

Role of Proton-Coupled Electron Transfer in the Redox Interconversion between Benzoquinone and Hydroquinone

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S Supporting Information

ABSTRACT: Benzoquinone/hydroquinone redox interconversion by the reversible $\text{Os}(\text{dmb})_3^{3+/2+}$ couple over an extended pH range with added acids and bases has revealed the existence of seven discrete pathways. Application of spectrophotometric monitoring with stopped-flow mixing has been used to explore the role of PCET. The results have revealed a role for phosphoric acid and acetate as proton donor and acceptor in the concerted electron–proton transfer reduction of benzoquinone and oxidation of hydroquinone, respectively.

Derivatives of benzoquinone/hydroquinone (Q/H₂Q) play essential roles in biology.¹ An important example appears in photosynthesis, in the reduction of plastoquinone (Q_B) to the mobile redox carrier plastoquinol (H₂Q_B), which is transported through the thylakoid membrane to cytochrome *b₆f*, where it is oxidized to Q_B with proton release to the lumen.²

Interconversion between Q and H₂Q in photosystem II (PSII) and amino acid redox mediators in biology utilize proton-coupled electron transfer (PCET) in transferring redox equivalents with the transfer of both electrons and protons.^{1a} In tyrosine and cysteine oxidation, concerted electron–proton transfer (EPT) pathways are utilized to avoid high-energy protonated radical intermediates.^{3,4} In these reactions, pendant bases or solvent molecules enable EPT by acting as H⁺ acceptors avoiding high-energy intermediates like TyrOH^{•+}.³ For tyrosine oxidation, $E^\circ \approx 1.5$ V (vs NHE) for 1e[−] oxidation to TyrOH^{•+}, compared to $E^\circ \approx 1.0$ V for oxidation of the tyrosine–histidine acid–base pair in PSII, TyrOH---His → TyrO^{•−}+H-His.^{2a–c}

Amino acid oxidation is irreversible, but the Q/H₂Q couple is reversible, providing an opportunity for mechanistic investigation in “both directions”. There is an extensive literature on Q/H₂Q redox interconversion,⁵ but very little is known about the role of acid- and base-assisted PCET pathways.

We report here mechanistic details of the redox interconversion between Q and H₂Q as a function of pH by the couple $\text{Os}(\text{dmb})_3^{3+/2+}$ (dmb = 4,4′-dimethyl-2,2′-bipyridine). Remarkably, our results provide evidence for seven distinct pathways for this interconversion, including an important role for concerted EPT that may be of relevance in biological Q/H₂Q reactions.

Results of extensive electrochemical measurements on Q/H₂Q interconversion are available,⁶ but interpretation is typically complicated by adsorption and mass-transfer effects. Following Laviron, a potential–pK_a diagram for the Q/H₂Q couple under standard conditions is shown in Figure 1a.⁷ From the diagram the 1e[−] semiquinone intermediate, HQ[•], is highly unstable toward disproportionation, 2HQ[•] → H₂Q + Q, with $\Delta G^\circ = -0.7$ eV.⁸

The implied importance of PCET and concerted EPT^{2a,b,9} in Q/H₂Q reactivity is apparent from the E° –pK_a diagram. For PCET reduction of Q to HQ[•], $E^\circ(Q/\text{HQ}^\bullet) = 0.34$ V (vs NHE). In a mechanism involving initial proton transfer, $\text{Q} + \text{H}^+ \rightleftharpoons \text{HQ}^+$, followed by electron transfer, $\text{HQ}^+ + \text{e}^- \rightarrow \text{HQ}^\bullet$ (PT-ET), protonation is unfavorable, with $\text{pK}_a(\text{HQ}^+) \approx -6$ and $\Delta G^\circ = -0.059(\text{pH}+6) = 0.35$ eV at pH 0. HQ⁺ is an enhanced oxidant with $E^\circ(\text{HQ}^+/\text{HQ}^\bullet) = 0.70$ V (vs NHE). For electron transfer followed by proton transfer (ET-PT), $E^\circ(Q/Q^{\bullet-}) = 0.099$ V for the initial electron transfer, with $\Delta G^\circ = -0.24$ eV for protonation of Q^{•−} at pH 0.

