

# A Method for Computing One-Electron Reduction Potentials and Its Application to *p*-Benzoquinone in Water at 300 K

Ralph A. Wheeler

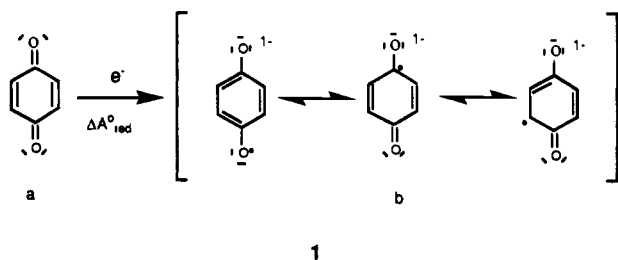
Contribution from the Department of Chemistry and Biochemistry, University of Oklahoma, 620 Parrington Oval, Room 208, Norman, Oklahoma 73019

Received April 21, 1994<sup>®</sup>

**Abstract:** Despite the importance of electron transfer in electrochemistry, photosynthesis, respiration, and chemical syntheses, the first-principles calculation of one-electron reduction potentials remains a significant challenge to modern computational chemistry. This contribution describes a thermodynamic cycle method, combined with hybrid Hartree–Fock/density-functional chemical and thermodynamic perturbation/molecular dynamics calculations, to estimate the one-electron reduction potential for the parent of quinone electron acceptors in photosynthesis and respiration, *p*-benzoquinone, in water at 300 K. Hybrid Hartree–Fock/density functional methods yield a calculated, gas-phase electron affinity of 1.85 eV (42.55 kcal/mol), in agreement with the experimental electron attachment free energy (42.9 kcal/mol) and thermodynamic perturbation/molecular dynamics simulations give a hydration free energy difference between *p*-benzoquinone and *p*-benzosemiquinone anion of 64.26 kcal/mol (2.79 eV). Together, the two numbers yield a computed reduction potential of 4.63 eV for *p*-benzoquinone, within approximately 90–100 mV of the experimental reduction potential of 4.54 eV. The exceptional accuracy attained for *p*-benzoquinone suggests the possible computer-aided design of molecules and their solvent or protein surroundings to achieve predictable electrochemical properties.

## Introduction

First-principles calculation of one-electron reduction potentials remains a significant challenge to modern computational chemistry, despite the importance of electron transfer to electrochemistry,<sup>1,2</sup> natural and artificial photosynthesis,<sup>3–5</sup> respiration,<sup>3</sup> and a number of enzymatic<sup>3</sup> and synthetic<sup>6,7</sup> chemical reactions. Broad classes of organic reactions catalyzed by electron transfer include S<sub>N</sub>1, S<sub>N</sub>2, cycloreversion, and cycloaddition reactions.<sup>6,7</sup> Even the classical thermal Diels–Alder reaction of *p*-benzoquinone is now believed to accelerate upon one-electron reduction of *p*-benzoquinone (**1a**) to form



the more reactive *p*-benzosemiquinone anion (**1b**).<sup>8</sup> And quinones are central to other one-electron reductions as well:<sup>9</sup>

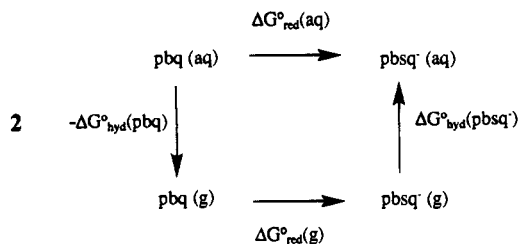
- <sup>®</sup> Abstract published in *Advance ACS Abstracts*, November 1, 1994.
- (1) Bard, A. J.; Faulkner, L. R. *Electrochemical Methods, Fundamentals and Applications*; John Wiley & Sons: New York, 1980.
- (2) Clark, W. M. *Oxidation–Reduction Potentials of Organic Systems*; The Williams & Wilkins Co.: Baltimore, 1960.
- (3) Stryer, L. *Biochemistry*, 3rd ed.; W. H. Freeman & Co.: New York, 1988.
- (4) Kirmaier, C.; Holten, D. *Photosynth. Res.* **1987**, *13*, 225–260.
- (5) Connolly, J. S.; Bolton, J. R. In *Photoinduced Electron Transfer*; Fox, M. A., Chanon, M., Eds.; Elsevier: Amsterdam, 1988; Vol. D, p 303–393.
- (6) Ebersson, L. *Electron Transfer Reactions in Organic Chemistry*; Springer-Verlag: Berlin, 1987.
- (7) Kochi, J. K. *Angew. Chem.* **1988**, *100*, 1331–1370; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1227–1266.
- (8) Fukuzumi, S.; Okamoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 11600–11601.

