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ARTICLE *in* THE JOURNAL OF PHYSICAL CHEMISTRY A · JANUARY 2006

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pK_a of Acetate in Water: A Computational Study

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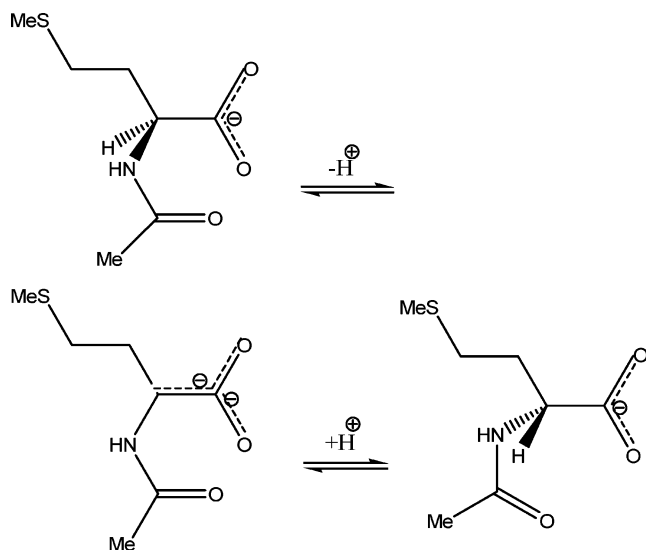
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Received: July 19, 2005; In Final Form: September 30, 2005

Several computational methods including the conductor-like polarizable continuum model, CPCM with both UAKS and UAHF cavities, Cramer and Truhlar's generalized Born solvation model, SM5.4(AM1), SM5.4-(PM3), and SM5.43R(mPW1PW91/6-31+G(d)), and mixed QM/MM-Ewald simulations were used to calculate the pK_a values of acetate and bicarbonate anions in aqueous solution. This work provided a critical and comprehensive assessment of the quality of these theoretical models in the calculation of aqueous solvation free energies for the singly charged acetate and bicarbonate ions, as well as the doubly charged acetate dianion and carbonate dianion. It was shown that QM/MM-Ewald simulations could give an accurate and consistent evaluation of the pK_a values of acetate and bicarbonate based on both the relative and absolute pK_a formulas, while other methods could yield satisfactory results only for certain calculations. However, this does not mean that the current QM/MM-Ewald protocol is superior to other methods. The useful information obtained in this investigation is that both the absolute and relative pK_a formulas should better be tested in accurate calculations of pK_a values based on any methods.

1. Introduction

The deprotonation of a carboxylate ion is important and widespread in chemistry and biochemistry, ranging from racemization of amino acids to carbon–carbon bond formation via carbon anion intermediates.^{1–3} For example, the following enzyme-catalyzed racemization reaction of *N*-acyl methionine proceeds through deprotonation and protonation of the α-carbon of the amino acid carboxylate.⁴



Carbonanions are reactive species, especially in aqueous solution where biological processes take place. The acidity of carbon acids is typically very low with large pK_a values. Consequently, these ions must be stabilized through delocal-

ization of charges or by electrostatic stabilization in the enzyme-active site. Experimental methods with flash photolysis⁵ and NMR measurement of the kinetic deuterium exchange rate^{6–11} have been instrumental for determining the equilibrium constants and pK_a values of weak organic carbon acids. Recently, the enolization of carboxylate ions and the related enzyme mechanisms have been investigated by Richard and co-workers, who determined the pK_a value of acetate anion in water using the newly developed kinetics methods.⁸ Their reported result is pK_a = 33.5. On the theoretical side, calculations of the pK_a values of an anion represent a great challenge due to the need of the accurate solvation free energies for the ionized, doubly charged dianions. Little work in this regard has been done so far. To provide insight into anionic solvation in aqueous solution, we have performed an extensive computational study of the pK_a calculations of the weak ionic carbon acid, acetate, in aqueous solution using a variety of easily accessible theoretical models. This work is important for the understanding of solute–solvent interactions, for the interpretation and confirmation of experimental results, and for the evaluations of the performance of different computational solvation models particularly for the calculations of highly charged anions. The deprotonation of acetate in water can serve as a reference reaction for the discussion of the mechanisms of the relevant enzymatic processes.

There have been many computational studies of pK_a values.^{12–24} Now the pK_a calculation of some small simple organic compounds has reached chemical accuracy^{16,17} thanks to the development of the powerful theoretical approaches and advances in computer hardware and software. However, previous work was basically focused on the calculations of neutral species or singly charged cations due to inaccurate computational evaluations of hydration and or solvation free energies for doubly charged ions. In this paper, we report our calculations of the pK_a values of two ionic species, acetate and the related

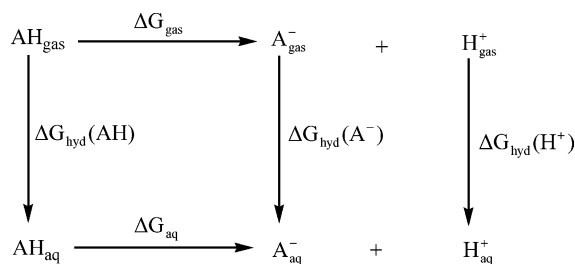
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bicarbonate, using several state-of-the-art computational models. In particular, this includes the calculation of hydration free energies for the doubly charged enolate dianion and carbonate.

Currently, both the dielectric continuum^{25–27} and explicit^{28–30} solvation models are widely used to calculate solvation energies. The continuum models have the advantage of computational efficiency and the treatment of long-range electrostatic interactions. The explicit models of solvent such as Monte Carlo and molecular dynamics simulation approaches can give detailed solvent structures surrounding the solute. But explicit models are computationally demanding and lack the accurate treatment of long-range solute–solvent interactions unless the Ewald lattice-sum technique or the fast multipole methods are employed.³¹ Since this work deals with the calculation of anions and in particular the highly charged dianions in solution, the impact of long-range electrostatic interactions could be significant. We used Monte Carlo simulations with the combined quantum mechanical and molecular mechanical (QM/MM) potentials augmented with the Ewald method in our calculations.³² Note that another well-known protocol—the Langevin dipole solvation model developed by Warshel and co-workers—would also be a good choice to efficiently calculate pK_a values.^{12a–c} More importantly, the use of the Ewald summation with the periodic boundary conditions to treat long-range electrostatics may not be a perfect solution for the infinitely dilute solutions because the formula was not developed to represent nonperiodic systems. The potential size dependence problems associated with the standard Ewald calculations could be overcome by the surface constraint all-atom solvent (SCAAS) model with the spherical boundary conditions and the local reaction field method.^{12d} We also used the conductor-like version of polarization continuum model (CPCM)^{33–35} implemented in Gaussian 03,³⁶ as well as Cramer and Truhlar's SMx continuum models which employ the generalized Born (GB) approximation.^{37–40} We will demonstrate the success and reliability of these theoretical models, in particular the Monte Carlo QM/MM methods. We will also show, for the first time, that the experimental values of the hydration free energies for the bicarbonate and carbonate anions reported by Marcus in 1994 are in serious error through our detailed analysis and justification (see section 4.5).⁴¹

