

# Computational electrochemistry: aqueous one-electron oxidation potentials for substituted anilines

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Semiempirical molecular orbital theory and density functional theory are used to compute one-electron oxidation potentials for aniline and a set of 21 mono- and di-substituted anilines in aqueous solution. Linear relationships between theoretical predictions and experiment are constructed and provide mean unsigned errors as low as 0.02 V over a training set of 13 anilines; the error rises to 0.09 V over a test set of eight additional anilines. A good correlation is also found between oxidation potential and a simple computed property, namely the energy of the highest occupied molecular orbital for neutral anilines in aqueous solution. For the particular case of the substituted anilines, a strong correlation between oxidation potential and  $pK_a$  is found, and a still stronger correlation between oxidation potential and physical organic descriptors for aromatic substituents is also found, albeit over a reduced data set.

## I. Introduction

Single-electron-transfer steps are involved in reaction pathways that lead to the transformation of certain classes of anthropogenic organic compounds in the environment.<sup>1</sup> These electron transfers can be either oxidative or reductive. Environmental fate constants (from which one can determine the half-lives of particular species in the environment) depend on the kinetics of individual steps in the transformation pathway. Because the initial electron-transfer step is often the rate-determining step, and its rate constant is correlated with its energetics, a key molecular descriptor in modeling electron-transfer kinetics is the one-electron redox potential. Successful linear free energy relationships (LFERs) based on one-electron redox potentials have been developed for the reduction rate constants of nitro-aromatics mediated by quinones and iron porphyrin,<sup>2</sup> ferrogenic aquifer material,<sup>3</sup> Fe(II) bound to magnetite<sup>4</sup> and goethite.<sup>5</sup> Likewise, successful LFERs have been developed relating redox potentials to rate constants of dehalogenation of chlorinated alkanes by zero-valent iron<sup>6</sup> and zinc.<sup>7</sup> The utility of such LFERs can often be rationalized using frontier molecular orbital theory or hard/soft acid–base theory.<sup>8,9</sup>

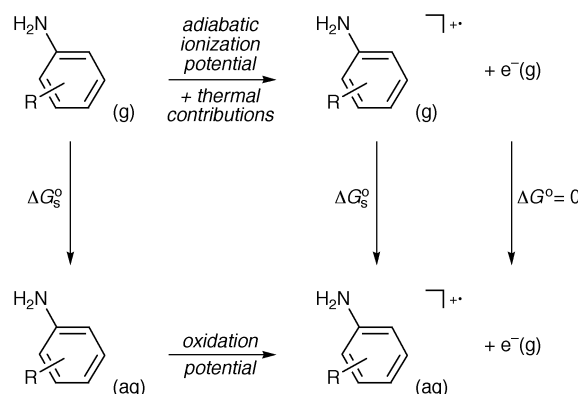
Cyclic voltammetry provides an experimental means for the measurement of redox potentials when the electron-transfer process is reversible. For non-reversible reactions, the experimental situation is more complicated, and accurate redox potentials are typically available only *via* rapid spectrophotometric techniques such as pulse radiolysis.<sup>10</sup>

To assist in the construction of kinetic schemes for the fates of various environmental contaminants for which experimental redox potentials are *not* available, useful models for the prediction of these potentials would be helpful. Just as reduction rate constants have been based on LFERs with redox potentials, the prediction of the redox potentials themselves has typically been based on LFERs between this property and related kinetic or thermodynamic quantities.<sup>11</sup> For

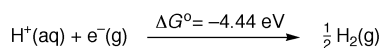
instance, Schwarzenbach *et al.*<sup>2</sup> have shown a linear relationship between certain nitro-aromatic reduction potentials and second-order rate constants for reduction of these species by the hydroquinone monophenol of juglone (8-hydroxy-1,4-naphthoquinone). This LFER was used in particular to estimate the one-electron reduction potential of 2,4,6-trinitrotoluene (TNT) and its aminonitrotoluene reduction products.<sup>5</sup> In the present study, in contrast, we are interested in predicting the redox potentials for cases where rate constants are *not* known.

Methods for predicting redox potentials that do not involve any experimental data typically make use of a free energy cycle; Scheme 1 is an illustration of such a cycle for the particular example of a substituted aniline as a reactant. The free

### Aniline oxidation half-reaction



### Normal hydrogen electrode half-reaction



Scheme 1

energy change associated with the top side of the cycle is the gas-phase oxidation potential, which is closely related to the adiabatic ionization potential (the distinction being that the adiabatic ionization potential is a difference in 0 K enthalpies, whereas the oxidation potential is a difference in 298 K free energies). Free energy changes associated with the left and right sides of the cycle are free energies of solvation (aqueous solvation in the case of Scheme 1), and thus the bottom side of the cycle refers to the oxidation potential in solution.

Oxidation potentials are usually reported relative to a reference potential, typically taken as the normal hydrogen electrode (NHE); this convention, then, refers to the free energy change for the net reaction resulting from addition of the NHE half-reaction to the half-reaction at the bottom of the free energy cycle (Scheme 1; note that, by definition, the NHE and aniline half-reactions involve a gas-phase electron, so the solvation free energy of the electron is not a relevant quantity in the free energy cycle). The free energy change associated with the NHE half-reaction is  $-4.44$  eV.<sup>12</sup> Thus, the aqueous oxidation potential of a closed-shell neutral solute X is determined from Scheme 1 as

$$\Delta G_{\text{ox}}^{\circ}(\text{X vs. NHE}) = \text{IP}(\text{X}) + \Delta G_{\text{evr, gas}}(\text{X} \rightarrow \text{X}^{+\cdot} + \text{e}^{-}) + \Delta G_{\text{s}}^{\circ}(\text{X}^{+\cdot}) - \Delta G_{\text{s}}^{\circ}(\text{X}) - 4.44 \text{ eV} \quad (1)$$

where IP(X) is the adiabatic ionization potential of X;  $\Delta G_{\text{evr, gas}}(\text{X} \rightarrow \text{X}^{+\cdot} + \text{e}^{-})$  is the difference in thermal contributions to the solute free energy deriving from changes in the electronic, vibrational and rotational partition functions upon ionization (note that the difference in zero-point vibrational energy is defined to be already included in the IP);  $\Delta G_{\text{s}}^{\circ}$  is the aqueous free energy of solvation; and X and  $\text{X}^{+\cdot}$  are the neutral and oxidized forms of the solute, respectively.

