Effects of Substituents on the Acidity of Acetic Acids

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The acidities of a wide range of substituted acetic acids have been determined in several solvents from potentiometric titrations. From multi-linear-regression (MLR) correlation equations in which substituent steric, polarizability, and field/inductive effects are considered, analysis of structural effects on the relative acidities was accomplished. The effects that alkyl substituents have on acidity variations come primarily from a substituent steric effect and not a substituent polarizability effect. The effect of polar substituents on acidity variations is caused mainly by a substituent field/inductive effect, and this effect is manifested most in polar basic solvents. The effect of the N,N-dimethylamino substituent differs from the other polar substituents studied. N,N-Dimethylglycine is less acidic than predicted by the MLR correlation equations in all solvents studied. The tautomeric equilibrium that governs the neutral/zwitterion formation is medium dependent, and the magnitude of that equilibrium constant dictates the observed acidity of N,N-dimethylglycine. The solubility of N,N-dimethylglycine gives an indication of the extent of zwitterion formation. N,N-Dimethylglycine is very soluble in solvents in which the zwitterion is favored, but the solubility decreases in solvents in which the neutral amino acid is the favored species.

Introduction

The chemical, physical, and biological properties of many compounds are usually dictated by acidic and/or basic groups that are present on the molecules. For example, the rate of gastrointestinal absorption of some ionizable drugs depends on the acidity (or basicity) of functionalities that are present.[1] Such structure–reactivity relationships have been recognized for a long time; the Hammett equation, for example, has been very useful for the analysis of the effects that substituents have on acidity variations of various molecules in aqueous media.[2] In order to gain a complete understanding of the different factors that affect reaction rates and equilibria, the effects that the reaction media have on the reactivity of molecules cannot be neglected.[3] Owing to the knowledge that is gained from the study of reactions in the gas phase,[4] the possibility exists to determine more precisely the intrinsic effects of substituents on the reactivity of molecules. As a result of such studies, the effects that substituents have on the reactivity of compounds can be separated from the effects that solvents have on their reactivity.

Quantitative structure–activity relationships (QSAR) have been used to correlate molecular structural features of compounds with their known biological, chemical, and physical properties.[5] For a particular compound, QSAR assumes that there is a quantitative relationship between its microscopic and macroscopic properties. Over the years, numerous substituent constants have been developed for different compounds. Such constants have been used to predict successfully the acidities of different compounds in different media.[6] One QSAR that is used widely for the analysis of substituent effects on the reactivity of compounds is shown below (eq 1)[7]

$$-\delta \Delta G = \rho_R \sigma_R + \rho_F \sigma_F + \rho_\alpha \sigma_\alpha + c \qquad (1)$$

where $\rho_R \sigma_R$ represents the substituent resonance effect, $\rho_F \sigma_F$ represents the substituent field/inductive effect, and $\rho_\alpha \sigma_\alpha$ represents the substituent polarizability effect. The coefficients are represented by ρ and the substituent constant by σ. In this study, the effects that substituents have on the acidity of substituted acetic acids will be assessed and analyzed in various media by MLR correlation equations of the format shown in eq 1. The effects that solvents have on the relative magnitude of the tautomeric equilibrium of N,N-dimethylglycine will be discussed.

Experimental Section

Substituted acetic acids and spectrophotometric grade solvents were purchased from Aldrich Chemical Co. Solvents were stored over molecular sieves (4A) before being used. Substituted acetic acids were purified by recrystallization or distillation before being used. The procedure used for acidity determinations from potentiometric titrations is similar to that outlined in the literature.[8] Tetrabutylammonium hydroxide (0.15 M) was used to titrate freshly prepared solutions of the acids. Titrations were carried out at 25.0 ± 0.1 °C. A constant temperature was maintained with a Fisher Scientific Isotemp refrigerated circulator (Model 9100). For each titration, a Fisher Accumet pH meter (Model 620) was used in conjunction with a Beckman glass electrode and a Pt/I⁻, I⁻₃ reference electrode. The connecting junction consisted of tetramethylammonium tetrafluoroborate dissolved in the solvent used for the titration. The reference