2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and tetrachloro-*p*-benzoquinone (*p*-chloranil) are powerful oxidizing agents in organic synthesis,<sup>10</sup> *p*-anthraquinone is a common industrial oxidant,<sup>11</sup> and *p*-benzoquinone (**1a**) is the parent of quinone electron acceptors in respiration and photosynthesis.<sup>3,4,12</sup> This contribution extends recent advances in thermodynamic cycle/free-energy perturbation theory<sup>13–20</sup> to estimate the reduction potential for one-electron reduction of *p*-benzoquinone to *p*-benzosemiquinone anion, **1**. Results reported here for *p*-benzoquinone evoke the possibility of computer-aided design of molecules and their solvent or protein surroundings to tailor a system's electrochemical properties.

Despite impressive, recent advances in computational methods based on thermodynamic cycles,<sup>13–20</sup> one-electron reduction potentials are extremely difficult to calculate accurately and the thermodynamic cycle shown in **2** reveals the reasons. The top reaction in **2** represents the reduction of *p*-benzoquinone (pbq) to *p*-benzosemiquinone anion (pbsq<sup>−</sup>) in aqueous solution, whereas the other reactions illustrate the conceptual decomposition of the reduction into (1) quinone desolvation, (2) gas-phase

- (9) *The Chemistry of the Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1988; Vol. 2, Parts 1 and 2.
- (10) Smith, J. G.; Fieser, M. *Reagents for Organic Synthesis*; Wiley-Interscience: New York, 1990; Vol. 12.
- (11) Bayer, O. In *Methoden der Organischen Chemie (Houben-Weyl-Müller)*, 4th ed.; Georg Thieme Verlag: Stuttgart, 1979; Vol. 7/3c, pp 270ff.
- (12) *Function of Quinones in Energy Conserving Systems*; Trumpower, B. L., Ed.; Academic: New York, 1982.
- (13) Straatsma, T. P.; McCammon, J. A. *Annu. Rev. Phys. Chem.* **1992**, *43*, 407–435.
- (14) Beveridge, D. L.; DiCapua, F. M. *Annu. Rev. Biophys. Chem.* **1989**, *18*, 431–492.
- (15) van Gunsteren, W. F.; Berendsen, H. J. C. *Angew. Chem.* **1990**, *102*, 1020–1051; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 992–1023.
- (16) Kollman, P. A. *Chem. Rev.* **1992**, *93*, 2395–2417.
- (17) Jorgensen, W. L. *Acc. Chem. Res.* **1989**, *22*, 184–189.
- (18) Reynolds, C. A.; King, P. M.; Richards, W. G. *Mol. Phys.* **1992**, *76*, 251–275.
- (19) McCammon, J. A.; Harvey, S. C. *Dynamics of Proteins and Nucleic Acids*; Cambridge University: Cambridge, 1987.
- (20) Allen, M. P.; Tildesley, D. J. *Computer Simulation of Liquids*; Clarendon Press: Oxford, 1987.

reduction, and (3) hydration of the *p*-benzosemiquinone anion.



