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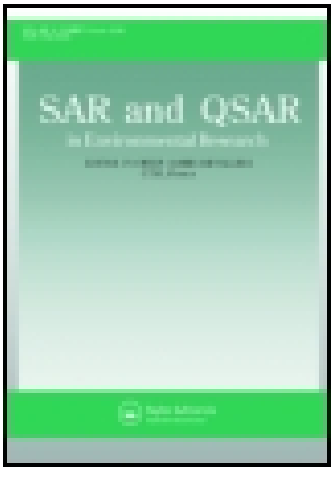

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ESTIMATING ONE-ELECTRON REDUCTION POTENTIALS OF QUINONES

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The one-electron reduction potential $^{*}E_7^1$ 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_7^1 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 di erences in parameters for the transition between intermediates were evaluated. The variation of E_7^1 was correlated with descriptors of the parent quinones and speci c 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 signi cantly correlated to E_7^1. With the exclusion of *ortho*-hydroxy-substituted compounds, the reaction enthalpies for the quinone-semiquinone couple, in combination with volume polarizability, were signi cantly correlated to E_7^1 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_7^1 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 e ects.

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_7^1 or E_7) of the quinone semiquinone radical couple ($Q\,Q^-$).[1,2] The observed dependence of redox cycling and oxidative stress on the E_7^1 of the $Q\,Q^-$ 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 O_2 O_2^- couple.[3,4,5,6] 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 E_7^1 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 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 signi cantly di erent manner, which suggested that hydrogen bonding and electrostatic interaction increased charge delocalization. The e ect of internal hydrogen bonding[8] and neighboring group interactions[9,10] on E_7^1 have been reported and associated with di culties in predicting potentials using the Hammett *para* substituent constant.[9,10]

It was also assumed in the previous study[7] that the one-electron reduction potential should be related to the free energy change of the equilibirium 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 signi cant 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 speci ed 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 e ects, 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.[1,12-17]

Transitions of the redox cycle were modeled to determine their signi cance in deriving QSARs. The following intermediates were evaluated: 91) 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 de ned by quantum chemical or force eld methods.

A dynamic QSAR approach,[11] which incorporates the exibility of chemicals in structure-toxicity studies, was also employed. This method assumes that in complex environments, such as biological tissues and uids, 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.[18] More importantly, solvation and binding interactions could more than compensate for energy di erences 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 e ect 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_{LUMO}, E_{HOMO}, and $E_{HOMO-LUMO}$, respectively. Conformers providing prevailing, minimum, and mean values of those para-meters were selected, and organized in correlation samples.

Computational Methods for Solvation E ect Assessment

Two computational methods were used to assess solvation e ects.

(i) COSMO (COnductor-like Screening Model Method;[19] MOPAC7[20]). The COSMO method is within the class of models where the solute molecule is embedded in a dielectric continuum of permeability ε. 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_{HOMO} and E_{LUMO}) for parent quinones and the E_{HOMO} variations for the quinone-semiquinone radical anion transitions (see Figure 1) were determined by gas phase PM3 calcualtions and the COSMO[19] method, respectively, using MOPAC7.[20]

	One-electron reduction potential (mV)					*Stereoelectronic descriptors*			
	Observed[a]	*Calculated*				E_{HOMO}	E_{LUMO}	ΔE_{HOMO}[b]	$E(BQ)_{HOMO}$[c]
Compound (#)		*Eq.(1)*	*Eq.(2)*	*Eq.(3)*	*Eq.(4)*	(*Eq.(1)*)	(*Eq.(2)*)	(*Eq.(3)*)	(*Eq.(4)*)
1,4-benzoquinone (#1)	99	62	62	60	100	−10.958	−1.665	5.670	−10.986
2-methyl-1,4-benzoquinone (#2)	23	−11	−15	−10	−17	−10.791	−1.611	5.461	−10.672
2,5-dimethyl-1,4-benzoquinone (#3)	−66	−40	−88	−46	−49	−10.723	−1.588	5.352	−10.587
2,6-dimethyl-1,4-benzoquinone (#4)	−80	−42	−86	−46	−48	−10.717	−1.560	5.351	−10.591
2,6-dimethoxy-1,4-benzoquinone (#5)	−150	−207	−168	−180	−194	−10.334	−1.501	4.948	−10.202
2,3,5-trimethyl-1,4-benzoquinone (#6)	−165	−175	−156	−151	−167	−10.409	−1.509	5.035	−01.274
2,-hydroxy-1,4-benzoquinoen (#7)	−165	−183	−12	−171	−171	−10.392	−1.613	5.199	−10.263
2,3,5,6-trimethyl-1,4-benzoquinone (#8)	−240	−188	−232	−160	−198	−10.380	−1.455	5.009	−10.191

