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Theoretical Study of X−H Bond Energetics (X = C, N, O, S): Application to Substituent Effects, Gas Phase Acidities, and Redox Potentials

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Bond dissociation energies, electron affinities, and proton affinities are computed for a variety of molecules containing C−H, N−H, O−H, and S−H bonds using density functional theory with the B3LYP functional. Thermochemistry in which these bonds are broken or ions are formed is particularly relevant to understanding proton transfer (acid−base), electron transfer (redox), and H-atom transfer (free radical) reactions. A series of basis set experiments has led to an optimum compromise between computational speed and accuracy. Several theoretical models are defined and tested, and the medium and higher-level models approach an accuracy of 1 kcal/mol. Use of the above methodology to obtain absolute bond dissociation energies for X−H bonds, isodesmic reaction schemes, substituent effects, redox potentials, and gas-phase acid dissociation constants shows the usefulness of this approach.

1. Introduction

Most biochemical reactions involve relatively small energy changes. This principle is axiomatic because large energy changes cannot be utilized by the cell and will lead to disruption of cellular processes or cell death.[1] Therefore biochemical reactions in which a bond is broken are invariably coupled to those in which a new bond is formed, as in steps in the respiratory chain where dioxygen is reduced in a stepwise fashion to water and ATP is generated in the various steps.

Many such reactions involve changes in single bonds to hydrogen, especially those involving C−H, N−H, O−H, and S−H. This includes proton-transfer reactions, where lone pairs of electrons on the basic atoms N, O, and S are protonated, electron-transfer reactions involved in biological redox cycles, and free radical reactions involving transfer of a hydrogen atom. To give but one example, the respiratory “mistakes” which generate superoxide ion, peroxyl radicals, and hydrogen peroxide during the biological conversion of dioxygen into water lead to subsequent reactions which involve the transfer of hydrogen atoms (or H^+,e^-) between reactive oxygen species and hydrogen/electron donors such as ascorbate (O−H bond), glutathione (S−H bond) and α-tocopherol (O−H bond). Highly reactive radicals such as hydroxyl can also oxidize N−H and C−H bonds, forming water and carbon-centered or nitrogen-centered free radicals.[2]

With recent advances in theoretical techniques we are now in a position to be able to calculate the thermochemistry for processes in which X−H bonds are made and broken, ideally with an accuracy approaching 1 kcal/mol in the gas phase. If the above is successful, relevance to organic chemistry in solution and to biochemistry in general must still consider solvent effects and even multiphase behavior (e.g. the membrane−solution interface) but these extensions will be less meaningful if gas-phase behavior cannot first be accurately determined.

In a recent paper on the thermochemistry of phenolic compounds related to vitamin E[3] we showed that the O−H bond dissociation energy (BDE) was significantly underestimated when using density functional theory (DFT) with the B3LYP functional[4,5] and standard basis sets. For example the BDE of the O−H bond in phenol itself was underestimated relative to the experimental value by 7.8, 10.2, and 4.5 kcal/mol for the 6-31G, 6-31G(d), and 6-31G(d,p) basis sets, respectively. Use of larger basis sets results in slow convergence toward experimental BDE’s, with the result that meaningful calculations on systems of biochemical interest containing 10 or more heavy (i.e. non-hydrogenic) centers becomes computationally very difficult. An alternative approach involving use of an unconventional basis set was suggested in our work as one way to obtain more accurate thermochemistry in phenolic systems.[3] The present paper adopts a somewhat different approach based on experience gained since that time, and we believe it will be more generally useful.

At the present time it is already possible to obtain accurate theoretical gas-phase thermochemistry, particularly when the same bond types are present in reactants and products (idodesmic reactions). The G2 method of Curtiss and co-workers[6,7] and its variants such as G2(MP2)[8] give heats of formation to within 2 kcal/mol for most systems but is much more computationally demanding than even large-basis DFT calculations. Use of the G2 method will continue to be impractical for large systems even given anticipated advances in computer technology, due to the high-order dependence of the QCISD component of the calculation on the number of basis functions. On the other hand, DFT methods scale much more favorably with size of basis set, particularly so with recent implementations of the method.[9,10] Given this situation it would be very desirable to develop a DFT-based approach capable of giving accurate thermochemical quantities while still using basis sets which are as compact as possible.

This area of research is undergoing intensive development, and there has already been considerable discussion in the literature of the results obtained using DFT methods. The subject is complicated by the wide variety of DFT functionals in use and their ongoing development, plus the necessity of testing a variety of basis sets for each functional. The original G2 test set of molecules was examined by Bauschlicher using five different DFT methods.[11] He found that the B3LYP functional

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TABLE 1: Bond Dissociation Energy (ΔH°_{298}) for H_2O Defined To Be Consistent with the Experimental Measurement of $H_2O \rightarrow OH + H$ at 298 K[a]

basis set	H°_{298} (H_2O)	H°_{298} (OH)	H°_{298} (H)	BDE
6-31G(d)	−76.38401	−75.71185	−0.49791	109.3
6-31+G(d)	−76.39770	−75.72190	−0.49791	111.6
6-311G(d,p)	−76.42236	−75.74280	−0.49980	112.8
6-311+G(2d,2p)	−76.43683	−75.75249	−0.49980	115.8
6-311++G(3df,3pd)	−76.43943	−75.75448	−0.49990	116.1

[a] Absolute enthalpy data are in hartree; relative enthalpy (BDE) in data are kcal/mol.

TABLE 2: B3LYP Bond Dissociation Energy (BDE) for Water at 298.15 K, Electron Affinity (EA) of OH at 0 K, and Proton Affinity (PA) of Water at 0 K, as a Function of Basis Set Size[a]

basis set	BDE	EA	PA
6-31G(d,p)	114.3	−1.7	171.6
6-31+G(d,p)	116.7	41.3	163.6
6-311+G(d,p)	117.4	41.7	162.9
6-311+G(2d,2p)	118.3	41.8	162.4
6-311++G(3df,3pd)	119.0	41.7	162.7
experiment	119.3 ± 0.05[b]	42.1 ± 0.001[c]	163.4[d]

[a] All values in kcal/mol. [b] Reference 38. [c] Drzaic, P. S.; Marks, J.; Brauman, J. I. In *Gas-Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1984; Vol. 3. [d] Szvlejko, J. E.; McMahon, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 7839.

was optimal but had a large average absolute deviation from experimental heats of formation *even when using large basis sets*. This is consistent with the results by Curtiss and coworkers,[7] who used the B3LYP functional with the 6-311+G(3df,2p) basis, i.e., the largest of the standard basis sets, and still obtained a relatively large average absolute deviation from experiment of 3.1 kcal/mol.