The overall reaction is characterized by a standard Gibbs free energy of reduction,  $\Delta G^\circ_{\text{red}}(\text{aq}) = -FE^\circ$ , where  $F$  is the Faraday constant ( $F = 23.06 \text{ kcal mol}^{-1} \text{ V}^{-1}$ ) and  $E^\circ$  is the standard reduction potential. The reduction free energy in water is equal to the sum of free energies for the indirect route from reactants to products in **2**,  $\Delta G^\circ_{\text{red}}(\text{aq}) = \Delta G^\circ_{\text{red}}(\text{g}) + [\Delta G^\circ_{\text{hyd}}(\text{pbsq}^-) - \Delta G^\circ_{\text{hyd}}(\text{pbq})]$ . Although molecular dynamics (MD) methods cannot yield accurate estimates for the gas-phase free energy change,  $\Delta G^\circ_{\text{red}}(\text{g})$ , and quantum chemical methods currently require too much computer time to be useful in calculating hydration free energy differences  $[\Delta G^\circ_{\text{hyd}}(\text{pbsq}^-) - \Delta G^\circ_{\text{hyd}}(\text{pbq})]$  for such a large molecule, MD and quantum chemical methods may be combined effectively by using the thermodynamic cycle shown in **2**.

To obtain accurate estimates of energy changes due to changes in covalent bonding and intermolecular contacts, represented by  $\Delta G^\circ_{\text{red}}(\text{g})$  and  $\Delta \Delta G_{\text{hyd}}^\circ = [\Delta G^\circ_{\text{hyd}}(\text{pbsq}^-) - \Delta G^\circ_{\text{hyd}}(\text{pbq})]$  respectively, one may appeal to quantum chemical calculations to approximate gas-phase reduction free energies as calculated electron affinities and molecular dynamics simulations to calculate hydration free energy differences. Work utilizing MD simulations and thermodynamic cycles similar to those in **2** was pioneered by several research groups,<sup>13–20</sup> but the work closest to that described here is the calculation by Reynolds and co-workers<sup>18,21–23</sup> of differences in two-electron reduction potentials between two different quinones. Because the net reactions studied by Reynolds *et al.* involved changes in covalent bonding within uncharged, closed-shell molecules, they could use molecular orbital (MO) methods<sup>24,25</sup> to calculate gas-phase free energy changes and MD simulations with thermodynamic perturbation theory<sup>13–20</sup> to compute accurate hydration free energy differences between very similar, uncharged molecules. However, calculating accurate gas-phase electron affinities by using MO methods requires estimating the correlation energy of charged, open-shell structures by using extended basis sets and sophisticated schemes for introducing electron correlation. To our knowledge, this has been accomplished only for relatively smaller molecules.<sup>9,26–29</sup> Because of the difficulties encountered in using MO methods to calculate energies of large, open-shell molecules and because the customary scaling of charges input to MD simulations<sup>30,31</sup> is impossible

(21) Reynolds, C. A.; King, P. M.; Richards, W. G. *Nature* **1988**, *334*, 80–82.

(22) Reynolds, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7545–7551.

(23) Lister, S. G.; Reynolds, C. A.; Richards, W. G. *Int. J. Quantum Chem.* **1992**, *41*, 293–310.

(24) Levine, I. N. *Quantum Chemistry*, 4th ed.; Prentice-Hall: Englewood Cliffs, NJ, 1991.

(25) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986.

(26) Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys.* **1991**, *94*, 7221–7230.

(27) Curtiss, L. A.; Jones, C.; Trucks, G. W.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **1990**, *93*, 2537–2545.

(28) Pople, J. A.; Head-Gordon, M.; Fox, D. J.; Raghavachari, K.; Curtiss, L. A. *J. Chem. Phys.* **1989**, *90*, 5622–5629.

(29) Petersson, G. A.; Tensfeldt, T. G.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1991**, *94*, 6091–6101.

for ions, estimating accurate electron affinities by using density functional methods and estimating hydration free energy differences without charge scaling represent the major computational challenges addressed here. Naturally, this strategy of separately calculating the solute's gas-phase electron affinity and the hydration free energy difference neglects the effects of solvent on quinone electronic structure, as well as the influence of a solute on the solvent's molecular structure and force field.

