Multilevel and Density Functional Electronic Structure Calculations of Proton Affinities and Gas-Phase Basicities Involved in Biological Phosphoryl Transfer[†]

Kevin Range,[‡,§] Carlos Silva López,[#] Adam Moser,[‡] and Darrin M. York*[,‡]

Department of Chemistry, University of Minnesota, 207 Pleasant Street SE, Minneapolis, Minnesota 55455-0431, and Departamento de Química Orgánica, Universidade de Vigo, Lagoas Marcosende, 36200 Vigo, Galicia, Spain

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Five multilevel model chemistries (CBS-QB3, G3B3, G3MP2B3, MCG3/3, and MC-QCISD/3) and seven hybrid density functional methods (PBE0, B1B95, B3LYP, MPW1KCIS, PBE1KCIS, and MPW1B95) have been applied to the calculation of gas-phase basicity and proton affinity values for a series of 17 molecules relevant to the study of biological phosphoryl transfer. In addition, W1 calculations were performed on a subset of molecules. The accuracy of the methods was assessed and the nature of systematic errors was explored, leading to the introduction of a set of effective bond enthalpy and entropy correction terms. The multicoefficient correlation methods (MCG3/3 and MC-QCISD), with inclusion of specific zero-point scale factors, slightly outperform the other multilevel methods tested (CBS-QB3, G3B3, and G3MP2B3), with significantly less computational cost, and in the case of MC-QCISD, slightly less severe scaling. Four density functional methods, PBE1KCIS, MPW1B95, PBE0, and B1B95 perform nearly as well as the multilevel methods. These results provide an important set of benchmarks relevant to biological phosphoryl transfer reactions.

1. Introduction

Proton affinities and gas-phase basicities are important thermochemical quantities required for the calculation of pK_a values[1,2] and linear free energy relations.[3] Biological phosphoryl transfer reactions[4] are particularly sensitive to the protonation state. The utility of theoretical methods to provide detailed atomic-level information that may aid in the interpretation and refinement of experimental data is intimately linked to the accuracy of the underlying models. Consequently, it is important to establish benchmark comparisons between theory and experiment such that the limitations of current models can be characterized, and new-generation models with increased reliability and computational performance can be developed. A promising strategy toward the elucidation of complex chemical mechanisms of RNA catalysis, for example, is to derive highly accurate quantum models for phosphoryl transfer reactions that are sufficiently fast to be applied in linear-scaling electronic structure methods[5−8] or hybrid quantum mechanical/molecular mechanical (QM/MM) simulations.[9−11]

Significant effort has been made to develop electronic structure methods that achieve chemical accuracy (±1 kcal/mol) for thermochemical properties.[12] Among two of the most promising classes of model chemistries for thermochemistry and kinetics are so-called “multilevel” and density functional methods. There is generally a tradeoff between accuracy and computational efficiency that often motivates a hierarchical strategy where a more affordable level of theory is first calibrated against experiment and/or higher level methods to establish error limits and determine sources of systematic errors.

“Multilevel” methods are model chemistries that combine the results of several electronic structure calculations, and in some cases additional empirical terms, to predict energies and related quantities to high accuracy. The multilevel methods discussed in the present work include the CBS methods by Petersson and co-workers,[13−16] the Gaussian-*n* methods by Pople and co-workers,[17−19] the Weizmann-*n* methods by Martin and co-workers,[20,21] and the multicoefficient correlation methods (MCCMs) of Truhlar and co-workers.[22−25] These methods have been extensively tested and shown to be generally reliable; however, they are too computationally intensive to apply to many large biological model systems. Methods based on Kohn−Sham density functional theory (DFT)[26] provide practical alternative to the multilevel methods for larger systems. The formal $O(N^3)$ scaling of DFT methods[26] is much less severe than that of most multilevel methods, and continue to improve in performance for thermochemistry and kinetics.[27,28]

In the present work, five multilevel and seven hybrid density functional methods have been applied to the calculation of gas-phase basicity and proton affinity values for a series of 17 molecules relevant to the study of biological phosphoryl transfer. In addition, W1 calculations were performed on a subset of molecules that warranted further study. The accuracy of the methods was assessed and the nature of systematic errors was explored, leading to the introduction of a set of effective bond enthalpy and entropy correction terms.

2. Methods

2.1. Multilevel Methods. All electronic structure and thermochemical calculations were performed using the GAUSSIAN03 (G03) suite of programs,[29] except for the coupled cluster

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* Corresponding author: Phone: (612)624-8042. Fax: (612)626-7541. E-mail: york@chem.umn.edu. Web site: http://theory.chem.umn.edu.

[‡] University of Minnesota.

[§] Present address: Department of Chemistry, Lock Haven University of Pennsylvania, Lock Haven, PA 17745.

[#] Universidade de Vigo.

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calculations used in the W1 method (see below) that were performed using MOLPRO.[30] The multicoefficient correlation method calculations were performed using the MULTILEVEL 3.1/G03 suite.[31] Five multilevel methods were studied: CBS-QB3,[14,15] G3B3,[32] G3MP2B3,[32] MCG3/3,[23] and MC-QCISD/3.[23] CBS-QB3 is a multilevel model chemistry that combines the results of several electronic structure calculations and empirical terms to predict molecular energies to around 1 kcal/mol accuracy.[33] The G3B3 and the related G3MP2B3 methods are both modifications of the Gaussian-3 multilevel theory for the calculation of molecular energies.[18] Like CBS-QB3, G3B3 uses density functional theory with the B3LYP functional for geometries and frequencies and combine the results of several electronic structure calculations and empirical terms to predict molecular energies to around 1 kcal/mol accuracy.[32] A close relative of the G3B3 method, the G3MP2B3 method[32] eliminates all of the MP4 calculations in G3B3, trading some accuracy for computational efficiency.

The MCG3/3 and the related MC-QCISD/3 methods are MCCMs that evolved from the original G3 method and predict molecular energies to around 1 kcal/mol. These methods introduce several coefficients that scale the various energy components in the multilevel energy expression (although the coefficients do not always sum to unity). Unlike the multilevel methods discussed above, MCG3/3 and MC-QCISD/3 were designed for potential energy surfaces and do not include a prescription for zero-point energy and thermal corrections to the enthalpy and free energy as part of the numerical recipe. The authors suggest, however, that the MCCMs may be used with any “reasonable geometry”.[23] In this work, we choose to use B3LYP/6-311G(2d,d,p) geometries and frequencies used for the zero-point and thermal vibrational corrections, because these are available from the CBS-QB3 calculations. The zero-point energies for the MCG3/3 and MC-QCISD/3 method were scaled so as to minimize the sum of the squared proton affinity and gas-phase basicity errors. The resulting scale factors are 1.088 and 0.918 for MCG3/3 and MC-QCISD/3, respectively. This procedure gives the MCG3/3 and MC-QCISD/3 methods an “advantage” in terms of error analysis of the PA and GPB data presented here, with respect to the CBS-QB3, G3B3, and G3MP2B3 methods that have zero-point scale factors determined from a more general data set. This issue will be discussed further in the Results. Analogous to the G3B3 and G3MP2B3 methods, the MC-QCISD/3 method is based on the MCG3/3 but eliminates the costly MP4SDQ calculation and the perturbative triples in the quadratic configuration interaction step, trading some accuracy for speed and more favorable scaling.