As shown in Figure 1b, $E^\circ = 0.63$ V (vs NHE) for the $\text{Os}(\text{dmb})_3^{3+/2+}$ couple, and it is pH-independent. The Os complexes are substitutionally inert and have minimal barriers to electron transfer.¹⁰ By contrast, E° for the Q/H₂Q couple is pH-dependent and varies with the Nernst slope of -0.059 V/pH unit for a 2e[−]/2H⁺ couple. E° values for the two couples cross at pH 1.2. Below this pH, $\text{Os}(\text{dmb})_3^{3+/2+}$ reduction of Q is spontaneous; above this pH, $\text{Os}(\text{dmb})_3^{3+/2+}$ oxidation of H₂Q is spontaneous. By varying the pH, the overall reaction can be studied in either direction.

In our experiments, the kinetics of reduction of Q by $\text{Os}(\text{dmb})_3^{2+}$ or oxidation of H₂Q by $\text{Os}(\text{dmb})_3^{3+}$ were investigated by stopped-flow mixing with spectrophotometric monitoring at 20 °C, *I* = 0.8 M (NaCl). Stock solutions of $\text{Os}(\text{dmb})_3^{2+}$ were freshly prepared and oxidized to Os^{III} by Cl₂,

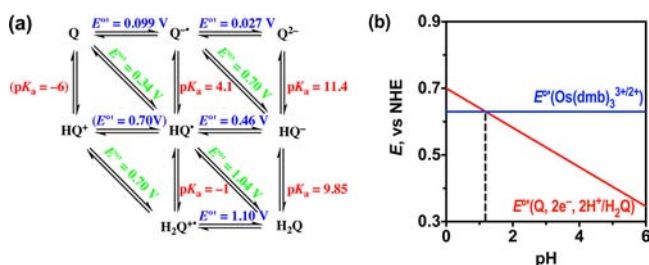


Figure 1. (a) E° (vs NHE)–pK_a diagram for the Q/H₂Q couple. Diagonal lines give potentials vs NHE for 1H⁺/1e[−] PCET couples at pH 0 in water. pK_a for HQ⁺ was obtained in the present work. (b) Calculated E° –pH diagram for Q/H₂Q (red) and $\text{Os}(\text{dmb})_3^{3+/2+}$ (blue) couples.

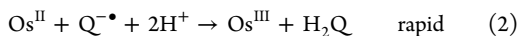
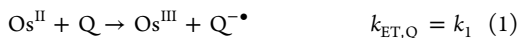
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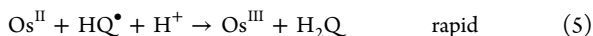
followed by an argon purge. All solutions were degassed with argon prior to stopped-flow mixing. *p*-Benzoquinone was purified by sublimation to give yellow crystals. The purities of Q and H₂Q were checked by ¹H NMR.

Absorption–time traces for either appearance of Os(dmb)₃²⁺ by Os(dmb)₃³⁺ oxidation of H₂Q, or its disappearance by oxidation by Q, were monitored at the metal-to-ligand charge transfer absorption, 480 nm. Under pseudo-first-order conditions in either Q or H₂Q, with added buffers or acids, both oxidation and reduction of Os^{II} followed first-order kinetics, with analysis of the data giving an observed rate constant *k*_{obs}. Typical absorption–time traces and kinetic analyses are shown in the Supporting Information, Figure SI.1.

