH_3, R_3 = Thienyl, R_5 = H, R4 = OCH_3	−376±9			
		R_1, R_2 = −$(CH_2)_3$−, R_3 = R_5 = H, R4 = OCH_3	−317±8			
9.10	3,3′,5,5′-Tetrabromodiphenoquinone		260			[1

No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H_2Q$) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
9.11	3,3′,5,5′-Tetrachlorodiphenoquinone		260			[1
9.12	Methoxatine		−114			[1
9.13	7-Hydroxy-2-[2-(2-hydroxyethyl) aminoethyl]-5-[[2-(2-hydroxyethyl) aminoethyl]amino}-anthra[1,9-cd] pyrazol-6-one		−538			[1
9.14	N1-(Acridinyl)-N4-methylsulfonyl-2-methoxycyclohexa-2,5-diene-1′, 4′-diimine		85			[1
9.15	N1-(Acridinyl)-N4-methylsulfonyl-2-dimethylaminocyclohexa-2, 5-diene-1′,4′-diimine		−10			[1
9.16	1,2,4-Trihydroxybenzene			−110±20		[3

No.	Compounds	Structure	$E^{o\prime}$ ($Q/SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}/H_2Q$) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
9.17	1,2,3-Trihydroxybenzene (Pyrogallol)(Pyrogallol)			−9±5		[3
9.18	Gallic acid			450 780 980		[9
9.19	Methyl gallate			560 910 1120		[9 9 9
9.20	Ethyl gallate			−54		[9
9.21	5-Hydroxydopamine			42		[9

No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
9.22	Epigallo-o gallate			420 730 930		[9
9.23	Epigallocatechin gallate			430		[1
9.24	Epicatechin			420 48		[1 [9
9.25	(+)-Catechin			570 910 1120 79		[9 [9 [9 [9
9.26	Quercetin			330 −37		[9 [9

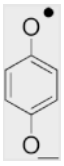
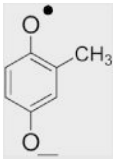
No.	Compounds	Structure	$E^{o\prime}$ (Q/$SQ^{\bullet-}$) /mV	$E^{o\prime}$ ($SQ^{\bullet-}$/H_2Q) /mV	$E^{o\prime}$ (Q/H_2Q) /mV	R
9.27	2,4,5-trihydroxypyrimidine			132		[9
9.28	Ellagic acid			187		[9

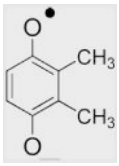
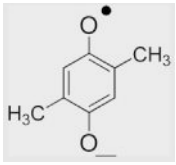
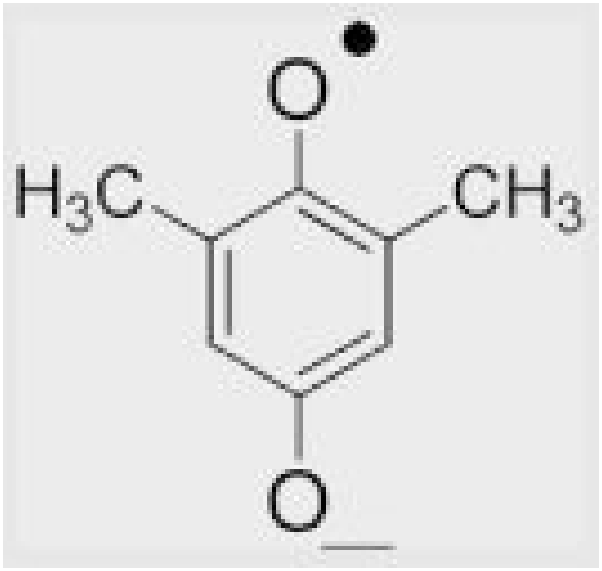
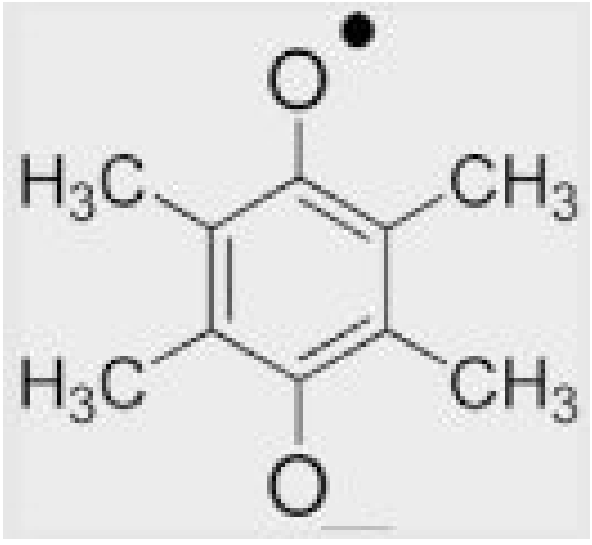
[a] Reduction potentials are at pH 7.0 unless indicated otherwise.

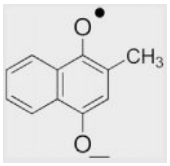
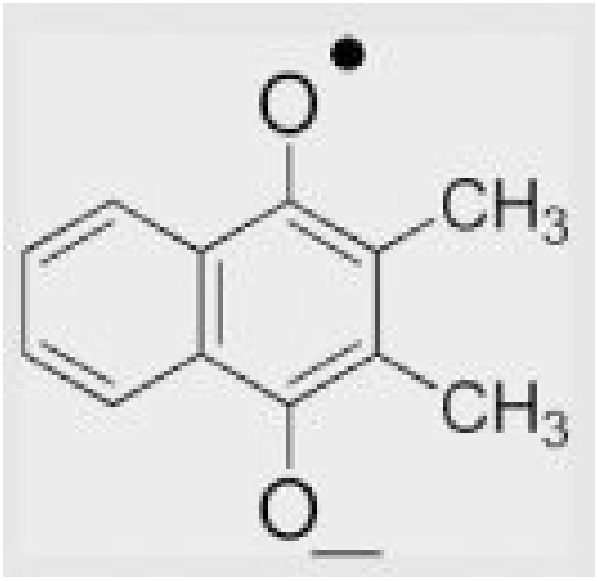
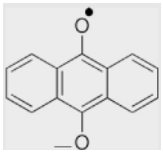
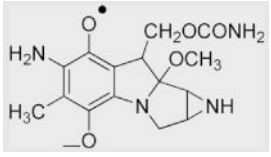
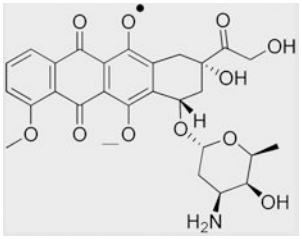
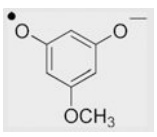
[b] We quote $E^{o\prime}$. Many references above provide midpoint potentials. These are nearly the same, typically within 1 mV [40].

