Reexamination of the Kirkwood–Westheimer Theory of Electrostatic Effects. 4. Effect of N-Substitution on the Dissociation Constants of Some α,ω-Amino Acids

John T. Edward,*[1a] Patrick G. Farrell,[1a] Jean-Claude Hallé,[1b] Jitka Kirchnerova,[1a]
Robert Schaal,*[1b] and François Terrier[1b]

Department of Chemistry, McGill University, Montreal, PQ, Canada H3A 2K6 and the Laboratoire de Physicochimie des Solutions, LA CNRS, 161, ENSCP, Université Pierre-et-Marie Curie, Paris 5e, France

Received July 18, 1978

pK values for the ionization of the carboxyl group and (where possible) of the ammonium group of several α,ω-amino acids, unsubstituted or substituted to varying extents on the ammonium group, have been determined in water and in water–Me_2SO mixtures of varying composition. Results are in fair agreement with the Kirkwood–Westheimer treatment of electrostatic effects when the charged centers are separated by four or more methylene groups, but diverge increasingly as the charged centers become closer. A possible effect of solvent composition on the extent of chain coiling is discussed.

The electrostatic "field-effect" model elaborated 40 years ago by Kirkwood and Westheimer[2] has proved moderately successful in predicting the effects of substituents on reaction rates and equilibria. In particular, it can account (at least qualitatively) for the effect of orientation of dipolar substituents,[3] which the rival "inductive effect" model would consider without effect. It can also account for the effect of charged substituents at relatively great distances, where the inductive mechanism would indicate a negligible effect.[4] In a preceding paper[5] we have examined critically the adequacy of the Kirkwood–Westheimer (KW) model to account for the variation in the pK of 3- and 4-substituted cyclohexanecarboxylic acids in solvent mixtures made up of varying proportions of water and dimethyl sulfoxide. In the present paper we examine its adequacy to account for the variation in the pK in these solvent mixtures of both carboxyl and ammonium groups when separated at varying distances from charged groups of different ionic radius.

According to KW theory the effect, ΔpK, of a charged substituent on an ionization constant is given by

$$\Delta pK = e^2/2.3kTRD_{\text{eff}} \qquad (1)$$

where e is the electronic charge, k Boltzmann's constant, T the absolute temperature, R the distance between the center of the charged substituent and the center of the ionizing group,[6] and D_{eff} the effective dielectric constant. For prolate ellipsoidal molecules in which the charges are located at the foci of the ellipsoid, D_{eff} may be calculated from the eccentricity λ_0 ($\equiv 2a/R$, where a is the major axis) and D_e, the dielectric constant of the solvent, assumed to be a continuum.[2] For short, fat, relatively spherical molecules (large λ_0), the lines of force between charges pass mostly through the hydrocarbon framework of the molecule (dielectric constant D_i, assumed to be 2.0) and D_{eff} can approach 2.0. For long thin molecules (λ_0 approaching 1.0 as a limit), the lines of force between the charges pass mostly through the solvent and D_{eff} approaches D_e.

A practical problem in applying this theory comes from the need to fit the real molecule into an ideal ellipsoid. In practice two approaches[7] have been followed:

(i) For a known R and molecular volume V, λ_0 can be calculated, according to the original KW approach,[2] from the geometrical relationship:

$$\lambda_0^3 - \lambda_0 = 6V/\pi R^3 \qquad (2)$$

and hence D_{eff} obtained from λ_0 and D_e.[2,9]

This equation makes use of a physically reasonable V, but as the ellipsoid becomes elongated, the foci approach the end surface more closely, and so depth d by which the charges are buried in the molecular cavity is continually decreased.

(ii) Tanford[10] recommended that for charged groups d be fixed at 1 Å; for a given R this then fixes $\lambda_0 = (R + 2d)/R$, but gives rise to unrealistically large values of V as the molecule becomes elongated. While $d = 1.0$ Å is more realistic than the values which emerge for long thin molecules by the KW approach (i), it is still unreasonably small;[8] even so, it must be reduced to 0.6 Å when one attempts to fit KW theory to the titration curves of proteins.[11]

In the present paper we investigate the effect on the pK of the carboxyl group of burying the positive charge of a nearby ammonium group to varying depths in the molecular cavity by progressive alkylation. These studies have used a wide range of water–Me_2SO mixtures as solvent. Up to fairly high Me_2SO contents, these have dielectric constants not grossly different from the dielectric constant of water;[12] however, the solvating properties of Me_2SO-rich mixtures differ appreciably from those of water. We can expect the $-NH_3^+$ group to be solvated strongly (by hydrogen bonding to Me_2SO), the $-NR_3^+$ group weakly, and the $-CO_2^-$ group very weakly.[13] On the other hand, $-CO_2^-$ should be strongly solvated by H_2O. Consequently, we considered it possible that large changes might become evident as Me_2SO replaced water in solvent mixtures.

