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ESTIMATING ONE-ELECTRON REDUCTION POTENTIALS OF QUINONES

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The one-electron reduction potential $E^\text{1}$ of benzo-, naphtho- and anthracenequinones is related to their ability to undergo redox cycling and elicit cytotoxicity through oxidative stress. To evaluate a general approach to estimate the $E^\text{1}$ of benzo-, naphtho- and anthracenequinones, QSAR approaches based on gas phase and solvation based methods were employed.

Stereoelectronic descriptors of ground state quinones, respective intermediates of the redox cycle, and the differences in parameters for the transition between intermediates were evaluated. The variation of $E^\text{1}$ was correlated with descriptors of the parent quinones and specific transition parameters. The energy of the highest occupied molecular orbital (the inverse of the ionization potential) and the energy of the lowest unoccupied molecular orbital of the parent benzoquinones were significantly correlated to $E^\text{1}$. With the exclusion of ortho-hydroxy-substituted compounds, the reaction enthalpies for the quinone-semiquinone couple, in combination with volume polarizability, were significantly correlated to $E^\text{1}$ across the entire dataset.

The QSARs obtained were found to be consistent with the hypothesis that quinones which have a greater ability to delocalize electron density should have more positive reduction potentials for the quinone-semiquinone couple. In general, models incorporating solvation descriptors were found to be better correlated to $E^\text{1}$ than those based on gas-phase descriptors, especially when evaluated across structural classes of quinones.

KEY WORDS: QSAR; quinones; one-electron reduction potential; redox cycling; solvation effects.

INTRODUCTION

A major factor in determining the rate of avoprotein-mediated reduction of quinones, and therefore their ability to undergo redox cycling and elicit cytotoxicity through oxidative stress, is the one-electron reduction potential ($E^\text{1}$ or $E^\text{2}$) of the quinone-semiquinone radical couple ($Q\cdot Q^-\cdot$).¹,² The observed dependence of redox cycling and oxidative stress on the $E^\text{1}$ of the $Q\cdot Q^-\cdot$ couple arises from the studies

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that have established narrow reduction potential windows that are based on the single-electron potential of the reductases, such as NADPH-cytochrome P-450 reductase (−240 mV) and NADH-cytochrome b5 reductase (−170 mV), and the reduction potential of the O₂/O⁻ couple.⁵,⁴,⁵,⁶ Hence, the estimates of one-electron reduction potentials for quinones would be extremely useful for assessing a toxic mode of action associated with oxidative stress.

In a recently reported study,⁷ the E₁⁺ of benzo- (BQs), naptho- (NQs) and anthracenequinones (AQs) were estimated using conventional semiempirical computational methods (PM3 Hamiltonian) to model electronic structure of the parent compounds and respective semiquinone intermediates. It was hypothesized in this previous study that quinones which have greater ability to delocalize electron density will have more positive reduction potentials for the Q⁻⁻couple. Such quinones should have lower values for aromaticity indices (higher evenness of electron distribution), lower-energy HOMO orbitals (lower electron donor ability; within the semi-empirical approximations being used HOMO is equal to the negative ionization potential) and lower-energy LUMO orbitals (higher electron acceptor ability). Consistent with this hypothesis, it was found that the more positive reduction potentials of 1,4-BQs and 1,4-NQs were correlated with more negative values of E_HOMO. However, 1,2-quinones, quinones with ortho-substituted hydroxyl groups and NQs with intramolecular hydrogen bonding or direct electrostatic interaction correlated with E_HOMO in a significantly different manner, which suggested that hydrogen bonding and electrostatic interaction increased charge delocalization. The effect of internal hydrogen bonding⁸ and neighboring group interactions⁹,¹⁰ on E₁⁺ have been reported and associated with difficulties in predicting potentials using the Hammett para substituent constant.⁹,¹⁰