2. Computational Design

We used the following thermodynamic cycle to calculate both the absolute and relative pK_a values of an acid AH in aqueous solution. We found this simple cycle appropriate in the present calculations. Other schemes that include an explicit water and a hydronium ion (H₃O⁺) were found to be inferior to this simple cycle in the calculation of pK_a values.^{16,24}



The pK_a of AH in water is related to the basicity of the conjugate base A[−], gas-phase acidity ΔG_{gas}, and aqueous solvation Gibbs free energies for AH, A[−], and proton H⁺.

$$\text{p}K_{\text{a}}(\text{AH}) = \frac{1}{2.303RT} [\Delta G_{\text{gas}}(\text{AH}) + \Delta G_{\text{hyd}}(\text{A}^{-}) + \Delta G_{\text{hyd}}(\text{H}^{+}) - \Delta G_{\text{hyd}}(\text{AH})] \quad (1)$$

$$\text{p}K_{\text{a}}(\text{AH}) = -\log K_{\text{a}} = \frac{\Delta G_{\text{aq}}}{2.303RT}$$

$$\Delta G_{\text{aq}}(\text{AH}) = \Delta G_{\text{gas}}(\text{AH}) + \Delta G_{\text{hyd}}(\text{A}^{-}) + \Delta G_{\text{hyd}}(\text{H}^{+}) - \Delta G_{\text{hyd}}(\text{AH})$$

In eq 1, ΔG_{gas} is the Gibbs free energy for the deprotonation of acid AH in the gas phase at 1 atm and 25 °C, which can be obtained by high-level ab initio calculations. ΔG_{hyd}(AH) and ΔG_{hyd}(A[−]) are the absolute free energies of hydration for the acid AH and its anion A[−]. The absolute hydration free energies are obtained through Monte Carlo QM/MM free energy perturbation (FEP)^{12b,30} calculations by perturbing AH and A[−] to nothing in solution, respectively. The absolute hydration free energies can also be easily collected with the use of continuum models with Gaussian 03 (for the CPCM) and Spartan 04 (for SM5.4/AM1 and SM5.4/PM3).⁴² There have been some discussions about the accuracy of the value of experimental absolute hydration free energy of proton. The value of ΔG_{hyd}(H⁺) seemed to converge to −264.0 kcal/mol in several recent experimental and theoretical publications.^{37,43–48} We used this value for our calculations in this work.

Although the calculation of the absolute pK_a is straightforward with eq 1, its accuracy depends on the determination of the absolute hydration free energies for AH, A[−], and H⁺, as well as the gas-phase acidity. To reduce the errors from solution-phase calculations and to avoid the uncertainty of the experimental free energy of hydration for proton, the absolute pK_a can be obtained alternatively through a relative formula by selecting another structurally similar acid BH whose pK_a value is well-known. This is done by subtraction of a similar equation for BH from eq 1.

$$\text{p}K_{\text{a}}(\text{AH}) - \text{p}K_{\text{a}}(\text{BH}) = \frac{1}{2.303RT} [\Delta \Delta_{\text{gas}}(\text{BH} \rightarrow \text{AH}) + \Delta \Delta G_{\text{hyd}}(\text{B}^{-} \rightarrow \text{A}^{-}) - \Delta \Delta G_{\text{hyd}}(\text{BH} \rightarrow \text{AH})] \quad (2)$$

Here in this work, AH represents CH₃CO₂[−], A[−] is CH₂=CO₂^{2−}, BH is HCO₃[−], and B[−] is CO₃^{2−}. The three terms in the brackets of eq 2 are differences in free energies of hydration for the anions and dianions, and in the gas-phase acidities (ΔΔ_{gas}(BH → AH) = ΔG_{gas}(AH) − ΔG_{gas}(BH)).

In this study, we took the experimental pK_a value of bicarbonate HCO₃[−] as 10.3⁴⁹ and eq 2 to calculate the pK_a of acetate in water. To critically examine the performance of different solvation models, we also used eq 1 to calculate the pK_a values of both acetate and bicarbonate. Useful information about the quality of different theoretical models can be obtained through comparing these computed pK_a values with the experimental values of both acetate and bicarbonate anions.

3. Computational Details

3.1. Gas-Phase Structures. The geometries of the four ions, acetate (CH₃CO₂[−]), enolate dianion (CH₂=CO₂^{2−}), bicarbonate (HCO₃[−]), and carbonate (CO₃^{2−}), were optimized at the Hartree–Fock level with the triple split valence 6-311+G(d,p) basis set.^{50–52} It is essential to include diffuse functions for anions.⁵³ All the optimized structures were confirmed to be energy minima by vibrational frequency calculations with all

TABLE 1: Computed Thermodynamic Properties for the Carbon Acid Ionization Reaction in the Gas Phase at 25 °C and 1 atm at the MP2/Aug-cc-pVTZ//HF/6-311+G(d,p) Level^a

	$\text{CH}_3\text{CO}_2^- \rightarrow \text{CH}_2=\text{CO}_2^{-2} + \text{H}^+$	$\text{HCO}_3^- \rightarrow \text{CO}_3^{-2} + \text{H}^+$
HF/6-311+G(d,p)	517.2	497.8
HF/aug-cc-pVTZ	516.9	499.4
MP2/aug-cc-pVTZ	503.1	488.0
ΔE_v^0	-9.0	-7.9
$\Delta(\Delta E_v)^{298,15}$	0.1	-0.2
$\Delta H^{298,15}$	495.7	481.3
$\Delta S^{298,15}$	21.1	21.4
$\Delta G^{298,15}$	489.4	475.0

^a Energies are given in kcal/mol, and entropies in cal/(mol·K).

real frequencies. The structures in terms of the Z-matrix are given in the Supporting Information.

3.2. Gas-Phase Acidities. Ab initio vibrational frequencies from HF/6-311+G(d,p) calculations were scaled by a factor of 0.9 for the evaluation of the zero-point energy, its thermal corrections, and entropies. Frequencies below 500 cm⁻¹ were treated as classical rotators.⁵³ The reaction enthalpy of the gas-phase ionization process of $\text{AH} \rightarrow \text{A}^- + \text{H}^+$ is given by eq 3

$$\Delta H^{298} = \Delta E_e^0 + \Delta E_v^0 + \Delta(\Delta E_v)^{298} + \Delta E_t + \Delta E_r + \Delta(\text{PV}) \quad (3)$$

where ΔE_e^0 is the change of the electronic energy including the electron correlations between the products and reactants at 0 K, ΔE_v^0 is the change in the vibrational zero-point energy, and $\Delta(\Delta E_v)^{298}$ is the change in the vibrational energy from 0 to 298.15 K. The final terms in eq 3 are for the changes in the translational and rotational energies and the work term. The gas-phase acidity at $T = 298.15$ K was calculated by eq 4

$$\Delta G^{298} = \Delta H^{298} - T\Delta S^{298} \quad (4)$$

where ΔS^{298} is the reaction entropy. These calculations were done by a locally written Fortran program according to standard statistical mechanics.⁵³

The optimized structures at the HF/6-311+G(d,p) level were used in single-point energy calculations with Dunning's augmented correlation-consistent triple- ζ basis function, aug-cc-pVTZ.⁵⁴ Electron correlation effects were considered by means of Møller–Plesset perturbation theory⁵⁵ up to the second order. Thus, the notation for the energy calculation is MP2/aug-cc-pVTZ//HF/6-311+G(d,p). The detailed results of this calculation are listed in Table 1.