Although in water a carboxylic acid is in general a much stronger acid than an ammonium ion, it becomes relatively weaker as solvent water is progressively replaced by Me_2SO, and in 100% Me_2SO it is generally a slightly weaker acid.[14] Consequently, it became necessary to consider the possibility that in the Me_2SO-rich mixtures the amino acids may exist in the molecular as well as, or rather than, in the tautomeric zwitterionic form (cf. ref 15). This possibility was investigated by NMR studies of *N,N*-dimethylglycine in Me_2SO-d_6–D_2O ca. 85:15 (w/w). (At higher Me_2SO concentrations solubility problems were encountered.)

Experimental Section

Materials and Methods. Me_2SO and water were purified as before.[16] The amino acids and their derivatives were commercial products of the highest purity available. They were recrystallized two or three times, first from water then from water–methanol solutions, and were dried in vacuo over P_2O_5. Betaines of ω-amino carboxylic acids were prepared by alkylation of the acids with methyl or ethyl iodide, following standard literature procedures. The neutral zwitterionic betaines[17] were recrystallized from water–methanol mixtures. Stock solutions (0.1 N) of hydrochloric acid and sodium hydroxide were prepared from Fisher 1 N standard solutions using freshly boiled, distilled water.

Experimental procedures for pK measurements have been described.[14,15] pK's were determined in triplicate, using three buffer

0022-3263/79/1944-0615$01.00/0

Table I. Dissociation Constants in Water and in 83.1% (mol/mol) Me_2SO

compd	registry no.	water		83.1% Me_2SO	
		pK_1	pK_2	pK_1	pK_2
glycine (**1**)	56-40-6	2.36 (2.36[a])	9.90 (9.91[a])	6.60	12.46
N-methylglycine (**2**)	107-97-1	2.14 (2.14[a])	10.32 (10.32[a])	6.25	12.40
N,N-dimethylglycine (**3**)	1118-68-9	1.94 (1.96[a])	10.05 (10.04[b])	5.76	11.64
N,N,N-trimethylglycine (**4**)	6915-17-9	1.83 (1.83[a])		5.40	
N,N,N-triethylglycine (**5**)	25079-99-6	1.85		5.58	
N-tris(hydroxymethyl)methylglycine (**6**)	5704-04-1	2.01 (2.042[c])	8.23 (8.228[c])	5.84	10.86
N,N-di(2-hydroxyethyl)glycine (**7**)	150-25-4	1.75 (1.77[d])	8.44 (8.41[d])	5.40	10.10
β-alanine (**8**)	107-95-9	3.57 (3.57[a])	10.38 (10.36[a])	8.45	12.25
N,N,N-trimethyl-*β*-alanine (**9**)	13441-31-1	3.25		8.65	
γ-aminobutyric acid (**10**)	56-12-2	4.05 (4.04[a])	10.71 (10.71[a])	9.35	12.73
N,N,N-trimethyl-*γ*-aminobutyric acid (**11**)	10329-41-6	3.98		9.85	
trans-4-aminocyclohexanecarboxylic acid (**12**)	3685-25-4		10.74		12.23
glycylglycine (**13**)	556-50-3	3.12 (3.14[a])	8.38 (8.37[a])	8.02	9.77
ω-trimethylammoniohexanoic acid (**14**)	68409-45-0	4.26		10.62	
ω-trimethylammoniododecanoic acid (**15**)	68409-46-1	4.59		11.01	
n-butylammonium chloride (**16**)	3858-78-4		10.72[e] (10.72[a])		10.82[e]

[a] References 18 and 19. [b] Reference 20. [c] Reference 21. [d] Reference 22. [e] Placed in pK_2 column because this column refers to ionization of substituted ammonium groups.

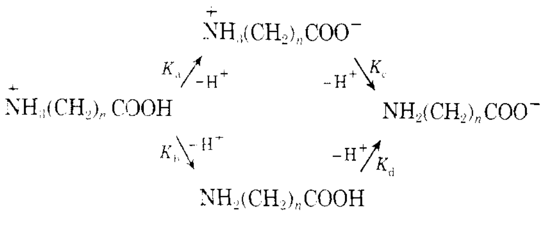
solutions having different acid/base ratios, for the following solvent compositions, 0, 2.7, 9.6, 13.5, 19.5, 26.6, 35.6, 48.7, 59.3, 69.7, and 83.1% (mol/mol) Me_2SO-water, and are reported in Table I and in Table IIIs (supplementary material) as averaged values (pK_1 for CO_2H, pK_2 for $\equiv NH^+$ ionization). The difference between three independently determined values never exceeded 0.06 pK units, the standard deviation being on the average ±0.01 for p$K \geq 4$ and ±0.02 for p$K < 4$. Where results can be compared with data in the literature (see footnotes) agreement is good.