In the present paper we begin with a careful look at the thermochemistry of water. We focus on the treatment of its bond dissociation energy ($H_2O \rightarrow OH + H$) and then consider the electron affinity of hydroxyl radical ($OH + e^- \rightarrow OH^-$) and the proton affinity of water ($H_2O + H^+ \rightarrow H_3O^+$). This reaction serves as our "benchmark", and we experiment with our theoretical approach until we approach as closely as is feasible the target accuracy of 1 kcal/mol. Several calculation models are defined and then checked in a wider context, which include C−H, N−H, O−H, and S−H bonds, and shown to be generally useful. Finally, several applications of our methodology are included: the relationship to the approach using isodesmic reactions; determination of substituent effects in *para*-substituted phenols; the correlation of computed BDE's with standard reduction potentials; the calculation of gas-phase acidity constants. These applications illustrate that we not only are able to calculate accurate thermochemistry using traditional isodesmic approaches, with attendant error canellation, but are also able to *directly* obtain accurate BDE's as well as gas-phase p*K*'s.

The methodology described in this paper is applied only to the study of X−H bond energetics. The methodology is general, but because of the extraordinary importance of reactions involving the X−H bond (where X = C, N, O, S) in biochemistry, the present work is restricted to this subset of possible reactions. Within this subset we consider a number of different examples. In future work we will consider the extension of these methods to more general bonding situations.

2. Test Calculations on Water

Jursic and Martin[12] showed total electronic energies E_e for H_2O, OH, and H and the dissociation energy ΔE_e for HO−H $\rightarrow$ OH + H, using the B3LYP functional and a variety of basis sets. To compare with the gas-phase experimental value for water, the electronic energy must be corrected by including zero-point energy, translational, rotational, vibrational, and pressure−volume contributions to the enthalpy (described more fully in the next section).

Table 1 shows BDE's using the same basis sets as Jursic and Martin and the necessary zero-point and enthalpy corrections. These data were obtained using the GAUSSIAN 94 program.[13] Here $H^\circ_{298} = E_e + \mathrm{ZPE} + H_{\mathrm{trans}} + H_{\mathrm{rot}} + H_{\mathrm{vib}} + RT$, where $H_{\mathrm{trans}} = {}^3/_2RT$, $H_{\mathrm{rot}} = {}^3/_2RT$ (nonlinear) or RT (linear) and H_{vib} is given by standard formulas.[14] From this table it can be seen that all of the calculated BDE's lie *well below* the experimental value, even when using their largest 6-311++G(3df,3pd) basis. Furthermore, the series of basis sets shows the slow approach (from below) toward the experimental BDE, with the biggest basis giving a BDE which is still over 3 kcal/mol too low! From this exercise we conclude that the standard DFT/B3LYP approach cannot achieve a 1 kcal/mol accuracy level for the BDE of water, even in the limit of large basis sets. Indeed, the results of Curtiss et al.[7] show that bond dissociation energies using large basis B3LYP are underestimated for most systems. This indicates that some refinement of the theoretical procedure is necessary.

First, consider the energy of atomic hydrogen in the DFT calculation. From Jursic's data[12] the electronic energy of hydrogen is −0.500 27 for the 6-31G basis set, −0.502 16 for the 6-311G basis set, and −0.502 26 hartree for the 6-311++G data set, a point which was discussed by Becke in connection with testing various functional forms.[15] The hydrogen atom is unique in this respect in the context of density functional theory. We therefore introduce a correction factor and set the energy of atomic hydrogen to its exact value of −0.500 00 hartree. This correction to the thermochemistry amounts to an increase in the BDE of 0.002 16 hartree (1.36 kcal/mol) for the 6-311+G(2d,2p) basis in Table 1, since the atomic energy is −0.502 16 hartree. Note that the high-level correction of Pople et al.,[16] which is quite essential in the G2 method to obtain accurate thermochemistry, is a correction which depends on the number of electrons with α and β spins, so that this would apply even in the case of an isolated hydrogen atom. The G2 correction factors were originally established so as to obtain the exact energy of the H atom and the H_2 molecule.

The second factor in calculating the BDE for water is the choice of methodology for treating open shells. The usual procedure is to use an unrestricted Hartree−Fock (UHF) starting point to generate the DFT orbitals. However, the LYP functional was derived starting from a restricted open-shell Hartree−Fock (ROHF) formalism.[4] Similarly, the gradient correction for exchange in the B3LYP functional ($\Delta E_x^{\mathrm{B88}}$) was determined through the use of "spherically averaged" atomic orbitals which are restricted Hartree−Fock atomic wave functions.[17] Under the circumstances it seemed appropriate to test the calculation of the remaining exchange terms in the B3LYP functional (Hartree−Fock and Slater exchange) by using the ROHF starting MO's.[18]

Table 2 shows the calculated bond dissociation energy for water (BDE, 298.15 K), electron affinity of the OH radical (EA, 0 K) and proton affinity of water (PA, 0 K) as a function of basis set size. These data were calculated using the H-atom correction and the ROB3LYP method for the OH radical. Zero-point energies and vibrational enthalpy corrections were scaled by a factor 0.9806 as described in the next section, a correction which causes an increase in BDE of ca. 0.2 kcal/mol.

For this table, the progression of basis sets which we used is slightly different from that of Jursic and Martin.[12] As is well-known and obvious from the results, it is necessary to have diffuse (+) functions in the basis set in order to calculate electron affinities. Less obvious is that diffuse functions are also important to obtain a reasonable proton affinity; i.e., once they have been added all the basis sets in the table give comparable values for the PA. Similarly, the EA is well described once the diffuse functions have been added (all basis sets except the smallest). The one property remaining which discriminates between the various basis sets is the BDE. If we adopt 1 kcal/mol as a target accuracy in this most important property, it can be seen that only the two largest basis sets satisfy this criterion: 6-311+G(2d,2p) and 6-311++G(3df,3pd). Since they are of similar accuracy in EA and PA and the former is much more economical (27 vs 39 basis functions per carbon atom, 9 vs 21 basis functions per H atom), we adopt the former 6-311+G(2d,2p) basis as our standard basis.

