The kinetics and thermodynamics of quinone–semiquinone–hydroquinone systems under physiological conditions

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The steady-state concentration of semiquinones ($Q^{\cdot -}$) determined by EPR in the mixtures of eleven alkyl-, methoxy- and chloro-substituted 1,4-benzoquinones as well as 1,4-naphthoquinone (Q) with corresponding hydroquinones (QH_2) in aqueous buffer, pH 7.40, was used to calculate a constant for equilibrium (1) $Q + QH_2 \rightleftharpoons Q^{\cdot -} + Q^{\cdot -} + 2H^+$ (k_1; $2k_{-1}$; $K_1 = k_1/2k_{-1}$). The rate constants for comproportionation between Q and QH_2, k_1, were calculated from the combination of K_1 determined in this work and $2k_{-1}$ reported previously. The Nernst equation was applied to calculate the change in one-electron reduction potential $\Delta E_1 = E(Q/Q^{\cdot -}) - E(Q^{\cdot -}/QH_2)$ in equilibrium (1). The $E(Q^{\cdot -}/QH_2)$ values were calculated from ΔE_1 and the values of $E(Q/Q^{\cdot -})$ known from the literature. The correlations between $E(Q^{\cdot -}/QH_2)$ and $E(Q/Q^{\cdot -})$ as well as between ΔE_1 (k_1) and $E(Q/Q^{\cdot -})$ are discussed. The values of ΔE_1 and k_1 are suggested to be the key factors governing the autoxidation of QH_2.

Introduction

The reactivity and thermodynamic properties of quinones (Q) and their reduced forms, semiquinones ($Q^{\cdot -}$) and hydroquinones (QH_2), are related to many biological problems including quinone cytotoxicity,[1,2] application of quinones as antitumor agents,[2,3] electron transfer,[4] and the functioning of the antioxidant defense system.[5] There are several equilibria involving Q, $Q^{\cdot -}$ and QH_2 in chemical and biological systems. The equilibrium (1) and its constituents, disproportionation of $Q^{\cdot -}$ (reaction (−1)) and comproportionation between Q

$$Q + QH_2 \underset{(-1)}{\overset{(1)}{\rightleftharpoons}} Q^{\cdot -} + Q^{\cdot -} + 2H^+ \qquad (1),(-1)$$

and QH_2 (reaction(1)), are the most fundamental. Knowledge of this equilibrium constant, $K_1 = k_1/2k_{-1}$, along with the rate constants for elementary reactions (−1) and (1), $2k_{-1}$ and k_1, opens up many opportunities to predict the reactivity of Q, $Q^{\cdot -}$, and QH_2 and the behavior of these species in various chemical and biological systems.

The value of $2k_{-1}$ determines to a significant degree the stability of $Q^{\cdot -}$ and its steady-state concentration. Other things being equal, the lower $2k_{-1}$ the more significant becomes the role of other reactions with participation of $Q^{\cdot -}$. Much attention has been given to the determination of $2k_{-1}$, basically using pulse radiolysis combined with UV-Vis spectrophotometry (refs. 6–9 and references therein). Surprisingly, the quantitative information on the disproportionation of substituted 1,4-benzosemiquinones was until recently very restricted though the kinetics of this process with $Q^{\cdot -}$ produced from substituted naphthoquinones and anthraquinones and Q with more complex structures have been studied in detail. Our recent work[9] has partly eliminated this gap. K_1 was previously reported for many Q/QH_2 couples but only a few of them were determined at physiological pH.[10–13] When K_1 and $2k_{-1}$ are known, this allows us to calculate the rate constant for reaction (1), a parameter which significantly governs the oxidizability of QH_2 by molecular oxygen.[14] Previously a k_1 value has been reported only for the non-substituted 1,4-benzoquinone/1,4-hydroquinone couple.[15] Using the Nernst equation, K_1 may be converted into the difference in one-electron reduction potential in equilibrium (1), ΔE_1, that represents the combination of $E(Q/Q^{\cdot -})$ and $E(Q^{\cdot -}/QH_2)$. Eqn. (2) may be used to calculate $E(Q^{\cdot -}/QH_2)$ from ΔE_1

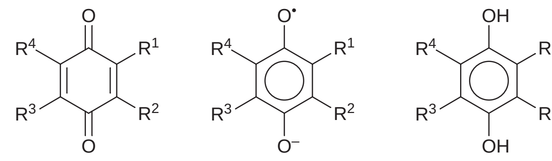
$$\Delta E_1 = E(Q/Q^{\cdot -}) - E(Q^{\cdot -}/QH_2) \qquad (2)$$

provided that $E(Q/Q^{\cdot -})$ is known. While considerable attention was paid to the determination of $E(Q/Q^{\cdot -})$, the values of $E(Q^{\cdot -}/QH_2)$ in aqueous solutions have been reported only for a few QH_2.[16] Meanwhile, $E(Q^{\cdot -}/QH_2)$ determines to a large extent the reactivity of $Q^{\cdot -}$ and QH_2, and thus this parameter is of vital interest for Q/QH_2 chemistry and biochemistry.

The present work is devoted to the EPR determination of K_1 from a steady-state concentration of $Q^{\cdot -}$ in the mixtures of Q and QH_2 for eleven Q/QH_2 couples presented in Scheme 1. These data were used to calculate k_1, ΔE_1, and $E(Q^{\cdot -}/QH_2)$ and to establish the correlation between various one-electron reduction potentials.