Finally, several key molecules were studied with the highly accurate (and expensive) W1 multilevel method that typically is able to predict molecular energies to around 0.8 kcal/mol with maximum errors of around 2 kcal/mol.[20,21]

2.2. Density Functional Methods. All density functional calculations were performed using the GAUSSIAN03 (G03) suite of programs,[29] using the 6-31++G(d,p) basis set for geometries and frequencies and the 6-311++G(3df,2p) basis set for refined energies with the standard numerical integration grid (a pruned grid based on 75 radial shells and 302 angular points per shell) and default geometry convergence criteria. Several hybrid density functionals were investigated: PBE0, B1B95, B3LYP, MPW1KCIS, PBE1KCIS, and MPW1B95.

B3LYP is a three parameter hybrid functional[34] that uses the B88 exchange functional of Becke[35] and the Lee, Yang, and Parr correlation functional.[36] PBE0 is a zero parameter hybrid functional[37] that uses the Perdew, Burke, Ernzerhof (PBE) exchange and correlation functional.[38] B1B95 is a one parameter hybrid functional[39] that uses the B88 exchange functional[35] and B95 correlation functional[39] of Becke. MPW1KCIS is a one parameter hybrid functional[27] that combines the modified Perdew−Wang (MPW1) exchange functional[40] and the Krieger, Chen, Iafrate, and Savin (KCIS) correlation functional.[41] PBE1KCIS is a one parameter hybrid functional[42] that uses the PBE exchange functional and the KCIS correlation functional. MPW1B95 is a one parameter hybrid functional[43] that uses the MPW exchange and B95 correlation functional.

2.3. Calculation of Proton Affinities and Gas-Phase Basicities. The proton affinity (PA) and gas-phase basicity (GPB) of a species A^- are related to the gas-phase reaction:

$$A^-_{(g)} + H^+_{(g)} \rightarrow AH_{(g)} \tag{1}$$

The proton affinity of A^- is defined as the negative of the enthalpy change (ΔH) of the process in eq 1, and the gas-phase basicity of A^- is defined as the negative of the corresponding Gibbs free energy change (ΔG).[44]

The required thermodynamic properties were obtained from the electronic structure calculations using standard statistical mechanical expressions for separable vibrational, rotational, and translational contributions within the harmonic oscillator, rigid rotor, ideal gas/particle-in-a-box models in the canonical ensemble.[45] The standard state in the gas phase was for a mole of particles at 298.15 K and 1 atm pressure.

The gas-phase enthalpy and entropy of the proton was calculated from the ideal gas expression and Sackur−Tetrode equation,[46] respectively, as in previous work.[47]

It is sometimes the case that a molecule and/or its conjugate base has more than one indistinguishable microscopic protonation state. All of the GPB values in this paper are *microscopic* gas-phase basicities, because that is what naturally comes out of electronic structure calculations of a single protonation state. The conversion between microscopic and macroscopic GPB values was estimated as follows.

The macroscopic equilibrium constant, K^M, for the reverse process to that of eq 1, assuming unit activity coefficients, is given by

$$K^M = \frac{[A^-]_M[H^+]}{[AH]_M} \tag{2}$$

If A^- has m indistinguishable microscopic protonation states and AH has n indistinguishable microscopic protonation states, then

$$K^M = \frac{m[A^-]_\mu[H^+]}{n[AH]_\mu} = K^\mu\left(\frac{m}{n}\right) \tag{3}$$

where μ indicates microscopic quantities and $K^\mu = [A^-]_\mu[H^+]/[AH]_\mu$. The free energy change (ΔG) for a process is related to the equilibrium constant by

$$\Delta G = -RT \ln K \tag{4}$$

Substitution of eq 4 into eq 3 yields the following equation for interconversion of microscopic and macroscopic free energy changes:

$$\Delta G^\mu = \Delta G^M + RT \ln\left(\frac{m}{n}\right) \tag{5}$$

3. Results and Discussion

In this section, calculated proton affinities and gas-phase basicities are compared with experimental values using the

TABLE 1: Gas-Phase Basicity Error Analysis for Multilevel Methods[a]

molecule[b]	CBS-QB3		G3B3		G3MP2B3		MCG3/3[c]		MC-QCISD/3[d]		expt
water	1.7	***2.3***	1.2	*1.3*	1.3	*1.1*	**−1.7**	*−1.4*	−1.7	*−1.4*	383.7(0.2)
hydronium	−1.1	*−0.6*	−0.4	*−0.4*	−0.5	*−0.7*	−1.1	*−0.8*	−1.0	*−0.8*	157.7(0.1)
methanol	1.3	*1.9*	**2.4**	***2.5***	**2.3**	***2.2***	1.3	***1.6***	1.7	*2.0*	374.8(0.7)
ethanol	0.4	*1.0*	1.3	*1.3*	1.4	*1.3*	0.7	*1.0*	1.1	*1.3*	371.3(1.0)
propanol	0.2	*0.8*	1.2	*1.2*	1.4	*1.2*	0.6	*0.9*	0.9	*1.2*	369.4(1.1)
2-propanol	0.3	*0.9*	1.0	*1.0*	1.3	*1.2*	0.3	*0.6*	0.6	*0.9*	368.8(1.0)
DMPH[e]	−1.7	*−1.1*	−1.2	*−1.1*	−0.7	*−0.8*	−0.1	*0.2*	−0.8	*−0.5*	324.6(4.0)
phosphoric acid	**−2.5**	*−1.9*	−1.9	*−1.9*	−1.5	*−1.6*	−1.3	*−1.0*	**−2.3**	***−2.0***	323.2(4.9)
formic acid	−1.3	*−0.8*	−0.6	*−0.5*	−0.1	*−0.2*	−0.5	*−0.2*	−0.5	*−0.2*	337.9(1.2)
acetic acid	−2.0	*−1.4*	−1.2	*−1.1*	−0.8	*−0.9*	−1.2	*−0.9*	−1.2	*−0.9*	341.4(1.2)
propanoic acid	−0.9	*−0.3*	−0.1	*−0.0*	0.3	*0.2*	0.6	*0.8*	0.6	*0.9*	340.4(1.4)
phenol	−0.6	*−0.1*	−0.5	*−0.4*	−0.5	*−0.7*	−0.7	*−0.5*	−0.6	*−0.3*	342.9(1.4)
o-chlorophenol	−0.8	*−0.2*	−0.4	*−0.3*	−0.4	*−0.6*	−0.3	*−0.1*	−0.4	*−0.1*	337.1(2.0)
m-chlorophenol	−1.2	*−0.6*	−0.9	*−0.8*	−0.9	*−1.0*	−0.9	*−0.7*	−0.8	*−0.6*	335.2(1.4)
p-chlorophenol	−0.9	*−0.3*	−0.5	*−0.5*	−0.5	*−0.7*	−0.5	*−0.2*	−0.5	*−0.2*	336.5(1.4)
p-methylphenol	−0.6	*−0.0*	−0.4	*−0.3*	−0.4	*−0.5*	−0.5	*−0.2*	−0.3	*−0.0*	343.8(1.2)
p-nitrophenol	−0.1	*0.4*	0.2	*0.2*	0.7	*0.5*	0.8	*1.1*	0.5	*0.7*	320.9(2.0)
MAXE	−2.5	*2.3*	2.4	*2.5*	2.3	*2.2*	−1.7	*1.6*	−2.3	*−2.0*	
RMSE	1.2	*1.1*	1.1	*1.1*	1.0	*1.0*	0.9	*0.8*	1.1	*1.0*	
MUE	1.0	*0.8*	0.9	*0.9*	0.9	*0.9*	0.8	*0.7*	0.9	*0.8*	
MSE	−0.6	*0.0*	0.0	*0.0*	0.1	*0.0*	−0.3	*0.0*	−0.3	*0.0*	