It was also assumed in the previous study⁷ that the one-electron reduction potential should be related to the free energy change of the equilibrium between the parent quinone and the radical anion. Thus, the semiquinones formed should be more likely to act as electron donors and the greater negative charge should cause displacement of the frontier HOMO and LUMO orbitals towards the higher energies, thereby increasing electron donor ability and decreasing electron acceptor properties. However, a signcant correlation with the heats of reaction or variation of frontier orbitals for the transition from the quinones to the radical anions was not obtained.⁷

Overall, our recent results showed that measures related to electron delocalization can be used to estimate one-electron reduction potentials, however, these estimations were restricted to specified chemical classes. In the search of adequate predictive models, independent of chemical class bias, we analyzed the structural transformations of quinones within the redox cycle by employing quantum chemical methods that included solvation effects, in addition to gas phase calculations. Quantitative structure-activity relationship (QSAR) approaches were based on both low energy conformers as well as sets of active conformers, which do not necessarily coincide with the lowest energy geometries.¹¹
METHODS

Chemicals Under Investigation

A series of eight 1,4-BQs, eleven 1,4- and 1,2-NQs and two AQs were studied (Tables I and II). The one-electron reduction potentials for these compounds have been experimentally determined by pulse radiolysis.\textsuperscript{1,12-17}

Transitions of the redox cycle were modeled to determine their significance in deriving QSARs. The following intermediates were evaluated: (1) quinone (Q); (2) semiquinone radical anion (SMQRA); (3) semiquinone radical (SMQR); (4) hydroquinone cation radical (HQCR); (5) hydroquinone (HQ); and (6) hydroquinone anion (HQA) (Figure 1).

QSAR APPROACHES

Single vs. Multiple Conformer Methods

Using conventional QSAR methods, the molecular structure of each chemical under investigation was represented by a single lowest energy conformer as defined by quantum chemical or force field methods.

A dynamic QSAR approach,\textsuperscript{11} which incorporates the flexibility of chemicals in structure-toxicity studies, was also employed. This method assumes that in complex environments, such as biological tissues and fluids, xenobiotics are likely to exist in conformations other than the lowest, gas phase energy state. In some instances, the most stable conformations may be the least likely to interact with solvent or macromolecules.\textsuperscript{18} More importantly, solvation and binding interactions could more than compensate for energy differences among many conformations of the same chemical. Through this method active conformers are selected in the context of the interaction under investigation. The chemical behaviour (activity, toxicity, reactivity, etc.) is subsequently modeled as an effect of a set of conformers, rather than a property of a single conformer.

In the present study, after an exhaustive conformer generation, a screening of 3-D isomers was performed based on distributions of electron acceptor and donor properties, as well as reactivity, as evaluated by $E_{\text{LUMO}}$, $E_{\text{HOMO}}$, and $E_{\text{HOMO-LUMO}}$, respectively. Conformers providing prevailing, minimum, and mean values of those parameters were selected, and organized in correlation samples.

Computational Methods for Solvation Effect Assessment

Two computational methods were used to assess solvation effects.

(i) COSMO (Conductor-like Screening Model Method;\textsuperscript{19} MOPAC\textsuperscript{20}). The COSMO method is within the class of models where the solute molecule is embedded in a dielectric continuum of permeability $\varepsilon$. Thus, the solute forms a cavity within the dielectric, typically termed the solvent accessible surface (SAS). The
Table I  Observed and calculated one-electron reduction potentials of benzoquinones, based on Eqs. (1)-(4), and associated electronic descriptors. Frontier orbital energies ($E_{\text{HOMO}}$ and $E_{\text{LUMO}}$) for parent quinones and the $E_{\text{HOMO}}$ variations for the quinone-semiquinone radical anion transitions (see Figure 1) were determined by gas phase PM3 calculations and the COSMO method, respectively, using MOPAC.