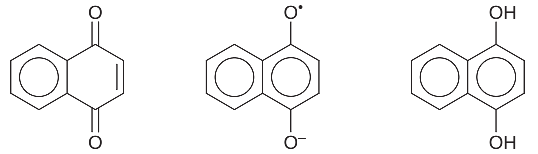
Experimental

The quinones and hydroquinones studied in this work are presented in Scheme 1. Q **1**, Q **5**, Q **6**, Q **7**, Q **10**, and Q **11** were purchased from Aldrich; Q **2** and QH_2 **2** from Merck; QH_2 **4** and QH_2 **11** from Fluka, Q **8** from Lancaster, Q **9** from Sigma. Q **3** and Q **4** were prepared *via* the oxidation of QH_2 **3** and QH_2 **4** with $K_3Fe(CN)_6$ in the 1 : 1 mixture of benzene and diethyl ether. QH_2 **1**, QH_2 **5**, QH_2 **6**, QH_2 **7**, QH_2 **8**, QH_2 **9** and QH_2 **10** were prepared by the reduction of corresponding Q by Zn powder in acetic acid followed by removing the solvent with a rotary evaporator and further extraction of QH_2 with an appropriate organic solvent. Both purchased and synthesized Q and QH_2 were purified by recrystallization, sublimation under vacuum or using a silica gel (40–100 μm) column with $CHCl_3$ as an eluent. Sodium phosphates, NaH_2PO_4 and Na_2HPO_4, of highest grade used to prepare buffer solutions, were purchased from Merck. Other reagents were of the highest available grade.



Q **Q•⁻** **QH₂**

	R^1	R^2	R^3	R^4
1	H	H	H	H
2	Me	H	H	H
3	Et	H	H	H
4	Bu^t	H	H	H
5	Me	H	H	Me
6	Me	H	Pr^i	H
7	Cl	H	Cl	H
8	OMe	H	H	OMe
9	Me	OMe	OMe	H
10	Cl	Cl	Cl	Cl



Q 11 **Q•⁻ 11** **QH₂ 11**

Scheme 1 The structures of quinones, hydroquinones and semiquinones studied.

Aqueous solutions were prepared with doubly distilled water. Experiments were performed at 37 °C with 50 mM phosphate buffer, pH 7.40 ± 0.02, (unless otherwise indicated), which was prepared by mixing fifty millimolar solutions of NaH_2PO_4 and Na_2HPO_4 without adding any acid or base. Solutions of the individual phosphates used for the buffer preparation were purged from traces of transition metals by Chelex-100 resin (Bio-Rad) using a batch method.[17] Stock solutions of Q and QH_2 were prepared, depending on solubility, with water or aqueous dimethyl sulfoxide (DMSO).

Steady-state concentration of $Q^{\bullet -}$ in the mixture of Q and QH_2 used to calculate K_1 was determined by EPR in a flat quartz cell with a Varian E12 spectrometer (Varian, USA) equipped with a TE_{104} dual cavity and temperature controller. Solutions containing Q and corresponding QH_2 were prepared by adding a certain volume of stock solutions of Q and QH_2. Both stock solutions and buffer were argon-bubbled prior to mixing. The reaction mixture was immediately transferred using a microsyringe into a flat EPR cell flushed with argon. 10 μM solution of the aminoxyl stable radical TEMPO in benzene placed into one of the cavities was used as a reference standard for the determination of the absolute concentration. Instrument settings were as follows: microwave power, 5 mW; modulation frequency, 12.5 kHz; modulation amplitude, 0.63 G (for determination of $[Q^{\bullet -}]$) or 0.05 G (for determination of hyperfine splitting parameters). The absolute concentration of $Q^{\bullet -}$ was calculated by double integrating EPR spectrum of $Q^{\bullet -}$ and normalizing the obtained value to the intensity of the standard. The protocol we followed for EPR determinations has been reported in more detail elsewhere.[13,18] A standard error in the determination of $[Q^{\bullet -}]$ was typically within ±15%.

Results and discussion

EPR determination of K_1

When Q and QH_2 were mixed in deaerated buffer, well-resolved multicomponent EPR spectra attributed to $Q^{\bullet -}$ were observed. Hyperfine splitting parameters of these spectra were in reasonable agreement with those reported in the literature[19,20] and are therefore not reported here. With most Q/QH_2 couples the intensity of the EPR spectrum remained constant for at least one hour as is exemplified by plot 1 in Fig. 1. This demonstrates that Q and QH_2 are the only products of $Q^{\bullet -}$ disproportionation and thus this reaction is completely reversible. By contrast, the concentration of $Q^{\bullet -}$ formed in the Q **7**/QH_2 **7** and Q **10**/QH_2 **10** systems decreased dramatically with time (plots 2 and 3, Fig. 1) suggesting that reaction (−1) in these cases is not the only pathway of $Q^{\bullet -}$ decay.

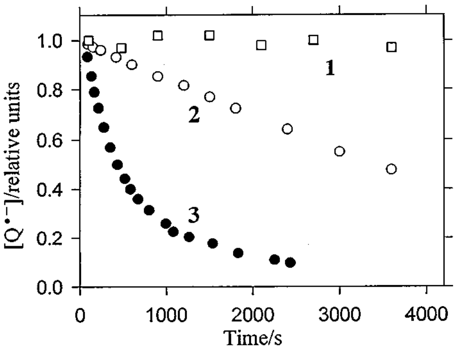


Fig. 1 Time dependence of $[Q^{\bullet -}]$ in 50 mM phosphate buffer, pH 7.40, at 37 °C for the mixtures of 0.5 mM Q **9** and 1 mM QH_2 **9** (plot 1); 25 μM Q **10** and 60 μM QH_2 **10** (plot 2); 62 μM Q **7** and 60 μM QH_2 **7** (plot 3).

