Thermodynamics of Acid–Base Equilibria. VI.[1-5] Ionization of Substituted Pyridinium Ions

Charles L. Liotta,* Edward M. Perdue, and Harry P. Hopkins, Jr.*

Contribution from the School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332, and the Department of Chemistry, Georgia State University, Atlanta, Georgia 30332. Received June 4, 1974

Abstract: The standard enthalpies of ionization of 12 3- and 4-substituted pyridinium ions have been determined calorimetrically in aqueous solution at 25°. Standard entropies of ionization have been calculated from the experimental enthalpies of ionization and the literature Gibbs free energies of ionization. Both the enthalpies and entropies of ionization show a good linear correlation with the Gibbs free energy of ionization. The experimental results have been analyzed in terms of Hepler's theory of substituent effects and have been compared with the predictions of electrostatic theory.

Substituent-induced changes in the acidities of organic acids can be attributed to electrostatic substituent effects, resonance interactions between the substituent and the reaction center, and differences in solvation phenomena involving the acid and its conjugate base. The thermodynamic quantity most commonly used as a measure of acidity is the standard Gibbs free energy of ionization ($\Delta \bar{G}_i^\circ$), which can easily be obtained from pK_a determinations. Consequently, most current theories tend to treat the acid ionization process only in terms of $\Delta \bar{G}_i^\circ$ values. Unfortunately, $\Delta \bar{G}_i^\circ$ represents the net effect of all the factors mentioned above and, therefore, provides very little information concerning the relative importance of each factor in determining the acidity of a given compound. However, an analysis of the thermodynamic components of $\Delta \bar{G}_i^\circ$, the standard enthalpy ($\Delta \bar{H}_i^\circ$) and entropy ($\Delta \bar{S}_i^\circ$), of ionization might be expected to contribute significantly to the refinement of current theories of the acid ionization process.

While reliable $\Delta \bar{G}_i^\circ$ values have now been obtained in aqueous solution for a majority of the known organic acids, $\Delta \bar{H}_i^\circ$ and $\Delta \bar{S}_i^\circ$ values are known for only a few acid systems. A recent review article by Larson and Hepler has summarized the available data.[6] In ionogenic processes, such as the ionization of phenols[6] and carboxylic acids,[7,8] it has been established that entropy changes are primarily responsible for substituent-induced changes in the acidities of these acids in aqueous solution. In contrast to these ionogenic processes, it has recently been established that, for an isoelectric reaction such as the ionization of 3- and 4-substituted anilinium ions in aqueous solution, relative acidities are primarily due to substituent-induced enthalpy changes.[3] In order to further investigate substituent effects in isoelectric processes, the study of cationic organic acids has been expanded to include the ionization of substituted pyridinium ions in aqueous solution. The possibility of resonance interactions between the substituent and cationic reaction center could substantially influence the substituent-induced enthalpy and entropy changes for pyridinium ions, whereas this mode of interaction should not be important for anilinium and alkylammonium ions. Furthermore, since the proton–dipole distance is shorter in pyridinium ions than in anilinium ions, electrostatic theory predicts that substituent-induced $\Delta \bar{G}_i^\circ / \Delta \bar{S}_i^\circ$ ratios should be more negative for substituted pyridinium ions than for the corresponding anilinium ions. Thus, a study of the thermodynamics of ionization of substituted pyridinium ions should provide a substantial amount of data which is needed for the evaluation of current acid ionization theories. At the same time, these data can be combined with the current gas phase studies on

the relative acidities to provide an unambiguous measure of the solvation contribution to the ionization thermodynamics parameter found in aqueous solutions.[9]

The pK_a's of a large number of substituted pyridinium ions in aqueous solution have been determined by Fischer and coworkers[10] who, on the basis of relative pK_a values, concluded that only electron-donating substituents located in the 4 position undergo resonance interactions with the reaction center.