In previous work, oxidation potentials of various solutes have sometimes been predicted by making use of computed values for some or all of the quantities on the right-hand side of eqn. (1) (or its analog for reduction potentials). For example, Rychnovsky *et al.*<sup>13</sup> computed the oxidation potentials of 11 nitroxyl radicals by using the semiempirical quantum mechanical Austin model 1<sup>14–16</sup> (AM1) molecular orbital method to compute ionization potentials and the semiempirical quantum mechanical (QM) generalized Born<sup>17</sup> (GB) solvation model 2<sup>18,19</sup> (SM2) to compute free energies of solvation. At the same level of theory but with AM1 used to compute gas-phase electron affinities (EAs, EA being the quantity corresponding to IP for a reduction), Wolfe *et al.*<sup>20</sup> predicted reduction potentials for 12 nitrofurans and nitrothiophenes; when a neural network was employed to correct for systematic errors, these authors achieved an average accuracy of 0.07 eV. Reynolds<sup>21</sup> followed an analogous procedure to calculate two-electron reduction potentials with an average error of 0.03 eV for five naphthoquinones by using density functional theory<sup>22,23</sup> (DFT) to compute gas-phase energy differences and the semiempirical QM solvation model 3<sup>19,24</sup> (SM3) for solvation free energies. Using the semiempirical QM parameterized model 3<sup>25</sup> (PM3) for IPs and SM3 for solvation free energies, Charles-Nicolas *et al.*<sup>26</sup> predicted oxidation potentials for eight aromatic hydrocarbons with an average error of 0.04 eV. Similarly, Harada *et al.*<sup>27</sup> predicted oxidation potentials for 18 aromatic hydrocarbons in acetonitrile with an average error of 0.07 eV by using experimental IPs and a semiempirical QM GB method.<sup>28</sup>

All of the solvation models mentioned above treat the solvent as a dielectric continuum, which is a particularly efficient approach for the computation of the electrostatic component of the absolute solvation free energy at a QM level, and the SMx models also compute the non-electrostatic component of the absolute solvation free energy.<sup>17–19,24,29</sup> As an alternative, *explicit* solvent models and statistical mechanical sampling techniques have been employed to compute *relative*

free energies of solvation (and hence relative reduction potentials) for substituted quinones to levels of accuracy similar to those noted above for the continuum solvent models.<sup>21,30–33</sup>

This article focuses on predicting the absolute oxidation potentials of a series of substituted anilines (aminobenzenes) using various levels of gas-phase theory and continuum solvation models. Aromatic amines comprise an important class of environmental contaminants—they are building blocks for many textile dyes, agrochemicals and other classes of synthetic chemicals. The reaction pathways of aromatic amines in natural systems are dominated by redox reactions with soil and sediment constituents. For example, the formation of anilino radicals through oxidative processes (*e.g.*, oxidation by manganese oxides or redox active enzymes) can result in the formation of bound residues by coupling with sediment-bound radicals and/or the formation of dimers resulting from head-to-head or head-to-tail coupling of pairs of anilino radicals.<sup>34,35</sup>

We focus first on the sensitivity of the quantities on the right-hand side of eqn. (1) to the employed level of theory. We test not only the direct prediction of  $\Delta G_{\text{ox}}^{\circ}$  but also its prediction by an LFER involving the directly predicted value as a theoretical input. We also compare the quality of both kinds of purely computational prediction schemes to other approaches using LFERs. Finally we examine the degree to which the best (practical) computational method for the anilines can be extended to other mono- and di-substituted anilines. Section II describes the computational methods. Section III assembles the relevant experimental and computational data. Section IV provides a discussion of the quality and robustness of various predictive approaches, and we present conclusions in Section V.

## II. Computational methods

Gas-phase molecular geometries for all species were optimized at three different levels of electronic structure theory, namely AM1, *ab initio* Hartree–Fock (HF) and DFT. At the AM1 level, Dewar's half-electron method<sup>37</sup> was used for the radical cations. At the HF level, both unrestricted<sup>38</sup> (UHF) and restricted open-shell<sup>39</sup> (ROHF) methods were employed for the radical cations. At the DFT level, only the unrestricted formalism was used; all DFT calculations made use of Becke's<sup>40</sup> exchange functional (B) and the correlation functional of Perdew and Wang<sup>41</sup> (PW91); the combination is denoted BPW91. Expectation values of the square of the electron spin operator  $\langle S^2 \rangle$  for the radical cations were typically between 1.1 and 1.3 at the UHF level (such a value is indicative of heavy contamination by incorrect spin multiplicities), and were always between 0.75 and 0.76 at the BPW91 level (whereas the exact value is 0.75).

All *ab initio* geometry optimizations were carried out with the MIDI! basis set,<sup>42,43</sup> which was optimized in previous work specifically to reproduce high-quality geometries. Single-point gas-phase energy calculations for specific geometries were carried out at the Møller–Plesset second-order perturbation theory<sup>44</sup> (MP2) and BPW91 levels using the cc-pVDZ basis set.<sup>45–47</sup>

Zero-point vibrational energies (ZPVEs) and thermal vibration–rotation contributions to gas-phase free energies for all species were computed at the BPW91/MIDI! level of theory. The analytic vibrational frequencies required for these computations also verified that all structures are local minima at this level. The electronic contributions to  $\Delta G_{\text{evr, gas}}(\text{X} \rightarrow \text{X}^{+\cdot} + \text{e}^{-})$  were estimated from the ground-state electronic spin degeneracies, which yields  $-RT \ln 4$  ( $-0.04$  eV at 298 K).

Aqueous solvation free energies were computed at semiempirical molecular orbital levels using the SM5.4/AM1<sup>48</sup>

and SM5.42R/AM1<sup>49</sup> models. At an *ab initio* level, SM5.42R/HF<sup>50,51</sup> calculations were carried out, and, with DFT, calculations were carried out at the SM5.42R/BPW91<sup>51,52</sup> level. The MIDI! basis set was used for all SM5.42R/HF calculations. The MIDI!, 6-31G\*<sup>53–56</sup> and DZVP<sup>57</sup> basis sets were used for SM5.42R/BPW91 calculations. Geometries were reoptimized in solution for the SM5.4/AM1 calculations; SM5.42R models are parameterized for gas-phase geometries so reoptimization is not carried out in solution.