<table>
<thead>
<tr>
<th>Compound (#)</th>
<th>Observed$^{a}$</th>
<th>Calculated</th>
<th>$E_{\text{HOMO}}$</th>
<th>$E_{\text{LUMO}}$</th>
<th>$\Delta E_{\text{HOMO}}$</th>
<th>$E(\text{BQ})_{\text{HOMO}}$</th>
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</thead>
<tbody>
<tr>
<td>1,4-benzoquinone (#1)</td>
<td>99</td>
<td>62</td>
<td>62</td>
<td>60</td>
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<tr>
<td>2-methyl-1,4-benzoquinone (#2)</td>
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<td>-17</td>
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<tr>
<td>2,5-dimethyl-1,4-benzoquinone (#3)</td>
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<td>-40</td>
<td>-88</td>
<td>-46</td>
<td>-49</td>
<td>-10.723</td>
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<td>2,6-dimethyl-1,4-benzoquinone (#4)</td>
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<td>-42</td>
<td>-86</td>
<td>-46</td>
<td>-48</td>
<td>-10.717</td>
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<td>2,6-dimethoxy-1,4-benzoquinone (#5)</td>
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<td>-207</td>
<td>-168</td>
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<td>2,3,5-trimethyl-1,4-benzoquinone (#6)</td>
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<td>-175</td>
<td>-156</td>
<td>-151</td>
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<td>-183</td>
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<td>-171</td>
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<td>2,3,5,6-trimethyl-1,4-benzoquinone (#8)</td>
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<td>-188</td>
<td>-232</td>
<td>-160</td>
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<td>-10.380</td>
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</table>

$^{a}$Reduction potentials experimentally determined.$^{1,12-17}$

$^{b}$Difference in $E_{\text{HOMO}}$ for the Q-SMQRA transition.

$^{c}$$E_{\text{HOMO}}$ for solvated benzoquinones.
Table II  Observed and calculated one-electron one-electron reduction potentials of benzoquinones, naphthoquinones and anthracenequinones, based on Eq.(5), and associated electronic descriptors (compounds #7 and #20 not included in the regression). Solvated anion radial formation enthalpies (\(\Delta H_{\text{SMQAR}}\)) and gas phase volume polarizability (Vol. P) of parent quinones were determined by AM SOL25 PM3-SM3 and PM3 methods, respectively.

<table>
<thead>
<tr>
<th>Compound (#)</th>
<th>One-electron Reduction Potential (MV)</th>
<th>Stereoelectronic Descriptors</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Observed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Calculated Eq.(5)</td>
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<td>1,4-benzoquinone (#1)</td>
<td>99</td>
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</tr>
<tr>
<td>2,hydroxy-1,4-benzoquinone (#7)</td>
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<td>-102</td>
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<tr>
<td>2,3,5,6-tetramethyl1,4-benzoquinone (#8)</td>
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<td>-152</td>
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<td>2,3-dichloro-1,4-benzoquinone (#9)</td>
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<td>-55</td>
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<td>1,4-napththoquinone-2-sulfonate (#10)</td>
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<td>1,2-napththoquinone (#11)</td>
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<td>9,10-anthraquinone-2-sulfonate (#21)</td>
<td>-375</td>
<td>-367</td>
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</table>

<sup>a</sup>Reduction potentials experimentally determined.<sup>1,12-17</sup>  
<sup>b</sup>Di erence in enthalpy for the Q-SMQAR transition (see Figure 1) in solution.  
<sup>c</sup>Volume polarizability of the parent quinone.

response of a homogeneous dielectric continuum to a charge distribution of the solute consists of a surface charge distribution on the interface; i.e., the SAS, arising from the polarization of the dielectric medium. An approximate, but accurate, non-iterative approach for the calculation of the screening charge densities is developed in the COSMO, for an arbitrary shaped surface, based on conductor screening.