While this research was in progress, a calorimetric study of the thermodynamics of ionization of several substituted pyridinium ions was published by Christensen and coworkers.[11] However, since only three 4-substituted pyridines (including 4-hydroxypyridine, which is believed to exist as the pyridone tautomer in aqueous solution) were included in this study, a thorough examination of resonance effects in the pyridine system was not possible. Furthermore, the positive slope obtained in a plot of $\Delta \bar{G}_i^\circ$ vs. $\Delta \bar{S}_i^\circ$ from the results of these workers is in contradiction with the negative slope which is predicted by electrostatic theory and with the experimental slopes found in other acid systems.[3,7,8]

Recently, the pK_a's of several pyridinium ions were determined at three different temperatures by an nmr technique.[12] The enthalpies and entropies of ionization reported by these workers do not compare favorably with those of Christensen, et al.[11]

This study was undertaken to accurately establish the enthalpies and entropies of ionization of a variety of 3- and 4-substituted pyridinium ions. The thermodynamic results of this investigation are analyzed in terms of current theories of the acid ionization process and compared with the published gas phase data.

Experimental Section

The calorimeter used in this investigation has been described.[4] The 4-chloropyridine and 4-bromopyridine are unstable[13] and can only be studied as the commercially available hydrochloride salts. Therefore, the enthalpies of ionization of 4-chloropyridinium ion and 4-bromopyridinium ion were calculated from the difference between the enthalpies of solution of the hydrochloride salts in aqueous perchloric acid and in aqueous sodium hydroxide, using a value of 13.34 kcal/mol for the enthalpy of ionization of water.[14,15] All the other pyridines included in this study were commercially available except 4-methoxypyridine, which was prepared by catalytic reduction of 4-methoxypyridine N-oxide.[16] These compounds were studied by the experimental procedure which was employed in the study of anilinium ions.[3]

At least five calorimetric determinations were made for each pyridine studied. All calculations were carried out using the computer facilities at Georgia State Univeristy.

Table I. Enthalpies of Ionization of Substituted Pyridinium Ions

Substituent	Run 1	Run 2	Run 3	Run 4	Run 5	Av	Lit. values
				$-\Delta H°$ of ionization, kcal/mol			
H	4.76	4.86	4.87	4.76	4.77	4.80 ± 0.06	4.795[b]
							4.000[e]
4-NH$_2$	11.31	11.28	11.24	11.18	11.36	11.27 ± 0.07	11.31[c]
							11.25[d]
4-OCH$_3$	6.63	6.79	6.86	6.92	7.05	6.85 ± 0.16	5.23[e]
4-CH$_3$	6.10	6.11	6.15	6.13	6.16	6.13 ± 0.03	6.02[b]
							6.10[c]
							6.54[e]
4-Cl[a]		($\Delta H_a = 3.35 \pm 0.05$ and $\Delta H_b = -6.41 \pm 0.22$)				3.58 ± 0.27	2.57[e]
4-Br[a]		($\Delta H_2 = 4.39 \pm 0.02$ and $\Delta H_b = -5.44 \pm 0.12$)				3.51 ± 0.14	2.38[e]
4-CN	1.25	1.25	1.18	1.30	1.30	1.26 ± 0.05	3.04[e]
3-NH$_2$	6.37	6.44	6.39	6.41	6.42	6.41 ± 0.03	6.43[c]
3-CH$_3$	5.86	5.86	5.83	5.90	5.90	5.87 ± 0.03	5.64[b]
							5.71[c]
							4.87[e]
3-Cl	2.62	2.54	2.56	2.65	2.65	2.60 ± 0.05	2.11[c]
							1.63[e]
3-Br	2.81	2.79	2.82	2.74	2.73	2.78 ± 0.04	1.35[c]
3-CN	0.90	0.86	0.82	0.80	1.02	0.88 ± 0.09	5.59[e]

[a] $\Delta H°$ values determined from the enthalpies of solution of the hydrochloride salts in aqueous perchloric acid (ΔH_a) and in aqueous sodium hydroxide (ΔH_b) in combination with the enthalpy of ionization of water (13.34 kcal/mol). [b] Reference 18. [c] Reference 11. [d] Reference 17. [e] Reference 12.