**Software.** Semiempirical calculations were carried out with AMSOL version 6.6.<sup>58</sup> *Ab initio* and density functional calculations were carried out with GAUSSIAN98<sup>56</sup> augmented with MN-GSM version g1.<sup>59</sup>

The standard state used for all experimental and computational data in this article is the ideal gas or ideal solution at a concentration of 1 mol L<sup>-1</sup>.

### III. Results

#### A. Geometries

Optimized structures for the anilines present no surprises. Neutral anilines all have pyramidalized nitrogen atoms while planar nitrogen atoms are observed for all radical cations; such a situation is expected given the much greater importance of nitrogen lone pair conjugation in the positively charged species. In general, molecular geometries were insensitive to the level of electronic structure theory, and we will not compare different levels of theory in any detail.

In cases where two different rotamers might be possible (*o*- and *m*-methoxy and -acetyl), we checked both geometries to see if they had populations large enough at 298 K to be included in the thermochemical calculations. For the two *meta*-substituted cases, the relative energies of *syn* and *anti* conformers were sufficiently close at several levels of theory that we computed all energies as averages over both conformers in the usual Boltzmann sense.<sup>60</sup> In neutral and cationic *o*-methoxyaniline, the methyl group orients away from the amine and no other rotamer could be found. In neutral and cationic *o*-acetylaniline, the conformation in which the amino group hydrogen bonds to the acetyl oxygen was in every instance at least 4 kcal mol<sup>-1</sup> lower in energy

than the alternative conformation (with methyl *syn* to amino) in the gas phase, but solvation effects occasionally reduced this difference to as little as 2 kcal mol<sup>-1</sup>, so we averaged over both conformers in this instance as well.

#### B. Gas-phase calculations

Table 1 lists computed and experimental (where available) IPs for 22 mono-substituted anilines. As we are interested in adiabatic IPs, changes in ZPVE (*i.e.*,  $\Delta ZPVE$  for  $X \rightarrow X^{+\cdot}$ ) are included as computed at the BPW91/MIDI! level. Absolute energies from all levels of theory, as well as ZPVEs and thermal free energy contributions from the BPW91/MIDI! level, are provided in Tables S1 and S2.† The  $\Delta ZPVE$  values never exceed 0.06 eV in magnitude, and are usually much smaller (*i.e.*, the vibrational frequencies do not change very much upon ionization). Mean unsigned errors (MUEs) *vs.* experiment are also tabulated for the different theoretical levels. Since the IP for *p*-chloroaniline is reported only as an upper bound, it is not included in the MUE calculation.

Table S3† lists the negative energies of the highest occupied molecular orbitals (HOMOs) for the neutral anilines at five levels of theory. Koopmans' theorem<sup>61</sup> establishes that the HOMO energy from a gas-phase Hartree–Fock calculation provides an estimate of the *vertical* ionization potential. While Koopmans' theorem does not apply to DFT HOMO eigenvalues or to orbital eigenvalues from a solvated wave function, they can still often be correlated with ionization potentials and are tabulated for this purpose. Further discussion of the HOMO energies is postponed until Section IV.D.

The rotational–vibrational part of the  $\Delta G_{\text{evr, gas}}(X \rightarrow X^{+\cdot} + e^-)$  term in eqn. (1) has also been calculated for all of the substituted anilines at the BPW91/MIDI! level (Tables S1 and S2†). In no case does this term exceed 0.03 eV in magnitude. Presumably because this term is often found to be small, one occasionally sees eqn. (1) written without it. However, it is not difficult to imagine systems where this term will be of greater

† Available as electronic supplementary information. See <http://www.rsc.org/suppdata/cp/a9/a909076b>

**Table 1** Gas-phase adiabatic IPs (eV) for substituted anilines<sup>a</sup>

Substituent	AM1 <sup>b</sup>	HF/MIDI!	(RO)HF/MIDI! <sup>c</sup>	BPW91/MIDI!	MP2/cc-pVDZ <sup>d</sup>	BPW91/cc-pVDZ <sup>d</sup>	Expt <sup>e</sup>
H	7.87	6.15	6.79	7.24	7.75	7.29	7.720 ± 0.002
<i>o</i> -Me	7.75	6.03	6.63	7.08	7.62	7.11	7.44 ± 0.02
<i>m</i> -Me	7.80	6.02	6.63	7.07	7.57	7.10	7.50 ± 0.02
<i>p</i> -Me	7.68	5.98	6.52	6.94	7.47	6.97	7.24 ± 0.02
<i>o</i> -CN	8.26	6.64	7.35	7.72	9.24	7.81	
<i>m</i> -CN	8.24	6.61	7.35	7.74	9.32	7.82	8.61 ± 0.05
<i>p</i> -CN	8.27	6.61	7.38	7.65	9.27	7.74	8.17
<i>o</i> -MeO	7.50	5.77	6.26	6.63	7.26	6.73	7.5 ± 0.1
<i>m</i> -MeO	7.79	6.00	6.50	6.82	7.14	6.90	7.8 ± 0.1
<i>p</i> -MeO	7.45	5.87	6.18	6.46	6.94	6.56	7.44
<i>o</i> -Cl	7.99	6.42	7.08	7.46	7.96	7.40	8.50
<i>m</i> -Cl	8.06	6.48	7.14	7.52	8.04	7.46	8.1 ± 0.1
<i>p</i> -Cl	7.93	6.43	7.02	7.33	7.86	7.24	≤ 8.18
<i>o</i> -Ac <sup>f</sup>	7.99	5.96	6.75	7.21	7.91	7.34	
<i>m</i> -Ac	8.00	6.17	6.90	7.28	8.70	7.36	
<i>p</i> -Ac	8.12	6.22	6.98	7.27	8.29	7.37	
<i>o</i> -CF <sub>3</sub>	8.35	6.51	7.16	7.48	8.18	7.37	
<i>m</i> -CF <sub>3</sub>	8.32	6.48	7.14	7.49	8.20	7.65	
<i>p</i> -CF <sub>3</sub>	8.44	6.55	7.26	7.50	8.27	7.63	
<i>o</i> -Br	8.04	6.32	6.97	7.27	8.35	7.67	8.45
<i>m</i> -Br	8.07	6.38	7.03	7.34	8.41	7.37	
<i>p</i> -Br	8.03	6.35	6.91	7.09	8.23	7.42	7.74
MUE <sup>g</sup>	0.23	1.63	1.07	0.70	0.27	0.61	

<sup>a</sup> Restricted calculations for all neutral anilines, unrestricted for radical cations unless otherwise indicated. All computed IPs include ZPVEs computed at the BPW91/MIDI! level. <sup>b</sup> Half-electron method for radical cations. <sup>c</sup> Restricted open-shell method for radical cations. <sup>d</sup> Geometries optimized at BPW91/MIDI! level. <sup>e</sup> Ref. 98. <sup>f</sup> Ac = acetyl. <sup>g</sup> MUE = mean unsigned error for 13 cases.

importance owing, for instance, to ionization-induced changes in very-low-frequency vibrational modes.

