Accurate Redox Potentials from Theoretical Calculations: Methyl-substituted Benzoquinones

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The redox potentials of 2-methylbenzoquinone and 2,5-dimethylbenzoquinone have been calculated theoretically to within about 25 mV of the experimental value using a combination of *ab initio* calculations and molecular dynamics simulations.

The ability to calculate redox potentials accurately using theoretical methods would be advantageous in a number of different areas,[1] particularly where the experimental measurement is difficult due to complex chemical equilibria and reactions of the chemical species involved. This article describes *ab initio* and free energy perturbation (FEP)[2–7] calculations of the redox potential of mono- and dimethyl benzoquinone. There have been very few instances of this combined *ab initio*–FEP approach.[2,8]

The difference in redox potential in aqueous solution of two quinones, Q and Q′ can be obtained from the thermodynamic cycle in Figure 1.

The difference in the gas phase free energy for the reaction, ΔG(g), is fairly straightforward to calculate using accurate *ab initio* calculations. For this we have used Møller–Plesset second order perturbation theory (MP2)[9] with a 6–31G* double zeta basis set including polarisation functions on the non-hydrogen atoms.[10] The geometries of the molecules were determined using Hartree–Fock (HF) self-consistent field gradient methods with a 3–21G basis set.[11] The 3–21G basis set was used for the geometry optimisation because it is computationally much cheaper than the 6–31G* basis set, it gives superior geometries for quinones compared to the 6–31G* basis set (particularly for the C=O bond) and because previous calculations on the difference in redox potentials gave good results when either the 3–21G or 6–31G* geometries were used.[8] The calculations were performed using the CADPAC and Gaussian 82 programs.[12,13]

The *ab initio* calculations give internal energies at 0 K; in order to obtain gas phase free energies at 298 K, it is necessary to calculate the zero-point energy, the entropy, and the thermal contributions to the enthalpy. These corrections were carried out using frequencies[14] calculated using the AM1 semi-empirical molecular orbital method with the program AMPAC.[15,16]

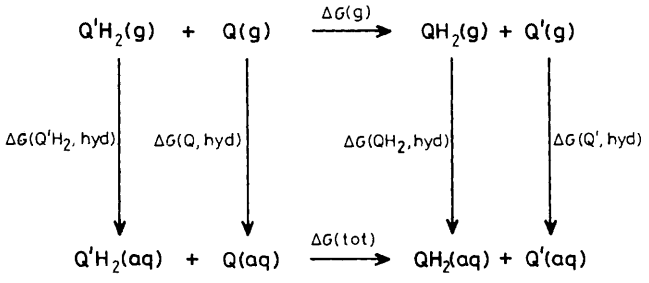

Figure 1. Equation (1): ΔG(tot) = ΔG(QH_2, hyd) − ΔG(Q, hyd) + ΔG(Q′, hyd) − ΔG($Q'H_2$, hyd) + ΔG(g).

Until recently, the calculation of free energies of hydration was a major obstacle to the theoretical study of reactions in solution. However, differences in free energy of hydration (ΔG) can be calculated using the free energy perturbation relationship[17] [equation (2)], where ΔH is the difference in Hamiltonian of states A and B and $<>_A$ indicate that an average is taken over the reference state A. We have used the implementation of the method incorporated in the AMBER suite of programs.[18,19,20]

In principle, equation (2) can be evaluated as a time average in which data is collected at each step of the molecular dynamics simulation of A by evaluating the total energy of A, and then changing the parameters to those of B, evaluating the energy and hence evaluating ΔH as the difference. However because the systems studied (hydroquinone and quinone) differ by more than 2 kT in their free energy of hydration, it was necessary to evaluate the change in several simulations (windows) to ensure that the reference system A contains sufficient important configurations that are representative of the system B. The change was therefore evaluated during 21 discrete simulations; the total difference in free energy is the sum of that obtained for each window.

$$\Delta G = -RT \ln <\exp(-\Delta H/RT)>_A$$

The simulation was performed as follows: the Hamiltonian of the system (solute plus about 610 TIP3P water molecules[21]) was formulated as a sum of bond, angle, torsional, non-bonded, and electrostatic terms. A molecular dynamics simulation was then carried out at constant temperature and pressure (1 atm, 298 K) using periodic boundary conditions. SHAKE[22] was used to constrain bonds, allowing a time step of 0.002 ps. The system was equilibrated for 5 ps. At each window, 500 steps of data collection were preceded by 500 steps of equilibration. The overall change therefore occurred over 42 ps.

Because only intra-molecular terms were used to evaluate ΔH in equation (2), only the change in the free energy of hydration was evaluated, and not the change in the free energy

Table 1. *Ab initio* energies/hartrees of methyl substituted quinones and hydroquinones (1 hartree = 2625.6 kJ mol^{-1}). ΔH_{ai} is the gas phase enthalpy/kJ mol^{-1} at 0 K for the reaction with respect to the benzoquinone system, without the zero-point correction.