[a] All quantities are in kcal/mol. Experimental values are the unweighted average of all values available from ref 48, corrected for degenerate protonation sites where appropriate to produce microscopic gas-phase basicities. Estimates of the experimental error are shown in parentheses immediately to the right of the experimental data and were calculated from the individual error estimates using standard propagation of errors.[49] The error metrics (error = calculated value − experimental value) shown are the maximum error (MAXE), root-mean-square error (RMSE), mean unsigned error (MUE), and mean signed error (MSE). The gas-phase basicity errors that include the empirical bond free energy correction ΔG^{C} for O−H bonds (see text) are shown in italics immediately to the right of the uncorrected data. The MAXE for each method is bold-face. [b] "Molecule" refers to AH in eq 1. [c] B3LYP/6-311G(2d,d,p) geometries and frequencies with zero point corrections scaled by 1.088 (see text). [d] B3LYP/6-311G(2d,d,p) geometries and frequencies with zero point corrections scaled by 0.918 (see text). [e] Hydrogen dimethyl phosphate.

TABLE 2: Proton Affinity Error Analysis for Multilevel Methods[a]

molecule[b]	CBS-QB3		G3B3		G3MP2B3		MCG3/3[c]		MC-QCISD/3[d]		expt
water	1.7	*1.8*	1.2	*0.8*	1.3	*0.7*	**−1.6**	***−1.8***	−1.7	*−1.8*	390.3(0.2)
hydronium	−1.0	*−0.9*	−0.3	*−0.7*	−0.4	*−1.0*	−0.9	*−1.1*	−0.9	*−1.0*	165.0(1.0)
methanol	1.1	*1.3*	**2.2**	*1.9*	**2.1**	*1.6*	1.6	*1.4*	**2.0**	***1.9***	381.5(1.0)
ethanol	0.7	*0.8*	1.5	*1.1*	1.7	*1.1*	1.0	*0.9*	1.3	*1.2*	378.2(0.8)
propanol	0.8	*0.9*	1.7	*1.3*	1.9	*1.4*	1.2	*1.1*	1.5	*1.4*	376.0(1.1)
2-propanol	0.8	*0.9*	1.4	*1.1*	1.7	*1.2*	0.8	*0.6*	1.1	*1.0*	375.7(0.8)
DMPH[e]	**−2.4**	***−2.2***	−1.8	***−2.2***	−1.3	***−1.8***	−0.8	*−0.9*	−1.5	*−1.6*	331.6(4.1)
phosphoric acid	−1.8	*−1.7*	−1.4	*−1.8*	−1.0	*−1.6*	−0.6	*−0.7*	−1.7	*−1.8*	330.5(5.0)
formic acid	−0.4	*−0.3*	0.4	*−0.0*	0.9	*0.3*	0.5	*0.3*	0.5	*0.4*	344.0(1.6)
acetic acid	0.2	*0.3*	1.0	*0.6*	1.4	*0.8*	1.0	*0.8*	1.0	*0.9*	347.2(1.1)
propanoic acid	−0.5	*−0.3*	0.3	*−0.1*	0.7	*0.1*	−0.3	*−0.5*	−0.3	*−0.4*	347.4(1.8)
phenol	−0.8	*−0.6*	−0.6	*−1.0*	−0.6	*−1.2*	−0.8	*−1.0*	−0.7	*−0.8*	350.1(1.1)
o-chlorophenol	0.7	*0.8*	1.0	*0.6*	1.0	*0.4*	1.1	*1.0*	1.0	*1.0*	343.4(2.3)
m-chlorophenol	−0.5	*−0.4*	−0.2	*−0.6*	−0.2	*−0.8*	−0.3	*−0.4*	−0.2	*−0.3*	342.1(3.1)
p-chlorophenol	−0.5	*−0.4*	−0.2	*−0.6*	−0.2	*−0.8*	−0.2	*−0.3*	−0.2	*−0.3*	343.4(1.6)
p-methylphenol	−0.3	*−0.1*	0.0	*−0.4*	0.0	*−0.6*	−0.1	*−0.3*	0.0	*−0.1*	350.7(1.3)
p-nitrophenol	−0.2	*−0.0*	0.2	*−0.2*	0.7	*0.1*	0.8	*0.7*	0.4	*0.3*	327.8(2.1)
MAXE	−2.4	*−2.2*	2.2	*−2.2*	2.1	*−1.8*	−1.6	*−1.8*	2.0	*1.9*	
RMSE	1.0	*1.0*	1.1	*1.1*	1.2	*1.0*	0.9	*0.9*	1.1	*1.1*	
MUE	0.8	*0.8*	0.9	*0.9*	1.0	*0.9*	0.8	*0.8*	0.9	*0.9*	
MSE	−0.1	*−0.0*	0.4	*−0.0*	0.6	*0.0*	0.1	*0.0*	0.1	*0.0*	

[a] All quantities are in kcal/mol. Experimental values are the unweighted average of all values available from ref 48. Estimates of the experimental error are shown in parentheses immediately to the right of the experimental data and were calculated from the individual error estimates using standard propagation of errors.[49] The error metrics (error = calculated value − experimental value) shown are the maximum error (MAXE), root-mean-square error (RMSE), mean unsigned error (MUE), and mean signed error (MSE). The proton affinity errors that include the empirical bond enthalpy correction ΔH^{C} for O−H bonds (see text) are shown in italics immediately to the right of the uncorrected data. The MAXE for each method is bold-face. [b] "Molecule" refers to AH in eq 1. [c] B3LYP/6-311G(2d,d,p) geometries and frequencies with zero point corrections scaled by 1.088 (see text). [d] B3LYP/6-311G(2d,d,p) geometries and frequencies with zero point corrections scaled by 0.918 (see text). [e] Hydrogen dimethyl phosphate.