### C. Solvation free energies

We have computed 298 K aqueous free energies of solvation at six different levels. Results for the neutral anilines are in Table S4,<sup>†</sup> and results for the radical cations are in Table S5.<sup>†</sup> For the AM1 Hamiltonian, we have examined both the SM5.4 solvation model, which involves geometry reoptimization in solution, and the SM5.42R solvation model, which is parameterized to provide accurate solvation free energies at gas-phase geometries. The two models also differ in the algorithm used for atomic charges and in the size of the training set. For only a few cases do the results from these two models differ by more than 10%, and in those instances the absolute magnitude of the difference remains less than or equal to 0.7 kcal mol<sup>-1</sup>.

For the radical cations, the SM5.42R/HF/MIDI! model has been applied using both UHF and ROHF wave functions. Some fairly large differences between the two types of calculations are observed, and given the high levels of spin contamination in the UHF wave functions for the radical cations, the UHF values are considered unreliable. ROHF/MIDI! solvation free energies agree well with those calculated from the DFT levels of theory, where spin contamination is not an issue.

### D. Oxidation potentials

Using the results in Table 1 of this article and Tables S1, S2, S4, and S5,<sup>†</sup> aqueous oxidation potentials have been computed according to eqn. (1) for six different combinations of wave function approximation and solvation model. These predictions are provided in Table 2 together with experimental data<sup>62</sup> (measured in aqueous solutions buffered to pH 7 with acetate) where available. The mean unsigned errors for the six models *vs.* experiment are also tabulated. Not included in Table 2 are any results from levels of theory making use of an unrestricted Hartree–Fock wave function for the radical

cation, since high levels of spin contamination make this level of theory unreliable.

Also included in Table 2 are the oxidation potentials that would be predicted from using *experimental* IPs and SM5.4/AM1 solvation free energies in eqn. (1). Since the IP for *p*-chloroaniline is reported only as an upper bound, the predicted oxidation potential is also an upper bound, and is not used in computing the MUE for this method.

## IV. Discussion

### A. Predicted ionization potentials

The smallest MUE in gas-phase IPs, 0.23 eV, is afforded by the semiempirical AM1 model. The MP2/cc-pVDZ level is next best in performance, with an MUE of 0.27 eV, but this probably represents fortuitously good agreement of theory and experiment. As noted above, the UHF wave functions used as references for the MP2 calculations are heavily spin contaminated [note that the (U)HF/MIDI! level of theory gives the *largest* error for predicted IPs], and perturbation theory is typically<sup>63</sup> quite sensitive to spin contamination. Errors of about 0.7 eV are found for the BPW91 level using either the cc-pVDZ basis set or the considerably smaller MIDI! basis set (the former has polarization functions on all atoms, while the latter has polarization functions only on atoms other than C and H). Finally, the (RO)HF/MIDI! level gives a fairly large MUE of 1.06 eV, as might be expected since this level fails to account for differences in electron correlation between the neutral and the radical cation.

It is important to point out, in this comparative analysis, that some caution is warranted with respect to the quality of the experimental numbers themselves. For instance, the experimental IP for *o*-chloroaniline is reported to be 0.4 ± 0.1 eV larger than that for *m*-chloroaniline. However, every level of theory predicts that the *meta* compound should be the one with the higher IP, by 0.05 to 0.08 eV. Similarly, the experimental differences in IP between *m*- and *p*-cyanoaniline and

**Table 2** Aqueous oxidation potentials (298 K, V relative to NHE) for substituted anilines<sup>a</sup>

Substituent	1	2	3	4	5	6	7	Expt <sup>b</sup>
	AM1	AM1	(RO)HF/MIDI!	BPW91/MIDI!	BPW91/cc-pVDZ	BPW91/cc-pVDZ	Expt	
	SM5.4/ AM1	SM5.42R/ AM1	SM5.42R/ (RO)HF/MIDI!	SM5.42R/ BPW91/DZVP	SM5.42R/ BPW91/DZVP	SM5.4/ AM1	SM5.4/ AM1	
H	1.25	1.15	0.03	0.50	0.56	0.67	1.15	0.63
<i>o</i> -Me	1.22	1.12	-0.05	0.43	0.49	0.58	0.97	0.60
<i>m</i> -Me	1.28	1.18	0.01	0.46	0.53	0.58	1.01	0.61
<i>p</i> -Me	1.19	1.09	-0.10	0.35	0.41	0.48	0.79	0.54
<i>o</i> -CN	1.51	1.35	0.44	0.88	0.98	1.06		
<i>m</i> -CN	1.33	1.19	0.29	0.76	0.86	0.91		
<i>p</i> -CN	1.42	1.31	0.44	0.80	0.91	0.89		
<i>o</i> -MeO	1.13	1.03	-0.24	0.17	0.29	0.36	1.14	0.50
<i>m</i> -MeO	1.33	1.24	0.01	0.37	0.46	0.45	1.35	0.62
<i>p</i> -MeO	1.08	0.97	-0.32	0.01	0.13	0.18	1.11	0.39
<i>o</i> -Cl	1.41	1.31	0.35	0.78	0.76	0.83	1.97	0.74
<i>m</i> -Cl	1.38	1.30	0.35	0.76	0.74	0.78	1.46	0.77
<i>p</i> -Cl	1.32	1.24	0.28	0.63	0.58	0.63	≤ 1.62	0.68
<i>o</i> -Ac <sup>c</sup>	1.48	1.33	0.17	0.66	0.83	0.87		0.85
<i>m</i> -Ac	1.35	1.23	0.13	0.66	0.72	0.70		0.76
<i>p</i> -Ac	1.48	1.38	0.14	0.74	0.83	0.73		0.82
<i>o</i> -CF <sub>3</sub>	1.66	1.51	0.37	0.75	0.92	0.96		
<i>m</i> -CF <sub>3</sub>	1.47	1.36	0.24	0.62	0.77	0.79		
<i>p</i> -CF <sub>3</sub>	1.59	1.49	0.39	0.67	0.83	0.81		
<i>o</i> -Br	1.48	1.37	0.30	0.64	0.77	0.81	1.65	
<i>m</i> -Br	1.40	1.31	0.27	0.64	0.76	0.75		
<i>p</i> -Br	1.42	1.33	-0.05	0.48	0.61	0.58	1.12	
MUE <sup>d</sup>	0.65	0.55	0.59	0.16	0.09	0.07	0.62	

