

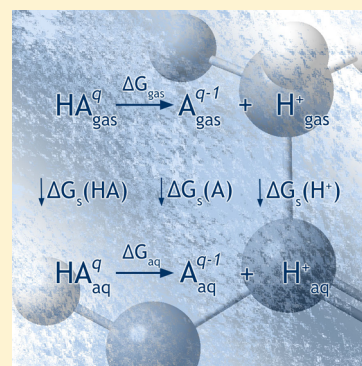
Solv-ccCA: Implicit Solvation and the Correlation Consistent Composite Approach for the Determination of pK_a

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Supporting Information

ABSTRACT: Direct theoretical methods are advantageous for the prediction of pK_a , as relative methods rely upon the experimental values of reference acid molecules that can limit application of the method to well-characterized systems. Here, a direct route is introduced, which incorporates the SMD universal solvation model¹ within the correlation consistent Composite Approach (ccCA). This Solv-ccCA methodology has been used for the prediction of theoretical pK_a values for nitrogen-containing species to within a mean absolute deviation (MAD) of 1.0 pK_a unit from experimental values by utilizing a thermodynamic cycle that combines gas-phase and solution-phase calculations. Several density functionals, including B3LYP, B97-1, B97-2, B98, BMK, M06, and M06-2X, were also evaluated for use with SMD and for comparison to Solv-ccCA.



1. INTRODUCTION

The pK_a of a molecule or functional group is an important chemical and biological property, aiding in the determination of protonation at a given pH as well as the likely protonation site of a molecule. Many thermodynamic schemes have been designed to calculate the pK_a of a system, varying in the degree to which they rely on experimental data.^{2–6} Generally, methods that use free energies from experiment to parametrize calculations are referred to as relative methods, and those that minimize the use of experimental reference energies are referred to as absolute or direct methods.

In previous studies, the accuracy of both direct and relative pK_a calculations was examined by Liptak and Shields.^{2,3,7,8} The direct thermodynamic cycle, depicted in Scheme 1, includes the deprotonation of an acid to form H_3O^+ . This is generally simplified in Scheme 2 as the dissociation of an acid (HA^q) into its conjugate base (A^{q-1}) and a lone proton (H^+).

Thus, the solvation free energy (ΔG_{aq}) for Scheme 2 can be calculated using

$$\Delta G_{aq} = \Delta G_{gas} - \Delta \Delta G_s \quad (1)$$

where

$$\Delta \Delta G_s = \Delta G_s - \Delta G_{gas} \quad (2)$$

$$\Delta G_{gas} = G_{gas}(A) + G_{gas}(H^+) - G_{gas}(HA) \quad (3)$$

$$\Delta G_s = \Delta G_s(A) + \Delta G_s(H^+) - \Delta G_s(HA) \quad (4)$$

Liptak and Shields calculated all ΔG values with ab initio composite methods, namely the Complete Basis Set (CBS) methods of Petersson et al.^{9–14} or the Gaussian- n (Gn) methods developed by Pople, Curtiss, Raghavachari, and co-

workers,^{15–18} and all ΔG_s values with a solvation approach, typically the conductor-like polarizable continuum solvation model (CPCM). The CBS methods are composite methods, designed to combine calculations from different levels of theory to minimize computational demand arising from electron correlation methods. CBS methods are so named for the explicit extrapolation of the correlation energy, which uses pair natural orbital expansion to asymptotic convergence. The Gn methods are also composite methods, which assume basis set additivity. The Gn methods do not include an explicit extrapolation, as in the CBS methods, but do include an empirical “high level correction” to minimize deviation from experimental values.

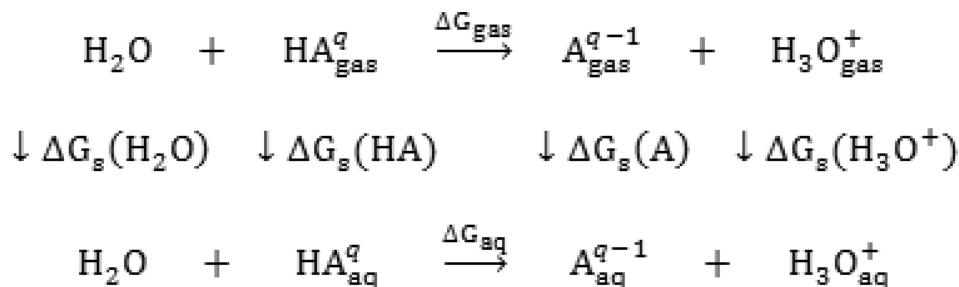
While there are several studies in the literature which incorporate the effects of solvation into composite methodologies, most include solvation as an additive energetic term at a density functional level of theory (DFT).^{19–22} A 2010 study by Ho and Coote¹⁹ calculated the pK_a values for a set of oxicams, nonsteroidal anti-inflammatory drugs (NSAIDs) with analgesic and antipyretic properties.²³ Various DFT methods were compared to the performance of G3MP2(+)-cc¹⁹ gas-phase calculations, with M05-2X yielding the most promising results. However, solvation effects were accounted for using B3LYP and a smaller basis set with CPCM, COSMO, and SMD continuum solvent models. Similarly, Dinescu et al.²¹ used the G3 composite method to calculate the free energies of solvation for oxygen transfer reactions in a variety of small systems. In this prior work, the effects of solvation were also included at the

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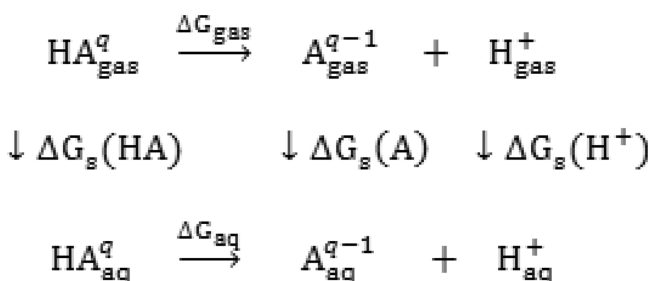
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Scheme 1. Direct Thermodynamic Cycle



Scheme 2. Dissociation of an Acid into Its Conjugate Base and a Lone Proton

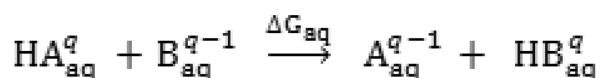


B3LYP level with a 6-31++G(2d,2p) basis set, using PCM, CPCM, IEFPCM, and COSMO continuum solvent models.

Liptak and Shields have shown that absolute solvation calculations using Scheme 2 are capable of producing pK_{a} values for a set of six small, uncharged carboxylic acids to within ~ 0.5 pK_{a} unit of experimental values when using CBS methods combined with CPCM. In the same studies, G_{n} methods used in conjunction with CPCM resulted in pK_{a} values within two units from experiment. Recently, the work of Casanovas and co-workers⁵ examined relative solvation schemes to determine the suitability of DFT methods and the CBS-QB3 composite method in calculating pK_{a} values of pyridines and carbon acids. The relative scheme used by Casanovas et al. is shown in Scheme 3, which depicts a proton exchange reaction between a reference acid (A)—with known experimental values—and an unknown acid (B). Alternatively, Casanovas et al. also investigated an isodesmic-style reaction that depicts the proton exchange reaction of Scheme 3 but excludes gas-phase calculations.

Casanovas and co-workers used Scheme 4 to examine 20 pyridine structures and 13 carbon acids, the building blocks of amino acids and deoxyribonucleosides. Using the relative scheme, pK_{a} values were calculated to within an MAD of 2.5 units of experimental values for both the pyridine and carbon

Scheme 4. Proton Exchange Reaction Excluding Gas-Phase Calculations

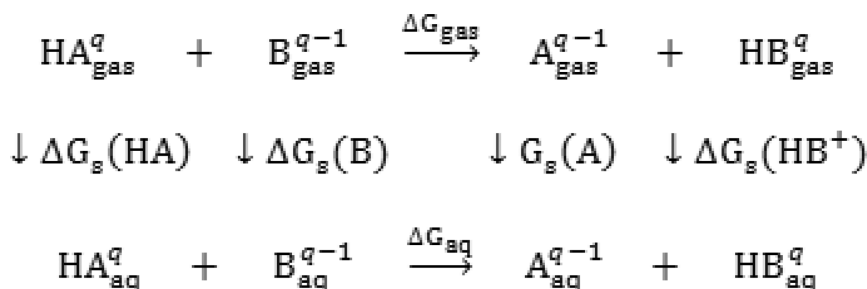


acid sets. DFT, specifically B3LYP, was able to produce pK_{a} values of comparable accuracy to CBS-QB3 (overall MAD within 3.5 pK_{a} units). For the substituted pyridines only, Casanovas and co-workers were able to achieve an MAD of 0.91 pK_{a} unit; however, the authors note that carbon acids are a known difficulty for computational solvation determinations, since these charged and zwitterionic species are poorly described by continuum solvent models.^{5,24,25} Some improvement in MAD (0.10–0.50 pK_{a} units) is observed by Casanovas when the carbon acids are microsolvated using individual water molecules, and similar results have subsequently been noted by Marenich et al.²⁶ and Sutton et al.⁶ in studies of carboxylic acids using various density functionals.