## Computational Methods

Spin-unrestricted Hartree–Fock (UHF),<sup>24,25</sup> second-order Møller–Plesset perturbation (UMP2),<sup>24,25,32</sup> density-functional,<sup>24,33</sup> and hybrid Hartree–Fock/density-functional (HF/DF)<sup>34–36</sup> methods were employed by using the GAUSSIAN92/DFT<sup>37</sup> quantum chemistry programs to solve UHF, UMP2, or Kohn–Sham density-functional equations. The semiempirical “B3LYP” hybrid Hartree–Fock/density-functional method<sup>36,37</sup> was found to give the most accurate electron affinities. The method is similar to methods developed by Becke<sup>34,35</sup> and expresses a molecule's energy as a functional of the electron density,  $E[\rho]$ , where the molecular energy is a weighted sum of Hartree–Fock ( $E_X^{\text{HF}}$ ), Slater's local ( $E_X^{\text{Slater}}$ ),<sup>38</sup> and Becke's gradient-corrected ( $E_X^{\text{Becke}}$ )<sup>39</sup> exchange energies, combined with the local correlation energy expression of Vosko, Wilk, and Nusair ( $E_C^{\text{VWN}}$ )<sup>40</sup> and the nonlocal, gradient-corrected correlation energy proposed by Lee, Yang, and Parr ( $E_C^{\text{LYP}}$ ):<sup>41</sup>

$$E[\rho] = AE_X^{\text{Slater}} + (1 - A)E_X^{\text{HF}} + BE_X^{\text{Becke}} + CE_C^{\text{LYP}} + (1 - C)E_C^{\text{VWN}}$$

The parameters  $A$ ,  $B$ , and  $C$  in this equation were chosen to reproduce thermochemical data accurately,<sup>34–36</sup> and we have shown that the hybrid HF/DF methods also yield extremely accurate structures for *p*-benzoquinones<sup>42</sup> and harmonic vibrational frequencies accurate to within an average of approximately 30–50  $\text{cm}^{-1}$  for phenoxyl radical,<sup>43</sup> *p*-benzoquinones,<sup>42</sup> and their *p*-benzosemiquinone radical anions.<sup>44</sup> Apparently, anharmonic corrections for these species are small and the three-parameter, HF/DF methods show considerable promise in providing accurate harmonic force fields, including the effects of electron correlation, for these molecules and radical anions.

A number of different basis sets were employed with several density-functional and hybrid HF/DF methods. The 6-31G(d) basis set was used initially because it gives accurate structures and vibrational frequencies for *p*-benzoquinones<sup>42,44</sup> and the 6-311G(d,p) basis was selected because it was optimized for post-Hartree–Fock calculations<sup>45</sup> and we believed that it might prove more compatible than other Gaussian basis sets with the correlation functionals tested. Larger basis

(30) Singh, U. C.; Kollman, P. A. *J. Comput. Chem.* **1984**, *5*, 129–145.

(31) Besler, B. H.; Merz, K. M., Jr.; Kollman, P. A. *J. Comput. Chem.* **1990**, *11*, 431–439.

(32) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618–622.

(33) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Clarendon Press: Oxford, 1989.

(34) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377.

(35) Becke, A. J. *J. Chem. Phys.* **1992**, *97*, 9173–9177.

(36) Stevens, P. J.; Devlin, F. J.; Chablowski, C. F.; Frisch, M. J. *J. Chem. Phys.* Submitted for publication.

(37) Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. GAUSSIAN92/DFT; Gaussian, Inc.: Pittsburg, 1992.

(38) Slater, J. C. *Quantum Theory of Molecules and Solids*; McGraw-Hill: New York, 1974; Vol. 4.

(39) Becke, A. *Phys. Rev. A* **1988**, *38*, 3098–3100.

(40) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200–1211.

(41) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

(42) Boesch, S. E.; Wheeler, R. A. *J. Phys. Chem.* Submitted for publication.

(43) Qin, Y.; Wheeler, R. A. *J. Chem. Phys.* **1995**, in press.

(44) Boesch, S. E.; Wheeler, R. A. *J. Phys. Chem.* In preparation.

(45) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650–654.

sets including diffuse functions, ranging in size from 6-31+G(d) to 6-311++G(d,p), were also tested, but the polarization basis sets gave the most accurate electron affinities. Although it is not unusual even for *ab initio* molecular orbital results to degrade as basis set size increases, the deterioration of B3LYP-derived electron affinities may be due instead to the parametrization of the semiempirical hybrid HF/DF methods without diffuse functions in the basis set.<sup>34,36</sup>