[a]Reduction potentials experimentally determined.[1,12–17]
[b]Di erence in E_{HOMO} for the Q-SMQRA transition.
[c]E_{HOMO} for solvated benzoquinones.

Table II Observed and calculated one-electron one-electron reduction potentials of benzoquinones, naph thoquinones and anthracenequinones, based on Eq.(5), and associated electronic descriptors (com pounds #7 and #20 not included in the regression). Solvated anion radial formation enthalpies ($\Delta\Delta H_f^{solv}$) and gas phase volume polarizability (Vol. P) of parent quinones were determined by AM SOL[21] PM3-SM3 and PM3 methods, respectively.

	One-electron Reduction Potential (MV)		*Stereoelectronic Descriptors*	
Compound (#)	*Observed*[a]	*Calculated Eq.(5)*	$\Delta\Delta H_f^{solv}$[b] *Eq.(5)*	*Vol.P*[c] *Eq.(5)*
1,4-benzoquinone (#1)	99	27	−102.891	−0.608
2-methyl-1,4-benzoquinone (#2)	23	−14	−101.884	−0.715
2,5-dimethyl-1,4-benzoquinone (#3)	−66	−54	−101.058	−0.823
2,6-dimethyl-1,4-benzoquinone (#4)	−80	−53	−101.118	−0.823
2,6-dimethoxy-1,4-benzoquinone (#5)	−150	−100	−98.820	−0.896
2,3,5-trimethyl-1,4-benzoquinone (#6)	−165	−102	−99.440	−0.930
2,hydroxy-1,4-benzoquinone (#7)	−165	–	−103.399	−0.641
2,3,5,6-tetramethyl1,4-benzoquinone (#8)	−240	−152	−97.726	−1.038
2,3-dichloro-1,4-benzoquinone (#9)	−36	−55	−104.999	−0.992
1,4-napththoquinone-2-sulfonate (#10)	−60	−92	−104.435	−1.102
1,2-napththoquinone (#11)	−89	−128	−97.629	−0.950
5-hydroxy-1,4-napththoquinone (#12)	−93	−113	−99.727	−0.981
5,8-dihydroxy-1,4-napththozoquinone (#13)	−110	−101	−101.547	−1.014
9,10-phenanthrenequinone (#14)	−124	−275	−93.206	−1.291
1,4-napththoquinone (#15)	−140	−131	−97.434	−0.949
5-hydroxy,2-methyl-1,4-natphthozoquinone (#16)	−156	−150	−99.112	−1.089
2-methyl-1,4-naphthoquinone (#17)	−203	−170	−96.630	−1.056
2,3-dimethoxy-1,4-naphthoquinone (#18)	−240	−195	−98.863	−1.239
2,3-dimethyl-1,4-naphthoquinone (#19)	−240	−224	−94.489	−1.161
2-hydroxy-1,4-naphthoquinone (#20)	−415	–	−97.786	−0.983
9,10-anthraquinone-2-sulfonate (#21)	−375	−367	−89.189	−1.455

[a]Reduction potentials experimentally experimentally determined.[1,12-7]
[b]Di erence in enthalpy for the Q-SMQAR transition (see Figure 1) in solution.
[c]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[21-23] (AMSOL, version 3.0.1c[24]). This aqueous solvation model incorporates continuum solvent polarization e ects 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., hydrophodic 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