Because the relative method is parametrized using experimental data, Scheme 4 is limited by the amount of available experimental data in the literature. Additionally, Casanovas identifies that accuracy in the relative method is dependent upon those systems wherein there is little change in the geometries of HA^q/HB^q and $\text{A}^{q-1}/\text{B}^{q-1}$ (i.e., relative calculations are limited to structures which have the same geometries, regardless of being in the gas- or solution-phase).⁵

In the spirit of ab initio or first principles calculations, it would be advantageous to be able to determine unknown pK_{a} values in the absence of experimental values. Thus, Scheme 2 is utilized for the direct calculation of pK_{a} with the solvated variant of the correlation consistent composite approach (ccCA). This ab initio-based solvation method has been termed Solv-ccCA. The ccCA method is a composite approach which utilizes the correlation consistent basis sets developed by Dunning et al.^{27–31} and includes several forms: the original main group ccCA,^{32–36} Transition Metal ccCA (ccCA-

Scheme 3. Proton Exchange Reaction Between Reference Acid and Unknown Acid



TM),^{37,38} relativistic pseudopotential ccCA (rp-ccCA),^{39,40} multireference ccCA (MR-ccCA),⁴¹ and ONIOM-type QM:QM multilayered ccCA (ONIOM-ccCA).^{40,42,43} To date, ccCA has successfully been applied to gas-phase calculations of thermodynamic properties, including ionization potentials, enthalpies of formation, electron affinities, activation energies, isomerization energies, and bond dissociation energies to within 1 kcal mol⁻¹ (on average) of well-established experiment for hundreds of chemical species but has not been utilized to accurately describe species with significant solvent interactions. Thus, a reliable solvated variant would be desirable to utilize the accuracy and flexibility of ccCA for calculations in a solvated medium, extending this reliable composite methodology to new systems beyond the limitations of the gas phase.

For this investigation, the Solv-ccCA methodology has been applied to the set of 20 pyridine structures and 13 carbon acids from the Casanovas study and examined by calculating solvation free energies and, subsequently, pK_a values. A variety of density functionals are also used to examine the pyridines and carbon acids, and results are compared to experimental values as well as the direct pK_a values calculated by Solv-ccCA. Finally, the Solv-ccCA methodology is then applied to calculate the pK_a values for a set of thirty-two aliphatic amine systems, previously selected by Sumon and co-workers⁴⁴ for their relevance in CO₂ capture.

2. SOLVATED CCCA METHOD

In considering a fundamental equation of thermodynamics, where the pK_a is related to free energies of solvation as

$$\text{pK}_a = \frac{\Delta G_{\text{aq}}}{2.303RT} \quad (5)$$

a deviation of 1.36 kcal mol⁻¹ in the ΔG_{aq} value results in an error of a full pK_a unit. While a full discussion of the accuracies of various direct and relative cycles and methodologies is outside of the scope of this paper, a study by Ho and Coote⁴ indicates that an accuracy of 3.5 pK_a units from experiment can be expected when employing a direct thermodynamic cycle. This is larger than the predicted accuracy of relative cycles, which can be within 2 pK_a units from experiment.⁴ Liptak and Shields² identify that one source of error for direct schemes is the choice of free energy of solvation from experiment for the lone proton— $\Delta G_s(\text{H}^+)$. The Ho and Coote study⁴ notes five values have been provided for the free energy of solvation, $\Delta G_s(\text{H}^+)$. These energies range from -259.5 to -264 kcal mol⁻¹, representing a spread of 3 pK_a units.

In the present study, we use Camaioni's and Schwerdtfeger's value⁴⁵ of -265.9 kcal mol⁻¹ for $\Delta G_s(\text{H}^+)$, as it has been produced both by experiment⁴⁶ and theoretical⁴⁷ calculations, and we use -4.39 kcal mol⁻¹ for the value of $G_{\text{gas}}(\text{H}^+)$, derived using the Sackur–Tetrode equation.⁴⁸ Additionally, ΔG_{gas} values calculated using Solv-ccCA take into account the conversion from standard state in units atm to molar,^{49,50} and ΔG_{solv} is calculated using $[(E_{\text{soln}} + G_{\text{nes}}) - E_{\text{gas}}]$, as defined in the parametrization of continuum solvent models (such as SMD).⁵⁰

All structures were optimized with two DFT methods: B3LYP and M06-2X, using a triple- ζ correlation consistent basis set (cc-pVTZ). Subsequently, single-point energy calculations were performed using the B3LYP, B97-1, B97-2, B98, BMK, and M06 functionals and the cc-pVTZ basis set on the B3LYP optimized structures, with M06-2X/cc-pVTZ

single-point calculations on the M06-2X optimized structures. Specifically, the M06-2X optimizations and energy calculations were chosen because SMD was extensively optimized and parametrized using M05-2X.¹

The Solv-ccCA methodology incorporates the main group ccCA methodology. The ccCA method consists of a set of single-point energy calculations performed using a B3LYP/cc-pVTZ optimized geometry, with harmonic vibrational frequencies scaled by 0.9890.³⁵ The reference energy is calculated by separately extrapolating Hartree–Fock (HF) and second-order Møller–Plesset (MP2) single-point energies, using the Feller extrapolation^{35,51} for the more rapidly converging HF energies:

$$E(n) = E_{\text{CBS(HF)}} + B \exp(-1.63n) \quad (6)$$

The Feller extrapolation is a three-point extrapolation, a scheme that we have applied to the HF energies computed at the aug-cc-pVTZ and aug-cc-pVQZ basis set levels, as suggested by Halkier et al.^{51,52} For the MP2 energies, the ccCA-P scheme is used, implying the use of the Peterson extrapolation:⁵³

$$E(x) = E_{\text{CBS}} + B \exp[-(x-1)] + C \exp[-(x-1)^2] \quad (7)$$

This scheme uses energies computed using the aug-cc-pVDZ, aug-cc-pVTZ, and aug-cc-pVQZ basis sets for extrapolation to the CBS limit. For comparison, extrapolations were also performed using the ccCA-S3 and ccCA-S4 schemes, which include inverse cubic and quartic equations colloquially referred to as the Schwartz 3 and Schwartz 4 extrapolations:

$$E(l_{\text{max}}) = E_{\text{CBS}} + \frac{B}{(l_{\text{max}})^3} \quad (8)$$

$$E(l_{\text{max}}) = E_{\text{CBS}} + \frac{B}{\left(l_{\text{max}} + \frac{1}{2}\right)^4} \quad (9)$$

Both are two-point extrapolations, using energies computed at either the aug-cc-pVDZ and aug-cc-pVTZ levels or the aug-cc-pVTZ and aug-cc-pVQZ levels.

Correlation effects beyond the MP2 level of theory are accounted for using coupled cluster with single, double, and perturbative triple excitations (CCSD(T)), with additional steps to account for the effects of core–core and core–valence correlation and scalar relativistic effects. Finally, ZPE contributions are included to give the final ccCA energy:

$$E_{\text{ccCA}} = E(\text{MP2/CBS}) + \Delta E(\text{CC}) + \Delta E(\text{CV}) + \Delta E(\text{SR}) + \Delta E(\text{ZPE}) \quad (10)$$

The full ccCA formulation is discussed in-depth in ref 35.