following error metrics: mean signed error (MSE), mean unsigned error (MUE), root-mean-square error (RMSE), and maximum error (MAXE), where the error for each data point is defined as the calculated value minus the experimental value. Tables 1−4 compare the errors with respect to experiment for proton affinity and gas-phase basicity values calculated with the various quantum model chemistries. The 17 molecules in these tables were selected from available experimental data to represent those most relevant to the study of phosphoryl transfer, including the most common types of biological phosphorus compounds, nucleophiles, and leaving groups that involve formation and cleavage of P−O bonds. Discussion of error

TABLE 3: Gas-Phase Basicity Error Analysis for Hybrid DFT Methods[a]

molecule[b]	MPW1KCIS		PBE1KCIS		MPW1B95		PBE0		B1B95		B3LYP		expt
water	1.8	***3.0***	2.1	***3.0***	**3.2**	***3.5***	**3.2**	***3.6***	**3.3**	***3.5***	0.1	***2.4***	383.7(0.2)
hydronium	−0.0	*1.2*	−0.1	*0.8*	−0.0	*0.3*	0.4	*0.8*	0.3	*0.5*	−1.2	*1.1*	157.7(0.1)
methanol	−1.4	*−0.1*	−0.8	*0.1*	−0.0	*0.3*	−0.4	*−0.0*	0.1	*0.2*	−2.1	*0.2*	374.8(0.7)
ethanol	−1.9	*−0.6*	−1.1	*−0.2*	−0.1	*0.2*	−0.5	*−0.1*	0.1	*0.2*	−2.4	*−0.1*	371.3(1.0)
propanol	−0.6	*0.6*	0.0	*0.9*	0.9	*1.3*	0.5	*0.8*	1.1	*1.3*	−2.0	*0.3*	369.4(1.1)
2-propanol	−1.2	*0.1*	−0.4	*0.5*	0.6	*0.9*	0.3	*0.7*	0.8	*1.0*	−1.7	*0.6*	368.8(1.0)
DMPH[c]	−0.1	*1.2*	0.1	*1.0*	−0.4	*−0.1*	0.1	*0.5*	−1.5	*−1.3*	−0.9	*1.4*	324.6(4.0)
phosphoric acid	−0.5	*0.8*	−0.2	*0.6*	−0.2	*0.2*	0.3	*0.6*	0.2	*0.4*	−2.5	*−0.2*	323.2(4.9)
formic acid	−1.7	*−0.4*	−1.5	*−0.7*	−1.2	*−0.9*	−1.1	*−0.8*	−0.8	*−0.6*	−2.9	*−0.6*	337.9(1.2)
acetic acid	−1.7	*−0.4*	−1.5	*−0.6*	−0.2	*0.1*	−0.1	*0.2*	−1.7	*−1.5*	−3.1	*−0.8*	341.4(1.2)
propanoic acid	−1.2	*0.1*	−0.9	*−0.1*	−0.0	*0.3*	0.7	*1.0*	0.4	*0.6*	−3.6	*−1.3*	340.4(1.4)
phenol	−1.8	*−0.6*	−1.5	*−0.6*	−0.9	*−0.6*	−1.4	*−1.0*	−0.7	*−0.5*	−2.4	*−0.1*	342.9(1.4)
o-chlorophenol	−1.8	*−0.5*	−1.4	*−0.5*	−0.6	*−0.3*	−1.1	*−0.8*	−0.5	*−0.3*	−2.4	*−0.1*	337.1(2.0)
m-chlorophenol	−2.3	*−1.0*	−1.9	*−1.0*	−1.3	*−1.0*	−1.7	*−1.4*	−1.2	*−1.0*	−2.9	*−0.6*	335.2(1.4)
p-chlorophenol	−2.0	*−0.7*	−1.7	*−0.8*	−1.1	*−0.8*	−1.5	*−1.2*	−1.0	*−0.8*	−2.6	*−0.3*	336.5(1.4)
p-methylphenol	−1.9	*−0.6*	−1.4	*−0.6*	−1.9	*−1.6*	−1.3	*−0.9*	−0.2	*−0.0*	−2.2	*0.1*	343.8(1.2)
p-nitrophenol	−**3.4**	*−2.1*	−**2.8**	*−1.9*	−2.0	*−1.7*	−2.4	*−2.1*	−1.8	*−1.6*	−**4.2**	*−1.9*	320.9(2.0)
MAXE	−3.4	*3.0*	−2.8	*3.0*	3.2	*3.5*	3.2	*3.6*	3.3	*3.5*	−4.2	*2.4*	
RMSE	1.7	*1.1*	1.4	*1.1*	1.2	*1.2*	1.3	*1.3*	1.2	*1.2*	2.5	*1.0*	
MUE	1.5	*0.8*	1.1	*0.8*	0.9	*0.8*	1.0	*1.0*	0.9	*0.9*	2.3	*0.7*	
MSE	−1.3	*−0.0*	−0.9	*0.0*	−0.3	*−0.0*	−0.4	*0.0*	−0.2	*−0.0*	−2.3	*−0.0*	

[a] All quantities are in kcal/mol. Experimental values are the unweighted average of all values available from ref 48, corrected for degenerate protonation sites where appropriate to produce microscopic gas-phase basicities. Estimates of the experimental error are shown in parentheses immediately to the right of the experimental data and were calculated from the individual error estimates using standard propagation of errors.[49] The error metrics (error = calculated value − experimental value) shown are the maximum error (MAXE), root-mean-square error (RMSE), mean unsigned error (MUE) and mean signed error (MSE). The gas-phase basicity errors that include the empirical bond free energy correction ΔG^C for O−H bonds (see text) are shown in italics immediately to the right of the uncorrected data. The MAXE for each method is bold-face. [b] ”Molecule” refers to AH in eq 1. [c] Hydrogen dimethyl phosphate.

