O−H Bond Dissociation Enthalpies of Oximes: A Theoretical Assessment and Experimental Implications

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By using a multilayer composite ab initio method ONION-G3B3, we calculated O−H bond dissociation enthalpies (BDEs) of 58 oximes that were measured experimentally. Experimental BDEs derived from thermal decomposition kinetics and calorimetric measurements were found to be consistent with the theory. However, the electrochemical method was found to give questionably high BDEs possibly due to errors in the measurement of pK_a's or redox potentials. Subsequently, the performances of a variety of DFT functionals including B3LYP, B3P86, B3PW91, BHandH, BHandHLYP, BMK, PBE1PBE, MPW1KCIS, mPWPW91, MPW1B95, and MPW1K were tested to calculate oxime O−H BDEs, where ROBHandHLYP was found to be the most accurate. By using this method, we calculated O−H BDEs of over 140 oximes in a systematic fashion. All of the calculated O−H BDEs fell in the range from 76.8 to 89.8 kcal/mol. An amino group on the azomethine carbon was found to strengthen the O−H bond, whereas bulky alkyl substituents on oximes decreased O−H BDEs due to their large steric-strain-relieving effects in the process of O−H bond cleavage. Para substituents had little effect on the BDEs of benzaldoximes and phenyl methyl ketoximes. Finally, on the basis of a spin distribution calculation, aryl-, alkyl-, and carbonyl-substituted iminoxyl radicals were found to be σ-radicals, whereas amino-substituted iminoxyl radicals were of π-structure.

1. Introduction

Oximes are among the most fascinating organic molecules.[1] Besides possessing interesting biological activities such as anti-inflammatory,[2,3] antiallergic,[3] antibacterial and fungicidal,[4] as well as hematotoxic[5,6] effects, they also find important practical applications as antidotes for nerve agents,[7] vasodilators,[8−11] anticancer drugs,[12] and prodrugs for pharmaceutically active ketones[13,14] such as ketoprofen and nabumetone.[15] Recent studies revealed that several oximes and oxime−ethers of hydroxylated benzaldehydes and acetophenones are powerful antioxidants[16] and tyrosinase inhibitors[17] for cosmetic or food use. Furthermore, as an important class of metal chelators,[18−20] oximes are useful for catalyst design,[21] removal of toxic metal ions,[22] and construction of supramolecular systems.[23,24] Additionally, oximes' photochemical activities[25] and involvement in the Beckmann rearrangement make them key starting materials for the synthesis of a variety of N-substituted amides,[26] heterocycles,[27,28] and nitriles.[29−31]

Note that in a number of the above applications of oximes, the O−H-bonding strength (as measured by the O−H homolytic bond dissociation enthalpy (BDE)) plays an important role in determining the activity. For instance, the metabolic stability of oxime drugs and the biological activity of oxime antioxidants in the physiological environment have a strong dependence on the stability of the iminoxyl radicals that are produced through the O−H homolysis.[32−38] Furthermore, according to the proposed mechanism for the photooxidation of aldoximes that can yield the corresponding aldehyde and nitrile, the aldehyde/nitrile product ratio is largely determined by the relative stability of the iminoxyl radical as compared with the iminoyl radical.[31,39] Due to these reasons, it is important to acquire a sound knowledge about the O−H BDEs of various types of oximes. Unfortunately, during the past several decades, there have been some heated controversies over the experimental values of oxime O−H BDEs.[40]

Briefly, most of the currently available oxime O−H BDEs were measured by an electrochemical (EC) method[41] on the basis of the following empirical equation[42−45]

$$\mathrm{BDE} = 1.37\mathrm{p}K_{\mathrm{HA}} + 23.06E_{\mathrm{ox}}(\mathrm{A}^-) + 73.3\ \mathrm{kcal}$$

However, a recent re-examination of the oxime O−H BDEs by measuring the thermolysis rates of corresponding *O*-benzyl oxime ethers (TR method)[40,46] led to some new BDE data that were dramatically lower than the electrochemical values.[42−45] It was further found that the new experimental data were consistent with the theoretical calculations at composite ab initio levels including G3MP2, G3, CBS-QB3, and CBS-APNO.[40] Nonetheless, it must be pointed out that while more than 40 oxime BDEs were measured by the EC method, only 6 of them have been re-evaluated and found erratic.[40] It is important at the present time to study whether the remaining ∼30 oxime BDEs measured by the EC method were problematic. Evidently, the previous composite ab initio methods such as G3 cannot be used for this purpose because they cannot handle molecules possessing over eight non-hydrogen atoms.[47,48]

Fortunately, we recently have developed a multilayer composite ab initio method named ONIOM-G3B3. We demonstrated that this method can predict the C−H, N−H, and O−H BDEs

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of various sizable molecules with a precision of ∼1.5 kcal/mol.[48,49] Thus, the ONIOM-G3B3 method provides us with a unique opportunity to re-examine all of the experimental oxime O−H BDEs measured by the EC method, which are reported in the present paper. In addition to the re-examination, we also want to answer the following two questions that have not been solved in the past. (1) What density functional theory (DFT) method can be used to replace ONIOM-G3B3 in calculating oxime BDEs so that the CPU cost can be significantly lowered yet the accuracy is still acceptable? Note that the DFT model (RO)B3LYP/6-311+G(2d,2p)//(U)B3LYP/6-31G(d) was previously reported to underestimate the oxime BDE values by 2 kcal/mol.[40] (2) What are the effects of various substitutions on the oxime O−H BDEs? This particular question has not been adequately studied previously, not only due to the lack of reliable experimental data but also because of the fact that the electronic structure of aryl- and alkyl-substituted iminoxyl radicals has been controversial for many years.[40,42,43,45,50−52]

2. Computational Methods

BDE is defined as the enthalpy change of the following reaction in the gas phase at 298.15 K and 1 atm

$$A{-}B(g) \rightarrow A^{\bullet}(g) + B^{\bullet}(g) \quad (1)$$

Specifically, the O−H BDE in the molecule RR′C═NOH is estimated from the expression

$$\mathrm{BDE(O{-}H)} = H_f(\mathrm{RR'C{=}NO^{\bullet}}) + H_f(\mathrm{H^{\bullet}}) - H_f(\mathrm{RR'C{=}NOH}) \quad (2)$$

The enthalpy of each species can be calculated from the following equation

$$H_f(298\ \mathrm{K}) = E + \mathrm{ZPE} + H_{\mathrm{trans}} + H_{\mathrm{rot}} + H_{\mathrm{vib}} + RT \quad (3)$$

where ZPE is the zero point energy; H_{trans}, H_{rot}, and H_{vib} are the standard temperature correction terms calculated with the equilibrium statistical mechanics with harmonic oscillator and rigid rotor approximations.

All calculations were performed by using the GAUSSIAN 03 package.[53] The geometries of oximes were fully optimized using the hybrid B3LYP density functional in conjunction with the 6-31G(d) basis set. An unrestricted open-shell wave function was utilized in the optimization of the iminoxyl radicals. For the molecules or radicals which have more than one possible conformation, the conformation with the lowest Gibbs free energy was singled out and used in the ensuing calculations. Each optimized geometry was confirmed to be a real minimum on the potential energy surface without any imaginary frequency. The harmonic vibrational frequencies were computed at the optimized geometry using the same level of theory. Single-point electronic energies were calculated using higher-level methods, as discussed below. ZPE and thermal correction to enthalpy were obtained at the B3LYP/6-31G(d) level. A scaling factor of 0.96 for the calculated ZPE was used in consistency with the ONIOM-G3B3 requirement.[49]

The re-evaluation of the experimentally measured O−H BDEs in oximes was conducted at the ONIOM-G3B3 level. Briefly speaking, a target system was divided into two layers in the ONIOM-G3B3 method. Then, a series of single-point energy calculations were performed at the ONIOM(MP2:B3LYP), ONIOM(MP4:B3LYP), and ONIOM(QCISD(T):B3LYP) levels of theory (The detailed procedure for using ONIOM-G3B3 to calculate BDEs can be found in our previous report[49]). In each of the ONIOM calculations, only the core layer was treated with the high-level theory, and the total energy was calculated with eq 4. The final ONIOM-G3B3 energy was calculated by using an extrapolation equation. 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 effective at the ONIOM(QCISD(T,FU)/G3Large:B3LYP) level[49]

$$E(\mathrm{ONIOM}) = E(\text{high, core layer}) + E(\text{low, whole system}) - E(\text{low, core layer}) \quad (4)$$

As to the search for a DFT method that can give the most accurate prediction of O−H BDEs in oximes, a variety of functionals in conjunction with the 6-311++G(2df, 2p) basis set were used to carry out single-point calculation on the optimized geometries of our chosen molecules whose experimental values have been confirmed with the ONIOM-G3B3 method. These functionals include B3LYP,[54,55] B3P86,[56] B3PW91,[57] BHandH,[58] BHandHLYP,[55] BMK,[59] PBE1PBE,[60] MPW1KCIS,[61] mPWPW91,[62] MPW1B95,[63] and MPW1K.[61] For the single-point calculation of radicals, both restricted open-shell and unrestricted open-shell wave functionals have been tested with the same training set.