Solvation free energies are calculated by optimizing the geometries using the SMD solvation model of Cramer and Truhlar at the B3LYP/cc-pVTZ level. SMD single-point energies are then calculated using ccCA, with the reference energies and various correlation contributions solvated at each step (i.e., SMD solvation energies were calculated using MP2 for each of the aug-cc-pVnZ basis sets to produce the extrapolated solvation free energy for the composite scheme, and then, SMD solvation energies were calculated using all other method/basis set combinations utilized within the steps of ccCA, including CCSD(T)/cc-pVTZ). This approach allows for an additive Solv-ccCA final energy similar to the gas-phase

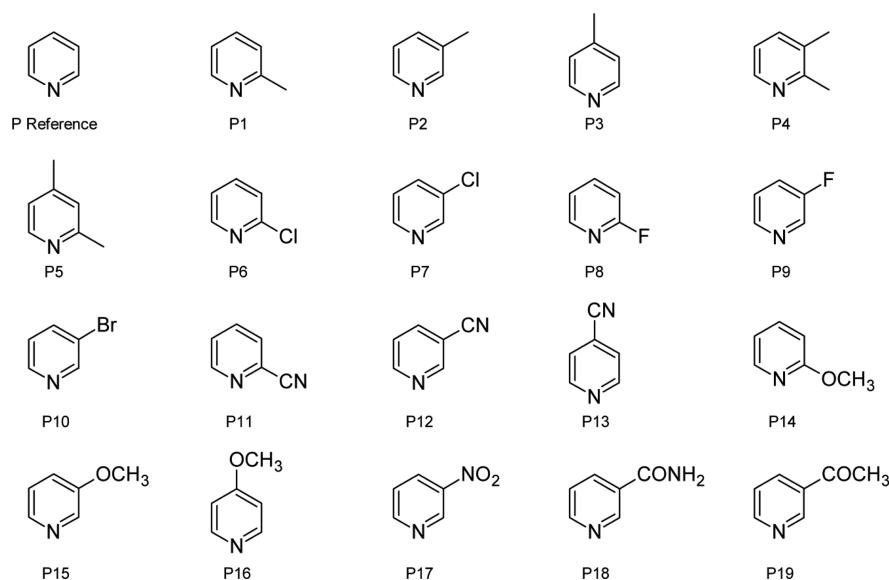


Figure 1. Pyridine systems.

composite approach explained above, wherein the difference between the gas-phase ccCA and Solv-ccCA calculations provides for the effects of solvation.

Free energies were calculated using the statistical thermodynamics of an ideal gas and harmonic oscillator rigid rotor approximation. All calculations were performed at 298.15 K using *Gaussian 2009*.⁵⁴

3. APPLICATION AND RESULTS

3.1. Pyridine Systems. The performance of DFT/pVTZ for the pyridine systems is within Ho's and Coote's accuracy of 3.5 pK_a units for each of the methods examined. Of the methods optimized using B3LYP, M06 yields the highest accuracy, with an MAD of 0.70 pK_a unit from experiment. Because the M06 family of functionals was developed by reparameterizing the M05 family of functionals, the superior accuracy of M06 is not unexpected: the SMD model was parametrized against a benchmark set of solvation data¹ using the M05-2X functional. The BMK functional also performs to within 1 pK_a unit (an MAD of 0.89), and the MAD of B3LYP is 1.05 pK_a units from experiment. In comparison to experiment, the B97-1, B97-2, B98, and M06-2X functionals yield pK_a values that differ by ~1.5 pK_a unit or more.

With the exception of M06 and M06-2X, the pK_a values for the density functional calculations result in maximum deviations that range from 1.92 to 4.04 pK_a units for the P1 structure (Figure 1), which is substituted with a methyl group connected ortho to the N1 position. Large deviations are also observed for the P4 and P5 structures (e.g., errors for B3LYP are 2.20 and 2.29 pK_a units, respectively), where both systems have methyl groups in the ortho position. When the methyl group is substituted by a halogen, such errors are not observed (e.g., errors for the chlorinated P6 structure and fluorinated P8 structure are ~0.8 pK_a unit for the B3LYP/cc-pVTZ calculations). This is in agreement with previous work by Casanovas et al.,^{5,55} in which the authors note that calculation of solvent effects on the pyridine nitrogen is hindered by the solvation spheres of neighboring atoms, which overlap the nitrogen sphere.

The M06 functional has a maximum deviation for the P6 structure (an error of 1.69 pK_a units), with similarly sized

deviations for the P1, P5, P8, and P11 structures (1.42, 1.27, 1.34, and 1.20 pK_a units, respectively). P6 and P8 pK_a values (for the halogenated structures discussed above) indicate that the M06 functional does not exhibit reduced deviations, as was shown for B3LYP. Additionally, performance of the BMK and M06-2X functionals for the P6, P8, and P11 structures do not show an improved description of the halogenated structures, with M06-2X yielding a maximum deviation of 3.75 pK_a units for the P8 structure and comparable deviations for P6 and P11. Overall, M06-2X pK_a values exhibit the largest deviations from experiment for the P6, P8, and P11 structures, and M06-2X yields a larger MAD (2.17 pK_a units) than for the pyridine pK_a values produced using B3LYP.

In general, each of the DFT methods examined tends to overestimate the experimental pK_a; however, the M06, M06-2X, and Solv-ccCA pK_a values generally underestimate experiment. The largest deviations for Solv-ccCA include structures P8 (maximum deviation of 3.03 pK_a units), P6, and P11—structures with pK_a values approaching zero. In contrast to the B3LYP calculations, Solv-ccCA exhibits a better description of structures with ortho-substituted methyl groups (P1, P4, and P5) but a larger overall MAD (1.35 pK_a units) in comparison to B3LYP.

Since the S3 and S4 ccCA formulations are two-point extrapolations, the quality of these calculations was also examined. On average, the S3 and S4 extrapolations using energies calculated with aug-cc-pVDZ and aug-cc-pVTZ basis sets (D,T notation) perform to comparable accuracy with the aug-cc-pVTZ, aug-cc-pVQZ two-point extrapolations (T,Q notation). The S4 (D,T) extrapolation scheme gives the smallest MAD (1.33 pK_a units from experiment), but the difference between it and the S3 extrapolations, which each exhibit the largest MAD (1.38 pK_a units) is only 0.05 pK_a unit. The improvement of S4 (D,T) over the Solv-ccCA Peterson extrapolation is even less—0.02 pK_a unit.

Because the S4 (D,T) extrapolation produced pK_a values with reduced deviations in comparison to the (T,Q) extrapolations, pK_s values were also calculated at each of the MP2/aug-cc-pVnZ levels, used in place of the extrapolated reference value, to better understand basis set behavior. The MP2/aug-cc-pVnZ pK_a values are provided in Table 1, along

Table 1. pK_a Values Determined for Pyridine Systems Using Solv-ccCA and Compared to Experiment^a

	Solv-ccCA (no extrapolation)			Solv-ccCA (various schemes)					expt. ⁵
	MP2/aug-cc-pVDZ	MP2/aug-cc-pVTZ	MP2/aug-cc-pVQZ	Peterson	S3 (D,T)	S4 (D,T)	S3 (T,Q)	S4 (T,Q)	
Pref	3.57	4.14	4.11	4.13	4.06	4.11	4.10	4.12	5.23
P1	5.47	6.07	6.02	6.04	6.01	6.05	6.01	6.03	5.97
P2	4.05	4.63	4.60	4.62	4.57	4.62	4.59	4.61	5.68
P3	4.34	4.96	4.93	4.96	4.90	4.95	4.93	4.95	6.02
P4	5.76	6.37	6.33	6.35	6.32	6.36	6.32	6.34	6.57
P5	6.08	6.73	6.68	6.70	6.69	6.73	6.68	6.70	6.99
P6	-2.66	-1.92	-2.04	-2.10	-1.98	-1.93	-2.14	-2.10	0.49
P7	0.50	1.12	1.06	1.04	1.05	1.09	1.01	1.04	2.81
P8	-4.17	-3.44	-3.49	-3.47	-3.50	-3.45	-3.51	-3.48	-0.44
P9	0.83	1.50	1.48	1.51	1.46	1.51	1.48	1.50	2.97
P10	0.13	0.76	0.72	0.77	0.75	0.80	0.74	0.76	2.84
P11	-3.37	-2.79	-2.89	-2.88	-2.88	-2.83	-2.92	-2.89	-0.26
P12	-0.64	-0.11	-0.16	-0.15	-0.20	-0.15	-0.18	-0.16	1.45
P13	-0.02	0.49	0.44	0.46	0.39	0.44	0.42	0.45	1.90
P14	1.93	2.59	2.49	2.49	2.53	2.58	2.46	2.49	3.28
P15	3.04	3.63	3.58	3.60	3.57	3.62	3.57	3.59	4.88
P16	5.16	5.81	5.79	5.82	5.76	5.81	5.79	5.81	6.62
P17	-1.57	-1.01	-1.08	-1.07	-1.09	-1.04	-1.11	-1.08	0.81
P18	1.73	2.28	2.24	2.26	2.21	2.26	2.23	2.25	3.40
P19	1.79	2.38	2.38	2.42	2.32	2.36	2.38	2.40	3.18
MAD	1.92	1.32	1.36	1.35	1.38	1.33	1.38	1.36	
RMSD	2.08	1.52	1.57	1.56	1.58	1.54	1.59	1.57	
MAX Dev	3.73	3.00	3.05	3.03	3.06	3.01	3.07	3.04	