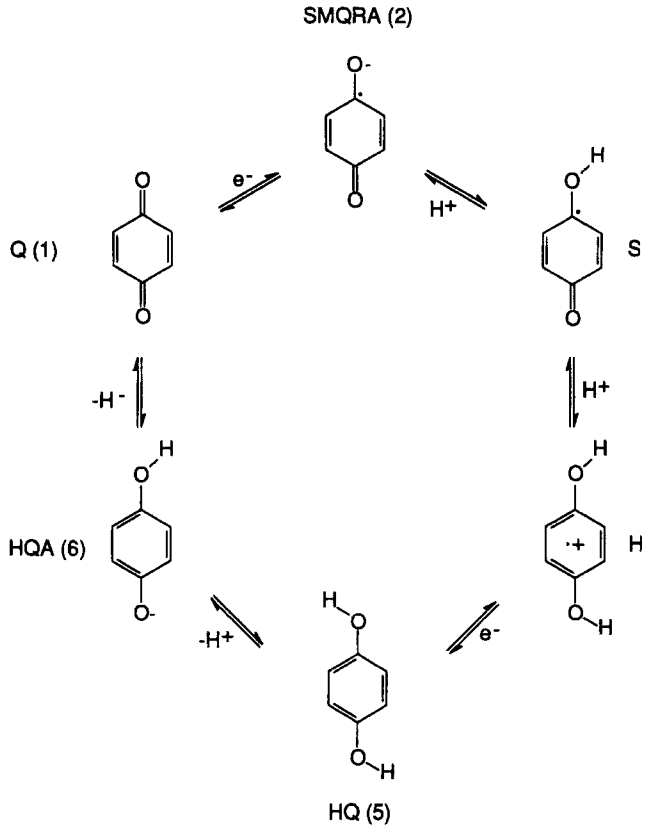


Figure 1 The complete scheme of the quinone redox cycle.

practical solution was possible to eliminate time consuming geometry optimization calculations when solvation e ects 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 e ects 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 di erent 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 $E_{\frac{1}{2}}$.

Using the COSMO method, descriptors such as the dielectric energy (E_D) and solvation enthalpies of formation($\Delta\Delta H_f^{solv}$) were assessed. Ionization potentials were also calculated, which are inversely related to E_{HOMO} of non-radical systems.

The following AMSOL-based molecular descriptors were used: heat of formation + ΔG-solvation (ΔH_f^{solv}); electronic energy + ΔG-solvation (E_E^{solv}); electronic-nuclear energy of solute (E-EN^{solv}); polarization free energy of solvation (G-P^{solv}); electronic-nuclear-polarization free energy of system (G-ENP)^{solve}); and cavity-dispersion-solvent structure free energy (G-CDS^{solv}).

Changes in descriptors were de ned 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 di erences 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 di erence for the hydroquinone-hydroquinone anion transition (65) could also be de ned as a pK_a descriptor; i.e., $\Delta\Delta H_f = -RT.\log K_a = RT.pK_a$, where K_a is the equilibrium constant for the reaction $AH = H^+ + A^-$.

RESULTS AND DISCUSSION

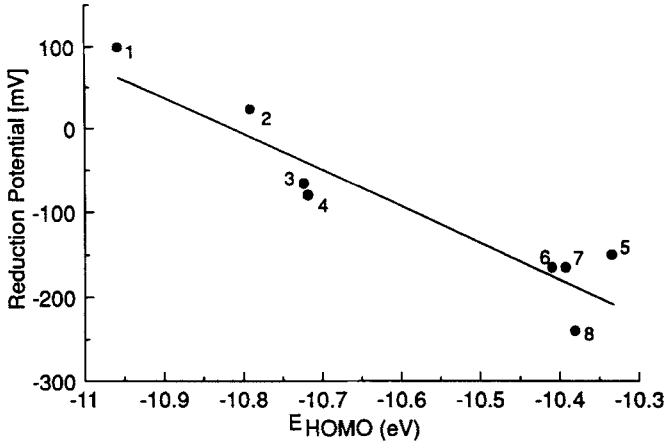
As way hypothesized previously,[7] we propose that quinones which have greater ability to delocalize electron density should have more positive reduction potentials for the $Q\ Q^-$ couple. Such quinones should have lower (higher) electron donor (acceptor) ability; i.e., lower (higher)-energy HOMO (LUMO) 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 rst 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_7^1 and energies of frontier orbitals for the neutral BQs were obtained. The highest correlations were obtained when E_{HOMO} was employed as a moelcular descriptor and conformers with mean values of frontier orbitals were selected. Regressions based on optimized conformers were not signi cantly di erent. The model with the non-optimized conformers associated with mean values of E_{HOMO} is described by Eq. (1) (see Figure 2a and Table I):