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Table 1. Relative Free Energy Change ($\delta\Delta G$) for the
Acidities of Substituted Acetic Acids (XCH_2COOH) in
Various Media at 298 K. Values (kcal/mol) Are Relative to
Acetic Acid[a]

substituent	gas[b]	AQ	MeOH	EtOH	2-PrOH	EG	DME
H	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CH_3	−1.2	0.1	0.6	0.5	1.1	0.5	0.2
C_2H_5	−2.0	0.1	0.6	0.7	1.3	0.6	0.7
C_3H_7	−2.3	0.1	0.6	0.6	1.4	0.6	0.8
$i\text{-}C_3H_7$	−3.0	0.1	0.5	0.7	1.3	0.6	0.8
$c\text{-}C_6H_{11}$	−3.2	0.1	0.9	0.9	1.6	0.8	0.8
$t\text{-}C_4H_9$	−3.7	0.4	0.9	1.3	1.7	0.8	1.4
$(CH_3)_3Si$		0.6	0.9	1.3	1.9	c	1.1
Ada		c	0.8	1.1	2.3	c	1.5
CH_3S		−1.5	−1.1	−1.1	−0.9	−1.0	−1.2
CH_3O	−6.2	−1.7	−1.4	−1.4	−1.6	−1.7	−1.9
C_6F_5		c	−1.5	−2.1	−2.6	−1.9	−2.6
Cl	−12.5	−2.7	−2.6	−2.9	−2.9	−2.7	−3.3
$(CH_3)_2N$		7.0	3.3	2.5	2.1	c	c
		(−0.6)	(−0.2)	(−0.2)	(0.2)		

[a] Key: gas, gas phase; AQ, water; MeOH, methanol; EtOH, ethanol;
2-PrOH, 2-propanol; EG, ethylene glycol; DME, dimethoxyethane.
[b] Reference 10c. [c] Not soluble.

electrode used is similar to that used for the basicity determi-
nations of amines.[9] The glass electrode was checked for respon-
siveness prior to each experiment. Best results were obtained
when the glass electrode was limited to 5 h of use and stored in
a pH 7 buffer solution when not in use. Each acidity measurement
was repeated at least three times, and acidity reproducibility is
within ±0.1 pK unit. Relative free energy changes ($\delta\Delta G$) shown
in Table 1 were calculated from the relationship $\Delta G = -RT \ln K$ (relative to acetic acid). The solubility of N,N-dimethylglycine
was determined in the solvents shown in Table 4 by adding an
excess of N,N-dimethylglycine to 10 mL of solvent. The mixture
was stirred vigorously for 2 days at 25.0 ± 0.1 °C. After the
excess N,N-dimethylglycine was filtered off, the density of the
filtrates was determined with a Anton Parr density meter. On
the basis of the linear relationships that exist between the
densities and the concentrations of five different solutions, the
concentrations of the saturated solutions were determined. The
reproducibilities shown in Table 4 are based on at least three
determinations.

Results and Discussion

Substituent Polarizability/Steric Effects. For the
acidity of substituted acetic acids (eq 2), examination of

the gas-phase acidity data[10] (Table 1) indicates that bulky
alkyl substituents increase the strength of each acid. That
is, for example, in the gas phase, *tert*-butylacetic acid is
a stronger acid than acetic acid. In the gas phase, charge-
induced stabilization[11] of the conjugate base is gained from
nearby substituents, and as a result, acids with bulky alkyl
substituents are more acidic than those with less bulky
substituents. Similar observations are made for the
acidities of most compounds in the gas phase.[12] The data