^aSeveral different reference schemes have been considered. In the “Solv-ccCA (no extrapolation)”, the level shown (i.e., MP2/aug-cc-pVDZ) serves as the reference energy. For “Solv-ccCA (various schemes)”, several extrapolation schemes have been considered for the MP2 reference energy. Both the S3 and S4 schemes were considered, using energies arising from calculations at the basis set levels indicated (e.g. (D,T) refers to a reference energy based upon a CBS extrapolation of the MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ energies).

Table 2. B3LYP/pVTZ pK_a Values for the Pyridine Systems Compared to Solv-ccCA (Peterson Extrapolation) and Solv-ccCA with MP2/pVTZ- and MP2/aug-cc-pVTZ-Based Reference Energies^a

	B3LYP	Solv-ccCA (Peterson)	Solv-ccCA (MP2/aug-cc-pVTZ)	Solv-ccCA (MP2/pVTZ)	expt. ⁵
Pref	6.29	4.13	4.14	5.58	5.23
P1	8.41	6.04	6.07	7.50	5.97
P2	6.90	4.62	4.63	6.07	5.68
P3	7.35	4.96	4.96	6.40	6.02
P4	8.77	6.35	6.37	7.74	6.57
P5	9.28	6.70	6.73	8.16	6.99
P6	-0.31	-2.10	-1.92	-0.50	0.49
P7	3.05	1.04	1.12	2.51	2.81
P8	-1.21	-3.47	-3.44	-1.72	-0.44
P9	3.54	1.51	1.50	3.02	2.97
P10	2.60	0.77	0.76	2.10	2.84
P11	-0.66	-2.88	-2.79	-1.45	-0.26
P12	1.68	-0.15	-0.11	1.22	1.45
P13	2.37	0.46	0.49	1.84	1.90
P14	4.75	2.49	2.59	3.94	3.28
P15	6.00	3.60	3.63	5.11	4.88
P16	8.39	5.82	5.81	7.38	6.62
P17	0.65	-1.07	-1.01	0.43	0.81
P18	4.49	2.26	2.28	3.75	3.40
P19	4.37	2.42	2.38	3.82	3.18
MAD	1.05	1.35	1.32	0.64	
RMSD	1.26	1.56	1.52	0.77	
MAX Dev	2.44	3.03	3.00	1.53	

^aAll deviations are from experimental pK_a values.

with Solv-ccCA values using the ccCA-P, ccCA-S3, and ccCA-S4 forms for extrapolation to the CBS limit. The Solv-ccCA

calculations using MP2/aug-cc-pVTZ as the reference energy (with no extrapolation) give a slight improvement (0.03 pK_a

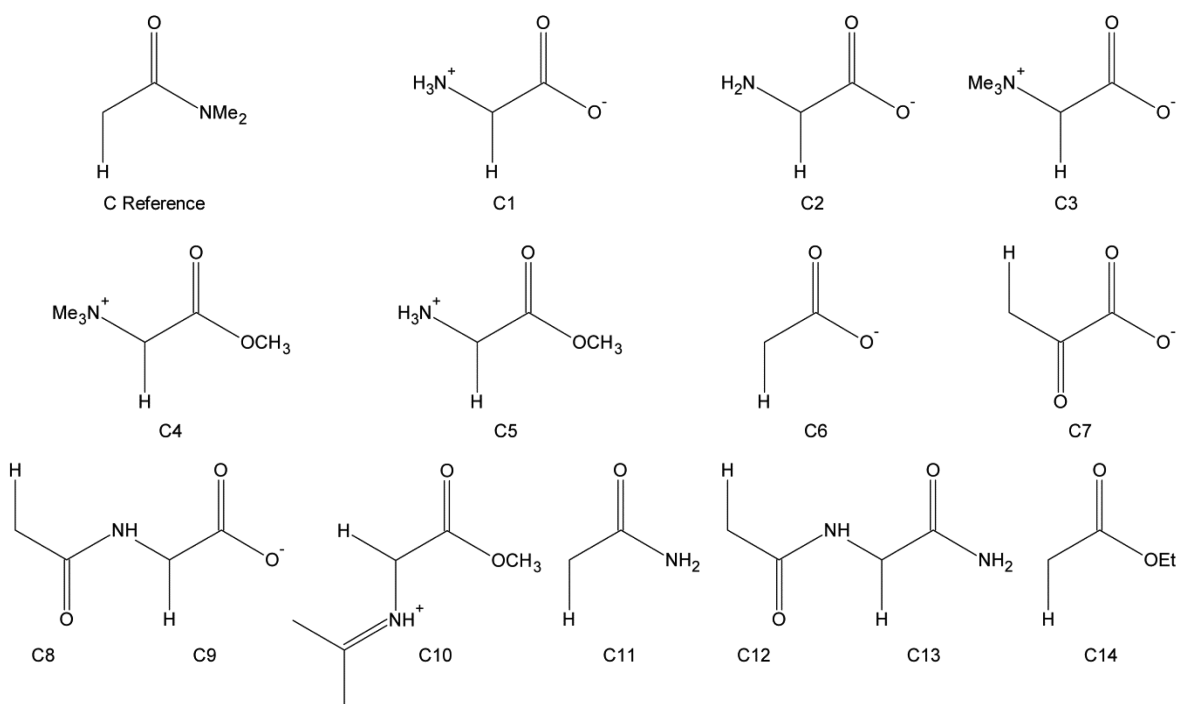


Figure 2. Carbon acids.

unit) over the full formalism. Overall, the pK_a values diverge from the experimental pK_a , with the MP2/aug-cc-pVDZ step performing most poorly (MAD = 1.92 pK_a units). A reduced deviation of 1.32 pK_a units is observed for the aug-cc-pVTZ step, while the aug-cc-pVQZ step exhibits another slight decrease in the accuracy (MAD = 1.36 pK_a units).

To further compare the Solv-ccCA reference energy to the DFT methods examined, pK_a values were also calculated based upon an MP2/pVTZ reference energy. Table 2 shows a comparison of these results against B3LYP and Solv-ccCA using the Peterson extrapolation and their deviations from experiment. Overall, Solv-ccCA with the MP2/pVTZ-based reference energy exhibits an MAD of 0.64 pK_a unit, outperforming the full Solv-ccCA. This deviation equates to an accuracy of 0.87 kcal mol⁻¹ on average, well within the desired 3.5 pK_a units but also within gas-phase chemical accuracy (1 kcal mol⁻¹).

As observed for the DFT/pVTZ calculations, Solv-ccCA with the MP2/pVTZ reference energy overestimates the experimental pK_a values, further highlighting the basis set dependence of the solvation calculations. Performance is significantly improved for the structures with pK_a values approaching zero, including P6, P8, P11, and P17, with a maximum deviation of 1.23 pK_a units (the P1 structure). In comparison, the maximum deviation from experiment for M06 is 1.69 pK_a units (P6). The accuracy of MP2/pVTZ-based Solv-ccCA is slightly decreased for P1, P4, and P5 in comparison to full Solv-ccCA. P1, P4, and P5 are structures with ortho- and para-substituted methyl groups that were previously identified as problematic for B3LYP-optimized solvation calculations, but overall, the MP2/pVTZ-based Solv-ccCA deviations from experiment are similar to M06 deviations and are improved in comparison to those calculated using B3LYP.