The thermodynamic perturbation method with molecular dynamics was chosen to calculate hydration free energy differences because it (and thermodynamic perturbation or thermodynamic integration with Monte Carlo methods) gives accurate hydration free energy differences between various organic and biological molecules and between halide ions and noble gas atoms.<sup>13–20</sup> The thermodynamic perturbation method was invented to minimize numerical errors by expressing the Hamiltonian, or energy operator, as a weighted sum of Hamiltonians for reactants and products. For changing *p*-benzoquinone into *p*-benzosemiquinone anion, the Hamiltonian is

$$H_{\delta} = \delta H(\text{pbsq}^{-}) + (1 - \delta)H(\text{pbq})$$

The parameter  $\delta$  was varied from 0 to 1 in small increments ("windows") as the geometry and MD parameters for *p*-benzoquinone were changed to those for *p*-benzosemiquinone anion. The free energy difference is a sum of small equilibrium free energy changes calculated for each of 21 windows. A second, independently equilibrated sample containing *p*-benzosemiquinone anion was then transformed into one containing *p*-benzoquinone and the average magnitude of the free energy changes for forward and reverse simulations gives the reported free energy difference. The difference between the average free energy change and the free energy change from either simulation is a lower limit for the error. Simulations were thus performed for a constant volume, temperature, and number of atoms by using the AMBER MD programs.<sup>46</sup> A temperature of  $300 \pm 20$  K was maintained by coupling the system to a heat bath with a time constant of 0.1 ps.<sup>47</sup> Bond distances were held constant by using the SHAKE coordinate re-setting algorithm<sup>48,49</sup> to allow use of a 0.001 ps time step and all structures were equilibrated for at least 100 ps before beginning thermodynamic perturbation. In solution, a single molecule (ion) was studied in a rectangular box containing the molecule (ion) and 360 water molecules, with periodic boundary conditions. Interactions in solution were cut off beyond 10 Å and the Born charging correction<sup>50–52</sup> was applied by using the first term from eq 15 of ref 54, a multipole expansion of the energy for a distribution of charges within a sphere imbedded in a structureless, polarizable dielectric.<sup>53,54</sup> Although the truncated multipole expansion is an approximation, higher-order terms in the expansion for *p*-benzoquinone in water are likely to be very small. First, the average structure of both the *p*-benzoquinone molecule and its radical anion have zero dipole moment, so the next largest term in the series expansion, the dipolar term, is zero. Moreover, terms in the expansion of higher order than the dipolar term fall off as  $1/r^5$  or faster, and are therefore likely to be insignificant for the cutoff distance employed. The 10 Å radius of the sphere was in fact used as the cutoff distance and the dielectric constant was assumed the same as the experimental dielectric constant of water, 78.

Because truncating long-range interactions and using the Born correction is an approximation, a large amount of work has been done to test its accuracy and to investigate alternatives such as generalized reaction field methods and Ewald sums.<sup>55–58</sup> Although Ewald sums

and generalized reaction fields are generally more accurate, especially for calculating potentials of mean force for ion pairs,<sup>56,59</sup> the Born charging correction reportedly recaptures approximately 95–98% of the hydration free energy lost by cutting off interactions between a single ion and distant water molecules.<sup>60–62</sup> We are nonetheless investigating ways to calculate long-range interactions more accurately and to attenuate the effects of cutoffs on calculated energy differences by considering thermodynamic cycles involving species of the same charge.

The Helmholtz hydration free energy difference between *p*-benzoquinone and *p*-benzosemiquinone anion,  $\Delta\Delta A^{\circ}_{\text{hyd}} = \Delta A^{\circ}_{\text{hyd}}(\text{pbsq}^{-}) - \Delta A^{\circ}_{\text{hyd}}(\text{pbq}) \approx \Delta\Delta G^{\circ}_{\text{hyd}}$ , was actually estimated from two sets of the thermodynamic perturbation/molecular dynamics simulations described above. The simulations transformed *p*-benzoquinone into *p*-benzosemiquinone anion in the gas phase [to estimate  $\Delta A^{\circ}_{\text{red}}(\text{g})$ ] and in water [to calculate  $\Delta A^{\circ}_{\text{red}}(\text{aq})$ ]. According to the thermodynamic cycle shown in 2, the difference between the aqueous and gas-phase free energies is the reported hydration free energy difference ( $\Delta A^{\circ}_{\text{red}}(\text{aq}) - \Delta A^{\circ}_{\text{red}}(\text{g}) = \Delta A^{\circ}_{\text{hyd}}(\text{pbsq}^{-}) - \Delta A^{\circ}_{\text{hyd}}(\text{pbq}) = \Delta\Delta A^{\circ}_{\text{hyd}}$ ). Gas-phase MD simulations were thus performed in the same way as those described above for solution simulations, but since no periodic boundary conditions were implemented, cutting off interactions beyond specified distances was unnecessary and the Born correction was not needed.