$$E_7^1(mV) = -4700(\pm 650) - 430(\pm 60)E_{HOMO}$$

$$n = 11; \quad r^2 = 0.85; \quad s^2 = 1674; \quad F = 49.8 \qquad (1)$$



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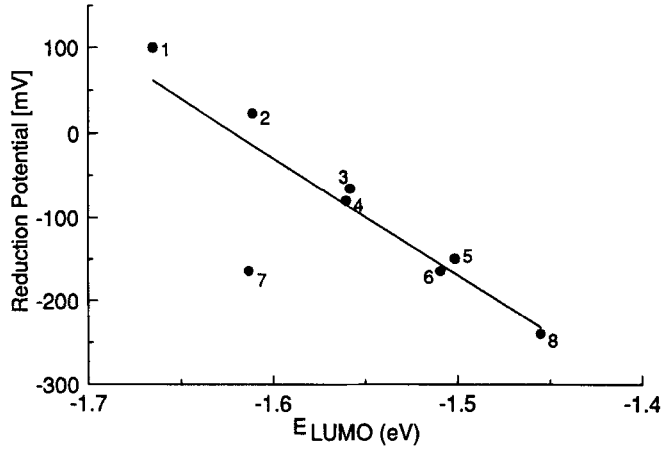

b

Figure 2 Variation of one-electron reduction potentials with E_{HOMO} (a) and E_{LUMO} (b) based on PM3[17] calculations for conformer sets of parent benzoquinones (see Eqs. (1) and (2), respectively).

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_7^1 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):

$$E_7^1(mV) = -2300\ (\pm 470) - 1400(\pm 300)E_{LUMO}$$

$$n = 11; \quad r^2 = 0.71; \quad s^2 = 3202; \quad F = 21.73 \qquad (2)$$

The conformers of 2-OH-BQ, however, were still found to be outliers for the relationship with E_{LUMO}. As can be seen from Figure 2b and Table I , based on an E_{LUMO} value of -1.61 eV, this chemical s E_7^1 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_{LUMO} relationship could be due 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 di erences 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_{HOMO} for Q and SMQRA to derive ΔE_{HOMO} values are summarized in Eq. (3) and Table I:

$$E_7^1(mV) = -1830(\pm 260) - 330(\pm 50)E_{HOMO} \tag{3}$$

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

The regression with ΔE_{LUMO} wa sless satisfactory ($r^2 = 0.55$); however, when 2-OH-BQ (#7) was eliminated from the sample, the correlations improved ($0.98 \leqslant r^2 \leqslant 1.00$ for di erent conformer subsets).

Compared to our previous study,[7] 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 di erences 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):

$$E_7^1(mV) = -4000(\pm 460) - 380(\pm 40)E(BQ)_{HOMO}$$

$$n = 8; \quad r^2 = 0.92; \quad s^2 = 1113; \quad F = 71.69 \tag{4}$$

In Eq. (4) (con dence level of 85), $-E(BQ)_{HOMO}$ is the ionization potential of the parent BQs. The increase in ionization potentials ($-E(BQ)_{HOMO}$) of neutral BQs is correlated to more positive reduction potentials, consistent with the hypothesis