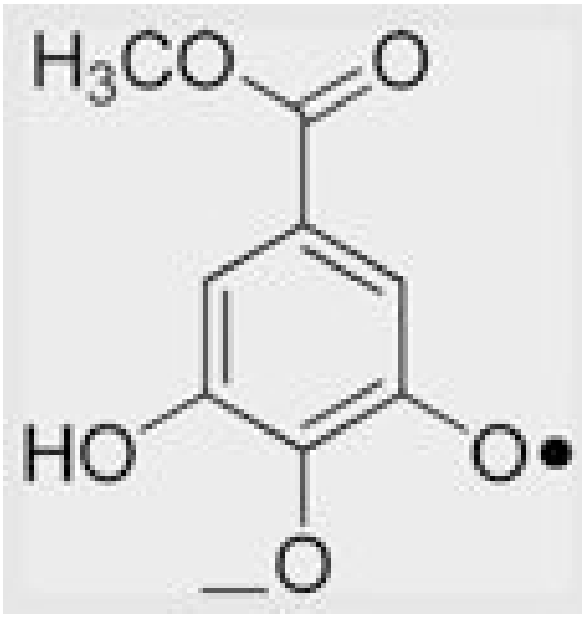
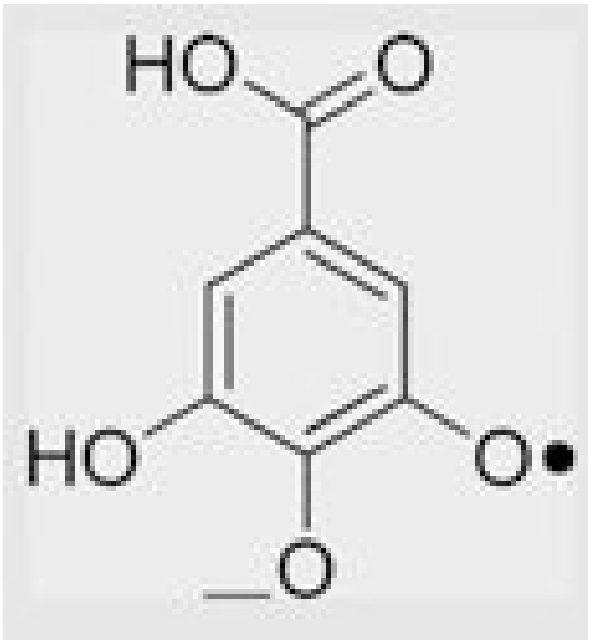
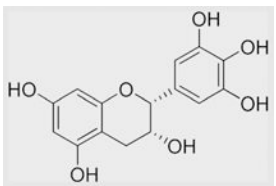
Table A2

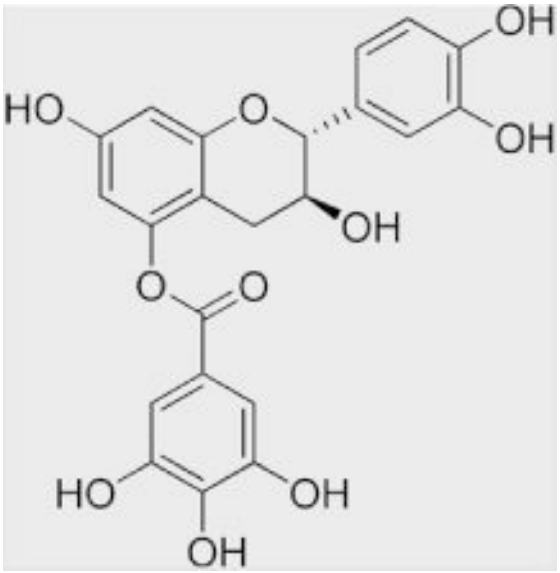
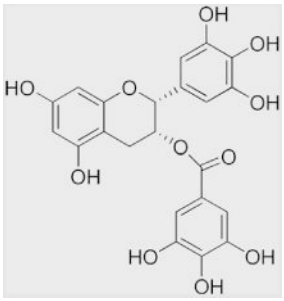
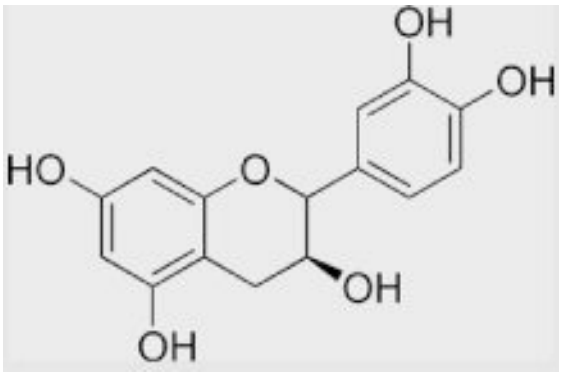
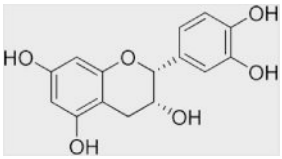
Reaction rate constants for $SQ^{\bullet-}$ with dioxygen to form superoxide

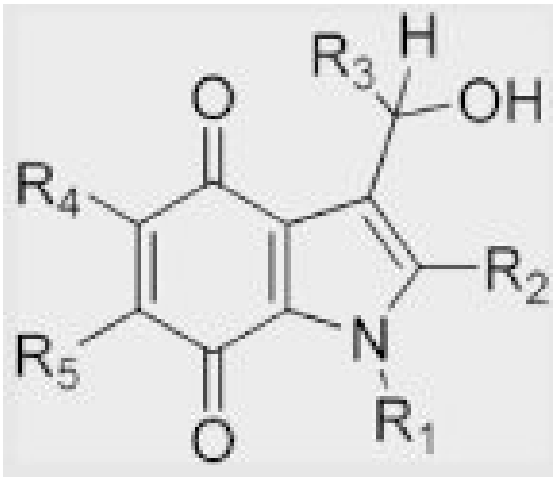
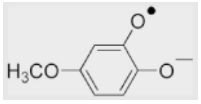
No.	Q or H_2Q	$SQ^{\bullet-}$ (or parent Q or H_2Q)	$k_{forward}$ (M^{-1} s^{-1}) Eq. (7)	$k_{reverse}$ (Eq. (7)
1	1,4-Benzoquinone		5×10^4	1×10^9
2	Methyl-1,4-benzoquinone		1.1×10^6	7.6×10^8

