Quantum-Chemical Predictions of Redox Potentials of Organic Anions in Dimethyl Sulfoxide and Reevaluation of Bond Dissociation Enthalpies Measured by the Electrochemical Methods

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A first-principle theoretical protocol was developed that could predict the absolute pK_a values of over 250 structurally unrelated compounds in DMSO with a precision of 1.4 pK_a units. On this basis we developed the first theoretical protocol that could predict the standard redox potentials of over 250 structurally unrelated organic anions in DMSO with a precision of 0.11 V. Using the two new protocols we systematically reevaluated the bond dissociation enthalpies (BDEs) measured previously by the electrochemical methods. It was confirmed that for most compounds the empirical equation (BDE $= 1.37$ p$K_{HA} + 23.1E^o +$ constant) was valid. The constant in this equation was determined to be 74.0 kcal/mol, compared to 73.3 kcal/mol previously reported. Nevertheless, for a few compounds the empirical equation could not be used because the solvation energy changed dramatically during the bond cleavage, which resulted from the extraordinary change of dipole moment during the reaction. In addition, we found 40 compounds (mostly oximes and amides) for which the experimental values were questionable by over 5 kcal/mol. Further analyses revealed that all these questionable BDEs could be explained by one of the three following reasons: (1) the experimental pK_a value is questionable; (2) the experimental redox potential is questionable; (3) the solvent effect cannot be neglected. Thus, by developing practical theoretical methods and utilizing them to solve realistic problems, we hope to demonstrate that ab initio theoretical methods can now be developed to make not only reliable, but also *useful*, predictions for solution-phase organic chemistry.

1. Introduction

The phenomenal increase in speed and computational power of computers—as well as their dramatic reduction in cost—has continued at an astonishing pace over the last several years. Chemistry, like many other disciplines, is being profoundly influenced by increased computing power. Chemists want to calculate the properties of molecules that have not yet been made, to select a likely medicine for synthesis. Chemists also want to calculate what catalyst would best speed a particular reaction with selectivity, so that new catalysts can be created and used in manufacturing. Furthermore, basic understanding of chemistry will require successful theoretical approaches, because simple experimental facts without a theory to interpret them do not satisfy our need for understanding.

Currently many high-level methods are available for solving the Schrödinger equation of molecular systems of 5 to 20 common atoms.[1] Various properties of small molecules as isolated species in the gas phase can be calculated with equivalent or greater accuracy than that obtained experimentally, provided that extended basis sets are used and that electron correlation effects are recovered through post-Hartree−Fock or density functional approaches.[2] The contemporary challenge is to devise more accurate ways to obtain predictions of properties for systems of increasing size. Additionally, because chemical reactions are most often carried out in solution, it is an *extremely* important objective to develop methodologies for solvated molecules in condensed systems.

To date, a few different approaches have been studied to deal with the solvation effects. These include molecular simulations,[3] Langevin dipole models,[4] integral equation techniques,[5] and dielectric continuum methods.[6] Among them, the dielectric continuum methods are the most popular because they are more cost-effective and more broadly applicable than the other methods.[7] A good representative of the dielectric continuum methods is the polarized continuum model (PCM) developed by Tomasi and co-workers.[8] With the PCM model (or more specifically, PCM-UAHF), the mean error with respect to the experimental absolute solvation energies in water can be as small as about 0.2 and 1 kcal/mol for some neutral molecules and ions, respectively.

It has been long known that chemistries in solution can be dramatically different from chemistries in the gas phase. Thus, the advent of the dielectric continuum methods opens an exciting door for chemists who want to obtain predictions of molecular structures, bond energies, molecular properties, and transition state energies for systems in condensed phases. Nonetheless, blind use of the dielectric continuum methods is not recommended, because these relatively new methods have not been adequately validated for being able to make correct predictions for each particular solution-phase chemical process. A long journey has to be undertaken by chemists to carefully, step-by-step validate as well as improve the prediction ability of the dielectric continuum methods for each type of chemical reaction in each type of solvent against the experimental data.

In the first step of the journey chemists tried to use the dielectric continuum methods to calculate the simplest reaction in solution, i.e., the acid−base equilibrium. A number of groups

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have demonstrated that the pK_a values of many types of molecules in water can be predicted with a precision of 1−2 pK_a units.[9] Successful predictions of pK_a values of molecules in organic solvents were also reported very recently by Pliego's group[10] and by us.[11] These newly developed pK_a calculation methods immediately find applications in many branches of chemistry ranging from medicine design to organometallic catalysis.[12] They have enabled chemists to acquire the pK_a values of many intriguing species that are not readily amenable to experimental characterization, such as phosphoranes, phenol radical cations, and *N*-heterocyclic carbenes.[13]

It is undoubted that more efforts are still required to improve the ability of the current methods to predict the acid−base equilibrium in different solvents. Nonetheless, at this point we and a few other groups have decided to start the next challenge, namely, how to accurately predict the redox potentials in the solution phase. This challenge is interesting not only from the quantum chemistry point of view, but also in a very practical sense because redox potentials are crucial to the study of the numerous electron-transfer reactions. Up to now several outstanding studies have been performed about how to calculate the redox potentials in water.[14] Very recently we also developed a protocol that could predict the redox potentials of 270 structurally unrelated (predominately neutral) organic molecules in acetonitrile with a precision of 0.17 V.[15] Despite these achievements, quantum chemical calculation of redox potentials is still an underdeveloped field.

Herein we wish to address the challenging problem of how to use a quantum chemical method to accurately calculate the redox potentials of diverse structurally unrelated organic anions in dimethyl sulfoxide (DMSO). This problem has never been studied before, but it is important and interesting for the following reasons. (1) Up to now there has not been a method that can predict the redox potentials in DMSO with confident reliability. The ability to predict the redox potentials in DMSO by using a coherent, well-defined theoretical approach, without any external approximations, would be valuable to the chemical community. (2) Over the past two decades a large number of redox potentials of organic anions have been measured in DMSO.[16] This accomplishment is a great milestone in the advance of physical organic chemistry, yet a systematic evaluation of these bulk data has not been performed. (3) An interesting method has been developed to estimate the homolytic bond dissociation enthalpies (BDE) from the pK_a and redox potential values in DMSO.[17] Although this method has been widely utilized, considerable controversy has arisen as to the reliability of the BDEs determined by this method. Accurate quantum chemical calculations of the pK_a and redox potential values in DMSO shall provide new insights into this important problem.

2. An Improved Protocol for Calculating pK_a Values in DMSO

Our ability to accurately predict the redox potentials in DMSO relies heavily on our ability to correctly calculate the solvation energies in DMSO. To find an appropriate solvation model, we decide to test the capability of the solvation model to calculate pK_a values in DMSO at first. It is worth noting that the experimental pK_a values are usually more reliable than many other types of experimental quantities. Thus, unless the theoretical pK_a values predicted by a certain solvation model can match the experimental values, we will not be confident about the reliability of the solvation model.

In a previous study we developed the first protocol to calculate pK_a values of structurally unrelated molecules in DMSO.[11] In the protocol the gas-phase acidities was calculated by using the MP2/6-311++G(d,p) methods. The solvation effect was calculated by using the original PCM method at the HF/6-31+G(d,p) level. The Bondi radii were utilized to construct the solvent-inaccessible cavity. We obtained a nice correlation between the predicted pK_a values and the experimental data for 105 organic molecules that contain less than 10 non-hydrogen atoms (the limitation of 10 non-hydrogen atoms was due to the expensive scaling of the MP2 method). However, there was a nontrivial systematic underestimation of pK_a values (i.e., −2.20 pK_a units) by the protocol.