<sup>a</sup> Columns labeled 1–7 are predictions; see eqn. (1). The method used to compute the potential energy part of the IP is indicated above, and the method used to compute the solvation free energies is indicated below the rule. All ZPVE and  $\Delta G_{\text{evr, gas}}(\text{X} \rightarrow \text{X}^{+\cdot} + \text{e}^-)$  values were computed at the BPW91/MIDI! level. <sup>b</sup> Ref. 62. <sup>c</sup> Ac = acetyl. <sup>d</sup> MUE = mean unsigned error for available number of data.

between *o*- and *p*-bromoaniline seem unduly large in light of the theoretical predictions.

Curtiss and Raghavachari<sup>64</sup> have compared the predictive abilities of different theoretical models for 38 IPs. They found that the MUE for the BPW91/6-311+G(3df,2p) level is 0.23 eV, which is smaller than that found here, using a smaller basis set, for the anilines. In order to evaluate whether this difference can be attributed to basis set saturation [the 6-311+G(3df,2p) basis is considerably larger than cc-pVDZ], we computed the IP for aniline at the BPW91/cc-pVTZ//BPW91/MIDI! level. The result is 7.39 eV, which is only a 0.15 eV improvement over the BPW91/MIDI! prediction. Curtiss and Raghavachari also reported that the MUEs in IPs computed by hybrid HF-DFT models like B3LYP<sup>65</sup> are about 25% smaller than those obtained from pure DFT functionals like BPW91. To examine the effect of adding HF character to the density functional, we also computed the IP of aniline at the B3LYP/cc-pVTZ//BPW91/MIDI! level. The result is 7.45 eV, which is an improvement of only 0.06 eV over the analogous pure BPW91 calculation. These results suggest that, at least for the anilines, the BPW91 functional is as good (or almost as good) a choice as B3LYP.

## B. Predicted solvation free energies

The only experimental number available for direct comparison to the predicted data for the neutral anilines is the aqueous solvation free energy of unsubstituted aniline itself, which is  $-5.5 \text{ kcal mol}^{-1}$  (ref. 66). Table S4† shows that all of the solvation models examined here predict values within 0.3  $\text{kcal mol}^{-1}$  of this measurement. For the remaining molecules where no experimental data are available, agreement between the predicted solvation free energies from the different models is within 1.1  $\text{kcal mol}^{-1}$  for all of the neutral anilines, and the range of predictions is often smaller than 1  $\text{kcal mol}^{-1}$  if the solvation free energy is not itself large.

With the exception of the UHF/MIDI! level of theory, the different SM $x$  models also predict similar solvation free energies, one compared to another, for each radical cation. We attribute the considerably larger solvation free energies predicted in every case by the UHF/MIDI! level compared to the other levels to be the result of the severe spin contamination observed for the radical cation wave functions. Except for the UHF/MIDI! results, differences in solvation free energies across the remaining six models are less than 10% of the total solvation free energy in each case.

An experimental solvation free energy is not available for any aniline radical cation. One possible model compound for the unsubstituted aniline radical cation is protonated pyridine, since both of these molecules delocalize a positive charge involving a nitrogen atom over similarly sized aromatic  $\pi$  systems. The experimental aqueous solvation free energy of protonated pyridine is  $-58 \text{ kcal mol}^{-1}$  (ref. 67), which is indeed quite close to the predictions made here for the aniline radical cation. On the other hand, the experimental solvation free energy for protonated *aniline*, which might also be considered a reasonable analog for aniline radical cation, is  $-68 \text{ kcal mol}^{-1}$  (ref. 67), which is a substantially larger value. We note that SM5.42R/BPW91/MIDI! predicts solvation free energies for these two ions that are within 0.8  $\text{kcal mol}^{-1}$  of experiment in each case.<sup>51</sup>

To further evaluate the reliability of the SM5.42R predictions, we computed the electrostatic component of the solvation free energy of all of the aniline radical cations using the polarized continuum model<sup>29,68,69</sup> (PCM) of Tomasi and co-workers at the BPW91/MIDI! level (using the same gas-phase BPW91/MIDI! geometries employed for analogous SM5.42R calculations). The atomic radii for this model were taken to be 1.2 times the van der Waals radii given by Bondi.<sup>70</sup> The average difference between the PCM and SM5.42R models at

this level was about 0.5  $\text{kcal mol}^{-1}$ . The close agreement between the two formalisms indicates that the result is not very sensitive to the details of the continuum model employed. As discussed further in the next section, however, there is reason to suspect that the continuum approximation may not be as accurate as usual in this instance.

## C. Predicted aqueous oxidation potentials

The most complete level of electronic structure theory (and the most expensive) in Table 2 computes the potential energy component of the IP at the BPW91/cc-pVDZ level and solvation free energies at the SM5.42R/BPW91/DZVP level (column 5). This combination provides an MUE of 0.09 V in predicted aqueous oxidation potentials. Column 6 in Table 2 uses the SM5.4/AM1 level for the solvation free energies and has a slightly smaller MUE; the overall close agreement between the results using these two solvation models is consistent with the earlier discussion, which noted the similar performance of all of the solvation models for individual solutes. Insofar as both of the just discussed sets of calculations make use of the “best” gas-phase approximation to the wave function, it is tempting to regard it as satisfying that they provide the highest raw predictive accuracy.