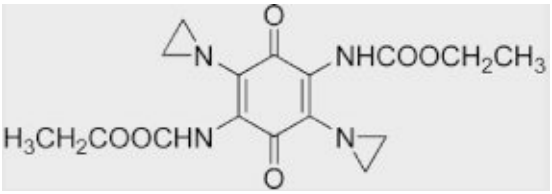
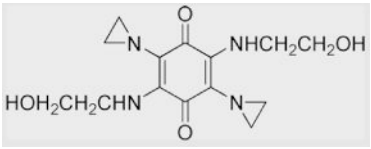
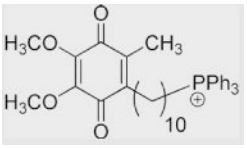
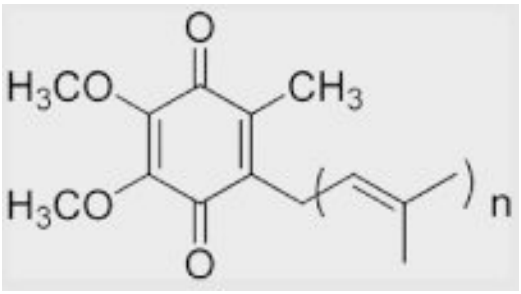
No.	Q or H_2Q	$SQ^{\bullet-}$ (or parent Q or H_2Q)	$k_{forward}$ (M^{-1} s^{-1}) Eq. (7)	$k_{reverse}$ (Eq. (7)
3	2,3-Dimethyl-1,4-benzoquinone		2.4×10^{7}	4.5×10^{8}
4	2,5-Dimethyl-1,4-benzoquinone		3.4×10^{6}	1.7×10^{8} 3.6×10^{9}
5	2,6-Dimethyl-1,4-benzoquinone		8.8×10^{6}	2.2×10^{8} 5.8×10^{9}
6	Duroquinone		2.2×10^{8}	1×10^{7}

No.	Q or H_2Q	$SQ^{\bullet-}$ (or parent Q or H_2Q)	$k_{forward}$ (M^{-1} s^{-1}) Eq. (7)	$k_{reverse}$ (Eq. (7)
7	2-Methyl-1,4-naphthoquinone (Menadione)		2×10^8 2.4×10^8	5×10^6 3.8×10^7
8	2,3-Dimethyl-1,4-naphthoquinone		2×10^8	4×10^6
9	Anthraquinone		5.0×10^8	1.2×10^4
10	Mitomycin C		$2.2(\pm0.2)\times10^8$	1.4×10^6
11	Adriamycin		$3.0(\pm 0.2)\times10^8$	3.8×10^6
12	3,5-Dihydroxyanisole			$<10^4$

No.	Q or H_2Q	$SQ^{\bullet-}$ (or parent Q or H_2Q)	$k_{forward}$ (M^{-1} s^{-1}) Eq. (7)	$k_{reverse}$ (Eq. (7)
13	Methyl gallate			2.5×10^5
14	Gallic acid			3.4×10^5
15	Epigallocatechin (Gallocatechol)			4.1×10^5

No.	Q or H_2Q	$SQ^{\bullet-}$ (or parent Q or H_2Q)	$k_{forward}$ (M^{-1} s^{-1}) Eq. (7)	$k_{reverse}$ (Eq. (7)
16	Epicatechin gallate			4.3×10^5
17	Epigallocatechin gallate			7.3×10^5
18	Epicatechin			6.8×10^4
19	Catechin			6.4×10^4

No.	Q or H_2Q	$SQ^{\bullet-}$ (or parent Q or H_2Q)	$k_{forward}$ (M^{-1} s^{-1}) Eq. (7)	$k_{reverse}$ (Eq. (7)
20	Indolequinones			
		$R_1 = CH_3$, $R_2 = R_3 = R_5 = H$, $R_4 = OCH_3$		
		$R_1 = R_2 = CH_3$, $R_3 = R_5 = H$, $R_4 = OCH_3$		
		$R_1 = R_2 = R_5 = CH_3$, $R_3 = H$, $R_4 = OCH_3$	$(4.4\pm0.1)\times10^8$	
		$R_1 = R_2 = CH_3$,$R_3 = R_5 = H$, R_4 = Morpholino	$(5.2\pm0.1)\times10^8$	
		$R_1 = CH_3$, R_2 = Ph, $R_3 = R_5 = H$, $R_4 = OCH_3$	$(1.2\pm1.2)\times10^8$	
		$R_1 = CH_3$, R_2 = 4-Ph-C_6H_4, $R_3 = R_5 = H$, $R_4 = OCH_3$	$(5.1\pm0.1)\times10^8$	
		$R_1 = CH_3$, R_2 = 2-Naphthyl, $R_3 = R_5 = H$, $R_4 = OCH_3$	$(1.2\pm0.1)\times10^8$	
		R_1 = *c*-Pr, $R_2 = CH_3$, $R_3 = R_5 = H$, $R_4 = OCH_3$	$(1.3\pm0.2)\times10^8$	
		$R_1 = CH_2Ph$, $R_2 = C_2H_5$, $R_3 = R_5 = H$, $R_4 = OCH_3$	$(1.5\pm0.3)\times10^8$	
		R_1 = Ph, $R_2 = CH_3$, $R_3 = R_5 = H$, $R_4 = OCH_3$	$(1.3\pm0.4)\times10^8$	
		R_1 = Ph, $R_2 = R_5 = CH_3$, $R_3 = H$, $R_4 = OCH_3$	$(2.2\pm0.3)\times10^8$	
		R_1 = *p*-F-C_6H_4, $R_2 = CH_3$, $R_3 = R_5 = H$, $R_4 = OCH_3$	$(1.4\pm0.4)\times10^8$	
		R_1 = *n*-Pr, $R_2 = CH_3$, $R_3 = R_5 = H$, $R_4 = OCH_3$	$(4.6\pm0.5)\times10^8$	
		R_1 = *n*-Pr, $R_2 = R_5 = CH_3$, $R_3 = H$, $R_4 = OCH_3$	$(1.8\pm0.6)\times10^8$	
		$R_1 = R_2 = R_3 = CH_3$, $R_5 = H$, $R_4 = OCH_3$	$(2.1\pm0.3)\times10^8$	
		$R_1 = R_2 = R_3 = CH_3$, $R_5 = H$,	$(2.4\pm0.3)\times10^8$	
		R_4 = 4-Methylpiperazin-1-yl		
		$R_1 = R_2 = CH_3$, R_3 = Ph, $R_5 = H$, $R_4 = OCH_3$	$(0.9\pm0.1)\times10^8$	
		$R_1 = R_2 = CH_3$, R_3 = Thienyl, $R_5 = H$, $R_4 = OCH_3$	$(1.1\pm0.1)\times10^8$	
		R_1, $R_2 = -(CH_2)_3-$, $R_3 = R_5 = H$, $R_4 = OCH_3$	$(0.9\pm0.1)\times10^8$	
			$(0.8\pm0.1)\times10^8$	
21	Anisyl-3,4-quinone		$\leq10^5$	8.7×10^8