The only problem with this choice is that the determination of geometries and particularly vibrational frequencies using the full (RO)B3LYP/6-311+G(2d,2p) method is extremely time-consuming for large molecules (e.g. more than 6 non-hydrogenic atoms). Further testing is therefore needed to obtain a faster but still reliable way to obtain optimized geometries and vibrational frequencies, while performing higher-level single-point energy calculations at the specified geometry. Many such computational experiments of this type have been described in the literature[19] and can be used as a guide. Our own approach is described in the next section.

3. Method of Calculation

A series of 15 molecules involving C−H, N−H, O−H, and S−H bonds were tested. The program GAUSSIAN 94 was used for most of the calculations described in this paper. First, optimized geometries and vibration frequencies for neutral molecules, anions, and cations were obtained using one of several procedures. Appropriate scale factors were applied to the frequencies to make the necessary zero-point and enthalpy corrections necessary to obtain H°_{298}. DFT calculations were carried out at the optimized geometries using the B3LYP functional[20] and a 6-311+G(2d,2p) basis set. The ROB3LYP method was used for open shells. The energy of the H atom was set equal to −0.500 00 hartree.

Four different methods were used to obtain the geometries and frequencies, defining the various theoretical models. In the low-level model (LLM), the semiempirical AM1 method[21,22] was used to obtain the geometry and frequencies.[23,24] Following the careful study of Scott and Radom,[25] for each model separate scale factors were applied to the vibrational frequencies to obtain the zero-point energy (ZPE) and the vibrational enthalpy correction H_{vib}. These scale factors were determined from test sets of molecules to give optimum agreement with experimental ZPE's and experimental enthalpy corrections. Separate scale factors are necessary since the ZPE is more dependent on the high-frequency vibrations, while the enthalpy correction, which contains $\exp(h\nu/kT)$ in the denominator, is more sensitive to the low-frequency modes. For the AM1 method, Scott and Radom (hereafter SR) give a scale factor 0.9532 for scaling AM1 harmonic frequencies but do not give any further data. Since ZPE's typically have a higher scale factor by ca. 0.02 in their compilation than do total frequencies,[25] we used a scale factor of 0.973 for AM1 ZPE's and retained 0.9532 for the (much less important) enthalpy correction. These values are close to the factor 0.947 used to scale frequencies in our work on phenolic compounds.[3] The single-point energy//geometry/frequency calculation for the LLM is then denoted (RO)B3LYP/6-311+G(2d,2p)//AM1/AM1, where it is understood that open shells are treated by using ROB3LYP. The LLM is computationally feasible for relatively large molecules (20 or more heavy atoms depending on the power of the workstation) since the determination of the geometry and frequencies is rapid using AM1.

The first medium-level model (MLM1) uses the MP2(full)/6-31G(d) method to obtain the optimized geometry at which the single-point DFT energy is determined. The geometry optimization is now much more time-consuming than using AM1 but also generally more accurate, particularly for systems involving O−O and S−S bonds. The geometry is then reoptimized using a (U)HF-6-31G(d) level of theory, and the vibration frequencies are obtained at the HF minimum. As described by SR, ZPE's are scaled by 0.9135 and vibrational enthalpy corrections by 0.8905. Note that this corresponds closely to the G2 prescription for geometry/frequency, which uses MP2(full)/6-31G(d) geometries and HF/6-31G(d) frequencies but with a single scale factor 0.8925. The MLM1 is denoted (RO)B3LYP/6-311+G(2d,2p)//(U)MP2(fu)/6-31G(d)/(U)HF/6-31G(d). The method can still be applied to relatively large molecules, i.e., up to ca. 15 heavy atoms, since the frequency determination is fast using analytical gradient procedures in GAUSSIAN 94. A similar "hybrid" method for obtaining heats of formation was also described by Smith and Radom.[26]

An alternative and more self-consistent medium level model, designated medium-level model 2 (MLM2), determines the geometry and vibrational frequencies using the same B3LYP/6-31G(d) procedure. This avoids possible situations which are occasionally encountered where the MP2 and HF minima correspond to different conformations, so that the relevance of the HF frequencies becomes questionable. The B3LYP/6-31G(d) calculation of open-shell systems (for geometry and frequencies) is now carried out using the (default) UHF starting orbitals, which leads to faster determination of vibrational frequencies than obtained with ROHF orbitals.[27] As recommended by SR the ZPE's are scaled by 0.9806 and the vibrational enthalpy corrections by 0.9989. The scaled DFT frequencies are considered very reliable and somewhat better than scaled HF frequencies (SR). This model is denoted (RO)B3LYP/6-311+G(2d,2p)//B3LYP/B3LYP/6-31G(d). With GAUSSIAN 94, geometry optimizations and especially frequency calculations are much more time-consuming than with MLM1. However, with the advent of low-order scaling DFT programs this model will become increasingly feasible as the computational power increases.

Finally, a high-level model (HLM) is similar to that used in the previous section except that both geometry and frequencies were obtained using the B3LYP method with the 6-311+G(2d,2p) basis, and open-shell calculations were treated with ROB3LYP. Again, ZPE's were scaled by 0.9806 and enthalpy corrections by 0.9989 since the DFT scale factors are relatively invariant to basis set.[25] The HLM is denoted (RO)B3LYP/(RO)B3LYP//(RO)B3LYP/6-311+G(2d,2p), where the same basis set is used throughout.

Some additional comments are needed to fully define the procedure. Each model begins by obtaining the geometry and vibrational frequencies. For parent molecule RH and radical R we add $^3/_2RT$ for translation and rotation (nonlinear molecule) and an additional RT to convert from energy to enthalpy (PV term). The vibrational contribution to the enthalpy requires a more careful treatment, since low-frequency torsional modes