3. Results and Discussion

3.1. Re-evaluation of experimental methods for measuring oxime O−H BDEs. In order to evaluate the reliability of the experimental oxime O−H BDEs, we first conducted the ONIOM-G3B3 calculation for oximes with controversial BDEs in the past. Theoretical results and experimental values by different methods are summarized in Table 1. Differences between experimental and ONIOM-G3B3 values are given in parentheses (that is, $\mathrm{BDE_{exp}} - \mathrm{BDE_{ONIOM-G3B3}}$). It is noteworthy that EC BDEs have an error bar of 2−3 kcal/mol[42−45] (the error bar for experimental pK_a values is about 0.5 pK_a units or 0.7 kcal/mol; the error bar for experimental redox potentials is about 0.1 V or 2.3 kcal/mol). While for (i-Pr)$_2$C═NOH, t-Bu(i-Pr)C═NOH, (t-Bu)$_2$C═NOH, E-/Z-t-Bu(1-Ad)C═NOH, differences between the EC and ONIOM-G3B3 BDEs border or slightly outreach this error bar, the former are dramatically higher than the latter by over 5 kcal/mol for Me$_2$C═NOH, Ph$_2$C═NOH, and fluorenone oxime.

We can also see that the ONIOM-G3B3 BDEs are in good agreement with experimental values by the TR method or from direct calorimetric measurement together with the REqEPR (radical equilibration electron paramagnetic resonance) technique. These results indicate that while these two experimental methods are generally sound, there are probably errors in the EC method when estimating O−H BDEs in oximes.

Before further examination of discrepancies between EC and ONIOM-G3B3 BDEs, a detailed review of the electrochemical methods for estimating the BDE is needed.

According to Scheme 1,[64] we have

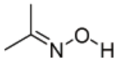
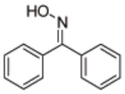
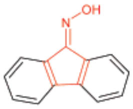
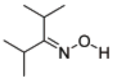
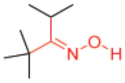
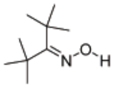
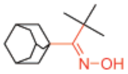
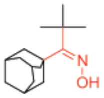
$$\Delta G_{\mathrm{solution}} = 1.37\mathrm{p}K_{\mathrm{HA}} + 23.1E^{\circ}(\mathrm{A}^{-}) - 23.1E^{\circ}(\mathrm{H}^{\bullet}) \quad (5)$$

where 1.37 and 23.1 are constants that convert the pK_a unit and volts to kilocalories/mole. At the same time, we have

$$\Delta G_{\mathrm{solution}} = \mathrm{BDE} - T\Delta S + \Delta G_{\mathrm{solvation}}^{\mathrm{A}^{\bullet}} + \Delta G_{\mathrm{solvation}}^{\mathrm{H}^{\bullet}} - \Delta G_{\mathrm{solvation}}^{\mathrm{HA}} \quad (6)$$

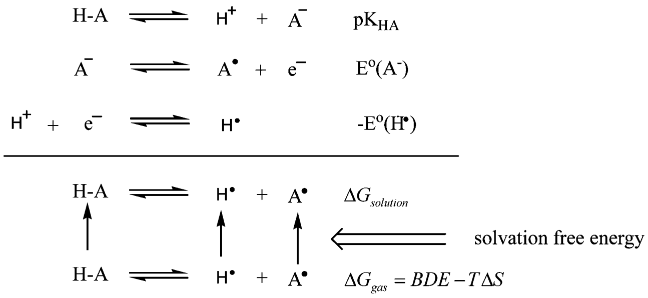
Since the redox potential of the hydrogen atom (i.e., $E^{\circ}(\mathrm{H}^{\bullet})$) and the solvation energy of the hydrogen atom (i.e., $\Delta G_{\mathrm{solvation}}^{\mathrm{H}^{\bullet}}$)

TABLE 1: Theoretical O−H BDEs in Oximes Compared with Various Experimental Values (at 298 K in kcal/mol)

	Calculated BDE		Experimental BDE		
oxime	ONIOM-G3B3	DFT^{c}	EC	TR^{g}	other
	85.7^{a}	84.3	95.8^{d}(10.1)	84.3(-1.4)	94.1^{i}(8.4)
	81.8^{a}	81.7	89.0^{d}(7.2)	82.4(0.6)	—
	80.4^{b}	82.3	87.5^{d}(7.1)	82.0(1.6)	—
	83.0^{a}	82.6	87.7^{e}(4.7)	79.7(-3.3)	86.0^{i}(3.0)
	83.0^{b}	81.5	86.0^{f}(3.0)	79.3(-3.7)	82.6^{h}(-0.4), 84.3^{i}(1.3)
	79.0^{a}	77.6	84.2^{e}(5.2), 82.6^{f}(3.6)	78.8(-0.2)	79.2^{h}(0.2), 80.9^{i}(1.9)
	78.7^{b}	77.1	81.7^{e}(3.0)	77.0(-1.7)	79.2^{h}(0.5), 80.0^{i}(1.3)
	78.3^{b}	76.8	81.7^{e}(3.0)	76.5(-1.8)	80.0^{i}(1.3)

[a] From ref 64. [b] This work. For oximes calculated in this work, the core layer is highlighted in red. [c] DFT = (RO)BHandHLYP/6-311++G(2df,2p)//(U)B3LYP/6-31G(d). [d] From ref 42. [e] From ref 43. [f] From ref 44. [g] From ref 40. [h] Revised calorimetric or REqEPR value from ref 46. [i] From ref 65.

SCHEME 1



are constants, with further assumptions that (1) the gas-phase entropy change (i.e., $T\Delta S$) is zero and (2) the solvation energy of $A^{\bullet}$ equals that of HA (i.e., $\Delta G_{\text{solvation}}^{A^{\bullet}} - \Delta G_{\text{solvation}}^{HA} = 0$) as well, we will have

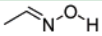
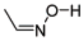
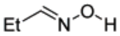
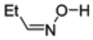
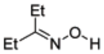
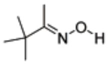
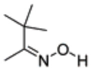
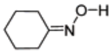
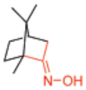
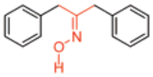
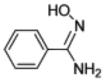
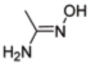
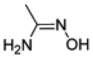
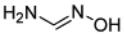
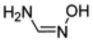
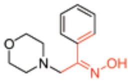
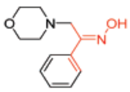
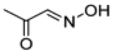
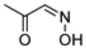
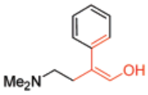
$$\text{BDE} = 1.37\text{p}K_{\text{HA}} + 23.1E^{\circ} + \text{constant} \qquad (7)$$

Possible reasons for the dramatic discrepancies between EC BDEs and ONIOM-G3B3 values include (1) that the gas-phase entropy change is not zero (i.e., $T(S_{A^{\bullet}} - S_{HA}) \neq 0$),[64] (2) the neglect of solvation effects (i.e. $\Delta G_{\text{solvation}}^{A^{\bullet}} - \Delta G_{\text{solvation}}{}^{HA} \neq 0$), especially the hydrogen bonding,[40,66] and (3) significant errors in the measurement of pK_a and redox potential values.