No.	Q or H_2Q	$SQ^{\bullet-}$ (or parent Q or H_2Q)	$k_{forward}$ (M^{-1} s^{-1}) Eq. (7)	$k_{reverse}$ (Eq. (7)
22	2,5-Diaziridinyl-3, 6-bis (carbethoxyamino)-1, 4-benzoquinone (AZQ)		$(1.1\pm0.1)\times10^7$	(2.7±0.2
23	2,5-Diaziridinyl-3, 6-bis (2-hydroxyethylamino)-1, 4-benzoquinone (BZQ)		$(8.2\pm0.5)\times10^8$	(1.5±0.1
23	Mitoquinone		$(2.9\pm0.2)\times10^7$	(2.0±0.3
24	Coenzyme Q (Ubiquinone)		2×10^8	5×10^6

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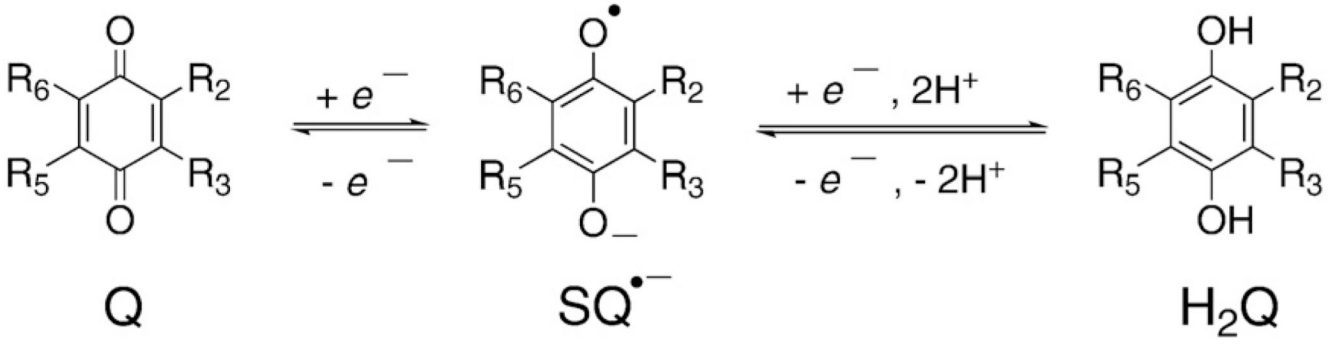

Fig. 1.

Shown are the basic structures of quinones, semiquinones, and corresponding hydroquinones. We show here the dominant species of each component of the triad that would be present in aqueous solution at pH 7. For example, for 1,4-hydroquinone the pK_a's are 9.8 and 11.4 for the first and second protons of the phenoxyl moieties, respectively [11,12]. The pK_a of the protonated 1,4-semiquinone radical (SQH$^\bullet$) is 4.1 [13,14]; thus, it is shown as the radical anion.