To improve the protocol we now make the following changes. (1) The gas-phase acidities are now calculated with the B3LYP/6-311++G(2df,2p) method. This method has a much better scaling than MP2 although it utilizes a much more flexible basis set. Thus, we can readily calculate organic molecules containing as many as 30 non-hydrogen atoms. (2) The solvation effect is calculated with the most recent PCM version called integral equation formalism (IEF-PCM).[18] As opposed to the original PCM model, IEF-PCM keeps the molecular symmetry and its computational time scales linearly with the solute size. IEF-PCM has been shown to have a significantly extended range of applications with dramatically improved accuracy. (3) The molecular cavity is built up by using the newly developed United Atom (UA0) model.[19] In this model a sphere is put around each solute heavy atom, using the atomic radii of the universal force field (UFF). Hydrogen atoms are enclosed in the sphere of the atom to which they are bonded.

It is worth mentioning that a central idea in the continuum solvation model is the construction of a solvent-inaccessible cavity in which the solute molecule resides. In practice, this solvent-inaccessible cavity is built as a union of overlapping spheres entered on the nuclei of atoms or chemical groups. The sphere radii are usually proportional to the atomic radii with a scale factor (*f*). The default scale factor ($f = 1.00$) of the UA0 cavity in Gaussian03 is a value specifically optimized for the aqueous solution.[19] On the basis of our previous studies, we postulate that a different scale factor is probably more appropriate for the DMSO solution.[11] Thus, we select 18 relatively small molecules with reliable experimental pK_a data (see Table 1). Our task is to find the optimal *f* value so that the standard deviation (i.e., sd as defined in eq 1) between the 18 experimental pK_a values and the theoretical predictions reaches the minimum.

$$\mathrm{sd} = \sqrt{\frac{1}{18}\sum(pK_a^{\mathrm{Theor}} - pK_a^{\mathrm{Exp}})^2} \qquad (1)$$

To accomplish the above plan, we first need to derive the equations for pK_a calculations. Thus, we consider the following proton-exchange reaction

$$\mathrm{AH} + \mathrm{HO}^- \rightarrow \mathrm{A}^- + \mathrm{H_2O} \qquad (2)$$

If the free energy change of the above reaction in the DMSO solution is defined as $\Delta G_{\mathrm{exchange}}$, the p$K_a$ of the acid AH can be calculated by eq 3.

$$\mathrm{p}K_a(\mathrm{AH}) = \mathrm{p}K_a(\mathrm{H_2O}) + \frac{\Delta G_{\mathrm{exchange}}}{2.303RT} \qquad (3)$$

Herein, pK_a(H$_2$O) = 31.4 is a highly trustworthy experimental value because its measurement does not require rigorously anhydrous conditions.[20] It is known from the previous studies that the gas-phase free energy change of eq 2 can be fairly

TABLE 1: Experimental and Theoretical pK_a Values for 18 Small Molecules in DMSO[a]

species	pK_a(exp)	$f = 0.80$	$f = 0.85$	$f = 0.90$	$f = 0.95$	$f = 1.00$	$f = 1.05$	$f = 1.10$	$f = 1.15$	$f = 1.20$
$\mathbf{H}$F	15.0	18.0	14.7	13.2	12.5	12.2	12.0	12.0	12.1	12.1
$\mathbf{H}$CN	12.9	18.3	15.4	13.8	12.7	11.8	11.0	10.3	9.6	9.1
$\mathbf{H}_2$O	31.4	31.4	31.4	31.4	31.4	31.4	31.4	31.4	31.4	31.4
PhC$\mathbf{H}_3$	43.0	46.4	46.4	46.4	46.0	45.5	44.8	44.1	43.4	42.6
$CH_3O\mathbf{H}$	29.0	37.1	33.5	32.0	31.4	31.2	31.1	31.2	31.3	31.4
$C_2H_5O\mathbf{H}$	29.8	38.2	34.1	32.3	31.0	30.6	30.4	30.2	30.1	30.0
i-PrO$\mathbf{H}$	30.3	38.7	34.7	33.0	32.1	31.6	31.3	31.1	31.0	30.8
$CH_3COC\mathbf{H}_3$	26.5	27.2	28.0	28.8	29.1	29.2	29.1	28.9	28.7	28.3
$CH_3SOC\mathbf{H}_3$	35.1	38.6	38.9	39.1	38.9	38.5	36.4	37.4	36.8	36.2
$C\mathbf{H}_3CN$	31.3	30.9	31.4	31.7	31.6	31.3	30.9	30.4	29.8	29.2
$CH_3CON\mathbf{H}_2$	25.5	29.6	29.0	28.6	28.0	27.4	26.8	26.2	25.6	25.1
$HCON\mathbf{H}_2$	23.5	28.9	27.5	26.9	26.0	25.1	24.3	23.5	22.8	22.1
PhN$\mathbf{H}_2$	30.6	37.0	35.9	35.3	34.5	33.7	33.0	32.2	31.4	30.6
PhS$\mathbf{H}$	10.3	33.0	21.8	16.5	13.6	11.8	10.5	9.5	8.7	8.0
$C\mathbf{H}_3NO_2$	17.2	14.7	15.5	16.1	16.3	17.0	16.2	15.9	15.6	15.1
PhO$\mathbf{H}$	18.0	30.9	25.7	22.6	20.6	19.2	18.0	17.0	16.1	15.3
t-BuO$\mathbf{H}$	32.2	38.8	35.6	34.4	33.5	33.2	32.9	32.2	32.2	32.1
$\mathbf{H}N_3$	7.9	21.2	15.6	12.8	10.9	9.5	8.4	7.5	6.7	6.0
r	-	0.788	0.941	0.975	0.986	0.991	0.993	0.994	0.993	0.993
sd	-	8.4	4.8	3.3	2.4	1.9	1.7	1.5	1.6	1.8

[a] Experimental data are taken from the following: Pliego, J. R., Jr.; Riveros, J. M. *Chem. Phys. Lett.* **2002**, *4*, 1622 (see ref 10).

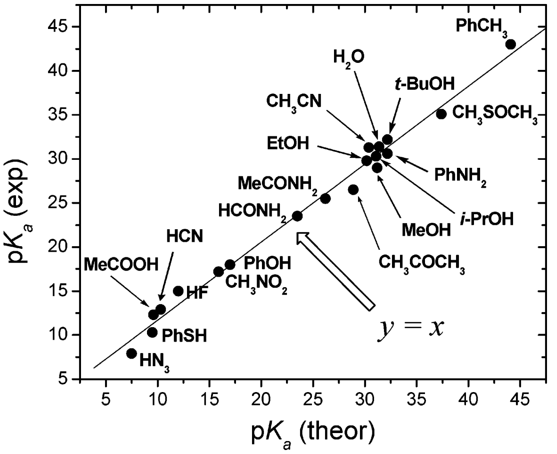


Figure 1. Comparison between the experimental and theoretical ($f = 1.10$) pK_a values for 18 small molecules.

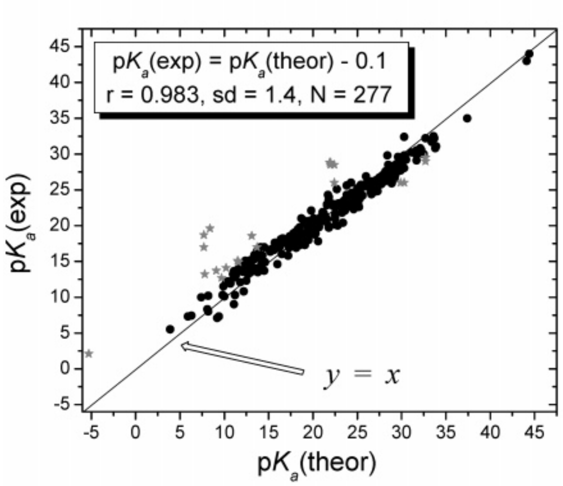


Figure 2. Comparison between the experimental and theoretical pK_a values for a large number of compounds in DMSO.

accurately calculated.[11] Thus, whether the theory can reproduce the experimental pK_a values mainly relies on the quality of the solvation energy calculations.

