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# Polar Group Enhanced Gas-Phase Acidities of Carboxylic Acids: An Investigation of Intramolecular Electrostatic Interaction

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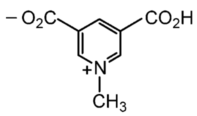
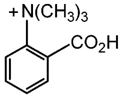
We studied the effects of polar groups on the gas-phase acidities of carboxylic acids experimentally and computationally. In this connection, the gas-phase acidities ($\Delta H_{acid}$, the enthalpy of deprotonation, and $\Delta G_{acid}$, the deprotonation free energy) of borane-complexed methylaminoacetic acid ($(CH_3)_2N(BH_3)CH_2CO_2H$) and methylthioacetic acid ($CH_3S(BH_3)CH_2CO_2H$) were measured using the kinetic method in a flowing afterglow-triple quadrupole mass spectrometer. The values of $\Delta H_{acid}$ and $\Delta G_{acid}$ of $(CH_3)_2N(BH_3)CH_2CO_2H$ were determined to be 328.8 ± 1.9 and 322.1 ± 1.9 kcal/mol, and those of $CH_3S(BH_3)CH_2CO_2H$ were determined to be 325.8 ± 1.9 and 319.2 ± 1.9 kcal/mol, respectively. The theoretical enthalpies of deprotonation of $(CH_3)_2N(BH_3)CH_2CO_2H$ (329.2 kcal/mol) and $CH_3S(BH_3)CH_2CO_2H$ (325.5 kcal/mol) were calculated at the B3LYP/6-31+G(d) level of theory. The calculated enthalpies of deprotonation of *N*-oxide−acetic acid ($CH_3NOCH_2CO_2H$, 329.4 kcal/mol) and *S*-oxide−acetic acid ($CH_3SOCH_2CO_2H$, 328.6 kcal/mol) are comparable to the experimental results for borane-complexed methylamino- and methylthioacetic acids. The enthalpy of deprotonation of sulfone−acetic acid ($CH_3SO_2CH_2CO_2H$, 326.1 kcal/mol) is about 2 kcal/mol lower than the *S*-oxide−acetic acid. The calculated enthalpy of deprotonation of sulfoniumacetic acid, $(CH_3)_2S^+CH_2CO_2H$, is 243.0 kcal/mol. Compared to the corresponding reference molecules, $CH_3NHCH_2CO_2H$ and $CH_3SCH_2CO_2H$, the dipolar group and the monopolar group substituted carboxylic acids are stronger acids by 11−14 and 97 kcal/mol, respectively. We correlated the changes of the acidity upon a polar group substitution to the electrostatic free energy within the carboxylate anion. The acidity enhancements in polar group substituted carboxylic acids are the results of the favorable electrostatic interactions between the polar group and the developing charge at the carboxyl group.

## Introduction

Polar groups, either monopolar or dipolar, are common in organic and biological molecules. Monopolar groups involve atoms bearing a unit charge, and dipolar groups involve atoms bearing separate formal charges. Polar groups can be found, for example, in zwitterionic amino acids and zwitterionic moieties in enzyme active sites, in salt bridges in peptides and proteins, and in polar covalent bonds in Lewis acid−base complexes.[1−5] Polar groups play important roles in controlling the stability and reactivity of molecular systems through intramolecular interactions among polar groups and between polar groups and reaction sites. These interactions often have significant influence on the thermochemical properties, such as acidities, metal cation affinities, electron affinities, and bond dissociation energies.[6−14] Studies have shown that the electric field generated by polar groups can influence the gas-phase acidities of carboxylic acids significantly.[8,13−17] The combination of photodetachment photoelectron spectroscopy, mass spectrometry, and computational studies show that the gas-phase deprotonation free energy of the zwitterionic pyridinium carboxylic acid (**1**, $\Delta G_{acid}$ = 303 kcal/mol) is about 30 kcal/mol stronger than that of the nonzwitterionic benzoic acid ($\Delta G_{acid}$ = 333 kcal/mol).[15] This acidity enhancement is mainly the result of the electrostatic interactions between the deprotonated carboxyl group and the two oppositely charged monopolar groups.[13−15] The increase in the gas-phase acidity will be even more dramatic if one positively charged monopolar group is placed nearer the carboxyl group. The gas-phase deprotonation free energy of trimethylammoniumbenzoic acid (**2**, $\Delta G_{acid}$ = 245 kcal/mol) is about 88 kcal/mol greater than that of benzoic acid.[16] Similarly, protonated betaine (**3**, $\Delta G_{acid}$ = 239 kcal/mol) is a stronger acid than sarcosine, $CH_3NHCH_2CO_2H$ ($\Delta G_{acid}$ = 335 kcal/mol), by about 96 kcal/mol.[8,17]


**1**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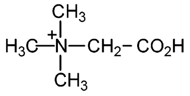
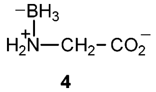

$H_3C-\overset{+}{N}(CH_3)_2-CH_2-CO_2H$

**3**

It seems reasonable to assume that the gas-phase acidity of a carboxylic acid can also be perturbed significantly if a dipolar group, such as a polar covalent bond of a Lewis acid−base complex, is introduced near the carboxyl group. There are no reports in the literature on the quantitative measurements of the gas-phase acidities of carboxylic acids with a nearby dipolar group induced by Lewis acid complexation. An interesting gas-phase study showed that complexation of deprotonated glycine with borane produced a remarkably stable carboxylate anion, **4**, suggesting a significant increase in the acidity of the carboxyl group.[18]