TABLE 3: Bond Dissociation Energy ΔH°_{298} for the Indicated Bond (in kcal/mol), as a Function of the Level of Model[a]

bond	LLM	MLM1	MLM2	HLM	G2[b]	expt
HO−H	119.2	118.3	118.3	118.3	119.2	119.3 ± 0.05[c]
HS−H	90.9	91.3	91.3	91.4	91.4	91.2 ± 0.7[d]
H_2N−H	108.5	107.5	107.4	107.6	107.9	108.2 ± 0.3[e]
Me−H	105.5	105.5	105.5	105.8	105.8	104.9 ± 0.1[g]
EtO−H	103.4	102.5	103.0	102.7	107.0	104.6 ± 0.8[h]
EtS−H	89.7	86.4	86.2	86.5	87.3[f]	87.3 ± 0.6[d,e]
MeNH−H	100.2	99.0	98.8	98.9	100.7	100.0 ± 2.5[d]
Et−H	101.0	101.1	101.0	101.0	102.6	101.1 ± 0.4[c]
ArO−H	87.1	86.8	*i*	*i*	*i*	87.3 ± 1.0[g]
ArS−H	80.7	79.1	*i*	*i*	*i*	79.1 ± 2.0[h]
ArNH−H	92.0	91.3	*i*	*i*	*i*	92.3 ± 2.0[j]
$ArCH_2$−H	89.3	89.7	*i*	*i*	*i*	88.5 ± 1.5[c]
HOO−H	91.0	85.4	85.8	85.8	87.8	88. 2 ± 1.0[d]
HSS−H	78.7	73.1	73.2	73.2	74.2	70.0 ± 1.5[k]
H_2NNH−H	76.9	81.2	81.5	81.4	83.5	82.2 ± 0.3[l]

[a] Abbreviations: Me = methyl, Et = ethyl, Ar = phenyl, LLM = low-level model, MLM1 = first medium-level model, MLM2 = second medium-level model, HLM = high-level model (see text for fuller definitions). [b] Taken from ref 7 or computed in this work. [c] Reference 38. [d] Reference 43. [e] Value in the literature is for MeS−H; should be close to EtS−H. [f] Value for MeS−H. [g] Wayner, D. D. M.; Lusztyk, E.; Pagé, D.; Ingold, K. U.; Mulder, P.; Laarhoven, L. J. J.; Aldrich, H. S. *J. Am. Chem. Soc.* **1995**, *117*, 8737. [h] Bordwell, F. G.; Zhang, X.-M.; Satish, A. V.; Cheng, J.-P. *J. Am. Chem. Soc.* **1994,** *116*, 6605. [i] Not calculated due to excessive requirement in computer time (>2 days on Sun UltraSparc 1 WorkStation). [j] Bordwell, F. G.;Zhang, X.-M.; Cheng, J.-P. *J.Org.Chem.* **1993**, *58*, 6410. [k] McMillen, D. F.; Golden, D. M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 493. [l] Corrected to 298 K from the BDE at 0 K reported in ref 38.

TABLE 4: Electron Affinity at 0 K (in kcal/mol) Obtained Using the Various Models (Definitions in Table 3)

radical	LLM	MLM1	MLM2	HLM	G2[a]	expt[b]
HO	41.9	42.0	41.9	41.8	43.1	42.1 ± 0.001
HS	54.5	54.8	54.8	54.7	53.0	53.4 ± 0.1
H_2N	17.4	17.1	16.8	16.9	17.8	17.2 ± 0.5
H_3C	0.1	1.3	1.0	2.7	0.9	1.8 ± 0.7
EtO	38.8	38.3	38.5	39.0	41.7	39.8 ± 0.8
EtS	46.9	44.7	44.7	44.7	45.2	45.0 ± 0.1
MeNH	9.9	9.7	9.2	10.2	11.0	
ArO	51.5	52.3				52.0
ArS	53.5	53.4				57.0 ± 1.4
ArNH	36.8	37.4				39.2 ± 0.7
$ArCH_2$	19.9	21.7				20.3 ± 0.2
HOO	16.2	24.5	24.7	24.7	25.6	24.9 ± 0.2
HSS	47.9	44.2	44.2	44.1	44.1	

[a] Computed in this work or taken from: Curtiss, L. A.; Redfern, P. C.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.*, **1998**, *109*, 42. [b] See Table 2, footnote *b*. [c] Oakes, J. M.; Harding, L. B.; Ellison, G. B. *J. Chem. Phys.* **1985**, *83*, 5400.

TABLE 5: Proton Affinity at 0 K (in kcal/mol), Calculated Using the Different Models (Definitions in Text)

molecule	LLM	MLM1	MLM2	HLM	G2[a]	expt[b]
H_2O	162.4	162.6	162.5	162.5	163.1	163.4[b]
H_2S	170.5	167.5	167.9	168.3	167.7	168.8
NH_3	203.2	202.0	202.1	201.9	202.5	202.5
EtOH	184.4	185.0	185.0	184.8	184.2	184.3
EtSH	188.5	188.5	188.2	189.2	187.5	189.3
$MeNH_2$	214.0	213.5	213.4	213.3	213.9	213.7
ArOH	176.2	177.5				176.1
ArSH	184.1	188.7				186.3
$ArNH_2$	209.0	209.1				208.0

[a] From ref 6 or computed in this work. [b] Experimental data from ref 44, corrected to 0 K, unless otherwise noted. [c] Szulejko, J. E.; McMahon, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 7839 (corrected to 0 K).

can make a significant contribution. Following SR we visually examine (scaled) modes below 260 cm^{-1} to see whether they represent torsional motions. At this point a "crossover" to the classical rotational limit ${}^1/_2RT$ occurs, so that all (scaled) torsional modes below 260 cm^{-1} are replaced by this value. The remaining (scaled) modes are used in the usual enthalpy correction, giving the final expression $H^\circ_{298} = E_e + \text{ZPE} + {}^3/_2RT + {}^3/_2RT + H_{vib} + RT = E^\circ_0 + 4RT + H_{vib}$. Since the H atom has no rotational or vibrational contribution, the expression for the enthalpy change for a reaction which produces a hydrogen atom from nonlinear RH and nonlinear R (i.e. for RH → R + H) is $\Delta H^\circ_{298} = \Delta E^\circ_0 + \Delta H_{vib} + {}^3/_2RT$, where the ΔE°_0 term contains the scaled ZPE correction to the electronic energy E_e for RH and R (first scale factor) and H_{vib} contains the scaled vibrational enthalpy correction (second scale factor).

4. Results and Discussion

4.1. BDE, EA, and PA. Our test set of C−H, N−H, O−H, and S−H bonds includes the categories of simple inorganic hydrides, alkyl hydrides, aromatic hydrides, and hydrides containing strong lone-pair interactions (H_2O_2, H_2S_2, N_2H_4). The data are grouped according to these categories in Tables 3−5. Table 3 shows bond dissociation energies (at 298.15 K) for the test set as a function of the level of model, with the computational expense increasing from left to right in the table. Table 4 shows the electron affinity of the radical at 0 K, and Table 5 shows the proton affinity of the neutral molecule, also at 0 K. Fewer entries are given in Tables 4 and 5, due to the lack of experimental data available for comparison, to the formation of unstable species (e.g. $C_2H_5^-$, where the electron is unbound) or to the formation of high-energy species (e.g. $C_2H_7^+$). For comparison, G2 values[6,7] are also included in Tables 3−5.

