Theoretical Calculations of Benzoquinone Redox Potentials using the COSMO Continuum Solvation Model

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Relative redox potentials for substituted benzoquinones are calculated to an accuracy of $\approx$50 mV at the AM1 or PM3 level using the COSMO continuum solvation model.

The kinetics of many important reductively activated alkylating drugs based on quinones such as **1** [2,5-bis(1-aziridinyl)-1,4-benzoquinones] (BABQ) have been shown to be related to their aqueous reduction potential.[1]

Accurate theoretical prediction of such electrode potentials has centred[2] around the use of a thermodynamic cycle (Scheme 1) in which the difference in energies of two quinones, Q and Q' and the two-electron reduced forms QH_2 and $Q'H_2$ can be related to the difference in electrode potential by eqn (1).

$$\Delta G_{(tot)} = \Delta G[Q'_{(hyd)}] + \Delta G[QH_{2(hyd)}] - \Delta G[Q'H_{2(hyd)}] - \Delta G[Q_{(hyd)}] + \Delta G(g) \quad (1)$$
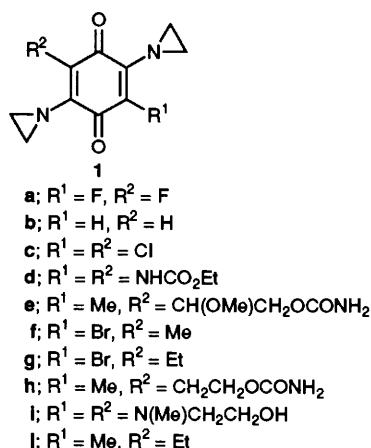
$$\Delta G_{(tot)} = -nF(E_Q - E_{Q'})$$

Such a scheme is necessary because accurate condensed phase *ab initio* energies at *e.g.* the MP2/6-31G* level for optimised molecular geometries together with correction for entropy and thermal contributions to 298 K are as yet unavailable. Instead, relatively reliable gas phase energies are combined with differences in solvation free energies obtained from a perturbation method based on molecular dynamics simulations. Each component of this cycle can become computationally very expensive for larger molecules such as **1**. Here we report a more direct approach based the COSMO continuum solvation model[3] involving calculation of ΔH(aq) for Q, Q', QH_2 and $Q'H_2$ employing full geometrical optimisation† and correction to ΔG(aq) using the calculated entropies obtained from a full vibrational analysis at the COSMO level. This approach yields results similar in accuracy to the *ab initio* approach, and which is readily extended to systems such as **1**.

In the COSMO (conductor screening) model, as applied to

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† Theoretical calculations were carried out at the restricted Hartree-Fock level (RHF) using the MNDO, AM1 or PM3 semi-empirical SCF-MO methods, as implemented in the MOPAC 93 program,[6] using a relative permittivity of 78.4 and 60 surface segments per atom. All structures were optimized and further refined to a gradient normal of <2 followed by a vibrational analysis, calculation of thermodynamic properties and hence correction of ΔH(aq) to ΔG_{298}(aq). For **1**, a prior molecular mechanics study of the side-chains conformations was carried out using the Macromodel program[7] (V 3.5a), with MM3 as the selected force field.

1

a; $R^1 = F$, $R^2 = F$
b; $R^1 = H$, $R^2 = H$
c; $R^1 = R^2 = Cl$
d; $R^1 = R^2 = NHCO_2Et$
e; $R^1 = Me$, $R^2 = CH(OMe)CH_2OCONH_2$
f; $R^1 = Br$, $R^2 = Me$
g; $R^1 = Br$, $R^2 = Et$
h; $R^1 = Me$, $R^2 = CH_2CH_2OCONH_2$
i; $R^1 = R^2 = N(Me)CH_2CH_2OH$
j; $R^1 = Me$, $R^2 = Et$

Table 1 Calculated electrode potentials (in mV) of the substituted hydroquinones 2–8 using 1,4-benzoquinone as a reference[a]

| Half-cell Reaction	Expt[b]	Ab initio[c]	MNDO	AM1	PM3
2S → Q	712	655 (57)[d]	715 (−3)[d]	711 (1)[d]	693 (19)[d]
2A → Q	712	685 (37)	726 (−14)	707 (5)	709 (3)
3 → Q	594	574 (20)	662 (−68)	674 (−80)	624 (−30)
4 → Q	792	798 (−6)	670 (122)	720 (72)	677 (115)
5 → Q	470	390 (80)	463 (7)	462 (8)	480 (10)
6 → Q	547	567 (−20)	461 (86)	491 (56)	442 (105)
7 → Q	644	670 (−26)	682 (−38)	648 (−4)	671 (−27)
8 → Q	590	578 (12)	625 (−35)	633 (−43)	630 (−40)

[a] The electrode potential of 1,4-benzoquinone is 699.76 mV. In this paper: 1 cal = 4.184 J; $F = 96\,485$ C mol^{-1}. [b] Experimental values; see ref. 2. [c] Calculated at MP2/6-31G* level; see ref. 2. [d] Differences (in mV) between experimental and calculated values, in parentheses.