Using the UA0 model, we have examined different f values ($f = 0.80, 0.85, 0.90, 0.95, 1.00, 1.05, 1.10, 1.15, 1.20$) for the IEF-PCM model in the calculation of pK_a values in DMSO. Comparing the experimental data and the theoretical predictions (see Table 1), we find that $f = 1.10$ is the most desirable. The standard deviation and correlation coefficient between the theoretical and experimental pK_a values with use of this scale factor are 1.5 pK_a units and 0.994 for 18 organic molecules, respectively (also see Figure 1).

Having successfully predicted the pK_a values of the compounds in Table 1, we next apply the same computational protocol to nearly all the pK_a data that have been experimentally measured (detailed data are tabulated in the Supporting Information).[20] It is gratifying to find that the computational protocol can successfully predict the pK_a values for 277 structurally unrelated compounds. The mean error between the experimental and theoretical pK_a values is only 0.1 pK_a unit (see Figure 2), which is certainly a great improvement over our previous protocol (where the mean error = 2.2 pK_a units). Furthermore, the correlation coefficient and the standard deviation between the experimental and theoretical pK_a values are 0.983 and 1.4 pK_a units, respectively. Nonetheless, we find 18 compounds (red stars in Fgure 2) for which the predicted pK_a values differ from the experimental data by over 3.0 pK_a units (see Table 2). Further analyses about these 18 suspicious data will be conducted in Section 6 of this report.

3. Computing Standard Redox Potentials of Organic Anions in DMSO

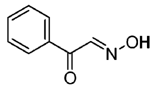
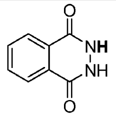
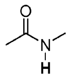
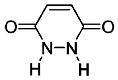
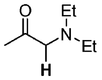
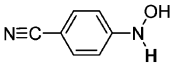
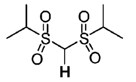
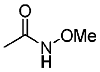
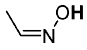
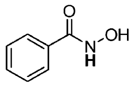
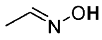
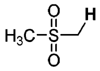
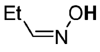
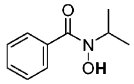
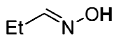
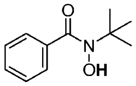
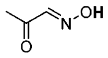
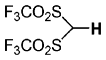
Through the above studies we have optimized a solvation model that can predict the pK_a values of a huge number of structurally unrelated compounds in DMSO with a mean error of 0.1 pK_a unit and a standard deviation of 1.4 pK_a units. The success of pK_a predictions provides us the confidence that the solvation free energies in DMSO can be reliably calculated. It is time to utilize this solvation model to develop a theoretical protocol to calculate the standard redox potentials of diverse organic anions in DMSO.

It should be noted that by convention the standard redox potential is defined for half reactions written in the order

$$E^o: \quad \text{reduced form} \rightarrow \text{oxidized form} + e^-(g) \qquad (4)$$

The value of E^o is usually measured relative to a reference electrode, for instance, the normal hydrogen electrode (NHE).

TABLE 2: The Compounds for Which the Theoretical pK_a Values Differ from the Experimental Values by Over 3.0 pK_a Units

Compound	pK_a (theor)	pK_a (exp)	Compound	pK_a (theor)	pK_a (exp)
	11.6	14.9		9.7	12.7
	28.9	25.9		7.8	13.2
	29.9	26.0		13.1	18.6
	10.2	14.1		7.7	17.0
	22.4	28.5		9.1	13.7
	22.0	28.5		32.7	29.0
	21.9	28.8		7.7	18.7
	22.0	28.8		8.4	19.6
	11.5	15.1		-5.3	2.1

The NHE half reaction is $H^+(aq) + e^-(g) \rightarrow {}^1/_2H_2(g)$. Thus, the E^o value is connected to the standard free energy change of the reaction

ΔG^o:

$$\text{reduced form} + H^+(aq) \rightarrow \text{oxidized form} + {}^1/_2H_2(g) \quad (5)$$

in the form of eq 6

$$E^o = \Delta G^o/F \quad (6)$$

where F is the Faraday constant equal to 23.06 kcal/(mol·V).

From a free energy cycle as shown in Figure 3, one can relate the redox potentials with the gas-phase adiabatic IPs and solvation energies using the following equation:

$$E^o(\text{vs. NHE}) = \text{IP} + \frac{1}{23.06}(-T\Delta S + \Delta G_{\text{solvation2}} - \Delta G_{\text{solvation1}}) - 4.44 \quad (7)$$

In eq 7, IP is the gas-phase adiabatic ionization potential (unit: eV), which equals the gas-phase enthalpy change from the reduced form to the oxidized form plus e^- at 298 K. According to our previous benchmarking work, the IP values of 160 structurally unrelated molecules were systematically underestimated by 0.28 eV with the B3LYP/6-311++G(2df,2p)//B3LYP/6-31+G(d) method.[15] Thus, we can calculate the IP values using the following empirical equation:

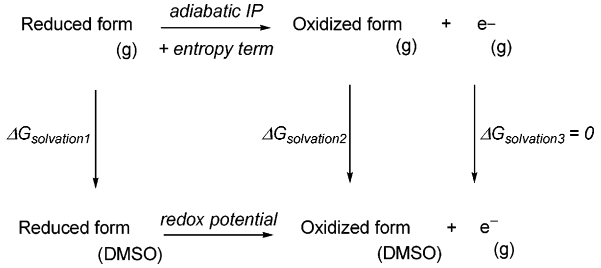


Figure 3. The free energy cycle for the redox reaction in DMSO.

$$\text{IP} = \text{IP(B3LYP)} + 0.28 \text{ eV} \quad (8)$$

The second term in eq 7, $-T\Delta S$ (unit: kcal/mol) is the gas-phase entropy term from the reduced form to the oxidized form plus e^- at 298 K. This term can be easily calculated with reasonable accuracy.[21] The next terms, $\Delta G_{\text{solvation1}}$ and $\Delta G_{\text{solvation2}}$ (unit: kcal/mol), correspond to the solvation free energies of the reduced and oxidized forms. They can be calculated by using the solvation model optimized in section 2 of this report. The last term, −4.44 (unit: eV), is the free energy change associated with the reference NHE half-reaction (i.e., $H^+(aq) + e^-(g) \rightarrow {}^1/_2H_2(g)$).[22]

It is worth noting that by convention the standard redox potentials of organic anions in DMSO are reported relative to the ferrocene/ferrocenium (Fc/Fc$^+$) reference electrode.[16] To be consistent with literature, we need to convert the E^o(vs. NHE) values to E^o(vs. Fc/Fc$^+$) using the following equation

$$E^o(\text{vs. Fc/Fc}^+) = E^o(\text{vs. NHE}) - \delta \quad (9)$$

where δ is the potential value of Fc/Fc$^+$ relative to NHE. Bordwell and co-workers reported that $\delta = 0.750$ V.[16] However, Parker and co-workers reported a much lower δ (0.537 V).[23] To determine which δ value is more appropriate, we decided to calculate the redox potential of 2,6-di-*tert*-butyl-4-nitrophenate in DMSO. This compound has a *reversible* anion oxidation potential in DMSO and its value has been measured to be 0.126

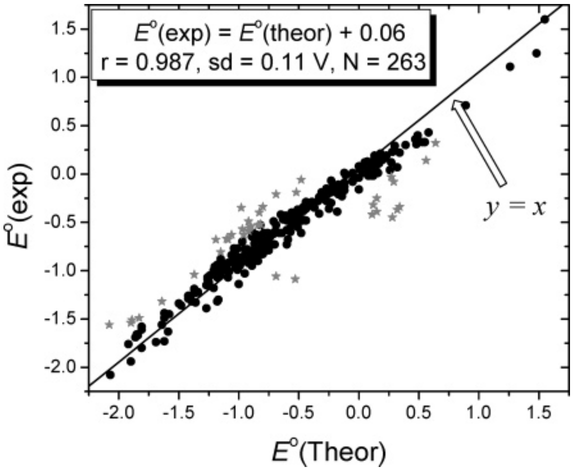


Figure 4. Comparison between the experimental and theoretical standard redox potentials for a large number of organic anions in DMSO.