In an initial set of experiments, Os(dmb)₃²⁺ reduction of Q was investigated under pseudo-first-order conditions in [Q] with *I* = 0.8 M (NaCl) at *T* = 20 °C. In 0.16 M HCl, reduction occurred with the rate law $-d[\text{Os}^{\text{II}}]/dt = k_{\text{obs}}[\text{Os}^{\text{II}}]$ (Figure SI.2). *k*_{obs} varied linearly with added quinone, [Q]_T, with the slope *k* = 270 ± 4 M⁻¹ s⁻¹ and negligible intercept. The acid dependence of the reaction was investigated over the pH range 0.6–2.0.¹¹ As shown in Figure SI.3a, *k*_{obs}/[Q]_T varied linearly with [H⁺], consistent with the expression $k_{\text{obs}}/[\text{Q}]_{\text{T}} = k_1 + k_2[\text{H}^+]$, with *k*₁ = 9.7 ± 2.6 M⁻¹ s⁻¹ and *k*₂ = (2.2 ± 0.1) × 10³ M⁻² s⁻¹ (Table SI.1). The term zero-order in [H⁺] is consistent with outer-sphere electron transfer with *k*₁ = *k*_{ET,Q}



and the pathway first-order in [H⁺] is consistent with pre-protonation of Q to give HQ⁺, followed by ET,



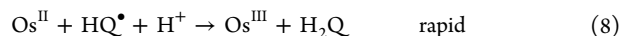
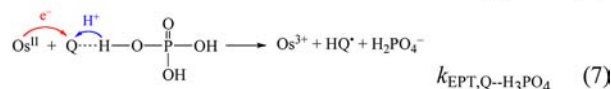
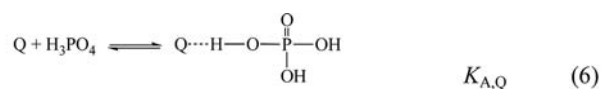
With this interpretation and p*K*_{a,HQ⁺} = -6, the rate constant for outer-sphere reduction of HQ⁺, $k_{\text{ET,HQ}^+} = (2.2 \pm 0.1) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, approaches the diffusion-controlled limit in H₂O.¹² The significant rate enhancement compared to reduction of Q is not surprising since $\Delta G^{\circ} = -0.07 \text{ eV}$ for Os^{II} reduction of HQ⁺ and 0.53 eV for reduction of Q. By comparison, HQ[•] disproportionation to ¹/₂Q + ¹/₂H₂Q occurs with $\Delta G^{\circ} = -0.7 \text{ eV}$ and *k*_{disp} = 1.1 × 10⁹ M⁻¹ s⁻¹.⁸

Reduction of Q was investigated in D₂O with added DCl with p*D* varied from 0.6 to 2.0.¹³ Variation of *k*_{obs}/[Q]_T with [D⁺] was linear (Figure SI.3b), with *k*₁^D = 8.8 ± 1.6 M⁻¹ s⁻¹ and *k*₂^D = (1.5 ± 0.1) × 10³ s⁻¹, yielding H₂O/D₂O solvent kinetic isotope effects (KIE; *k*_{H₂O}/*k*_{D₂O}) of 1.1 ± 0.4 for *k*₁ and 1.4 ± 0.1 for *k*₂ (Table SI.1). Although the magnitude of KIE for *k*₁ implies sequential ET-PT, a contribution by concerted EPT with water as the proton donor cannot be ruled out.

We also searched for a possible EPT pathway for reduction with added H₃PO₄ at fixed pH (1.3). In these experiments, the buffer ratio was held constant at [H₃PO₄]/[H₂PO₄⁻] = 4, and [H₃PO₄] was varied by increasing the total buffer concentration. Ionic strength was adjusted to 0.8 M by adding NaCl.¹⁴ As shown in Figure SI.4a, *k*_{obs} increased linearly with [H₃PO₄], with no sign of saturation up to [H₃PO₄] = 0.48 M. From a plot of $k_{\text{obs}}/[\text{Q}]_{\text{T}} = k' + k_3[\text{H}_3\text{PO}_4]$, *k*₃ = 570 ± 20 M⁻² s⁻¹ with an intercept, *k*' = *k*₁ + *k*₂[H⁺], of 123 ± 4 M⁻¹ s⁻¹. The experiment was repeated in D₂O by adding varying concentrations of D₃PO₄.¹⁵ As shown in

Figure SI.4b, *k*_{obs}/[Q]_T increased linearly with [D₃PO₄], with *k*₃^D = 654 ± 28 M⁻² s⁻¹ and *k*₃^H/*k*₃^D = 0.87 ± 0.05.