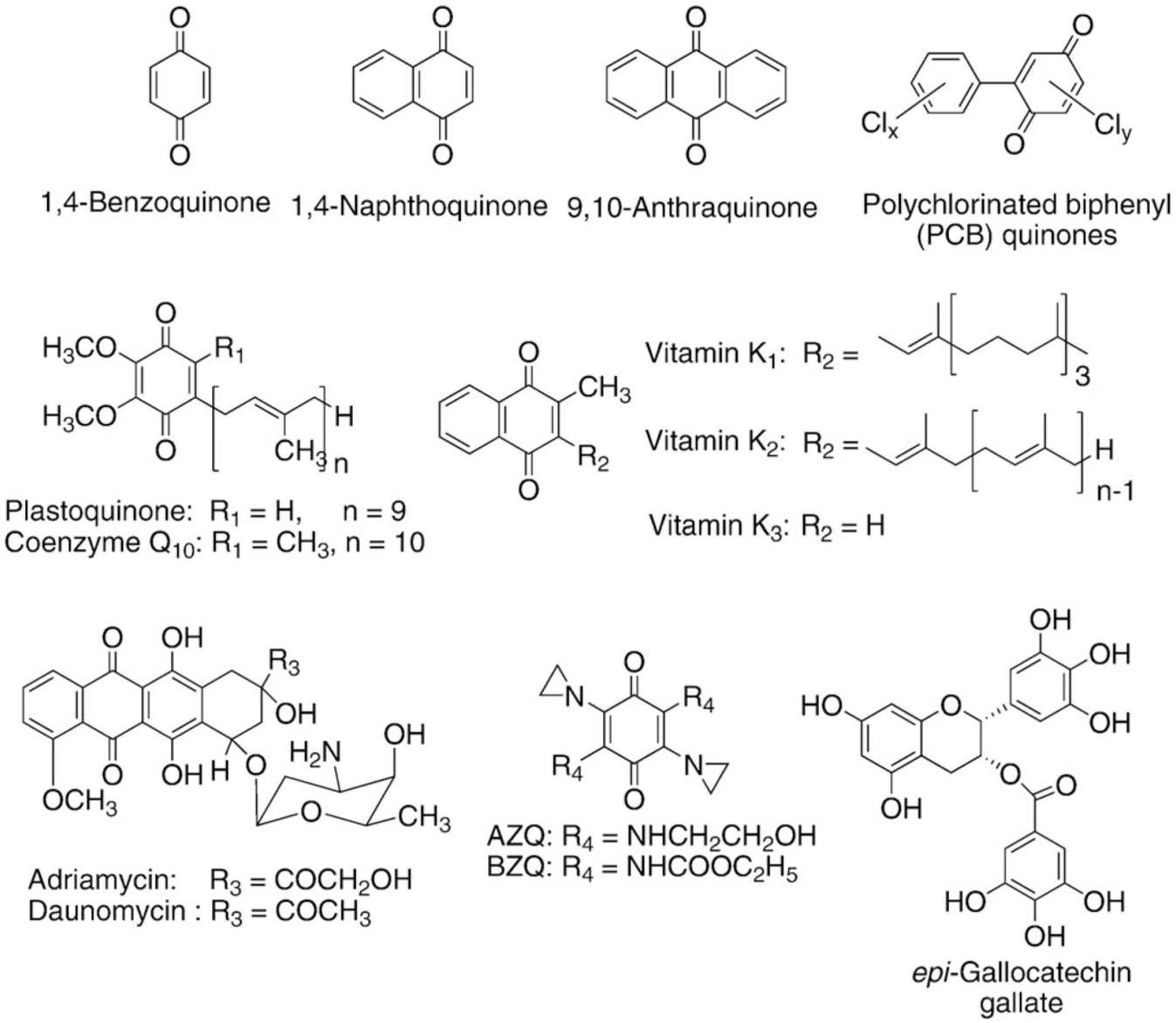

Fig. 2.
Chemical structures of quinones.

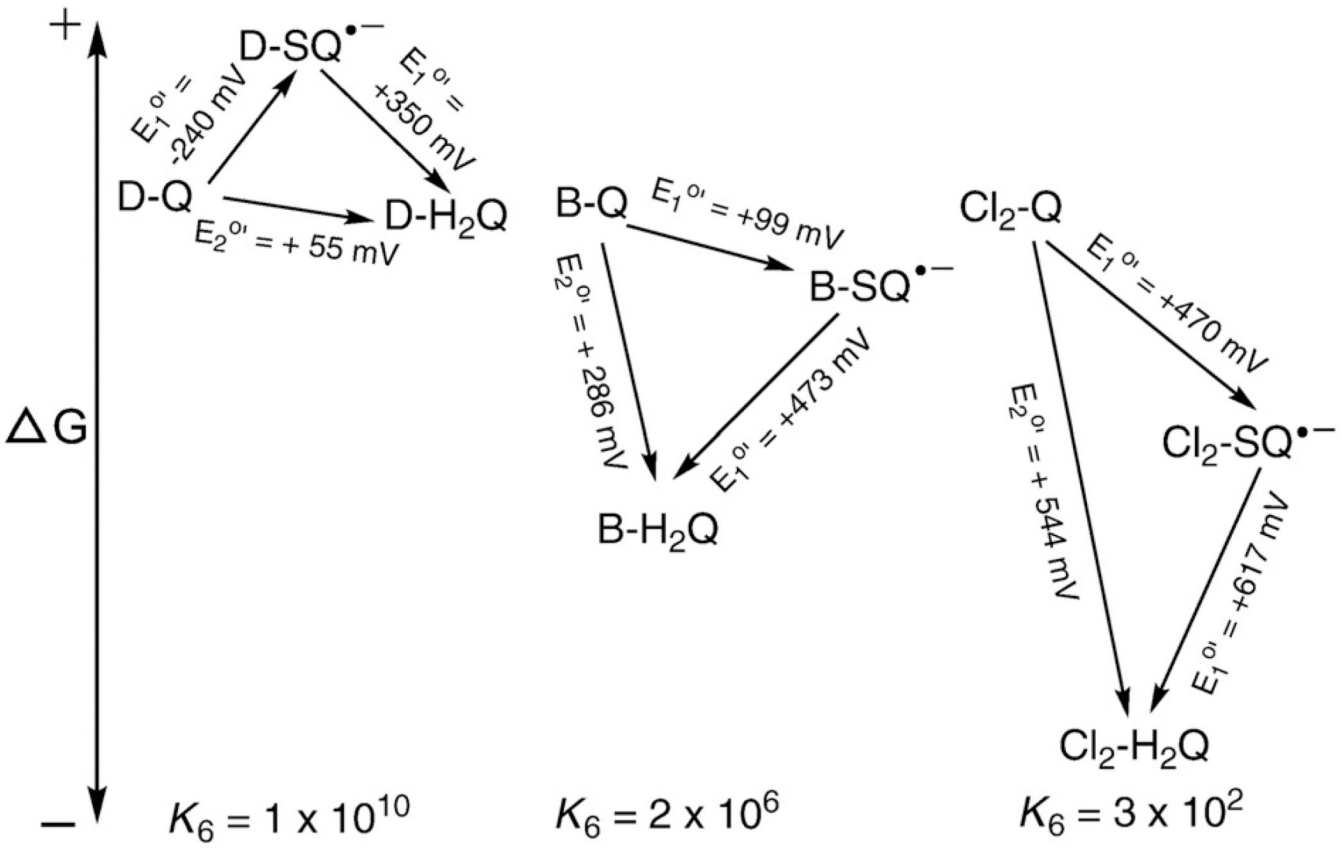

Fig. 3.

The disproportionation (dismutation) reaction of semiquinone radicals is spontaneous and reversible at pH 7. Shown are the standard one-electron $\left(E_1^{\circ\prime}\right)$ and two-electron $\left(E_2^{\circ\prime}\right)$ reduction potentials for the duroquinone (D-Q), benzoquinone (B-Q), and 2,5-dichlorobenzoquinone (Cl_2-Q) triads. Under standard conditions, i.e., ≈ 1.0 M concentration for each species, the dismutation reaction will be spontaneous because the overall change in the Gibbs free energy is favorable. A positive change in ΔE will yield a negative value for the change in the Gibbs free energy ($\Delta G=-n\mathrm{F}\Delta E$), indicating a spontaneous process. However, comproportionation of Q and H_2Q to yield $SQ^{\bullet-}$ is also possible when the value of the mass action expression for the system is not equal to the equilibrium constant. For Eq. (6), the complete mass action expression will be $Q_r=[Q][H_2Q]/[SQ^{\bullet-}]^2[H^+]^2$. However, $E^{\circ\prime}$ is the reduction potential at pH 7; thus, at this fixed pH, the mass action expression can be simplified to $Q_r=[Q][H_2Q]/[SQ^{\bullet-}]^2$, because $[H^+]$ is constant. The equilibrium constants shown were determined with this form of Q_r. The equilibrium constant for the disproportionation reaction (Eq. (6)) for a $Q/SQ^{\bullet-}/H_2Q$ triad can be determined using $\Delta E=((E_1^{\circ\prime})_{Q/SQ^{\bullet-}}-(E_1^{\circ\prime})_{SQ^{\bullet-}/H2Q})-(RT/n\mathrm{F})\ln K$. At equilibrium $\Delta E = 0$. If $Q_r<K$, the reaction will proceed to the right until equilibrium is achieved; if $Q_r>K$ the reaction will proceed to the left; K is the equilibrium constant. (The quinones of each triad are shown with the same relative free energies. This was done only to conveniently show the relative changes in the free energy of each triad; it is not meant to imply they have the same Gibbs free energy.)