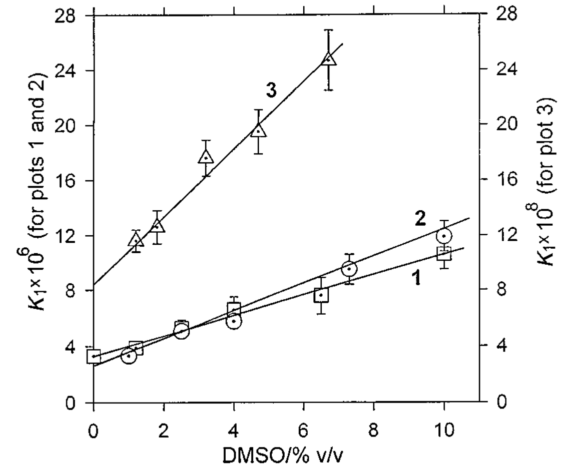


Fig. 2 Plots of K_1 against DMSO concentration for equilibrium (1) determined in the mixtures of Q **2** with QH_2 **2** (plot 1); Q **9** with QH_2 **9** (plot 2); Q **4** with QH_2 **4** (plot 3); in 50 mM phosphate buffer, pH 7.40, at 37 °C.

A constant of equilibrium (1), K_1, was calculated from $[Q^{\bullet -}]$ by using eqn. (3), where $[Q]_0$ and $[QH_2]_0$ are initial

$$K_1 = [Q^{\bullet -}]^2/([Q]_0 - 0.5[Q^{\bullet -}])\,([QH_2]_0 - 0.5[Q^{\bullet -}]) \quad (3)$$

concentrations of the reagents. Typically, K_1 was determined in four or more separate runs at several concentrations of [Q] and $[QH_2]$. The K_1 value was found to be independent of [Q] or $[QH_2]$. With the Q **7**/QH_2 **7** couple, the concentration of $Q^{\bullet -}$ extrapolated to zero time was used to calculate K_1. With the Q **10**/QH_2 **10** mixture, the starting concentration of $Q^{\bullet -}$ was close to the sum of [Q] and $[QH_2]$; an exact value of K_1 could not therefore be calculated.

In some cases K_1 was determined in aqueous buffer containing a small amount of DMSO that was added to increase the solubility of Q. As is exemplified by Fig. 2, K_1 increased nearly linearly with [DMSO]. The K_1 values presented in Table 1 were determined either in solution without DMSO or by using linear extrapolation of the measured K_1 values to zero concentration of DMSO as shown in Fig. 2. For several Q/QH_2 couples these values may be compared with those reported in ref. 10 (Q **1**/QH_2 **1**, Q **2**/QH_2 **2** and Q **11**/QH_2 **11**) and ref. 11 (Q **3**/QH_2 **3**). The reported values differ from those determined in this

Table 1 Parameters of equilibrium (1) $Q + QH_2 \rightleftharpoons Q^{\bullet -} + Q^{\bullet -} + 2H^+$ ($K_1 = k_1/2k_{-1}$) determined by EPR (K_1) and pulse radiolysis ($2k_{-1}$) in 50 mM sodium phosphate buffer

Q/QH_2[a]	K_1[b] at 37 °C, pH 7.4	ΔH_1/kJ mol^{-1}[c]	K_1 at 37 °C, pH 7.4	$2k_{-1}/10^8$ M^{-1} s^{-1}[f]	k_1/M^{-1} s^{-1}
1	$(8.1 \pm 1.4) \times 10^{-6}$	50 ± 4 (39)	2.4×10^{-6}[d]	1.6 ± 0.2	1300 ± 400
2	$(3.3 \pm 0.6) \times 10^{-6}$	50 ± 5 (49)	1.1×10^{-6}[d]	1.35 ± 0.02	450 ± 90
3	$(3.1 \pm 0.7) \times 10^{-6}$	54 ± 6		0.91 ± 0.04	290 ± 80
4	$(8.5 \pm 2.3) \times 10^{-8}$	50 ± 5	2.2×10^{-8}[e]	0.35 ± 0.17	~3
5	$(4.4 \pm 0.9) \times 10^{-7}$	nd		1.15 ± 0.20	50 ± 20
6	$(7.9 \pm 2.2) \times 10^{-7}$	nd		0.38 ± 0.08	30 ± 14
7	$(5.5 \pm 0.7) \times 10^{-2}$	64 ± 8		nd	nd
8	$(2.6 \pm 0.4) \times 10^{-5}$	46 ± 4		0.32 ± 0.03	800 ± 200
9	$(2.6 \pm 0.5) \times 10^{-6}$	54 ± 5		0.54 ± 0.03	140 ± 35
10	>1	nd		nd	nd
11	$(5.2 \pm 1.4) \times 10^{-6}$	nd (57)	1.0×10^{-5}[d]	2.76 ± 0.10	1400 ± 400

nd — Not determined. [a] The structures of Q/QH_2 are given in Scheme 1. [b] Values of K_1 mean ±SD from four or more independent experiments conducted at various concentrations of Q and QH_2. [c] ΔH_1 in parentheses were reported in ref. 10. [d] Reported in ref. 10 at 25 °C and recalculated to 37 °C using ΔH_1 determined there. [e] K_1 reported in ref. 11 at 22 °C and pH 7.0 and recalculated to 37 °C and pH 7.4 using $\Delta H_1 = 50$ kJ mol^{-1} and d(log K_1)/d(pH) = 2. [f] The averaged values determined by pulse radiolysis of Q and QH_2 at room temperature in our previous work[9] (see text for more detail).