$H_2\overset{+}{N}(\overset{-}{B}H_3)-CH_2-CO_2^-$

**4**

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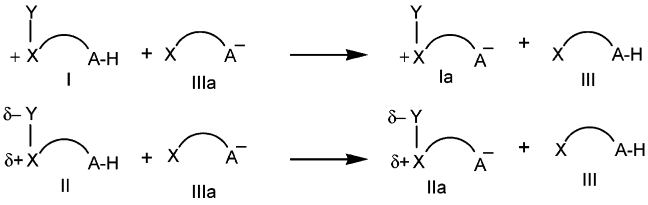
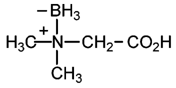
**SCHEME 1**

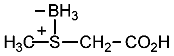


We have quantitatively studied dipolar as well as monopolar group effects on the gas-phase acidities of carboxylic acids. In this paper, we describe the experimental measurements and theoretical studies of the gas-phase acidities of borane-complexed methylamino- and methylthioacetic acids (**5** and **6**). For comparison, we report the results of quantum calculations for amine oxide−acetic acid (**7**), sulfoxide−acetic acid (**8**), sulfone−acetic acid (**9**), and sulfonium−acetic acid (**10**). We also show quantitative correlations between polar group induced acidity enhancements and intramolecular electrostatic interactions in the carboxylate anions.



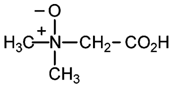
$\mathrm{H_3C{-}\overset{+}{N}(\overset{-}{B}H_3)(CH_3){-}CH_2{-}CO_2H}$

**5**



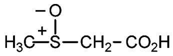
$\mathrm{H_3C{-}\overset{+}{S}(\overset{-}{B}H_3){-}CH_2{-}CO_2H}$

**6**



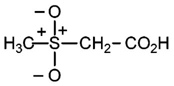
$\mathrm{H_3C{-}\overset{+}{N}(\overset{-}{O})(CH_3){-}CH_2{-}CO_2H}$

**7**



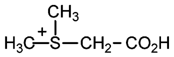
$\mathrm{H_3C{-}\overset{+}{S}(\overset{-}{O}){-}CH_2{-}CO_2H}$

**8**



$\mathrm{H_3C{-}\overset{+}{\underset{}{S}}(\overset{-}{O})_2{-}CH_2{-}CO_2H}$

**9**



$\mathrm{H_3C{-}\overset{+}{S}(CH_3){-}CH_2{-}CO_2H}$

**10**

## Experimental Methods

**The Kirkwood and Westheimer (K−W) model**. The polar group effects on the acidities of carboxylic acids (**5**−**10**) were examined using the K−W model.[19,20] According to this model, an organic acid can be treated as a cavity of low dielectric constant embedded in the solvent continuum with its macroscopic dielectric constant. Upon the acid ionization, where the acid has a polar substituent, the departing proton (with charge $q_1$) will interact with the monopolar group (with charge $q_2$) or dipolar group (with dipolar moment $\mu$) via electrostatic interaction. The electrostatic free energy (U) of interaction between $q_1$ and $q_2$, separated by a distance $r$, can be calculated using eq 1a, where $D_e$ is the effective dielectric constant. Similarly, the electrostatic free energy for the interaction between $q_1$ and the dipole moment $\mu$ can be calculated using eq 1b, where $r$ is the distance between the charge and the dipole, and $\theta$ is the angle between the dipole axis and the line connecting the charge to the dipole. A direct application of the K−W model is the comparison of the dissociation constants of two related organic acids, I and III (Scheme 1). If the two acids are similar in structures, except for the presence of an additional monopolar group in I, then the ratio of the dissociation constants ($K/K_o$) is related to the electrostatic free energy for the interaction between the polar group and the departing proton in the neutral acid, I, eq 2a, where $R$ is the gas constant and $T$ is the temperature.[21,22] The term $RT\ln(K/K_o)$ corresponds to the free-energy change for the proton-transfer reactions between I and III. The same idea applies to the two related acids II and III, where II has an additional dipolar group. The relationship between the acid dissociation constants and the electrostatic free energy in acid II can be described using eq 2b.

**SCHEME 2**

$$U = (q_1 q_2)/D_e r \tag{1a}$$

$$U = (q_1 \mu \cos\theta)/D_e r^2 \tag{1b}$$

$$RT\ln(K/K_o) = (q_1 q_2)/D_e r \tag{2a}$$

$$RT\ln(K/K_o) = (q_1 \mu \cos\theta)/D_e r^2 \tag{2b}$$

If the geometries of I and II do not change upon deprotonation, then the magnitude of the electrostatic interaction between the negative charge at $A^-$ and the polar group (X−Y) in the anions, Ia and IIa, will be comparable to the interaction between the departing proton and the polar group (X−Y) in the neutral acids, I and II, but with opposite sign. Therefore, the free-energy change for the proton transfer can also be calculated from the electrostatic free energy in Ia and IIa. Furthermore, if the reaction occurs in the gas phase, then the free-energy change for the proton-transfer reaction is equal to the difference in the gas-phase acidity (the deprotonation free energy, $\delta\Delta G_{\mathrm{acid}}$) of the pair of neutral acids in the reaction, I versus III and II versus III. Equations 2a and 2b can be converted to eqs 3a and 3b.

$$\delta\Delta G_{\mathrm{acid}}{}^{\mathrm{I}} = -(q_1 q_2)/D_e r \tag{3a}$$

$$\delta\Delta G_{\mathrm{acid}}{}^{\mathrm{II}} = -(q_1 \mu \cos\theta)/D_e r^2 \tag{3b}$$

**Gas-Phase Acidity Measurement**: The gas-phase acidities ($\Delta H_{\mathrm{acid}}$ and $\Delta G_{\mathrm{acid}}$) of the borane-complexed amino- and thioacetic acids, **5** and **6**, were determined using the kinetic method. The kinetic method, introduced by Cooks and coworkers, has been widely used to determine gas-phase thermochemical quantities.[23−25] Relevant publications can be found in the current literature.[26−29] The method used to determine the gas-phase acidity of an organic acid, HA, is described in brief as follows. A series of proton-bound cluster ions ($[A{\cdot}H{\cdot}A_i]^-$) of $A^-$ with a set of reference acids ($HA_i$) will be generated in the mass spectrometer. The reference acids have known gas-phase acidities. Each proton-bound cluster ion will be activated by collisions with argon atoms. Competitive unimolecular dissociations will occur to produce two ionic products, $A^-$ and $A_i^-$, with the rate constants of $k$ and $k_i$, respectively, as shown in Scheme 2. The ratio of the rate constants ($k/k_i$) can be assumed to be equal to the ratio of the intensities of the product ions ($[A^-]/[A_i^-]$), if secondary fragmentation is negligible.