Table II. Thermodynamics of Ionization of Substituted Pyridinium Ions in Water at 298 °K[a]

Substituent	$\Delta G_i°$	$\Delta H_i°$	$\Delta S_i°$
H	7.11	4.80	-7.75
4-NH$_2$	12.44	11.27	-3.92
4-OCH$_3$	8.98	6.85	-7.14
4-CH$_3$	8.23	6.13	-7.04
4-Cl	5.23	3.58	-5.53
4-Br	5.12	3.51	-5.40
4-CN	2.54	1.26	-4.29
3-NH$_2$	8.24	6.41	-6.14
3-CH$_3$	7.74	5.87	-6.27
3-Cl	3.83	2.60	-4.13
3-Br	3.89	2.78	-3.72
3-CN	1.84	0.88	-3.22

[a] $\Delta G_i°$ and $\Delta H_i°$ values in kcal/mol; $\Delta S°$ values in cal/(deg mol).

Results

The enthalpies of ionization of 12 3- and 4-substituted pyridinium ions in aqueous solution were determined calorimetrically at an ionic strength of 0.0287. The results of five determinations along with the average value and standard deviation for each pyridinium ion are shown in Table I. It has previously been shown that enthalpies of dilution are negligible at this ionic strength[3] so the average values shown in Table I are the standard enthalpies of ionization of the corresponding pyridinium ions with an estimated uncertainty of ±0.05 kcal/mol.

For comparison, the enthalpies of ionization determined by other workers are included in Table I. The results of this research are in excellent agreement with the results recently published by Christensen and coworkers,[11] with the exception of the 3 chloro- and 3-bromopyridinium ions. However, since the pK_a's of the two acids are almost equal, and since the enthalpies of ionization of 3-Cl and 3-Br substituted acids are almost identical for other acid systems,[3,7,8,10] the results of this research (2.60 and 2.78 kcal/mol, respectively) are preferred over the results of Christensen and coworkers (2.11 and 1.35 kcal/mol, respectively). It appears from this comparison that the enthalpies and entropies of ionization determined from the nmr techniques are questionable.

Bates and Hetzeer[17] have reported a value for the enthalpy of ionization of 4-aminopyridinium ion which is in excellent agreement with the results of this research. Sacconi and coworkers[18] have determined the enthalpies of ionization of pyridinium ion and the 2-, 3-, and 4-methylpyridinium ions in aqueous solution. Their results are in good agreement with the results obtained in this study.

Using the calorimetrically determined standard enthalpies of ionization ($\Delta \bar{H}_i°$) from this study and the standard Gibbs free energies of ionization ($\Delta \bar{G}_i°$) from the pK_a data of Fischer and coworkers,[10] the standard entropies of ionization ($\Delta \bar{S}_i°$) have been calculated. These results have been tabulated in Table II for the 12 pyridinium ions included in this study.

A plot of $\Delta \bar{G}_i°$ vs. $\Delta \bar{S}_i°$ is given in Figure 1. Clearly, the 4-aminopyridinium ion deviates markedly from the general $\Delta \bar{G}_i°/\Delta \bar{S}_i°$ correlation which is exhibited by the other substituents. If this substituent is omitted from a least-squares analysis, there is a fair correlation between $\Delta \bar{G}_i°$ and $\Delta \bar{S}_i°$ with a least-squares slope of $-1490°$ and a correlation coefficient of 0.906. As in the study of substituted anilinium ions[3] ($\Delta \bar{G}_i°/\Delta \bar{S}_i°$ slope = $-900°$), the $\Delta \bar{G}_i°/\Delta \bar{S}_i°$ slope is much more negative than the value of $-218°$ predicted from the Bjerrum electrostatic theory.[19]

The plot of $\Delta \bar{G}_i°$ vs. $\Delta \bar{H}_i°$ which is shown in Figure 2 is linear with a slope of 1.190 and a correlation coefficient of 0.996 (4-aminopyridinium ion has been omitted from least-squares calculations). The factors which influence the thermodynamics of ionization of pyridinium ions appear to be quite similar to those involved in the ionization of anilinium and alkyl ammonium ions.[3] For both of the acid systems, the predominant substituent effects in aqueous solution are manifested in the enthalpy rather than the entropy of ionization.