Since all theoretical models use the same evaluation of the total energy, i.e., (RO)B3LYP/6-311+G(2d,2p), it is most relevant to compare the lower-level theoretical results to those obtained using the high-level model. Discrepancies then occur because of different optimum geometries, different (scaled) vibrational frequencies, and/or different (scaled) vibrational enthalpy corrections, the latter being almost insignificant. Since the HLM geometries are in very good agreement with experimental values, in general (bond distances ≤ 0.01 Å, angles ≤ 1°), the most serious differences occur because of errors in the optimized geometries for the lower-level models. Let us now consider the quality of the results according to different groupings of the molecules.

Simple Hydrides (H_2O, H_2S, NH_3, CH_4). BDE's for the medium-level models MLM1 and MLM2 are in good agreement with the BDE values obtained with the HLM, the differences being less than 0.4 kcal/mol (Table 3). The LLM values show more scatter, up to 1.0 kcal/mol. Note however that the LLM values are in agreement with the experimental values to within about 1.0 kcal/mol. Electron affinities obtained with the MLP's also agree well with the HLM (Table 4), except for the case of methyl radical which shows more scatter. Analysis of the discrepancy in the case of methyl showed that the HLM geometry of the methyl anion is more pyramidal, the MLM geometries being somewhat too flattened (but still nonplanar). Addition of a set of diffuse functions to the MLM2, i.e., repeating the calculation using B3LYP/6-31+G(d), led to an electron affinity of 2.7 kcal/mol in agreement with the HLM, i.e., the diffuse functions in the smaller basis caused a geometry change so that the optimum geometry was in essentially perfect agreement with the high-level model. This increases the cost of the geometry/frequency calculation but might be considered as an alternative to MLM2 when higher accuracy is required, e.g. for radicals and anions. The AM1 geometry is even worse for CH_3, resulting in an EA of 0.1 kcal/mol, which is outside the 1 kcal/mol level for deviation from either HLM or experiment. Proton affinities for H_2O, H_2S, and NH_3 (Table 5) show that the PA for water is fairly consistently treated using all the models, with an error less than or equal to 1 kcal/mol relative to the most recent experimental value. The results for H_2S and NH_3 are quite close ($\leq$1 kcal/mol) except for the LLM, which shows a deviation of 2.2 and 1.3 kcal/mol, respectively, from the HLM. However, the LLM results compare more favorably to the experimental values.

Alkylated Hydrides (EtOH, EtSH, MeNH$_2$, EtH). BDE's deviate by up to 1.5 kcal/mol between the HLM and the experimental values, the largest deviation occurring for ethanol. Again, good consistency is obtained among MLM1, MLM2, and HLM. For EtSH (ethanethiol) the LLM deviates by 3.2 kcal/mol from the HLM value and by 2.7 kcal/mol from experiment, indicating a problematic treatment of the molecular geometry involving sulfur.[23]

Electron affinities for EtO and EtS are in very good agreement with experimental values, with LLM again showing the most error for sulfur. The EA for ethyl radical has not been given since it is (correctly calculated to be) negative, whereas experimental data for CH_3NH are not available for comparison. Proton affinities for this group (excluding ethane) show very good agreement between the HLM and experiment ($\leq$0.5 kcal/mol) and good consistency among all the models.

Phenyl-Substituted Hydrides (ArOH, ArSH, ArNH$_2$, ArCH$_3$). Due to the computational expense, only the LLM and MLM1 were calculated for this set of molecules. The MLM1 results show excellent agreement with experiment for the BDE values ($\leq$1.0 kcal/mol). The LLM values are also very good. EA's show slightly larger scatter. The MLM1 values deviate from experiment by almost 4 kcal/mol for thiophenol (note, however, the large experimental error bar). Proton affinities are actually treated better by LLM than by MLM1. Overall (but less so for sulfur), the reasonably good agreement between use of LLM and MLM1 in these molecules helps to explain our good results in earlier work using AM1 geometries and frequencies for vitamin E analogues[3] and gives grounds for optimizm in use of the lowest-level models for large molecules (which is usually the only practical alternative).

Hydrides with Strong Lone-Pair Interactions (H$_2$O$_2$, H$_2$S$_2$, N$_2$H$_4$). There is good consistency in BDE among MLM1, MLM2, and HLM, although the BDE for hydrogen peroxide differs from the experimental value by 2.4 kcal/mol. Wider discrepancies are observed for the LLM values of the BDE. This was traced to the incorrect geometries predicted by the AM1 calculation for the starting geometries of all three compounds: in the case of hydrogen peroxide, the optimized AM1 O−O distance is only 1.30 Å instead of the correct value 1.46 Å! This appears to be due to an incorrect handling of the lone pair−lone pair interactions and is obviously a major problem for the AM1 method. It also shows up dramatically in the EA's, where the LLM results are poor. The three other models give consistent results, which are in good agreement with the most recent experimental value. Proton affinities have not been measured for these species and were not calculated.

Considering all results from Tables 3−5 shows that for the most part there is good consistency between the two medium-level models. This is a fortunate result since the MP2 geometry/HF frequency calculation (MLM1 prescription) is much faster the B3LYP/6-31G(d) geometry/frequency determination (MLM2 calculation). In general, the MLM1 model gives results almost as good as using the full HLM, the only significant deviation between the two (i.e. $\geq$0.5 kcal/mol) occurring in the case of the methyl anion, whose potential surface is very sensitive to the choice of basis set, particularly the presence of diffuse functions. The LLM results are also rather good for CH, NH, and OH BDE's, although they show larger deviations for SH bonds. More severe difficulty is encountered using the LLM for the peroxide OH and disulfide SH bonds and for the NH bond in hydrazine. Here the biggest problem is in the AM1 geometry determination where lone-pair repulsions are important.