With the assumption that there are no reverse activation barriers for both dissociation channels and the two channels have a similar entropy at their transition states, the ratio of the dissociation rate constants (the product ion intensity ratio) can be related to the gas-phase acidities of HA ($\Delta H_{\mathrm{acid}}$ or $\Delta G_{\mathrm{acid}}$) and $HA_i$ ($\Delta H_{(\mathrm{acid})i}$ or $\Delta G_{(\mathrm{acid})i}$) by eqs 4 and 5, where $T_{\mathrm{eff}}$ is the effective temperature of the activated cluster ion.[30,31] A plot of $\ln([A^-]/[A_i^-])$ against $\Delta H_{(\mathrm{acid})i}$ or $\Delta G_{(\mathrm{acid})i}$ produces a straight line with the slope of $1/RT_{\mathrm{eff}}$ and the intercept of $-\Delta H_{\mathrm{acid}}/RT_{\mathrm{eff}}$ or $-\Delta G_{\mathrm{acid}}/RT_{\mathrm{eff}}$. The values of $\Delta H_{\mathrm{acid}}$ and $\Delta G_{\mathrm{acid}}$ are obtained as the ratios of the negative intercepts to the slopes. The entropy contribution (the differences in activation entropies between the two dissociation channels) can be very small and negligible if structurally similar carboxylic acids are used as the reference acids and the structures of the reference acids are also similar to the unknown acid.[32−36] In our previous studies of the gas-phase acidity of methylthioacetic acid, we found that the entropy contribution was negligible by using a set of acetic acid derivatives as reference acids.[37] Other studies of the proton affinities of nitriles using a flowing afterglow-triple quadrupole instrument also show small entropy effects (0.6−1.5 kcal/mol) providing that a suitable set of reference molecules are chosen.[38,39]

$$\ln([A^-]/[A_i^-]) = \Delta H_{(acid)i}/RT_{eff} - \Delta H_{acid}/RT_{eff} \quad (4)$$

$$\ln([A^-]/[A_i^-]) = \Delta G_{(acid)i}/RT_{eff} - \Delta G_{acid}/RT_{eff} \quad (5)$$

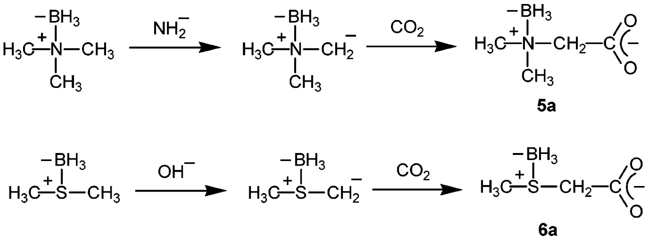
The experiments with the kinetic method were carried out at room temperature using a flowing afterglow-triple quadrupole apparatus that has been described extensively elsewhere.[40,41] Briefly, the instrument consists of an electron ionization ion source, a flow reactor with helium buffer gas at a pressure of 0.4 Torr, and an EXTREL triple quadrupole mass analyzer. The primary ions, $NH_2^-$ and $OH^-$, were generated by electron ionization of $NH_3$ and a mixture of $N_2O$ and $CH_4$, respectively. Other negative ions were formed by ion−molecule reactions of the primary ions with corresponding neutral molecules introduced via leak valves. Proton-bound cluster ions were also generated in the flow reactor by complex formation between the ions and neutral molecules added downstream in the flow reactor. All of the ionic species produced in the flow reactor were thermalized by multiple collisions (ca. $10^5$) with the helium buffer gas. A fraction of the ions, including the proton-bound clusters, were extracted into the triple quadrupole mass analyzer.

The proton-bound cluster ions were isolated with the first quadrupole (Q1) and were subjected to collision-induced-dissociation (CID) experiments in the gastight, rf-only quadrupole collision chamber (q2). Argon was used as the target molecule with the pressure around (1.0−1.5) × $10^{-4}$ Torr. The laboratory axial kinetic energy ($E_{lab}$) of the cluster ion was determined by the q2 rod offset voltage. The center-of-mass ($E_{cm}$) energy was calculated using the equation $E_{cm} = E_{lab}[m/(M + m)]$, where $E_{lab}$ is the collision energy in the laboratory frame, $m$ is the mass of argon, and $M$ is the mass of the proton-bound cluster ion. The CID product ions were analyzed by the third quadrupole (Q3). The ion intensities were measured using a digital counter operating with a gate time of 10 s. Ten successive readings were recoded for each ion and the average values were used for data analysis. Uncertainties were calculated by assuming that the ion intensity measurements follow a Poisson distribution. Thus, the uncertainty in an individual reading of the counter is the square root of the intensity. Error propagation was carried out in the standard manner. To examine the energy dependence of each fragmentation channel, the CID appearance curves were collected over a 9 eV ($E_{cm}$) energy range.

