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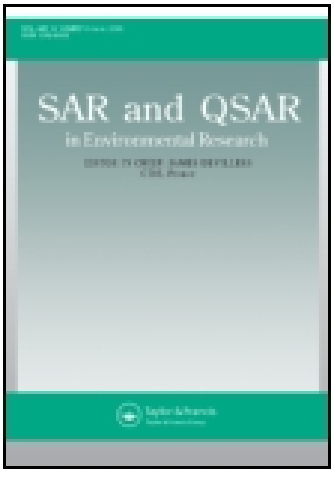

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SAR MODELS FOR FUTILE METABOLISM: ONE-ELECTRON REDUCTION OF QUINONES, PHENOLS AND NITROBENZENES

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Benzoquinones, naphthoquinones and aziridinylbenzoquinones, can be reduced by flavoproteins to semiquinones that react with molecular oxygen to form superoxide anion with the subsequent regeneration of the parent compounds. This redox cycling, a form of futile metabolism, produces reactive oxygen species and depletes the reducing equivalents of cells without concomitant energy production. The ability of a toxicant to redox cycle is related to its one-electron reduction potential, and this study attempted to estimate reduction potential from structure using semi-empirical quantum chemical models for a diverse set of chemicals. The results of this study suggest that one-electron reduction potentials, within structural classes of benzoquinones, naphthoquinones, phenols and nitrobenzenes, can be estimated from local and global electronic indices that are related to delocalization. Smaller absolute charge on the carbonyl carbon in the quinone moiety correlated with more positive one-electron reduction potentials of 1,4-benzoquinones, naphthoquinones and two-electron reduction potentials of aziridinylbenzoquinones. The energy of frontier orbitals of the quinones, phenols and nitrobenzenes also co-varied with reduction potential. More positive reduction potentials of 1,4-benzoquinones, 1,4-naphthoquinones and phenols were correlated with more negative values of E_{HOMO}, while more negative values of E_{LUMO} were correlated with more positive potentials of nitrobenzenes and aziridinylbenzoquinones. Delocalization of electron density also correlated with reduction potentials within individual classes.

KEY WORDS: quinones; phenols; nitrobenzenes; one-electron reduction potential; redox cycling.

INTRODUCTION

Predicting the toxicity of reactive chemicals using quantitative structure activity relationships (QSARs) is a complex challenge in predictive toxicology. The difficulty of this challenge is due, in part, to the large variety of toxic mechanisms for reactive chemicals as well as for the stereoelectronic descriptors associated with reactivity. Development of toxicologically-relevant approaches for classifying xenobiotics as

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"reactive" requires the evaluation of stereoelectronic descriptors using toxic response databases that are carefully defined with regard to the biological model, effect endpoint and exposure regime.[1] A critical appreciation of underlying toxicological processes is necessary because predicting reactivity in a biological system can be further complicated by metabolic activation. As a result, there is a fundamental need to develop a predictive capability to assess metabolic activation for toxicity estimations.

To address this research need, we have been developing the basic principles for incorporating metabolic activation into structure-toxicity models for reactive chemicals. Chemical reactivity can be classified according to the metabolic rate controlling perturbation of the chemical structure, whether measured as reactions of the parent structure with biomolecules or as metabolism rates in forming highly reactive intermediates. At least in the context of QSAR modeling, perturbations involving changes in heavy atom bonds seem quite different from those which involve absorption of light energy or exchange of electrons, protons and hydride anions.[2] Our initial efforts were focused on the formation of cations through hydride abstraction and protonation[2] and photoactivation of polycyclic aromatic hydrocarbons.[3] The present study addresses one-electron reductions that can lead to redox cycling and cytotoxicity through oxidative stress.[4]

Benzoquinones (BQs), naphthoquinones (NQs), and nitroaromatics, comprise several classes of drugs, pesticides and industrial chemicals[4] that are commonly released into the environment. They can be reduced to anion radicals by the transfer of an electron from an enzyme, typically a flavoprotein, to the parent molecule. Semiquinone anion radicals reduce molecular oxygen to superoxide anions, and in the process, the semiquinone radicals are oxidized to the parent structure; hence the term, "futile metabolism".[4] The net reaction is oxidation of the cellular flavoprotein coenzymes, a decrease in reduced glutathione with an associated increase in oxidized glutathione, and reduction of molecular oxygen to superoxide anions. Bioreductive activation also has been proposed as an explanation for the antitumor activity of aziridinylbenzoquinones (AZBQs). Reduction of the quinone fragment activates the alkylating group by facilitating protonation and reactions of the aziridine ring. Acute cytotoxicity as a side effect of such drugs is due, in part, to redox cycling.[5,6]

A major factor in the rate of flavoprotein-mediated reduction of quinones, and thus their ability to undergo redox cycling and cause cytotoxicity through oxidative stress, is the one-electron reduction potential (E^1_7 or E_7) of the quinone/ semiquinone radical couple ($Q/Q^{\cdot -}$).[7] The dependence of redox cycling on E^1_7 arises from activity in narrow ranges of reduction potential and the lack of substrate specificity of flavoprotein enzymes for xenobiotic electron acceptors.[8,9,10,11] For example, all quinones with E^1_7 greater than -240 mV are substrates for NADPH-cytochrome P-450 reductase, whereas -170 mV is the lower limit for NADH-cytochrome b_5 reductase. The upper reduction potential limit for quinones capable of undergoing redox cycling is determined by the single-electron reduction potential of the $O_2/O_2^{\cdot -}$ couple.[8]

Evidence to date suggests that the one-electron reduction potentials for quinones would be extremely useful for assessing a toxic mode of action associated with oxidative stress. We postulate that indices of aromaticity, energies of frontier

orbitals (e.g., E_{HOMO}, which is inversely related to the ionization potential) and charges on the carbonyl atoms should be correlated to reduction potential. This proposal is based on the hypothesis that aromatic compounds with greater delocalization of electron density should have a more positive reduction potential. To evaluate this hypothesis, the present study examines local and global descriptor(s) that could be related to electron density delocalization and one-electron reduction potentials. This investigation incorporated a diverse set of BQs, NQs and AZBQs, whose propensity to redox cycle and elicit oxidative stress has been well studied,[5,6,12,13,14,15] and a set of phenols and nitrobenzenes.