In view of the size of these molecules, gas-phase acidities were also calculated by using the Gaussian-2, Gaussian-3,^{56–58} and Complete Basis Sets (CBS)^{59,60} model chemistries. These methods were developed for accurately calculating thermochemical quantities. These highly automated procedures that were implemented in Gaussian 03 incorporate a series of electron correlation energy calculations, including extrapolation of basis sets, based on an initial optimized geometry. However, one needs to pay attention to make sure that all the optimized structures in these calculations are energy minima. We carried out these calculations on the four ions at the G2, G2MP2, G3, CBS-QB3, and CBS-APNO levels. An excellent description about these methods has been given by Shields and Liptak.¹⁷ Absolute Gibbs free energy for the anions and dianions at 1 atm and 25 °C was collected in the output of these calculations. The optimized geometries and the final thermodynamic properties of each ion with every model are given in the Supporting Information. Note that to calculate the gas-phase acidity,

TABLE 2: Computed Gas-Phase Acidity ΔG_{gas} (in kcal/mol) for the Carbon Acid Ionization Reaction at 25 °C and 1 atm with Different Models

	$\text{CH}_3\text{CO}_2^- \rightarrow \text{CH}_2=\text{CO}_2^{-2} + \text{H}^+$	$\text{HCO}_3^- \rightarrow \text{CO}_3^{-2} + \text{H}^+$
G2	495.6	477.2
G2MP2	496.4	478.8
G3	496.0	479.0
CBS-QB3	496.0	479.4
CBS-APNO	492.9	478.5
MP2/aug-cc-pVTZ// HF/6-311+G(d,p)	489.4	475.0
exptl	N/A	N/A

$\Delta G_{\text{gas}}(\text{AH}) = G_{\text{gas}}(\text{A}^-) + G_{\text{gas}}(\text{H}^+) - G_{\text{gas}}(\text{AH})$, for the ionization reaction of $\text{AH} \rightarrow \text{A}^- + \text{H}^+$, the absolute value of Gibbs free energy of proton, $G_{\text{gas}}(\text{H}^+)$, at 1 atm and 25 °C, is needed. This was obtained through statistical mechanics approximations. Using the Sackur–Tetrode equation,⁶¹ we obtained the entropy $S_{\text{gas}}(\text{H}^+) = 13.1R$ (R is the universal gas constant). Therefore, $G_{\text{gas}}(\text{H}^+) = H(\text{enthalpy}) - TS = E_{\text{trans}} + PV - TS = \frac{3}{2}RT + RT - 13.1RT = -10.6RT = -6.28$ kcal/mol.

The calculated gas-phase acidity $\Delta G_{\text{gas}}(\text{AH})$ at all levels for acetate and bicarbonate ions is summarized in Table 2.

3.3. Hydration Free Energies. The CPCM model was used in the calculation of hydration free energies with the Gaussian 03 program. Our experiences with other solvation models, such as IEF-PCM, D-PCM, or I-PCM, indicate that these models are either similar to the CPCM or inferior to the CPCM in the calculation of solvation energies. Thus, we used the CPCM model in this study. We also optimized the structures of the four anions in solution at the CPCM/HF/6-311+G(d,p) level. Frequency calculations in solution at the same level confirmed that the four optimized structures which are given in the Supporting Information are all true energy minima.

We first calculated the hydration free energy for the four anions at the CPCM/HF/6-311+G(d,p) and the CPCM/B3LYP/6-311+G(d,p) level, based on the gas-phase HF/6-311+G(d,p) and the solution-phase CPCM/HF/6-311+G(d,p) geometries, respectively. Next, based on the same gas-phase HF/6-311+G(d,p) and the solution-phase CPCM/HF/6-311+G(d,p) geometries, we performed the nondefault CPCM calculations with the HF/6-31G(d) wave function for the solutes in which the atomic radii of the solute cavity were built on the united atom topological model. These radii were optimized by the HF/6-31(d) calculations to give accurate solvation free energies of some ions and neutral compounds.⁶² This was done through the following keywords, SCRF = READ plus SCFVAC and RADII = UAHF. This model is recommended in the Gaussian 03 manual, which was used by Thomson, Cramer, and Truhlar in a recent paper to evaluate their latest New Universal Solvation Model (SM5.43R).³⁷ It was also used by Lopez in the calculation of the $\text{p}K_a$ values of several twisted amides.⁶³ In addition, as Takano and Houk^{23b} recommended in a more recent computational study of aqueous solvation free energies of neutral and ionic organic molecules, we also performed the CPCM/HF/6-31+G(d) calculations based on the HF/6-311+G(d,p) gas-phase geometries, as well as the solution-phase CPCM/6-311+G(d,p) geometries, with the UAKS cavities in which the radii were optimized for the PBE0/6-31G(d) level of theory.³⁶

The Minnesota Solvation Models, SM5.4/AM1 and SM5.4/PM3, were used to obtain the free energies of hydration for the four anions with Spartan 04. Note that these numbers are somewhat different from those originally published by Cramer and Truhlar with their AMSOL program.⁶⁴

3.4. Monte Carlo Simulations. To calculate the hydration free energies for the four anions with an explicit model of water and make comparisons, statistical mechanical Monte Carlo simulations were carried out to calculate the hydration free energies by making use of a combined quantum mechanical and molecular mechanical (QM/MM) potential. In this approach, the solute molecule is treated quantum mechanically with Dewar's semiempirical Austin Model 1 (AM1) theory,⁶⁵ whereas the solvent is represented classically by the TIP3P three-point charge model for water.⁶⁶ Thus, the effective Hamiltonian of the solution system is given by eq 5^{67–68}

$$\hat{H}_{\text{eff}} = \hat{H}_X^0 + \hat{H}_{\text{Xs}} + \hat{H}_{\text{ss}} \quad (5)$$

where \hat{H}_X^0 is the Hamiltonian of the solute in the gas phase, \hat{H}_{Xs} is the solute (X)–solvent (s) interaction Hamiltonian, and \hat{H}_{ss} represents the solvent–solvent interaction energy. Details of the computational procedure and the Lennard-Jones parameters can be found in ref 67. In the current work, the Lennard-Jones parameters for the carboxylic oxygen were approximated by the sp² oxygen from ref 67b. Note that only the first two terms in eq 5 involve the electronic degrees of freedom of the solute, which are explicitly included in the Hartree–Fock molecular orbital calculations, while there are no geometrical relaxations for the solute molecules in the simulations.