MD energies were derived from kinetic energies and potential energy expressions for interactions between atom pairs—including Lennard-Jones and Coulombic nonbonded terms, harmonic bond angle bending, and sinusoidal torsional angle twisting terms. For water, the well-known TIP3P model<sup>63</sup> was used; for quinones, Lennard-Jones parameters were adopted from those for similar atom types in the AMBER database<sup>64</sup> and other parameters were derived from UMP2 calculations. Atomic charges were derived from UMP2 calculations of the electrostatic potential on a grid of approximately 9000 points, spaced 1 Å apart and located outside the van der Waals radius of each atom, but within 2.8 Å of any atom. The potential was calculated by using the program GAUSSIAN92/DFT<sup>37</sup> with the 6-31G(d) basis set<sup>25,65</sup> and a least-squares-fitting procedure<sup>66</sup> was used to determine the partial atomic charges that best reproduce the electrostatic potential on the grid of points. Force constants were obtained for *p*-benzoquinone and *p*-benzosemiquinone anion by calculating uniformly scaled, harmonic force constants<sup>42,44</sup> for internal coordinates chosen according to the procedure recommended by Boatz and Gordon.<sup>67</sup> For torsional angle twisting, the harmonic force constants were adapted for use in AMBER by using a trigonometric identity to relate the functional form of the AMBER torsional potential,  $V_n/2[\cos(n\phi - \phi_0)]$ , to sines and cosines of the individual angles  $n\phi$  and  $\phi_0$ , noting that the equilibrium torsional angle,  $\phi_0$ , is 180° for each torsional angle required, and expanding  $\cos n\phi$  in a Taylor series to obtain the approximate relation  $V_n/2 = K_{\phi}n^2$  (where  $K_{\phi}$  are scaled harmonic force constants obtained from the molecular orbital calculations<sup>42,44</sup>).

## Results

Table 1 compares the experimental electron attachment free energy at 300 K ( $42.9 \text{ kcal mol}^{-1}$ )<sup>68,69</sup> with electron affinities

(55) An excellent review of electrostatics in simulations is: Davis, M. E.; McCammon, J. A. *Chem. Rev.* **1990**, *90*, 509–521.

(56) Alper, H.; Levy, R. M. *J. Chem. Phys.* **1993**, *99*, 9847–9852.

(57) Belhadj, M.; Alper, H. E.; Levy, R. M. *Chem. Phys. Lett.* **1991**, *179*, 13–20.

(58) Rick, S. W.; Berne, B. J. *J. Am. Chem. Soc.* **1994**, *116*, 3949–3954.

(59) Bader, J. S.; Chandler, D. J. *Phys. Chem.* **1992**, *96*, 6423–6427.

(60) Buckner, J. K.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 2507–2516.

(61) Hirata, F.; Redfern, P.; Levy, R. M. *Int. J. Quantum Chem. Biol. Symp.* **1989**, *15*, 179–190.

(62) Chan, S. L.; Lim, C. J. *Phys. Chem.* **1994**, *98*, 692–695.

(63) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926–935.

(64) Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230–252.

(65) Davidson, E. R.; Feller, D. *Chem. Rev.* **1986**, *86*, 681–696.

(66) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361–373.

(67) Boatz, J. A.; Gordon, M. S. *J. Phys. Chem.* **1989**, *93*, 1819–1826.

(46) Pearlman, D. A.; Case, D. A.; Caldwell, J. C.; Seibel, G. L.; Singh, U. C.; Weiner, P. K.; Kollman, P. A. *AMBER Version 4.0*; University of San Francisco, 1991.

(47) Andersen, H. C. *J. Chem. Phys.* **1980**, *72*, 2384–2393.