3.2. Carbon Acids. As shown in the Casanovas study, the performance of DFT/pVTZ for the calculation of carbon acid pK_a values is markedly decreased. It was previously noted by

Ho and co-workers⁵⁶ that many continuum solvation models (such as SMD) are parametrized using small, rigid molecules with little structural change between their gas- and solvent-phase structures. However, the carbon acid molecule set contains larger, more complex systems in comparison to the rigid pyridine structures, and the proposed methodology used in this study would be expected to yield larger deviations. In addition, Casanovas and co-workers⁵ note that while the experimental error of well-characterized systems is generally within 0.01–0.1 pK_a unit, the uncertainties of the carbon acids are can be expected to be within 0.1 to 1.0 pK_a unit or greater, due to their weak acidities in water. This error may contribute to large deviations when comparing experiment and calculated values.

On average, the B3LYP-optimized DFT/pVTZ calculations are within 12.0 pK_a units from experiment, and of these methods, M06 results in the best performance, with an MAD of 9.8 pK_a units from experiment. In contrast to the pyridine results, B3LYP performs comparably to M06 for the set of carbon acids (MAD = 10.2 pK_a units), which is slightly more accurate than the pK_a calculations using BMK (MAD = 10.6 pK_a units). In comparison to the B3LYP-calculated values, the B97-1, B97-2, and B98 pK_a values deviate by 1.0–2.0 pK_a units.

The resulting pK_a values from the DFT/pVTZ calculations each have a maximum deviation for the C2 structure (Figure 2), which consists of a carboxylate anion and an amine group connected beta to the site of deprotonation. For the pyridine systems, large deviations in pK_a were exhibited for multiple structures, but for the carbon acids, none of the pK_a values deviate as much as for C2. However, there are deviations for the zwitterionic structures (C1 and C3) around ~12.0 pK_a units, and large errors for the structures containing carboxylate anions (C2, C6, C7, and C9). Not taking C2 into account, deviations for the carbon anion structures are between 11.0 and 17.0 pK_a units. When the negatively charged oxygen is replaced by a methoxy group, the deviations for the B3LYP-calculated

Table 3. pK_a Values Determined for Carbon Acid Systems Using Solv-ccCA and Compared to Experiment^a

	Solv-ccCA (no extrapolation)			Solv-ccCA (various schemes)					expt. ⁵
	MP2/aug-cc-pVDZ	MP2/aug-cc-pVTZ	MP2/aug-cc-pVQZ	Peterson	S3 (D,T)	S4 (D,T)	S3 (T,Q)	S4 (T,Q)	
CRef	35.9	36.8	36.8e	36.8	36.8	36.9	36.7	36.8	29.4 (± 0.5)
C1	33.9	33.6	33.3	33.4	49.2	33.7	33.4	33.4	28.9 (± 0.5)
C2	47.0	47.4	47.1	47.7	48.2	48.2	47.7	47.7	34.0
C3	37.8	38.1	37.9	33.1	33.5	33.5	33.1	33.1	27.3 (± 1.2)
C4	24.6	24.5	24.2	18.5	18.8	18.9	18.4	18.5	18.0 (± 1.0)
C5	24.8	24.7	24.3	24.1	24.5	24.6	24.1	24.2	21.0 (± 1.0)
C6	43.8	44.4	44.1	44.0	44.4	44.5	43.9	44.0	33.5
C7	25.0	25.2	24.8	24.7	25.2	25.3	24.6	24.7	17.0
C8	36.3	36.8	36.6	36.7	36.9	37.0	36.7	36.6	30.3
C9	41.5	41.8	41.5	41.4	41.8	41.9	41.4	41.3	30.8
C10	20.0	19.9	19.5	13.8	14.2	14.2	13.7	13.8	14.0 (± 1.0)
C11	34.7	35.1	34.9	34.8	35.0	35.0	34.7	34.7	28.4 (± 0.5)
C12	35.5	36.0	35.8	30.9	31.1	31.1	30.8	30.9	29.1
C13	32.6	32.4	32.1	27.2	27.4	27.5	27.2	27.3	23.9
C14	31.2	31.5	31.2	31.1	31.5	31.6	31.1	31.1	25.6 (± 0.5)
MAD	7.6	7.8	7.5	5.8	7.2	6.2	5.8	5.8	
RMSD	8.0	8.2	8.0	6.9	8.8	7.2	6.9	6.9	
MAX Dev	13.0	13.4	13.1	13.7	20.3	14.2	13.7	13.7	

^aSeveral different reference schemes have been considered. In the “Solv-ccCA (no extrapolation)”, the level shown (i.e., MP2/aug-cc-pVDZ) serves as the reference energy. For “Solv-ccCA (various schemes)”, several extrapolation schemes have been considered for the MP2 reference energy. Both the S3 and S4 schemes were considered using energies arising from calculations at the basis set levels indicated (e.g. (D,T) refers to a reference energy based upon a CBS extrapolation of the MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ energies). Experimental uncertainties are included, where available.

pK_a values are substantially reduced (e.g., errors for the positively charged C4, C5, and C10 structures are 6.5, 3.6, and 4.4 pK_a units, respectively). To a lesser extent, the deviation of the ethoxy-substituted C14 is also reduced (an error of 7.4 pK_a units).

Surprisingly, the pK_a values calculated with the M06-2X functional exhibit the most favorable performance of all the DFT/pVTZ methods examined. Overall, M06-2X yields an MAD of 7.6 pK_a units from experiment, with a maximum deviation of 14.9 pK_a units for the C2 structure. As in the B3LYP-optimized structures, M06-2X shows worsened performance for the zwitterionic and carboxylate anionic structures and improved performance for the methoxy- and ethoxy-substituted structures. The maximum deviation for M06-2X is ~ 2.5 pK_a units lower than for B3LYP (17.6 pK_a units).

In general, each of the DFT methods examined overestimates the experimental pK_a , including the M06, M06-2X, and Solv-ccCA methods which previously underestimated pyridine experimental values. As in the case of the DFT calculations, the largest deviations for Solv-ccCA include structures C2 (maximum deviation of 13.7 pK_a units), C6, C7, and C9—zwitterionic and carboxylate anionic structures—but in comparison to M06-2X, the deviations are slightly decreased overall. When compared to M06-2X, Solv-ccCA exhibits a smaller MAD (5.8 pK_a units), despite slightly weaker performance for C5, C8, and C14, but improves upon the maximum deviation.

On average, Solv-ccCA is most consistent for both the pyridine and carbon acid structures; nevertheless, the reference energies were still examined to analyze possible basis set dependence shown previously. The values for pK_a calculated at each of the MP2/aug-cc-pVnZ levels for the carbon acids are provided in Table 3. In comparison to the full Solv-ccCA formalism, calculations using MP2/aug-cc-pVnZ (where an aug-cc-pVnZ level serves as the reference energy) are less

accurate. The MAD for MP2/aug-cc-pVDZ-based Solv-ccCA is 7.6 pK_a units, in comparison to the full Solv-ccCA MAD of 5.8, while the MADs for the MP2/aug-cc-pVTZ and MP2/aug-cc-pVQZ variants are 7.8 and 7.5 pK_a units, respectively. Overall, the pK_a values for the individual contributions of the MP2 steps converge toward the experimental pK_a as the basis set quality increases, with the MP2/aug-cc-pVQZ step performing most favorably, a slight decrease in accuracy observed for the aug-cc-pVTZ step, but slightly higher accuracy for the DZ step. As shown for the pyridine calculations, this behavior suggests a strong basis set dependence.

Solv-ccCA calculations with the S3 and S4 extrapolation schemes revealed that the (T,Q) extrapolations yield smaller MADs than their (D,T) counterparts. On average, the S3 MAD using energies calculated with the (T,Q) basis sets is smaller in comparison to the (D,T) extrapolation by ~ 1.5 pK_a units, but the S4 (T,Q) MAD is smaller than its (D,T) counterpart by only ~ 0.4 pK_a units. While the (T,Q) extrapolation schemes give the smallest MAD (5.8 pK_a units from experiment), the difference between these and S3 (D,T) (7.2 pK_a units) is 1.4 pK_a units. In addition, the performance of the (T,Q) extrapolations is comparable to the accuracy of the Solv-ccCA Peterson extrapolation—5.8 pK_a units from experiment.