The NMR measurements were carried out using a Varian A 60 spectrometer. Chemical shifts are quoted in ppm relative to Me_4Si and the solvent was Me_2SO-d_6–D_2O (85:15 w/w). The test solutions were prepared from stock solutions 0.8 M in *N,N*-dimethylglycine, *N,N,N*-trimethylglycine, KOH, and benzenesulfonic acid; they were made up so as to give a total solute concentration equal to 0.067 M.

Results and Discussion

The pK_1 and pK_2 values of the 16 compounds of Table I were found to vary smoothly with solvent composition over the range 0–83.1% (m/m) Me_2SO, as shown for seven of them in Figure 1. The variation of the chemical shifts of the methyl protons of *N,N*-dimethylglycine and *N,N,N*-trimethylglycine in 85% Me_2SO-d_6–15% D_2O on the addition of acid or alkali is shown in Figure 2.

Variation of the First and Second Dissociation Constants with Solvent Composition. The dissociation of the cationic species $NH_3^+(CH_2)_nCOOH$ to the anion $H_2N(CH_2)_nCOO^-$ involves four equilibria:



With respect to these equilibria, which cannot be directly determined, the apparent equilibrium constant for the first dissociation step (K_1) is given by

$$K_1 = K_a + K_b \tag{3}$$

or

$$\mathrm{p}K_1 = \mathrm{p}K_a - \log\left(1 + \frac{K_b}{K_a}\right) \tag{4}$$

and that for the second dissociation (K_2) is given by

$$K_2 = \frac{K_c K_d}{K_c + K_d} \tag{5}$$

or

$$\mathrm{p}K_2 = \mathrm{p}K_c + \log\left(1 + \frac{K_c}{K_d}\right) \tag{6}$$

In water, the value of K_a is generally several orders larger than K_b, and so the pK_1 of an aliphatic amino acid is virtually equal to pK_a. Similarly, since $K_c \ll K_d$, the aqueous value of pK_2 corresponds to the value of pK_c. However, on going from water to Me_2SO the ratios K_a/K_b and K_c/K_d can be expected to change significantly: this could result in values of pK_1 and pK_2 no longer equal to pK_a or pK_c, respectively. However, given the precision of our measurements, unless the ratios K_b/K_a and K_c/K_d are larger than 0.1, no measurable contributions of K_d or K_b to the constant K_1 or K_2, respectively, would be observed.

The variation in pK_1 of glycine with the concentration of Me_2SO shown in Figure 1 parallels closely that for the corresponding methylbetaine **4**. This is good evidence for the pK_1 value of glycine being virtually equal to pK_a up to 0.831χ (χ = mole fraction) of Me_2SO, although the presence of a small amount of the uncharged form (<10%) in equilibrium with the zwitterionic form cannot be excluded.

NMR Studies of *N,N*-Dimethylglycine and *N,N,N*-Trimethylglycine. The marked preference for the zwitterionic form over the uncharged form of *N,N*-dimethylglycine is indicated by the NMR measurements. In Figure 2 are shown the changes in chemical shift of the methyl protons of *N,N,N*-trimethylglycine on addition of acid: the protonation of the relatively distant carboxyl group causes a small upfield displacement of the chemical shift. On addition of acid, the chemical shift of the methyl groups of *N,N*-dimethylglycine suffers an exactly parallel displacement, which accordingly must be caused by protonation of the distant carboxyl, and not of the adjacent nitrogen atom, i.e., *N,N*-dimethylglycine must be substantially all in the zwitterionic form. This is supported by the much larger changes in chemical shift accompanying the addition of alkali to the solution of *N,N*-dimethylglycine, the ammonium group now undergoing deprotonation.

While similar arguments probably apply to other short-chain *α,ω*-amino acids, it seems likely that very long *α,ω*-amino acids prefer the molecular form. Thus it can be seen from Table I that while the *n*-butylammonium ion (**16**) is a much weaker acid than $Me_3N^+(CH_2)_{11}CO_2H$ (**15**) in water, in 83.1% (mol/mol) Me_2SO it is appreciably stronger than **15**, which in turn is appreciably stronger than unsubstituted carboxylic acids such as butyric or valeric (see below). Evidently the