Discussion

Hepler's Theory of Substituent Effects. The relative acidities of two organic acids are clearly demonstrated in a symmetrical proton transfer reaction such as

$$HA_1 + A_2 \rightleftharpoons A_1 + HA_2 \tag{1}$$
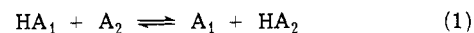
where HA$_1$ and HA$_2$ are two structurally similar acids differing only by a charged or dipolar substituent and A$_1$ and

Figure 1. A plot of $\Delta G_i°$ vs. $\Delta S_i°$ for the ionization of the 12 pyridinium ions included in this study.

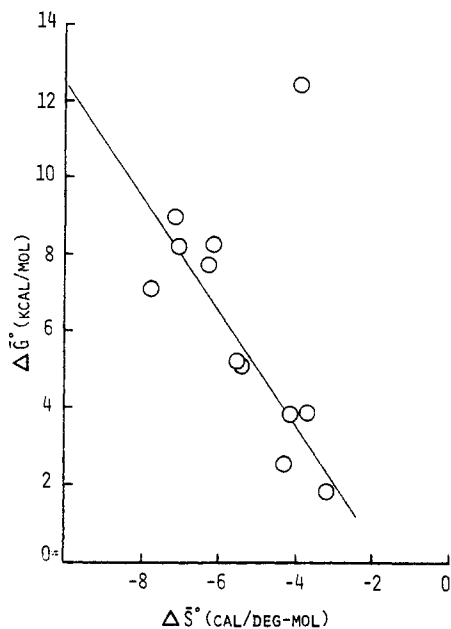**Figure 2.** A plot of $\Delta G_i°$ vs. $\Delta H_i°$ for the ionization of the 12 pyridinium ions included in this study.

A_2 are the respective conjugate bases. Hepler[20,21,22] has proposed that the overall effect of a substituent may be divided into "internal" and "external" contributions. Based on the assumptions that (a) the "external" contributions to the enthalpy and entropy changes are related by a constant β and (b) the "internal" contribution to the entropy is negligible, the following equation is obtained.

$$\Delta G° = \Delta H_{int} + (\beta - T)\Delta S° \qquad (2)$$

If β is assigned a value of 280°K as Hepler has suggested, it follows that the $\Delta G° = \Delta H_{int}$ at 25° since the assigned β value is very close to T (298°K). On the basis of results recently obtained in a comparison of the thermodynamics of ionization of anilinium ions and phenols,[3,23] it has been suggested that β may actually vary from one reaction to another and might be quite different from the value of 280°K originally suggested by Hepler.

Since ΔH_{int} is actually the gas phase enthalpy of proton transfer, a knowledge of the relative gas phase enthalpies of ionization of acid systems which have also been studied in aqueous solution would provide the necessary experimental data for direct calculation of β. Recently, the relative gas phase proton affinities of several 4-substituted pyridines[9a] have been determined. It was reported that a plot of the relative gas phase enthalpies of ionization vs. the relative aqueous Gibbs free energies of ionization is linear with a slope of 3.5 ± 0.5, indicating that ΔH_{int} values are much larger than $\Delta G°$ (298°K) values for substituted pyridinium ions. Combining $\Delta H_{int} = 3.5 \Delta G°$ from the results of Taft[9a] and coworkers with $\Delta G_i°/\Delta S_i° = -1490°$ from this research, a value of $\beta = 4023 ± 745°$ is obtained from eq 2. This β value is far greater than the value employed in Hepler's theory, suggesting that either β varies from one acid system to another or a second parameter must be added to eq 2.