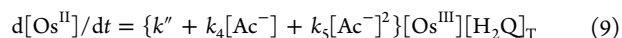
A [H₃PO₄]-dependent pathway is a novel observation, consistent with pre-association of H₃PO₄ (eq 6) followed by concerted multiple-site electron–proton transfer (MS-EPT)^{2a} (eq 7) with proton transfer to Q and electron transfer from Os^{II}. It is analogous to related base-catalyzed pathways in the oxidation of tyrosine, TyrOH---His + Os^{III} → TyO[•] + ⁺H-His + Os^{II}.^{3c,d,16} For the EPT pathway, $\Delta G^{\circ} = E^{\circ}(\text{Os}^{\text{III/II}}) - E^{\circ}(\text{Q}^{\bullet/\bullet}) - 0.059(\text{p}K_{\text{a,HQ}^{\bullet}} - \text{p}K_{\text{a1,H}_3\text{PO}_4}) = 0.39 \text{ eV}$.



The appearance of the inverse KIE for the EPT pathway was unexpected. For EPT oxidation of tyrosine by Os(bpy)₃³⁺ with histidine as the proton acceptor, $k_{\text{EPT},K_{\text{A}}(\text{H}_2\text{O})}/k_{\text{EPT},K_{\text{A}}(\text{D}_2\text{O})} = 3.2$.¹⁶ As shown in eq 7, *k*₃ = *k*_{EPT,Q-H₃PO₄}*K*_{A,Q} and the inverse isotope effect may originate in the pre-equilibrium. Small KIEs have been reported for other EPT reactions^{17a} and discussed by Hammes-Schiffer and Cukier.^{17b-d}

The reverse reaction, oxidation of H₂Q by Os(dmb)₃³⁺, was investigated under the same conditions with H₂Q in pseudo-first-order excess from 0.2 to 4 mM over the pH range 3.5–5.6. As shown in Figures SI.1b and SI.5, under these conditions, the reaction is first-order in both Os^{III} and H₂Q, consistent with the rate law $d[\text{Os}^{\text{II}}]/dt = k_{\text{obs}}[\text{Os}^{\text{III}}]$. At pH 4.0, *k*_{obs} varied linearly with [H₂Q]_T, with $k_{\text{obs}}/[\text{H}_2\text{Q}]_{\text{T}} = (1.1 \pm 0.1) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ and a negligible intercept.

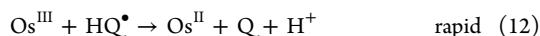
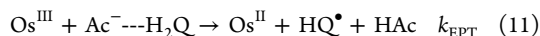
Evidence for EPT pathways was found with acetate (Ac⁻) added as the acceptor base. These experiments were conducted at fixed pH (3.5) and buffer ratio [HAc]/[Ac⁻] = 10/1, varying the concentrations of both acid and base. As shown in Figure SI.6a, *k*_{obs}/[H₂Q]_T varies quadratically with [Ac⁻] over the buffer concentration range 0.05–4 M, consistent with the rate law



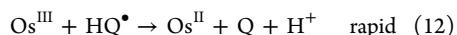
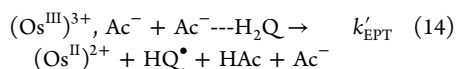
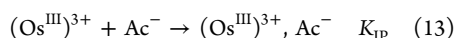
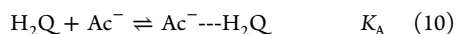
As determined from the intercept, *k*' = (4.8 ± 0.2) × 10³ M⁻¹ s⁻¹. This is consistent with the value obtained by direct measurement (*k*' = *k*₆ + *k*₇/[H⁺], see below). As shown in Figure SI.6a, the rate constants *k*₄ and *k*₅ were obtained by fitting the extended data set to give *k*₄ = (2.6 ± 0.1) × 10⁵ M⁻² s⁻¹ and *k*₅ = (8.2 ± 0.1) × 10⁵ M⁻³ s⁻¹.