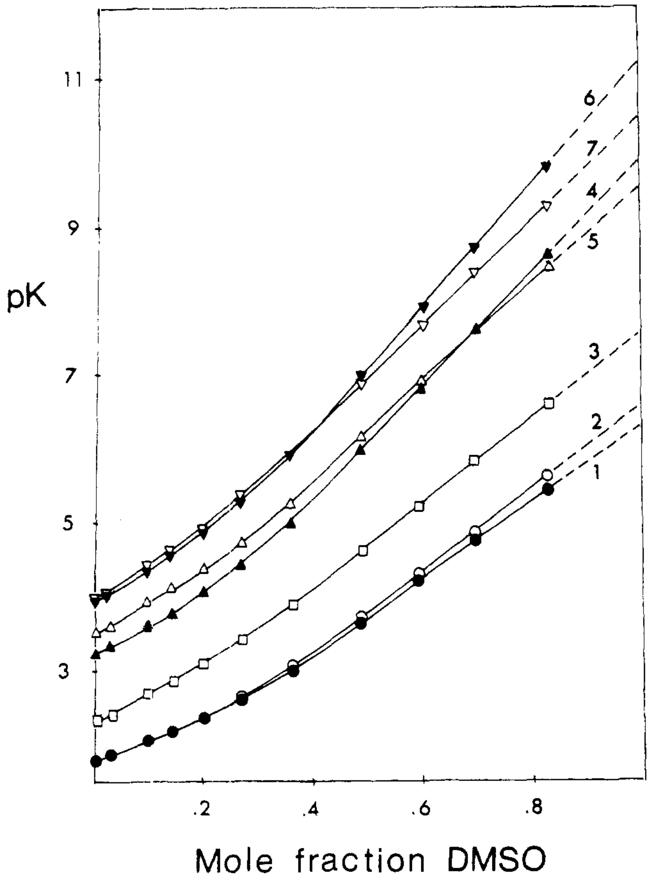


Figure 1. Effect of solvent composition on pK (carboxyl) of $Me_3N^+CH_2CO_2H$ (1), $Et_3N^+CH_2CO_2H$ (2), $H_3N^+CH_2CO_2H$ (3), $Me_3N^+(CH_2)_2CO_2H$ (4), $H_3N^+(CH_2)_2CO_2H$ (5), $Me_3N^+(CH_2)_3CO_2H$ (6), and $H_3N^+(CH_2)_3CO_2H$ (7).

acid-strengthening electrostatic influence in **15** is insufficient to overcome the intrinsically weaker acidity of the carboxyl group in this solvent caused by the poor solvation of CO_2^- and good solvation of CO_2H. Consequently, it seems likely that the corresponding α,ω-amino acid exists in 83.1% (mol/mol) Me_2SO primarily in the molecular form[23] $H_2N(CH_2)_{11}CO_2H$ rather than as the zwitterion $H_3N^+(CH_2)_{11}CO_2^-$, and that only at some shorter intercharge distance does the electrostatic stabilization of a zwitterion become more important than the better solvation of the corresponding molecular form. Obviously further NMR studies are indicated, but for the moment we shall assume that all the compounds of Table I exist in the zwitterionic form.

Qualitative Assessment of the Effect of Alkylation of the Ammonium Group on Acidity of the Carboxyl Group of Amino Acids. Qualitatively, the KW model predicts that the more deeply the positive charge of the ammonium group is buried in the molecular cavity, the more strongly acidic a neighboring carboxyl group should become.

In water this prediction is to some extent confirmed: The progressive replacement of hydrogen of the NH_3^+ group of glycine by the methyl groups (compare **1**, **2**, **3**, and **4** of Table I) leads to a progressive increase in acid strength. Similarly, the bulky trimethylolmethyl group of tricine (**6**) is more effective than the less bulky methyl of N-methylglycine (**2**). However, N,N,N-triethylglycine (**5**) should be a stronger acid than N,N,N-trimethylglycine (**4**) but is of essentially the same strength in water and is weaker in Me_2SO. There is no obvious explanation for these deviations from KW theory.

For the longer acids, alkylation again increases the acid strength of the carboxyl (compare **8** and **9**; **10** and **11**; ω-amino hexanoic acid[4] and **14**), although the effect becomes weaker, as expected, as the interchange distance R becomes greater.