± 0.005 V (vs. Fc/Fc$^+$) (Note: the redox potentials of other organic anions in DMSO are usually irreversible potentials).[23] Using eq 7 we calculate that the redox potential of the same anion in DMSO is 0.691 V (vs. NHE). Subtracting 0.691 V by 0.126 V, we calculate that the theoretical δ value should be 0.565 V, which is more consistent with Parker's experiment.

Combining all of the above results, we finally derive the equation for the calculation of standard redox potentials relative to Fc/Fc$^+$ reference electrode:

$$E^{\mathrm{o}}(\text{vs Fc/Fc}+) = \text{IP(B3LYP)} + \frac{1}{23.06}(-T\Delta S + \Delta G_{\text{solvation2}} - \Delta G_{\text{solvation1}}) - 4.72 \quad (10)$$

where the last term (−4.72 V) takes into account the free energy change associated with the reference NHE half-reaction (−4.44 V), the systematic error in the gas-phase calculation (+0.28 eV), and the potential value of Fc/Fc$^+$ relative to NHE (0.565 V). Using eq 10 we have calculated the redox potentials in DMSO of nearly all the organic anions that have been experimentally measured (detailed data are tabulated in the Supporting Information).[16] It is found that the theoretical predictions agree with the experimental data for 263 structurally unrelated anions (see Figure 4). The mean error between the theoretical predictions and experimental data is only 0.06 V. The correlation coefficient and the standard deviation are 0.987 and 0.11 V, respectively.

It is important to note that most of the experimental redox potentials are estimated from irreversible cyclic voltammetry. According to the studies by Arnett et al., some of the irreversible potentials measured by this method differ from the reversible potentials by about 50 mV.[24] Bordwell and co-workers estimated that the error bar for the redox potential values was around 0.1 V.[16] Compared to these error bars, it is obvious that our theoretical protocol is fairly successful because its standard deviation from the experiment is 0.11 V. At the same time, our predictions also indicate that most of the irreversible redox potentials measured with the electrochemical method agree within about 100 mV with the reversible redox potentials. Nevertheless, we find 32 compounds for which the theoretical and experimental redox potentials differ by more than 0.3 V (see Table 2). Further analyses about these 32 questionable data will be conducted in Section 6 of this report.

4. From pK_a Values and Redox Potentials to Bond Dissociation Enthalpies

The thermodynamic cycle in Scheme 1 has been used by many groups to estimate the gas-phase homolytic bond dissociation enthalpies from readily available solution-phase experimental data.[17]

According to Scheme 1, we have

$$\Delta G_{\text{solution}} = 1.37\text{p}K_{\text{HA}} + 23.1E^{\mathrm{o}}(\text{A}^-) - 23.1E^{\mathrm{o}}(\text{H}^\bullet) \quad (11)$$

where 1.37 and 23.1 are constants that convert the pK_a unit and volt to kcal/mol. At the same time, we also have

$$\Delta G_{\text{solution}} = \text{BDE} - T\Delta S + \Delta G^{\text{A}^\bullet}_{\text{solvation}} + \Delta G^{\text{H}^\bullet}_{\text{solvation}} - \Delta G^{\text{HA}}_{\text{solvation}} \quad (12)$$

It is noteworthy that the redox potential of the hydrogen atom (i.e., $E^{\mathrm{o}}(\text{H}^\bullet)$) and the solvation energy of hydrogen atom (i.e., $\Delta G^{\text{H}^\bullet}_{\text{solvation}}$) are constants. If we further assume that (1) the gas-phase entropy change (i.e., $T\Delta S$) is a constant and (2) the solvation energy of A$^\bullet$ equals that of HA (i.e., $\Delta G^{\text{A}^\bullet}_{\text{solvation}} - \Delta G^{\text{HA}}_{\text{solvation}} = 0$), we will have

$$\text{BDE} = 1.37\text{p}K_{\text{HA}} + 23.1E^{\mathrm{o}} + \text{constant} \quad (13)$$

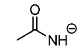
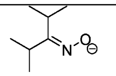
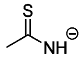
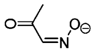
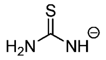
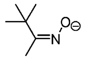
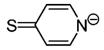
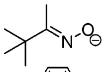
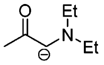
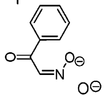
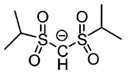
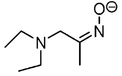
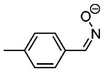
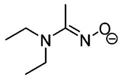
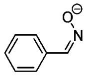
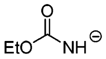
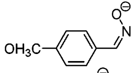
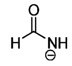
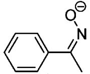
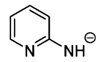
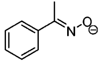
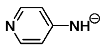
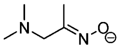
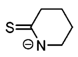
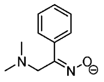
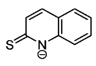
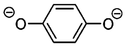
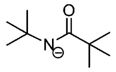
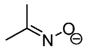
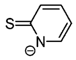
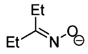
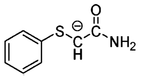
The validity of eq 13 has been examined by several groups for the BDEs of a few compounds.[17] Nonetheless, because it is difficult to obtain pK_a, redox potential, and BDE independently for every single compound, no one has ever examined the validity of eq 13 for the BDEs of a large number of structurally unrelated molecules. In the above work we have developed theoretical protocols that can reliably predict the pK_a values and redox potentials independently. If we can develop another protocol that can independently predict the BDEs accurately, we will be able to investigate, for the first time, whether eq 13 is generally applicable. At this point, it occurs to us that the newly developed ONIOM-G3B3 method will help us to accomplish this goal.[25]

Briefly speaking, in the ONIOM-G3B3 method a target system is divided into two layers. The geometry of the whole system is optimized with the B3LYP/6-31G(d) method. Then a series of single-point energy calculations are performed at the ONIOM(MP2: B3LYP), ONIOM(MP4:B3LYP), and ONIOM-(QCISD(T):B3LYP) levels of theory (see Table 4). In each of the ONIOM calculations only the core layer is treated with the high level theory and the total energy is calculated with eq 14. The final ONIOM-G3B3 energy is calculated by using an extrapolation equation as shown in Table 4. This energy also includes a B3LYP/6-31G(d) zero-point energy correction, a spin−orbit correction, and a higher level correction. The ONIOM-G3B3 theory is effectively at the ONIOM(QCISD-(T,FU)/G3Large:B3LYP) level.