The experiments with added HAc/Ac⁻ were repeated in D₂O at p*D* 4.1 with the same rate law behavior (Figure SI.6b). Analysis of the results gave *k*'(D₂O) = (1.8 ± 0.1) × 10³ M⁻¹ s⁻¹, consistent with the value obtained in D₂O with no added Ac⁻ (see below), with *k*₄^D = (9.9 ± 0.3) × 10⁴ M⁻² s⁻¹ and *k*₅^D = (2.9 ± 0.2) × 10⁵ M⁻³ s⁻¹. Based on these results and those obtained in H₂O, the H₂O/D₂O KIE values are 2.6 ± 0.1 for *k*₄ and 2.8 ± 0.2 for *k*₅.

The most straightforward interpretation of the term first-order in Ac⁻ is that, as found for tyrosine oxidation by Os(bpy)₃³⁺, pre-association occurs between Ac⁻ and H₂Q, followed by MS-EPT:



Given the similarity in KIE values and the high concentrations of Ac^- used, the squared term in $[\text{Ac}^-]$ may arise from a parallel mechanism, but with ion-pairing with the tri-cationic metal complex oxidant by a second Ac^- , followed by MS-EPT oxidation of $\text{H}_2\text{Q} \cdots \text{Ac}^-$ (eqs 13 and 14):



Other interpretations are possible, including formation of a doubly H-bonded Ac^- adduct with H_2Q .

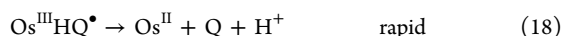
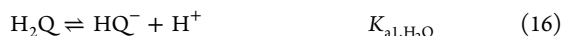
With this interpretation, $k_4 = K_A k_{\text{EPT}}$ and $k_5 = K_{\text{IP}} K_A k'_{\text{EPT}}$, with K_A the association constant between Ac^- and H_2Q and K_{IP} the ion pair constant between $\text{Os}(\text{dmb})_3^{3+}$ and Ac^- . The observed KIEs include contributions from the pre-equilibria but are presumably dominated by the KIEs for the EPT steps.^{3b-d}

An additional pH-dependent term appears in the rate law from oxidation of HQ^- . This term was investigated by stopped-flow measurements over the pH range 3.5–5.6 with added 0.05 M Ac^- buffer at $I = 0.8$ M. Under these conditions, there are contributions to k_{obs} from the pathways first- and second-order in $[\text{Ac}^-]$ (eq 9). A correction was made to k_{obs} for their contributions by using the known values for k_4 and k_5 with $[\text{Ac}^-] = K_{\text{a,HAc}}[\text{buffer}]/([\text{H}^+] + K_{\text{a,HAc}})$. As shown in Figure SI.7a, under these conditions $k_{\text{obs}}/[\text{H}_2\text{Q}]_{\text{T}}$ varied linearly with $[\text{H}^+]$ with $k_6 = (3.5 \pm 0.1) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ and $k_7 = 0.54 \pm 0.01 \text{ s}^{-1}$:

$$\frac{k_{\text{obs}}}{[\text{H}_2\text{Q}]_{\text{T}}} = k_4[\text{Ac}^-] + k_5[\text{Ac}^-]^2 + k_6 + \frac{k_7}{[\text{H}^+]} \quad (15)$$

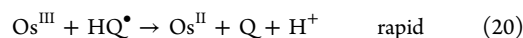
The pD dependence was also investigated for this pathway in D_2O solutions dilute in added Ac^- (0.01 M) free of contributions from the MS-EPT pathways. A fit of a plot of $k_{\text{obs}}/[\text{H}_2\text{Q}]$ vs pD (Figure SI.7b) to the expression $k_{\text{obs}}/[\text{H}_2\text{Q}]_{\text{T}} = k_6^{\text{D}} + k_7^{\text{D}}/[\text{D}^+]$ gave $k_6^{\text{D}} = (1.0 \pm 0.1) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ and $k_7^{\text{D}} = (9.8 \pm 0.2) \times 10^{-2} \text{ s}^{-1}$. As noted above, $k''^{\text{D}} = k_6^{\text{D}} + k_7^{\text{D}}/[\text{D}^+]$.¹³ Based on these values, $\text{H}_2\text{O}/\text{D}_2\text{O}$ KIEs were 3.5 ± 0.2 for k_6 and 5.5 ± 0.1 for k_7 .