METHODS

The series of compounds investigated in this study are listed in Table I. The compounds included a series of eight BQs (#1–3 and #5–9), twelve NQs (# 10–21), 9,10-anthraquinone-2-sulfonate (#22), indigodisulfonate (#23), 35 phenols (#24–58), 27 nitrobenzenes (#59–85) and 20 AZBQs (#4 and #86–105) (Figure 1). Recent studies with quinones have related their flavoprotein-mediated reduction and associated cytotoxicity to their one-electron potentials.[6,8,15] The potentials for these compounds, excluding the AZBQs, have been experimentally determined, most by pulse radiolysis, and were obtained from several sources.[12,15,16,17,18] The values reported for the AZBQs are two-electron reduction potentials,[6] except for AZQ.[18] One-electron reduction potentials for the phenolic compounds in Table I (#24–#58) are for the $ArO^{\cdot}/ArO^{-}$ couple.

The electronic structure of the parent BQs, NQs, AZBQs and nitrobenzenes, as well as their corresponding radical anions, were modeled. In the case of the phenolic compounds, the protonated form of the reduced metabolite (ArOH) was modeled, because of difficulties in modeling radicals (see results and discussion). In general, the molecular structures of parent compounds were modeled assuming that the potential is solely a function of an unperturbed chemical. However, if the potential is a function of the anion radicals formed after a one-electron reduction, it would be necessary to compute the electron parameters for these metabolites. Finally, it is possible that potentials are a function of the neutral semiquinone radicals or protonated phenolic anions (see Figure 2).

For each species within a couple, the reactivity approach of the isolated molecule was applied using the OASIS package.[19] Geometries were optimized by the PM3 quantum chemical method. The AM1 and PM3 Hamiltonians were used to calculate the electronic indices, assuming fixed optimized molecular geometries, to detect any biases of the Hamiltonians. In general, no significant differences were noted, and the results from the PM3 methods are presented.

The electronic indices [20,21,22] tested for significance as molecular descriptors were atomic charges (q_i), superdelocalizabilities (S_i^E and S_i^N), self-polarizabilities (π_i) and frontier charges (f_i^{LUMO}, f_i^{HOMO}). Global electronic parameters such as energies of frontier orbitals (E_{LUMO} and E_{HOMO}), HOMO-LUMO gap, heats of formation (ΔH_f°) and volume polarizabilities (Vol. P) were also evaluated as to their ability to predict one electron reduction potentials. Three global measures of aromaticity were also

Table I Observed and predicted electron reduction potentials for benzoquinones, naphthoquinones, aziridinylbenzoquinones, nitrobenzenes and phenols.

#	*Chemical name*	*Reduction potentials [m V]*								
		Obs (a)	*pH*	*Predicted (b)*						
				Eq. (1) q(4)	Eq. (2) E(HOMO)	Eq. (3) E(HOMO)	Eq. (4) E(HOMO)	Eq. (5) Ar(SE)	Eq. (6) Ar(q)	Eq. (7) E(LUMO)
1	1,4-Benzoquinone	99	7.0	57	49			17	−97	
2	2-Me-1,4-Benzoquinone	23	7.0	−8	−3			−14	−100	
3	2,5-Me-1,4-Benzoquinone	−66	7.0	−100	−23			−50	−110	
4	AZQ (Diaziquinone)	−70	7.0	−140				−71	−130	
5	2,6-Me-1,4-Benzoquinone	−80	7.0	−56	−29			−52	−110	
6	2,6-OMe-1,4-Benzoquinone	−150	7.0	−130	−200			−250	−180	
7	2,3,5-Me-1,4-Benzoquinone	−165	7.0	−160	−170			−69	−110	
8	2-OH-1,4-Benzoquinone	−165	7.0	−60	−190			−160	−120	
9	2,3,5,6-Me-1,4-Benzoquinone	−240	7.0	−170	−200			−84	−110	
10	2,3-$(Cl)_2$-1,4 Naphthoquinone	−36	7.0					−140	−100	
11	1,4-Naphthoquinone-2-sulfonate	−60	7.0	−29	−94			−140	−180	
12	1,2-Naphthoquinone	−89	7.0						−140	
13	5-OH-1,4-Naphthoquinone	−93	7.0					−150	−120	
14	5,8-$(OH)_2$-1,4-Naphthoquinone	−110	7.0					−150	−100	
15	9,10-Phenanthrenequinone	−124	7.0						−180	
16	1,4-Naphthoquinone	−140	7.0	−180	−190			−140	−110	
17	5-OH, 2-Me-1,4-Naphthoquinone	−156	7.0					−180	−120	
18	2-Me-1,4-Naphthoquinone	−203	7.0	−220	−200			−170	−120	
19	2-3-$(OMe)_2$-1,4-Naphthoquinone	−240	7.0	−300	−340			−290	−190	
20	2,3-$(Me)_2$-1,4-Naphthoquinone	−240	7.0	−300	−220			−190	−120	
21	2-OH-1,4-Naphthoquinone	−415	7.0	−330	−240			−320		
22	9,10-Anthraquinone-2-sulfonate	−375	7.0	−360				−370		
23	Indigodisulfonate	−247	7.0					−140		
24	Phenol(c)	860	7.0			840				
25	4-Aminophenol	410	7.0			260				
26	4-Hydroxybenzoic acid	500	13.5				320			
27	*p*-Cresol	770	7.0			690				
28	4-Methoxyphenol	655	7.0			520				
29	4-(Methylamino)phenol	146	7.0			230				
30	4-Acetamidophenol	460	7.0			760				
31	4-(Dimethylamino)phenol	174	7.0			190				
32	Tyrosine	930	7.0			790				
33	DL-Tyrosine, methyl ester	870	7.0			750				