The first two reasons, if true, would cause a nonlinear correlation between BDEs and 1.37pK_{HA} + 23.1$E°$ values for many systems, a circumstance that has been ruled out in our previous study.[64] In that study, pK_a values and redox potentials of 295 structurally unrelated compounds were accurately calculated, and their ONIOM-G3B3 BDEs were then plotted against the expression 1.37pK_{HA}(theor) + 23.1$E°$(theor) (where "theor" refers to theoretical values). The excellent linearity indicates that for most of the compounds, including some of the oximes in the current report, eq 7 is generally valid to predict BDEs, although the constant was found to be 74.0 kcal/mol instead of 73.3 kcal/mol, as reported before.[42−45,64]

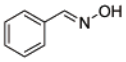
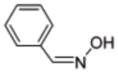
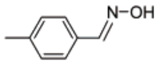
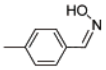
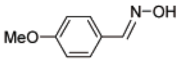
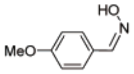
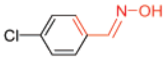
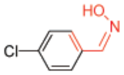
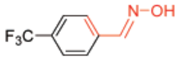
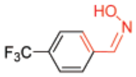
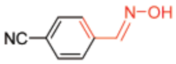
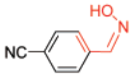
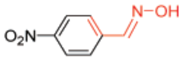
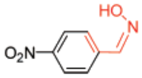
It is noteworthy that the theories we employed to calculate pK_a's and redox potentials have been carefully benchmarked against experimental data. The protocol to calculate pK_a values in DMSO[64,67] (the solvent employed in the EC method[42−45]) successfully reproduced the experimental pK_a's for 277 structurally unrelated compounds. The mean error, correlation coefficient, and standard deviation between the experimental and theoretical pK_a's are 0.1, 0.983, and 1.4 pK_a units, respectively.[64] On the other hand, the theory we developed to calculate redox potentials in DMSO[64,68] was found to produce predictions that agree well with the experimental data for 263 structurally unrelated anions. The mean error, correlation coefficient, and the standard deviation between the experimental and theoretical data are 0.06, 0.987, and 0.11 V, respectively. With these calibrated theoretical tools, we are confident about the calculated pK_a's and redox potentials and believe that in most cases, questionable EC BDEs are due to errors in the measurement of pK_a and redox potential values (mainly because most of the oxidation potentials are irreversible), rather than significant solvation effect problems.[64]

TABLE 2: O−H BDEs, pK_a's, and Redox Potentials in Oximes (RR′C═NOH) (Mainly Alkyl- and Amino-Substituted) at 298 K in kcal/mol, pK_a Units, and Volts, Respectively

	Calculated BDE			Experimental BDE	p*K*a		$E^\circ(A^-)$	
oxime	ONIOM-G3B3[a]	DFT[e]	Eq.7[f]	EC	Exp	Theor[f]	Exp	Theor[f]
	85.9[b]	84.6	85.9(0.0)	98.2[g](12.3)	28.5[g]	22.0	-0.61[g]	-0.79
	84.9[b]	83.5	84.4(-0.5)	98.2[g](13.3)	28.5[g]	22.4	-0.61[g]	-0.88
	85.8[b]	84.5	85.7(-0.1)	98.1[g](12.3)	28.8[g]	22.0	-0.64[g]	-0.80
	84.8[b]	83.5	84.4(-0.4)	98.1[g](13.3)	28.8[g]	21.9	-0.64[g]	-0.85
	83.9[b]	83.9	83.9(0.0)	92.3[g](8.4)	25.2[h]	25.1	-0.67[h]	-1.10
	85.2[b]	83.7	82.9(-2.3)	91.1[h](5.9)	24.4[h]	24.9	-0.68[h]	-1.09
	82.1[b]	80.8	80.6(-1.5)	91.1[h](9.0)	24.4[h]	24.9	-0.68[h]	-1.19
	85.1[b]	83.8	84.5(-0.6)	90.3[h](5.2)	24.2[h]	24.0	-0.70[h]	-0.97
	86.7[c]	84.9	—	88.1[h](1.4)	—	—	—	—
	83.3[c]	81.8	—	88.1[h](4.8)	—	—	—	—
	85.7[c]	84.0	—	89.1[g](3.4)	—	—	—	—
	85.5[b]	84.4	85.0(-0.5)	86.9[g](1.4)	23.0[g]	23.7	-0.78[g]	-0.93
	88.8[d]	85.0	88.0(-1.3)	86.7[g](-2.6)	25.8[g]	26.9	-0.95[g]	-0.99
	89.8[d]	86.7	88.9(-1.8)	86.7[g](-4)	25.8[g]	25.9	-0.95[g]	-0.89
	89.8[d]	86.3	89.2(-0.5)	88.8[g](-1.0)	25.6[g]	25.9	-0.85[g]	-0.88
	90.4[b]	88.5	89.7(-0.7)	88.8[g](-1.6)	25.6[g]	25.6	-0.85[g]	-0.84
	80.7[c]	79.9	—	89.1[g](8.4)	—	—	—	—
	82.1[c]	82.1	—	88.6[g](6.5)	—	—	—	—
	81.5[b]	83.0	84.2(2.7)	89.6[g](8.1)	15.1[g]	11.5	-0.19[g]	-0.24
	80.2[b]	80.2	79.0(-1.2)	89.6[g](9.4)	15.1[g]	12.4	-0.19[g]	-0.52
	84.1[c]	83.2	—	88.6[g](4.5)	—	—	—	—
	81.2[b]	80.9	—	88.7[g](7.5)	—	—	—	—

[a] The core layer is highlighted in red. [b] From ref 64. [c] This work. [d] Calculated by the G3B3 method for containing less than six heavy atoms. [e] DFT = (RO)BHandHLYP/6-311++G(2df,2p)//(U)B3LYP/6-31G(d). [f] From ref 64. The eq 7 column refers to BDEs calculated according to eq 7 using theoretical pK_a's and redox potential values. [g] From ref 42. [h] From ref 43.

TABLE 3: O−H BDEs in p-Substituted Benzaldoximes (*p*-$GC_6H_4CH{=}NOH$) at 298 K in kcal/mol

	Calculated BDE			Experimental BDE
oxime	ONIOM-G3B3[a]	DFT[d]	Eq 7[f]	EC[g]
	84.2[b]	84.0	85.0	88.1
	80.6[b]	—[e]	81.7	88.1
	84.3[b]	84.0	84.8	88.0
	80.7[b]	80.7	82.0	88.0
	84.5[b]	84.2	85.0	87.8
	81.0[b]	80.9	82.3	87.8
	84.5[c]	84.3	—	87.8
	81.0[c]	81.0	—	87.8
	84.4[c]	84.3	—	87.9
	80.8[c]	80.8	—	87.9
	84.4[c]	84.3	—	87.8
	80.8[c]	80.9	—	87.8
	84.4[c]	84.3	—	88.4
	80.7[b]	80.9	—	88.4

[a] The core layer is highlighted in red. [b] From ref 64. [c] This work. [d] The ROBHandHLYP model. [e] The given DFT model chemistry fails to reach a SCF convergence when running the single point energy calculation for the corresponding radical. [f] From ref 64, calculated with theoretical pK_a and redox potential values. [g] The most recent EC values from ref 45.

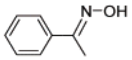
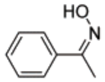
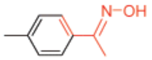
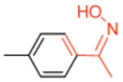
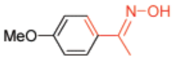
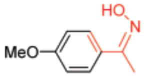
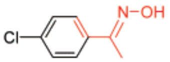
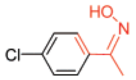
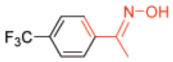
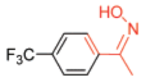
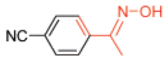
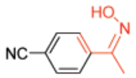
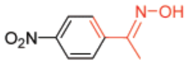
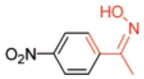
To depict a more detailed portrayal of the accuracy of the EC method for our specific system and further recommend high-accuracy theoretical BDEs, herein, we conduct ONIOM-G3B3 calculations for virtually all of the oximes investigated with the EC procedure. These BDE values are summarized in Tables 2−4. In the parentheses, we show the differences from corresponding ONIOM-G3B3 BDEs.

The 23 BDEs deduced from eq 7 (constant = 74.0 kcal/mol) using theoretical pK_a and $E°(A^-)$ data reported in our previous work[64] are also involved in the tables above. In Table 2, we list theoretical and experimental pK_a and $E°(A^-)$ values for 15 oximes as examples to show differences between theoretical and experimental data. More theoretical results are available in our previous report[64] and its Supporting Information. While differences between EC and ONIOM-G3B3 BDEs vary from −4 to 13.3 kcal/mol, the corresponding BDEs derived from eq 7 are generally in good agreement with ONIOM-G3B3 values (differences between them are within ±3 kcal/mol).

In Figure 1, we show the comparison between ONIOM-G3B3 and EC BDEs as well as that between ONIOM-G3B3 and BDEs derived from eq 7. While virtually no linear relationship is found between ONIOM-G3B3 and EC BDEs (as shown in Figure 1a), a remarkable improvement of linear correlation is found when experimental pK_a's and redox potentials are replaced by theoretical data (as shown in Figure 1b).