To examine Solv-ccCA in comparison to the DFT methods, Table 4 shows the results of the MP2/pVTZ-based variant of Solv-ccCA alongside B3LYP and Solv-ccCA using the Peterson extrapolation and their deviations from experiment. Overall, Solv-ccCA with the MP2/pVTZ-based reference energy exhibits an MAD of 11.9 pK_a units, which is the largest deviation in comparison to both B3LYP and Solv-ccCA using the Peterson extrapolation. As stated previously, Solv-ccCA (Peterson) achieves higher accuracy than M06-2X for the carbon acids, also more accurate than B3LYP or the pVTZ/aug-cc-pVTZ variants of Solv-ccCA. Unfortunately, the pVTZ-based variant is not as accurate for the carbon acid systems as

Table 4. B3LYP/pVTZ pK_a Values for the Carbon Acid Systems Compared to Solv-ccCA (Peterson Extrapolation) and Solv-ccCA with MP2/pVTZ- and MP2/aug-cc-pVTZ-Based Reference Energies^a

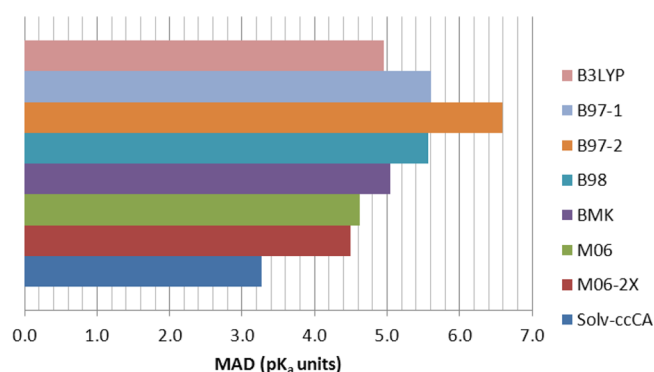
	B3LYP	Solv-ccCA (Peterson)	Solv-ccCA (MP2/aug-cc-pVTZ)	Solv-ccCA (MP2/pVTZ)	expt. ⁵
CRef	40.0	36.8	36.8	40.3	29.4 (± 0.5)
C1	40.0	33.4	33.6	36.2	28.9 (± 0.5)
C2	51.6	47.7	47.4	54.6	34.0
C3	40.2	33.1	38.1	42.3	27.3 (± 1.2)
C4	24.5	18.5	24.5	26.7	18.0 (± 1.0)
C5	24.6	24.1	24.7	27.1	21.0 (± 1.0)
C6	48.5	44.0	44.4	50.8	33.5
C7	28.1	24.7	25.2	30.3	17.0
C8	39.7	36.7	36.8	40.7	30.3
C9	44.2	41.4	41.8	48.1	30.8
C10	18.4	13.8	19.9	22.0	14.0 (± 1.0)
C11	38.1	34.8	35.1	39.2	28.4 (± 0.5)
C12	38.6	30.9	36.0	39.5	29.1
C13	33.9	27.2	32.4	36.7	23.9
C14	33.0	31.1	31.5	34.9	25.6 (± 0.5)
MAD	10.2	5.8	7.8	11.9	
RMSD	10.8	6.9	8.2	12.5	
MAX Dev	17.6	13.7	13.4	20.6	

^aAll deviations are from experimental pK_a values with uncertainties included, where available.

for the pyridine systems; however, Solv-ccCA (Peterson) is shown to be more consistent overall for the pyridine and carbon acid systems.

The MAD for the combined carbon acid and pyridine data sets reveals that Solv-ccCA (Peterson extrapolation) yields the highest overall accuracy (3.3 pK_a units) (Table 5). Of the DFT

Table 5. Overall MADs of Pyridine and Carbon Acid pK_a Values Calculated Using DFT/pVTZ in Comparison to Solv-ccCA (Peterson)



methods, B97-2 has the largest MAD (6.6 pK_a units), and while M06 and M06-2X may be expected to perform more favorably (due to the parametrization of SMD), the MADs for both are ~ 4.5 pK_a units with maximum deviations of 17.3 and 14.9 pK_a units, respectively.

3.3. Amine Systems. Table 6 shows the overall performance of Solv-ccCA for the amine systems (Figure 3) and the value of pK_a calculated at each of the MP2/aug-cc-pVnZ levels. Solv-ccCA using the Peterson extrapolation yields an MAD of 0.67 pK_a unit. Some Solv-ccCA pK_a values slightly overestimate

Table 6. Comparison of Amine pK_a Values Calculated Using Solv-ccCA (Peterson Extrapolation) and Solv-ccCA with an aug-cc-pVnZ-Based Reference Energy^a

	Solv-ccCA (Peterson)	Solv-ccCA (MP2/aug-cc-pVDZ)	Solv-ccCA (MP2/aug-cc-pVTZ)	Solv-ccCA (MP2/aug-cc-pVQZ)	expt. ⁴⁴
A01	10.99	10.98	11.25	11.12	10.84
A02	10.17	9.96	10.32	10.23	10.80
A03	10.16	10.13	10.38	10.25	10.73
A04	13.27	12.01	12.15	11.93	10.75
A05	9.36	10.77	11.11	11.05	10.68
A06	10.15	9.98	10.31	10.22	10.65
A07	10.60	10.37	10.73	10.65	10.63
A08	10.13	9.95	10.31	10.22	10.56
A09	10.03	9.85	10.20	10.11	10.54
A10	10.00	9.81	10.17	10.07	10.55
A11	9.56	9.38	9.71	9.64	10.66
A12	9.60	9.44	9.79	9.69	9.96
A13	8.46	9.81	9.93	9.72	9.80
A14	9.56	9.36	9.69	9.60	9.92
A15	9.16	9.26	9.46	9.30	9.85
A16	10.23	10.48	10.61	10.39	9.75
A17	9.05	8.85	9.21	9.14	9.68
A18	8.43	8.28	8.60	8.51	9.50
A19	8.38	8.26	8.55	8.45	9.45
A20	9.12	9.62	9.66	9.40	9.22
A21	8.32	8.34	8.60	8.45	8.88
A22	7.84	8.17	8.32	8.09	8.56
A23	7.41	7.84	7.88	7.61	7.78
A24	10.05	10.05	10.30	10.16	9.73
A25	10.05	10.03	10.30	10.16	9.57
A26	9.83	9.82	10.08	9.95	9.20
A27	9.71	9.75	10.02	9.88	9.14
A28	9.67	9.67	9.92	9.79	9.09
A29	9.27	9.51	9.67	9.46	8.38
A30	8.57	8.62	8.84	8.68	8.50
A31	8.77	9.07	9.23	8.98	7.67
A32	8.17	8.48	8.61	8.37	7.38
MAD	0.67	0.64	0.59	0.56	
RMSD	0.82	0.75	0.71	0.65	
MAX Dev	2.52	1.40	1.56	1.31	

^aAll deviations are from experimental pK_a values.

experimental values, while others underestimate, with the largest deviation for A04 (2.52 pK_a units), a triethylamine structure. Methyl group rotations often prove problematic for optimizations, but by adding hydroxyl substituents (as in A22 and A23), these rotations are effectively eliminated and accuracy is improved—0.72 and 0.37 pK_a unit, respectively.

The pK_a values from the MP2/aug-cc-pVnZ steps show that—unlike for the pyridine and carbon acid calculations—the deviations for the amine pK_a values decrease as basis set size increases. The Solv-ccCA calculations using MP2/aug-cc-pVQZ as the reference energy (with no extrapolation) give a slight improvement over the full formalism. The MAD for MP2/aug-cc-pVQZ-based Solv-ccCA is 0.56 pK_a unit, compared to the full Solv-ccCA MAD of 0.67 pK_a unit. The MP2/aug-cc-pVDZ step yields an MAD of 0.64 pK_a unit, with improvement observed for the TZ step (MAD = 0.59 pK_a unit) and further improvement in the accuracy for the QZ step.