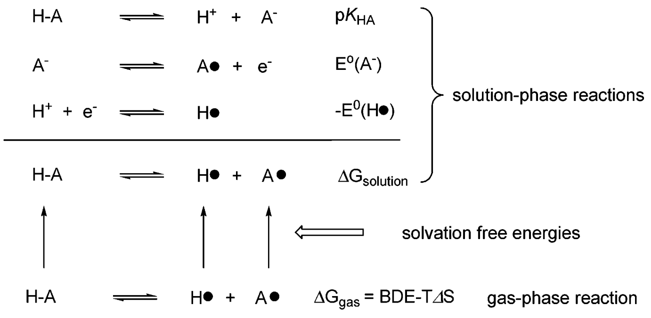
$$E(\text{ONIOM}) = E(\text{high, core layer}) + E(\text{low, whole system}) - E(\text{low, core layer}) \quad (14)$$

The detailed procedure for how to use ONIOM-G3B3 to calculate BDEs can be found in our previous report.[25] In that report the performance of the ONIOM-G3B3 method was also evaluated by comparing its predictions with the experimental BDEs for over 60 sizable molecules. It was found that the accuracy of the ONIOM-G3B3 method was about 1.4 kcal/mol for BDE calculations. Compared to the original G3B3 method, the ONIOM-G3B3 method is more powerful because it can

TABLE 3: The Compounds for Which the Theoretical Redox Potentials Differ from the Experimental Values by Over 0.3 V (vs. Fc/Fc$^+$; units in V)

Compound	E^o (theor)	E^o (exp)	Compound	E^o (theor)	E^o (exp)
	0.27	-0.03		-1.15	-0.80
	0.12	-0.32		-0.52	-0.19
	0.15	-0.39		-1.19	-0.68
	0.34	-0.34		-1.09	-0.68
	-1.90	-1.54		-0.69	-0.21
	0.64	0.32		-1.06	-0.63
	-0.83	-0.53		-0.96	-0.63
	-0.80	-0.47		0.29	-0.08
	-0.84	-0.53		0.56	0.14
	-0.92	-0.49		-0.69	-1.06
	-0.82	-0.52		-0.53	-1.09
	-0.92	-0.59		0.11	-0.42
	-0.91	-0.56		0.32	-0.37
	-2.08	-1.56		-0.48	-0.06
	-0.97	-0.57		0.28	-0.45
	-1.10	-0.67		-0.98	-0.35

SCHEME 1



handle a system containing as many as 20−50 non-hydrogen atoms, whereas G3B3 can only deal with a system containing less than 8 non-hydrogen atoms. Thus, the ONIOM-G3B3 method can be applied to virtually all of the common organic compounds.

Using the ONIOM-G3B3 method we have calculated the BDE values for 295 structurally unrelated compounds that have been studied using the electrochemical methods (detailed data are tabulated in the Supporting Information).[16] Plotting the ONIOM-G3B3 BDEs against the pK_a values and redox potentials calculated in Sections 2 and 3, we find that most of the compounds indeed obey eq 13 (see Figure 5). The constant in eq 13 is determined to be 74.0 kcal/mol, which is very close to the value reported by Bordwell, 73.3 kcal/mol.[17] The correlation coefficient is 0.957 and the standard deviation is 3.2 kcal/mol. Thus, the thermodynamic cycle in Scheme 1 is truly utilizable for the measurement of some BDEs. Nonetheless, it is important to point out that for 15 compounds the BDEs estimated with eq 13 severely differ from the real BDE values by over 5 kcal/mol (see Table 5).

According to Scheme 1, the only possible reasons that the BDEs estimated from eq 13 dramatically differ from the real BDE values are as follows: (1) the gas-phase entropy change is not a constant (i.e. $T(S_{A^\bullet} - S_{HA}) \neq 0$) or (2) the solvation energy of A$^\bullet$ does not equals that of HA (i.e. $\Delta G^{A^\bullet}_{solvation} - \Delta G^{HA}_{solvation} \neq 0$).[26] As shown in Table 4, the entropy change is actually not a problem because for most entries in Table 4 we do observe that $T(S_{A^\bullet} - S_{HA}) \approx 0$. On the other hand, it is clear that for the 18 compounds in Table 4 the solvation energy of A$^\bullet$ remarkably differs from that of HA. This is somehow

TABLE 4: Detailed Procedure of the ONIOM-G3B3 Theory

	ONIOM-G3B3
geometry	B3LYP/6-31G(d)
single-point energies[c]	ONIOM(MP4(FC)[a]/6-31G(d):B3LYP/6-31G(d)) (**A**) ONIOM(MP2(FC)/6-31G(d):B3LYP/6-31G(d)) (**A1**) ONIOM(MP4(FC)/6-31+G(d):B3LYP/6-31G(d)) (**B**) ONIOM(MP2(FC)/6-31+G(d):B3LYP/6-31G(d)) (**B1**) ONIOM(MP4(FC)/6-31G(2df,p):B3LYP/6-31G(d)) (**C**) ONIOM(MP2(FC)/6-31G(2df,p):B3LYP/6-31G(d)) (**C1**) ONIOM(QCISD(T,FC)/6-31G(d):B3LYP/6-31G(d)) (**D**) ONIOM(MP2(FU)[b]/G3large: B3LYP/6-31G(d)) (**E**)
higher level correction (ΔHLC)[d]	$A = 6.760$ $B = 3.233$
zero-point energy (ZPE)[e]	B3LYP/6-31G(d)

[a] FC = frozen core approximation for the correlation calculation. [b] FU = all electrons included in the correlation calculation. [c] E^{o}(ONIOM-G3B3) = $E[\mathbf{A}] + \Delta(+) + \Delta(\text{2df,p}) + \Delta(\text{QCI}) + \Delta + \Delta\text{HLC} + \text{ZPE}$, where $\Delta(+) = E[\mathbf{B}] - E[\mathbf{A}]$, $\Delta(\text{2df,p}) = E[\mathbf{C}] - E[\mathbf{A}]$, $\Delta(\text{QCI}) = E[\mathbf{D}] - E[\mathbf{A}]$, and $\Delta = E[\mathbf{E}] - E[\mathbf{C1}] - E[\mathbf{B1}] + E[\mathbf{A1}]$. [d] $\Delta H\text{LC} = -An_a - B(n_\alpha - n_\beta)$. n_α and n_β are the number of α and β valence electrons, respectively, with $n_\alpha \geq n_\beta$. A and B are in mhartrees. [e] Scale factor of 0.96 for B3LYP/6-31G(d).

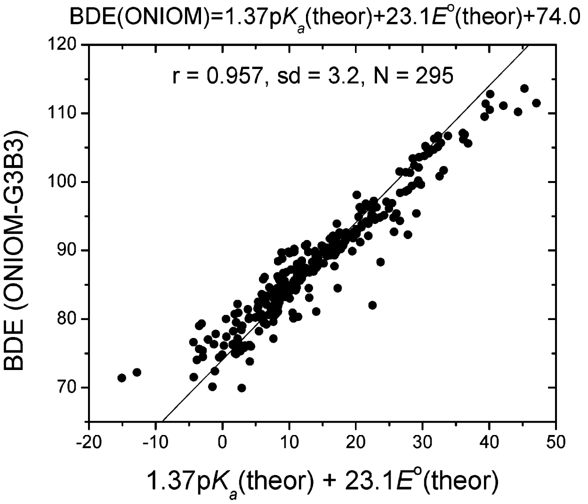


Figure 5. Correlation between the ONIOM-G3B3 BDEs (kcal/mol) and theoretical pK_a values and redox potentials (V).

surprising because for most cases both $A^\bullet$ and AH are neutral compounds.