For the pathway through k_7 , the appearance of the inverse first-order dependence in $[\text{H}^+]$ is consistent with deprotonation of H_2Q to give HQ^- , followed by ET:

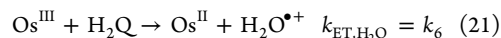


With $\text{p}K_{\text{a1,H}_2\text{Q}} = 9.82^{18}$ and $k_7 = 0.54 \pm 0.01 \text{ s}^{-1}$, $k_{\text{ET,HQ}^-} = (3.6 \pm 0.1) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ was obtained, near the diffusion-controlled limit of $7 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.¹⁹ Given $\text{p}K_{\text{a1,D}_2\text{Q}} \approx 10.4$ in D_2O ,²⁰ $K_{\text{a1,H}_2\text{Q}}(\text{H}_2\text{O})/K_{\text{a1,D}_2\text{Q}}(\text{D}_2\text{O}) \approx 4.0$, and the KIE for $k_{\text{ET,HQ}^-}$ is ~ 1.4 , consistent with outer-sphere oxidation as in eq 17.

The rate law and KIE for the k_6 term are consistent with electron-transfer oxidation of H_2Q but with simultaneous proton transfer to the solvent (eq 19):

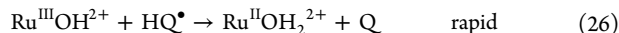
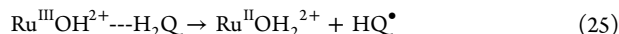
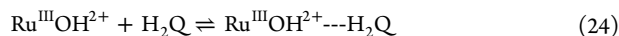


This pathway is kinetically indistinguishable from outer-sphere oxidation of H_2Q to $\text{H}_2\text{Q}^{\bullet+}$ followed by proton equilibration from $\text{H}_2\text{Q}^{\bullet+}$ with $K_{\text{a,H}_2\text{Q}^{\bullet+}} = 10$ (eqs 21 and 22):



However, the magnitude of the KIE points to a dominant role for MS-EPT with the solvent as the proton acceptor. Once again, EPT is energetically favored. For the initial ET step in eq 21, $\Delta G^{\circ'} = +0.47 \text{ eV}$ based on $E^{\circ'}$ values for the two couples. For the MS-EPT step (eq 19), $\Delta G^{\circ'} = -[E^{\circ'}(\text{Os}^{\text{III/II}}) - E^{\circ'}(\text{H}_2\text{Q}^{\bullet+}/\text{H}_2\text{Q})] - 0.059(\text{p}K_{\text{a}}(\text{H}_3\text{O}^+) - \text{p}K_{\text{a}}(\text{H}_2\text{Q}^{\bullet+})) = 0.41 \text{ eV}$.²¹

This result highlights an important role for an EPT pathway in the oxidation of H_2Q in water, in this case with a solvent molecule or water cluster acting as the proton acceptor as reported earlier for phenol oxidation by Stanbury^{22a} and Saveant.^{22b} By comparison, oxidation of H_2Q by the Ru^{III} oxidant, $\text{Ru}^{\text{III}}(\text{bpy})_2(\text{py})(\text{OH})^{2+}$, occurs by direct EPT with both electron and proton transfer to the $\text{Ru}^{\text{III}}\text{-OH}^{2+}$ acceptor,



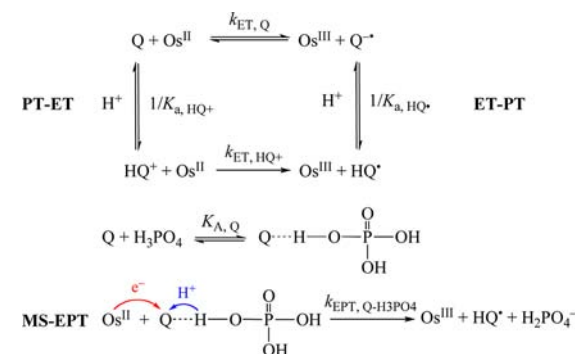
This reaction occurs with a KIE of 9.7 ± 0.1 .^{5c}