3.4. Examination of Solvent Effects and Solv-ccCA Contributions. Additional calculations were performed to

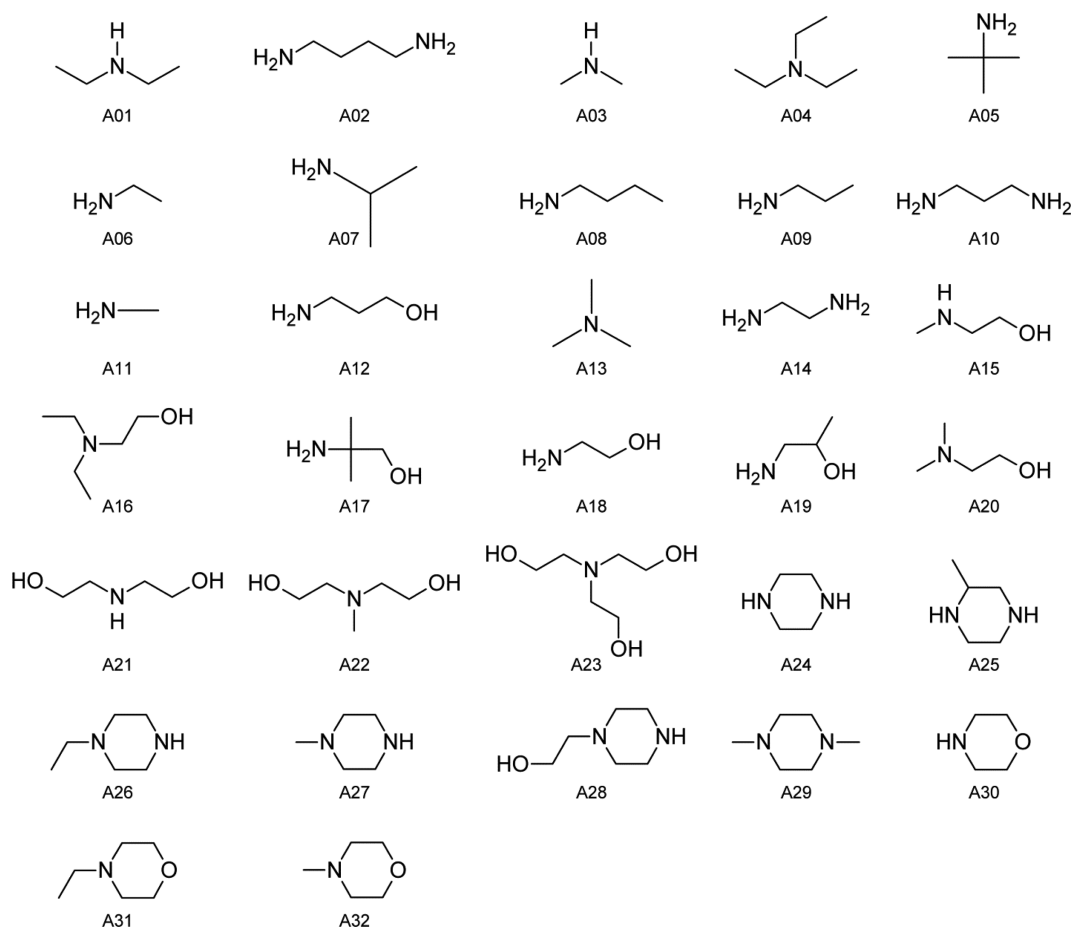


Figure 3. Amine systems.

further examine the effects of solvation in the Solv-ccCA method by incorporating solvation energies from SMD at the B3LYP/cc-pVTZ level in the main group ccCA methodology. Table 7 shows the comparison between the two styles of calculation for the set of pyridine structures, with a slightly larger MAD for ccCA with B3LYP solvent effects. The accuracy of main group ccCA with contributions from B3LYP is ~ 0.3 pK_a units larger than full B3LYP/cc-pVTZ calculations (1.38 versus 1.05 pK_a units, respectively) but is of comparable accuracy to Solv-ccCA with solvation incorporated in a stepwise fashion (1.35 pK_a units). The similar accuracies indicate that the decreased deviation in Solv-ccCA in comparison to DFT/cc-pVTZ calculations can be attributed to the improved treatment of the electronic energies alone, with only very limited benefit from calculating solvation energies at high levels of theory.

A similar comparison with the carbon acid set yield suggests that there is some computational savings to be gained from calculating solvation energies once at the B3LYP level, rather than at each step of Solv-ccCA. The MAD for Solv-ccCA on the carbon acid set is 5.8 pK_a units, with the deviation for main group ccCA with B3LYP solvent effects is 0.5 pK_a units smaller (5.3 pK_a units). However, ccCA calculations with solvation energies computed using B3LYP for the amine structures indicate that resource savings may not give comparable accuracies for all molecule types. While the MAD for Solv-ccCA on the amine set is 0.67 pK_a unit, the deviation for main group ccCA with added solvent effects from B3LYP/cc-pVTZ is larger (0.97 pK_a unit).

The contribution of the steps of Solv-ccCA to the overall accuracy was also analyzed for the pyridine and amine sets, revealing that the higher-order correlation energies provided by the CCSD(T) step are most significant in comparison to the core-core/core-valence and relativistic calculations. For the pyridine structures, the accuracy of the MP2/aug-cc-pVnZ Peterson extrapolation is within a deviation of 3.13 pK_a units from experiment, but by including contributions from higher-order correlation, the deviation decreases to 1.37 pK_a units (Table 8). Incorporation of the core-core/core-valence and scalar relativistic contributions, decreases the deviation only slightly (from 1.37 pK_a units to 1.32 and 1.35 pK_a units, respectively). Similarly, the accuracy for the MP2/aug-cc-pVnZ extrapolation for the amines achieves an overall MAD of 1.42 pK_a units from experiment, and the CCSD(T) contribution decreases this deviation to 0.67 pK_a units. Changes in the accuracy due to core-core/core-valence and relativistic calculations are comparatively small (resultant MADs for the amine structures are 0.68 and 0.67 pK_a units, respectively), further indicating that the recovered correlation from the higher-order CCSD(T) calculation is the significant energetic contribution in Solv-ccCA.

4. CONCLUSIONS

The Solv-ccCA solvated composite approach has been designed using an absolute thermodynamic cycle and yields an overall accuracy of 3.3 pK_a units for the pyridine and carbon acid species examined. The accuracy of Solv-ccCA is within Ho's and Coote's recommended accuracy of 3.5 pK_a units for a direct

Table 7. B3LYP/pVTZ pK_a Values for the Pyridine Systems Compared to Solv-ccCA (Peterson Extrapolation) and Main Group ccCA with Solvation Energies Incorporated at the B3LYP/pVTZ level^a

	B3LYP	Solv-ccCA (Peterson)	Solv-ccCA (B3LYP/cc-pVTZ)	expt. ⁵
Pref	6.29	4.13	4.32	5.23
P1	8.41	6.04	6.28	5.97
P2	6.90	4.62	4.79	5.68
P3	7.35	4.96	5.06	6.02
P4	8.77	6.35	6.57	6.57
P5	9.28	6.70	6.87	6.99
P6	−0.31	−2.10	−1.87	0.49
P7	3.05	1.04	1.24	2.81
P8	−1.21	−3.47	−3.33	−0.44
P9	3.54	1.51	1.46	2.97
P10	2.60	0.77	6.57	2.84
P11	−0.66	−2.88	−2.85	−0.26
P12	1.68	−0.15	−0.08	1.45
P13	2.37	0.46	0.30	1.90
P14	4.75	2.49	2.42	3.28
P15	6.00	3.60	3.54	4.88
P16	8.39	5.82	5.79	6.62
P17	0.65	−1.07	−0.98	0.81
P18	4.49	2.26	2.22	3.40
P19	4.37	2.42	2.56	3.18
MAD	1.05	1.35	1.38	
RMSD	1.26	1.56	1.66	
MAX Dev	2.44	3.03	3.73	

^aAll deviations are from experimental pK_a values.

Table 8. MADs for Individual Contributions to the Solv-ccCA Energy for the Pyridine Structures^a

	MAD (pK_a units)
MP2/aug-cc-pVnZ (Peterson extrap.)	3.13
...+[CCSD(T)/cc-pVTZ−MP2/cc-pVTZ]	1.37
...+[MP2(FC1)/aug-cc-pCVTZ−MP2/aug-cc-pVTZ]	1.32
...+[MP2(DK)/cc-pVTZ-DK−MP2/cc-pVTZ]	1.35

^aDeviations are from experimental pK_a values.

thermodynamic cycle, and in comparison to the DFT methods investigated in this study, Solv-ccCA is the only method that achieves this accuracy.