Next, consider the comparison of BDE, EA, and PA values obtained using our methods with the G2 values of Curtiss et al.[6,7] The G2 values for the BDE's (Table 3) are generally within 1 kcal/mol, except for EtOH, and are slightly better than the HLM values. For electron affinities, however (Table 4), the G2 values show larger errors than the HLM values. In Table 5 the G2 proton affinities are slightly better than the HLM values; both are within 1 kcal/mol of experiment except for the G2 value for EtSH. Since the medium-level models are both close to the HLM, this shows that the methods given here are competitive with the well-established G2 method for this class of molecules. At the same time, the DFT energy calculation scales more favorably than that of the G2 calculation, making the methods given in this paper applicable to larger molecules.

4.2. Isodesmic Reactions. The usual approach to calculating thermochemistry where bonds are broken is to perform an indirect calculation such that the maximum cancellation of errors occurs. Thus instead of calculating the enthalpy change directly for ROH → RO + H, where for example RO is an alkoxyl radical, the enthalpy change is calculated for ROH + OH → RO + HOH. Using this approach a relative scale of BDE's can be set up using thermochemical cycles. Thus if we have

$$\mathrm{ROH} \rightarrow \mathrm{RO} + \mathrm{H} \qquad (1)$$

$$\mathrm{OH} + \mathrm{H} \rightarrow \mathrm{HOH} \qquad (2)$$

$$\text{net:}\quad \mathrm{ROH} + \mathrm{OH} \rightarrow \mathrm{RO} + \mathrm{HOH} \qquad (3)$$

then consideration of the above shows that the energy of the H atom, which is not well treated in the DFT calculation, completely cancels out. The (U)B3LYP calculation on RO and OH will also lead to partial cancellation of error, so that the restricted open-shell (RO)B3LYP calculation plays a less important role in arriving at the correct overall enthalpy change. Finally, a BDE scale can still be constructed if the HOH BDE (reverse of eq 2) is assigned a reference value, e.g. the experimental value of 119.3 kcal/mol, rather than the (low) calculated DFT value (see Table 1 results for standard DFT approach, with errors greater than 3 kcal/mol). In that case the BDE of ROH can be obtained from eq 3 − eq 2, and a scale of *relative* BDE's can be established.

Using the experimental value 119.3 kcal/mol for the BDE of water, and the highest-level model calculations of H°_{298} available from our data which led to Table 3, gives a set of BDE's relative to water, obtained from our calculations. These are shown in Table 6. We note that, for the LLM, BDEs relative to water would be vitually unchanged since the water BDE is calculated to be only 0.1 kcal/mol below the experimental value. Furthermore, MLM1 and MLM2 BDEs are sufficiently close the HLM results so as to make their inclusion in Table 6 redundant. Inspection of Table 6 shows that for the conventional bonding situations (no lone-pair−lone-pair interactions) the BDE's are in very good agreement with experiment, with all

TABLE 6: BDE's (in kcal/mol) Obtained from Highest-Level H°_{298} Data (Table 3) and the Reaction Scheme RX−H + OH → RX + HOH, Using the Experimental BDE for Water (See Text)

bond	BDE(calcd)	BDE(expt)[a]
HO−H	119.3[b]	119.3
HS−H	92.4	91.2
H_2N−H	108.6	108.2
H_3C−H	106.8	104.9
EtO−H	103.7	104.6
EtS−H	87.5	87.0
MeNH−H	99.9	100.0
Et−H	102.0	101.1
ArO−H	87.8	87.3
ArS−H	80.1	79.1
ArNH−H	92.3	92.3
$ArCH_2$−H	90.7	90.0
HOO−H	86.8	88.2
HSS−H	74.2	70.0
H_2NNH−H	82.4	80.8

[a] Experimental data shown in Table 3. [b] Reference value for BDE table, adjusted to experimental value for water.

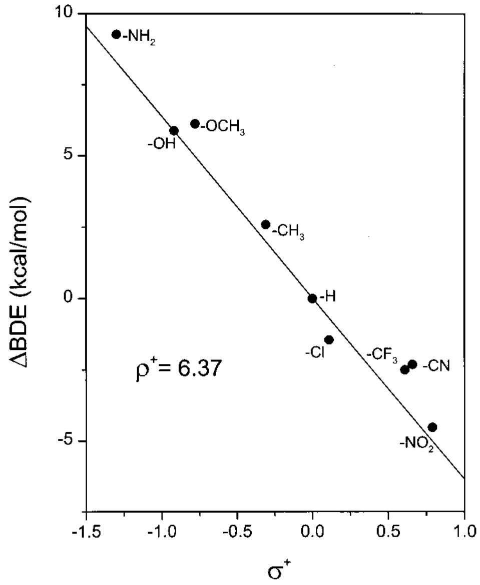

Figure 1. Hammett plot for *para*-substituted phenols using the low-level model (see text for model definitions).

data being within about 1 kcal/mol except for methane, which is in error by almost 2 kcal/mol. The only large error (4.2 kcal/mol) is for HSS−H, again suggesting that the 6-311+G(2d,2p) basis is inadequate for describing sulfur−sulfur interactions (in HSS) and should be increased in size.

This example shows that the error cancellation common to isodesmic schemes will also occur in the present case. A very significant difference, however, is that our method is capable of giving accurate absolute BDE's as well as relative BDE's; i.e., we do not need to incorporate experimental data in order to arrive at a very useful table of BDE's. This has the advantage that as experimental data undergo revision, we do not need to perform continuous updates to our table of X−H BDE's.

4.3. Substituent Effects. A second example using the isodesmic scheme is calculation of substituent effects on the O−H BDE of *para*-substituted phenols. Here we take BDE($H-C_6H_4O-H$) as our zero and calculate a ΔBDE using the LLM approach for various $X-C_6H_4O-H$ species. The results are illustrated in Figure 1 as a Hammett plot. As can be seen from the figure, there is an excellent correlation (correlation coefficient 0.971) between calculated ΔBDE values and the corresponding σ^+ constants.[28] A ρ^+ value of 6.37 kcal/mol is seen to be in fairly good agreement with the experimentally determined value of 7.3 kcal/mol.[29] As in the results shown in Table 6, the use of ΔBDE values results the complete cancelation of H atom energy corrections and almost full cancelation of energy changes due to the restricted open-shell treatment of radicals. This example illustrates that the LLM can be successfully applied to physical organic chemistry problems of current interest.