However, the small MUEs in this instance appear to derive from a fortuitous cancellation of errors. To argue this point, it is instructive to compute aqueous oxidation potentials taking *experimental* IPs in eqn. (1), so that only the solvation free energies [and the very small  $\Delta ZPVE$  and  $\Delta G_{\text{evr, gas}}(X \rightarrow X^{+\cdot} + e^-)$  terms] are derived from computation. With this approach (column 7 of Table 2) the MUE over nine data points is a surprisingly large 0.62 V. Since solvation free energies are largely invariant to choice of model, the magnitude of this MUE is not sensitive to the particular choice of the SM5.4/AM1 model for these calculations. Significantly, however, the mean unsigned error is equal in magnitude to the mean signed error—that is, every predicted value represents an overestimation of the oxidation potential. Indeed, if each predicted value is adjusted by subtraction of 0.62 V, the MUE drops 67% to 0.20 V, a considerable improvement.

As has been noted above, there is reason to suspect that a few of the experimental IPs may be in error by up to several tenths of an electronvolt, and thus it might be worth while to repeat this kind of check with the most empirically accurate theoretical IPs. The AM1 level gave excellent agreement with experiment over the broad range of available experimental IPs and showed similar trends to other levels of theory for those IPs where experiment is missing or may be suspect. So, let us now consider the two columns of Table 2 that use AM1 for potential energies of ionization and either the SM5.4/AM1 or SM5.42R/AM1 solvation models for solvation free energies. The MUEs for these models are 0.65 and 0.55 V, respectively. Again, the errors are large and entirely in one direction. If we adjust the predicted values in columns 1 and 2 of Table 2 by subtraction of 0.65 and 0.55 V, respectively, the MUEs for the “corrected” models are reduced to 0.03 V in each case. Such improved agreement between theory and experiment over 13 data points is noteworthy.

Of course, the observation that the raw predicted oxidation potentials require correction indicates that some aspect of the overall computational procedure is not accurate. Recalling that theory is being used to compute the top, left, and right sides of the free energy cycle in Scheme 1, and noting that the predicted errors are about as large whether theoretical or experimental IPs are used, we must conclude that the problem lies in the computation of the solvation free energies. Furthermore, since the solvation models provide an accurate prediction for the known solvation free energy of aniline, and since the total variation in solvation free energy over the neutrals is small, it appears likely that the error is in the computation of

the solvation free energy for the aniline radical cations. Indeed, it follows from this analysis that the solvation free energy of the radical cations is consistently underestimated by about 14 kcal mol<sup>-1</sup> (0.6 eV). Note that, were the solvation free energy of the aniline radical cation indeed to be more negative by this amount, that would put it in the range of the protonated aniline cation whose solvation free energy was noted above.

What might be the cause of the underestimation of the radical cation solvation free energies? The agreement between the SM<sub>x</sub> models, which employ the generalized Born equation,<sup>17,29,71–77</sup> and the PCM model, which solves the Poisson equation,<sup>29,68,78–81</sup> suggests that it is not any particular model formulation that is at fault, but rather perhaps a breakdown in the continuum approximation. The SM<sub>x</sub> models already account for the breakdown of the bulk continuum approximation in the first solvation shell, by incorporating parameters for “average” specific interactions. The radical cation, however, may have a specific interaction with an individual water molecule that stabilizes it above and beyond the average. For instance, an unusually strong hydrogen bond might be formed between the radical cation and a first-shell water molecule.

An alternative possibility is a strong interaction between the electron-deficient aromatic ring and a water molecule. Closed-shell phenylnitrenium ions, which are very similar to aniline radical cations but have only one hydrogen atom on nitrogen instead of two, are well known to attack a water molecule electrophilically (without an activation energy in aqueous solution) to form a so-called aromatic  $\sigma$ -complex.<sup>82–86</sup> Were this also to be the case with the aniline radical cation, it would not so much be that the solvation models are wrong, as that the solutes are. Accounting for the formation of such a complex would require an expansion of the free energy cycle in Scheme 1 to account for the free energies of specific interactions, and, while intriguing, is beyond the scope of this article.

#### D. Quality and generality of predictive methodologies

Prior to further discussion of approaches for the *direct* computation of the oxidation potentials of substituted anilines, it is appropriate to consider practical alternatives for estimating oxidation potentials that do not involve the solution of the Schrödinger equation. As noted in Section I, when some experimental data are available, simple LFER or quantitative structure–property relationship (QSPR) correlations are often useful in this regard. Table 3 illustrates the utility of several such correlations. In every case, a simple linear regression is performed over one correlating variable; variables derived

from computation, like the HOMO energy, have been shown to be useful in QSPRs<sup>87,88</sup> and are also included. Some variables were not available for all 13 mono-substituted anilines whose oxidation potentials are known, and the table indicates the total number of data used in the correlation, together with the best-fit slope, intercept, correlation coefficient *R*, and mean unsigned error from the correlating equation. The data used in the correlations are provided in Table 2 of this article and Tables S3 and S6.† The null hypothesis, which is listed in Table 3, consists of assuming that all neutral anilines have an oxidation potential of 0.65 V (the average of the 13 available data), and this assumption leads to an MUE of 0.11 V. Thus, correlations that do not significantly improve on this MUE cannot be regarded as useful.

Regressing on the nine available experimental IPs leads to an MUE of 0.06 V. While one does expect some correlation between IP and oxidation potential, it is not particularly good, and difficulties in obtaining gas-phase IPs make it unlikely that this would ever be a method of choice in any case. A simpler quantity to measure, at least for the anilines, is p*K*<sub>a</sub> (in this case the p*K*<sub>a</sub> of the protonated aniline cations). Regressing all 13 oxidation potentials on p*K*<sub>a</sub> values<sup>89</sup> gives a reasonable correlation coefficient of 0.910 and an MUE of 0.04 V. As the subject anilines are simple substituted benzenes, the LFER descriptors of Hammett<sup>90,91</sup> ( $\sigma$ ) and Brown<sup>92,93</sup> ( $\sigma^+$ ) are available for many of the substituents. Regressing the experimental data on the nine available  $\sigma$  descriptors correlates the data with an MUE of 0.03, which is one of the lowest in Table 3. As is typical for systems carrying a formal positive charge, using the  $\sigma^+$  values of Brown and co-workers for *para* substituents further improves the correlation and indeed gives the smallest MUE in Table 3, albeit over only eight of the experimental data. These correlations, then, provide further proof of the strength of LFER analysis for substituted benzenes. Regrettably, such analysis is not easily generalizable to other classes of organic molecules (at least not without the extensive experimental effort required to generate new descriptors analogous to  $\sigma$  and  $\sigma^+$ ).