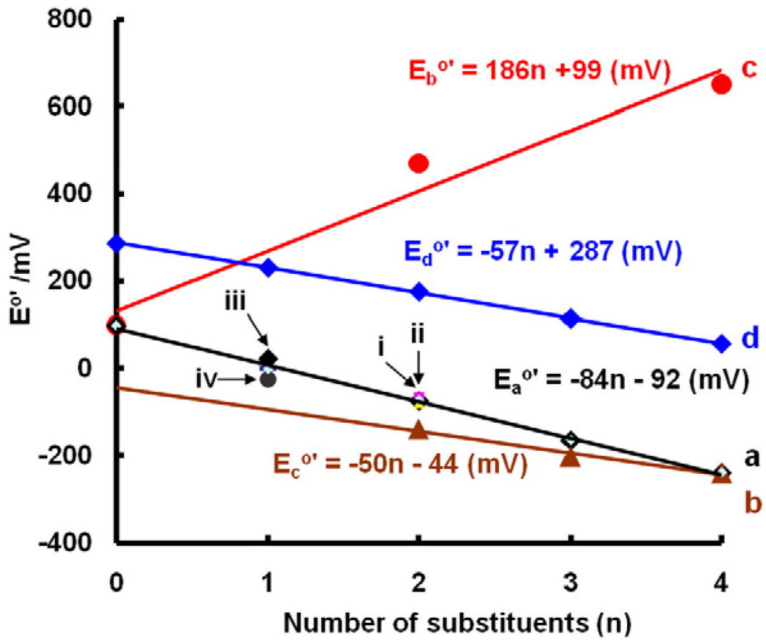

Fig. 4.

Substituents influence $E°'(Q/SQ^{\bullet -})$ and $E°'(Q, 2H^+/H_2Q)$ of quinones. (a) $E°'(Q/SQ^{\bullet -})$ vs number of alkyl groups on the benzoquinone ring: (i) all three isomers of dimethyl-benzoquinone are included (2,3-dimethyl, 2,5-dimethyl, and 2,6-dimethyl); they are similar so the points overlap on this plot; (ii) 2-methyl-5-*iso*-propyl-benzoquinone; again it is similar and overlap; (iii) ethyl-1,4-benzoquinone; (iv) *tert*-butyl-1,4-benzoquinone. (b) $E°'(Q/SQ^{\bullet -})$ vs number of methyl groups on 1,4-naphthoquinone; here we treat the second ring as benzoquinone with two alkyl groups. (c) $E°'(Q/SQ^{\bullet -})$ vs number of chlorines on benzoquinone. (d) $E_2^{\circ'}(Q, 2H^+/H_2Q)$ vs number of methyl groups on benzoquinone. Note these are two-electron half-cell reduction potentials.

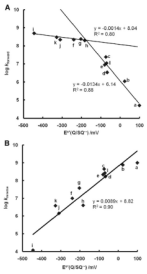

Fig. 5.

Second-order rate constants for formation of superoxide by $SQ^{\bullet -}$ (Eq. (7)), as well as the reverse reactions, are a function of $E^{\circ\prime}$. (A) For the forward reaction, the rate constants fall into two categories: (i) when $E^{\circ\prime}<-150$ mV the rate constants appear to be influenced by the diffusion limit, i.e., $> 10^8$ M^{-1} s^{-1}; and (ii) when $E^{\circ\prime}>-150$ mV the rate constants appear to follow the Marcus theory for electron transfer, here approximated by a linear relationship. (B) For the reverse reaction of Eq. (7), the rate constants correlate well with the one-electron reduction potential of the quinones. The specific semiquinone radical for each point has as the parent quinone: a, 1,4-benzoquinone; b, methyl-1,4-benzoquinone; c, 2,3-dimethyl-1,4-benzoquinone; d, 2,5-dimethyl-1,4-benzoquinone; e, 2,6-dimethyl-1,4-benzoquinone; f, duroquinone; g, 2-methyl-1,4-naphthoquinone; h, 2,3-dimethyl-1,4-naphthoquinone; i, anthraquinone (estimated here for B); j, Mitomycin (estimated here for B); k, Adriamycin (estimated here for B); l, AZQ: 2,5-diaziridinyl-3,6-bis(carbethoxyamino)-1,4-benzoquinone.

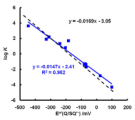

Fig. 6.

Experimental equilibrium constants match theoretical equilibrium constants closely. The dashed black line represents the theoretical values of *K* for Eq. (7) using the Nernst equation (Eq. (7)) with $E^{\circ\prime}(O_2/O_2^{\bullet-})= -180$ mV; the slope of this line is 1/(59.1 mV) and the intercept is (−180 mV)/(59.1 mV). The variation in the experimental values represents the uncertainties of measurement. (Solid line, a fit of experimental data by linear regression.) However, if the very fast reactions of Eq. (7) are influenced by limitations from diffusion, then the largest forward rate constants are lower than theoretical rate constants, resulting in the corresponding *K*s being underestimated. Likewise, when $E^{\circ\prime}(Q/SQ^{\bullet-})$ is very positive, the experimental, very fast rate constants for the reverse reactions of Eq. (7) are lower than theoretical rate constants and, thus *K* would be overestimated. These two extremes may account for the shallower slope and the underestimation of the intercept for experimental values.

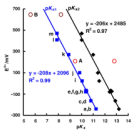

Fig. 7.