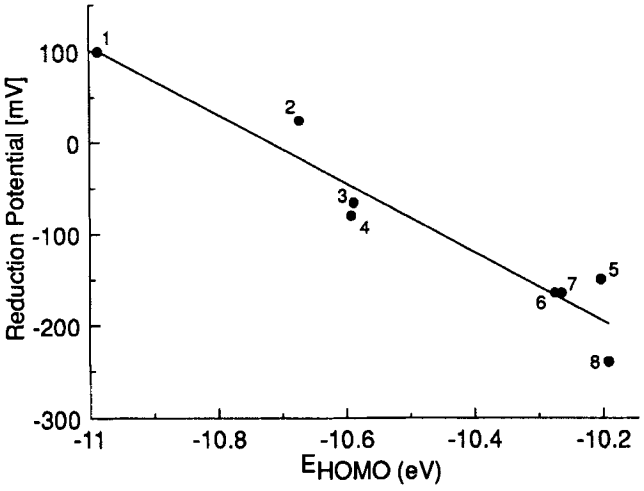

Figure 3 Variation of one-electron reduction potentials with E_{HOMO} based on COSMO[19] calculations of single conformer calculations of solvated patent benzoquinones (see Eq. (4)).

concerning electron delocalization. For these descriptors, incorporating solvation e ects 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 e ects claculated by the COSMO method did not signi cantly enhance the correlations (e.g., based on $E(BQ)_{HOMO}$ an $r^2 = 0.95$ was obtained). Due to either class-speci city 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 $E(BQ)_{HOMO}$). As with the gas phase calculations, solvation-based analyses incorporating E_{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 in uence of multiple conformers, solvation, and the potential role of transition di erences 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 di erence 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):

$$E_7^1(mV) = -1{,}000(\pm 540) - 12(\pm 5.0)\Delta\Delta H_f^{solv}(21) + 280(\pm 92)\text{Vol. P.} \quad (5)$$

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

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 e ects of neighboring quinone interactions.

Interestingly, similar correlations were obtained for the 51 transition, which is consistent with the assumption that in water di erences in one- and two-electron reduction potentials across the quinones should be similar.[29] Although the use of aromaticity indices in our previous study[7] improved regressions involving classes of quinones, these parameters did not signi cantly improve correlations that incorporated di erences in enthalpies for the Q-SMQRA transitions.

Consistent with our overall hypothesis, $E_7^1$was negatively correlated with the solvation-based transition reaction enthalpies. Thus, couples showing a greater propensity to form the radical anion (more negative di erneces in formation enthalpies) had more posutuve reduction potentials. Consistent with this relationship, a high positive intercorrelation (r^2 of approximately 0.80) was found between the di erences in enthalpies for the Q-SMQRA transitions and E_{LUMO} of the quinones, consistent with the basic hypothesis that the stronger electron accepting quinones should

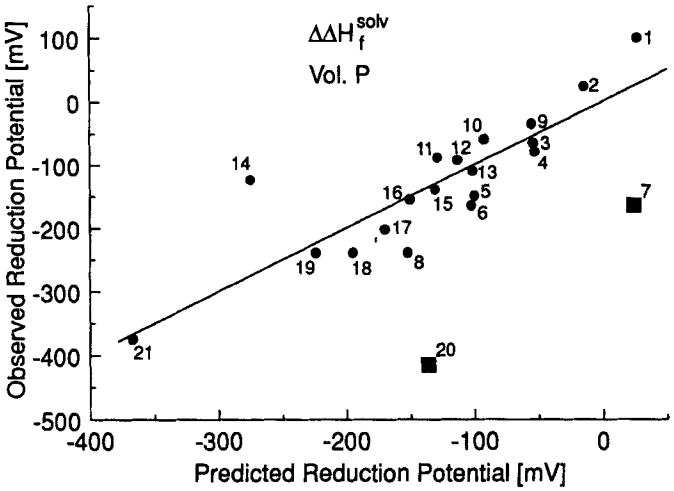

Figure 4 Plot of observed versus calculated reduction potentials of benzoquinones, napthoquinones and anthracenequinones based on Eq. (5), where predictions were based on solvated anion radical formation enthalpies ($\Delta\Delta H_f^{solv}$) and volume polarizability (Vol.P).