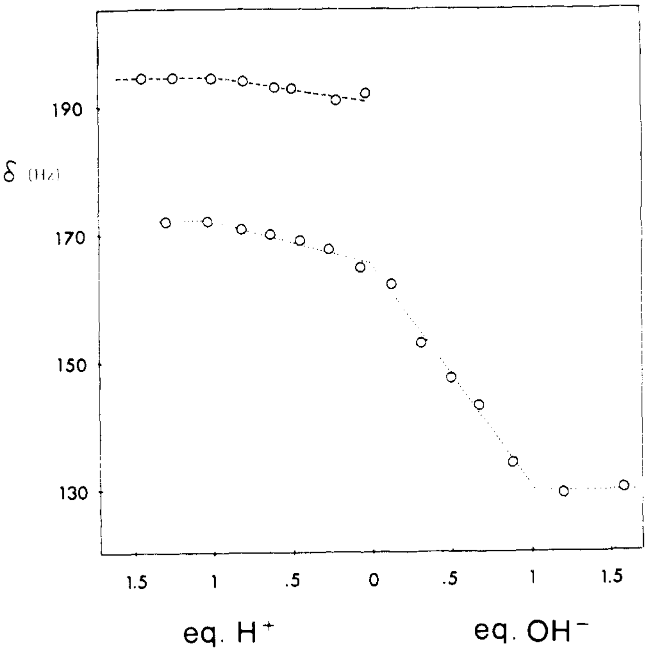
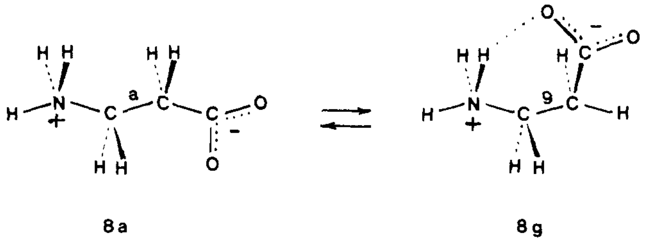


Figure 2. Effect of addition of benzenesulfonic acid or potassium hydroxide on the chemical shifts of the methyl protons of dimethylglycine (. . .) and trimethylglycine (- - -) in Me_2SO-D_2O 84.3:15.7 (w/w).

As the solvent water is progressively replaced by Me_2SO, the pK values of compounds **1–7**, for which R cannot be affected by conformational change, change in roughly parallel fashion. This is shown in Figure 1 for **1**, **4**, and **5**. However, for the acids $R_3N^+(CH_2)_2CO_2H$ and even more $R_3N^+(CH_2)_3CO_2H$, the protonated betaines (R = Me) become *weaker* acids in 100% Me_2SO, as shown by the crossing over of the curves in Figure 1.

This may be explained by a conformational change possible for $H_3N^+(CH_2)_nCO_2H$, but not for $Me_3N^+(CH_2)_nCO_2H$. In water, conformational equilibria seem to be unaffected by electrostatic effects,[4,17,25] presumably because hydration of both $-CO_2^-$ and $-NH_3^+$ is extensive. Consequently, it seems reasonable that about two-thirds of β-alanine (**8**) molecules in water exist in the anti conformation (**8a**) and about one third in the two enantiomeric gauche conformations (**8g**).[4,26,27] This results in the average intercharge distance R being somewhat smaller than the intercharge distance R_{max} for the fully extended form **8a**, so that $R = \rho R_{max}$, where $\rho = 0.95$.[4] However, as the solvent composition changes toward 100% Me_2SO, the protective solvation of the CO_2^- group by water can be expected to diminish greatly, so that both electrostatic and hydrogen-bonding effects should begin to favor **8g**. This will have the effect of diminishing ρ and hence R, and increasing ΔpK more than would be expected merely from diminishing D_e. Hydrogen-bonding effects shown in **8g** may also play a part in increasing acid strength.[28]



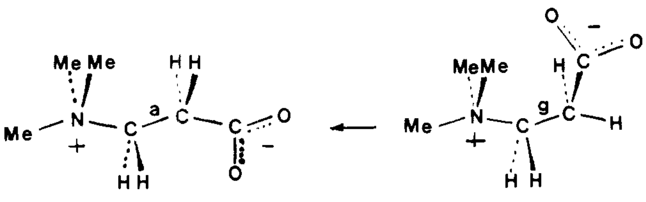
8a **8g**

A similar conformational change is not possible for **9**, which should exist essentially completely in the fully extended conformation **9a**; the enthalpy of the alternative conformation

Table II. Experimental and Calculated Values of ΔpK of Carboxyl and Ammonium Groups in Water and in 83.1% (mol/mol) Me_2SO