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Table 2. Coefficients for the MLR Analysis (Eq 1) for the
Substituent Effects (Polarizability and Field/Inductive
Effects) on the Acidities of Substituted Acetic Acids in
Various Media[a]

medium	ρ_α	ρ_F	c	r	sd	n
gas[b]	5.1 ± 0.4	−23.8 ± 0.5	−0.4 ± 0.2	0.9969	0.4	13
aq	−0.4 ± 0.3	−6.5 ± 0.2	−0.1 ± 0.1	0.9916	0.2	11
MeOH	−0.8 ± 0.2	−7.2 ± 0.3	0.2 ± 0.1	0.9953	0.1	13
EtOH	−1.1 ± 0.2	−7.8 ± 0.2	0.1 ± 0.1	0.9938	0.2	13
2-PrOH	−1.9 ± 0.3	−9.7 ± 0.2	0.3 ± 0.2	0.9905	0.3	13
EG	−1.0 ± 0.1	−7.1 ± 0.2	0.0 ± 0.1	0.9971	0.1	13
DME	−1.5 ± 0.2	−8.9 ± 0.4	−0.1 ± 0.1	0.9934	0.2	13

[a] Key: gas, gas phase; aq, water; MeOH, methanol; EtOH, ethanol;
2-PrOH, 2-propanol; EG, ethylene glycol; DME, dimethoxy ethane.
[b] Acidities obtained from ref 10c.

shown in Table 1 for the acidity of substituted acetic acids
in the condensed phase reveal the opposite trend. That
is, acetic acids with bulky substituents are weaker acids
than those with less bulky substituents. The acidities of
other carboxylic acids show a similar trend in solution.[13]
From these results, the effects that alkyl substituents have
on the acidity of substituted acetic acids are different in
the gas phase from those in the condensed phase. The
two possible modes by which alkyl substituents affect the
reactivity of compounds are polarizability and steric
effects. We have demonstrated recently that substituent
polarizability effect, even though small, is measurable in
the condensed phase.[14] On the basis of the trend of the
acidity of the substituted acetic acids of this study (Table
1), alkyl substituents apparently do not stabilize carbox-
ylate anions by substituent polarizability effect. If this
type of substituent effect existed, an acidity trend similar
to that for the gas phase would have been observed.

Further evidence that substituents affect the acidities
of these acids differently in the gas phase compared to the
condensed phase comes from the analysis of the data (Table
1) with MLR correlation equations. Table 2 shows the
correlation coefficients for the dual parameter equations
in which substituent polarizability and field/inductive
effects are considered. In order to include a larger number
of substituents that are capable of substituent polariz-
ability effect, the nonalkyl substituents shown in Table
1 were included in these correlations. Since the substit-
uents and the reaction center are separated by a methylene
unit, the resonance substituent effect was not included in
the analyses. The standard deviation and correlation
coefficients for these equations are very good as shown in
Table 2. It is noticeable, however, that the sign of the
coefficient for the substituent polarizability (ρ_α) effect in
solution is opposite from that in the gas phase. If the
strength of an acetic acid is increased due to the substi-
tution of a polarizable substituent in the α-position, a
positive coefficient is achieved. The sign of ρ_α for reactions
in which the substituent polarizability effect is present is
positive for both the gas-phase and solution-phase reac-
tions.[15] From Table 2, based on the different signs of ρ_α,
the substituent polarizability constants used in these MLR
correlation equations do not reflect the substituent
polarizability effect, but another property. Bowden,
Chapman, and Shorter showed that the steric effect plays
an important role in the dissociation of carboxylic acids.[16]

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Table 3. Coefficients for the MLR Analysis (Eq 3) for the Substituent Effects (Steric and Field/Inductive Effects) on the Acidities of Substituted Acetic Acids in Various Media

medium[a]	ρ_{St}	ρ_F	c	r	sd	n
gas[b]	1.5 ± 0.2	−25.0 ± 1.0	−1.6 ± 0.2	0.9935	0.5	10
aq	−0.1 ± 0.1	−6.2 ± 0.2	0.1 ± 0.0	0.9961	0.1	10
MeOH	−0.3 ± 0.1	−6.6 ± 0.3	0.5 ± 0.1	0.9964	0.1	10
EtOH	−0.4 ± 0.1	−7.1 ± 0.2	0.6 ± 0.1	0.9965	0.1	10
2-PrOH	−0.6 ± 0.1	−8.2 ± 0.5	1.0 ± 0.1	0.9932	0.2	10
EG	−0.3 ± 0.1	−6.8 ± 0.3	0.4 ± 0.1	0.9956	0.1	10
DME	−0.5 ± 0.1	−8.0 ± 0.5	0.5 ± 0.1	0.9923	0.2	10

[a] See Table 2 for abbreviations. [b] Acidities obtained from ref 10c.