Our results highlight a remarkable versatility in the redox interconversion between quinone and hydroquinone by the outer-sphere $\text{Os}(\text{dmb})_3^{3+/2+}$ couple. This versatility arises from the nature of the reagents themselves with accessibility to $1e^-$ intermediates $\text{Q}^{\bullet-}$ and $\text{H}_2\text{Q}^{\bullet+}$ by $1e^-$ reduction of Q or oxidation of H_2Q , or to HQ^\bullet and by their use of EPT pathways with concerted e^-/H^+ transfer to Q or from H_2Q . A summary is given in Scheme 1 for the reduction of Q and in Scheme 2 for the oxidation of H_2Q .

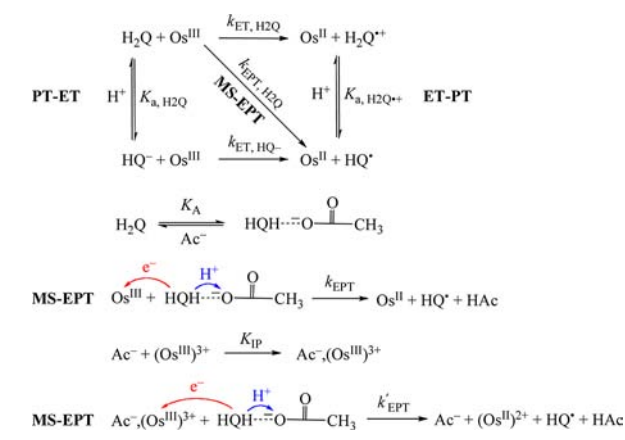
Important insights also emerge for the individual pathways:

(i) Specific acid and base catalysis occur for both reduction of Q and oxidation of H_2Q . This is due to the relatively high energy of the $1e^-$ intermediates $\text{Q}^{\bullet-}$ and $\text{H}_2\text{Q}^{\bullet+}$, which favors pathways involving PT-ET or ET-PT with prior formation of HQ^\dagger or HQ^- .

Scheme 1



Scheme 2



(ii) General acid and base catalysis appears with the acid (H_3PO_4) or base (Ac^-) forms of added buffers due to the intervention of concerted EPT pathways which give $\text{HQ} \cdot$ directly by reduction of $\text{Q} \cdots \text{HA}$ or oxidation of $\text{Q} \cdots \text{H}_2\text{Q}$. This is, no doubt, a general phenomenon and, as for tyrosine, will appear generally with added proton acceptor bases including use of these couples in biology.

(iii) In the oxidation of H_2Q by Os^{III} , the dominant mechanism is EPT with concerted proton transfer to the solvent.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental details and analyses. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (13) $\text{pD} = -\log [\text{D}^+] - \log \gamma_{\text{D}^+}$, assuming that $\gamma_{\text{D}^+} = \gamma_{\text{H}^+}$.

- (14) $\text{p}K_{\text{a}1, \text{H}_3\text{PO}_4} = -1.79$ at $I = 0.8 \text{ M}$ was converted from the reported values, 2.127 at zero ionic strength; see SI.

- (15) $\text{p}K_{\text{a}1, \text{D}_3\text{PO}_4} = 2.06$ at $I = 0.8 \text{ M}$ in D_2O was converted from the reported values, 2.3981 at zero ionic strength with $\gamma_{\text{H}^+} = \gamma_{\text{D}^+}$. $\text{pD} = \text{pH}$ meter reading + 0.4; see SI.

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- (19) The bimolecular diffusion control limit, $k_{\text{D}} = 3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, was corrected for the electrostatic interaction between $(\text{Os}^{\text{III}})^{3+}$ and HQ^- ; see SI.

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