In the recent extension of this theory of substituent effects, Hepler and coworkers[20,23] suggest that a second parameter, γ, must be introduced to account for possible incomplete compensation of ΔH_{ex} by $\beta \Delta S_{ex}$. Furthermore, Ives and Marsden[24] have presented arguments that β is actually the temperature, T, of the measurements. If these two modifications of the original theory of Hepler are ac-
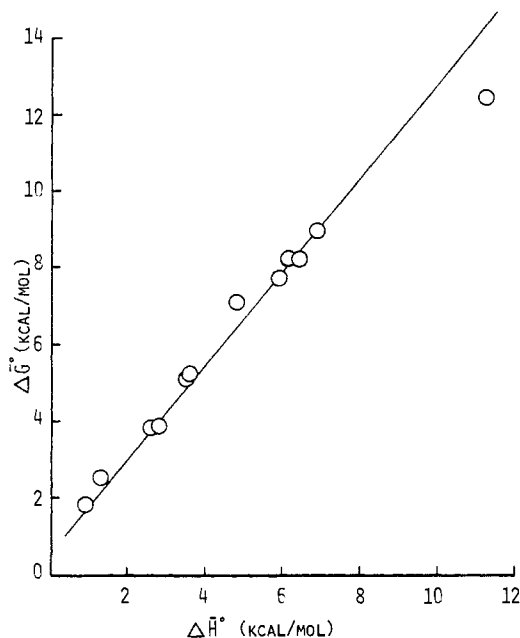
cepted, a value of $\gamma = -0.78$ can be obtained from the results of this research and the gas phase data. However, an extensive set of gas phase thermodynamic data for eq 2 will be required to unambiguously establish the validity of Hepler's theory.

4-Aminopyridinium Ion. In the previous discussion of Figures 1 and 2, it was noted that the 4-aminopyridinium ion deviates markedly from the general $\Delta G_i°/\Delta S_i°$ and $\Delta G_i°/\Delta S_i°$ correlations exhibited by the other substituents. The possibility that this deviation might result from protonation of the amino group is excluded by prior studies which have clearly shown that monoprotonation of 4-aminopyridine (I) occurs on the ring nitrogen rather than on the amino group.[25,26] Furthermore, while the monoprotonated species (II) is only weakly acidic, $pK_a = 9.12$, the diprotonated species (III) for which the reported pK_a value is -6.3 can only be obtained in strongly acidic solutions.[27] All of these observations indicate that the monoprotonated species is unusually stable and that this stability is destroyed by diprotonation. Substantial resonance stabilization by structures such as IIa and IIb is in accord with these observations.
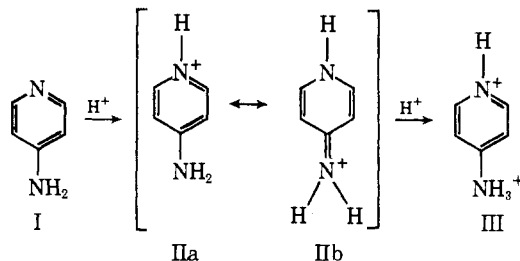
The entropy of ionization of the 4-aminopyridinium ion is approximately 6 cal/(deg mol) more positive than predicted by the $\Delta G_i°/\Delta S_i°$ correlation shown in Figure 1. Since the deviation of the 4-aminopyridinium ion from the correlation demonstrated in Figure 1 could in part be an enthalpy and/or an entropy effect, any analysis of the magnitude of the deviation is tenuous at best. However, for all other substituted pyridinium ions studied, the difference between the entropies of ionization for the 3 and 4 isomer is 0.77 to 1.68 cal/(deg mol), whereas this difference is -2.22 cal/(deg

mol) for the amino substituent. A substantial resonance contribution by structures IIa and IIb will increase the barrier to free rotation around the carbon–nitrogen bond of the amino group, but will decrease the polarization of the solvent owing to increased charge delocalization. While the latter effect may increase the entropy of the ion–solvent system,[6] an entropy decrease of as much as 3 cal/(deg mol) could occur because of the increase of the carbon–nitrogen rotational barrier.[28]

Entropy Analysis. In a previous study, it was found that the experimental substituent-induced $\Delta \bar{G}_i^\circ / \Delta \bar{S}_i^\circ$ ratios of 4-substituted anilinium ions were in good agreement with the values predicted by Kirkwood–Westheimer electrostatic theory.[3] A similar analysis for 4-substituted pyridinium ions predicts that the substituent-induced $\Delta \bar{G}_i^\circ / \Delta \bar{S}_i^\circ$ ratios should be approximately 1.5 times more negative for pyridinium ions than for anilinium ions. This value is in excellent agreement with the value of 1.66 which is derived from experimental data. The favorable comparison between calculated and experimental $\Delta \bar{G}_i^\circ / \Delta \bar{S}_i^\circ$ ratios indicates that both acid systems obey the predictions of electrostatic theory.