Table I (*continued*)

#	*Chemical name*	*Reduction potentials [mV]*								
		Obs (a)	*pH*	*Predicted (b)*						
				Eq. (1) q(4)	Eq. (2) E(HOMO)	Eq. (3) E(HOMO)	Eq. (4) E(HOMO)	Eq. (5) Ar(SE)	Eq. (6) Ar(q)	Eq. (7) E(LUMO)
34	L-Alanyl-L-tyrosine	850	7.0			790				
35	1,2-Dihydroxybenzene	530	13.5				660			
36	2,3-Dihydroxybenzoic acid	126	13.5				120			
37	3,4-Dihydroxyphenylacetic acid	119	13.5				190			
38	3,4-Dihydroxybenzoic acid	21	13.5				88			
39	3-Hydroxytyramine	18	13.5				−22			
40	Norepinephrine	44	13.5				−11			
41	*trans*-3,4-Dihydroxycinnamic acid	84	13.5				79			
42	Adrenalone	180	13.5				160			
43	2-Hydroxy-tyrosine	22	13.5				3			
44	1,3-Dihydroxybenzene	810	7.0			810				
45	3,5-Dihydroxybenzoic acid	280	13.5				260			
46	1,4-Dihydroxybenzene	459	7.0			560				
47	Methylhydroquinone	460	7.0			500				
48	Methoxyhydroquinone	−85	13.5				−37			
49	2′,5′-Dihydroxyacetophenone	118	13.5				24			
50	Homogentisic acid	−50	13.5				180			
51	2,3-Dimethylhydroquinone	430	7.0			460				
52	2,5-Dimethylhydroquinone	420	7.0			420				
53	Trimethylhydroquinone	385	7.0			400				
54	Tetramethylhydroquinone	350	7.0			340				
55	1,2,3-Trihydroxybenzene	−9	13.5				−16			
56	5-Hydroxydopamine	42	13.5				−48			
57	Ethyl gallate	−54	13.5				53			
58	1,2,4-Trihydroxybenzene	−110	13.5				−96			
59	1,2-Dinitrobenzene	−287	7.0						−370	−340
60	1,3-Dinitrobenzene	−345	7.0						−310	−320
61	1,4-Dinitrobenzene	−257	7.0						−380	−260
62	2,4-Dinitrobenzoic acid	−345	7.0						−330	−230
63	2,5-Dinitrobenzoic acid	−272	7.0						−390	−240
64	3,4-Dinitrobenzoic acid	−271	7.0						−370	−260

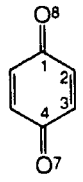
Table I (*continued*)

#	*Chemical name*	*Reduction potentials [mV]*								
		Obs (a)	*pH*	*Predicted (b)*						
				Eq. (1) q(4)	Eq. (2) E(HOMO)	Eq. (3) E(HOMO)	Eq. (4) E(HOMO)	Eq. (5) Ar(SE)	Eq. (6) Ar(q)	Eq. (7) E(LUMO)
65	3,5-Dinitrobenzoic acid	−344	7.0						−250	−280
66	2,4-Dinitrophenol	−500	7.0							−340
67	3-Nitroacetophenone	−437	7.0						−390	−440
68	4-Nitroacetophenone	−358	7.0						−400	−430
69	Nitrobenzene	−486	7.0						−390	−490
70	2-Nitrobenzaldehyde	−355	7.0						−380	−400
71	4-Nitrobenzaldehyde	−322	7.0						−390	−380
72	2-Nitrobenzoic acid	−412	7.0						−400	−450
73	3-Nitrobenzoic acid	−433	7.0						−370	−420
74	4-Nitrobenzoic acid	−396	7.0						−400	−360
75	2-Nitrobenzonitrile	−308	7.0						−390	−380
76	4-Nitrobenzyl alcohol	−477	7.0						−470	−490
77	4-Nitro-(3'-dimethylamino)-propiophenone	−315	7.0						−400	−390
78	1,3-Dinitro-4-aziridinyl-6-$CONH_2$-benzene	−385	7.0						−310	−330
79	1,3-Dinitro-4-aziridinyl-6-$CONHCH_3$-benzene	−387	7.0						−310	−330
80	1,3-Dinitro-4-aziridinyl-6-$CON(CH_3)_2$-benzene	−377	7.0						−310	−330
81	1,3-Dinitro-4-aziridinyl-6-$CONHCH_2CH(OCH_3)_2$-benzene	−384	7.0						−350	−290
82	1,3-Dinitro-4-amino-6-$CONH_2$-benzene	−460	7.0						−270	−340
83	1,3-Dinitro-4-dimethylamino-6-$CONH_2$-benzene	−464	7.0						−270	−360
84	1,3-Dinitro-4,6-$CONH_2$-benzene	−515	7.0						−470	−440
85	3-Amino-4-aziridinyl-6-$CONH_2$-nitrobenzene	−431	7.0						−440	−480
86	BABQ(d)	−105	7.5							−180
87	BMABQ(e)	−115	7.5							−180
88	3,6-Dichloro-BABQ	−113	7.5							−160

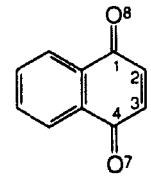
Table 1 (*Continued*)