	ΔpK in H_2O			ΔpK in 83.1% Me_2SO		
compd	exptl	calcd[a]	calcd[b]	exptl	calcd[a]	calcd[b]
1 (CO_2H)	−2.51[c]	−5.70	−5.70	−4.46[g]	−6.12	−6.12
2 (CO_2H)	−2.67[c]	−7.19	−7.19	−4.83[g]	−7.65	−7.65
3 (CO_2H)	−2.83[c]	−8.70	−8.70	−5.43[g]	−8.99	−8.99
4 (CO_2H)	−2.94[c]	−9.73	−9.73	−6.04[g]	−9.73	−9.73
5 (CO_2H)	−2.92[d]	−12.3	−12.3	−5.86[h]	−12.3	−12.3
8 (CO_2H)	−1.24[d]	−1.67	−2.01	−2.69[g]	−2.04	−2.40
9 (CO_2H)	−1.54[c]	−3.06	−3.06	−2.54[h]	−3.20	−3.20
10 (CO_2H)	−0.80[d]	−0.90	−1.22	−1.84[g]	−1.24	−1.52
11 (CO_2H)	−0.87[d]	−1.36	−1.60	−1.34[h]	−1.62	−1.91
14 (CO_2H)	−0.59[d]	−0.52	−0.67	−0.57[h]	−0.74	−0.91
15 (CO_2H)	−0.26[d]	−0.23	−0.32	−0.18[h]	−0.33	−0.47
1 ($\equiv NH^+$)	−0.81[e]	+5.70	+5.70	+1.64[e]	+6.12	+6.12
8 ($\equiv NH^+$)	−0.34[e]	+1.67	+2.01	+1.43[e]	+2.04	+2.40
10 ($\equiv NH^+$)	−0.01[e]	+0.90	+1.22	+1.91[e]	+1.24	+1.52
12 ($\equiv NH^+$)	+0.04[f]	+0.78	+0.78	+1.21[f]	+1.07	+1.07

[a] Calculations based on R_{max} and eq 2. [b] Calculations based on R_R and eq 2. [c] pK (Table I) − pK (homomorph, from ref 19). [d] pK (Table I) − pK (nearest homomorph, ref 19). [e] pK (Table I) − pK (butylammonium, Table I). [f] pK (Table I) − pK (cyclohexylammonium, ref 14). [g] pK (Table I) − pK (homomorph). [h] pK (Table I) − pK (nearest homomorph).



9a 9g

9g would be about 5 kcal mol^{-1} higher because of the g^+g^- interaction shown,[27] so that it should make up a negligible proportion of the total. Consequently $R = R_{max}$ and $\rho = 1.0$.

Similar arguments apply to the α,ω-amino acids and betaines of longer chain length, to account for the greater reversal in pK observed for $Me_3N^+(CH_2)_3CO_2H$ and $H_3N^+(CH_2)_3CO_2H$.[29]

The betaine 15 has about the same acid strength in water as ω-amino dodecanoic acid (pK = 4.648 at 25 °C[19]); both are appreciably stronger than the corresponding unsubstituted acid (p$K \sim 4.8$), showing the great distances to which electrostatic effects operate.

According to KW theory, the ionization of the ammonium group should be made more difficult by the proximity of a negative group; in fact, for short intercharge distances the acid strength of the ammonium group in water is enhanced by the proximity of the negative carboxylate group. A tentative explanation based on electrostatic interference with the hydration of the ammonium group was advanced.[4] Regardless of the merits of this explanation, the effect is solvent dependent; when Me_2SO replaces water as the solvent, a nearby carboxyl group weakens the acidity of the ammonium group (compare pK_2 of **1** with pK of **16** in Table I), as required by theory.

The acid strengths of the ammonium groups in **6**, **7**, and **13** reflect the presence of neighboring dipoles as well as of a neighboring charged group. In 100% Me_2SO the effects of the dipoles and of the charge are about in balance in **6**; however, for **7** and **13** the effect of the dipoles (or possibly, in the case of **7**, of special hydrogen-bonding effects) predominates.

Calculations of the Electrostatic Effect. The electrostatic effect ΔpK on the dissociation constants of the carboxyl group of 11 compounds, and on the ammonium group of four compounds, is shown in Table II. ΔpK values were calculated from eq 1 for R values corresponding both to the fully extended chain (R_{max}) and to the randomly coiled chain ($R_R = \rho R_{max}$). The shrinkage factor ρ was calculated for compounds **1**–**11** in the manner already described,[4] which ignores any possible coulombic effect on chain coiling. For the betaines **3**, **9**, and **11** ρ was found to be equal to ρ of the α,ω-amino acids shorter by one methylene group (the reasons are apparent from the discussion above), and it was assumed that the same would be true for **14** and **15**. λ_0 was calculated from V_w[30] and R_{max} or R_R by use of eq 2, and hence D_{eff} and ΔpK.

To obtain, for comparison, experimental values of ΔpK, it is necessary to have pK values of reference acids lacking charged substituents. Since the dissociation constant is affected slightly by relatively remote alkyl groups (probably because of solvation effects[14]), the most desirable reference acid is the homomorph having a carbon in place of the nitrogen atom of the ammonium group; thus, ΔpK (experimental) for **9** is the difference between the pK of **9** and of $(CH_3)_3C(CH_2)_2CO_2H$ (4.79[19]). The pK values in water at 20 or 18 °C are available for homomorphs of **1**, **2**, **3**, and **9**; for the other carboxylic acids pK values were estimated from those of homomorphs of the most closely similar structure found in ref 19. Because of the paucity of data for 83.1% (mol/mol) Me_2SO, we have determined the following pK values in this solvent: $CH_3CH_2CO_2H$ (homomorph of **1**), 11.06; $CH_3CH_2CH_2CO_2H$ (homomorph of **2** and **8**), 11.14; $CH_3CH_2CH_2CH_2CO_2H$ (homomorph of **10**), 11.19; $(CH_3)_2CHCH_2CO_2H$ (homomorph of **3**), 11.19; $(CH_3)_3CCH_2CO_2H$ (homomorph of **4**), 11.44.