TABLE 4: Proton Affinity Error Analysis for Hybrid DFT Methods[1]

molecule[b]	MPW1KCIS		PBE1KCIS		MPW1B95		PBE0		B1B95		B3LYP		expt
water	1.8	***2.6***	2.1	***2.6***	**3.2**	***3.1***	**3.2**	***3.3***	**3.3**	***3.0***	0.1	*1.9*	390.3(0.2)
hydronium	0.1	*0.9*	0.0	*0.5*	0.1	*0.0*	0.5	*0.7*	0.4	*0.1*	−1.1	*0.6*	165.0(1.0)
methanol	−1.6	*−0.7*	−0.9	*−0.5*	−0.2	*−0.2*	−0.5	*−0.4*	−0.1	*−0.4*	−2.3	*−0.6*	381.5(1.0)
ethanol	−1.6	*−0.8*	−0.8	*−0.4*	0.1	*0.1*	−0.2	*−0.1*	0.3	*0.0*	−2.2	*−0.4*	378.2(0.8)
propanol	0.2	*1.1*	0.9	*1.4*	1.8	*1.7*	1.4	*1.5*	1.9	*1.7*	−1.4	*0.3*	376.0(1.1)
2-propanol	−0.8	*0.1*	0.0	*0.5*	1.0	*0.9*	0.7	*0.9*	1.2	*0.9*	−1.3	*0.4*	375.7(0.8)
DMPH[4]	−0.6	*0.2*	−0.5	*−0.1*	−1.1	*−1.1*	−0.6	*−0.4*	−0.8	*−1.1*	−1.5	*0.3*	331.6(4.1)
phosphoric acid	−1.2	*−0.4*	−1.0	*−0.5*	−0.9	*−1.0*	−0.5	*−0.4*	−0.6	*−0.9*	−1.7	*0.1*	330.5(5.0)
formic acid	−0.8	*0.1*	−0.6	*−0.1*	−0.2	*−0.3*	−0.2	*−0.0*	0.1	*−0.2*	−2.0	*−0.2*	344.0(1.6)
acetic acid	0.4	*1.2*	0.6	*1.0*	0.3	*0.3*	0.4	*0.6*	1.2	*1.0*	−0.8	*1.0*	347.2(1.1)
propanoic acid	−0.2	*0.7*	0.0	*0.5*	0.3	*0.2*	−0.2	*−0.1*	0.6	*0.3*	−1.3	*0.4*	347.4(1.8)
phenol	−1.9	*−1.0*	−1.5	*−1.1*	−1.0	*−1.1*	−1.5	*−1.3*	−0.8	*−1.1*	−2.5	*−0.7*	350.1(1.1)
o-chlorophenol	−0.4	*0.5*	−0.0	*0.5*	0.8	*0.7*	0.3	*0.4*	0.9	*0.7*	−1.0	*0.7*	343.4(2.3)
m-chlorophenol	−1.7	*−0.8*	−1.3	*−0.8*	−0.7	*−0.8*	−1.1	*−1.0*	−0.5	*−0.8*	−2.3	*−0.6*	342.1(3.1)
p-chlorophenol	−1.7	*−0.8*	−1.3	*−0.9*	−0.8	*−0.9*	−1.2	*−1.0*	−0.6	*−0.9*	−2.3	*−0.6*	343.4(1.6)
p-methylphenol	−1.3	*−0.5*	−0.9	*−0.4*	0.2	*0.2*	−0.8	*−0.7*	−0.2	*−0.5*	−1.8	*−0.1*	350.7(1.3)
p-nitrophenol	−**3.3**	*−2.5*	−**2.7**	*−2.3*	−2.0	*−2.0*	−2.4	*−2.2*	−1.8	*−2.1*	−**4.2**	*−**2.4***	327.8(2.1)
MAXE	−3.3	*2.6*	−2.7	*2.6*	3.2	*3.1*	3.2	*3.3*	3.3	*3.0*	−4.2	*−2.4*	
RMSE	1.4	*1.1*	1.2	*1.1*	1.2	*1.2*	1.2	*1.2*	1.2	*1.2*	1.9	*0.9*	
MUE	1.1	*0.9*	0.9	*0.8*	0.9	*0.9*	0.9	*0.9*	0.9	*0.9*	1.7	*0.7*	
MSE	−0.9	*−0.0*	−0.5	*0.0*	0.1	*0.0*	−0.2	*−0.0*	0.3	*−0.0*	−1.7	*0.0*	

[a] All quantities are in kcal/mol. Experimental values are the unweighted average of all values available from ref 48. Estimates of the experimental error are shown in parentheses immediately to the right of the experimental data and were calculated from the individual error estimates using standard propagation of errors.[49] The error metrics (error = calculated value − experimental value) shown are the maximum error (MAXE), root-mean-square error (RMSE), mean unsigned error (MUE), and mean signed error (MSE). The proton affinity errors that include the empirical bond enthalpy correction ΔH^C for O−H bonds (see text) are shown in italics immediately to the right of the uncorrected data. The MAXE for each method is bold-face. [b] ”Molecule” refers to AH in eq 1. [c] Hydrogen dimethyl phosphate.

metrics, unless indicated otherwise, will refer to the magnitude of these quantities (and not their sign).

3.1. Performance of Multilevel Methods. In general, the multilevel methods are fairly comparable. MCG3/3 and CBS-QB3 each predict 7 data points outside the experimental error bars. MC-QCISD/3, G3B3, and G3MP2B3 have 9, 10, and 12 points outside the experimental error bars, respectively. The MCG3/3 method has the smallest MAXE, RMSE, and MUE for gas-phase basicities (−1.7, +0.9, and +0.8 kcal/mol, respectively), and the smallest MAXE and RMSE for proton affinities (−1.6 and +0.9 kcal/mol, respectively). The G3B3 method has the smallest GPB MSE (less than 0.005 kcal/mol). CBS-QB3 and MCG3/3 both have PA MUE of 0.8 kcal/mol. The PA MSE is of the same magnitude for CBS-QB3, MCG3/3, and MC-QCISD/3 (−0.1, +0.1, and +0.1 kcal/mol, respectively). Given the cost of the MCG3/3 method compared to

CBS-QB3 and G3B3 and the reduced scaling of MC-QCISD/3 (O(N^6) versus O(N^7)), the performance of the MCCM methods of Lynch and Truhlar[23] is impressive.

The zero-point energies used for the MCCM methods were scaled by a parameter (the zero-point scale factor) selected especially for this data set, and hence the results reported here are a best-case scenario in this respect. When these scale factors are set to unity the MAXE, RMSE, MUE, and MSE increase to 2.3, 1.0, 0.8, and 0.5 kcal/mol, respectively, for the MCG3/3 GPB values and 2.5, 1.3, 1.1, and 0.9 kcal/mol, respectively, for the MCG3/3 PA values. More dramatically, the MAXE, RMSE, MUE, and MSE increase to −2.9, +1.4, +1.1, −1.0 kcal/mol, respectively, for the MC-QCISD/3 GPB values and −2.4, +1.2, +1.0, −0.6 kcal/mol, respectively, for the MC-QCISD/3 PA values. Even without the zero-point scale factor, MCG3/3 is still quite competitive with the other multilevel methods, although it moves from best to worst of the O(N^7) methods for prediction of the PA values in this set (assuming that the experimental measurements are sufficiently reliable). The MC-QCISD method without the zero-point scale factor has an RMSE within the experimental error bar for each quantity (1.9 and 2.1 for the experimental GPB and PA, respectively).