**Materials.** Gas purities were as follows: He (99.995%), Ar (99.955%), $N_2O$ (99%), $CH_4$ (99%), $NH_3$ (anhydrous, 99.5%), $NF_3$ (99%), and $CO_2$ (99.5%). Borane dimethylsulfide (10 M in $(CH_3)_2S$) and borane trimethylamine were obtained from Aldrich Chemical Co. and were used as supplied. All other reagents were obtained from commercial vendors and were used as supplied except for degassing of liquid samples by freeze−thaw cycles prior to use.

**Computational Method.** The density functional theory at the B3LYP/6-31+G(d) level was employed to calculate geometries and vibrational frequencies.[42−47] True-energy minima were determined by checking the absence of imaginary frequencies from the set of obtained frequencies. Several representative conformations were calculated for each neutral and ionic species to determine the lowest energy conformation. Thermochemical quantities were obtained from frequency calculations where a scaling of the calculated harmonic vibrational frequencies was not considered to be important. Charge distributions were calculated using the natural population analysis (NPA)[48] method at the B3LYP/6-31+G(d) level. All calculations were carried out using the Gaussian 03 suite of programs.[49]

**SCHEME 3**



The electrostatic free energies of the anionic species were calculated via eqs 1a and 1b using the point-charge model. The point charges were estimated from the calculated charge distributions. The distances between the point charges were obtained from optimized geometry. For example, the sum of the charge around the $BH_3$ group is centered at the boron atom and the charge around the $CO_2$ group is located at the center of the $CO_2$ group.

## Experimental Results

The borane-complexed aminoacetate, **5a**, was synthesized in the flow reactor following the reaction sequence shown in Scheme 3. Proton abstraction from borane trimethylamine by $NH_2^-$ yielded the borane complexed carbanion, $(CH_3)_2N(BH_3)CH_2^-$. Addition of one $CO_2$ to the carbanion produced the carboxylate, **5a**. The borane-complexed thioacetate, **6a**, was synthesized in a similar manner. Proton abstraction from boranemethyl sulfide (BMS) by $OH^-$ produced borane-complexed carbanion, $CH_3S(BH_3)CH_2^-$, followed by the addition of $CO_2$ yielding the carboxylate, **6a** (Scheme 3). Previous studies show that the borane-complexed carbanions are stable and do not undergo borane shifts.[18,50]

The carboxylates ($A^-$ = **5a** and **6a**) were allowed to react with a set of reference organic acids, $HA_i$, in the flow reactor to form a series of proton-bound cluster ions, $[A{\cdot}H{\cdot}A_i]^-$. The set of reference acids are $ClCH_2CO_2H$ ($\Delta H_{acid} = 336.5 \pm 2.2$, $\Delta G_{acid} = 329.0 \pm 2.0$ kcal/mol), $BrCH_2CO_2H$ ($\Delta H_{acid} = 334.8 \pm 2.3$, $\Delta G_{acid} = 328.2 \pm 2.0$ kcal/mol), $F_2CHCO_2H$ ($\Delta H_{acid} = 331.0 \pm 2.2$, $\Delta G_{acid} = 323.8 \pm 2.0$ kcal/mol), and $F_3CCO_2H$ ($\Delta H_{acid} = 323.9 \pm 2.9$, $\Delta G_{acid} = 317.4 \pm 2.0$ kcal/mol).[51,52] Each cluster ion (the clusters with **6a** contain the $^{32}S$ isotope) was activated by CID in the collision chamber (q2) of the triple-quadrupole analyzer. Two competing dissociation product ions were produced, the borane-complexed carboxylate ($A^-$) and the deprotonated reference acid ($A_i^-$). Two representative CID spectra are shown in Figure 1. Figure 1a shows the spectrum for the dissociation of $[\mathbf{5a}{\cdot}H{\cdot}F_2CHCO_2]^-$, and Figure 1b shows the dissociation of $[\mathbf{5a}{\cdot}H{\cdot}F_3CCO_2]^-$. In Figure 1a, the intensity of **5a** is about 5 times higher than the deprotonated reference acid, $F_2CHCO_2^-$. While in Figure 1b, the intensity of **5a** is less than $^1/_{10}$ of the deprotonated reference acid, $F_3CCO_2^-$. The CID spectra suggest that the acidity of **5** is stronger than that of $F_2CHCO_2H$ but weaker than that of $F_3CCO_2H$. For the cluster ions with $BrCH_2CO_2H$ and $ClCH_2CO_2H$, about 5% of the secondary product ions produced by the loss of $BH_3$ from $A^-$

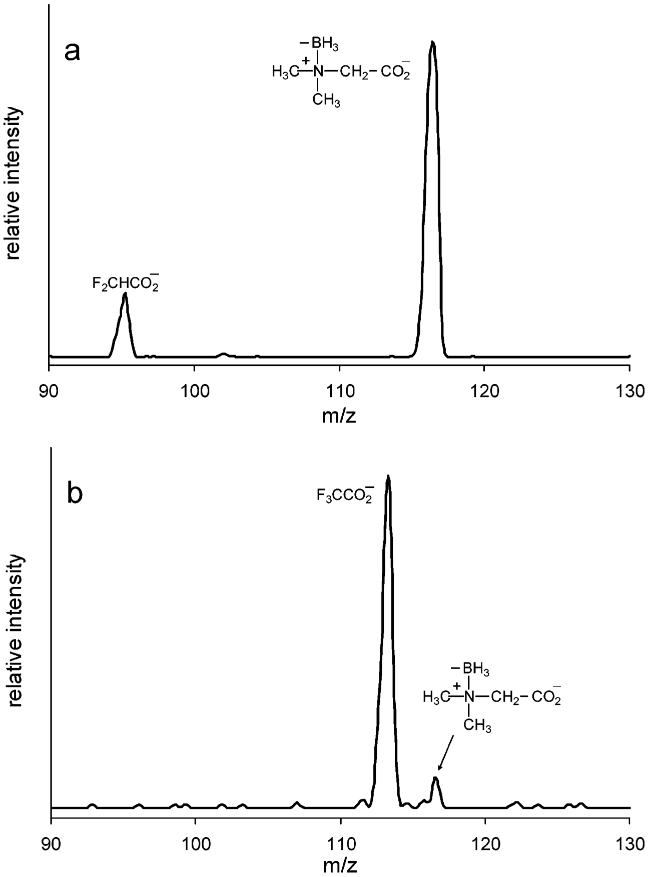


**Figure 1.** The CID spectra of (1a) $[\mathbf{5a}\cdot H\cdot F_2CHCO_2]^-$ and (1b) $[\mathbf{5a}\cdot H\cdot F_3CCO_2]^-$ at 4.5 eV ($E_{cm}$).