(ii) PM3-SM3 Method<sup>21-23</sup> (AMSOL, version 3.0.1c<sup>24</sup>). This aqueous solvation model incorporates continuum solvent polarization effects directly into the Fock matrix of the solute NDDO (neglect of diatomic di erential overlap) calculations and includes rst hydration shell e ects via a surface tension term. The resulting free energies of solvation may be partitioned into (i) a term which includes the e ects of solvent electric polarization and the associated solvent-induced electronic and nuclear relaxation of the solute, and (ii) a term which accounts for solvent-accessible-surface-area e ects like cavitation, dispersion, and local modi cation of the water structure (e.g., hydrophobic structural changes and hydrophobic hydrogen bonding).

It was assumed in the present study that the gas phase energy minima of solute molecules do not change due to the solvation e ects. Under this assumption, a
practical solution was possible to eliminate time consuming geometry optimization calculations when solvation effects were incorporated; i.e., solvation-based ISCF calculations were performed using optimized gas phase geometries. The PM3 quantum-chemical method was used as a background Hamiltonian when solvation effects were evaluated. This particular Hamiltonian was required to make the results compatible with our previous study.7

Molecular Descriptors Investigated

Gas phase and solvation assessments of molecular electronic structure were undertaken. Energies of frontier orbitals (E_LUMO and E_HOMO), HOMO-LUMO gap, ionization potential (IP) formation enthalpies (ΔH_f) and aromaticity indices,25,26 based on the distribution evenness of charges and superdelocalizabilities,27 were evaluated for the neutral quinones and different intermediates of the redox cycle, by making use of the OASIS computer system.28 Variation of those indices for the transitions between redox intermediates were also studied as regressors for E_f. 

Figure 1 The complete scheme of the quinone redox cycle.
Using the COSMO method, descriptors such as the dielectric energy ($E_D$) and solvation enthalpies of formation ($\Delta \Delta H_{f}^{\text{solv}}$) were assessed. Ionization potentials were also calculated, which are inversely related to $E_{\text{HOMO}}$ of non-radical systems.

The following AMSOL-based molecular descriptors were used: heat of formation + $\Delta G$-solvation ($\Delta H_{f}^{\text{solv}}$); electronic energy + $\Delta G$-solvation ($E_{e}^{\text{solv}}$); electronic-nuclear energy of solute ($E_{\text{EN}}^{\text{solv}}$); polarization free energy of solvation ($G_{\text{P}}^{\text{solv}}$); electronic-nuclear-polarization free energy of system ($G_{\text{ENP}}^{\text{solv}}$); and cavity-dispersion-solvent structure free energy ($G_{\text{CDS}}^{\text{solv}}$).

Changes in descriptors were defined for the following transitions: SMQRA-Q (denoted as transition 21; see Figure 1); SMQR-SMQRA (32); HQCR-SMQR (43); HQ-HQCR (54); HQA-HQ (65); and HQA-Q (61). Descriptor differences were also determined for the following transitions: Q-SMQR (31); SMQR-HQ (53) and HQ-Q (51). These transitions are characterized by the combined exchange of a proton and or charge. The enthalpy difference for the hydroquinone-hydroquinone anion transition (65) could also be defined as a $pK_a$ descriptor; i.e., $\Delta H_f = -RT \log K_a$, where $K_a$ is the equilibrium constant for the reaction $AH = H^+ + A^-$. 

RESULTS AND DISCUSSION

As way hypothesized previously, we propose that quinones which have greater ability to delocalize electron density should have more positive reduction potentials for the $Q Q^-$ couple. Such quinones should have lower (higher) electron donor (acceptor) ability; i.e., lower (higher)-energy HOMO (LUMO) orbitals, and lower values for aromaticity indices (higher evenness of electron distribution). In addition, the semiquinones formed through the reduction of quinones should be more likely to act as electron donors. The greater negative charge should cause displacement of the frontier HOMO and LUMO orbitals towards the higher energies, thereby increasing electron donor ability and decreasing electron acceptor properties.