To adequately treat long-range electrostatic interactions for these highly charged solute anions, we employed a hybrid semiempirical QM and the Ewald-sum methods that were recently developed in fluid simulations.³² Model studies indicate that the methods can be effectively used to account for long-range electrostatic effects in quantum mechanical calculations of the condensed media. Monte Carlo simulations were performed for a cubic primary unit cell consisting of 267 water molecules plus one solute ion, using the isothermal–isobaric ensemble (NPT) at 1 atm and 25 °C. Periodic boundary conditions and minimum image convention along with a 9 Å spherical cutoff were used in the evaluation of the real space Ewald potential and the Lennard-Jones terms. A value of 0.4 is used for the parameter κ . For the k -space potential, the maximum number of k -vectors included in each Cartesian direction is 5, with a constraint of $|n| \leq 27$, resulting in a total of 674 k -vectors.

Free energy perturbation (FEP) calculations, in which acetate was converted to bicarbonate to nothing and acetate dianion was converted to carbonate to nothing, are performed with use of the double-wide sampling technique with $\Delta\lambda = \pm 0.05$ and 0.1 for the dianions and monoanions, respectively. In each simulation window, at least 10⁶ configurations were discarded for equilibration, which were followed by an additional 1.5 × 10⁶ configurations of averaging.⁶⁹

In summary, the gas-phase acidity calculations were performed at the G2, G2MP2, G3, CBS-QB3, CBS-APNO, and MP2/aug-ccpVTZ//HF/6-311+G(d,p) levels. Solvation models used in the discussion of this study are listed below, along with the corresponding short-hand notations for convenience in the following discussion.

- S1:** CPCM/HF/6-311+G(d,p)//HF/6-311+G(d,p)
- S2:** CPCM/B3LYP/6-311+G(d,p)//HF/6-311+G(d,p)
- S3:** CPCM/HF/6-311+G(d,p)//CPCM/HF/6-311+G(d,p)
- S4:** CPCM/B3LYP/6-311+G(d,p)//CPCM/HF/6-311+G(d,p)
- S5:** CPCM/HF/6-31G(d) (Radii=UAHF)//HF/6-311+G(d,p)
- S6:** CPCM/HF/6-31G(d) (Radii=UAHF)//CPCM/HF/6-311+G(d,p)
- S7:** SM5.4/AM1 calculated from Spartan 04
- S8:** SM5.4/PM3 calculated from Spartan 04
- S9:** SM5.4/AM1 taken from ref 64 (AMSOL)

S10: SM5.4/PM3 taken from ref 64 (AMSOL)

S11: SM5.43R/mPW1PW91/6-31+G(d)//mPW1PW91/MI-DI!

S12: CPCM/HF/6-31+G(d) (Radii=UAKS)//HF/6-311+G(d,p)

S13: CPCM/HF/6-31+G(d) (Radii=UAKS)//CPCM/HF/6-311+G(d,p)

S14: Monte Carlo QM/MM

S15: experimental free energy of hydration for acetate, bicarbonate, and carbonate

Hydration free energies obtained from all of the above models are provided in Table 3.

TABLE 3: Computed and Experimental Gibbs Free Energy of Hydration ΔG_{hyd} (in kcal/mol) for the Four Anions with Different Solvation Models

	CH ₃ CO ₂ [−]	CH ₂ =CO ₂ ^{2−}	HCO ₃ [−]	CO ₃ ^{2−}
S1	−68.2	−234.4	−72.3	−254.5
S2	−66.3	−231.0	−70.2	−250.8
S3	−70.9	−239.8	−75.9	−254.9
S4	−67.8	−236.1	−73.4	−251.2
S5	−75.7	−262.8	−76.8	−267.4
S6	−77.4	−266.2	−79.8	−267.9
S7 (Spartan)	−75.2	−263.9	−71.1	−271.2
S8 (Spartan)	−76.8	−265.9	−73.8	−273.3
S9	−76.6	−264.7	−76.9	−273.8
S10	−78.6	−267.1	−79.2	−275.0
S11	−72.2	−264.2	−73.4	−275.2
S12	−78.9	−255.7	−78.0	−268.2
S13	−80.8	−260.4	−81.8	−268.7
S14 (QM/MM)	−77.0 ± 0.4	−255.6 ± 0.6	−75.8 ± 0.5	−270.2 ± 0.6
S15 (exptl) ^a	−77	N/A	−94	−314

^a Reference 41.

4. Results and Discussion

4.1. Gas-Phase Geometries and Acidities. Some drastic geometrical changes for these ions on going from the gas phase to aqueous solution were observed. Selected bond lengths are given in Figure 1. A common feature for acetate, enolate dianion, and bicarbonate is that the central C₄–C₂ bond (see Figure 1 for the numbering of the atoms) or O₄–C₂ bond (for bicarbonate) is shortened by ca. 0.02 Å to 0.07 Å, and the C₂–O₁ or C₂–O₃ bonds are lengthened by ca. 0.01 Å on going from the gas phase to aqueous solution. The C–O bond in carbonate is shortened by 0.01 Å in water. Note that the gas-phase HF/6-311+G(d,p) structure of enolate dianion is nonplanar with the two hydrogen atoms flipping above the carboxylate plane, giving the dihedral angle of H₅C₄C₂O₁ of 21.7°, while solution-phase optimization yields almost a planar structure. The origin for these geometrical changes comes from strong electrostatic interactions between the charged ions and the highly polar water solvent. This geometry relaxation in solution is due to localization of the anionic charges on the oxygen atoms resulting in stronger solvation.

Since the gas-phase acidities are determined separately, independent from the calculation of solvation free energies in the evaluation of pK_a values, we have used several affordable high-level ab initio methods to evaluate the gas-phase acidities (free energies) of the two systems. There are some interesting features in the gas-phase acidity calculations of acetate and bicarbonate at all levels in Table 2. MP2/aug-ccpVTZ calculations with use of scaled vibrational frequencies computed at the HF level give the deprotonation free energy of 489.4 kcal/mol for CH₃CO₂[−] and 475.0 kcal/mol for HCO₃[−], suggesting that the carbon acid of acetate ion is 14.4 kcal/mol less acidic than bicarbonate. The origin for the stronger acidity of bicarbon-

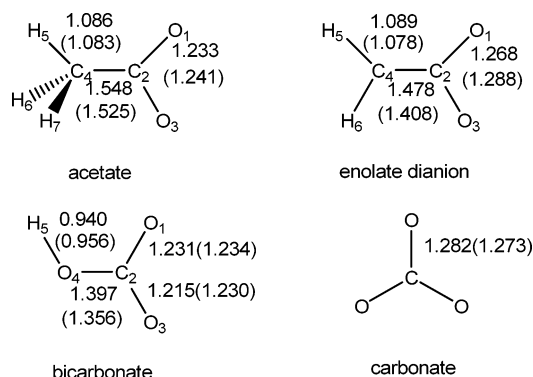


Figure 1. Selected optimized bond lengths (in Å) in the gas phase at the HF/6-311+G(d,p) level and in solution (in parentheses) with CPCM/HF/6-311+G(d,p) optimizations.

ate than acetate was investigated by Wiberg.⁷⁰ It was suggested that the stronger acidity of bicarbonate was caused by the electrostatic effect from a greater electronegativity of oxygen and it is not necessary to postulate a resonance stabilization.