Turning to using a *theoretical* descriptor in a linear regression, we first consider the HOMO energy, since it is clear that this property should be physically correlated with oxidation potential. Regressing on AM1 gas-phase HOMO energies provides the poorest correlation in Table 3, with an MUE of 0.07 V.

Continuum solvation calculations at QM levels are typically carried out within the self-consistent reaction field (SCRF) formalism.<sup>94–96</sup> In this approach, which is used for the SM<sub>x</sub> models, polarization of the surrounding dielectric medium is included in the QM Hamiltonian, and the solute

**Table 3** Linear regressions of aqueous aniline oxidation potentials on other quantities

Correlating variable	No. of data	Slope	Intercept	<i>R</i>	MUE <sup>a</sup> /V
Exptl IP/eV	9	0.23	−1.20	0.791	0.06
p <i>K</i> <sub>a</sub>	13	−0.12	1.11	0.910	0.04
Hammett $\sigma$	9	0.47	0.59	0.960	0.03
Brown $\sigma^+$	8	0.32	0.63	0.981	0.02
AM1 HOMO	13	−0.24	−1.35	0.711	0.07
SM5.42R/AM1 HOMO	13	−1.15	−9.22	0.901	0.04
BPW91/MIDI! HOMO	13	−0.40	−1.21	0.854	0.05
SM5.42R/BPW91/MIDI! HOMO	13	−0.56	−1.97	0.888	0.04
Table 2 column 1	13	1.03	−0.68	0.967	0.03
Table 2 column 2	13	1.03	−0.59	0.947	0.03
Table 2 column 3	13	0.55	0.62	0.855	0.05
Table 2 column 4	13	0.53	0.39	0.940	0.03
Table 2 column 5	13	0.62	0.30	0.988	0.02
Table 2 column 6	13	0.64	0.27	0.937	0.04
Null hypothesis	13	<sup>b</sup>	0.65	<sup>b</sup>	0.11

<sup>a</sup> MUE = mean unsigned error for indicated number of data. <sup>b</sup> The null hypothesis is not a linear regression, but rather assumes every oxidation potential to be 0.65 V.

wave function distorts from its gas-phase optimum so as to take maximum advantage of favorable interactions with the surrounding reaction field. One consequence of this distortion is that the orbital eigenvalues for the SCRf wave function are different from those for the gas-phase wave function. If aqueous SM5.42R/AM1 HOMO eigenvalues are used in place of gas-phase AM1 eigenvalues, the correlation has a much smaller MUE of 0.04 V. Using gas-phase BPW91/MIDI! HOMO energies provides some improvement over gas-phase AM1 HOMO energies, but solvated HOMO energies at the SM5.42R/BPW91/MIDI! level do not yield better correlations than SM5.42R/AM1 HOMO energies. While not shown in Table 3, results using HF/MIDI! and SM5.42R/HF/MIDI! HOMO energies are essentially the same as for the DFT level.

Finally, we consider treating the oxidation potentials predicted from eqn. (1) as theoretical regression variables, taking the data from the six purely computational columns of Table 2. As noted previously, values predicted from levels of theory using the AM1 Hamiltonian both for the gas phase and for aqueous solution have a roughly constant error, and thus the slope of the regression line is predicted to be near unity. As a result, this two-parameter fitting approach does not provide much improvement over adjustment by a constant (the intercept) as already described above. For the *ab initio* levels of theory, on the other hand, predictive utility is substantially enhanced by linear regression, particularly when the data from column 5 of Table 2 (BPW91/cc-pVDZ for the gas phase and SM5.42R/BPW91/DZVP for aqueous solution) are employed. In this instance, the MUE is reduced to 0.02 V. The other *ab initio* levels fail to improve on the AM1-based levels.

In terms of the best balance of generality, accuracy, and computational effort, the most accurate method in Table 3 for predicting aniline oxidation potentials is to regress linearly on quantities predicted from eqn. (1) where AM1 and SM5.4/AM1 are used to compute gas-phase and aqueous quantities, respectively. While some improvement can be had by regressing on oxidation potentials predicted from eqn. (1) using high-level DFT-based energies, this comes at a significantly higher cost in terms of computational effort. Moreover, the DFT-based fit is less physical, since the correlating line deviates considerably from unit slope, and this is some cause for concern. Indeed, given our above analysis it appears that a portion of the accuracy of this method derives from a fortuitous cancellation of errors in IPs with errors in radical cation solvation free energies.

### E. Extension to substituted anilines not in the training set

Having assessed the utility of various predictive schemes for substituted aniline oxidation potentials, we now apply some of

these procedures to molecules not included in the training set over which the schemes were developed but for which experimental oxidation potentials are available. In particular, we consider *o*-, *m*-, and *p*-nitroaniline, 2,5-dichloroaniline, 2,4-, 2,5-, 2,6-, and 3,5-dimethylaniline, and 2,6-diethylaniline (the structure of 2,6-diethylaniline is approximately  $C_2$  with one terminal methyl group above and one below the plane of the aromatic ring). Table 4 gives the results of using the regression equations listed in Table 3 to predict aqueous oxidation potentials accurately for these compounds; the raw data required for the regression equations are compiled in Table S7.†

With respect to regression on descriptors derived from experiment, protonated aniline  $pK_a$  values are robust predictors of the oxidation potentials, providing an MUE of 0.05 V over eight of the nine compounds (a  $pK_a$  value for 2,6-diethylaniline is not available). This MUE is only 0.01 V larger than the MUE calculated over the training set used for the regression equation. For the three additional anilines for which Brown  $\sigma^+$  values are available, there is essentially quantitative agreement between the predicted and measured oxidation potentials for *m*-nitroaniline and 3,5-dimethylaniline, and a somewhat larger error is manifest for *p*-nitroaniline, but the overall performance is still excellent, with an MUE of only 0.02 V over the three compounds.

In considering regressions on HOMO energies, for simplicity we limit ourselves to HOMO energies from only a single level of theory, namely SM5.42R/AM1. Predictive accuracy is reduced relative to the training set, with an MUE of 0.07 V. However, this remains a respectable accuracy, particularly given the computational efficiency of the approach—the only calculation required is one for a solvated neutral solute.