To understand why the solvation energy of $A^\bullet$ can differ from that of HA so dramatically, we have calculated the dipole moments of HA and $A^\bullet$ for each entry in Table 5. According to the Bell model of solvation,[27] the solvation free energy of a ball that contains a point dipole μ at the center follows eq 15

$$\Delta G_{\text{solvation}} = -\frac{\epsilon - 1}{2\epsilon + 1}\frac{\mu^2}{R^3} \tag{15}$$

where ϵ is the dielectric constant of the solvent and R is the radius of the ball. If we assume that the volumes of all the molecules in Table 4 are close to each other, it will be straightforward to derive the following equation

$$\Delta G^{A^\bullet}_{\text{solvation}} - \Delta G^{\text{HA}}_{\text{solvation}} = -\frac{\epsilon - 1}{2\epsilon + 1}\frac{1}{R^3}({\mu_{A^\bullet}}^2 - {\mu_{\text{HA}}}^2) \tag{16}$$

Thus, the dramatic change of solvation energy from $A^\bullet$ to HA can be explained by the dramatic change of molecular dipole moment from $A^\bullet$ to HA. Indeed, when we plot ($\Delta G^{A^\bullet}_{\text{solvation}} - \Delta G^{\text{HA}}_{\text{solvation}}$) against (${\mu_{A^\bullet}}^2 - \mu\text{HA}^2$), we obtain a nice straight line (See Figure 6).

5. Reevaluating Experimental BDEs Measured by the Electrochemical Methods

In the above studies we have developed a theoretical method that can predict the pK_a values of a huge number of structurally unrelated compounds in DMSO with a precision of 1.4 pK_a units (i.e., 1.9 kcal/mol). We have also developed a theoretical method that can predict the redox potentials of the same group of compounds with a precision of 0.11 eV (i.e., 2.5 kcal/mol). Furthermore, we have developed an ONIOM-G3B3 method that can predict the gas-phase BDEs of sizable molecules with a precision of about 1.4 kcal/mol. At this point, we are sufficiently armed to reevaluate the experimental BDE data measured by the electrochemical methods.

In Figure 7 we show the comparison between the ONIOM-G3B3 BDEs and the experimental BDE values calculated by the pK_a values and redox potentials. It is obvious from Figure 7 that for most of the cases the predicted BDEs agree with the reported values fairly well. The correlation coefficient and the standard deviation for 254 compounds are 0.966 and 2.2 kcal/mol. Moreover, the mean error between the predicted and reported BDEs is almost zero (i.e., 0.1 kcal/mol). The nice correlation not only confirms that the ONIOM-G3B3 method can reliably predict BDEs, but also demonstrates that the BDEs measured by the electrochemical methods are generally valid as long as we remember that *they have an error bar of* about 2−3 kcal/mol (the error bar for experimental pK_a values is about 0.5 pK_a unit or 0.7 kcal/mol; the error bar for experimental redox potentials is about 0.1 V or 2.3 kcal/mol).[16] Nevertheless, we also identify a number of compounds whose experimental BDEs dramatically differ from the ONIOM-G3B3 BDEs by over 5 kcal/mol (see Table 5).

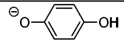
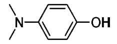
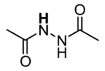
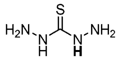
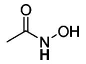
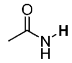
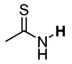
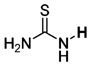
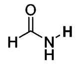
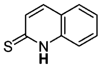
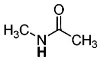
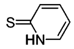
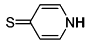
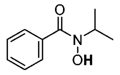
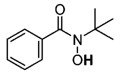
First, for 13 compounds in Table 6 (entries 1−13) we find that their experimental pK_a values are different from the theoretical values by over 3.0 pK_a units. Using the theoretical pK_a values for these 13 compounds we have recalculated the BDE values according to eq 17,

$$\text{BDE}^{\text{eq17}} = 1.37\text{p}K_a^{\text{theor}} + 23.1E^{\text{o theor}} + 74.0 \tag{17}$$

It is found that the BDE$^{\text{eq17}}$ values are mostly in agreement with BDE$^{\text{ONIOM}}$, except for two compounds (entries 11 and 12). For these two compounds the solvation energy of $A^\bullet$ remarkably differs from that of HA and therefore eq 17 cannot be used.

Second, for 26 compounds in Table 6 (entries 14−39) we find that their experimental redox potentials are different from the theoretical values by over 0.3 V. Using the theoretical redox potentials for these 26 compounds we have recalculated the BDE values according to eq 17. It is found that the BDE$^{\text{eq17}}$ values are mostly in agreement with BDE$^{\text{ONIOM}}$, except for four compounds (entries 21, 32, 36, and 38). For these four compounds the solvation energy of $A^\bullet$ remarkably differs from that of HA and therefore eq 17 cannot be used.

TABLE 5: The Compounds for Which the BDEs Estimated from Eq 13 (where the constant equals 74.0 kcal/mol) Differ from the BDE Values Calculated with ONIOM-G3B3 by Over 5 kcal/mol

Compound	BDE$^{\text{ONIOM}}$–BDE$^{\text{eq 13}}$	$\Delta G^{A\bullet}_{solvation} - \Delta G^{HA}_{solvation}$	$T(S_{A\bullet} - S_{HA})$	$\mu_{A\bullet}{}^2 - \mu_{HA}{}^2$
	8.5	-7.0	3.6	-85.6
	-5.4	5.2	-0.6	123.9
	7.0	-6.5	0.0	-39.3
	7.0	-7.1	-0.3	-72.0
	6.8	-3.9	-1.4	-14.2
	5.0	-3.5	0.4	-20.7
	6.3	-5.0	-0.3	-40.1
	7.7	-5.9	-0.1	-42.2
	5.7	-4.0	0.1	-24.2
	7.0	-5.6	-2.8	-61.0
	5.2	-3.7	0.1	-19.5
	9.4	-7.2	-0.3	-58.2
	14.5	-11.1	0.3	-150.7
	11.0	-3.3	0.4	-17.5
	6.5	-3.4	0.3	-21.3

Finally, for one compound in Table 6 (entry 40) the experimental value is not consistent with the ONIOM-G3B3 value simply because the solvation energy of A$^\bullet$ remarkably differs from that of HA. In other words, it is not valid to use eq 17 to calculate the BDE for this compound from the pK_a value and redox potential.

Thus, all the questionable experimental BDE values can be explained by one of the three following reasons: (1) the experimental pK_a value is questionable; (2) the experimental redox potential is questionable; or (3) the solvent effect cannot be neglected. It is interesting to note that most of the questionable experimental BDEs are not due to the solvation effect problem,[28] but are due to the experimental errors in the measurement of pK_a and redox potential values. We also find a number of cases where correct BDEs values were fortuitously measured from questionable pK_a or redox potential values because of error cancellation (see Table 7).

It is noteworthy that the questionable BDE values are mostly associated with the O−H bonds of oximes and the N−H bonds of amides. To further confirm that these experimental values are problematic, we have utilized other high-level theoretical

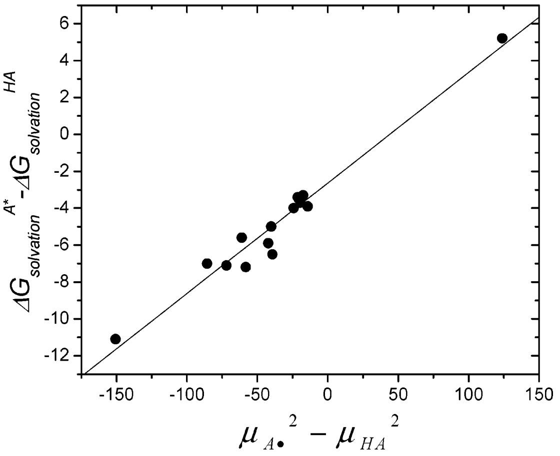


Figure 6. Correlation between $\Delta G^{A^\bullet}_{\text{solvation}}$ and $\Delta G^{\text{HA}}_{\text{solvation}}$ for all the molecules shown in Table 4.