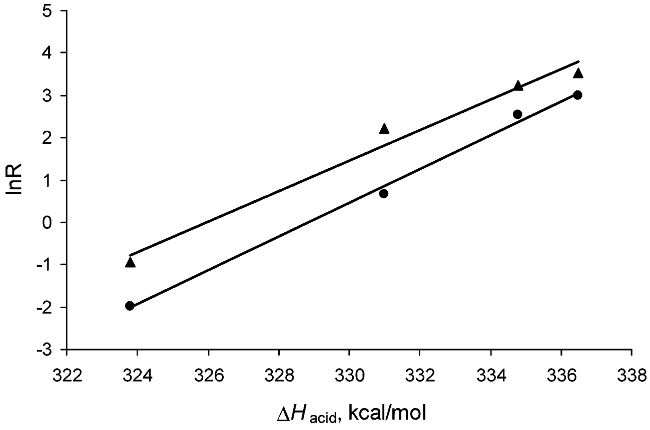


**Figure 2.** The thermokinetic plots of $\ln([\mathbf{5a}^-]/[A_i^-])$ (●) and $\ln([\mathbf{6a}^-]/[A_i^-])$ (▲) against the gas-phase enthalpies of deprotonation ($\Delta H_{acid}$) of the reference acids.

was observed. In the data analysis, the intensities of the secondary ion were added to those of the corresponding $A^-$.

The intensities of the CID product ions from the dissociation of $[\mathbf{5a}\cdot H\cdot A_i]^-$ and $[\mathbf{6a}\cdot H\cdot A_i]^-$ were measured at 4.5 eV (CM) collision energy to yield the ratios of the product ions, $[\mathbf{5a}^-]/[A_i^-]$ and $[\mathbf{6a}^-]/[A_i^-]$. The logarithms of the ratios, $\ln([\mathbf{5a}^-]/[A_i^-])$ and $\ln([\mathbf{6a}^-]/[A_i^-])$, were plotted against the gas-phase acidities of the reference acids ($\Delta H_{(acid)i}$) to generate two sets of thermokinetic data, Figure 2. Linear regression of each set of the data gives a straight line with the slope of $1/RT_{eff}$ and the intercept of $-\Delta H_{acid}/RT_{eff}$ (eq 4). The ratio of the negative intercept to the slope gives the values of $\Delta H_{acid}$, 328.8 kcal/mol for aminoacetic acid (**5**) and 326.0 kcal/mol for thioacetic acid (**6**). On the basis of error analysis, we assign ±1.9 kcal/mol as the uncertainty.[53] The gas-phase acidity of acid **5** was determined to be 328.8 ± 1.9 and of acid **6** to be 326.0 ± 1.9 kcal/mol. The corresponding effective temperatures are 1262 and 1420 K. We examined the collision energy effect on the measured acidity by performing the CID experiments at several lower and higher collision energies. The results are about the same as that measured at 4.5 eV of collision energy.

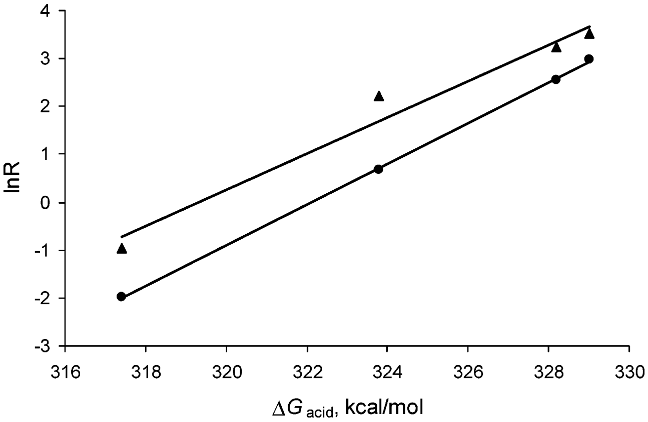


**Figure 3.** The thermokinetic plots of $\ln([\mathbf{5a}^-]/[A_i^-])$ (●) and $\ln([\mathbf{6a}^-]/[A_i^-])$ (▲) against the gas-phase deprotonation free energies ($\Delta G_{acid}$) of the reference acids.

Using a similar approach, we determined the deprotonation free energy ($\Delta G_{acid}$) for acids **5** and **6** using eq 5. The plot of $\ln([\mathbf{5a}^-]/[A_i^-])$ and $\ln([\mathbf{6a}^-]/[A_i^-])$ against $\Delta G_{(acid)i}$ (deprotonation free energies of the reference acids) gives two linear plots each with the slope of $1/RT_{eff}$ and the intercept of $-\Delta G_{acid}/RT_{eff}$, Figure 3. The plots yielded the values of $\Delta G_{acid}$ for **5** and **6** to be 322.1 ± 1.9 and 319.3 ± 1.9 kcal/mol, respectively. The uncertainty was assigned using the method similar to that for $\Delta H_{acid}$.