#	*Chemical name*	*Reduction potentials [m V]*								
		Obs (a)	*pH*	*Predicted (b)*						
				Eq. (1) q(4)	Eq. (2) E(HOMO)	Eq. (3) E(HOMO)	Eq. (4) E(HOMO)	Eq. (5) Ar(SE)	Eq. (6) Ar(q)	Eq. (7) E(LUMO)
89	3,6-Dichloro-BMABQ	−125	7.5							−190
90	3,6-Difluoro-BABQ	−87	7.5							−99
91	3,6-Difluoro-BMABQ	−93	7.5							−120
92	3-Bromo-6-methyl-BABQ	−185	7.5							−200
93	3-Bromo-6-methyl-BMABQ	−194	7.5							−200
94	3-Bromo-6-ethyl-BABQ	−210	7.5							−180
95	3-Bromo-6-[(2-carbamoyloxy)-1-ethyl]-BABQ	−201	7.5							−200
96	3-Chloro-6-methyl-BABQ	−197	7.5							−230
97	3-(1-Aziridinyl)-BABQ	−171	7.5							−150
98	3-(1-Aziridinyl)-6-fluoro-BABQ	−171	7.5							−64
99	3,6-bis(Ethoxycarbonylamino)-BABQ	−149	7.5							−200
100	3,6-bis(Ethoxycarbonylamino)-BMABQ	−145	7.5							−250
101	3-Methyl-6-ethyl-BABQ	−227	7.5							−270
102	3-Methyl-6-(2-hydroxyethyl)-BABQ	−209	7.5							−270
103	3-Methyl-6-(2-hydroxyethylcarbamate)-BABQ	−213	7.5							−250
104	3-Methyl-6-(2-hydroxyethylcarbamate)-BMABQ	−235	7.5							−200
105	CQ(f)	−182	7.5							−250

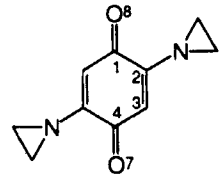
(a) One-electron reduction potentials, except for #86 − 105 which are two electron reduction potentials.
(b) Electronic descriptors based on the PM3 Hamiltonian.
(c) Reduction potentials for #24 − #58 are for the $ArO^{\cdot}/ArO^{-}$ couple.
(d) BABQ is 2,5-bis(1-aziridinyl)-1,4a-benzoquinone.
(e) BMABQ is 2,5-bis(2-methyl-1-aziridinyl)-1,4-benzoquinone.
(f) CQ is 2,5-bis(1-aziridinyl)-3-methyl-6-{2-(carbamoyloxy)-1-(methoxyethyl)}-1,4-benzoquinone.



1, 4 - benzoquinone (#1)



1, 4 - naphthoquinone (#16)



2, 5 - bis (1-aziridinyl) - 1, 4 - benzoquinone (#86)

Figure 1 Examples of benzoquinone, naphthoquinone, and aziridinylbenzoquinone structures modeled in this study.

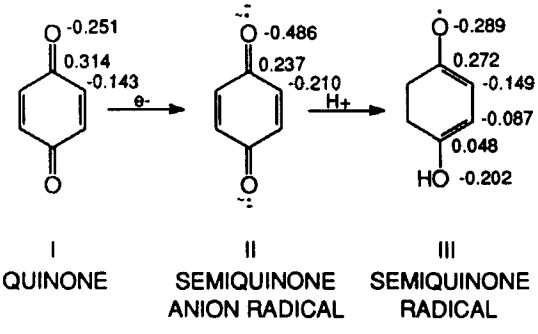


Figure 2 The modeling scheme evaluated, using 1,4-benzoquinone as an example: (I) parent quinone; (II) semiquinone as anion radical; (III) semiquinone as a neutral radical. The PM3 charge distributions for 1,4-benzoquinone (I), its semiquinone radical anion (II) and protonated semiquinone radical (III) derived from a one-electron reduction are presented.

used to evaluate possible relationships between electron density delocalization and one electron reduction potentials. Indices of aromaticity used were based on atomic charges (I^{q}_{Ar}) and donor- (I^{SE}_{Ar}) and acceptor- superdelocalizabilities (I^{SN}_{Ar}). These aromaticity indices were derived using an information-theoretic approach based on the evenness of the local electronic parameters' distribution over the atoms of the conjugated molecules.[23,24]

RESULTS AND DISCUSSION

Our hypothesis is that the addition of an electron to a quinone results in delocalization of the negative charge throughout all the atoms of the aromatic system and the charge on all atoms decrease (see Figure 2).

In theory, quinones and nitrobenzenes that have a greater ability to delocalize electron density in the molecule, will have more positive reduction potentials for the $Q/Q^{\cdot -}$ or $RNO_2/RNO_2^{\cdot -}$ couple. Such compounds should have more even electron distribution (lower values for aromaticity indices), lower-energy HOMO orbitals (lower electron donor ability), lower-energy LUMO orbitals (higher electron acceptor ability) and greater frontier charges on LUMO. In addition, the semiquinones and nitro aromatic anion radicals formed through the reduction would be more likely to act as electron donors, as opposed to the parent quinone or nitro aromatic. 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.

Theoretically, the one-electron reduction potential should be related to the free energy change of the equilibrium between the parent and the radical anion; however, a significant correlation with the heats of reaction for the transition from the BQs, NQs, and nitrobenzenes, to the radical anions was not obtained (data not shown). The results also failed to show the significance of changing LUMO energy in explaining potential as might be expected from equilibria considerations. The lack of significant correlations may be due to limitations with the semi-empirical methods and particularly their failure to adequately quantify proximity interactions, which perturb frontier orbitals (especially noteworthy for the open-shelled structures).

This study did not show any significance of the electronic indices for protonated semiquinone radicals in explaining reduction potentials. It is possible that semi-empirical methods are simply inadequate for these open-shell systems and future modeling with *ab initio* methods is planned.

The difficulty in modeling radicals with semi-empirical methods also precluded an attempt to assess the potential relationship between electron delocalization in phenoxyl radicals and one-electron reduction potentials. However, the hypothesis concerning electron density delocalization can be expanded in that more positive reduction potentials should also be related to reduced products that readily delocalize electron density in association with their higher thermodynamic stability. Thus, we also tested the hypothesis that more positive one-electron reduction potentials would be correlated with those reduced species that are less likely to act as electron donors because of the higher stability. To assess this hypothesis, E_{HOMO} values were derived for the protonated reduction products of phenoxyl radicals and related to potentials of $ArO^{\cdot}/ArO^{-}$ couples.