Again, we believe experimental errors in the measurement of pK_a's and redox potentials for oximes are the major reason

TABLE 4: O−H BDEs in p-Substituted Ketoximes (p-GC$_6$H$_4$C(Me)=NOH) at 298 K in kcal/mol

	Calculated BDE			Experimental BDE
oxime	ONIOM-G3B3[a]	DFT[d]	Eq 7[f]	EC[g]
	83.0[b]	82.9	84.1	88.4
	80.5[b]	80.1	81.8	88.4
	83.0[c]	82.9	—	89.0
	79.7[c]	79.4	—	89.0
	83.3[c]	83.1	—	88.9
	80.3[c]	80.0	—	88.9
	83.3[c]	—[e]	—	89.0
	80.6[c]	80.3	—	89.0
	83.3[c]	83.3	—	88.9
	80.6[c]	80.5	—	88.9
	83.3[c]	83.4	—	88.8
	80.7[c]	80.5	—	88.8
	83.3[c]	83.4	—	88.8
	80.8[c]	80.7	—	88.8

[a] The core layer is highlighted in red. [b] From ref 64. [c] This work. [d] The ROBHandHLYP model. [e] The given DFT model chemistry fails to reach a SCF convergence when running the single-point energy calculation for the corresponding radical. [f] From ref 64, calculated with theoretical pK_a and redox potential values. [g] The most recent EC values from ref 45.

for their problematic O−H BDEs with the EC method. Our previous broad conclusion[64] works well for this specific system.

3.2. Comparison of Various DFT Methods for Calculating O−H BDEs in Oximes. Before we conduct a comparative study on the performance of various DFT-based methods in predicting O−H BDEs in oximes, a training set with valid experimental values is needed. In Table 1, we have shown eight oximes whose theoretical O−H BDEs (at the ONIOM-G3B3 level) agree well with TR values or revised calorimetric or REqEPR measurements. Our training set includes all of the oximes in Table 1 except (i-Pr)$_2$C=NOH, where the difference between the ONIOM-G3B3 and experimental values is larger than 3 kcal/mol. We omit this oxime so that the different degree of linearity between experimental and theoretical BDEs for each DFT method can be more definitely owed to the performance of the DFT method itself rather than experimental errors.

For the established molecule set, TR values are taken as experimental reference, except for t-Bu(i-Pr)C=NOH, whose TR BDE is significantly lower than our ONIOM-G3B3 value. Its experimental value derived from REqEPR measurement[40] is taken instead.

With this training set, performances of both RODFT and UDFT were tested for all of the functionals in conjunction with the 6-311++G(2df,2p) basis set. Table 5 lists the mean absolute deviation (MAD) and root-mean-square deviation (rmsd) over the whole set of oximes for each DFT method.

Table 5 shows that (RO)BHandHLYP, (RO)BMK, (RO)-B3P86, and (U)BHandH yield BDEs for the molecule set with

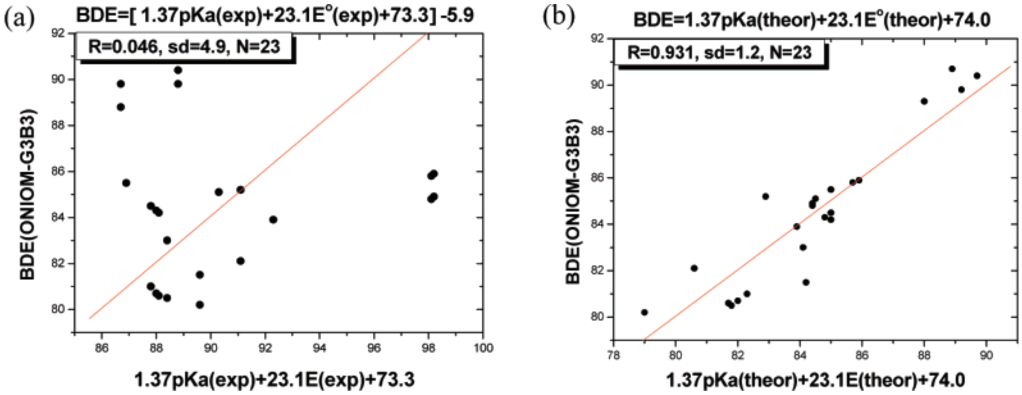


Figure 1. Comparison between ONIOM-G3B3 BDEs (kcal/mol) and (a) EC BDEs deduced from experimental pK_a and $E°(A^-)$ values and (b) eq 7 values calculated with theoretical pK_a and $E°(A^-)$ values.

TABLE 5: Mean Deviation (MAD) and Root-Mean-Square Deviation (rmsd) for Each DFT-Based Method (in kcal/mol)

UDFT	MAD[a]	rmsd[b]	*R*[c]	RODFT	MAD	rmsd	*R*
BHandH	1.4	1.5	0.970	BHandHLYP	0.5	0.7	0.974
BMK	2.3	2.4	0.973	BMK	0.9	1.1	0.973
BHandHLYP	3.2	3.3	0.975	B3P86	1.9	2.0	0.974
B3P86	3.3	3.3	0.974	MPW1K	2.9	2.9	0.977
MPW1B95	5.2	5.2	0.972	MPW1B95	3.7	3.8	0.975
MPW1K	5.3	5.4	0.977	BHandH	4.0	4.0	0.971
B3LYP	5.6	5.7	0.973	B3LYP	4.2	4.3	0.973
B3PW91	7.3	7.3	0.975	PBE1PBE	5.7	5.7	0.976
PBE1PBE	7.3	7.3	0.975	B3PW91	5.9	5.9	0.975
mPWPW91	10.6	10.7	0.970	mPWPW91[d]	9.8	9.8	0.970
MPW1KCIS	12.9	12.9	0.973	MPW1KCIS	11.8	11.8	0.973

[a] Mean absolute deviation (MAD). [b] Root-mean-square deviation (rmsd) from experimental values. [c] Correlation coefficient obtained by plotting BDE(expt) against BDE(DFT). [d] (RO)mPWPW91 fails to reach a SCF convergence when running the single-point energy calculation for the fluorenone iminoxy radical; thus, all of its parameters are deduced from the left six BDEs calculated with this level of theory.

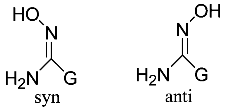
a rmsd less than 2 kcal/mol.[69−71] (RO)BHandHLYP gives the best results. It reproduces the valid experimental BDEs with a MAD of 0.5 kcal/mol and a rmsd of 0.7 kcal/mol, which even outperforms the ONIOM-G3B3 method in predicting O−H BDEs for the given molecule set. The MAD and rmsd of the latter are 1.07 and 1.3 kcal/mol, respectively.

Except for the BHandH and BHandHLYP functionals, the DFT methods generally underestimate BDEs for this specific system. RODFTs and UDFTs cost almost the same CPU time in our study, while RODFTs outperform UDFTs for all of the functionals except for BHandH. It is observed that ROBHandH significantly overestimates BDEs and is less accurate than UBHandH. Although most DFT functionals investigated here predicted absolute O−H BDEs significantly lower than experimental values, their relative BDEs were found to agree with each other. We have plotted experimental BDEs against theoretical values for each DFT functional. With the slopes fixed to 1, nice linear correlations were obtained, which have been reflected by the correlation coefficients in Table 5.

To further examine the accuracy of ROBHandHLYP and to facilitate the later discussions about effects of substituents on the O−H bond strength, we recalculated O−H BDEs in Tables 1− 4 with this DFT procedure. These results are shown in the same tables. Nice agreement between the ONIOM-G3B3 and ROBHandHLYP results can be clearly observed for the 56 oximes, which adds to our confidence in the ROBHandHLYP prediction of oxime O−H BDEs without experimental values.