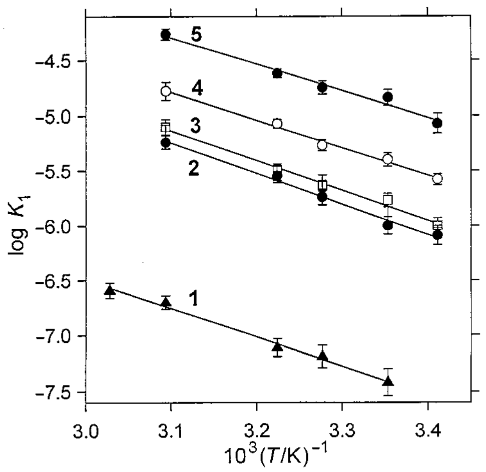


Fig. 3 Van't Hoff plots of K_1 determined in phosphate buffer, pH 7.40, for the following couples: Q **4**/QH_2 **4** (plot 1); Q **9**/QH_2 **9** (plot 2); Q **3**/QH_2 **3** (plot 3); Q **1**/QH_2 **1** (plot 4); Q **8**/QH_2 **8** (plot 5).

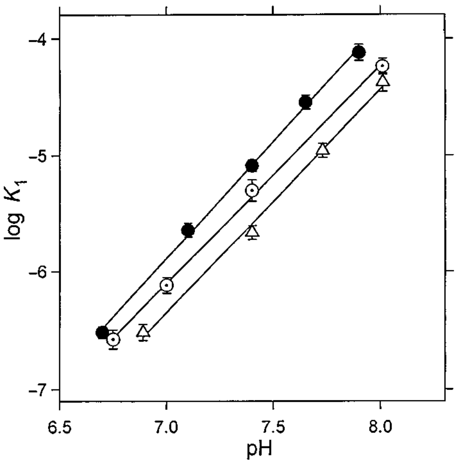


Fig. 4 Plots of K_1 against pH determined in phosphate buffer at 37 °C for the following couples: Q **1**/QH_2 **1** (●), Q **2**/QH_2 **1** (△), Q **9**/QH_2 **9** (○).

study typically by a factor of 2–4; this is not too significant a difference, as it corresponds to the difference in absolute concentration of $Q^{\bullet -}$ of about 1.5–2 times.

The temperature effect was studied for several Q/QH_2 couples. A steady-state concentration of $Q^{\bullet -}$ and thus K_1 increased with increasing temperature (Fig. 3). The determined enthalpies of equilibrium, ΔH_1, varied within a rather narrow range from 46 to 64 kJ mol^{-1} (Table 1). With $Q^{\bullet -}$ **1** and $Q^{\bullet -}$ **2**, it was possible to compare the ΔH_1 values determined in this study with those reported in ref. 10; they were in excellent agreement with each other (Table 1). K_1 was found to rise with pH evidently due to the larger contribution of an ionized form of QH_2, QH^-, to equilibrium (1). The linear plots of log K_1 against pH with slopes of 2.00 ± 0.04 ($Q^{\bullet -}$ **1**); 1.93 ± 0.06 ($Q^{\bullet -}$ **2**); 1.91 ± 0.05 ($Q^{\bullet -}$ **9**) were observed (Fig. 4). The slope of nearly 2 is in agreement with previous works (refs. 11, 12, 15) and predicted by the theory for the case when pH is far from the pK[16] of QH_2.

Determination of k_1

The rate constants for reaction (1) between Q and QH_2 were calculated from the combination of the values of K_1 determined in this study and $2k_{-1}$ previously reported, largely in ref. 9.

$$k_1 = K_1(2k_{-1}) \qquad (4)$$

The values of k_1 calculated in this way are given in Table 1. With several $Q^{\bullet -}$, the $2k_{-1}$ values measured in ref. 9 *via* pulse radiolysis experiments with Q and QH_2 solutions were found to be somewhat different. For this reason and because of the fact that both Q and QH_2 are present in the system, $2k_{-1}$ values were averaged for calculations of k_1. Although the values of $2k_{-1}$ used in these calculations were determined at *ca.* 22 °C rather than at 37 °C, it is unlikely that the difference in $2k_{-1}$ between 22 °C and 37 °C is significant. Previously k_1 has been reported only for the Q **1**/QH_2 **1** couple (58 M^{-1} s^{-1} at 25 °C and pH 7.0).[15] To compare this value of k_1 with that determined in the present work, it has to be recalculated for our conditions. When passing from pH 7.0 to pH 7.4 (with d(log k)/d(pH) = 2, see Fig. 4), k_1 will increase 6.3 times; when passing from 25 °C to 37 °C, k_1 (with $\Delta H = 50$ kJ mol^{-1} (Table 1)) will increase 2.2 times. Hence, the value of k_1 reported in ref. 15, being recalculated for our conditions, is expected to equal $58 \times 6.3 \times 2.2 \approx 800$ M^{-1} s^{-1}. The latter value is in reasonable agreement with 1300 ± 400 M^{-1} s^{-1} determined in the present study (Table 1). As seen from Table 1, k_1 in the series of methyl-substituted 1,4-benzoquinones/hydroquinones decreases dramatically with the number of methyl groups, *i.e.* in the direction of decreasing $E(Q/Q^{\bullet -})$; k_1 also decreases with the volume of alkyl substituent (*cf.* Q **2** with Q **3** and Q **4**). However, k_1 increases when methyl groups are replaced by methoxy groups (*cf.* Q **5** with Q **8**) despite the decrease in $E(Q/Q^{\bullet -})$.