(48) Ryckaert, J. P.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* **1977**, *23*, 327–341.

(49) van Gunsteren, W. F.; Berendsen, H. J. C. *Mol. Phys.* **1977**, *34*, 1311–1327.

(50) Born, M. *Z. Phys.* **1920**, *1*, 45.

(51) Rashin, A. A.; Honig, B. J. *Phys. Chem.* **1985**, *89*, 5588–5593.

(52) Jayaram, B.; Fine, F.; Sharp, K.; Honig, B. J. *Phys. Chem.* **1989**, *93*, 4320–4327.

(53) Kirkwood, J. G. *J. Chem. Phys.* **1934**, *2*, 351–361.

(54) Beveridge, D. L.; Schnuelle, G. W. *J. Phys. Chem.* **1975**, *79*, 2562–2566.

**Table 1.** Electron Affinity of *p*-Benzoquinone, Calculated by a Variety of Computational Methods,<sup>24,25,33</sup> Compared to the Experimental, Gas-Phase Electron Attachment Free Energy at 300 K<sup>68,69</sup>

method/basis set <sup>24,25,33</sup>	energy (kcal mol <sup>-1</sup> )
UHF/6-31G(d)	16.86
UMP2/6-31G(d)	20.32
B3LYP/6-31G(d)	36.53
B3LYP/6-311G(d,p)	42.55
experiment <sup>68,69</sup>	42.9

**Table 2.** Helmholtz Hydration Free Energy Differences between *p*-Benzoquinone (pbq, **1a**) and *p*-Benzosemiquinone Anion (pbsq<sup>-</sup>, **1b**),  $\Delta\Delta A^\circ_{\text{hyd}} = \Delta A^\circ_{\text{red}}(\text{aq}) - \Delta A^\circ_{\text{red}}(\text{g}) = \Delta A^\circ_{\text{hyd}}(\text{pbsq}^-) - \Delta A^\circ_{\text{hyd}}(\text{pbq})$ , Computed by Using Various Simulation Conditions<sup>a</sup>

simulation	no. of equilibration steps per window	no. of data collection steps per window	total time (ps)	$\Delta\Delta A^\circ_{\text{hyd}}$ (kcal mol <sup>-1</sup> )
pbq → pbsq <sup>-</sup>	250	250	10.5	-62.93
pbsq <sup>-</sup> → pbq	250	250	10.5	67.46
pbq → pbsq <sup>-</sup>	500	500	21	-64.09
pbsq <sup>-</sup> → pbq	500	500	21	64.61
pbq → pbsq <sup>-</sup>	2000	3000	105	-64.26
pbsq <sup>-</sup> → pbq	2000	3000	105	64.25

<sup>a</sup> The best estimate for the reduction potential of *p*-benzoquinone (-106.81 kcal mol<sup>-1</sup> = 4.63 eV) is obtained by averaging the magnitude of the free energy differences for the longest total simulation times (-39.11 kcal mol<sup>-1</sup>), subtracting the MD-derived, gas-phase free energy difference (8.80 kcal mol<sup>-1</sup>), subtracting the Born charging correction<sup>50-54</sup> (16.35 kcal mol<sup>-1</sup>) to obtain the Helmholtz hydration free energy difference (-64.26 kcal mol<sup>-1</sup>), and then subtracting the calculated electron affinity (1.85 eV = 42.55 kcal mol<sup>-1</sup>).

for *p*-benzoquinone calculated by using several different methods. The table shows that the B3LYP method with a 6-311G(d,p) basis set yields a calculated electron affinity for *p*-benzoquinone (42.55 kcal mol<sup>-1</sup>) in excellent agreement with experiment. We have therefore begun to examine the generality of the B3LYP method with polarization basis sets for calculating the electron affinities of a variety of other molecules. For example, the electron affinity for tetrafluoro-*p*-benzoquinone (*p*-fluoranil), calculated by using the B3LYP method with the 6-311G(d,p) polarization basis set, is within approximately 85 meV of the experimentally measured electron affinity.