$E°'$(Q/SQ$^{\bullet-}$) correlates with the pK_a's of the corresponding *para*-hydroquinones. The squares (■, blue) are the first pK_a of a particular hydroquinone; the diamonds (◆, black) are the second pK_a of the hydroquinone; pK_a's are from [11,12,39]. The *para*-quinones/hydroquinones a–m show a linear relationship between the one-electron reduction potential of the quinone ($E°'$(Q/SQ$^{\bullet-}$)) and the first and second pK_a's of the corresponding hydroquinone. The one-electron reduction potentials for quinones k and l have been estimated from Fig. 4; compounds A (catechol) and B (tetrachloro-1,4-hydroquinone) are not included in the linear regression of the two lines. We anticipate that *ortho*-hydroquinones would behave similarly to *para*-hydroquinones, but there would most likely be a systematic offset relative to the plots for *para*-hydroquinones. (A note on tetrachloro-1,4-hydroquinone: $E°'$(Q/SQ$^{\bullet-}$) for tetrachloro-1,4-hydroquinone (B) has been estimated from the correlation of the reduction potentials determined in methyl cyanide [40,78]; knowing that pK_{a1} for tetrachloro-1,4-hydroquinone is 5.6 [12] suggests that the one-electron reduction potential is actually about +800 mV in aqueous solution.) The compounds are: a. ubiquionol-1, coenzyme Q-1; b, tetramethyl-1,4-hydroquinone; c, 2,3,5-trimethyl-1,4-hydroquinone; d, plastoquinol-1; e, 2,6-dimethyl-1,4-hydroquinone; f, 2-methyl-5-isopropyl-1,4-hydroquinone; g, 2,3-dimethyl-1,4-hydroquinone; h, 2,5-dimethyl-1,4-hydroquinone; i, 2-methyl-1,4-hydroquinone; j, 1,4-hydroquinone; k, 2-chloro-1,4-hydroquinone; l, 2,6-dichloro-1,4-hydroquinone; m, 2,5-dichloro-1,4-hydroquinone; A, catechol; B, tetrachloro-1,4-hydroquinone.

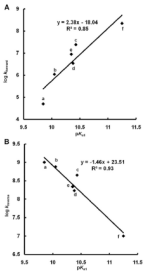

Fig. 8.

Second-order rate constants for formation of superoxide by $SQ^{\bullet -}$ (Eq. (7)) as well as the reverse reactions are a function of pK_{a1}. pK_a's are from Fig. 5. The *para*-hydroquinones a–f show a linear relationship between the rate constant of formation of semiquinone (Eq. (7)) as well as corresponding reverse Eq. (7) vs the first pK_a's of the corresponding hydroquinone. The compounds are: a, 1,4-benzoquinone; b, methyl-1,4-benzoquinone; c, 2,3-dimethyl-1,4-benzoquinone; d, 2,5-dimethyl-1,4-benzoquinone; e, 2,6-dimethyl-1,4-benzoquinone; f, duroquinone.

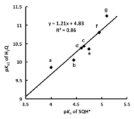

Fig. 9.

There is a linear relationship of pK_{a1} of H_2Q with pK_a of the corresponding $SQH^{\bullet}$. (a) 1,4-Benzoquinone; (b) methyl-1,4-benzoquinone; (c) 2,3-dimethyl-1,4-benzoquinone; (d) 2,5-dimethyl-1,4-benzoquinone; (e) 2,6-dimethyl-1,4-benzoquinone; (f) 2,3,5-trimethyl-1,4-benzoquinone; (g) duroquinone.

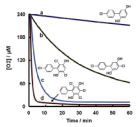

Fig. 10.

Time course of oxygen consumption during the autoxidation of PCB hydroquinones with different degrees of chlorination on the oxygenated phenyl ring. (a) 4′-Cl-2,5-H_2Q; (b) 4,4′-Cl-2,5-H_2Q; (c) 3,6,4′-Cl-2,5-H_2Q; and (d) 3,4,6-Cl-2,5-H_2Q. Solutions contained [H_2Q] = 2.0 mM in pH 7.4 phosphate buffer at 25 °C. Adapted from [56].

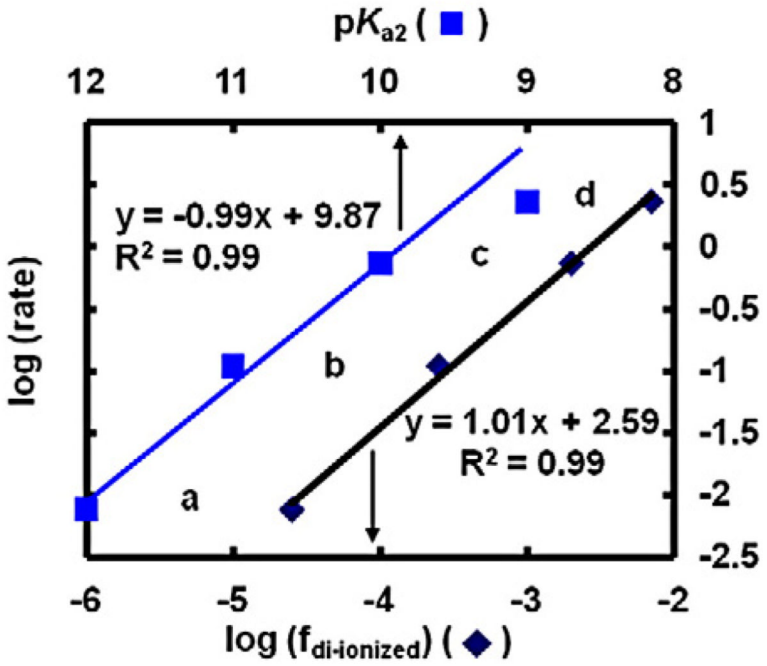

Fig. 11.

The rate of O_2 consumption (μM s^{-1}) increases with the fraction of the di-ionized hydroquinone, which is determined by the number of chlorines on the ring. Rates were determined from the initial slopes for the uptake of oxygen in Fig. 10. (a) 4′-Cl-2,5-H_2Q; (b) 4,4′-Cl-2,5-H_2Q; (c) 3,6,4′-Cl-2,5-H_2Q; and (d) 3,4,6-Cl-2,5-H_2Q. A plot of log(rate) vs pK_{a2} of the hydroquinone works well except for (d). However, pK_{a1} for (d) is 7; thus there is not an approximate factor of 10 increase in the concentration of Q^{2-}, compared to (c), because the solution pH is 7.4. However, when the log of fraction di-ionized ($f_{di\text{-}ionized}$) is plotted against log(rate), all points fit. The fraction of di-ionized ($f_{di\text{-}ionized}$) H_2Q was determined in pH 7.4 buffer, by using pK_{a2} of the H_2Q's as 12, 11, 10, and 9 for H_2Q with 0, 1, 2, and 3 chlorines on the oxygenated ring, respectively [56]. The values are pK_{a1} + 2, as indicated by Fig. 7. A slope of 1.0 indicates the reaction is first-order in [di-ionized hydroquinone].