We estimated the entropy of deprotonation ($\Delta S_{acid}$) of **5** and **6** by using the thermochemical relationship $\Delta S_{acid} = (\Delta H_{acid} - \Delta G_{acid})/T$, where $T = 298$ K. The value of $\Delta S_{acid}$ for **5** is 22.6 and for **6** is 22.2 cal/mol K (we did not assign uncertainties to these values).

## Computational Results

The geometries of the carboxylic acids and carboxylate anions were calculated at the B3LYP/6-31+G(d) level of theory using unconstrained optimization. For each species, several optimized conformations were identified. The initial geometries for these conformations were generated by adjusting the corresponding bond orientations, especially the N—B, S—B, N—O, and S—O bonds. The relative stabilities of the conformers were compared by examining the corresponding total electronic energies. Schematic drawings of the most stable conformers of the carboxylate anions are shown in Figure 4. For both the aminoacetic acid and the thioacetic acid series, the most stable conformers have the polar bonds (N—B, N—O, S—B and S—O) anti to the carboxyl group.

Frequency calculations were carried out using the most stable conformations to determine the thermochemical quantities. The theoretical enthalpies of deprotonation ($\Delta H_{acid}$) of these carboxylic acids were calculated using the isodesmic proton-transfer reaction with acetic acid serving as the reference standard (eq 6). The difference in the enthalpies of deprotonation between the carboxylic acid (HA) and acetic acid ($\Delta H_{acid} = 348.1 \pm 2.2$ kcal/mol)[52,54] is the enthalpy change ($\Delta H_{rxn}$) of the isodesmic reaction. The enthalpy of deprotonation of HA was then obtained using eq 7. We tested the suitability of the computational

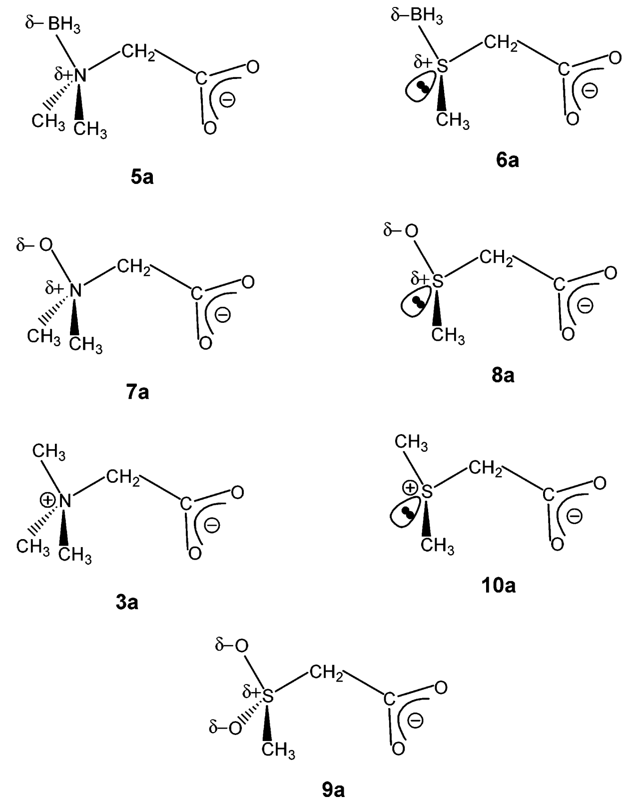


**Figure 4.** Schematic drawings of the most stable conformations of the carboxylate anions with charge sites calculated using the B3LYP/6-31+G(d) method.

**TABLE 1: Gas-Phase Thermochemical Quantities, $\Delta H_{\mathrm{acid}}$, $\Delta G_{\mathrm{acid}}$, and $\Delta S_{\mathrm{acid}}$, Obtained Experimentally and Computationally**

| acid | $\Delta H_{\mathrm{acid}}$, expt (kcal/mol) | $\Delta H_{\mathrm{acid}}$, calc[b] (kcal/mol) | $\Delta G_{\mathrm{acid}}$, expt (kcal/mol) | $\Delta S_{\mathrm{acid}}$[e] (cal/mol K) |
|---|---|---|---|---|
| $CH_3NHCH_2CO_2H$ | 341.5[a] | 340.9 | 334.6[a] | 23.1 |
| $(CH_3)_2N(BH_3)CH_2CO_2H$, **5** | 328.8[b] | 329.2 | 322.1[b] | 22.6 |
| $CH_3NOCH_2CO_2H$, **7** | | 329.4 | | |
| $(CH_3)_3N^+CH_2CO_2H$, **3** | | 248.3 | 239.2[d] | |
| $CH_3SCH_2CO_2H$, **MTA** | 340.0[c] | 338.9[c] | 333.0[c] | 22.8 |
| $CH_3S(BH_3)CH_2CO_2H$, **6** | 325.8[b] | 325.5 | 319.2[b] | 22.2 |
| $CH_3SOCH_2CO_2H$, **8** | | 328.6 | | |
| $CH_3SO_2CH_2CO_2H$, **9** | | 326.1 | | |
| $(CH_3)_2S^+CH_2CO_2H$, **10** | | 243.0 | | |

[a] Obtained from refs 52 and 55. [b] Determined in this work. The uncertainty is ±1.9 kcal/mol for the expt value. [c] Obtained from ref 37. [d] Obtained from refs 8 and 17. [e] Derived from $\Delta H_{\mathrm{acid}}$ and $\Delta G_{\mathrm{acid}}$.