Note that deprotonation free energies for both anions calculated at all other higher levels are all larger than the MP2 results. Although the Gaussian and CBS methods are believed to be developed for “high accuracy” thermochemical calculations, they were not very well documented for acidity calculations of anions. There have been enormously good applications of MP2 calculations, giving excellent energetic results for deprotonation or protonation reactions.^{71–73} Since no experimental acidity data are available for the two anions, we cannot make a definite conclusion which method is superior to others. A recent study indicated that the MP2/6-311+G(d,p) level gave protonation free energies of several amines in better agreement with experimental values than the G3 model.²¹ For acetate ion, there is a 7 kcal/mol difference in acidity between G2MP2 and MP2/aug-ccpVTZ calculations, while the difference for bicarbonate is reduced to 4.4 kcal/mol between CBS-QB3 and MP2/aug-ccpVTZ levels. For other new developments and improvement of the Gaussian methods for accurate thermochemistry calculations, readers may check out the work recently published by Truhlar’s group.^{74,75} The CBS-APNO method is usually regarded as the best among these Gaussian and CBS models.⁵⁹ In CBS-APNO calculations, the initial structure of the molecule is optimized at the standard QCISD/6-311G(d,p) level, followed by a series of electron correlation calculations and extrapolation of basis sets. The CBS-APNO model gives the same relative acidity (14.4 kcal/mol) as that with the MP2/aug-ccpVTZ/HF/6-311+G(d,p) calculations between acetate and bicarbonate. There is only a 3.5 kcal/mol increase in absolute acidities with the CBS-APNO method. It can be expected that using these two methods of gas-phase free energy calculations will yield close results of pK_a values in solution in conjunction with hydration energies.

4.2. Hydration Free Energies. S1 through S6 solvation models (see Table 3) are ab initio CPCM calculations with Gaussian 03 in which both the gas-phase and solution-phase geometries were used and electron correlation effects were also considered at the B3LYP level.^{76,77} S7 and S8 were Cramer and Truhlar SM5.4 model implemented in Spartan 04 based on AM1 and PM3⁷⁸ Hamiltonian. For comparison, S9 and S10 were original published results from SM5.4/AM1 and SM5.4/PM3 calculations by Cramer and Truhlar.⁶⁴ S11 is the latest SM5.43R/mPW1PW91/6-31+G(d)/mPW1PW91^{79,80}/MIDI!⁸¹ model in which the restricted gas-phase geometry at the mPW1PW91/MIDI! level is used. S12 is the CPCM/HF/6-31+G(d) (Radii=

UAKS)/HF/6-311+G(d,p) and level of theory recommended by Takano and Houk. S13 is the same calculation as S12 but based on the solution phase CPCM/6-311+G(d,p) geometry. S14 is the QM/MM Monte Carlo FEP calculation.

In view of the large hydration free energies of these charged anions, inclusion of electron correlation in the B3LYP-CPCM calculations has little effect on the absolute value of solvation energy over the HF calculations. In general, electron correlations make the anions less hydrophilic by 2–3 kcal/mol. Use of solution-phase geometry gave somewhat larger hydration free energies than the fixed gas-phase geometry at the same theoretical level, indicating favorable interactions between solvent and the relaxed solute in solution. This is particularly obvious for the enolate dianion, where the free energy of hydration calculated from the solution geometry is ca. 5 kcal/mol more negative than that calculated with the use of gas-phase geometry at both HF and B3LYP levels. It is interesting to note that geometry has little effect on the calculated hydration free energy for the carbonate dianion. This may be caused by the nature of nonpolarity of the carbonate dianion. As for the accuracy of the calculated absolute free energy of hydration, S5–S10, S12, S13, and S14 all gave results for acetate which are in excellent agreement with the widely cited experimental value of –77 kcal/mol.^{17,64,82} S11 underestimated the free energy of hydration for acetate by about 5 kcal/mol. Note that to try to accurately calculate solvation free energies for ions with the continuum model, some researchers incorporate one or more explicit solvent molecules with the solute ion to form a cluster with the purpose of simulating the first solvation shell. However, this kind of supermolecule-continuum model was not rigorously justified and it sometimes could not improve the results of pK_a calculations.^{21,23b} In this study, we did not consider this approach. S5–S11 gave very similar hydration free energies for enolate dianion, which is about 9 kcal/mol more negative than the results from QM/MM S14 and S12. There is about a 30 kcal/mol difference between the hydration free energies of enolate dianion calculated by S1–S4 and by other models. Unfortunately there is no experimental data of enolate dianion for comparison. The values of hydration free energy for both acetate and bicarbonate calculated by S9–S14 are similar. But the computed values of hydration free energy for bicarbonate are 15–20 kcal/mol smaller than the reported experimental hydration free energy of –94 kcal/mol.⁴¹ We will show that the experimental values of hydration free energy for both bicarbonate and carbonate are not consistent with aqueous pK_a values and are therefore not reliable (see section 4.5). Note that S12, S13, and S14 gave similar hydration free energies for carbonate. In view of the good performance of the SM5.4 model, CPCM-UAKS, and Monte Carlo QM/MM simulations for other systems,^{83,23b} the computed free energies of hydration for the current monoanions and dianions are in a reasonable range. Hydration free energies for both the anions and dianions from S1–S4 deviated from other models and were underestimated as compared to those from S5–S14. However, this does not necessarily indicate that these models will give low-quality relative pK_a values. To critically test the consistent performance and quality of these different models, the evaluation of the pK_a values from both the relative pK_a formula of eq 2 and the absolute pK_a formula of eq 1 should be used.