It is noteworthy that the zero-point scale factor for MCG3/3 is greater than one, when conventional methods[45] and other multilevel thermochemical methods[14,20,32] typically have scale factors that are less than one. Because the zero-point energy contribution to GPB and PA is always negative (due to the loss of the A−H bond), this may be indicative of a systematic overestimation of the electronic energy difference between AH and A^- in the MCG3/3 method.

3.2. Performance of Hybrid Density Functional Methods. Although multilevel methods are considerably reliable, they are also quite costly and have highly nonlinear (i.e., O(N^6) or O(N^7)) scaling behavior, making many important biological model compounds inaccessible to practical calculation. On the other hand, density functional methods are sufficiently efficient to apply over a broad range of biological systems, and are the methods of choice in modern applications. The seven density functional methods examined here give comparable results for prediction of GPB and PA values, with MAXE of around ±3 kcal/mol, RMSE just over 1 kcal/mol, and MUE of ≈1 kcal/mol, except for MPW1KCIS and B3LYP, which have errors up to a kcal/mol higher. It is interesting to note that the two best functionals for these systems, B1B95 and MPW1B95, both use Becke's B95 meta-GGA correlation functional. These results make B95 containing functionals promising candidates to supersede B3LYP as the functional of choice for most calculations.

3.3. Bond Enthalpy, Entropy, and Free Energy Corrections. It has be previously observed that systematic errors in GPB and PA calculations (manifested when |MSE| ≈ RMSE) may be considerably reduced by introduction of (constant) effective enthalpic and entropic correction terms.[47] The corrected change in enthalpy ($\Delta H'$), entropy ($\Delta S'$), and free energy ($\Delta G'$) of the process in eq 1 take the form

$$\Delta H' = \Delta H + \Delta H^{\mathrm{C}} \tag{6}$$

$$\Delta S' = \Delta S + \Delta S^{\mathrm{C}} \tag{7}$$

$$\Delta G' = \Delta G + \Delta G^{\mathrm{C}} = \Delta H' - T\Delta S' \tag{8}$$

where ΔH^{C} and ΔS^{C} are the effective bond enthalpy and entropy corrections, respectively, and $\Delta G^{\mathrm{C}} = \Delta H^{\mathrm{C}} - T\Delta S^{\mathrm{C}}$. These terms correct for enthalpy and entropy difference between a protonated (XO−H) and deprotonated (XO^-) states for O−H bonds, and are listed in Tables 5 and 6.

TABLE 5: Thermodynamic O−H Bond Corrections for Multilevel Methods[a]

	CBS-QB3	G3B3	G3MP2B3	MCG3/3[b]	MC-QCISD/3[c]
ΔH^{C}	0.1	−0.4	−0.6	−1.1	0.6
ΔS^{C}	−1.4	−1.4	−1.4	−1.3	−1.3
ΔG^{C}	0.6	0.0	−0.1	−0.7	1.0

[a] ΔH^{C} and ΔG^{C} are in kcal/mol and correspond to 298.15 K. ΔS^{C} is in cal/(mol K). [b] B3LYP/6-311G(2d,d,p) geometries and frequencies with zero point corrections scaled by 1.088 (see text). [c] B3LYP/6-311G(2d,d,p) geometries and frequencies with zero point corrections scaled by 0.918 (see text).

TABLE 6: Thermodynamic O−H Bond Corrections for Hybrid DFT Methods[a]

	MPW1KCIS	PBE1KCIS	MPW1B95	PBE0	B1B95	B3LYP
ΔH^{C}	0.9	0.5	−0.1	0.2	−0.3	1.7
ΔS^{C}	−1.4	−1.4	−1.2	−0.7	−1.6	−1.9
ΔG^{C}	1.3	0.9	0.3	0.4	0.2	2.3

[a] ΔH^{C} and ΔG^{C} are in kcal/mol and correspond to 298.15 K. ΔS^{C} is in cal/(mol K).

The multilevel methods are not significantly affected by the bond enthalpy and entropy corrections (see Tables 1 and 2) as they are already considerably accurate, and the residual error is not sufficiently systematic that a simple correction of this form makes appreciable difference. On the other hand, for certain density functional methods, especially B3LYP, the bond energy corrections greatly reduce the errors in GPB and PA calculation (see Tables 3 and 4). Indeed, with bond enthalpy and entropy corrections, the B3LYP method performs as well as or slightly better than the best corrected or uncorrected DFT and multilevel methods with GPB and PA MAXE, RMSE, and MUE values of approximately 2.4, 1.0, and 0.7 kcal/mol, respectively.

3.4. Extended Analysis and Discussion of Errors. The purpose of this work is to benchmark PA and GPB values of most relevance for biological phosphoryl transfer using a wide range of modern thermochemical and density functional methods. As such, the data set used in this work represents the intersection of those molecules for which experimental GPB and PA values are available and that are of importance in the study of phosphoryl transfer reactions. Often the experimental error bars for this data set exceed the differences between the PA and GPB values, which brings into question the resolution of the gas-phase basicity scale. Although this is cause for some skepticism, it is likely that the trends in relative PA and GPB values for sets of molecules with similar functional groups and the relative average PA and GPB values between these sets are more reliable.

Phosphoric acid and DMPH are, to our knowledge, the only two relevant phosphate derivatives for which GPB and PA values are available. Unfortunately, the error bars on these experiments are the largest of all the molecules in the data set at 4−5 kcal/mol. This lack of accurate and abundant experimental GPB and PA data for phosphate derivatives emphasizes the need for theoretical benchmarks, such as those presented here, that may, in conjunction with experiment, lead to further refinement of these values and generation of a more diverse set of GPB and PA values relevant to biological phosphoryl transfer. Nonetheless, the limited current availability of experimental GPB and PA values, and hence limited number of phosphate derivatives in the dataset, precludes one from drawing general conclusions about the reliability of the current methods for these compounds. This prompted us to consider an additional cationic

TABLE 7: GPB and PA Values Predicted by W1 Theory[a]

molecule[b]	GPB	err	PA	err
water	384.1	0.4	390.7	0.4
hydronium	157.5	−0.2	165.0	−0.0
methanol	376.6	1.8	383.1	1.6
ethanol	372.6	1.3	379.8	1.6
phosphoric acid	321.6	−1.6	328.9	−1.6

[a] All quantities are in kcal/mol. "err" is the difference between the W1 value and the experimental value. [b] "Molecule" refers to AH in eq 1.

phosphate derivative in the calculations, and in the case of phosphoric acid, a higher level set of W1 calculations.