Calculation of ΔE_1 and mid-point potential $E(Q^{\bullet -}/QH_2)$

The change of the one-electron reduction potential in equilibrium (1), ΔE_1 (in mV), was calculated from K_1 using the

Table 2 One-electron reduction mid-point potentials (in mV) in the system Q–$Q^{\bullet -}$–QH_2 at 25 °C and pH 7.0

Q/QH_2[a]	ΔE_1[b]	$E(Q/Q^{\bullet -})$[c]	$E(Q^{\bullet -}/QH_2)$	$E(Q^{\bullet -}/QH_2)$[c]
1	−370	+78	+448	+459
2	−391	+23	+414	+460
3	−395	0[d]	+395	
4	−485	−32[11]	+453	+489[f]
5	−443	−80	+363	+430
6	−428	−70[d]	+358	
7	−147	+470[e]	+617	623[1]
8	−337	−150[11]	+187	
9	−399	−110[g]	~+290	
10	>0	+650[e]	>+650	+726[1]
11	−380	−140	+240	+212[2]

[a] The structures of Q/QH_2 are given in Scheme 1. [b] Recalculated from data given in Table 1 using an experimental value of ΔH_1 if available (or $\Delta H_1 = 50$ kJ mol^{-1} when not available) and assuming that d(log K_1)/d(pH) = 2. [c] Taken from ref. 16, unless otherwise indicated. [d] Estimated based on the correlation of $E(Q/Q^{\bullet -})$ with the structures of alkyl-substituted 1,4-benzoquinones reported in refs. 16, 21. [e] Estimated from the correlation of $E(Q/Q^{\bullet -})$ in aqueous buffer and that in MeCN[21] (see below). [f] Calculated on the basis of data reported in ref. 11. [g] Estimated from the correlation of $E(Q/Q^{\bullet -})$ in aqueous buffer and that in MeCN.[22]

$$\ln K_1 = 0.0389 \Delta E_1 \qquad (5)$$

Nernst equation. Eqn. (5) shows ΔE_1 at the standard temperature, 25 °C. The values of ΔE_1 for the standard conditions (25 °C, pH 7.0) are given in Table 2. As mentioned above, ΔE_1 is the difference between two one-electron potentials, $E(Q/Q^{\bullet -})$ and $E(Q^{\bullet -}/QH_2)$† (eqn. (2)). If $E(Q/Q^{\bullet -})$ is known, eqn. (2) allows us to calculate the second potential $E(Q^{\bullet -}/QH_2)$ from ΔE_1. As a rule, the values of $E(Q/Q^{\bullet -})$ applied to calculate $E(Q^{\bullet -}/QH_2)$ were taken from ref. 16. The values of $E(Q^{\bullet -}/QH_2)$ calculated from ΔE_1 by eqn. (2) are listed in Table 2. While $E(Q^{\bullet -}/QH_2)$ for $Q^{\bullet -}$ **1**, $Q^{\bullet -}$ **7**, and $Q^{\bullet -}$ **11** reported in refs. 16, 23 and those determined in our work were in reasonable agreement, the difference for $Q^{\bullet -}$ **2**, $Q^{\bullet -}$ **4** and $Q^{\bullet -}$ **5** was rather significant (Table 2). It should be noticed that the $E(Q^{\bullet -}/QH_2)$ values reported in ref. 23 were calculated using a sophisticated protocol rather than directly. With $Q^{\bullet -}$ **3**, $Q^{\bullet -}$ **6**, $Q^{\bullet -}$ **8** and $Q^{\bullet -}$ **9**, the $E(Q^{\bullet -}/QH_2)$ was determined in our work for the first time.

The correlation between various one-electron reduction potentials

By contrast to aprotic organic solvents, direct determination of one-electron reduction potentials, $E(Q/Q^{\bullet -})$ and $E(Q^{\bullet -}/QH_2)$, in an aqueous medium using a routine electrochemical technique (polarography or potentiometry) is almost impossible because of the instability of $Q^{\bullet -}$. Under these circumstances, the determination of $E(Q/Q^{\bullet -})$ and $E(Q^{\bullet -}/QH_2)$ in aqueous solution requires much more complicated non-direct methods, mostly pulse radiolysis and the combination of pulse radiolysis and EPR technique using reference compounds with known reduction potentials. This is probably the reason why the information on $E(Q/Q^{\bullet -})$ and especially $E(Q^{\bullet -}/QH_2)$ in aqueous solution is much more limited as compared to organic solvents. Thus the approach using various correlations for prediction of unknown one-electron reduction potentials in aqueous solution looks very promising. Wardman[24] has drawn attention to an excellent correlation between $E(Q/Q^{\bullet -})$ determined for methyl-substituted 1,4-benzoquinones in aqueous buffer and those in aprotic organic solvents and the application of the correlation as a promising way to predict $E(Q/Q^{\bullet -})$ in water. As Fig. 5 demonstrates, this correlation is also workable for a larger assortment of Q including *tert*-butyl- and methoxy-substituted benzoquinones, several 1,4-naphthoquinones (NQ), and 9,10-anthraquinones (AQ) (see Scheme 2). However, hydroxy-substituted NQ and AQ visibly do not fit this correlation (Fig. 5). Without regard for hydroxy-substituted NQ and AQ, the correlation between $E(Q/Q^{\bullet -})$ in aqueous buffer, pH 7.0 (standard hydrogen electrode, SHE, as a reference electrode), $E(Q/Q^{\bullet -})_{aq}$, and that in acetonitrile (saturated calomel electrode, SCE, as a reference electrode), $E(Q/Q^{\bullet -})_{MeCN}$, is described by the eqn (6). Reduction potentials