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_7^1 are associated with more polar quinones, which may be re ective 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 signi cantly di erent. The di culty 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 e ort. Attempts to compare the gas-phase and solvation-phase minima in the energy surface are in progress.

CONCLUSIONS

In an attempt to nd 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 e ecs. Two QSAR approaches were employed, the rst 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 signi cantly improve the results of the conventional (single conformer based) QSAR methods, likely due to the small conformational exibility of the chemicals studied. The ionization potential ($-E_{HOMO}$) and energy of the lowest unoccupied molecular orbital ($-E_{LOMO}$) 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 e ects 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 signi cantly 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 di erences in formation

enthalpies). Thus, the reaction enthalpy for this signi cant redox cycle transition appears to be the main factor controlling E_7^1.

Althoguh encouraging, the results to date have not resolved the problem of neighboring group interactions and internal hydrogen bonding, even with the incorporation of solvation e ects. Further analysis may require the use of optimized solvated geometries and or *ab initio* calculations to assess molecular stereoelectronic structure.

Disclaimer

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

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References

1. Wardman, P. (1989). Reduction potentials of one-electron couples involving free radicals in aqueous solution. *J. Phys. Chem. Ref. Data* **18,** 1637–1745.
2. Mason, R. (1990). Redox cycling of radical anion metabolites of toxic chemicals and drugs and the Marcus theory of electron transfer. *Environ. Health Perspect.* **87,** 237–249.
3. Powis, G., Hodnett, E.M., Santone, K.S., Lee See, K., and Melder, D.C. (1989). Role of metabolism and oxidation-reduction cycling in the cytotoxicity of antitumor quinoneimines and quinonediimines. *Cancer Res.* **47,** 2363–2370.
4. Bilmoria, M.H. and Kamin, H. (1973). The e ect of high salt concentration upon cytochrome C_1, cytochrome C_5, and iron EDTA reductase activities of liver microsomal NADPH-cytochrome C reductase. *Ann. N. Y. Acad. Sci.* **212,** 428–430.
5. Mason, R.P. and Holtzman, J.L. (1975). The mechanism of microsomal and mitochondrial nitroreductase. Electron spin resonance evidence for nitroaromatic free radical intermediates. *Biochem.* **14,** 1626–1632.
6. O Brien, P.J. (1991). Molecular mechanisms of quinone cytotoxicity. *Chem. -Biol. Interactions* **80,** 1–41.
7. Bradbury, S.P., Mekenyan, O.G., Veith, G.D., and Zaharieva, N. (1995). SAR modeling of futile metabolism; One-electron reduction of quinones, phenols and nitrobenzenes. *SAR QSAR Environ. Res.* **4,** 109–124.
8. Ashnagar, A., Bruce, J.M., Dutton, P.L., and Prince, R.C. (1984). One- and two-electron reductions of hydroxy-1,4-naphthoquinones and hydroxy-9,10-anthraquinones. The role of internal hydrogen bonding and its bearing on the redox chemistry of the anthracycline antitumor quinones. *Biochem. Biophys. Acta.* **801,** 351–259.
9. Prince, R.C., Dutton, P.L., and Bruce, J.M. (1983). Electrochemistry of ubiquinones, menaquinones and plastoquinones in aprotic solvents. *FEBS Lett.* **160,** 273–276.
10. Wardman, P. (1990). Bioreductive activation of quinones: Redox properties and thiol reactivity. *Free Rad. Res. Comms.* **8,** 219–229.
11. Mekenyan, O.G., Ivanov, J.M., Veith, G.D., and Bradbury, S.P. (1994). Dynamic QSAR: A new search for active conformations and signi cant stereoelectronic indices. *Quant. Struct.-Act. Relat.* **13,** 302–307.
12. Mason, R.P. (1979). Free radical metabolites of foreign compounds and their toxicological signi cance. In, *Reviews in Biochemical Toxicology*, Vol. 1 (E. Hodgson, Y. Bend, and R. Philpot, Eds.). Elsevier, New York, pp. 151–200.