Consistent with our hypothesis concerning the relationship between electron density delocalization and one-electron reduction potential, those parameters which showed the most significant correlation with reduction potential of BQs, NQs, phenols and nitrobenzenes were the charges on the carbonyl carbons in the quinone moiety (BQs and NQs only), i.e., phenols and nitrobenzenes do not have a quinone moiety), energy of the HOMO (BQs, NQs and phenols) and LUMO (nitrobenzenes) orbitals and the aromaticity index based on atomic charges (I^q_{Ar}).

As illustrated in Figure 3, one-electron reduction potential tends to decrease with increasing positive charge on the carbonyl carbon (q_4) within the quinone moiety (see also Figure 1). With the exception of *ortho*-NQs (#12 and #15), NQs with intramolecular hydrogen bonding (#13, #14, #17) or direct electrostatic interaction (#10) and indigodisulfonate (#23), the potentials of the quinones under study were correlated to the charge on q_4 as summarized in Eq. (1) (all regressions cited are significant at the 95% confidence limit):

$$E_7^1\,(\text{mV}) = 2700(\pm 330) - 8500(\pm 970)q_4 \qquad (1)$$

$$n = 16;\ r^2 = 0.845;\ s^2 = 2942;\ F = 76.56$$

The data show that the *ortho*-NQs do not fit Eq. (1). The results associated with compounds #10, #13, #14 and #17 are interesting because they indicate that for a similar calculated carbonyl carbon charge, the one electron reduction potential is approximately 350 mV more positive when intramolecular hydrogen bonding is, presumably, increasing charge delocalization (e.g., q_4 of 0.360 for #10 and #21, but E_7^1 of -415 mV and -36 mV, respectively). Consistent with our hypothesis, the decreasing negative charge on the carbonyl oxygen of BQs and NQs was also correlated with increasing one-electron reduction potentials ($r^2 = 0.76$), when *ortho*-NQs were excluded.

Based on the overall findings in regard to local descriptors for BQs and NQs, it appears that increasing absolute charge on either of the carbonyl atoms is related to a decrease in the reduction potential. This finding is encouraging because smaller absolute charge should be associated with a greater delocalization of electron density. However, reduction potential should be related to a global molecular property

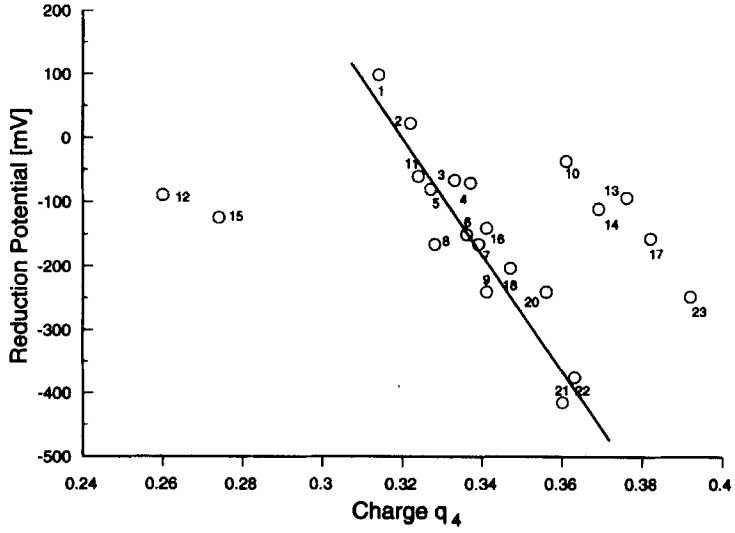


Figure 3 Variation of one-electron reduction potentials with charges on the carbonyl carbon within the quinone moiety (q_4; computed by PM3) for benzoquinones and naphthoquinones (see Figure 1 for atom numbering convention).

and the correlations described for atomic charges must be viewed with extreme caution, unless there is mechanistic process involving electrostatic charge of a micro-environment in the molecule. Even assuming Eq. (1) reasonably predicts one-electron reduction potentials for a select group of BQs and NQs, its utility is of limited value in a global sense because it incorporates an electronic descriptor that is only applicable to quinones.

In support of our hypothesis that global electronic measures should correlate with reduction potentials, more negative HOMO energies corresponded with more positive reduction potentials for BQs, NQs and phenols. Usually, E_{HOMO} is an inverse expression of the ability to accept electrons, and quinones and phenols which more readily accept electrons will have more positive potentials. For the reduced products in the $ArO^{\cdot}/ArO^{-}$ couple, the negative correlation between reduction potential and E_{HOMO} should be related to the higher electron density delocalization (and respectively higher stabilization) of ArOH. Four relationships between one-electron reduction potential and E_{HOMO} were obtained (Figure 4). The different relationships reflect, in part, the fact that reduction potentials are highly dependent upon pH[18] and for the compounds modeled here, measurements were made at pHs of 7.0 (BQs; non-*ortho*-NQs; non-hydrogen bonding and direct electrostatic interaction NQs – Eq. (2); and phenols – Eq. (3)) and 13.5 (phenols – Eq. (4)):