To assess hypotheses concerning electron delocalization using single and multiple conformers, both in the gas phase and a solvated environment, QSARs were first developed using the series of BQs. Based on results from these analyses, subsequent models were developed for the entire set of BQs, NQs, and AQs.

Consistent with our basic premise, negative correlations between $E_1^+$ and energies of frontier orbitals for the neutral BQs were obtained. The highest correlations were obtained when $E_{\text{HOMO}}$ was employed as a molecular descriptor and conformers with mean values of frontier orbitals were selected. Regressions based on optimized conformers were not significantly different. The model with the non-optimized conformers associated with mean values of $E_{\text{HOMO}}$ is described by Eq. (1) (see Figure 2a and Table I):

$$E_1^+(\text{mV}) = -4700(\pm 650) - 430(\pm 60)E_{\text{HOMO}}$$

$$n = 11; \quad r^2 = 0.85; \quad s^2 = 1674; \quad F = 49.8$$

(1)
where \( n \) stands for the cardinality of the correlation sample, which is the number of conformers included in the regression (all regressions in the present work were at the 95\% confidence level, unless otherwise noted).

In our previous study,\(^7\) \( E_{LUMO} \) did not correlate with \( E_i \) due to the deviation of the ortho-alkoxy and hydroxy substituted BQs (\#5 and \#7). The dynamic method, however, provided a statistically better model than that obtained with single low energy conformers only, primarily by 'incorporating' one of the two outlying ortho-derivatives (2,6-(OMe)\(_2\)-BQ; \#5) into the relationship with \( E_{LUMO} \) (Eq. (2), see Figure 2a and Table I):

\[
E_i^\dagger (mV) = -2300 (\pm 470) - 1400 (\pm 300)E_{LUMO}
\]

\[ n = 11; \quad r^2 = 0.71; \quad s^2 = 3202; \quad F = 21.73 \] (2)
The conformers of 2-OH-BQ, however, were still found to be outliers for the relationship with $E_{\text{LUMO}}$. As can be seen from Figure 2b and Table I, based on an $E_{\text{LUMO}}$ value of $-1.61$ eV, this chemical's $E^\dagger$ is estimated to be much higher than that observed. Elimination of 2-OH-BQ from the correlation sample increased the $r^2$ to 0.98. The failure to fully incorporate 2-OH-BQ in a $E_{\text{LUMO}}$ relationship could be due to it being partially protonated at a pH of 7.0. Partially protonated structures can not be readily assessed by the virtual orbitals of gas phase semi-empirical quantum chemical approaches.

Based on the hypothesis that the one-electron reduction potential is related to the free energy change of the equilibrium between the parent (Q) and the radical anion (SMQRA), as depicted in Figure 1, we expected larger increases in the differences of frontier orbital energies, during the transition of BQs to the semiquinone radical anions, to be associated with more positive one-electron reduction potentials. Results derived from the multiple conformer approach (non-optimized) using mean values of $E_{\text{HOMO}}$ for Q and SMQRA to derive $\Delta E_{\text{HOMO}}$ values are summarized in Eq. (3) and Table I:

$$E^\dagger_{\text{aq}}(\text{mV}) = -1830(\pm 260) - 330(\pm 50)E_{\text{HOMO}}$$

$$n = 15; \quad r^2 = 0.77; \quad s^2 = 2033; \quad F = 44.78$$

The regression with $\Delta E_{\text{LUMO}}$ was less satisfactory ($r^2 = 0.55$); however, when 2-OH-BQ (#7) was eliminated from the sample, the correlations improved ($0.98 \leq r^2 \leq 1.00$ for different conformer subsets).

Compared to our previous study, where the lowest energy gas-phase conformers were used, implementation of the multiple conformer approach did result in a modest improvement in that the ortho-substituted alkoxy derivative was incorporated in the models. However, a global solution was still not attained even for this restricted set of BQs. As a consequence, a solvation-based QSAR study was undertaken. First, the properties of the parent BQs were evaluated, which was followed by an examination of the intermediates in the redox cycle, including differences associated with the transitions. Ultimately, these analyses incorporated the entire quinone dataset.