Further evidence that the steric effect plays a role in the acidity variations of alkyl-substituted carboxylic acids comes from the observation that there is a pK_a variation of 0.67 pK_a unit in 50% (v/v) aqueous methanol for carboxylic acids that have substituents with the empirical formula C_7H_{15}. These substituents have the same empirical formula and, therefore, based on the molar refractivities have the same polarizability; thus, acidity variations arise from the steric effect rather than the polarizability effect.[17] For the alkyl substituents used in this study, the correlation coefficient for the least-squares equation of E_s, a measure of steric substituent effect,[18] versus σ_α is 0.9725. Since there is a direct relationship between the substituent polarizability constants and the substituent steric constants, the polarizability constant may reflect substituent steric effect.

The carboxylate group, being a fairly large functionality,[19] is susceptible to steric interactions from nearby substituents. The acetate anion that has bulky substituents in the α-position is less favored than the carboxylate anion with a less bulky substituent in the same position. Table 3 shows the coefficients for the dual-parameter MLR correlation equations for reaction 1 in which substituents steric, E_s, and field/inductive effects are considered (eq 3). The coefficient of the steric property (ρ_{st}) is negative

$$-\delta\Delta G = \rho_F\sigma_F + \rho_{st}E_s + c \qquad (3)$$

for the gas-phase reaction but positive for the solution-phase reaction. For the acidity of carboxylic acids in the gas phase, alkyl groups influence the acidity of carboxylic acids by the polarizability effect and not the substituent steric effect,[20] whereas the substituent steric effect plays an important role for the reactivity of most compounds in solutions. Another important factor for the solution-phase acidity is that theoretical calculations show that hydration of the substituted acetate anion plays an important role for the acidity of substituted acetic acids. The $-\Delta E$ for adding three water molecules to an acetate anion is about 51.1–63.6 kcal/mol, whereas similar additions are about 8.2–10.2 kcal/mol for the neutral acid.[21] The relatively small ρ_{st} in aqueous solution indicates that steric effects do not play a major role in acidity variations compared to the other solvents. From Table 1, the small variations of aqueous acidity indicate that alkyl substit-

uents effect is minimal. For the other solvents, however, substituents effects do play a major role—the ρ_{st} values are much larger. A number of workers have shown that bulky groups inhibit the solvation of the carboxylate anions of aliphatic and arylaliphatic carboxylic acids.[22,23] These findings that the steric effect plays a measurable role in the acidity of acetic acids contradict the implication of Bartnicka et al.[24] that the steric effect is either completely absent or approximately the same as the methyl group for the acidity of carboxylic acids. The substituent constant used for their correlation analysis is σ^*, which is a measure of inductive effects, and as a result, the slope of such a correlation reveals the inductive effect of the substituent on the reaction rather than other possible substituents effects. As will be shown in the next section, acidity variations caused by field/inductive effects are much larger than those caused by other types of substituent effects. Since substituent polarizability is the only electronic effect of alkyl groups,[6] such effects would have been ignored (or overwhelmed) if only the σ^* constant was used.