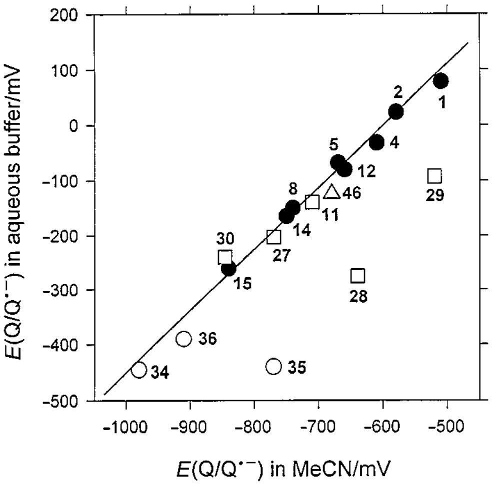


Fig. 5 The correlation between mid-point potential $E(Q/Q^{\bullet -})$ in aqueous buffer, pH 7.0, (SHE as a reference electrode) and $E(Q/Q^{\bullet -})$ in acetonitrile (SCE as a reference electrode) for 1,4-benzoquinones (●), 1,4-naphthoquinones (□), 9,10-anthraquinones (○) and miscellaneous compounds (△). Data were taken from ref. 14 and 18, respectively. Numbers at symbols represent $Q/Q^{\bullet -}/QH_2$ structures as they are given in Schemes 1 and 2.

$$E(Q/Q^{\bullet -})_{aq} = 650 + 1.1\ E(Q/Q^{\bullet -})_{MeCN} \qquad (6)$$

are given in mV. Such a correlation may be very useful in estimating $E(Q/Q^{\bullet -})_{aq}$ when $E(Q/Q^{\bullet -})_{MeCN}$ is known. Nearly the same correlation may be suggested with $E(Q/Q^{\bullet -})$ determined in other organic solvents.

Chambers[21] reported a linear correlation between $E(Q/Q^{\bullet -})$ determined in acetonitrile and the sum of the Hammett substituent constants, $\Sigma\sigma$, for substituted 1,4-benzoquinones and the related correlation for $E(Q^{\bullet -}/QH_2)$ for substituted 1,4-hydroquinones. A parallel existence of these two linear correlations suggests a linear correlation between $E(Q/Q^{\bullet -})$ and $E(Q^{\bullet -}/QH_2)$. The latter is given in Fig. 6. With a few exceptions, the values of $E(Q^{\bullet -}/QH_2)$ and $E(Q/Q^{\bullet -})$ demonstrate the excellent correlation for various kinds of Q and QH_2 that is described by eqn. (7).

$$E(Q^{\bullet -}/QH_2) = -680 + 0.81\ E(Q/Q^{\bullet -}) \qquad (7)$$

From the standpoint of quantum chemistry, the occurrence of this correlation means that, when Q transforms into $Q^{\bullet -}$ and $Q^{\bullet -}$ transforms into QH_2, an additional electron falls into the same lowest uncoupled molecular orbital (refs. 21, 22 and references therein). Fig. 7 depicts the same correlation for the case of aqueous solution. Although the general tendency remains the same—$E(Q^{\bullet -}/QH_2)$ decreases when $E(Q/Q^{\bullet -})$ decreases—the quality of the correlation is considerably worse, besides, it becomes non-linear. This is not a surprise since $E(Q^{\bullet -}/QH_2)$ depends on a prototropic equilibrium (characterized by p*K*) which varies significantly from one QH_2 to another; the latter results in a different contribution

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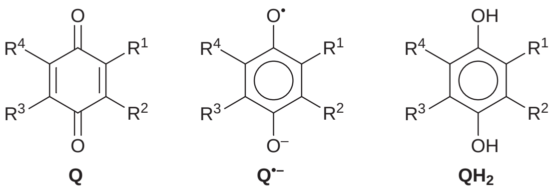
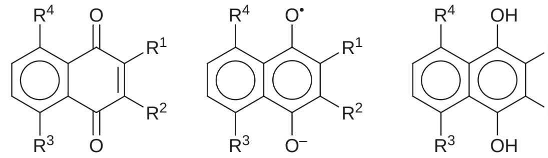
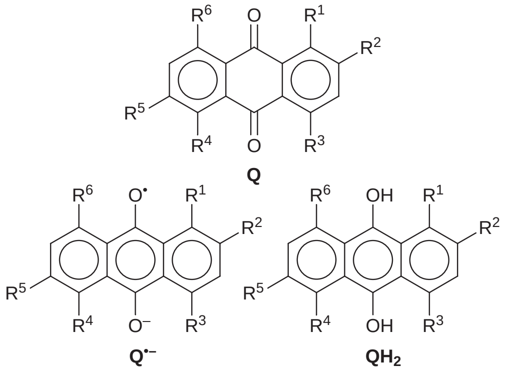
† In principle, the form $E(Q^{\bullet -}, 2H^+/QH_2)$ should be used instead of the short form $E(Q^{\bullet -}/QH_2)$. For simplicity, we use the short form ignoring protonation in the text.