Using the the COSMO method with the single lowest energy conformers, the following regression, consistent with the basic hypothesis, was obtained (Eq. (4) see Figure 3 and Table I):

$$E^\dagger_{\text{aq}}(\text{mV}) = -4000(\pm 460) - 380(\pm 40)E_{\text{HOMO}}$$

$$n = 8; \quad r^2 = 0.92; \quad s^2 = 1113; \quad F = 71.69$$

In Eq. (4) (confidence level of 85), $-E_{\text{HOMO}}$ is the ionization potential of the parent BQs. The increase in ionization potentials ($-E_{\text{HOMO}}$) of neutral BQs is correlated to more positive reduction potentials, consistent with the hypothesis
Figure 3 Variation of one-electron reduction potentials with $E_{\text{HOMO}}$ based on COSMO calculations of single conformer calculations of solvated patent benzoquinones (see Eq. (4)).

Concerning electron delocalization. For these descriptors, incorporating solvation effects with the COSMO method slightly improved the models over those obtained using gas-phase optimizations (see Eq. (1)). A multiple conformer study based on solvation effects calculated by the COSMO method did not significantly enhance the correlations (e.g., based on $E(\text{BQ})_{\text{HOMO}}$ an $r^2 = 0.95$ was obtained). Due to either class-specificity in the quantum-chemical methods or because of the limited set of quinones studied, the correlations with PM3-SM3 reactivity parameters were found to be comparable to those obtained from gas-phase calculations (an $r^2 = 0.85$ with $E(\text{BQ})_{\text{HOMO}}$). As with the gas phase calculations, solvation-based analyses incorporating $E_{\text{LUMO}}$ did not result in satisfactory regressions ($r^2 < 0.5$), mainly due to the ortho-alkoxy and hydroxy BQs. Use of the multiple conformer approach did not improve these relationships.

To more completely evaluate the influence of multiple conformers, solvation, and the potential role of transition differences in the redox cycle, a modeling exercise was subsequently undertaken on the entire set of BQs, NQs, and AQs. Inclusion of the entire set resulted in poor regressions based on gas-phase ionization potentials (PM3-MOPAC7), using both the single and multiple conformer approach. In addition, incorporation of solvation using the COSMO method did not improve the regressions, even when analyses incorporated intermediates in the redox cycle. Models based on calculations derived from the AMSOL package were also unsatisfactory when restricted to one parameter correlations. However, more encouraging results were obtained using the solvation phase (PM3-SM3) calculations in the AMSOL package when two parameter models based on stereoelectronic descriptors of the parent quinones were combined with the transition values for the intermediates in the redox cycle.

Based on single conformer analyses for solvated intermediates, reasonable regressions were obtained with the difference in enthalpies for the Q-SMQRA transi-
tions (21 in Figure 1) and Vol. P for the parent quinones, when the ortho-hydroxy-substituted compounds (#7 and #20) were excluded (Eq. (5), see Figure 4 and Table II):

\[
E^*_1 (\text{mV}) = -1,000 (\pm 540) - 12 (\pm 5.0) \Delta \Delta H_f^{\text{solv}} (21) \\
+ 280 (\pm 92) \text{Vol. P},
\]

\(n = 19; \quad r^2 = 0.75; \quad s^2 = 3212; \quad F = 23.71\)

Elimination of 9,10-phenanthrenequinone (#14) from the data set improved the correlation \(r^2 = 0.90\) and indicates that inclusion of a solvation-based approach did not completely eliminate the effects of neighboring quinone interactions.

Interestingly, similar correlations were obtained for the 51 transition, which is consistent with the assumption that in water differences in one- and two-electron reduction potentials across the quinones should be similar.\(^7\) Although the use of aromaticity indices in our previous study\(^7\) improved regressions involving classes of quinones, these parameters did not significantly improve correlations that incorporated differences in enthalpies for the Q-SMQRA transitions.