Substituent Field/Inductive Effect. Polar substituents are known to increase the acidity of carboxylic acids in both the condensed and gas phases.[18] For the acids in this study, acidity variations in the gas phase are caused by substituent field/inductive and polarizability effects,[25] but as noted in the previous section, the substituent steric (and not the polarizability effect) is an important factor for the determination of the acidity of substituted acetic acids. Thus, in order to characterize the overall effects that substituents have on the acidity variations of acetic acids in solution, eq 3 should be utilized. The coefficients of these MLR correlation equations are shown in Table 3. In this case, the sign for the field/inductive effect (ρ_F) is the same for the gas-phase and solution acidities. If the magnitude of a particular coefficient is large, then inherent stabilization of the carboxylate anion plays a dominant role in acidity variations and solvation effect is minimal, whereas smaller magnitudes of the coefficients mean the opposite. The coefficient is largest for the gas-phase reaction since there are no solvent molecules present. From Table 3, the largest magnitude of ρ_F for solution-phase acidity is for 2-propanol and dimethoxyethane (DME). Solvation of the carboxylate anion depends on the solvent's ability to solvate the negatively charged ion by electrostatic interactions and by the effective formation of hydrogen bonds to the anion. The solvatochromic parameters[26] are often used to quantify such solvent properties. For DME, the values for the dipolarity/polarizability effect (π^*) and hydrogen bond acidity (α) parameters are 0.53 and 0, respectively. Compared to water (solvatochromic parameters are shown in Table 4), the solvation of the acetate anions by DME is minimal, hence, a large ρ_F value. 2-Propanol, in addition to having relatively small solvatochromic parameters for these properties (Table 4), is a bulky solvent and *cannot solvate effectively the acetate*

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Table 4. Solubility (mol/L) of *N,N*-Dimethylglycine in Various Alcohols (and Water) at 298 K along with Selected Solvatochromic Parameters[26]

solvent	solubility	π^*	α	β
water	∞	1.09	1.17	0.45
methanol	3.6464 ± 0.0087	0.60	0.98	0.62
ethanol	1.2331 ± 0.0037	0.54	0.86	0.77
2-propanol	0.3539 ± 0.0288	0.46	0.78	0.90

anions—as a result, ρ_F is large also. The trend for ρ_F for the other solvents is consistent with the magnitude for these solvatochromic parameters.

For the results of the MLR analyses that are shown in Tables 2 and 3, the correlations do not include the *N,N*-dimethylamino substituent. The excellent correlation coefficients shown in these tables were destroyed if this substituent was included in the MLR analyses. The experimental acidities shown in Table 1 for *N,N*-dimethylglycine are lower than the values predicted by eqs 1 and 3. The values in parentheses (Table 1) are those calculated from eq 3. A possible cause for the lower than expected acidity is that *N,N*-dimethylglycine forms zwitterions in solution. The tautomeric equilibrium that governs the formation of the zwitterions of N,N-dialkylated amino acids is medium dependent.[27] In the gas phase, amino acids are known to exist as neutral molecules,[28] whereas glycine and other soluble amino acids exist as zwitterions in aqueous solution and in the solid crystalline state.[29] Table 4 shows the solubility of *N,N*-dimethylglycine in different solvents. *N,N*-Dimethylglycine is infinitely soluble in water but not very soluble in 2-propanol. Solvents with large dipole moments and

dielectric constants and that have good hydrogen bond donor and acceptor abilities solvate zwitterions very well. The solvatochromic parameters (Table 4), which reflect these properties, can be used to analyze the solvation of the zwitterions. Owing to the limited data set, it is difficult to determine which factor plays the dominant role in the solubility of dimethylglycine; however, the sum of these parameters gives a good indication of the ability of the solvent to solvate the zwitterions. The sum of the parameters is largest for water and smallest for 2-propanol; thus, since the solubility is greatest in water, a greater percentage of zwitterion exists in water compared to other less polar solvents, such as 2-propanol. In addition, a bulky solvent such as 2-propanol cannot solvate effectively species where a charged center is very close to another charge (or dipole),[30] as is the case of the zwitterions. The solvent molecules must gain access between the lines of force of the two charged groups (or dipoles) to effectively solvate such a system. Also, since the pK_a of *N,N*-dimethylglycine in water (9.88)[31] is close to that of trimethylammonium ion (9.75)[32] and not acetic acid (4.75), *N,N*-dimethylglycine exists in water as zwitterions and as a result is very soluble in this medium. As a result, the acidity of *N,N*-dimethylglycine is closer to the calculated acidity in 2-propanol (Table 1). The closeness of these values, compared to those in water, suggests that the tautomeric equilibrium favors the neutral amino acid. As a result, the solvation of the zwitterion by 2-propanol must be minimal. These results indicate that the solubility of *N,N*-dimethylglycine depends on the ability of the solvent to solvate the zwitterion.

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