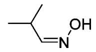
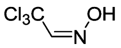
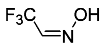
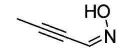
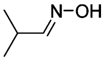
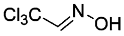
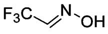
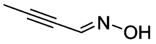
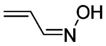
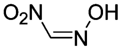
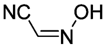
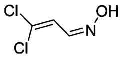
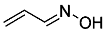
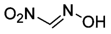
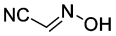
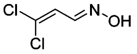
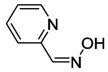
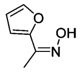
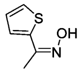
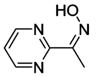
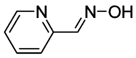
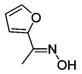
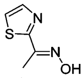
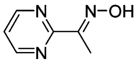
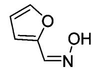
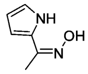
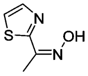
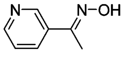
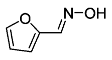
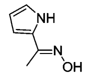
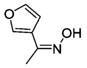
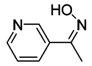
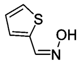
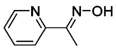
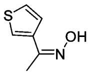
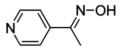
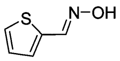
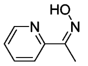
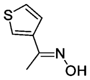
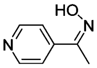
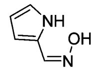
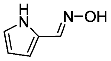
3.3. Systematic Study of Oxime O−H BDEs with ROBHandHLYP. By using the ROBHandHLYP procedure, we have predicted O−H BDEs in more than 140 oximes. Special interest is aroused in oximes (GG′C═NOH) with substituents G = NO_2, NH_2, Cl, carbonyl, and heterocycles. Nineteen hydroxyimino oximes are included, and all of their O−H BDEs have been calculated. To the best of our knowledge, no experimental O−H BDEs for the above oximes are reported. However, since they are crucial for chemical synthesis and the O−H bond is one of the weakest bonds, our theoretical prediction would help understand the chemistry of oximes as well as a large number of reactions in which they are involved. These BDEs are available in Tables 6−8.

All of the oxime O−H BDEs calculated at this DFT level fall in the range from 76.8 to 89.8 kcal/mol. Geometrical isomerism, intramolecular hydrogen bonds, dipole−dipole interactions, and steric effects are found to affect BDEs. Interestingly, while most O−H BDEs are below 86 kcal/mol, the amino group bonded to the azomethine carbon in amidoximes seems to significantly strengthen their O−H bond. Virtually all of the BDEs larger than 88 kcal/mol belong to those O−H bonds syn to an amino substituent. BDEs (at the DFT level) in oximes with amino substituents are listed in Table 8.



Although the unpaired electron in radicals of amidoximes can delocalize in a much wider area than that of iminoxyl radicals with other substituents (vide infra), it seems that the delocalization fails to significantly stabilize these radicals considering the appreciable increase of the O−H BDEs. As previous studies[72] revealed that RSEs for heteroallylic-type radicals decrease dramatically as the electronegativities of the terminal atoms increase from carbon in C═C−C$^•$ (RSE = 18 kcal/mol[73]) to nitrogen in N═C(Ph)−N$^•$ (5 kcal/mol) to oxygen in O═

TABLE 6: Gas-Phase O−H BDEs of Aldoximes and Ketoximes Substituted by Nitro, Cloro, Carbonyl Groups, Heteroatomic Rings, and So Forth (at 298 K in kcal/mol)

Aldoximes							
	83.0		81.9		82.6		83.3
	84.4		84.6		84.4		83.8
	82.9		82.3		84.2		83.4
	84.0		84.0		84.5		88.1
aldoximes and ketoximes containing heteroatomic rings							
	80.7		83.1		83.3		81.4
	83.7		84.0		84.9		80.8
	83.1		83.9		83.1		83.5
	84.5		88.4		83.2		80.5
	83.7		83.6		81.5		83.1
	84.9		79.8		81.5		80.2
	84.4		85.7				
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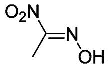
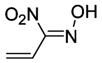
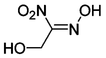
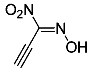
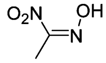
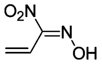
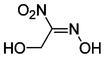
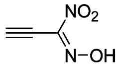
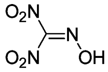
	83.9		81.6		81.7		83.6
	82.2		80.7		83.2		81.3
	84.9						
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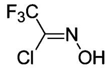
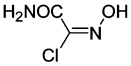
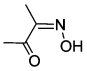
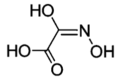
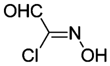
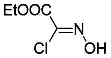
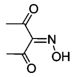
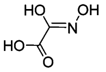
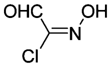
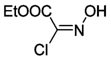
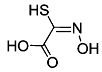
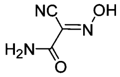
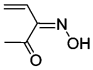
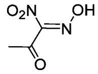
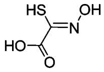
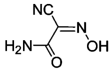
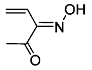
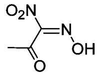
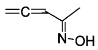
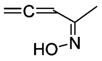
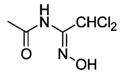
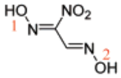
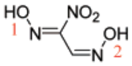
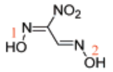
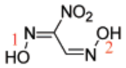
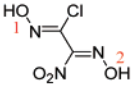
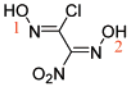
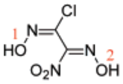
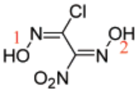
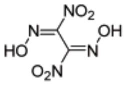
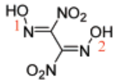
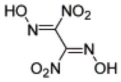
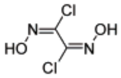
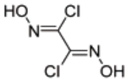
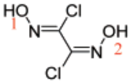
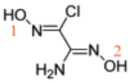
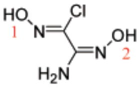
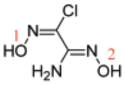
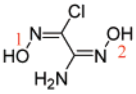
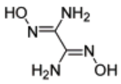
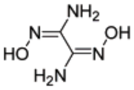
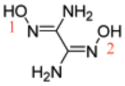
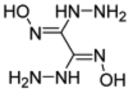
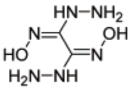
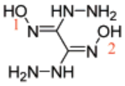
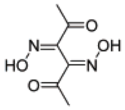
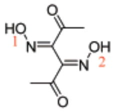
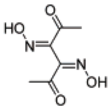
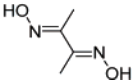
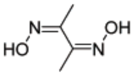
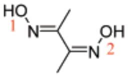
	86.2		85.5		78.6		87.1
	85.0		83.8		81.3		87.4
	82.1		83.7		83.6		84.6
	78.3		84.5		86.9		84.3
	79.4		82.0				
other oximes							
	84.1		83.9		87.3		86.8

C(Ph)−O$^\bullet$ (0 kcal/mol[74]), the small RSE of oxygen-terminal iminoxyl radicals seems understandable. In contrast, however, for molecules, the electron-donating nature of the amino group can increase the electron density of the whole system including the hydroxyl group, which seems to be the primary reason for the strengthened O−H bond.

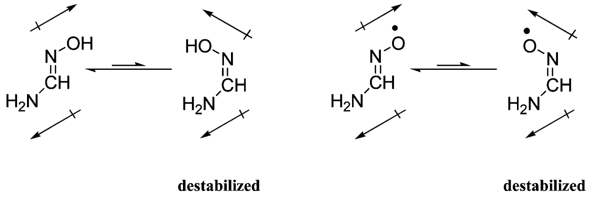
For amidoximes, syn isomers have O−H BDEs almost constantly larger than corresponding anti isomers. Take HC-

TABLE 7: Gas-Phase O−H BDEs of Hydroxyimino Oximes (at 298 K in kcal/mol)

Oxime	BDE	Oxime	BDE	oxime	BDE	oxime	BDE
	85.9^1, 84.9^2		82.2^1, 83.4^2		85.5^1, 84.2^2		84.5^1, 83.5^2
	89.5^1, 83.8^2		89.0^1, 81.9^2		86.9^1, 82.6^2		87.9^1, 83.9^2
	78.9		83.7^1, 84.0^2		82.5		
	86.3		85.0		86.2^1, 83.7^2		
	86.3^1, 89.0^2		86.3^1, 84.6^2		83.5^1, 87.8^2		86.3^1, 86.6^2
	87.0		85.6		85.3^1, 82.7^2		
	85.8		86.9		83.7^1, 79.4^2		
	84.9		82.1^1, 81.0^2		82.5		
	83.8		83.8		82.9^1, 80.7^2		

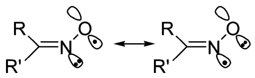
(NH_2)═NOH for example, the *syn*-iminoxyl radical and *syn*-oxime are stabilized by 1.2 and 3.4 kcal/mol, respectively, relative to their anti isomers. Two factors would possibly influence the relative stability of these isomers, that is, intramolecular hydrogen bonds and dipole−dipole interactions. The syn isomer preference is possibly a consequence of an intramolecular hydrogen bond between oxygen and a hydrogen bonded to the amino nitrogen, which is observed in both *syn*-oxime molecule and *syn*-iminoxyl radical of formamidoxime. The hydrogen bond is stronger in the radical than that in the molecule as the distances between unbonded oxygen and hydrogen show in Figure 2.