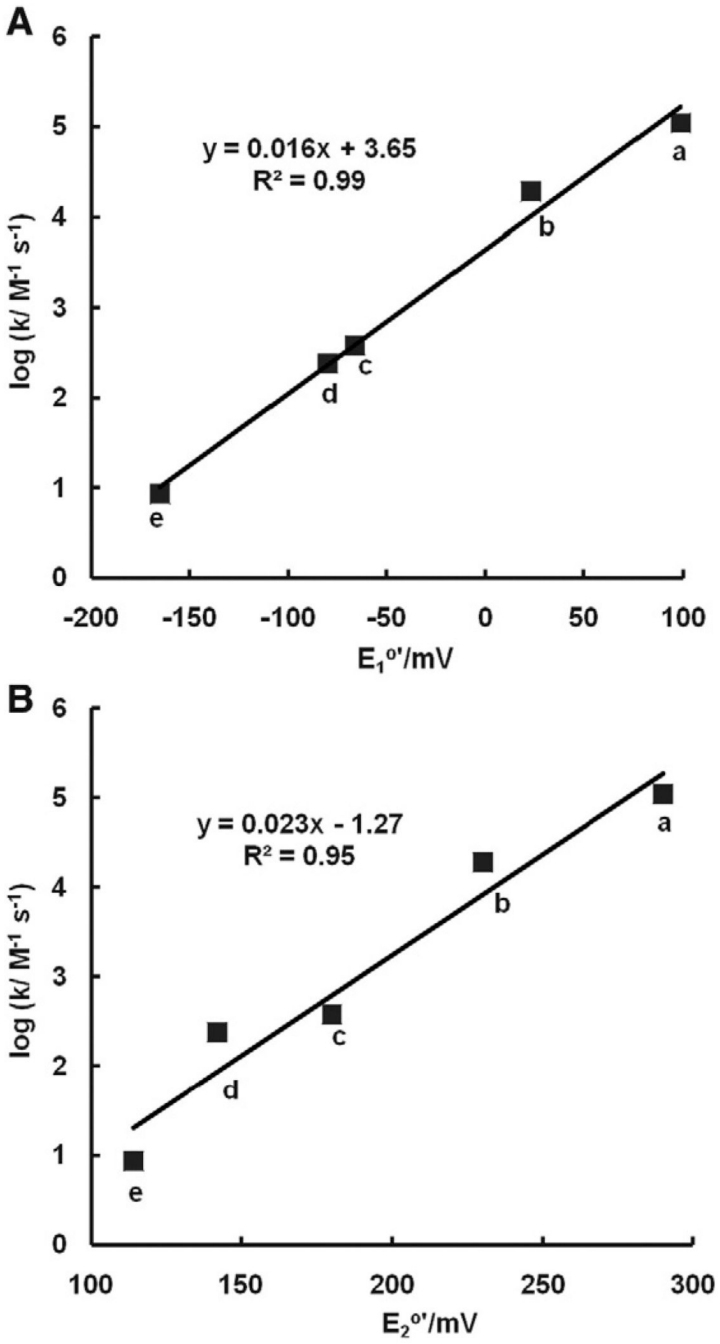

Fig. 12.

The rate constants for the Michael reaction of glutathione with various quinones are a function of $E^{\circ\prime}$. The rate constants for reductive addition of GSH to benzoquinone and methylated benzoquinones decrease linearly with increasing degrees of methylation; methyl groups donate electrons into the quinone ring. (A) One-electron reduction potential for $Q/SQ^{\bullet -}$; and (B) two-electron reduction potential of the quinones, $Q,2H^+/H_2Q$. (a) 1,4-Benzoquinone; (b) methyl-1,4-benzoquinone; (c) 2,6-dimethyl-1,4-benzoquinone; (d) 2,5-dimethyl-1,4-benzoquinone; (e) 2,3,5-trimethyl-1,4-benzoquinone. Data from [70]. The kinetic data are at pH 6.0. Because it is actually the ionized thiol, here GS^-, that dominates the reaction of Eq. (14), rate constants at pH 7 will be about 10 times larger.

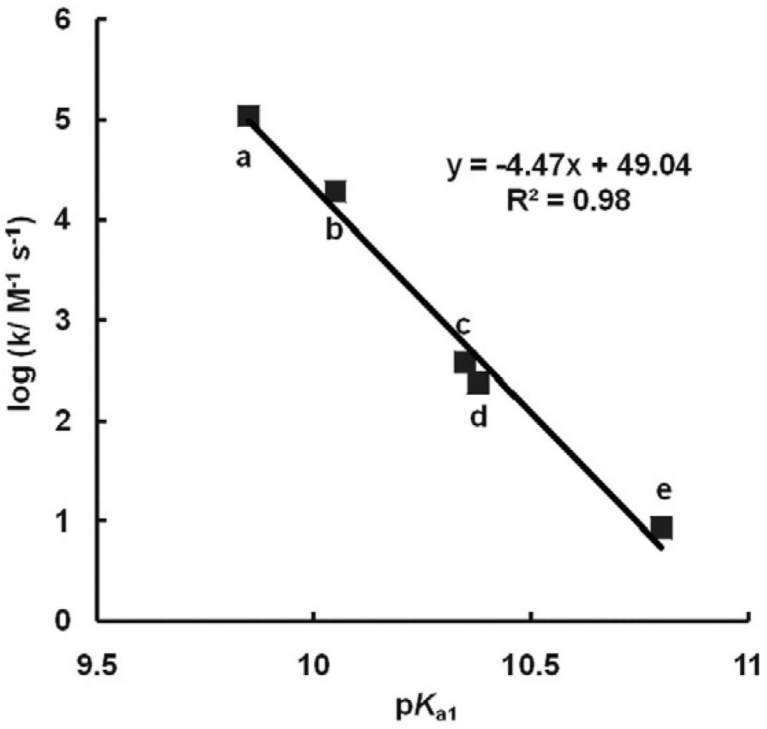

Fig. 13.

The rate constants for the Michael reaction of glutathione with various quinones are a function of pK_{a1} of the corresponding hydroquinone. The rate constants for reductive addition of GSH to benzoquinone and methylated benzoquinones decrease linearly with increase of pK_{a1}. (a) 1,4-Benzoquinone; (b) methyl-1,4-benzoquinone; (c) 2,6-dimethyl-1,4-benzoquinone; (d) 2,5-dimethyl-1,4-benzoquinone; (e) 2,3,5-trimethyl-1,4-benzoquinone.