4.4. Correlation with Redox Potentials: BDE vs E°. In a recent review paper, Buettner[30] discussed the relative oxidizing or reducing nature of free radicals of biochemical importance. This provided a useful overview of the relative antioxidant capabilities of various systems. The different systems were ranked according to their standard 1-electron reduction potentials in water at pH 7, giving the "pecking order" of free radicals and antioxidants. The most oxidizing free radical is OH, which reacts according to $OH + e^- + H^+ \rightarrow H_2O$ with a standard reduction potential $E^{\circ} = +2.310$ V. At the opposite end of the range of systems encountered in biochemistry (most reducing) is the hydrated electron, which can be generated by pulse radiolysis in water, with $E^{\circ} - 2.87$ V. A large number of free radicals were given in Buettner's table, including alkoxyl, peroxyl, phenoxyl, radicals derived from ascorbate and Vitamin E (α-tocopherol), and a number of others of biochemical significance.

Many of the above reactions involve the formation of an O−H bond during the reduction (formally the oxygen atom of the radical is reduced to oxide and then protonated. This is thermodynamically indistinguishable from H-atom transfer). It was shown by Bordwell and Cheng[31] that there is a linear relationship between BDE and the pK_a of the corresponding acid RO−H, corresponding to the ionization $RO-H \rightarrow RO^- + H^+$. By use of thermodynamic cycles these authors derived the relationship BDE = $1.37pK_a - 23.06E^{\circ} + C$, where the constant C contains the free energy of formation of the hydrogen atom together with estimates of solvation energies needed to related free energies in solution to gas phase ΔH° values. However, in this and related papers Bordwell and co-workers[32,33] and Jonsson et al.[34] showed that the pK_a values were strongly linearly correlated with the standard reduction potentials. It therefore follows that a plot of BDE vs E° should also be linear. This assumes that all reductions were carried out in the same solvent (so that solvation effects are constant) and that substituents were to be varied on the same basic structure, in their case a series of substituted phenols.[31]

In Figure 2 we show a plot of the *experimental* gas-phase BDE vs experimental standard reduction potentials E°, using the data given by Buettner for the E° values. We restrict the data to only those containing RO−H bonds in order to equalize solvation effects, but we allow the entire range of R groups for which data are available. The figure includes, in addition to small molecules, the biological antioxidant α-tocopherol (α-TOH), for which an accurate gas-phase BDE = 77.3 kcal/mol is known.[35] There is an excellent linear correlation with slope 24.3 kcal mol^{-1} V^{-1} and correlation coefficient 0.997.

Figure 3 shows our *calculated* BDE's vs the experimental E° values. To construct this figure we used the highest-level model calculated in each case. This figure includes calculations for the $H_2O_2 + H \rightarrow H_2O + OH$ reaction, for which all necessary data were calculated using the HLM. It also includes calculated data for an α-TOH model compound, in which the hydrocarbon tail is omitted, which gives 77.0 kcal/mol (using LLM),[36] and the ascorbate anion $AscOH^-$ (69.6 kcal/mol using

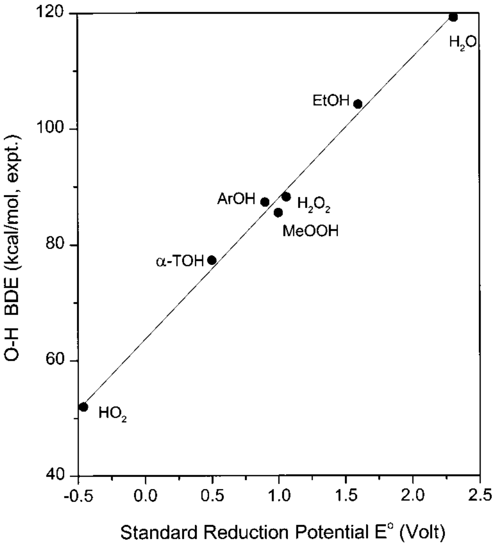

Figure 2. Correlation of experimental gas-phase bond dissociation energy (ΔH°_{298}) vs the standard reduction potential ($E°$) in aqueous solution.

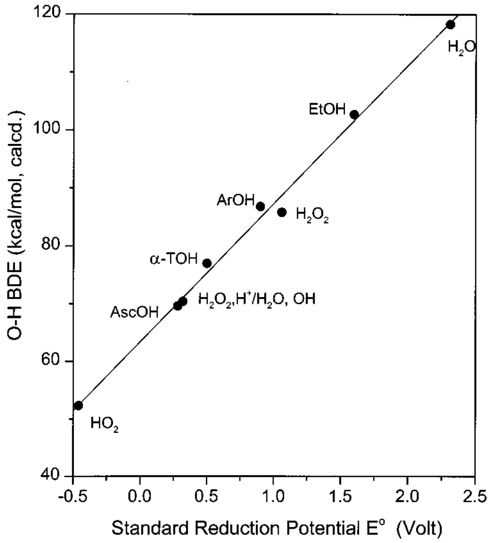

Figure 3. Correlation of calculated gas-phase bond dissociation energy (ΔH°_{298}) vs the standard reduction potential ($E°$) in aqueous solution.

LLM).[37] The correlation is again excellent, with slope = 23.9 kcal mol^{-1} V^{-1} and correlation coefficient 0.997.

The point of this application is to show that our theoretical procedure is useful in an important biochemical problem (relative strengths of oxidants and antioxidants) and is capable of giving calculated BDE values which are nearly as accurate as experimental values. Furthermore, our calculated values show no pathological effects, even though the range of BDE values for RO−H go from a maximum of 119 kcal/mol (water) to a minimum of 52 kcal/mol (HO_2) and cover a wide range of substituents R. In addition, we are also able to provide information beyond that obtainable by experimental measurement of reduction potentials or gas-phase BDE's. For molecules containing more than one OH group (e.g. ascorbic acid, which is a dialcohol) we can distinguish which O−H bond is weakest and therefore which will be the first to break. It appears that with the models described above we should certainly be able to distinguish similar bonds which differ in energy by 2 kcal/mol or greater. Such polyhydroxyl bonds are active not only in the ascorbate system but also in the biological hydroquinones (including ubiquinone, of central importance in the respiratory chain), uric acid, the catechols (adrenaline and dopamines), and many other species of biological significance.