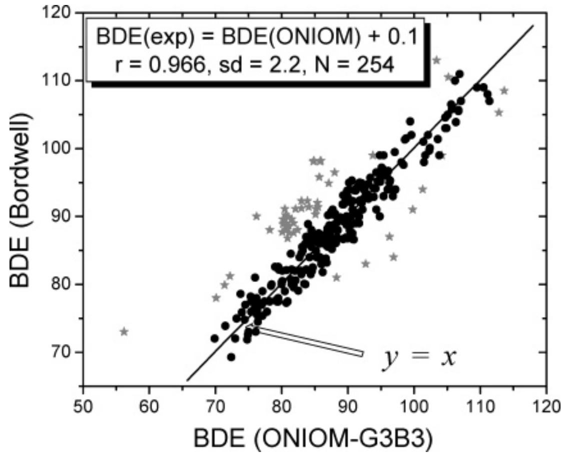


Figure 7. Comparison between the ONIOM-G3B3 BDEs and the experimental BDEs measured by the electrochemical methods.

TABLE 6: The Compounds for Which the Experimental BDE Values Differ from the Theoretical BDE Values Calculated by ONIOM-G3B3 by Over 5 kcal/mol

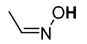
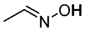
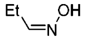
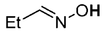
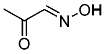
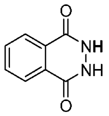
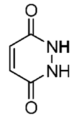
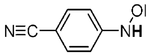
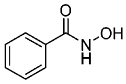
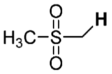
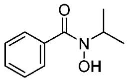
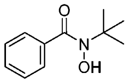
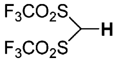
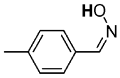
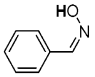
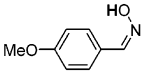
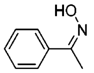
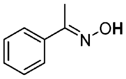
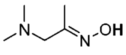
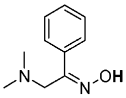
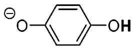
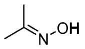
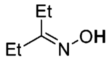
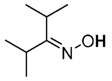
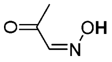
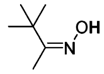
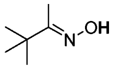
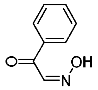
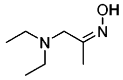
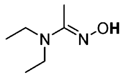
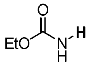
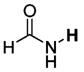
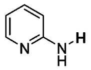
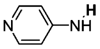
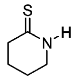
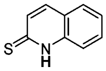
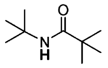
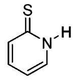
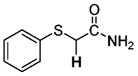
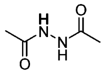
Entry	Compound	pK_a^{exp}	pK_a^{theor}	$E^{o\ exp}$	$E^{o\ theor}$	BDE^{exp}	$BDE^{eq\ 17}$	BDE^{ONIOM}
		Experimental pK_a's are questionable						
1		(28.5)	22.4	-0.61	-0.88	(98.2)	84.4	84.9
2		(28.5)	22.0	-0.61	-0.79	(98.2)	85.9	85.9
3		(28.8)	21.9	-0.64	-0.85	(98.1)	84.4	84.8
4		(28.8)	22.0	-0.64	-0.80	(98.1)	85.7	85.8
5		(15.1)	11.5	-0.19	-0.24	(89.6)	84.2	81.5
6		(12.7)	9.7	-0.17	-0.12	(86.8)	84.5	80.9
7		(13.2)	7.8	-0.16	0.00	(87.7)	84.7	80.1
8		(18.6)	13.1	-0.90	-0.84	(78.0)	72.5	70.1
9		(13.7)	9.1	-0.17	-0.17	(88.0)	82.5	82.4
10		(29.0)	32.7	-0.73	-0.60	(96.2)	104.9	104.2
11		(18.7)	7.7	-0.77	-1.01	(81.2)	(61.2)	72.2
12		(19.6)	8.4	-0.88	-1.15	(79.9)	(58.9)	71.4
13		(2.1)	-5.3	1.60	1.55	(113.0)	102.5	103.4
		Experimental redox potentials are questionable						
14		20.6	19.8	(-0.53)	-0.83	(89.0)	82.0	80.7
15		20.2	19.1	(-0.47	-0.80	(90.2)	81.7	80.6
16		20.9	20.2	(-0.53)	-0.84	(89.9)	82.3	81.0
17		21.2	21.2	(-0.49)	-0.92	(91.1)	81.8	80.5
18		21.8	21.2	(-0.52)	-0.82	(91.2)	84.1	83.0
19		23.5	23.5	(-0.59)	-0.92	(92.0)	84.9	85.4
20		20.5	20.4	(-0.56)	-0.91	(88.5)	80.9	80.6
21		26.5	28.3	(-1.56)	-2.08	(73.0)	(64.7)	56.2
22		26.0	24.3	(-0.57)	-0.97	(95.8)	84.9	85.7
23		25.2	25.1	(-0.67)	-1.10	(92.3)	83.0	83.9
24		25.2	25.0	(-0.80)	-1.15	(89.3)	81.7	83.0
25		15.1	12.4	(-0.19)	-0.52	(89.6)	79.0	80.2

TABLE 6 (Continued)

Entry	Compound	pK_a^{exp}	pK_a^{theor}	$E^{o\ exp}$	$E^{o\ theor}$	BDE^{exp}	$BDE^{eq\ 17}$	BDE^{ONIOM}
	Experimental redox potentials are questionable							
26		24.4	24.9	(-0.68)	-1.19	(91.1)	80.6	82.1
27		24.4	24.9	(-0.68)	-1.09	(91.1)	82.9	85.2
28		14.9	14.6	(-0.21)	-0.69	(88.9)	78.1	80.2
29		23.8	25.3	(-0.63)	-1.06	(91.4)	84.2	84.1
30		23.8	24.0	(-0.63)	-0.96	(91.4)	84.7	85.5
31		24.6	24.4	(-0.08)	0.29	(105.3)	114.1	112.8
32		23.4	23.6	(0.14)	0.56	(108.5)	(119.3)	113.6
33		27.7	28.5	(-1.06)	-0.69	(87.0)	97.1	96.3
34		26.5	27.5	(-1.09)	-0.53	(84.0)	99.4	96.9
35		20.1	19.5	(-0.42)	0.11	(91.0)	103.2	99.8
36		13.7	13.4	(-0.37)	0.32	(83.0)	(99.8)	92.7
37		28.0	30.3	(-0.06)	-0.48	(110.5)	104.4	105.2
38		13.3	12.6	(-0.45)	0.28	(81.0)	(97.7)	88.3
39		23.0	24.7	(-0.35)	-0.98	(96.5)	85.2	88.0
	Solvation energy of A• remarkably differs from that of HA							
40		16.7	15.5	-0.19	-0.31	(91.8)	(88.1)	81.1

methods including CBS-Q, CBS-QB3, G3, and G3B3 to calculate the BDEs of three oximes and two amides that contain less than seven non-hydrogen atoms (see Table 8). All these high-level methods have been benchmarked previously to be able to calculate the BDE values with an accuracy of about 1−2 kcal/mol.[29]

As shown in Table 8, all the high-level methods predict almost the same BDE values for the five compounds, strongly suggesting that the corresponding experimental values are questionable. For the O−H BDEs of *cis*-acetaldehyde oxime, *trans*-acetaldehyde oxime, and propan-2-one oxime the theoretical O−H BDEs are about 85 kcal/mol, which are in agreement with the very recent predictions by Pratt et al.[30] Both Pratt's and our BDE values are over 10 kcal/mol lower than the experimental data (95−98 kcal/mol). On the other hand, the N−H BDEs of formamide and ethyl carbamate are calculated to be about 113 kcal/mol, which are over 5 kcal/mol higher than the experimental values. It is worth noting that in a recent study by Radom et al., the N−H BDE of formamide is calculated to be 113.4 kcal/mol using the W1 method.[31] It is obvious that Radom's prediction is in agreement with our value.