4.3. Relative pK_a Values. Table 4 listed the computed absolute pK_a values of acetate based on the relative pK_a formula of eq 2. In this equation, only the differences in the gas-phase acidity, free energy of hydration for anions and dianions are needed, while the absolute free energy of hydration of proton

TABLE 4: Computed pK_a Values^a of Acetate by Use of Eq 2 (formula for the relative pK_a calculation) with Different ab Initio Gas-Phase Acidities and Solvation Models, while pK_a(exptl) = 33.5⁸

	G2	G2MP2	G3	CBS-QB3	CBS-APNO	MP2/aug-ccpVTZ// HF/6-311+G(d,p)
S1	36.1(2.6)	35.6(2.1)	35.2(1.7)	34.9(1.4)	33.2(−0.3)	33.2(−0.3)
S2	35.4(1.9)	34.9(1.4)	34.4(0.9)	34.1(0.6)	32.4(−1.1)	32.5(−1.0)
S3	31.2(−2.3)	30.7(−2.8)	30.2(−3.3)	29.9(−3.6)	28.2(−5.3)	28.3(−5.2)
S4	30.7(−2.8)	30.2(−3.3)	29.8(−3.7)	29.5(−4.0)	27.8(−5.7)	27.8(−5.7)
S5	26.4(−7.1)	25.9(−7.6)	25.4(−8.1)	25.1(−8.4)	23.4(−10.1)	23.5(−10.0)
S6	23.2(−10.3)	22.6(−10.9)	22.2(−11.3)	21.9(−11.6)	20.2(−13.3)	20.3(−13.2)
S7(Spartan)	32.1(−1.4)	31.6(−1.9)	31.1(−2.4)	30.8(−2.7)	29.2(−4.3)	29.2(−4.3)
S8(Spartan)	31.4(−2.1)	30.8(−2.7)	30.4(−3.1)	30.1(−3.4)	28.4(−5.1)	28.5(−5.0)
S9	30.2(−3.3)	29.7(−3.8)	29.2(−4.3)	28.9(−4.6)	27.3(−6.2)	27.3(−6.2)
S10	29.1(−4.4)	28.6(−4.9)	28.1(−5.4)	27.8(−5.7)	26.2(−7.3)	26.2(−7.3)
S11	30.9(−2.6)	30.4(−3.1)	30.0(−3.5)	29.7(−3.8)	28.0(−5.5)	28.0(−5.5)
S12	33.6(0.1)	33.0(−0.5)	32.6(−0.9)	32.3(−1.2)	30.7(−2.8)	30.7(−2.8)
S13	30.5(−3.0)	30.0(−3.5)	29.6(−3.9)	29.3(−4.2)	27.6(−5.9)	27.6(−5.9)
S14(QM/MM)	35.3(1.8)	34.8(1.3)	34.4(0.9)	34.1(0.6)	32.4(−1.1)	32.4(−1.1)

^a Deviations relative to the experimental value are given in parentheses.

is avoided. The absolute pK_a values in Table 4 were obtained by making use of the experimental pK_a(HCO₃[−]) = 10.3⁴⁹ and the gas-phase acidity calculated at different levels of theory.

With MC QM/MM simulations (**S14**) and MP2/aug-ccpVTZ gas-phase acidities, we obtained a predicted pK_a difference of 22.1 between CH₃CO₂[−] and HCO₃[−] in water. This is the result of nearly equal contributions from the intrinsic (gas-phase) acidity difference between the acetate anion and the bicarbonate anion, and solvation effects. In the gas phase, HCO₃[−] is more acidic than CH₃CO₂[−] by 14.4 kcal/mol, whereas in aqueous solution, CO₃^{2−} is better solvated than CH₂=CO₂^{2−} by 14.6 kcal/mol. The small difference in the free energy of hydration between CH₃CO₂[−] and HCO₃[−] makes up an overall free energy difference of 30.2 kcal/mol for the deprotonation in water, or a difference in acidity of 22.1 pK_a units. In combination with the experimental pK_a for bicarbonate in water, we estimated that the pK_a of acetate ion is 32.4, which is in excellent agreement with the experimental value of 33.5.⁸

From Table 4, it is observed that use of gas-phase acidities at other levels than MP2 and CBS-APNO with MC QM/MM simulations gave higher pK_a values by ca. 2.5 pK_a units. This is due to an overestimation of relative gas-phase acidity at the same level between acetate and bicarbonate. As discussed before, the MP2 and CBS-APNO calculations yield the most reliable results.

It is not surprising that **S1** and **S2** gave very good pK_a values for the acetate anion due to the fortuitous cancellation of errors in solution calculations for both acetate and bicarbonate anions, even though the computed absolute hydration free energy of acetate deviated from the experimental value by ca. 10 kcal/mol. **S7** and **S8** models (from Spartan 04) as well as **S9** and **S10** with MP2 gas-phase acidities underestimated the pK_a value of acetate by about 4–6 pK_a units. Note that the newly developed SM5.43R (**S11**) did not show an improvement over the original SM5.4 model in these calculations. CPCM-UAKS-(HF/6-31+G(d)) calculations (**S12**) gave a pK_a value of 30.7 of acetate that is smaller than the experimental value by 2.8 pK_a units. This is the next best estimation of the pK_a value of acetate with use of the relative formula of eq 2 among all these models.

Since the experimental pK_a values in water for both acetate and bicarbonate are known, it is essential and interesting to calculate the pK_a values of these two ions by using the absolute pK_a formula of eq 1 to further assess the quality of these theoretical models.

4.4. Absolute pK_a Values. Four quantities are needed to obtain an accurate value of pK_a according to eq 1. The free

energy of hydration of proton is taken as −264.0 kcal/mol from the experimental value.^{43,46} The gas-phase acidity is reliable with the MP2 and CBS-APNO level. These two quantities are essential in the evaluation of absolute pK_a values, but the most crucial component is the difference in hydration free energy between the anion and its dianion. The pK_a values calculated by eq 1 could be used to estimate the quality of different solvation models when the experimental values are available. Tables 5 and 6 list the computed pK_a values for both acetate and bicarbonate, using different models and gas-phase acidities. Again, **S14** model-MC QM/MM simulations gave a good value of pK_a of 34.3 of acetate at the MP2 level as compared to the experimental value of 33.5. **S12** and **S13** also gave a good estimation of the pK_a of acetate. Note that **S7** and **S8**, as well as **S9** and **S10** did not give satisfactory results. Moreover, **S11** underestimated the pK_a value of acetate by 9 pK_a units. There are some discrepancies between Spartan implementation (**S7** and **S8**) and Cramer and Truhlar's original SM5.4/AM1(**S9**) and SM5.4/PM3(**S10**) calculations.⁶⁴ **S1**–**S4** overestimated the pK_a value of acetate by more than 8 pK_a units due to inaccurate calculations of hydration free energies for the ions, though **S1** and **S2** gave excellent pK_a values by relative pK_a calculations (Table 4). **S5** and **S6** gave much improved numbers over **S1**–**S4**, which is still unacceptable in view of the large deviations from the experimental value.

For bicarbonate (Table 6), **S7**–**S10** and **S14** all gave reasonable computed pK_a values at the MP2 level as compared to the experimental value of 10.3. In particular the **S9** model performed slightly better than the other four models, **S7**, **S8**, **S10**, and **S14**. **S11** underestimated the pK_a value of bicarbonate by about 4 pK_a units, while **S12** and **S13** overestimated the pK_a by 5 pK_a units, which is unacceptable. Note that the gas-phase acidity was calculated based on the standard states of 1 atm and 25 °C. If gas-phase standard states of 1 M and 25 °C were applied, then gas-phase acidity ΔG_{gas}(1M) = ΔG_{gas}(1atm) + RT ln24.47 would be used.⁸⁴ This would increase all the calculated pK_a values in Tables 5 and 6 by 1.4 pK_a units based on the absolute pK_a formula of eq 1. This change of gas-phase standard will not affect the pK_a values in Table 4 calculated by the relative formula of eq 2 due to cancellations.