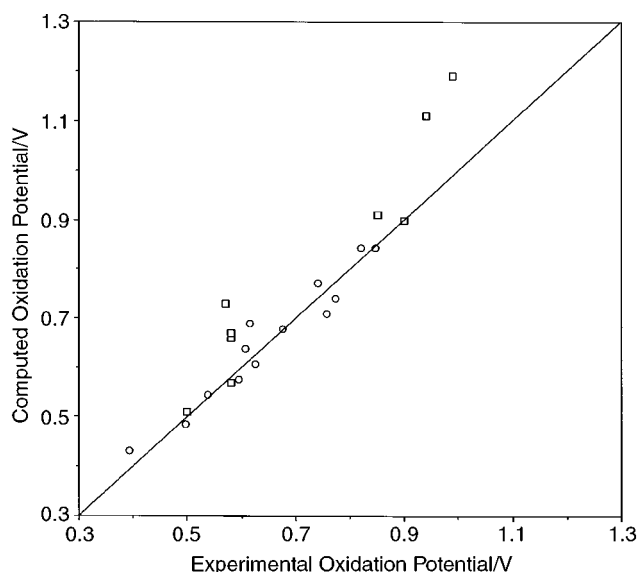
With respect to regressions using results obtained from eqn. (1), we consider the two most accurate regressions listed in Table 3. Using the AM1 Hamiltonian for the gas phase and the SM5.4/AM1 model for solvation free energies (column 1 of Table 2), the mean unsigned error over all nine additional compounds is 0.09 V (Fig. 1). This is a threefold increase in the error compared to the parameterization set. Much of this increase is associated with the nitro-substituted anilines. The MUE over the six non-nitro-substituted anilines is 0.06 V, which is still considerably larger than the MUE over the parameterization set. On the other hand, this MUE probably should not be interpreted too closely insofar as all of the dialkylanilines but one have experimental oxidation potentials within 0.01 V of one another, thereby reducing the diversity of the set and the significance of the error.

Semiempirical molecular orbital methods often give rather poor results for compounds containing nitro groups.<sup>19,97</sup> In this instance, however, more complete levels of electronic structure theory fail to improve matters. From the regression

**Table 4** Aqueous oxidation potentials (298 K, V relative to NHE) for additional substituted anilines predicted from regression equations in Table 3

Substituent	Predictions from regression on					Expt <sup>a</sup>
	$pK_a$	Brown $\sigma^+$	SM5.42R/AM1 HOMO	Table 2 column 1	Table 2 column 5	
<i>o</i> -NO <sub>2</sub>	1.14		1.04	1.19	1.16	0.99
<i>m</i> -NO <sub>2</sub>	0.82	0.85	1.09	0.91	1.02	0.85
<i>p</i> -NO <sub>2</sub>	0.99	0.88	0.94	1.11	1.12	0.94
2,4-diMe	0.54		0.44	0.51	0.57	0.50
2,5-diMe	0.58		0.56	0.67	0.64	0.58
2,6-diMe	0.65		0.54	0.73	0.63	0.57
3,5-diMe	0.55	0.58	0.65	0.67	0.68	0.58
2,6-diEt			0.51	0.57	0.62	0.58
2,5-diCl	0.93		0.83	0.90	0.94	0.90
MUE <sup>b</sup>	0.05	0.02	0.07	0.09	0.10	

<sup>a</sup> Ref. 62. <sup>b</sup> MUE = mean unsigned error for available number of data.



**Fig. 1** Computed vs. experimental oxidation potentials. Circles represent data from Table 2 column 1 treated with the regression equation listed in Table 3 for that data set. Squares represent data from Table 4 treated by the same regression equation. The ideal line (unit slope, zero intercept) is shown.

on the most complete level of theory, BPW91/cc-pVDZ for the gas phase and SM5.42R/BPW91/DZVP for aqueous solution (column 5 of Table 2), the MUE is 0.10 V, and again errors are large for the nitro-substituted anilines (the MUE over the six non-nitro-substituted anilines is again 0.06 V). The predictions from the two different regressions on eqn. (1) values are quite close to one another for the nitroanilines, so we speculate that the systematic error derives from an overestimation of the solvation free energies of the nitro-substituted aniline radical cations, but this point cannot be addressed with certainty in the absence of additional experimental data.

## V. Conclusions

Theoretical prediction of aqueous oxidation potentials is a challenging task, but computational chemistry is accurate enough to meet the challenge for practical applications that require semiquantitative accuracy. Although levels of theory that do not demand large amounts of computational resources can be inaccurate for ionization potentials and/or free energies of aqueous species, thereby leading to errors in directly calculated absolute oxidation potentials, these errors are sometimes systematic, in which case a linear correction scheme can be efficacious. Here, the very inexpensive AM1 gas-phase model combined with the also inexpensive SM5.4/AM1 aqueous solvation model was employed in a linear regression that gave a mean unsigned error of 0.03 V over 13 oxidation potentials for aniline and a set of mono-substituted anilines. Although the mean unsigned error was reduced to 0.02 V when theoretically more complete (and computationally more expensive) density functional levels of theory were employed, the semiempirical level was slightly more accurate than the density functional level when the regression equations were applied to an additional nine substituted anilines not in the original training set.

Computationally inexpensive HOMO energies for neutral anilines in aqueous solution were also found to give reasonable correlations with experimental oxidation potentials. For cases where experimental data for properties correlated with the oxidation potential are lacking, this may be an attractive approach if more complete computations are not practical.

When experimental data for molecular properties that might reasonably be correlated with the oxidation potential are available, predictive accuracy from assumed linear relationships can be quite high. Thus, for instance, aniline  $pK_a$  values were found to be more robust for predicting aniline oxidation potentials than were any of the purely theoretical methods. More accurate still, albeit over a reduced set of data, were classical linear free energy relationships based on descriptors tabulated for use in substituted aromatic systems; however, such descriptors are typically not available for more general systems, which limits the applicability of this technique. Thus, a very significant conclusion from the present study is that LFERs based purely on electronic structure calculations, which are universally applicable, are typically approximately as good as or better than classical LFERs, which are reasonably accurate when they can be applied but which are of use only for certain classes of compounds.

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