However, the dipole−dipole interaction would serve to offset such a syn isomer preference since such an unfavorable interaction in the syn isomers destabilizes both the molecule and the radical (arrows represent the directions of dipole moments).



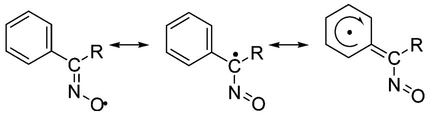
In fact, the more effective intramolecular hydrogen bond in the syn radical naturally causes a shorter distance between the amino nitrogen and oxygen (2.55 Å) than that in the syn molecule (2.59 Å) and, in turn, a more intense dipole−dipole repulsion. The two contradictory effects finally strike the balance that the syn molecule is more stabilized than the syn radical by 2.2 kcal/mol relative to their corresponding anti isomers. For that reason, O−H BDEs in *syn*-oximes are larger than those in *anti*-oximes.

3.4. Spin Distribution on Heavy Atoms in Iminoxyl Radicals. The electronic structure of iminoxyl radicals has been a controversial problem. From EPR spectroscopy, Thomas[50] found significant spin density on nitrogen in an orbital with considerable s character and therefore deduced a σ-structure for iminoxyl radicals, a conclusion confirmed by subsequent workers.[40,51,52] Iminoxyl radicals are described as



(8)

However, on the basis of the EC measurement, the increased RSEs for the radical of benzaldoxime, relative to acetaldoxime, were owed to delocalization of the single electron into π-electron clouds above the Ph ring, which suggests a π-structure for aryl-substituted iminoxyl radicals.[42,43,45] That is



(9)

For a series of dialkyl ketoximes ranging from *t*-Bu(1-Ad)C═NOH to Me_2C═NOH, the 14.1 kcal/mol increase in O−H BDEs

TABLE 8: Gas-Phase O−H BDEs of Oximes $GC(NH_2){=}NOH$ at 298 K in kcal/mol

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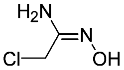
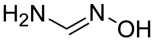
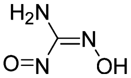
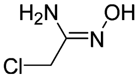
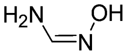
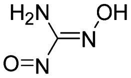
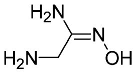
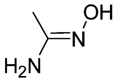
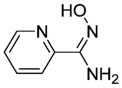
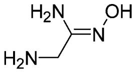
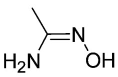
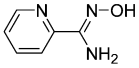
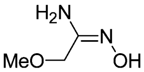
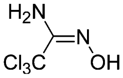
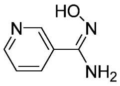
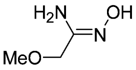
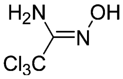
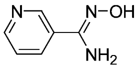
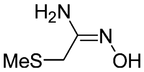
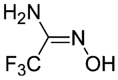
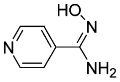
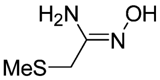
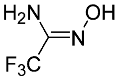
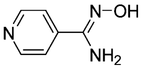
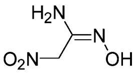
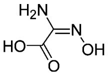
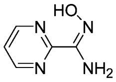
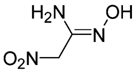
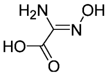
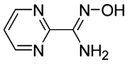
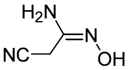
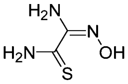
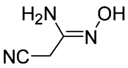
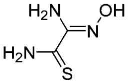
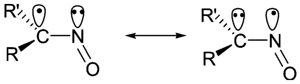
	85.5		86.3		88.3
	88.7		88.5		88.1
	83.7		85.0		82.9
	86.2		86.7		85.0
	83.5		86.7		84.6
	86.0		88.9		85.9
	85.9		88.5		83.4
	89.0		89.4		86.9
	86.5		82.8		83.5
	89.5		89.8		86.6
	85.5		82.1		
	88.5		86.7		

(EC values) was attributed to a decrease in steric strain in the parent oximes.[43] A rotation around the C−N bond was proposed to accompany the cleavage of the O−H bond to best relieve the strain between oxygen and R groups, which generated a perpendicular structure for iminoxyl radicals (eq 10).[43]

 (10)

The study of the spin distribution on various iminoxyl radicals shows that although most of the iminoxyl radicals investigated act as σ-radicals, radicals of amidoximes possess a π-behavior. Figure 3 shows the Mulliken spin densities on heavy atoms in aryl-, alkyl-, carbonyl-, and amino-substituted iminoxyl radicals.

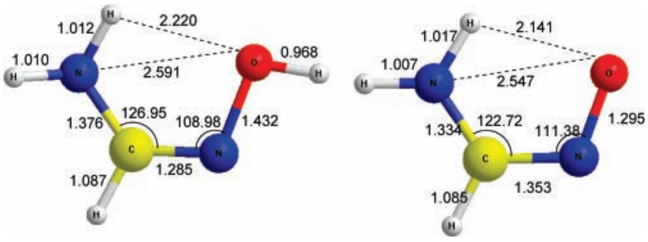


Figure 2. (U)B3LYP/6-31G(d) Structures of *syn*-formamidoxime and its radical (bond length and atom distances in Angstroms; bond angles in degree).

The calculation of spin densities was performed at the UB3LYP/6-31+G** level, a chemistry model which proved to generate spin densities for $H_2C{=}NO^{\bullet}$[75] in satisfactory agreement with the EPR estimate.[76,77] For comparison, the spin distribution of the phenyl propenyl radical, whose single electron was reported to delocalize over the Ph ring,[78] was calculated at the same level.

Turn to the aryl-substituted iminoxyl radicals first. While the spin densities on the O and N atoms for all of these calculated radicals are 0.56 ± 0.02 and 0.46 ± 0.01, respectively, carbons are left with hardly any spin densities, in agreement with EPR and previous calculated evidence.[75−77] The two structures as shown in eqs 9 and 10, if true, would find significant spin densities on the azomethine carbon. The largest spin density on the azomethine carbon is found to be −0.16 in the benzophenone iminoxyl radical, while for other radicals, the absolute value is no more than 0.10. In sharp contrast, however, the phenyl propenyl radical, whose configuration is very similar to that of the benzaldehyde iminoxyl radical, has the spin density as large as 0.64 on the counterpart carbon. The fact clearly indicates different characteristics of the two radicals in terms of delocalization, that is, σ-type and π-type, respectively. Moreover, while the *ortho*- and *para*-carbons in the Ph ring of the phenyl propenyl radical have spin densities around 0.2, these values fall below 0.05 for aryl-substituted iminoxyl radicals. These facts, along with the obviously shortened N−O distance and increased angle ∠(CNO) in iminoxyl radicals compared

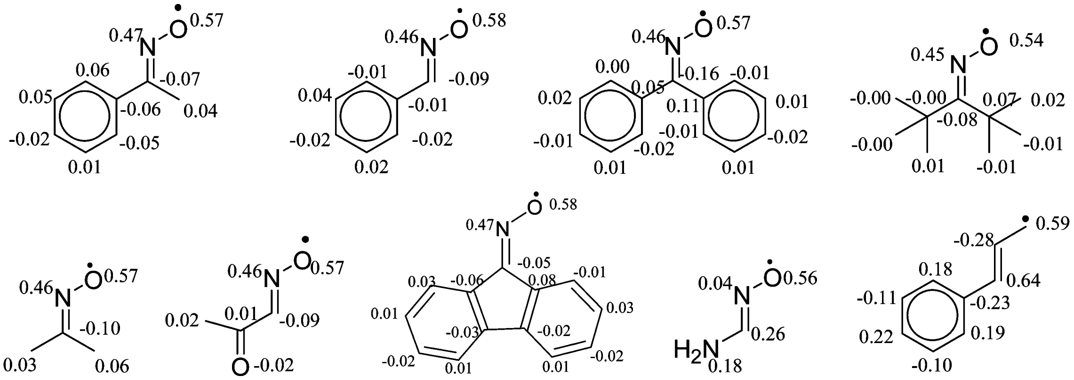
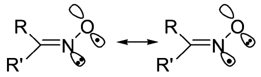


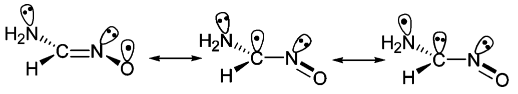
Figure 3. Spin densities for some typical iminoxy radicals compared with the phenyl propenyl radical.

with parent oximes (vide infra), can lead to the σ-structure of iminoxyl radicals, whose substituents on the azomethine carbon are aryl, alkyl, and carbonyl groups, as shown below.