semiempirical MNDO, AM1 or PM3 Hamiltonians, the dielectric screening energy and derivative terms for a solute are evaluated within a realistic solvent-accessible cavity for a charge distribution derived from an atom rather than cavity centred distributed multipole analysis involving dipole and quadrupole terms, allowing efficient geometry optimisation for not only closed shell but also open shell species. This results in good predictions of absolute solvation enthalpies for reasonably polar molecules where free energy dispersion terms are less important, and performs better where relative solvation enthalpies of related species are compared, as for example reaction path calculations.[4]

We have applied this model for two-electron reduction to the substituted hydroquinones 2–8 to obtain relative electrode potentials, normalised to the value for benzoquinone itself. The ab initio results (RMS error 38.8 mV) are slightly better than AM1 (45.6) with MNDO (61.1) and PM3 (59.1) being less accurate. Interestingly, all three semiempirical procedures independently result in large errors for the ortho-hydroquinone 4.

The errors calculated for 1a–j (AM1: 68; PM3: 67) are slightly larger (Table 2), but for a wider range of substituents. There is also significantly greater conformational mobility for the side chains which may result in significant errors in the entropic contributions, and side chain hydrogen bonding as in 1h vs. 1j may also play a role. We also note that where a significant difference in the size of the alkyl side chain occurs, dispersion contributions[5] to the solvation terms, which are not currently included in the COSMO treatment, may become important. Since the COSMO model can in principle be applied to ab initio wavefunctions, and since corrections for dispersion terms based on surface area can be included, the intrinsic accuracy of this type of treatment should be readily improvable.

2A   **2S**   **3**   **4**

5   **6**   **7**   **8**
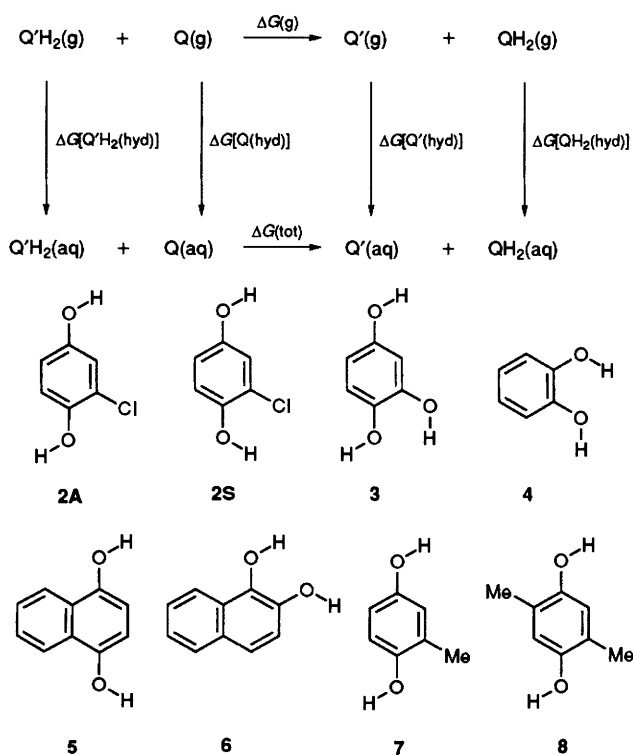
Table 2 Experimental[1] and calculated electrode potentials for systems 1a–j

BABQ derivative 1	$E_{1/2}$/V	AM1/V	PM3/V
a	−0.087	−0.037 (−50)[a]	−0.162 (75)
b	−0.105	−0.095 (−10)	−0.079 (−26)
c	−0.113	−0.086 (−27)	−0.013 (−100)
d	−0.149	−0.081 (−68)	−0.153 (4)
e	−0.182	−0.113 (−69)	−0.175 (−7)
f	−0.185	−0.129 (−56)	−0.145 (−40)
g	−0.210	−0.100 (−110)	−0.121 (−89)
h	−0.213	−0.078 (−135)[−0.116][b]	−0.113 (−100)
i	−0.225	−0.227 (2)	−0.253 (28)
j	−0.227	−0.228 (1)	−0.320 (93)

[a] Differences (in mV) between experimental and calculated values, in parentheses. [b] This value is obtained using ΔH_{298}(aq) instead of ΔG_{298}(aq).

References

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7 Macromodel V3.5a Copyright Columbia University, New York, USA, 1992.

The scheme at the top right of the page:

$$Q'H_2(g) + Q(g) \xrightarrow{\Delta G(g)} Q'(g) + QH_2(g)$$

$$\Delta G[Q'H_2(hyd)] \quad \Delta G[Q(hyd)] \quad \Delta G[Q'(hyd)] \quad \Delta G[QH_2(hyd)]$$

$$Q'H_2(aq) + Q(aq) \xrightarrow{\Delta G(tot)} Q'(aq) + QH_2(aq)$$