	R^1	R^2	R^3	R^4
12	Me	H	Me	H
13	Me	Me	H	H
14	Me	Me	Me	H
15	Me	Me	Me	Me
16	Ph	H	H	H
17	Cl	H	H	H
18	$\mathrm{NMe_2}$	H	H	H
19	COMe	H	H	H
20	OCOMe	H	H	H
21	$\mathrm{CF_3}$	H	H	H
22	$\mathrm{NO_2}$	H	H	H
23	$\mathrm{CONH_2}$	H	H	H
24	Cl	H	Cl	H
25	Cl	Cl	Cl	H
26	Cl	CN	Cl	CN



	R^1	R^2	R^3	R^4
27	Me	H	H	H
28	OH	H	H	H
29	H	H	OH	H
30	Me	Me	H	H
31	$\mathrm{NH_2}$	H	H	H
32	Cl	Cl	H	H
33	OMe	OMe	H	H



	R^1	R^2	R^3	R^4	R^5	R^6
34	H	H	H	H	H	H
35	H	OH	H	H	H	H
36	H	$\mathrm{SO_3Na}$	H	H	H	H
37	Me	H	Me	H	H	H
38	Me	H	Me	Me	H	Me
39	$\mathrm{SO_3Na}$	H	H	$\mathrm{SO_3Na}$	H	H
40	H	$\mathrm{SO_3Na}$	H	H	$\mathrm{SO_3Na}$	H
41	OH	$\mathrm{SO_3Na}$	OH	H	H	H
42	OH	H	OH	H	$\mathrm{SO_3Na}$	H

Scheme 2 The structures of quinones, hydroquinones and semiquinones taken into the correlations between various reduction potentials (see Figs. 4–7).

of solvation energy to the reduction potential $E(\mathrm{Q}^{\bullet-}/\mathrm{QH_2})$. Nevertheless, the correlation presented in Fig. 7 may be useful for a rough estimation of unknown values of $E(\mathrm{Q}^{\bullet-}/\mathrm{QH_2})$ when $E(\mathrm{Q}/\mathrm{Q}^{\bullet-})$ is available.

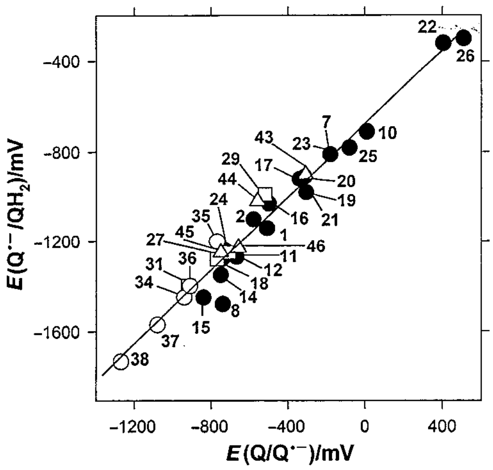


Fig. 6 The correlation between $E(\mathrm{Q}^{\bullet-}/\mathrm{QH_2})$ and $E(\mathrm{Q}/\mathrm{Q}^{\bullet-})$ determined in acetonitrile (SCE as a reference electrode) for 1,4-benzoquinones (●), 1,4-naphthoquinones (□), 9,10-anthraquinones (○) and miscellaneous compounds (△). Data were taken from ref. 18. Numbers at symbols represent $\mathrm{Q}/\mathrm{Q}^{\bullet-}/\mathrm{QH_2}$ structures as they are given in Schemes 1 and 2.

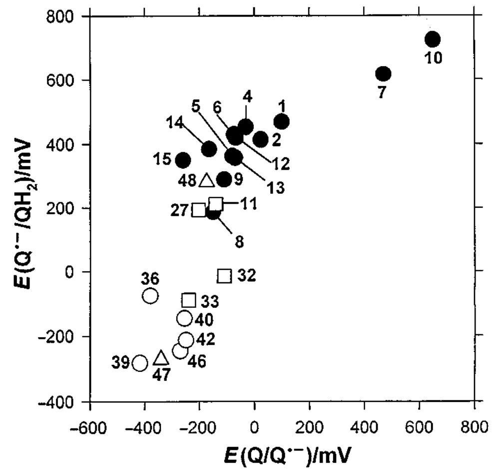


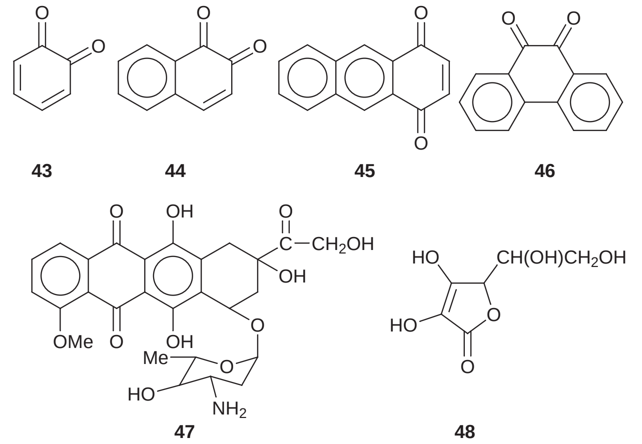
Fig. 7 The correlation between mid-potential $E(\mathrm{Q}^{\bullet-}/\mathrm{QH_2})$ and $E(\mathrm{Q}/\mathrm{Q}^{\bullet-})$ determined in aqueous buffer, pH 7.0, (SHE as a reference electrode) for benzoquinones (●), 1,4-naphthoquinones (□), 9,10-anthraquinones (○) and miscellaneous compounds (△). Data were taken largely from ref. 14 and partly from Table 2 of the present work. Numbers at symbols represent $\mathrm{Q}/\mathrm{Q}^{\bullet-}/\mathrm{QH_2}$ structures as they are given in Schemes 1 and 2.