The one other currently available experimental GPB and PA values, to our knowledge, is for the hydrogen trimethyl phosphate cation ($TMPH^+$). The $TMPH^+$ ion is considerably different from the other neutral molecules studied here (the only other cation being hydronium) and is an unlikely species directly related in biological phosphoryl transfer. Indeed, the errors for $TMPH^+$ (much like those for hydronium) are qualitatively different than those for the other phosphates.[53] For example, the G3B3 DMPH GPB error is −1.2 kcal/mol, whereas for $TMPH^+$ it is 0.6 kcal/mol. For most of the DFT methods (MPW1KCIS, PBE1KCIS, MPW1B95, and PBE0) the phosphate errors are less than ±1 kcal/mol, but for $TMPH^+$ the errors are ≈2 kcal/mol. Given that $TMPH^+$ is chemically diverse from the other phosphates and of limited relevance to phosphoryl transfer, it is not present in the tables or statistics.

There are several other data points in Tables 1 and 2 that warrant further study, specifically water, hydronium, and methanol, which are consistently outside the experimental error bars for almost all of the multilevel methods, and phosphoric acid and hydrogen dimethyl phosphate, which have large experimental error bars (4−5 kcal/mol) and are associated with the MAXE for several of the multilevel methods. In an effort to further probe the reliability of both the calculated and experimental GPB and PA values for these molecules, the W1 method[20,21] was employed for a subset of molecules (Table 7).

The W1 GPB and PA values for water and hydronium are quite close to the experimental values, suggesting that there is no deficiency in the experiments or in the standard assumptions of the multilevel methods that are shared with W1. The W1 GPB and PA values for methanol, on the other hand, differ from the experimentally reported values by 1.8 and 1.6 kcal/mol, respectively, around 2 times the expected error for this method and outside the experimental error bars by a factor of ≈1.5. Similar results are obtained for ethanol. Examination of the individual experimental results making up the NIST GPB and PA values for methanol and ethanol reveals that every reported value is lower than the corresponding W1 values with the smallest difference being 0.7 kcal/mol for the PA of ethanol, as measured by DeTuri and Ervin,[50] and the largest difference being 2.6 kcal/mol for the GPB of methanol, as measured by Bartmess et al.[51] It is known that the W1 method underpredicts the heat of formation of methanol by 1.0 kcal/mol[21] (i.e., W1 predicts that methanol is too stable). Taking this into account, the GPB and PA errors for methanol are reduced to 0.8 and 0.6 kcal/mol, respectively, which are within the expected performance of W1. The origin of this disagreement between W1 and experiment is not clear and warrants further study.

The W1 GPB and PA values for phosphoric acid differ from the experimentally reported values by −1.6 kcal/mol, which, though within the experimental error bars, is around 2 times the expected error in the W1 method. All of the methods tested here agree qualitatively with the W1 results for phosphoric acid PA values (i.e., all of them predict smaller PA values with errors that range from −0.6 to −1.8 for the multilevel methods and from −0.5 to −1.7 for the DFT methods), and with the exception of some of the DFT methods, also agree qualitatively with the W1 GPB values (e.g., the multilevel methods GPB errors range from −1.3 to −2.5 kcal/mol). These results suggest that the actual GPB and PA values of phosphoric acid may be 1−2 kcal/mol lower than the current reported NIST value, although with the limited number of phosphate compounds in the data set, this suggestion is not conclusive.

The two most troublesome molecules for the density functional methods studied here are water and *p*-nitrophenol. Because the GPB and PA errors for the two molecules are large and often of opposite sign, one might be tempted to eliminate them from the data set. Although this would indeed reduce the errors reported below, it would also have the affect of eliminating two of the most important molecules in the data set. Water is of course a key player in phosphate hydrolysis and related reactions; *p*-nitrophenol has been used as an enhanced leaving group in experimental studies of phosphate hydrolysis.[52] Additionally, the DFT errors for *p*-nitrophenol are often not much larger than the experimental error bar of 2.1 kcal/mol. If certain methods (like current state-of-the-art hybrid DFT methods) are unable to correctly calculate the GPB and/or PA of key molecules such as water and *p*-nitrophenol, then this needs to be documented. In the present work, we endeavor neither to eliminate perceived experimental outlier points in the data set nor to obscure the most pertinent trends by inclusion of molecules that are significantly outside the area of biological interest (i.e., predominantly phosphates and oxyanion leaving groups). At the same time, it should be emphasized that the data set used here, though relevant for phosphoryl transfer, is not sufficiently large to draw more broad generalizations. It is likely that other more diverse chemical species will exhibit a larger range of errors.

4. Conclusion

Five multilevel and seven hybrid density functional methods have been tested against experimental gas-phase basicity and proton affinity values for a series of 17 molecules relevant to the study of biological phosphoryl transfer. The multilevel methods all have MAXE of around 2 kcal/mol, RMSE of around 1 kcal/mol, MUE ≤ 1 kcal/mol, and |MSE| ≤ 0.6 kcal/mol, with typical values less than 0.4 kcal/mol. The multicoefficient correlation methods (MCG3/3 and MC-QCISD), with inclusion of specific zero-point scale factors, slightly outperform the other multilevel methods tested (CBS-QB3, G3B3, and G3MP2B3), with significantly less computational cost, and in the case of MC-QCISD, slightly less severe scaling.

Four density functional methods, PBE1KCIS, MPW1B95, PBE0, and B1B95 perform nearly as well as the multilevel methods. The widely used B3LYP functional shows a relatively large, but systematic, error in the calculation of GPB and PA values, which may be largely offset by a set of effective O−H bond enthalpy and entropy correction terms. Two of the best performing density functional methods use Becke's B95 meta-GGA correlation functional, suggesting that a density functional method incorporating this functional (e.g., B1B95 or MPW1B95) shows promise in computational biochemistry applications where protonation/deprotonation events play an important role, such as in the prediction of pK_a shifts and linear free energy relations.

W1 calculations of the GPB and PA of water and hydronium support the accuracy of the experimental values. The same calculations on methanol and ethanol, however, deviate by 1.3–1.8 kcal/mol from the experimental values (although the calculations of the relative GPB and PA are in closer agreement). All of the multilevel methods tested in this work, including W1, predict that the GPB and PA of phosphoric acid are approximately 1–2 kcal/mol lower than the best current experimental values. Although this discrepancy is within the experimental error bars for this system, the calculated results, although not conclusive, are suggestive that the true value may indeed be lower than the experimental value. The fact that there currently exists only a few phosphate derivatives with available experimental GPB and PA values, and that these values have fairly large error bars, underscores the need for theory and experiment to work together to provide GPB and PA values at higher resolution and over a broader spectrum of biologically relevant phosphate compounds. Such a data set would be extremely useful in the design of next-generation quantum models for the study of phosphoryl transfer reactions in solution, enzymes and ribozymes.

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References and Notes

(1) Pliego, J. R., Jr.; Riveros, J. M. *J. Phys. Chem. A* **2002**, *106*, 7434–7439.