13. Miller, M.G., Rodger, A., and Cohen, G.A. (1986). Mechanisms of toxicity of napthoquinones to isolated hepatocytes. *Biochem. Pharmacol.* **35,** 1177–1184.
14. Orna, M.V. and Mason, R.P. (1989). Correlation of kinetic parameters of nitroreductase enzymes with redox properties of nitroaromatic compounds. *J. Biol. Chem.* **264,** 12379–12384.
15. Powis, G. P. and Appel. (1980). Relationship of the singlet electron reduction potential of quinones to their reduction by avoproteins *Biochem. Pharmacol.* **29,** 2567–2572.
16. Meisel, D. and Czapsik, G. (1975). One-electron transfer equilibria and redox potentials of radicals. I. The oxygen superoxide system. *J. Phys. Chem.* **79,** 1503.
17. Ilan, Y.A., Czapsik, G., and Meisel, D. (1976). The one-electron transfer redox potentials of free radicals. I. The oxygen superoxide system. *Biochem. Biophys. Acta* **430,** 209–224.
18. Eliel, E.L. (1993). Chemistry in three dimensions. In, *Chemical Structures,* Vol. 1 (W.A. Warr, Ed.). Springer, Berlin, pp. 1–8.
19. Klamt, A. and Schuurmann, G. (1993). COSMO: A new approach to dielectric screening in solvents with explicit expressions for the screening energy and its gradient. *J. Chem. Soc. Perkin Trans.* **2,** 99–805.
20. Steward, J.J.P. (1995). MOPAC mannual v.7.0. Quantum chemistry program exchange, University of Indiana, Bloomington, ID.
21. Cramer, C.J. and Truhlar, D.G. (1991). General parameterized SCF model for free energies of solvation in aqueous solution. *J. Am. Chem. Soc.* **113,** 8305–8311.
22. Cramer, C.J. and Truhlar, D.G. (1992). PM3-SM3: A general parameterization for including aqueous solvation e ects in the PM3 molecular orbital model. *J. Comput. Chem.* **13,** 1089–1097.
23. Rauhat, G., Clark, T., and Steinke, T. (1993). A numerical self-consistent reaction eld (SCRF) model for ground and excited states in NDDO-based methods. *J. Am. Chem. Soc.* **115,** 9174–9181.
24. Cramer, C.J., Lynch, G.L., and Truhlar, D.G. (1993). QCPE program 606-version 3.0.1c. Quantum chemistry program exchange, Chemistry Department, Indiana University, Bloomington. *QCPE Bull.* **13,** 9.
25. Fratev, F., Bonchev, D., and Enchev, V. (1980). A theoretic information approach to ring and total aromaticity in ground and exicted states. *Croat. Chem. Acta* **530,** 545–554.
26. Mekenyan, O.G., Bonchev, D.G., and Dimitrov, D.N. (1991). Information-theoretic approach to the aromaticity of chemical compounds based on superdelocalizability indices. *Rev. Roumaine Chim.* **36,** 363–377.
27. Klopman, G. (1974). The generalized perturbation theory of chemical reactivity and its applications. In, *Chemical Reactivity and Reaction Paths* (G. Klopman, Ed.). John Wiley & Sons, New York, pp. 55–166.
28. Mekenyan, O., Karabunarliev, S., Ivanov, J., and Dimitrov, D. (1994). A new development of the OASIS computer system for modeling molecular properties. *Comput. Chem.* **18,** 173–187.
29. Lusthof, K.J., Richter, W., de Mol, N.J., Janssen, L.H.M., Verboom, W., and Reinholdt, D.N. (1990). Reductive activation of potential antitumorbis (aziridinyl) benzoquinones by xanthine oxidase: Competition between oxygen and quinone reduction. *Arc. Biochem. Biophys.* **227,** 137–142.