Despite known difficulties in describing electrostatic interactions for charged and zwitterionic species, Solv-ccCA is also able to achieve smaller deviations for carbon acid species in comparison to DFT methods, with no empirical parametrization or fitting to experimental reference values required. Though computational savings will be gained by determining solvation effects using B3LYP rather than higher level electron correlation methods, this does result in a slight decrease in the overall accuracy. When applied to the set of amine systems, Solv-ccCA yields an MAD of 0.67 pK_a unit, contributing to an average deviation of 0.93 kcal mol^{−1} for the nitrogen-containing systems and indicating that the better performance of Solv-ccCA over the DFT methods examined is a direct result of the improved treatment of the electronic energies.

■ ASSOCIATED CONTENT

■ Supporting Information

pK_a values calculated using DFT/pVTZ and Solv-ccCA (Peterson) for the pyridine and carbon acid systems and their deviations from experiment. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.
- (2) Liptak, M. D.; Shields, G. C. *Int. J. Quantum Chem.* **2001**, *85*, 727.
- (3) Liptak, M. D.; Shields, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 7314.
- (4) Ho, J.; Coote, M. *Theor. Chem. Acc.* **2010**, *125*, 3.
- (5) Casasnovas, R.; Fernández, D.; Ortega-Castro, J.; Frau, J.; Donoso, J.; Muñoz, F. *Theor. Chem. Acc.* **2011**, *130*, 1.
- (6) Sutton, C. C. R.; Franks, G. V.; da Silva, G. J. *Phys. Chem. B* **2012**, *116*, 11999.
- (7) Toth, A. M.; Liptak, M. D.; Phillips, D. L.; Shields, G. C. *J. Chem. Phys.* **2001**, *114*, 4595.
- (8) Liptak, M. D.; Gross, K. C.; Seybold, P. G.; Feldgus, S.; Shields, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6421.
- (9) Nyden, M. R.; Petersson, G. A. *J. Chem. Phys.* **1981**, *75*, 1843.
- (10) Petersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081.
- (11) Petersson, G. A.; Yee, A. K.; Bennett, A. J. *J. Chem. Phys.* **1985**, *83*, 5105.
- (12) Montgomery, J. A., Jr.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **1994**, *101*, 5900.
- (13) Ochterski, J. W.; Petersson, G. A.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1996**, *104*, 2598.
- (14) Montgomery, J. A., Jr.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **1999**, *110*, 2822.
- (15) Pople, J. A.; Head-Gordon, M.; Fox, D. J.; Raghavachari, K.; Curtiss, L. A. *J. Chem. Phys.* **1989**, *90*, 5622.
- (16) Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys.* **1991**, *94*, 7221.
- (17) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Pople, J. A. *J. Chem. Phys.* **1997**, *106*, 1063.
- (18) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Pople, J. A. *J. Chem. Phys.* **2000**, *112*, 7374.
- (19) Ho, J.; Coote, M. L.; Franco-Pérez, M.; Gómez-Balderas, R. J. *Phys. Chem. A* **2010**, *114*, 11992.
- (20) Sastre, S.; Casasnovas, R.; Muñoz, F.; Frau, J. *Theor. Chem. Acc.* **2012**, *132*, 1.

- (21) Dinescu, A.; Whiteley, C.; Combs, R. R.; Cundari, T. R. *J. Phys. Chem. A* **2006**, *110*, 4053.
- (22) Namazian, M.; Coote, M. L. *J. Phys. Chem. A* **2007**, *111*, 7227.
- (23) Olkkola, K. T.; Brunetto, A. V.; Mattila, M. J. *Clin. Pharmacokinet.* **1994**, *26*, 107.
- (24) Takano, Y.; Houk, K. N. *J. Chem. Theory Comput.* **2004**, *1*, 70.
- (25) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Theory Comput.* **2005**, *1*, 1133.
- (26) Marenich, A. V.; Ding, W.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. Lett.* **2012**, *3*, 1437.
- (27) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007.
- (28) Xantheas, S. S.; Dunning, T. H., Jr. *J. Phys. Chem.* **1993**, *97*, 18.
- (29) Dunning, T. H., Jr.; Peterson, K. A.; Wilson, A. K. *J. Chem. Phys.* **2001**, *114*, 9244.
- (30) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796.
- (31) Woon, D. E.; Dunning, T. H., Jr. *J. Chem. Phys.* **1994**, *100*, 2975.
- (32) DeYonker, N. J.; Cundari, T. R.; Wilson, A. K. *J. Chem. Phys.* **2006**, *124*, 114104.
- (33) DeYonker, N. J.; Grimes, T.; Yockel, S.; Dinescu, A.; Mintz, B.; Cundari, T. R.; Wilson, A. K. *J. Chem. Phys.* **2006**, *125*, 104111.
- (34) DeYonker, N. J.; Ho, D. S.; Wilson, A. K.; Cundari, T. R. *J. Phys. Chem. A* **2007**, *111*, 10776.
- (35) DeYonker, N. J.; Wilson, B. R.; Pierpont, A. W.; Cundari, T. R.; Wilson, A. K. *Mol. Phys.* **2009**, *107*, 1107.
- (36) Prascher, B. P.; Lai, J. D.; Wilson, A. K. *J. Chem. Phys.* **2009**, *131*, 044130.
- (37) DeYonker, N. J.; Williams, T. G.; Imel, A. E.; Cundari, T. R.; Wilson, A. K. *J. Chem. Phys.* **2009**, *131*, 024106.
- (38) Jiang, W.; DeYonker, N. J.; Determan, J. J.; Wilson, A. K. *J. Phys. Chem. A* **2012**, *116*, 870.
- (39) Laury, M. L.; DeYonker, N. J.; Jiang, W.; Wilson, A. K. *J. Chem. Phys.* **2011**, *135*, 214103.
- (40) Oyedepo, G. A.; Wilson, A. K. *ChemPhysChem* **2011**, *12*, 3320.
- (41) Oyedepo, G. A.; Wilson, A. K. *J. Phys. Chem. A* **2010**, *114*, 8806.
- (42) Das, S. R.; Williams, T. G.; Drummond, M. L.; Wilson, A. K. *J. Phys. Chem. A* **2010**, *114*, 9394.
- (43) Riojas, A. G.; John, J. R.; Williams, T. G.; Wilson, A. K. *J. Comput. Chem.* **2012**, *33*, 2590.
- (44) Sumon, K. Z.; Henni, A.; East, A. L. *Ind. Eng. Chem. Res.* **2012**, *51*, 11924.
- (45) Camaioni, D. M.; Schwerdtfeger, C. A. *J. Phys. Chem. A* **2005**, *109*, 10795.
- (46) Tissandier, M. D.; Cowen, K. A.; Feng, W. Y.; Gundlach, E.; Cohen, M. H.; Earhart, A. D.; Coe, J. V.; Tuttle, T. R. *J. Phys. Chem. A* **1998**, *102*, 7787.
- (47) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2006**, *110*, 16066.
- (48) McQuarrie, D. A. *Statistical Mechanics*; University Science Books: Sausalito, CA, 2000.
- (49) Liptak, M. D.; Gross, K. C.; Seybold, P. G.; Feldgus, S.; Shields, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6421.
- (50) Hodgson, J. L.; Roskop, L. B.; Gordon, M. S.; Lin, C. Y.; Coote, M. L. *J. Phys. Chem. A* **2010**, *114*, 10458.
- (51) Halkier, A.; Helgaker, T.; Jørgensen, P.; Klopper, W.; Olsen, J. *Chem. Phys. Lett.* **1999**, *302*, 437.
- (52) Halkier, A.; Helgaker, T.; Jørgensen, P.; Klopper, W.; Koch, H.; Olsen, J.; Wilson, A. K. *Chem. Phys. Lett.* **1998**, *286*, 243.
- (53) Peterson, K. A.; Woon, D. E.; Dunning, T. H., Jr. *J. Chem. Phys.* **1994**, *100*, 7410.
- (54) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochtershi, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Revision A.02 ed.; Gaussian, Inc.: Wallingford, CT, 2009.
- (55) Casanovas, R.; Frau, J.; Ortega-Castro, J.; Salvá, A.; Donoso, J.; Muñoz, F. J. *Mol. Struct. THEOCHEM* **2009**, *912*, 5.
- (56) Ho, J.; Klamt, A.; Coote, M. L. *J. Phys. Chem. A* **2010**, *114*, 13442.