Consistent with our overall hypothesis, \(E^*_1\) was negatively correlated with the solvation-based transition reaction enthalpies. Thus, couples showing a greater propensity to form the radical anion (more negative differences in formation enthalpies) had more positive reduction potentials. Consistent with this relationship, a high positive intercorrelation \((r^2 \text{ of approximately } 0.80)\) was found between the differences in enthalpies for the Q-SMQRA transitions and \(E_{\text{LUMO}}\) of the quinones, consistent with the basic hypothesis that the stronger electron accepting quinones should

![Figure 4](image-url)
be associated with couples showing a greater propensity to form the radical anions. A mechanistic explanation for the inclusion of Vol. P in Eq. (5) is not straightforward. Attributes such as orbital energies and charge distributions are associated with Vol. P. The regressions indicate that more positive values of \( E_i \) are associated with more polar quinones, which may be reflective of partitioning or distribution characteristics associated with the aqueous environment in which the measurements are made.

The analyses associated with Eqs. (4) and (5) were based on gas-phase optimized geometries and 1SCF solvation calculations, under the assumption that deep gas-phase and solvation-phase minima in the energy surface are not significantly different. The difficulty in achieving a single descriptor model based on solvation calculations that included ortho-hydroxylated compounds may be a function of this assumption. To assess the impact of this approach on the results of the current study requires the calculation of solvation geometries, which is a computationally intensive effort. Attempts to compare the gas-phase and solvation-phase minima in the energy surface are in progress.

CONCLUSIONS

In an attempt to find a general approach to estimate one-electron reduction potentials of quinones, the structural transformations of the redox cycling process were studied. In addition to gas phase calculations, a set of molecular descriptors was used to incorporate solvation effects. Two QSAR approaches were employed, the first based on the low energy conformer representations of the chemicals, whereas the second employed conformer sets. To more completely evaluate stereoelectronic structure on the reduction potential, a broad series of BQs, NQs, and AQs were analyzed.

It was determined that the multiple conformer-based modeling approach does not significantly improve the results of the conventional (single conformer based) QSAR methods, likely due to the small conformational flexiblity of the chemicals studied. The ionization potential \( (-E_{\text{HOMO}}) \) and energy of the lowest unoccupied molecular orbital \( (-E_{\text{LUMO}}) \) were descriptors associated with parent BQs that were highly correlated to the one-electron reduction potential. Correlations found with frontier molecular orbitals are consistent with the assumption that quinones with higher (lower) electron acceptor (donator) properties should be associated with more positive reduction potentials. Although solvation-based molecular descriptors only moderately improved QSARs for the restricted set of BQs, the inclusion of solvation effects did result in QSARs for reduction potentials when BQs, NQs and AQs were modeled together. Ultimately, a reasonable regression based on the reaction enthalpies \( (\Delta \Delta H_f) \) for the quinone-semiquinone anion radical transition and Vol. P. for the parent quinone was obtained when the ortho-hydroxy-substituted compounds were excluded \( (r^2 = 0.75) \). Removal of 9,10-phenanthrenequinone signally improved the relationship \( (r^2 = 0.90) \). Consistent with our overall hypothesis, couples with more positive one-electron reduction potentials were correlated with a greater propensity to form the radical anion (greater negative differences in formation
enthalpies). Thus, the reaction enthalpy for this significant redox cycle transition appears to be the main factor controlling $E^\dagger$.

Although encouraging, the results to date have not resolved the problem of neighboring group interactions and internal hydrogen bonding, even with the incorporation of solvation effects. Further analysis may require the use of optimized solvated geometries and or $ab\ initial$ calculations to assess molecular stereoelectronic structure.

Disclaimer

Mention of trade names or specific products or approaches does not constitute endorsement on the part of the U.S. Environmental Protection Agency.

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References