Amine pK's vary little with chain length,[31] and the butylammonium ion was chosen as the reference compound for **1**, **8**, and **10**, and the cyclohexylammonium ion[14] for **12** in Table II.

A comparison of calculated with experimental ΔpK values reveals the limitations of KW theory. The increase in magnitude (positive or negative) of ΔpK on alkylation of the ammonium group is very modest and much less than calculated by eq 1. As noted already,[4] the theory works badly when postive and negative charges of the zwitterion are separated by less than three carbon atoms. With greater charge separation (e.g., **14** and **15**), the theory is moderately successful for solutions in water, but less in 83.1% (mol/mol) Me_2SO. For compounds **1** and **9**, in which uncertainties about R are absent, ΔpK in 83.1% Me_2SO is greater than in water, and the difference is more than expected from eq 1 on the basis of the macroscopic dielectric constant and its effect on D_{eff}. If any appreciable sorting out of solvent molecules from the mixture were taking place under the influence of the charged centers,[32] the reverse would be expected. The changes in pK with changing solvent composition shown in Table IIIs (supplementary material) do not seem to depend on the nature of the charged groups, as they might if very specific solvating properties were of overriding importance. This indicates that the macroscopic dielectric constant may not be a bad parameter for mixed solvents but that the results obtained using it in the KW treatment are only very approximate.

Calculations using D_{eff} derived by Tanford's method are beset by uncertainty because of our ignorance of the correct value for d of the variously substituted ammonium groups. The results obtained with d = 1.72 Å for the trimethylammonium group[33] were in poorer agreement with experimental ΔpK values than those shown in Table II.

Acknowledgments. We are grateful to the National Research Council for financial support and to Coopération Franco-québécoise for financing the exchanges between our laboratories, in particular for the mission of J.K. to Paris where the dissociation constants were measured. We thank Dr. Bo-Long Poh for checking many calculations and Mrs. Annie Corlaville for NMR measurements.