6. Concluding Remarks

One of the grandest challenges for chemists is to learn how to design and produce new compounds with properties that can be predicted, tailored, and tuned before production. Although impressive progress has been made in theoretical predictions of molecular properties of isolated molecules in the gas phase, a lot remains to be done for predicting the properties of solvated molecules in condensed systems. Systematic studies toward this end are therefore extremely important.

In the present work we studied how to accurately calculate the properties of structurally unrelated molecules in DMSO. By benchmarking the theory against a huge number of experimental data, we developed a theoretical protocol that could predict the pK_a values of 277 structurally unrelated compounds in DMSO with a precision of 1.4 pK_a units. On the basis of this accomplishment, we developed the first theoretical protocol that

TABLE 7: The Compounds for Which Correct BDEs Values Were Fortuitously Obtained from Questionable Experimental pK_a Or Redox Potential Data

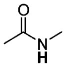
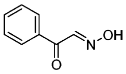
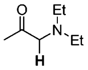
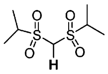
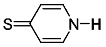
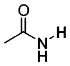
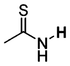
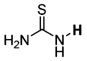
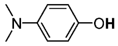
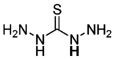
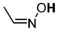
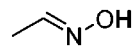
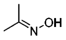
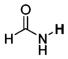
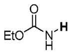
Entry	Compound	pK_a^{exp}	pK_a^{theor}	$E^{o\ \mathrm{exp}}$	$E^{o\ \mathrm{theor}}$	BDE$^{\mathrm{exp}}$	BDE$^{\mathrm{eq\ 17}}$	BDE$^{\mathrm{ONIOM}}$
1		(25.9)	28.9	-0.09	-0.12	106.5	(110.8)	105.6
2		(14.9)	11.6	-0.21	-0.26	88.9	83.8	84.0
3		(26.0)	29.9	(-1.54)	-1.90	76.0	71.1	75.4
4		(14.1)	10.2	(0.32)	0.64	100.1	102.8	102.4
5		11.9	10.7	(-0.34)	0.34	82.0	(96.5)	82.0
6		25.5	26.2	(-0.03)	0.27	108.0	(116.1)	111.1
7		18.5	17.4	(-0.32)	0.12	91.0	(100.6)	94.3
8		21.0	18.7	(-0.39)	0.15	93.0	(103.1)	95.4
9		19.8	19.8	-1.05	-1.15	80.3	(74.6)	80.0
10		16.6	15.6	-0.83	-0.80	72.0	(76.9)	69.9

TABLE 8: The Questionable BDEs Recalculated by Several Different High-Level Theoretical Methods (kcal/mol)

Compound	BDE$^{\mathrm{exp}}$	BDE$^{\mathrm{ONIOM}}$	CBS-Q	CBS-QB3	G3	G3B3
	(98.2)	84.9	82.9	83.9	84.4	85.1
	(98.2)	85.9	84.0	84.2	85.9	86.0
	(95.8)	85.7	83.5	84.3	85.8	86.0
	(108.5)	113.6	114.4	112.8	114.5	113.6
	(105.3)	112.8	112.5	112.7	112.6	112.6

could predict the standard redox potentials of 263 structurally unrelated organic anions in DMSO with a precision of 0.11 eV.

Armed with the newly developed pK_a and redox potential calculation methods, we were able to reevaluate all the bond dissociation enthalpy values measured by the electrochemical methods. It was confirmed that most of the redox potential values reported previously were reliable despite that irreversible cyclic voltammetry experiments were conducted. It was also confirmed that for most of the compounds the empirical equation (BDE $= 1.37\mathrm{p}K_{\mathrm{HA}} + 23.1E^{\mathrm{o}} +$ constant) was valid. The constant in this equation was determined to be 74.0 kcal/mol, compared to 73.3 kcal/mol reported previously. Nevertheless, we also identified a few compounds for which the above empirical equation could not be utilized because of the dramatic change of solvation free energy during the bond cleavage. It was revealed that such a dramatic change of solvation free energy was caused by the extraordinary change of dipole moment during the bond cleavage.

Next we utilized our ONIOM-G3B3 method to calculate all the BDE values measured by the electrochemical methods. It was demonstrated that the ONIOM-G3B3 method could nicely reproduce the experimental BDEs for 254 compounds. Nonetheless, we identified 40 compounds for which the theoretical BDEs differed from the experimental values by over 5 kcal/mol. These compounds were mostly oximes and amides. Further analyses revealed that all the questionable experimental BDEs could be explained by one of the three following reasons: (1) erratic measurement of pK_a; (2) erratic measurement of redox potential; or (3) the solvent effect cannot be neglected.

Thus, on the basis of bulky experimental data we have developed powerful theoretical methods that can make reliable predictions for realistic, solution-phase organic chemistry. Using the newly developed theoretical methods we have also solved some important problems that have remained difficult to settle by experiments. It is worth emphasizing that our ability to make a detailed picture of every aspect of a chemical reaction will come most readily from theories in which those aspects can be calculated, but theories whose predictions have been validated by particular experimental data.

7. Computational Methodology

All of the theoretical calculations were conducted with the Gaussian 03 programs.[19] The geometry of each species was optimized by using the B3LYP/6-31+G(d) method. For the molecules which have more than one possible conformation, the conformation with the lowest electronic energy was singled out and used in the ensuing calculations. Each final optimized geometry was confirmed by the B3LYP/6-31+G(d) frequency calculation to be a real minimum on the potential energy surface without any imaginary frequency.

Harmonic vibrational frequencies were calculated with the B3LYP/6-31+G(d) method for the optimized geometries. Single-point electronic energies were then calculated at B3LYP/6-311++G(2df,2p) levels. The free energy was obtained by combining the B3LYP/6-311++G(2df,2p) single-point electronic energies with ZPE, thermal corrections (0→298 K), and the entropy terms obtained at B3LYP/6-31+G(d) level (unscaled).

Free energy of solvation values were calculated by using the integral equation formalism version of PCM (IEF-PCM),[18] as implemented in Gaussian 03. PCM methods used here represent the solute as a cavity made up of a set of interlocking spheres. The cavity is built by the United Atom model (UA0). In this model a sphere is put around each solute heavy atom, using the atomic radii of the universal force field (UFF). Hydrogen atoms are enclosed in the sphere of the atom to which they are bonded. All the IEF-PCM calculations were performed at the

B3LYP/6-31+G(d,p) level. Both the electrostatic and nonelectrostatic contributions were included for the total solvation energies.

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Supporting Information Available: Experimental and theoretical pK_a values, standard redox potentials, and bond dissociation enthalpies for over 298 compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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