TABLE 7: Gas-Phase Acidity Values, I.e., the Enthalpy Change ΔH°_{298}, Corresponding to the Ionization $R{-}H \rightleftharpoons R^- + H^+$, in kcal/mol

R−H	MK[a]	HLM	expt[b]
HO−H	394.4	390.3	390.7 ± 0.1
HS−H	353.5	350.5	351.1 ± 2.0
H_2N−H	407.5	404.5	404.0 ± 0.4
H_3C−H	419.5	416.9	416.7 ± 0.7
HOO−H	379.5	374.9	375.9 ± 2.1
EtO−H		377.5	378.6 ± 0.8
EtS−H	357.7[c]	355.6	356.9 ± 2.2
$ArCH_2$−H	383.2	381.8[d]	380.8 ± 0.2

[a] Reference 39. [b] Experimental data from ref 38. [c] Calculated value in ref 39 is for MeS−H; experimental data are also for MeS−H. EtS−H will have a similar but not identical value. [d] In this case the calculated value used MLM1, the highest-level model for which the necessary quantities were obtained.

4.5. Gas-Phase Acidity. Another application of interest possible using data generated in this paper is the calculation of the gas-phase acidity. For $RH \rightarrow H^+ + R^-$, the relevant (gas-phase) thermodynamic quantity is $\Delta H^\circ_{acid}(RH) = PA(R^-)$. A clear discussion of the relationship between the relevant thermodynamic quantities has been given by Berkowitz and coworkers,[38] who showed that $\Delta H^\circ_{acid} = BDE_{298}(RH) + IP_0(H) - EA_0(R)$. This is derived from the thermodynamic cycle

$$RH \rightarrow R + H \quad \Delta H° = BDE_{298}(RH)$$

$$H \rightarrow H^+ \quad \Delta H° = IP_0(H)$$

$$R + e^- \rightarrow R^- \quad \Delta H° = EA_0(R)$$

Calculations of a number of gas-phase acidities were given by Smith and Radom,[26] who tested a variety of theoretical methods, and more recently by Merrill and Kass (ref 39, hererafter MK), using a methodology similar to that in the present paper. In this latter work MK used B3LYP (and other functionals), and their largest basis was 6-311++G(2df,2pd), which has more polarization functions than ours and also includes diffuse functions on hydrogen. Using our own theoretical methods we have set the ionization potential of H = +0.500 00 hartree and obtained the BDE and EA values given in Tables 3 and 4, respectively. We can now compare our calculated acidities to those given by MK and also to the experimental values. Table 7 shows the result of such gas-phase acidity calculations. In this table we show data only for our highest-level model calculated in each case (HLM except for toluene).

This table shows that the acidity values of MK are in error by 3−4 kcal/mol, typically in the direction of overestimation of the acidity. On the other hand our own data are very accurate and generally within ca. 1 kcal/mol of the experimental values. Inspection of Tables 3 and 4 shows that our calculated (HLM) values for the combined quantity (BDE−EA) is invariably closer to experiment than the individual BDE and EA; i.e., there is some error cancellation involved in obtaining ΔH°_{acid}. This occurs because each species (HA, A^-) contains the same number of electrons. The resulting error cancellation helps to obtain the remarkable agreement with gas-phase acidities shown in Table 7.

5. Conclusions

We have examined the BDE, EA, and PA for a variety of X−H bonds of most significance to biochemistry, but also of great relevance to organic chemistry, using a density functional approach with the B3LYP functional to calculate the total energy. Various basis sets have been examined. On the basis of our comparison to previous theoretical calculations and to experimental data, we have introduced some modifications into the usual procedure for calculating the relevant thermodynamic quantities. A variety of theoretical models have been introduced which we have termed LLM, MLM1, MLM2, and HLM. These models define procedures used to obtain the geometry and the vibration frequency. On the basis of our results, a prescription for use of these models for X−H thermochemistry is the following:

1. Use LLM for large molecules which do not contain sulfur or lone-pair−lone-pair interactions. Expect errors of less than ±2 kcal/mol for BDE, EA, and PA. For substituent effects and gas-phase acidity studies, the cancellation of the errors plus the computational speed in the LLM approach make this the method of choice for larger systems.

2. Use MLM1 instead of MLM2—it is cheaper and just about as accurate. Expect errors of ±1 kcal/mol in most cases with occasional outliers of ±2 kcal/mol, particularly when sulfur or peroxyl radicals are involved.

3. Consider adding diffuse functions to the basis for geometry optimization when very floppy radicals are involved where significant distortions can occur. The same applies to anions when low-frequency modes are important.

The application to isodesmic schemes, correlation of ΔBDEs with Hammett σ^+ values, and correlation of BDE values vs measured redox potentials ($E°$) values and to the calculation of gas-phase acidity values was extremely successful and shows the power of the modified DFT approach. By extension, it should be possible using these methods to determine the weakest single bond in a polyatomic molecule containing C−H, N−H, O−H, and S−H bonds and in so doing to determine the preferred oxidation sites. We have not presented data on other combinations of interest to organic chemists or in biochemistry, e.g. BDE's for C−C bonds or disulfide linkages in this paper, but further studies along these lines are in progress in our laboratory and in many others as well.

We also introduce a note of caution. In the application of these methods to calculation of energetics for large molecules, some difficulties have been encountered. The most serious of these is the balky convergence of the ROB3LYP calculation which often occurs for radicals when using the 6-311+G(2d,2p) basis set. It appears that this is caused by the presence of diffuse functions on many centers, since omission of these functions usually solves the problem. As we showed, the diffuse functions are needed to give accurate electron and proton affinities as well as improving the description of hydrogen bonding. They can probably be eliminated if only BDE's are required, with little loss in accuracy. At the present time we are experimenting with various approaches to improve the convergence properties of the procedure. Applications using these models are currently in progress on the reactivity of vitamin C, vitamin E, and a number of other antioxidants.

To extend these techniques further into the realm of large, biologically interesting molecules will require some additional modifications to the models described in this paper. It is reasonable to expect that the BDE, for example, is a property which requires a very accurate treatment in the region of the bond of interest but less accurate at distant regions of the molecule. One such approach to the calculation of the BDE of an OH bond in a large molecule would be to use the DFT procedures and basis sets for an "active region" surrounding the OH bond, while describing more distant parts of the molecule with an empirical force field. This is the basis of the ONIOM method of Morokuma and co-workers.[40]

A different approach which we are exploring is the use of "locally dense" basis sets (LDBS)[41] for the active region. The LDBS method appears to be capable of reproducing the accuracy of thermochemical quantities obtained with the various DFT models described in this paper. For example, we were able to accurately calculate the OH BDE in α-tocopherol (vitamin E), a molecule of considerable biochemical significance which contains 81 atoms. This combination of DFT/LDBS methods will be reported in future publications.[42]

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