Method and basis set	2-Methylbenzoquinone			2,5-Dimethylbenzoquinone		
	Oxidised	Reduced	ΔH_{ai}	Oxidised	Reduced	ΔH_{ai}
HF/3–21G	−415.92832	−417.12041	−13.44	−454.75602	−455.94473	−22.33
HF/6–31G*	−418.27538	−419.44518	−10.04	−457.31715	−458.48277	−21.00
MP2/6–31G*	−419.50182	−420.69549	−8.01	−458.67245	−459.86297	−16.28

Table 2. Relative hydration energies/kJ mol^{-1} of oxidised and reduced forms obtained using the free energy perturbation method. The table also shows the AM1 contributions/kJ mol^{-1} to the zero-point energy, thermal enthalpy, and entropy (as $-T\Delta S$). (The AM1 heat of formation is included).

	2-Methylbenzoquinone		2,5-Dimethylbenzoquinone	
Contribution	Oxidised	Reduced	Oxidised	Reduced
$\Delta G(Q, hyd) - \Delta G(QH_2, hyd)$	−23.102	0.000	−14.077	0.000
Zero-point	306.156	365.364	378.819	437.977
Thermal enthalpy	23.511	25.303	28.300	30.133
Entropy ($-T\Delta S$)	−112.455	−113.248	−123.485	−123.824
Heat of formation	−137.323	−302.585	−69.910	−331.609

Table 3. Individual contributions to the redox potential differences between benzoquinone and methyl substituted benzoquinones. The individual contributions are taken from Tables 1 and 2 and ref. 8.

	2-Methylbenzoquinone		2,5-Dimethylbenzoquinone	
Contribution	Free energy /kJ mol^{-1}	$E^{\ominus}$/V	Free energy /kJ mol^{-1}	$E^{\ominus}$/V
ΔH_{ai}	−8.01	0.042	−16.28	0.084
Thermal enthalpy	0.05	0.000	0.009	0.000
Entropy ($-T\Delta S$)	−0.67	0.003	−1.13	0.006
Zero-point	−0.35	0.002	−0.30	0.002
Hydration	3.31	−0.017	−5.72	0.030
Total (theory)	−5.67	0.029	−23.42	0.121

Table 4. Variation of calculated redox potential with method and basis set. The table also shows the difference between the experimental and theoretical redox potentials.

	2-Methylbenzoquinone		2,5-Dimethylbenzoquinone	
Method	$E^{\ominus}$/V	Difference/mV	$E^{\ominus}$/V	Difference/mV
HF/3–21G	0.642	−2	0.547	40
HF/6–31G*	0.660	−16	0.554	40
MP2/6–31G*	0.670	−26	0.578	10
Experiment	0.644		0.59	

of the solute. However, the total free energy change can be obtained by combining the quantum mechanical results with those from the molecular dynamics stimulation.

Using this method it is possible to calculate differences in redox potentials only. However, as calculations on benzoquinone have already been carried out and reported elsewhere,[8] the results from the benzoquinone system can be used to calculate absolute values of redox potentials.

The *ab initio* energies are reported in Table 1. The differences in hydration energies of the oxidised and reduced forms are shown in Table 2, along with the zero-point, enthalpy, and entropy data. The individual contributions to the difference in redox potentials, relative to benzoquinone are shown in Table 3 (using the MP2/6–31G* results), and the calculated redox potentials are shown in Table 4, using the experimental value for benzoquinone[23] of 0.6998 V.

The agreement between all the theoretical results given in Table 4 and the experimental value is remarkable. For the results obtained using the self-consistent field method with the 3–21G and 6–31G* basis sets the agreement may be fortuitous. However, the MP2 method with a 6–31G* basis set is able to account for up to 85% of the electron correlation energy[24] (for that basis set) and should give quite accurate results, particularly as the calculation involves taking differences in the *ab initio* energies for similar molecules. The corrections to the *ab initio* results (Table 3) obtained using the AM1 method are on the whole insignificant, except for the entropy correction, which should be accurate as it depends primarily on the calculated geometry, rather than the frequencies.

In this system, unlike the results for the benzoquinone–*ortho*-benzoquinone system,[8] reasonable results are obtained by ignoring the hydration contribution. However, we believe that it is important to calculate the hydration energies wherever possible, and the free energy perturbation method appears to be eminently suitable for calculating hydration energy differences.

These calculations show that it may be possible to calculate redox potentials and the shift in redox potential due to substituents to an accuracy comparable with experimental error using a combined approach which involves both accurate *ab initio* calculations and free energy perturbation calculations implemented within the framework of molecular dynamics. This approach would have many applications, particularly within the realms of molecular design where the properties of a molecule are dependent upon its redox potential.

Moreover, as the free energy perturbation calculations and the *ab initio* calculations (particularly with full geometry optimisation of molecules of this size) require similar computational resources, it appears that some treatment of hydration should now be carried out in all quantitative *ab initio* studies of energies of reaction in solution; for larger molecules this will be even more appropriate as the cost of the *ab initio* calculations grows significantly more rapidly than the cost of the free energy perturbation calculations.

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