(2) da Silva, C. O.; da Silva, E. C.; Nascimento, M. A. C. *J. Phys. Chem. A* **1999**, *103*, 11194–11199.

(3) Jencks, W. P. *Chem. Rev.* **1985**, *85* (6), 511–527.

(4) Perreault, D. M.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 432–450.

(5) Goedecker, S. *Rev. Mod. Phys.* **1999**, *71*, 1085–1123.

(6) Yang, W.; Pérez-Jordá, J. M. In *Encyclopedia of Computational Chemistry*; von Schleyer, P. R., Ed.; John Wiley and Sons: New York, 1998; pp 1496–1513.

(7) Khandogin, J.; Musier-Forsyth, K.; York, D. M. *J. Mol. Biol.* **2003**, *330*, 993–1004.

(8) Khandogin, J.; York, D. M. *Proteins* **2004**, *56*, 724–737.

(9) Warshel, A.; Levitt, M. *J. Mol. Biol.* **1976**, *103*, 227–249.

(10) Gao, J.; Truhlar, D. G. *Annu. Rev. Phys. Chem.* **2002**, *53*, 467–505.

(11) Garcia-Viloca, M.; Gao, J.; Karplus, M.; Truhlar, D. G. *Science* **2004**, *303*, 186–195.

(12) Head-Gordon, M. *J. Phys. Chem.* **1996**, *100*, 13213–13225.

(13) Ochterski, J. W.; Petersson, G. A.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1996**, *104* (7), 2598–2619.

(14) Montgomery, J. A., Jr.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **1999**, *110* (6), 2822–2827.

(15) Montgomery, J. A., Jr.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **2000**, *112*, 6532–6542.

(16) Petersson, G. A.; Tensfeldt, T. G.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1991**, *94* (9), 6091–6101.

(17) Curtiss, L. A.; Jones, C.; Trucks, G. W.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **1990**, *93* (4), 2537–2545.

(18) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 7764–7776.

(19) Curtiss, L. A.; Redfern, P. C.; Rassolov, V.; Kedziora, G.; Pople, J. A. *J. Chem. Phys.* **2001**, *114* (21), 9287–9295.

(20) Martin, J. M. L.; de Oliveira, G. *J. Chem. Phys.* **1999**, *111*, 1843–1856.

(21) Parthiban, S.; Martin, J. M. L. *J. Chem. Phys.* **2001**, *114* (14), 6014–6029.

(22) Fast, P. L.; Truhlar, D. G. *J. Phys. Chem. A* **2000**, *104*, 6111–6116.

(23) Lynch, B. J.; Truhlar, D. G. *J. Phys. Chem. A* **2003**, *107* (19), 3898–3906.

(24) Zhao, Y.; Lynch, B. J.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2005**, *7*, 43–52.

(25) Lynch, B. J.; Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 1643–1649.

(26) Parr, R.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

(27) Zhao, Y.; González-García, N.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 2012–2018.

(28) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 5656–5667.

(29) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B.05; Gaussian, Inc.: Wallingford, CT, 2003.

(30) Werner, H.-J.; Knowles, P. J.; Lindh, R.; Schütz, M.; Celani, P.; Korona, T.; Manby, F. R.; Rauhut, G.; Amos, R. D.; Bernhardsson, A.; Berning, A.; Cooper, D. L.; Deegan, M. J. O.; Dobbyn, A. J.; Eckert, F.; Hampel, C.; Hetzer, G.; Lloyd, A. W.; McNicholas, S. J.; Meyer, W.; Mura, M. E.; Nicklass, A.; Palmieri, P.; Pitzer, R.; Schumann, U.; Stoll, H.; Stone, A. J.; Tarroni, R.; Thorsteinsson, T. MOLPRO, version 2002.6, a package of ab initio programs. 2003.

(31) Rodgers, J. M.; Lynch, B. J.; Fast, P. L.; Zhao, Y.; Pu, J.; Chuang, Y.-Y.; Truhlar, D. G. Multilevel version 3.1/g03. University of Minnesota, Minneapolis, 2002.

(32) Baboul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **1999**, *110*, 7650–7657.

(33) Pokon, E. K.; Liptak, M. D.; Feldgus, S.; Shields, G. C. *J. Phys. Chem. A* **2001**, *105*, 10483–10487.

(34) Becke, A. D. *J. Chem. Phys.* **1993**, *98* (7), 5648–5652.

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

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

(37) Adamo, C.; Scuseria, G. E. *J. Chem. Phys.* **1999**, *111*, 2889–2899.

(38) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865–3868.

(39) Becke, A. D. *J. Chem. Phys.* **1996**, *104* (3), 1040–1046.

(40) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108* (2), 664–675.

(41) Kurth, S.; Perdew, J. P.; Blaha, P. *Int. J. Quantum Chem.* **1999**, *75*, 889–909.

(42) Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2005**, *1* (3), 415–432.

(43) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908–6918.

(44) McNaught, A. D.; Wilkinson, A. *Compendium of Chemical Terminology: IUPAC Recommendations*, 2nd ed.; Blackwell Science, Inc.: Oxford, U.K., 1997.

(45) Cramer, C. J. *Essentials of Computational Chemistry: Theories and Models*, 2nd ed.; John Wiley & Sons: Chichester, England, 2002.

(46) McQuarrie, D. A. *Statistical Mechanics*; University Science Books: Mill Valley, CA, 1973.

(47) Range, K.; Riccardi, D.; Cui, Q.; Elstner, M.; York, D. M. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3070–3079.

(48) Linstrom, P., Mallard, W., Eds. *NIST Chemistry WebBook, NIST Standard Reference Database Number 69*; National Institute of Standards and Technology: Gaithersburg, MD; 2003.

(49) Harris, H. C.; Harris, D. C. *Quantitative Chemical Analysis*, 6th ed.; W. H. Freeman Co.: New York, 2002.

(50) DeTuri, V. F.; Ervin, K. M. *J. Phys. Chem. A* **1999**, *103*, 6911–6920.

(51) Bartmess, J. E.; Scott, J. A.; Robert T. McIver, J. *J. Am. Chem. Soc.* **1979**, *101*, 6056–6063.

(52) Hengge, A. C. *Acc. Chem. Res.* **2002**, *35*, 105–112.

(53) The experimental GPB and PA values for TMPH$^+$ are 205.7 and 212.9 kcal/mol, respectively (see ref 48). The corresponding GPB/PA errors in kcal/mol are −0.8/−1.0 for CBS-QB3, +0.6/−0.4 for G3B3, 1.1/0.1 for G3MP2B3, 1.0/0.9 for MCG3/3, 0.8/0.7 for MC-QCISD/3, 2.4/1.3 for MPW1KCIS, 2.2/1.1 for PBE1KCIS, 1.8/0.4 for MPW1B95, 1.6/0.5 for PBE0, 1.1/1.0 for B1B95, and 1.9/0.7 for B3LYP.