$$E_7^1\,(mV) = -4100(\pm 690) - 380(\pm 66)\,E_{HOMO} \qquad (2)$$

$$n = 14;\quad r^2 = 0.730;\quad s^2 = 4743;\quad F = 32.20$$

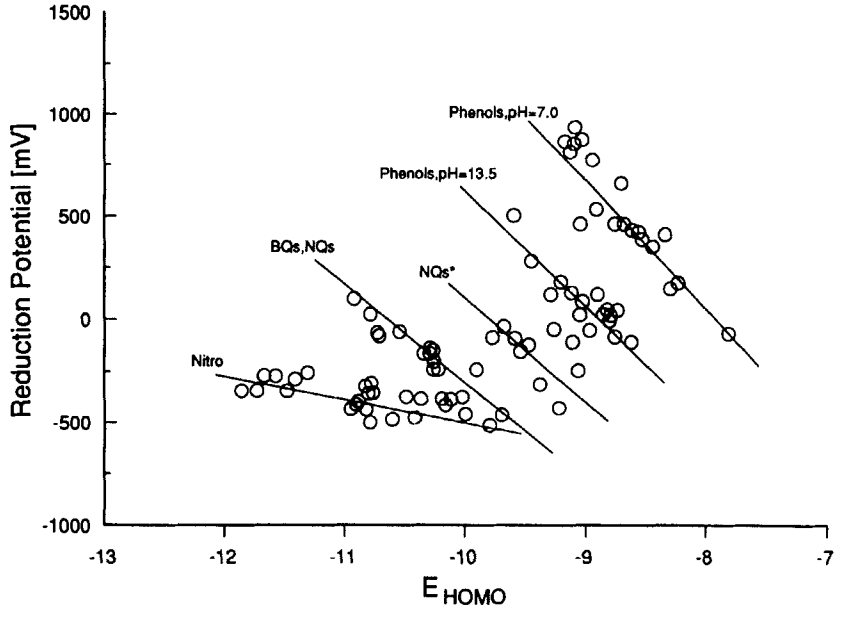


Figure 4 Variation of one-electron reduction potentials with E_{HOMO} (computed by PM3) for benzoquinones (BQs), naphthoquinones (NQs), NQs* (#4, #10, #12, #13, #14, #15, #17, #22, #23), phenols and nitrobenzenes.

$$E_7^1\,(mV) = -5600(\pm 790) - 700(\pm 90)E_{HOMO} \quad (3)$$

$$n = 18;\ r^2 = 0.792;\ s^2 = 1.32 \times 10^4;\ F = 60.4$$

$$E_{13.5}^1\,(mV) = -3800(\pm 780) - 430(\pm 86)E_{HOMO} \quad (4)$$

$$n = 17;\ r^2 = 0.624;\ s^2 = 8706;\ F = 25.2$$

4-Acetamidophenol (#30) and homogentisic acid (#50) deviated from Eqs. (3) and (4) respectively; elimination of these compounds significantly improved the correlations ($r^2 = 0.89$ for Eq. (3) and $r^2 = 0.79$ for Eq. (4)). Thus, the observation of distinct, but approximately parallel, relationships for phenols at pH = 7.0 and pH = 13.5 is not unexpected. However, the different quinone and phenol relationships at a pH of 7.0 (Eqs. (2) and (3)) is likely due to the different components being modeled within the redox couples. The differences may also suggest that semi-empirical calculations of E_{HOMO} may be biased by chemical class.

Similar to the findings with q_4, NQs capable of hydrogen bonding (#13, #14 and #17) or direct electrostatic interactions (#10), the *ortho*-NQs (#12 and #15), and compounds #22, #23 and #4 did not correlate with E_{HOMO} in the same manner as the remaining BQs and NQs. Instead, the potentials for these compounds correlated with E_{HOMO} ($r^2 = 0.5$) in a nearly parallel fashion to that of the remaining BQs and NQs, as depicted in Figure 4. In general, the failure of these NQs to fit Eq. (2) may reflect a substructural bias in the PM3 Hamiltonian and we are investigating this possibility. However, we are also examining the influence of solvation energy associated with the different chemical classes on the one-electron reduction potential. In this regard, the results associated with compounds #10, #13, #14 and #17 are interesting because they suggest increasing charge delocalization through hydrogen bonding or direct electrostatic interactions, results in an increased ability to accept electrons (i.e., for reduction potentials comparable to quinones without hydrogen bonding or direct electrostatic interactions, these NQs have significantly less negative HOMO energies).

When examining the relationship between one-electron reduction potential and E_{HOMO} (Figure 4) and E_{LUMO} for the nitrobenzenes (after elimination of chemicals #66 and #77), less significant correlations were obtained ($r^2 = 0.46$ and 0.49, respectively). This lack of consistency with E_{HOMO} and E_{LUMO} most likely reflect the inability of the semi-empirical method to uniformly model the diverse structure set under investigation.

In general, the results based on frontier orbitals indicate that more negative E_{LUMO} and E_{HOMO} values (higher electron acceptor and lower electron donor ability) were correlated with more positive reduction potentials, which is consistent with the overall hypothesis. The finding that semi-empirically-derived E_{LUMO} and E_{HOMO} values did not uniformly correlate with reduction potentials for all the compounds studied, may also indicate shortcomings of the single (energetically favorable) conformer-based QSAR modeling approach. It is possible that E_{HOMO} and E_{LUMO} derived from an appropriate group of 3D isomers selected among the set of all possible conformers[25] may fit the one-electron reduction potential data with less chemical class bias.

The aromaticity indices I^{q}_{Ar}, I^{SN}_{Ar} and I^{SE}_{Ar} are the most robust global estimates of electron density delocalization used in this investigation. Lower values for the aromaticity indices, which are related to greater evenness of electron density delocalization, were found to be associated with more positive one-electron reduction potentials. As indicated in Eq. (5), one-electron reduction potentials for BQs and NQs increased with a decrease in I^{SE}_{Ar} (see Figure 5):

$$E^{1}_{7}\,(mV) = 3200(\pm 5605) - 7.0 \times 10^{4}(\pm 1.2 \times 10^{4})\, I^{SE}_{Ar} \qquad (5)$$

$$n = 21;\ r^2 = 0.66;\ s^2 = 5323;\ F = 36.3$$

where the SE parameter distribution was analyzed for the entire quinone moiety. The regression can be improved significantly ($r^2 = 0.74$; $F = 50.5$), if the two *ortho*-quinones (#12–15) and 2-Me-1,4-NQ (#9) are eliminated from the correlation sample. Similar relationships were also found with I^{SN}_{Ar} ($r^2 = 0.72$) after elimination of NQs capable of hydrogen bonding (#13, #14 and #17) or direct electrostatic interactions (#10), the *ortho*-NQs (#12 and #15) and compound #23 from the correlation sample. The correlation with I^{q}_{Ar} was less pronounced.