Although CPCM-UAKS(**S12**, **S13**) gave acceptable pK_a calculations for acetate ion based on both the relative and absolute formulas, it overestimated the absolute pK_a of bicarbonate by 5 pK_a units. The MC QM/MM simulations (**S14**) with explicit representation of the solvent gave a superior and consistent performance on the calculations of pK_a values of acetate and bicarbonate based on both the relative and absolute

TABLE 5: Computed pK_a Values^a of Acetate by Use of Eq 1 (formula for the absolute pK_a calculation) with Different Gas-Phase and Solution Models, while $pK_a(\text{exptl}) = 33.5^8$

	G2	G2MP2	G3	CBS-QB3	CBS-APNO	MP2/aug-ccpVTZ// HF/6-311+G(d,p)
S1	48.6(15.1)	49.2(15.7)	48.9(15.4)	48.9(15.4)	46.7(13.2)	44.1(10.6)
S2	48.9(15.4)	49.6(16.1)	49.3(15.8)	49.3(15.8)	47.0(13.5)	44.4(10.9)
S3	45.9(12.4)	46.6(13.1)	46.3(12.8)	46.3(12.8)	44.0(10.5)	41.4(7.9)
S4	46.4(12.9)	47.0(13.5)	46.7(13.2)	46.7(13.2)	44.4(10.9)	41.8(8.3)
S5	32.6(−0.9)	33.2(−0.3)	33.0(−0.5)	33.0(−0.5)	30.6(−2.9)	28.1(−5.4)
S6	31.3(−2.2)	31.9(−1.6)	31.6(−1.9)	31.6(−1.9)	29.3(−4.2)	26.8(−6.7)
S7(Spartan)	31.4(−2.1)	32.0(−1.5)	31.7(−1.8)	31.8(−1.7)	29.4(−4.1)	26.9(−6.6)
S8(Spartan)	31.1(−2.4)	31.7(−1.8)	31.4(−2.1)	31.5(−2.0)	29.1(−4.4)	26.6(−6.9)
S9	31.8(−1.7)	32.5(−1.0)	32.2(−1.3)	32.2(−1.3)	29.9(−3.6)	27.3(−6.2)
S10	31.6(−1.9)	32.2(−1.3)	31.9(−1.6)	31.9(−1.6)	29.6(−3.9)	27.0(−6.5)
S11	29.0(−4.5)	29.6(−3.9)	29.3(−4.2)	29.3(−4.2)	27.0(−6.5)	24.5(−9.0)
S12	40.2(6.7)	40.7(7.2)	40.5(7.0)	40.5(7.0)	38.2(4.7)	35.6(2.1)
S13	38.0(4.5)	38.7(5.2)	38.4(4.9)	38.4(4.9)	36.1(2.6)	33.5(0.0)
S14(QM/MM)	38.8(5.3)	39.4(5.9)	39.1(5.6)	39.1(5.6)	36.8(3.3)	34.3(0.8)

^a Deviations relative to the experimental value are given in parentheses.**TABLE 6: Computed pK_a Values^a of Bicarbonate (HCO_3^-) by Use of Eq 1 (formula for the absolute pK_a calculation) with Different Gas-Phase and Solution Models, while $pK_a(\text{exptl}) = 10.3^{49}$**

	G2	G2MP2	G3	CBS-QB3	CBS-APNO	MP2/aug-ccpVTZ// HF/6-311+G(d,p)
S1	22.8(12.5)	23.9(13.6)	24.1(13.8)	24.4(14.1)	23.8(13.5)	21.2(10.9)
S2	23.9(13.6)	25.0(14.7)	25.2(14.9)	25.5(15.2)	24.8(14.5)	22.3(12.0)
S3	25.0(14.7)	26.2(15.9)	26.3(16.0)	26.7(16.4)	26.0(15.7)	23.4(13.1)
S4	25.9(15.6)	27.1(16.8)	27.2(16.9)	27.5(17.2)	26.9(16.6)	24.3(14.0)
S5	16.5(6.2)	17.7(7.4)	17.8(7.5)	18.2(7.9)	17.5(7.2)	14.9(4.6)
S6	18.4(8.1)	19.6(9.3)	19.7(9.4)	20.0(9.7)	19.4(9.1)	16.8(6.5)
S7(Spartan)	9.6(−0.7)	10.8(0.5)	10.9(0.6)	11.2(0.9)	10.6(0.3)	8.0(−2.3)
S8(Spartan)	10.0(−0.3)	11.2(0.9)	11.3(1.0)	11.7(1.4)	11.0(0.7)	8.4(−1.9)
S9	12.0(1.7)	13.1(2.8)	13.2(2.9)	13.6(3.3)	12.9(2.6)	10.3(0.0)
S10	12.8(2.5)	13.9(3.6)	14.0(3.7)	14.4(4.1)	13.7(3.4)	11.1(0.8)
S11	8.4(−1.9)	9.5(−0.8)	9.7(−0.6)	10.0(−0.3)	9.3(−1.0)	6.7(−3.6)
S12	16.9(6.6)	18.0(7.7)	18.2(7.9)	18.5(8.2)	17.8(7.5)	15.2(4.9)
S13	19.2(8.9)	20.4(10.1)	20.5(10.2)	20.9(10.6)	20.2(9.9)	17.6(7.3)
S14(QM/MM)	13.8(3.5)	14.9(4.6)	15.1(4.8)	15.4(5.1)	14.7(4.4)	12.2(1.9)
S15(exptl)	−5.0(−15.3)	−3.8(−14.1)	−3.7(−14.0)	−3.4(−13.7)	−4.0(−14.3)	−6.6(−16.9)

^a Deviations relative to the experimental value are given in parentheses.

formulas, even though the QM/MM-Ewald calculations are not perfect with the use of the periodic boundary conditions for dilute solutions.