procedure by calculating the enthalpies of deprotonation of $CH_3NHCH_2CO_2H$ (sarcosine) and $CH_3SCH_2CO_2H$ (MTA). The calculated values for sarcrosine (339.3 kcal/mol) and MTA (338.9 kcal/mol) agree well with the experimental values obtained from the literature, 341.5 ± 2.1 kcal/mol[52,55] and 340.0 ± 1.7 kcal/mol,[37] respectively. The calculated theoretical enthalpies of deprotonation of the series of carboxylic acids are summarized in Table 1. The results are in good agreement with the available experimental data. For borane aminoacetic acid (**5**) and borane thioacetic acid (**6**), we also calculated the enthalpy of deprotonation using a different theoretical method, MP2/6-311+G(2d,p)//B3LYP/6-31+G(d). The results are essentially the same as those calculated at the B3LYP/6-31+G(d) level.

$$\mathrm{HA} + \mathrm{CH_3CO_2}^- \rightarrow \mathrm{A}^- + \mathrm{CH_3CO_2H} \qquad (6)$$

$$\Delta H_{\mathrm{acid}}(\mathrm{HA}) = \Delta H_{\mathrm{rxn}} + \Delta H_{\mathrm{acid}}(\mathrm{CH_3CO_2H}) \qquad (7)$$

Schematic drawings of the charge sites, on the basis of calculated charge distributions, are also shown in Figure 4. For both **5a** and **6a**, the sum of the charge density at $BH_3$ is about −0.5*e* and at the carboxyl group is about unit negative charge. About 0.5*e* is distributed over the nitrogen. The geometries of the oxide analogues, **7a** and **8a**, resemble those of **5a** and **6a**. The calculated charge density at the oxide oxygen is about −0.9*e*. For **9a**, each of the two oxygen atoms at the sulfone group bears about −0.5*e* charge and the sulfur has a unit positive charge. For betaine (**3a**) and sulfonium−acetate (**10a**), a unit positive charge is distributed over the nitrogen and the sulfur atoms, and a unit negative charge is at the carboxyl group.

## Discussion

The gas-phase enthalpies of deprotonation ($\Delta H_{\mathrm{acid}}$) of borane−aminoacetic acid (**5**) and borane thioacetic acid (**6**) were measured to be 328.8 and 326.0 kcal/mol, respectively. Compared to sarcosine ($CH_3NHCH_2CO_2H$, $\Delta H_{\mathrm{acid}} = 341.5$ kcal/mol) and MTA ($CH_3SCH_2CO_2H$, $\Delta H_{\mathrm{acid}} = 340.0$ kcal/mol), the dipole-modified carboxylic acids, **5** and **6**, are stronger acids by 12.7 and 14.0 kcal/mol. The gas-phase deprotonation free energy ($\Delta G_{\mathrm{acid}}$) of **5** and **6** was determined to be 322.1 and 319.3 kcal/mol. The same magnitudes of acidity enhancements were obtained when compared to the gas-phase deprotonation free energies of sarcosine ($\Delta G_{\mathrm{acid}} = 334.6$ kcal/mol) and MTA ($\Delta G_{\mathrm{acid}} = 333.0$ kcal/mol). The gas-phase enthalpies of deprotonation of the two oxide analogues, **7** and **8**, were calculated to be 329.5 kcal/mol and 328.7 kcal/mol, respectively, and are comparable to those of **5** and **6**. The calculated enthalpy of deprotonation for sulfone−acetic acid (**9**) was 326.1 kcal/mol, about 2.5 kcal/mol lower than that of **8**. The enthalpy of deprotonation of sulfoniumacetic acid (**10**) was calculated to be 243.0 kcal/mol, comparable to that of protonated betaine, **3** (248.3 kcal/mol). Compared to MTA, **10** is a stronger acid by 97.0 kcal/mol.

The enhanced gas-phase acidity from sarcosine to **5** and from MTA to **6** can be analyzed qualitatively in the following manner. Upon an acid dissociation, a pair of opposite charges is generated at the carboxyl group, the departing proton and the carboxylate anion. In the presence of a dipole (the N−B or the S−B bond) oriented in such a way that the developing negative charge at the carboxyl group is stabilized by the charge−dipole interaction, the deprotonation energy will be reduced, and hence the acidity will be increased (**5a** and **6a** in Figure 4).

The magnitude of the acidity enhancements can be correlated to the electrostatic free energies of the dipole−charge interaction in the carboxylate ions through the application of the K−W model (Scheme 1 and eq 3b). Acids **5** and **6** are the examples of organic acids containing a dipolar substituent (II). Sarcosine and MTA are the corresponding acids without the dipolar group (III). The change in the gas-phase acidity ($\delta\Delta G_{\mathrm{acid}}$) from sarcosine to **5** and from MTA to **6** can be related to the electrostatic interaction between the dipolar group and the negatively charged carboxyl group in **5a** and **6a** (Scheme 4). The calculated electrostatic free energies in **5a** ($\Delta G_{\mathrm{elec}} = 15.2$ kcal/mol) and **6a** ($\Delta G_{\mathrm{elec}} = 14.9$ kcal/mol) are indeed comparable to the increase in the gas-phase acidity from sarcosine to **5** ($\delta\Delta G_{\mathrm{acid}} = -12.7$ kcal/mol) and from MTA to **6** ($\delta\Delta G_{\mathrm{acid}} = -14.2$ kcal/mol), Table 2.