Further expansion of this approach to include the nitrobenzenes was encouraging in that the aromaticity parameter based on charge distribution over the quinone moiety and the respective N = O fragment in the nitrobenzenes was correlated to reduction potential as indicated in Eq. (6):

$$E^{1}_{7}\,(mV) = -70(\pm 20) - 310(\pm 30)\, I^{q}_{Ar} \qquad (6)$$

$$n = 46;\ r^2 = 0.71;\ s^2 = 7063;\ F = 107.0$$

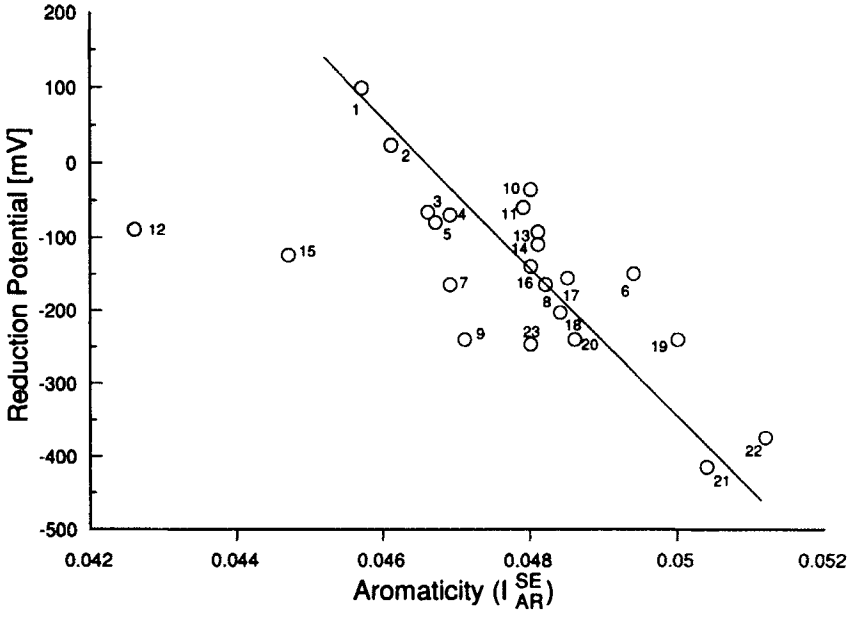


Figure 5 Variation of one-electron reduction potentials with I^{SE}_{Ar} (an aromaticity index based on donator superdelocalizabilities; computed by PM3) for benzoquinones and naphthoquinones.

where 2-OH-1,4-NQ (#21), 9,10-anthraquinone-2-sulfonate (#22), indigosulfonate (#23) and 2,4-dinitrophenol (#66) were eliminated from the correlation sample. Significant correlations were not, however, obtained with I_{Ar}^{SN} and I_{Ar}^{SE}, which likely reflects the fact that global measures of aromaticity through charge distribution are less influenced by variability in chemical structure than electron acceptor- and donator- superdelocalizability.

As discussed previously, bioreductive activation has been proposed as an explanation of the antitumor activity of AZBQs and acute cytotoxicity as a side effect of such drugs has been postulated to be related to redox cycling.[5,6] Superoxide anion formation for 22 AZBQs correlated with the electronic substituent constant, σ_{para}, summed for all substituents ($r^2 = 0.74$), but did not correlate with measured two-electron half-wave potentials.[6] Since the generation of reactive oxygen species through redox cycling should be related to the one-electron reduction potential, this finding may not be unexpected.[6] However, it has been suggested that even if the reduction of AZBQs is mediated through a two-electron reduction, the production of semiquinone-mediated superoxide production could be facilitated by a dismutation equilibrium of the two-electron reduced quinone (Q^{2-}) and the oxidized quinone (Q) with the semiquinone ($Q^{-\cdot}$).[26]

Because the propensity to accept the first electron in a two-electron reduction should be related to the ability of the parent quinone to delocalize electron distribution, and because differences between one- and two-electron reduction potentials in water should be similar,[26] we also investigated whether or not the local or global stereoelectronic descriptors examined thus far would also be correlated with measured two-electron reduction potentials of AZBQs (measured values for one-electron reduction potentials of AZBQs are not available in the literature). As with the BQs and NQs, q_4 was found to correlate with the two-electron reduction potential of AZBQs ($r^2 = 0.62$). Although a correlation of AZBQ reduction potentials with E_{HOMO} was not obtained, a significant correlation with E_{LUMO} was determined ($r^2 = 0.61$, after elimination of compounds #94, #98 and #104). Interestingly, the slope and intercept of this regression were not significantly different from that noted for the relationship between E_{LUMO} and the one-electron reduction potentials of the nitrobenzenes. Although the dependent variable represents one- and two-electron reduction potentials for nitrobenzenes and AZBQs, respectively, a significant correlation was obtained when these datasets were combined as shown in Eq. (7):

$$E_{1/2}^{7} = -710(\pm 38) - 200(\pm 17)\,E_{LUMO} \qquad (7)$$

$$n = 47;\ r^2 = 0.76;\ s^2 = 4005;\ F = 134.5$$

Certainly these results must be viewed with caution; however, they suggest that within the limitations of the semi-empirical methods used, the propensity of a compound to undergo a one- or two-step reduction is related to the ability of the parent compound to delocalize electron distribution.