Supplementary Material Available: First and second dissociation constants of some amino acids and derivatives in water and water-Me_2SO mixtures at 20 °C, Table III (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) McGill University; (b) Université Pierre-et-Marie Curie.
(2) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506, 513 (1938).
(3) C. L. Liotta, W. F. Fisher, E. L. Slighton, and C. L. Harris, *J. Am. Chem. Soc.*, **94**, 2129 (1972); C. T. Wang and E. J. Grubbs, *J. Org. Chem.*, **42**, 534 (1977); L. M. Stock, *J. Chem. Educ.*, **49**, 400 (1972), and references therein; S. Acevedo and K. Bowden, *J. Chem. Soc., Chem. Commun.*, 608 (1977), and references therein.
(4) J. T. Edward, P. G. Farrell, J. L. Job, and B. L. Poh, *Can. J. Chem.*, **56**, 1122 (1978).
(5) J. Kirchnerova, P. G. Farrell, J. T. Edward, J. C. Hallé, and R. Schaal, *Can. J. Chem.*, **56**, 1130 (1978).
(6) This differs from Kirkwood and Westheimer's original definition of R, and has been justified previously.[4]
(7) Recently Ehrenson[8] has removed the constraint of locating charges or dipoles at the foci of the ellipsoids[2,9] and has obtained more realistic distances d between charge or dipole and the solute-solvent interface. However, Ehrenson's calculated effective dielectric constants seem to us on intuitive grounds to be unreasonable for small values of λ_0: for an infinitely long ellipsoid (λ_0 = 1.0), $D_{\mathrm{eff}} = D_{\mathrm{e}}$, which is reasonable, but for long thin ellipsoids having $\lambda_0 > 1.0$, $D_{\mathrm{eff}} > D_{\mathrm{e}}$ until a maximum is reached, which we think unreasonable. We defer to a later paper a detailed discussion of D_{eff}.
(8) S. Ehrenson, *J. Am. Chem. Soc.*, **98**, 7510 (1976).
(9) J. T. Edward, P. G. Farrell, and J. L. Job, *J. Chem. Phys.*, **57**, 5251 (1972).
(10) C. Tanford, *J. Am. Chem. Soc.*, **79**, 5348 (1957).
(11) C. Tanford and R. Roxby, *Biochemistry*, **11**, 2192 (1972).
(12) G. Douheret, *Bull. Soc. Chim. Fr.*, 3122 (1968).
(13) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
(14) J. T. Edward, P. G. Farrell, J. Kirchnerova, J. C. Hallé, and R. Schaal, *Can. J. Chem.*, **54**, 1899 (1976).
(15) J. C. Hallé and R. Schaal, *Anal. Chim. Acta*, **60**, 197 (1972).
(16) J. C. Hallé, R. Gaboriaud, and R. Schaal, *Bull. Soc. Chim. Fr.*, 1851 (1969).
(17) J. Kirchnerova, P. G. Farrell, and J. T. Edward, *J. Phys. Chem.*, **80**, 974 (1976).
(18) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides", Reinhold, New York, 1943; R. A. Robinson and R. H. Stokes, "Electrolyte Solutions", Butterworths, London, 1959.
(19) G. Kortum, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution", Butterworths, London, 1961.
(20) S. P. Datta and A. K. Grzybowski, *Trans. Faraday Soc.*, **54**, 1179 (1958).
(21) R. N. Roy, R. A. Robinson, and R. G. Bates, *J. Am. Chem. Soc.*, **95**, 8231 (1973).
(22) S. P. Datta, A. K. Grzybowski, and R. G. Bates, *J. Phys. Chem.*, **68**, 275 (1964).
(23) The isolated molecule of an α-amino acid is more stable in the molecular than in the zwitterionic form;[24] the latter predominates only in the solid phase, because of stabilization by lattice energies, and in some polar solvents, because of solvation.
(24) J. S. Gaffney, R. C. Pierce, and L. Friedman, *J. Am. Chem. Soc.*, **99**, 4293 (1977), and references therein.
(25) J. T. Edward, P. G. Farrell, and J. L. Job, *J. Am. Chem. Soc.*, **96**, 902 (1974); J. A. Walder, *J. Phys. Chem.*, **80**, 2777 (1976).
(26) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Academic Press, New York, 1965, pp 10 and 11.
(27) G. Mann, *Tetrahedron*, **23**, 3375 (1967).
(28) H. C. Brown, D. H. McDaniel, and D. Hafliger, "Determination of Organic Structures by Physical Methods", E. A. Brande and F. C. Nachod, Ed., Academic Press, New York, 1955, p 567.
(29) We are presently engaged in attempting to test this explanation by measurements of the effect of composition of H_2O-Me_2SO solvents on the dielectric increments of α,ω-amino acids and betaines.
(30) J. T. Edward, *J. Chem. Educ.*, **47**, 261 (1970).
(31) I. M. Kolthoff, M. K. Chantooni, and S. Bhowmik, *J. Am. Chem. Soc.*, **90**, 23 (1968).
(32) J. B. Hyne, *J. Am. Chem. Soc.*, **85**, 304 (1963).
(33) C. F. Wilcox and J. S. McIntyre, *J. Org. Chem.*, **30**, 777 (1965).

Dioxolenium Ion Trapping in the Hydrolysis of Cyclic Ortho Esters: The Rate-Determining Step

Y. Chiang, A. J. Kresge,* and C. I. Young

Department of Chemistry, University of Toronto, Scarborough College, West Hill, Ontario M1C 1A4, Canada

Received September 8, 1978

The dioxolenium ion formed during the acid-catalyzed hydrolysis of 2-(p-methoxyphenyl)-2-methoxy-1,3-dioxolane in NH_3OH^+/NH_2OH aqueous buffer solutions at 25 °C is trapped efficiently by hydroxylamine without producing a corresponding increase in reaction rate; this indicates that trapping occurs after the rate-determining step and that dioxolenium ion formation is rate limiting in this hydrolysis reaction. Quantitative treatment of the data gives $N_+(NH_2OH) = 1.44 \pm 0.04$, much lower than the standard value of 5.05, but this discrepancy could be due to reversibility of the hydroxylamine trapping reaction.

The effect of phenyl substitution at the proacyl carbon atom of simple acyclic ortho esters is anomalous in that it leads to rate reductions instead of the accelerations expected in a carbonium ion forming reaction such as this (eq 1). We demonstrated recently that this unusual behavior is produced by steric inhibition of resonance in the dialkoxy carbonium ion intermediate of this reaction, **1**; when steric hindrance is removed by forming the alkoxy groups into a small ring, as in the 1,3-dioxolenium ion **3**, phenyl substitution does give the anticipated rate acceleration.[1]

This explanation is based upon an argument which requires dialkoxy carbonium ion formation to be the rate-determining step of these hydrolyses under the conditions of the study, i.e., at acidities less than pH ~ 6. All of the available evidence in-

0022-3263/79/1944-0619$01.00/0