The oxide analogues, **7** and **8**, have similar geometrical and electronic structures as the borane-complexed acids, **5** and **6**. The N−O and S−O bonds resemble the corresponding N−B

**SCHEME 4**

**5a** **6a**

**TABLE 2: Gas-Phase Acidity Enhancements ($\delta\Delta G_{acid}$) and Electrostatic Free Energies ($\Delta G_{elec}$) Calculated for the Corresponding Carboxylic Anions**

| acid | $\delta\Delta G_{acid}$ (kcal/mol) | $\Delta G_{elec}$ (kcal/mol)[c] |
|---|---|---|
| $(CH_3)_2N(BH_3)CH_2CO_2H$, **5** | 12.7[a] | 15.2 |
| $CH_3S(BH_3)CH_2CO_2H$, **6** | 14.2[b] | 14.9 |
| $CH_3NOCH_2CO_2H$, **7** | 12.0[a] | 13.0 |
| $CH_3SOCH_2CO_2H$, **8** | 11.3[b] | 12.8 |
| $CH_3SO_2CH_2CO_2H$, **9** | 13.9[b] | 15.5 |
| $(CH_3)_3N^+CH_2CO_2H$, **3** | 93.2[a] | 100.9 |
| $(CH_3)_2S^+CH_2CO_2H$, **10** | 97.0[b] | 95.2 |

[a] Reference acid: sarcosine. [b] Reference acid: MTA. [c] Calculated using eq 1.

and S—B dipolar bonds, respectively, in both the neutral acids and the carboxylate anions (**7a** and **8a** in Figure 4). As expected, the calculated enthalpies of deprotonation of **7** and **8** are similar to those of **5** and **6**. The acidity enhancements from sarcosine to **7** ($\delta\Delta G_{acid} = 12.0$ kcal/mol) and from MTA to **8** ($\delta\Delta G_{acid} = 11.3$ kcal/mol) are also comparable to the electrostatic free energies ($\Delta G_{elec}$) in the corresponding carboxylate anions, **7a** (13.0 kcal/mol) and **8a** (12.8 kcal/mol). The similarity of the gas-phase acidities between the oxides and the corresponding borane-complexed molecules can also be found in dimethylsulfoxide (DMSO, $(CH_3)_2S—O$) and boranemethylsulfide (BMS, $(CH_3)_2S—BH_3$). The gas-phase enthalpy of deprotonation of the methyl hydrogen in DMSO is the same as that in BMS (372.5 kcal/mol).[50] The sulfone group (O—S—O) in **9** can be viewed as one group dipole (Figure 4). The small increase in the acidity (2.5 kcal/mol) from **8** to **9** suggests that the sulfone group has a slightly stronger stabilization effect on the carboxyl group in **9a** than the S—O bond in **8a**. Nonetheless, the increase in the acidity from MTA to **9** (13.9 kcal/mol) is qualitatively comparable to the electrostatic free energy in **9a** (15.5 kcal/mol).

The sulfoniumacetic acid (**10**) is similar to the protonated betaine (**3**) insofar as it is an example of an organic acid with a monopolar substituent. The electronic structures of **3** and **10** can be related to those of borane-complexed acids, **5** and **6**. Upon deprotonation, both **5** and **6** form negatively charged ions, while **3** and **10** form overall neutral molecules. Compared to that in sarcosine and MTA, the deprotonation energy in **5** and **6** is smaller because of the favorable electrostatic interaction between the dipole and the carboxylate anion upon deprotonation. In **3a** and **10a**, interaction with the positively charged monopole will greatly stabilize the carboxylate anion (**3a** and **10a** in Figure 4), and the deprotonation energy of **3** and **10** will be significantly reduced. The acidity enhancement from MTA to **10** can be quantitatively correlated to the electrostatic free energy in **10a** through the application of the K−W model (Scheme 1 and eq 3a). Acid **10** is related to I and MTA is related to III. The results in Table 2 clearly show that the acidity enhancement of **10** ($\delta\Delta G_{acid} = 97.0$ kcal/mol) is about the same magnitude as the calculated electrostatic free energy in **10a** (95.2 kcal/mol). Similarly, the measured acidity enhancement of **3** ($\delta\Delta G_{acid} = 93.2$ kcal/mol) is also comparable to the electrostatic free energies in **3a** ($\Delta G_{elec} = 100.9$ kcal/mol).

The magnitude of the acidity enhancements will be smaller in the condensed phase. Since the solvation energy of IIIa will be larger than that of Ia and that of IIa, the change in solvation energies will be positive values for both of the reactions in Scheme 1. The positive solvation energy will offset the changes in the acidity from III to I and from III to II. A comparable example can be found in an earlier study of the α-CH acidity enhancement of $BF_3$ complexed acetaldehyde. The magnitude of the acidity enhancement is reduced by one-third from the gas-phase results to those in aqueous solution.[56]

In these polar group substituted carboxylic acids, the averaged distance from the polar group to the carboxyl group is about 3.7 Å. The acidity enhancement of the carboxyl group is about 11−14 kcal/mol in the dipolar group substituted acids and about 93−97 kcal/mol in monopolar substituted cases. These values can be valuable in estimating the effective acidity of an acidic group in the active site of a protein, since most active sites of proteins are located near the interior region where solvent effects are minimized.

## Conclusion

The polar group effects on the gas-phase acidities of carboxylic acids were studied experimentally and computationally. The gas-phase enthalpies of deprotonation and deprotonation free energies of borane-complexed methylamino- and methylthioacetic acids were determined using the kinetic method. The gas-phase enthalpies of deprotonation of several prototype monopole and dipole substituted carboxylic acids were calculated using the DFT method. The magnitudes of the acidity enhancement were correlated to the electrostatic free energies in the carboxylate anions through the application of the Kirkwood and Westheimer model. Introducing a dipolar group at the *β*-atom of a carboxylic acid can cause an increase in the gas-phase acidity up to 14 kcal/mol, corresponding to a reduction of 10 $pK_a$ units. Introducing a positively charged monopolar group can cause an increase in the acidity up to 97 kcal/mol, corresponding to a reduction of 67 $pK_a$ units. The magnitude of the acidity enhancements is comparable to the electrostatic free energies calculated for the carboxylate anions. The gas-phase acidity enhancements in polar group substituted carboxylic acids are the results of the favorable electrostatic interaction between the polar group and the developing charge at the carboxyl group.

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