Table 2 shows Helmholtz hydration free energy differences between *p*-benzoquinone and *p*-benzosemiquinone anion, calculated by using a variety of simulation conditions. Because the calculated Helmholtz hydration free energy differences presented in Table 2 are similar for total simulation times ranging from 20 to 100 ps, calculations appear to be converged. Since the difference between free energies calculated in the forward or reverse directions and their average magnitude is only 0.01 kcal mol<sup>-1</sup> for the 100 ps simulation, relative statistical error is also small. Moreover, the most reliable computed hydration free energy difference between *p*-benzoquinone and *p*-benzosemiquinone anion, 64.26 kcal mol<sup>-1</sup>, is within 4% of

(68) Heinis, T.; Chowdhury, S.; Scott, S. L.; Kebarle, P. *J. Am. Chem. Soc.* **1988**, *110*, 400-407.

(69) Chowdhury, S.; Grimsrud, E. P.; Kebarle, P. *J. Phys. Chem.* **1986**, *90*, 2747-2752.

the experimentally-derived value of 61.8 kcal mol<sup>-1</sup>. Computational accuracy for the *p*-benzoquinone molecule is thus comparable to the accuracy of calculated hydration free energy differences for atomic anions.<sup>13-18</sup> Finally, combining the density-functional-derived, gas-phase electron affinity for *p*-benzoquinone (42.55 kcal mol<sup>-1</sup>) with the calculated hydration free energy difference yields a calculated reduction potential for *p*-benzoquinone of 4.63 eV, approximately 90 to 100 meV greater than the experimental value of 4.54 ± 0.03 eV. We note that the absolute reduction potential for *p*-benzoquinone was obtained by following the current IUPAC recommendation<sup>70</sup> to add 4.44 ± 0.02 V to the experimental reduction potential of 0.099 ± 0.02 V, measured relative to the normal hydrogen electrode.<sup>71,72</sup>

## Conclusions

The exceptionally close agreement between the one-electron reduction potentials for *p*-benzoquinone determined experimentally (4.54 ± 0.03 eV)<sup>71,72</sup> and calculated here (4.63 eV) suggests the possibility of combining thermodynamic cycles with hybrid Hartree-Fock/density-functional quantum chemical and thermodynamic perturbation/molecular dynamics methods to estimate accurate one-electron reduction potentials from molecular properties of quinones and their solvent or protein surroundings. Although this result is provocative, a great deal of work remains to generalize the method. It may in fact be desirable to explore (1) other basis sets<sup>25,65,73</sup> and ultimately MO methods with electron correlation<sup>26-29,74</sup> for calculating accurate electron affinities and partial atomic charges for dipolar molecules, (2) more accurate methods for developing intra- and intermolecular force fields for both solvents and solutes,<sup>75</sup> (3) more sophisticated methods of correcting for finite interaction distances in MD simulations,<sup>55,76</sup> and perhaps (4) alternative thermodynamic cycles for estimating solvation free energy differences.<sup>13-16</sup> Work to generalize the method and to study trends in one-electron reduction potential differences between molecules with various chemical substituents is currently underway.

**Acknowledgment.** This work was made possible by the OCAS award for project no. HN3-011, from the Oklahoma Center for the Advancement of Science and Technology, and by a Junior Faculty Research Fellowship, from the University of Oklahoma Research Council. We are very grateful to Professor Gregory D. Reinhart for his generous donation of computer time, to Professor C. LeRoy Blank for helpful discussions, to Mr. Scott E. Boesch for providing calculated electron affinities, and to an anonymous reviewer for pointing out ref 70.

(70) Trasatti, S. *Pure Appl. Chem.* **1986**, *58*, 956-966.

(71) Ilan, Y. A.; Czapski, G.; Meisel, D. *Biochem. Biophys. Acta* **1976**, *430*, 209-224.

(72) Meisel, D.; Fessenden, R. W. *J. Am. Chem. Soc.* **1976**, *98*, 7505-7510.

(73) Andzelm, J.; Wimmer, E. *J. Chem. Phys.* **1992**, *96*, 1280-1302.

(74) Pettersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081-6090.

(75) St. Amant, A.; Cornell, W. D.; Halgren, T. A.; Kollman, P. A. Private communication.

(76) Sharp, K. A.; Honig, B. *Annu. Rev. Biophys. Biophys. Chem.* **1990**, *19*, 301-332.