For these radicals, a π-structure is clearly inappropriate.

However, it is interesting to point out that when connected to an amino group, the azomethine carbon, together with the amino nitrogen in iminoxyl radicals, can obtain significant spin density, as shown in Figure 3. This fact, together with a calculated C$-$NH$_2$ distance of 1.34 Å, close to that of the C=N bond (1.32 Å),[79] indicates significant delocalization of the single electron onto the azomethine carbon and the amino nitrogen, which can only occur in a π-system as described below.



(11)

We find the unusual π-behavior of amino-substituted iminoxyl radicals can be attributed to the strong π-electron-donating disposition of the amino group. Due to the hyperconjugation effect, the nitrogen lone pair can overlap with the 2p orbital of the azomethine carbon (perpendicular to the radical plane) so that the carbon-centered radical is stabilized.

3.5. Steric Effects on O$-$H BDEs in Oximes. Ever since the di-*tert*-butyl iminoxyl radical was first isolated in 1971,[80] considerable interest has been aroused on the unusual stability of some iminoxyl radicals.[50,77] It is generally acknowledged that BDEs of the O$-$H bonds become progressively weaker as the size of the alkyl groups R and R′ in RR′C=NOH increase. In other words, corresponding iminoxyl radicals become more stable.[81] In 1995, Bordwell and his co-workers analyzed steric effects on O$-$H BDEs in alkyl oximes on the basis of values given by the EC method. With the X-ray crystal structures of di-*tert*-butyl ketoxime and dimethyl ketoxime, the increasing size of the alkyl groups were deemed to increase ground-state energies and, in turn, decrease BDEs as a result of progressively larger relief of steric strain together with the homolytic O$-$H bond cleavage.[43] Rotation around the C$-$N bond to form a "perpendicular" radical (eq 10) was also proposed in this process for it would decrease the steric strain in iminoxyl radicals to the largest degree.[43]

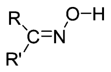
Unfortunately, however, since their O$-$H BDEs measured by the EC method have been found unconvincing in the present work as well as several previous works,[40,64] conclusions following these data need to be re-examined.

It can be seen from Tables 1 and 2 that theoretical O$-$H BDEs decrease as the size of the substituents (alkyl groups) bonded to the azomethine carbon increase. Take a series of symmetric ketoximes (that is, substituents R and R′ on the azomethine carbon are the same) for example, when R = Me, Et, *i*-Pr, and *t*-Bu, BDEs (at the DFT level) gradually decrease as 84.3, 83.9, 82.6, 77.6 kcal/mol, respectively. For asymmetric ketoximes and aldoximes, the same trend is clearly observed. For oximes with alkyl groups bonded to the azomethine carbon, O$-$H BDEs of Z isomers (highest priority cis to oxygen) are always lower than those of E isomers, a conclusion that can be easily drawn from E/Z pairs of MeCH=NOH, EtCH=NOH, Me(*t*-Bu)C=NOH, and camphor oxime in Table 2.

Bond lengths and angles of some optimized oximes and iminoxyl radicals are listed in Table 9. Oximes with dipolar substituents on the azomethine carbon are not involved here for their dipole$-$dipole interactions would distract us from the examination of steric effects.

It is noteworthy that the dihedral angles *D*(RCNO) and *D*(R′CNO) are within 5° for all oximes and iminoxy radicals optimized in this work, which is in agreement with Ingold et al.[40] Again, it strongly refutes the "perpendicular" structure of iminoxyl radicals,[43] which requires a 90° dihedral angle instead.

We can see that while in the parent the oximes angles around the sp^2-hydridized carbon atom ($\angle$(RCN), $\angle$(R′CN), and $\angle$(RCR′)) significantly deviate from the regular value of 120° mainly due to the steric repulsion between R and R′ groups, in corresponding iminoxyl radicals, these angles become much closer to 120°. Clearly, O$-$H bond cleavage relieves such steric strain. From Table 9, differences in $\angle$(RCN), $\angle$(R′CN), and $\angle$(RCR′) between oxime/iminoxyl radical pairs for symmetric ketoximes (R$_2$C=NOH) increase as the R group increases from Me to *t*-Bu, which indicates progressively greater relief of steric strain in company with the O$-$H bond dissociation as the R group grows more bulky. The increased steric relief aptly illustrates the decreasing O$-$H BDEs. Bordwell's earlier explanation of steric effects in alkyl oxime O$-$H BDEs is sound on the new basis of theoretical values.



A similar phenomenon can be seen between E/Z pairs for methyl phenyl ketoxime and methyl *tert*-butyl ketoxime. The smaller O$-$H BDEs of the Z isomers of these ketoximes can be attributed to the larger relief of steric strain that happens during its homolytic bond dissociation. The conclusion of

TABLE 9: Bond Lengths (Å) and Bond Angles (deg) of Optimized Structures in Selected Oximes and Their Iminoxyl Radicals[a]

R	R′	*r*(R−C)	*r*(R′−C)	*r*(C═N)	*r*(N−O)	*r*(O−H)	∠(RCN)	∠(R′CN)	∠(CNO)	∠(RCR′)	*D*(RCNO)	*D*(R′CNO)
Me	Me	1.507	1.504	1.282	1.415	0.970	123.861	116.396	111.088	119.743	0.0000	0.0000
		1.508	*1.503*	*1.286*	*1.239*		*121.368*	*118.490*	*133.673*	*120.142*	*0.0000*	*0.0000*
		(0.001)	*(−0.001)*	*(0.004)*	*(−0.176)*		*(−2.493)*	*(2.094)*	*(22.585)*	*(0.399)*		
Et	Et	1.512	1.512	1.283	1.418	0.969	124.564	115.645	111.743	119.781	1.2048	0.0176
		1.517	*1.508*	*1.287*	*1.242*		*119.566*	*118.447*	*132.410*	*121.977*	*1.4536*	*0.3391*
		(0.005)	*(−0.004)*	*(0.004)*	*(−0.176)*		*(−4.998)*	*(2.802)*	*(20.667)*	*(2.196)*		
i-Pr	*i*-Pr	1.521	1.531	1.282	1.416	0.969	125.112	114.765	113.430	120.122	0.0132	0.0168
		1.527	*1.524*	*1.286*	*1.240*		*119.972*	*117.708*	*134.434*	*122.320*	*0.4462*	*0.4599*
		(0.006)	*(−0.007)*	*(0.004)*	*(−0.176)*		*(−5.140)*	*(2.943)*	*(21.004)*	*(2.198)*		
t-Bu	*t*-Bu	1.558	1.558	1.287	1.413	0.970	123.407	110.679	116.172	125.823	0.1250	3.415
		1.561	*1.545*	*1.289*	*1.239*		*116.617*	*114.293*	*135.854*	*128.942*	*0.5613*	*3.462*
		(0.003)	*(−0.013)*	*(0.002)*	*(−0.174)*		*(−6.790)*	*(3.614)*	*(19.682)*	*(3.119)*		
Me	*t*-Bu	1.510	1.531	1.282	1.416	0.970	122.206	117.010	111.388	120.785	0.0000	0.0047
		1.513	*1.527*	*1.287*	*1.240*		*118.872*	*118.897*	*132.984*	*122.224*	*1.2332*	*0.2560*
		(0.003)	*(−0.004)*	*(0.005)*	*(−0.176)*		*(−3.334)*	*(1.887)*	*(21.596)*	*(1.439)*		
t-Bu	Me	1.542	1.513	1.285	1.416	0.969	127.017	112.360	114.352	120.623	0.0082	0.0042
		1.544	*1.507*	*1.287*	*1.242*		*120.158*	*116.401*	*134.220*	*123.441*	*0.0033*	*0.0095*
		(0.002)	*(−0.006)*	*(0.002)*	*(−0.174)*		*(−6.859)*	*(4.041)*	*(19.868)*	*(2.818)*		
Me	Ph	1.508	1.487	1.288	1.404	0.970	124.060	115.988	113.076	119.951	0.0928	0.0698
		1.511	*1.475*	*1.294*	*1.235*		*119.575*	*118.301*	*133.634*	*122.124*	*0.0175*	*0.0000*
		(0.003)	*(−0.012)*	*(0.006)*	*(−0.169)*		*(−4.485)*	*(2.313)*	*(20.558)*	*(2.173)*		
Ph	Me	1.488	1.514	1.289	1.407	0.970	128.236	113.045	114.369	118.719	2.0361	1.8649
		1.478	*1.508*	*1.295*	*1.236*		*122.748*	*115.619*	*135.058*	*121.633*	*0.0128*	*0.0292*
		(−0.010)	*(−0.006)*	*(0.006)*	*(−0.171)*		*(−5.488)*	*(2.574)*	*(20.689)*	*(2.914)*		
Ph	Ph	1.493	1.490	1.291	1.403	0.970	125.156	115.073	113.344	119.770	2.2136	2.5272
		1.486	*1.486*	*1.299*	*1.235*		*121.279*	*115.648*	*134.477*	*123.072*	*0.4906*	*0.7348*
		(−0.007)	*(−0.004)*	*(−0.008)*	*(−0.168)*		*(−3.877)*	*(0.575)*	*(21.133)*	*(3.302)*		