Redox potentials and the kinetics of $\mathrm{QH_2}$ autoxidation

Traditionally, the autoxidation of $\mathrm{QH_2}$ is considered to be triggered by the direct interaction of $\mathrm{QH_2}$ with molecular oxygen (eqn. (8)). This is a reason why repeated attempts have

$$\mathrm{QH_2 + O_2 \longrightarrow Q^{\bullet-} + O_2^{\bullet-} + 2H^+} \qquad (8)$$

been made to correlate the oxidizability of $\mathrm{QH_2}$ with the one-electron potential $E(\mathrm{Q}^{\bullet-}/\mathrm{QH_2})$[1,2] and the two-electron reduction potential $E(\mathrm{Q}/\mathrm{QH_2})$.[25] These attempts had only moderate success and many $\mathrm{QH_2}$ dropped out of the correlation. Furthermore, reaction (8) is spin-restricted[26] and is thus expected to be extremely slow under physiological conditions. In addition to this theoretical argument against reaction (8) as a triggering step of $\mathrm{QH_2}$ autoxidation, experimental counter arguments can be found in the literature. For many types of $\mathrm{QH_2}$, *e.g.* 1,4-hydroquinone,[14] 1,4-naphthoquinones,[27] and catecholamines,[28] $\mathrm{QH_2}$ autoxidation was reported to be a self-accelerated autocatalytic process, with Q being a catalyst. It was shown that the initial step of the oxidation of many $\mathrm{QH_2}$



Scheme 3 The structures of quinones (**43**–**47**) and ascorbic acid (**48**) taken into the correlations between various reduction potentials (see Figs. 4–7).

was accelerated by adding Q.[14,28] These observations suggest reaction (1) between Q and QH_2 resulting in the formation of $Q^{\bullet -}$ to be the main trigger reaction of QH_2 autoxidation. If it is the case, the efficiency of this process may be characterized by either K_1, *i.e.* the difference $\Delta E_1 = E(Q/Q^{\bullet -}) - E(Q^{\bullet -}/QH_2)$, or, to be more precise, by k_1.

To provide support for this view, a correlation between the rate of QH_2 autoxidation and ΔE_1 or k_1 is required. The major problem is the evident shortage in the systematic and comparable kinetic information on the process under consideration. As a rule, we have a chance to correlate the oxidizability of QH_2 determined within a single work only. For this reason we restrict our consideration to a few remarks and specific examples. Doing this, we should take into account that the rate of QH_2 oxidation is expected to depend not only on the rate of reaction (1) but also on other factors including the reactivity of $Q^{\bullet -}$ towards oxygen in the equilibrium (9). If $E(Q/Q^{\bullet -}) > -150$ mV,

$$Q^{\bullet -} + O_2 \rightleftharpoons Q + O_2^{\bullet -} \qquad (9)$$

equilibrium (9) is shifted to the left.[29] The situation may be altered by adding superoxide dismutase (SOD) that effectively purges the system from $O_2^{\bullet -}$. O'Brien[1] reported the elevated oxidizability of chloro-substituted 1,4-hydroquinones though the values of $E(Q^{\bullet -}/QH_2)$ for these QH_2 are very high (Table 2). The non-substituted 1,4-benzoquinone for which $E(Q^{\bullet -}/QH_2)$ is also very positive (Table 2) was reported to display rather high oxidizability when SOD was added.[14] The oxidizability of methyl-substituted 1,4-hydroquinones decreases (with adding SOD) with the increase of the number of methyl groups[30] although $E(Q^{\bullet -}/QH_2)$ becomes less positive in this direction (Table 2). In the meantime, the oxidizability of methyl-substituted 1,4-hydroquinones correlates reasonably with ΔE_1 and k_1.[30] Besides, the elevated oxidizability of QH_2 **8** and QH_2 **11**[1,2] is in line with a rather high value of k_1 (Table 1). Elevated oxidizibility of several other QH_2[1,2] combines, as a rule, with elevated values of ΔE_1. 1,4,5,8-Tetrahydroxynaphthalene ($\Delta E_1 = -95$ mV), 2,3-dimethoxy-1,4-dihydroxynaphthalene ($\Delta E_1 = -130$ mV) and adriamycine ($\Delta E_1 = +70$ mV) are examples of this.

This approach probably may be applied to the oxidation of substrates other than QH_2. Ascorbate was reported to oxidize very slowly in the absence of a catalyst and not to display any tendency for autoacceleration of this process.[17,18] This suggests that the rate of the reaction between ascorbate, $AscH^-$ and its oxidized form, dehydroascorbic acid, DAsc, with the formation of the ascorbyl radical, $Asc^{\bullet -}$, (an analog of reaction (1)) is very low. The latter may be roughly estimated. One-electron reduction potentials $E(DAsc/Asc^{\bullet -})$ and $E(Asc^{\bullet -}/AscH^-)$ were reported to be -174 mV[31] and $+282$ mV[16], respectively; the rate constant for $Asc^{\bullet -}$ disproportionation at pH 7.0 is as much as 3×10^6 M^{-1} s^{-1}.[32] It is possible to calculate from these data $E(DAsc/Asc^{\bullet -}) - E(Asc^{\bullet -}/AscH^-) = -456$ mV and $k_1 = 0.7$ M^{-1} s^{-1}. Such a low value of k_1 could explain the main features of $AscH^-$ autoxidation.

In conclusion, the above observations strongly suggest that the rate of reaction (1) and the value of ΔE_1 are the key factors controlling QH_2 oxidizability.

Acknowledgements

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