CONCLUSIONS

The one-electron reduction potential of quinones, nitro aromatics and phenolic compounds is an important indicator of the potential toxic effects that are mediated through redox cycling and oxidative stress, and which have been observed in both mammals[4] and aquatic life.[27] The goal of the current effort was to assess if global descriptors related to electron density delocalization, and independent of chemical class bias, could be found that would be correlated to reduction potential. We have shown that the one-electron reduction potential for a diverse set of 105 quinones, phenols and nitrobenzenes can be estimated from chemical structure using conventional semi-empirical computational methods for modeling electronic structure of the parent compound. Within the different chemical classes studied, energies of frontier orbitals were found to be correlated with reduction potentials, with E_{HOMO} (which is inversely related to the ionization potential) correlated with the one-electron reduction potential of 58 BQs, NQs and phenols and E_{LUMO} correlated with the one-electron reduction potentials of nitrobenzenes and the two-electron reduction potentials of AZBQs. Indices of aromaticity, such as I_{Ar}^{SE} (for BQs and NQs combined) and I_{Ar}^{q} (for BQs, NQs, and nitrobenzenes combined) were also correlated with reduction potential. These findings were consistent with a hypothesis that parent compounds with greater delocalization of electron density should have more positive reduction potentials. In the case of phenolic compounds, the higher electron density delocalization reflects a greater stabilization of the reduced products of the couple, leading to more positive reduction potentials.

Overall, the results of this study have established that local and global measures related to electron delocalization can be used to predict one-electron reduction potentials; however, with the limitation of currently available semi-empirical parameterizations, these predictions must be based on specified chemical classes. The establishment of an electron delocalization-based predictive model independent of chemical class bias may require the use of *ab initio* calculations and the estimation of solvation energy for the chemical species.

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References

1. Bradbury, S.P. (1994). Predicting modes of toxic action from chemical structure: an overview. *SAR QSAR Environ. Res.* **2,** 89–104.
2. Mekenyan, O.G., Veith, G.D., Bradbury, S.P., and Zaharieva, N. (1995). SAR models for metabolic activation: stability of organic cation intermediates. *Quant. Struct.-Act. Relat.* (in press).
3. Mekenyan, O., Ankley, G., Veith, G., and Call, D. (1993). QSARs for photoinduced toxicity: I. Acute effect of polycyclic aromatic hydrocarbons to *Daphnia magna*. *Chemosphere* **28,** 546–582.
4. Mason, R. (1990). Redox cycling of radical anion metabolites of toxic chemical and drugs and the Marcus theory of electron transfer. *Environ. Health Perspect.* **87,** 237–249.

5. Lin, A.J., Cosby, L.A., Shanksky, C.W., and Sartorelli, A.C. (1972). Potential bioreductive alkylating agents. 1. Benzoquinone derivatives. *J. Med. Chem.* **15,** 1247–1252.
6. Prins, B., Koster, A.S., Verboom, W., and Reinhoudt, D.N. (1989). Microsomal superoxide anion production and NADPH-oxidation in a series of 22 aziridinylbenzoquinones. *Biochem. Pharmacol.* **38,** 3753–3757.
7. Hernandez, P.H., Gillette, J.R., and Mazel, P. (1967). Studies on the mechanism of action of mammalian hepatic azoreductase. I. Azoreductase activity of reduced nicotinamide adenine dinucleotide phosphate-cytochrome c reductase. *Biochem. Pharmacol.* **16,** 1859–1875.
8. 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.
9. Bilmoria, M. H. and Kamin, H. (1973). The effect of high salt concentration upon cytochrome c_1, cytochrome c_s, and iron-EDTA reductase activities of liver microsomal NADPH-cytochrome c reductase. *Ann. N.Y. Acad. Sci.* **212,** 428–430.
10. Mason, R.P. and Holtzman, J.L. (1975). The mechanism of microsomal and mitochondrial nitroreductase. Electron spin resonance evidence for nitroaromatic free radical intermediates. *Biochemistry* **14,** 1626–1632.
11. O'Brien, P.J. (1991). Molecular mechanisms of quinone cytotoxicity. *Chem. Biol. Interactions* **80,** 1–41.
12. Mason, R.P. (1979). Free radical metabolites of foreign compounds and their toxicological significance. 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 naphthoquinones 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, P.L. (1980). Relationship of the singlet-electron reduction potential of quinones to their reduction by flavoproteins. *Biochem. Pharmacol.* **29,** 2567–2572.
16. Meisel, D. and Czapski, 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., Czapski, 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. Wardman, P. (1989). Reduction potentials of one-electron couples involving free radicals in aqueous solution. *J. Phys. Chem. Ref. Data* **18,** 1637–1745.
19. Mekenyan, O., Karabunarliev, S., and Bonchev, D. (1990). The microcomputer OASIS system for predicting the biological activity of chemical compounds. *Comput. Chem.* **14,** 93–200.
20. 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.
21. Pearson, R.G. and Sorgstad, J. (1967). Application of the principle of hard and soft acids and bases to organic chemistry. *J. Am. Chem. Soc.* **89,** 1827–1831.
22. Parr, R.G. and Poolson, R.G. (1983). Absolute hardness: companion parameter to absolute electronegativity. *J. Am. Chem. Soc.* **105,** 7512–7516.
23. Fratev, F., Bonchev, D., and Enchev, V. (1980). A theoretic information approach to ring and total aromaticity in ground and excited states. *Croat. Chem. Acta* **53,** 545–554.
24. Mekenyan, O.G., Bonchev, D.G., and Dimitrov, D.N. (1991). Information-theoretic approach to the aromaticity of chemical compounds based on superdelocalizability indices. *Revue Roumaine de Chimie* **36,** 363–377.
25. Mekenyan, O.G., Ivanov, J.M., Veith, G.D., and Bradbury, S.P. (1994). Dynamic QSAR: a search for active conformations and significant stereoelectronic indices. *Quant. Struct.-Act. Relat.* **13,** 302–307.
26. Lusthof, K.J., Richter, W., de Mol, N.J., Janssen, L.H.M., Verboom, W., and Reinhoudt, D.N. (1990). Reductive activation of potential antitumor bis(aziridinyl)benzoquinones by xanthine oxidase: competition between oxygen and quinone reduction. *Arch. Biochem. Biophys.* **277,** 137–142.
27. Digiullo, R.T., Washburn, P.C., Wenning, R.J., Winston, G.W., and Jewell, C.S. (1989). Biochemical responses in aquatic animals: a review of determinants of oxidative stress. *Environ. Toxicol. Chem.* **8,** 1103–1123.