[a] Values in italics correspond to the iminoxyl radical of the oxime right above it, and differences in structural parameters of the iminoxyl radical from the corresponding oxime are given in parentheses

Bordwell et al. in their 1992 work that "*anti*-benzaldoximes (E isomers) were found to have BDEs 2 kcal/mol lower than for *syn*-benzaldoximes (Z isomers)"[42] now seems problematic. According to our calculated results (ONIOM-G3B3 level), conversely, *E*-benzaldoximes constantly have BDEs 3.6 ± 0.1 kcal/mol higher than those of the Z isomers. While our results fit well with the general isomeric effects on O−H BDEs in oximes observed in the current work, Bordwell's conclusion is built on a problematic basis, that is, their questionable measurement of redox potentials for *Z*-benzaldoximes. Previous calculation[64] shows these experimental redox potentials differ from our high-accuracy theoretical values by over 0.3 V, which significantly affects the accuracy of BDE values and, in turn, leads to the questionable conclusions.

Moreover, while the 6.8 kcal/mol decrease of the O−H BDE in the benzophenone oxime from that in acetone oxime according to the EC measurement was attributed to the single-electron delocalization as described by eq 9,[43] this difference is now revised to only 3.9 kcal/mol by our ONIOM-G3B3 calculation. For the σ-structure of aryl-substituted iminoxyl radicals confirmed by the spin density study above, we consider that the steric effects instead would properly explain this trend in oxime O−H BDEs.

3.6. Remote-Substituent Effects on O−H BDEs in Oximes. To depict a complete image of the remote substituent effects on the O−H BDEs in p-substituted benzaldoximes (p-GC$_6$H$_4$-CH═NOH), some oximes that have been synthesized but not covered by the EC measurement are also investigated in our present work. These G groups include F, NH$_2$, NMe$_2$, and OH. For consistency, discussion of remote substituent effects on O−H BDEs are based on their DFT values. However, it is noteworthy that ONIOM-G3B3 BDEs give the same trends as those calculated at the DFT level. O−H BDEs of all the p-substituted benzaldoximes (p-GC$_6$H$_4$CH═NOH) and methyl p-substituted ketoximes (p-GC$_6$H$_4$C(Me)═NOH) are plotted in Figure 4.

Figure 4 shows that changes of para substituents have little effect on the BDEs of benzaldoximes and phenyl methyl ketoximes. According to the existence of a methyl on the azomethine carbon and geometrical isomerism, these oximes can be clearly divided into four groups regardless of different remote substituents. For each series, the O−H BDEs remain almost constant. To be specific, O−H BDEs in *Z*-benzaldoximes vary from 84.0 to 84.4 kcal/mol, while this range for corresponding E isomers is from 80.7 to 81.1. P-substituted phenyl methyl ketoximes show strikingly similar behavior as that of benzaldoximes with the BDE range from 79.4 to 80.7 kcal/mol and from 82.9 to 83.4 kcal/mol for Z and E isomers, respectively.

Although significant differences exist between our calculated BDEs and the EC measurement, they show similar remote-substituent effects. Compared to the large substituent effects observed in p-substituted phenols,[82] Bordwell et al. believed the negligible para-substituent effects on BDEs in the p-GC$_6$H$_4$-CH═NOH and p-GC$_6$H$_4$C(Me)═NOH series were due to the long distance between substituents and the radical center.[45] While this explanation works on the field and inductive effects of substituents, which decrease significantly with increasing distance, we consider the σ-structure of aryl-substituted iminoxyl radicals another important reason. According to the σ-structure, the unpaired electron is in an orbital lying in the plane of the radical framework, so that little delocalization of the single electron into π-electron clouds above Ph ring happens. This probably results in little resonance effects of para substituents and, in turn, constant O−H BDEs as the para substituent varies.

4. Conclusions

In the present study, we carried out a high-accuracy ONIOM-G3B3 calculation for O−H BDEs of 58 oximes. It was found that most of the experimental BDEs given by the EC method

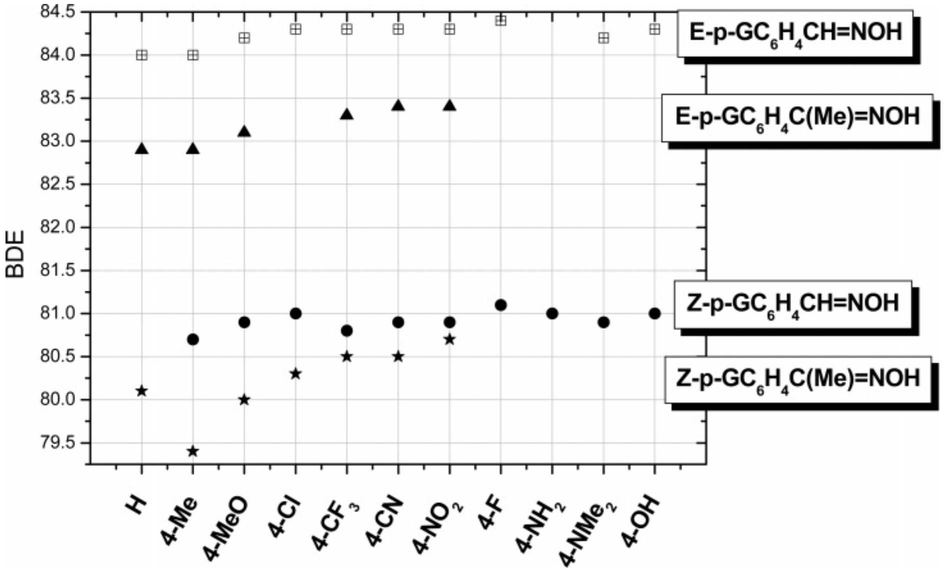


Figure 4. O−H BDEs in *p*-$GC_6H_4CH{=}NOH$ and *p*-$GC_6H_4C(Me){=}NOH$.

were problematic possibly due to errors in the measurement of pK_a's and redox potential values. On the other hand, the O−H BDEs in eight oximes given by calorimetric measurement or the TR method were verified to be reliable. Against a set of reference oximes with confirmed experimental O−H BDEs, several DFT functionals were benchmarked, among which the ROBHandHLYP model was found to give the best performance with an error bar of 0.7 kcal/mol. Systematic studies of O−H BDEs in over 140 oximes were then conducted with this DFT method.

A series of conclusions drawn on the basis of the questionable EC BDEs were re-examined. Two of the earlier conclusions about substituent effects on oxime O−H BDEs were confirmed according to our theoretical BDEs. (1) Bulky substituents on the azomethine carbon decrease O−H bond strength because the homolytic O−H bond cleavage in these oximes can relieve the steric strain. (2) Para substituents do not show a significant remote-substituent effect on the O−H BDEs in benzaldoximes and phenyl methyl ketoximes.

However, contrary to the earlier conclusion that *E*-benzaldoximes have O−H BDEs 2 kcal/mol lower than those for *Z*-benzaldoximes, we found that BDEs of *E*-benzaldoximes are about 3.6 kcal/mol higher than those of Z isomers.

According to our optimized iminoxyl radical structures, the "perpendicular" framework for bulky alkyl iminoxyl radicals proved to be problematic. The π-structure of aryl-substituted iminoxyl radicals was refuted by a study of spin distribution on heavy atoms. While amino-substituted iminoxyl radicals show a π-behavior, all the other iminoxyl radicals under investigation are of the σ-type.

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Supporting Information Available: Calculated single-point energies of radicals and molecules with different DFTs are shown in Table S1−3. Calculated BDEs with corrected TCE are given in Tables S4 and S5. This material is available free of charge via the Internet at http://pubs.acs.org.

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