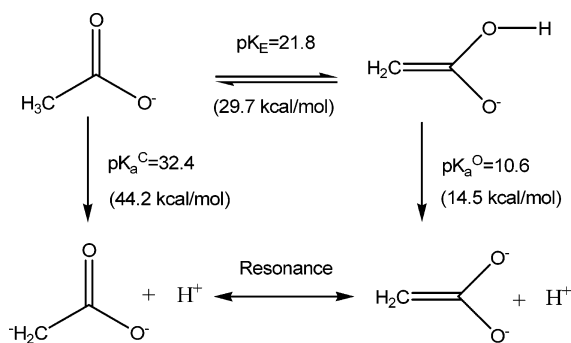
4.5. Experimental Hydration Free Energies. Finally, it is time to evaluate the experimental values of hydration free energies for bicarbonate and carbonate reported by Marcus in 1994.⁴¹ The computed pK_a values of bicarbonate based on the experimental hydration free energies are listed in the last row in Table 6. These values were obtained based on eq 1 by making use of the gas-phase acidities at all levels, absolute free energy of hydration for proton ($\Delta G_{\text{hyd}}(\text{H}^+) = -264$ kcal/mol), and experimental free energies of hydration for bicarbonate and carbonate. Surprisingly, all these pK_a numbers are quite far off from the literature pK_a value of 10.3⁴⁹ for the weak acid bicarbonate ion in aqueous solution. These computed and even negative pK_a numbers for bicarbonate based on the experimental hydration free energies of bicarbonate and carbonate would make bicarbonate as strong as the acid HBr in water whose $pK_a(\text{HBr}) = -5.8$.⁸⁵ The origin of the unexpected results must come from the experiments, because the computed ab initio gas-phase acidities at the MP2 level should be close to the true values. From Table 6, it can be seen that switching from MP2 gas-phase acidity to CBS-QB3 acidity brings about a 3.2 pK_a unit increase. Variation of the current hydration free energy of proton (−264 kcal/mol) by 5 kcal/mol can lead to a difference of 3.7 pK_a units. Variations from hydration energy for proton or gas-phase acidity or even their combinations would make no great improvement over the computed pK_a values to the true

pK_a value of bicarbonate. Checking the experimental hydration free energy for bicarbonate and acetate, the $\Delta G_{\text{hyd}}(\text{HCO}_3^-) = -94$ kcal/mol is apparently too low in comparison with the well-established data for acetate (−77 kcal/mol), which is structurally similar to bicarbonate. Note that the experimental complexation free energies for the acetate water complex, $\text{CH}_3\text{CO}_2^-(\text{H}_2\text{O})_n$, and bicarbonate water complex, $\text{HOCO}_2^-(\text{H}_2\text{O})_n$ where $n = 1-3$, were recently determined by Kebarle and co-workers.⁸⁶ In that study, acetate was found to be slightly better hydrated than bicarbonate with a favorable complexation free energy for the successive addition of water molecules (when $n = 1, 2$, and 3) by 0.9, 0.6, and 0.6 kcal/mol, respectively. Kebarle and co-workers explained this observation by taking the acetate and bicarbonate as the same acid group but with two different substituents, CH_3 and OH. The field and inductive effect of OH in bicarbonate as compared to the CH_3 group in acetate is counteracted by the π electron donor ability of OH, making the binding of the bicarbonate and water molecules slightly weaker than that of acetate and water molecules. Kebarle's experimental observation renders additional support of our theoretical calculations that similar hydration free energies for acetate and bicarbonate were obtained. Therefore, based on the consistent good performance in the evaluations of pK_a values for both acetate and bicarbonate by **S14** and the good performance of **S7–S10** models for calculations of the absolute pK_a value of bicarbonate, the computed free energies of hydration for bicarbonate and carbonate by **S14** and **S7–S10** should be very close to the true experimental values, while **S14** and **S12**

and S13 should give the best estimation of the experimental hydration free energies for acetate and acetate dianion. In view of the long history of both the experimental and computational study of ion solvations,^{86,87} the current computational study of these four highly charged anions and dianions demonstrates the power and reliability of these theoretical models.

In summary, MC QM/MM simulation is a reliable choice for both relative and absolute pK_a calculations for the anions, acetate, and bicarbonate. But, one needs to be cautious when evaluating pK_a values for charged systems by SM5.4 models and CPCM continuum models with Gaussian 03 because these models could not give a consistent performance based on eqs 1 and 2 as demonstrated here. It is noted that a generalized Born model based on the original procedure of Still and co-workers was recently incorporated into Monte Carlo simulations by Jorgensen's group.⁸⁸ A test of this model on the current acetate and bicarbonate systems would be an interesting future study.

4.6. Biological Relevance. Recently, the enol content of acetate ion in water was determined by using similar methodologies.⁸⁹ The predicted pK_E for the equilibrium constant between acetate ion and its enol form CH₂=CO₂H[−] is 21.8. The thermodynamic cycle below allows us to provide an estimate of the pK_a for CH₂=CO₂H[−], which is 10.6 in aqueous solution.



Note that the computed pK_a⁰ of 10.6 for the enol form CH₂=CO₂H[−] of acetate CH₃CO₂[−] is larger than the pK_a⁰ of 7.3 for the enol form CH₂=C(OH)₂ of acetic acid CH₃COOH by 3.3 pK_a units.⁸⁹ This is because it is the second pK_a of the enol form of acetic acid and the second ionization results in the unfavorable electrostatic repulsive interactions in the enolate dianion CH₂=CO₂^{2−}.

The deprotonation of acetate ion to enolate dianion in water is a formidable process, endergonic by ca. 44.2 kcal/mol, which can be regarded as a reference reaction for the related corresponding enzymatic processes. For example, in biological systems, the racemization reaction of α-amino acids proceeds through an amino acid enolate intermediate, which has to be catalyzed by enzymes. The formation and stability of the enolate by the enzyme enolase or racemase is a complicated process.^{90–94} Several proposals have been suggested, such as the stabilization of enolate or its dianion arises from the interactions with one or two metal dications that are bound in the enzyme active site, or through electrostatic interactions with the protonated amino acids.^{95–99} There are many factors that control the activities of enzymes. Although it was hard to draw a clear picture of enzyme mechanisms so far,⁹⁶ Warshel and co-workers have been able to give a consistent electrostatic picture of enzyme mechanisms.¹⁰⁰ However, investigations of enzymatic mechanisms are still continuing activities.^{101–105}

5. Conclusions

We have used several different solvation models including CPCM continuum methods, SMx models, and Monte Carlo QM/MM-Ewald simulations to calculate free energies of hydration for the four ionic species—acetate, acetate dianion, bicarbonate, and carbonate. In combination with the gas-phase acidities calculated at different ab initio levels, hydration free energy of proton and both the absolute and relative pK_a formula, we obtained the computed pK_a values of acetate and bicarbonate. We found that reliable pK_a values of acetate and bicarbonate anions can be obtained by MC QM/MM simulations augmented with the Ewald method to account for the long-range electrostatic effect based on both the absolute and relative pK_a calculations, while the SMx and CPCM models can only give satisfactory results for individual cases. We thus conclude that the MC QM/MM augmented with an appropriate long-range electrostatic treatment would be one of the good methods for studying the chemistry of highly charged ions in solution.

Acknowledgment. This work was supported by a grant from The City University of New York PSC-CUNY Research Award Program, CUNY Community College Collaborative Incentive Research Grant, and Queensborough Community College. We thank Dr. Jason Thompson of Professors Cramer and Truhlar groups for providing us with the results of the SM5.43R calculations.

Supporting Information Available: Optimized gas-phase structures of acetate, acetate dianion, bicarbonate, and carbonate ions at the HF/6-311+G(d,p) level, structures and energies from the G2, G3, and CBS calculations, and the optimized aqueous solution-phase structures at the CPCM/HF/6-311+G(d,p) level. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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