An unusual and perhaps significant result which emerges from the entropy analysis for this acid system concerns the relative magnitudes of the absolute entropies of pyridines and pyridinium ions in aqueous solution. Assuming the entropy of the hydrogen ion to be -5.5 cal/(deg mol) in aqueous solution,[29] it can be shown that, whenever $\Delta \bar{S}_i^\circ$ is more negative than -5.5 cal/(deg mol), the entropy of a pyridinium ion must be greater than the entropy of the corresponding pyridine. This effect is observed only for pyridinium ions with electron-donating substituents and for the unsubstituted compound. These results suggest the possible importance of hydrophobic bonding for the neutral species.

The preceding analysis clearly demonstrates that, while several aspects of acid–base equilibria are fairly well understood, there are a number of problems that remain unresolved. Most of these are in the area of solute–solvent interactions, especially insofar as the interpretation of entropy changes is concerned. It is clearly evident that further research in the gas phase and in other solvent systems is necessary if a comprehensive theoretical formulation of the acid ionization process is to be obtained.

References and Notes

(1) Part V: C. L. Liotta, E. M. Perdue, and H. P. Hopkins, Jr., *J. Amer. Chem. Soc.*, in press.
(2) Part IV: C. L. Liotta, A. Abidaud, and H. P. Hopkins, Jr., *J. Amer. Chem. Soc.*, **94**, 8624 (1972).
(3) Part III: C. L. Liotta, E. M. Perdue, and H. P. Hopkins, Jr., *J. Amer. Chem. Soc.*, **95**, 2439 (1973).
(4) Part II: C. L. Liotta, D. F. Smith, Jr., H. P. Hopkins, Jr., and K. A. Rhodes, *J. Phys. Chem.*, **76**, 1909 (1972).
(5) Part I: C. L. Liotta, K. H. Leavell, and D. F. Smith, Jr., *J Phys. Chem.*, **71**, 3091 (1967).
(6) J. W. Larson and L. G. Hepler, "Solute–Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N.Y., 1969.
(7) J. J. Christensen, R. M. Izatt, and L. D. Hansen, *J. Amer. Chem. Soc.*, **89**, 213 (1967).
(8) P. D. Bolton, K. A. Fleming, and F. M. Hall, *J. Amer. Chem. Soc.*, **94**, 1033 (1972).
(9) (a) M. Taagepera, W. G. Henderson, R. T. C. Brownlee, J. L. Beauchamp, D. Holtz, and R. W. Taft, *J. Amer. Chem. Soc.*, **94**, 1369 (1972); (b) M. T. Bowen and D. H. Aue, University of California, Santa Barbara, private communication.
(10) A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964).
(11) J. J. Christensen, D. E. Smith, M. D. Slade, and R. M. Izatt, *Thermochim. Acta*, **5**, 35 (1972).
(12) M. R. Chahoakarty, C. S. Handloren, and M. W. Mosher, *J. Chem. Soc., Perkin Trans. 2*, 939 (1973).
(13) J. P. Wibaut and W. J. Homes-Kamminga, *Bull. Soc. Chim. Fr.*, 424 (1958).
(14) J. D. Hale, R. M. Izatt, and J. J. Christensen, *J. Phys. Chem.*, **67**, 2605 (1963).
(15) C. E. Vanderzee and J. A. Swanson, *J. Phys. Chem.*, **67**, 2608 (1963).
(16) A. R. Katritzky and A. M. Monro, *J. Chem. Soc.*, 1263 (1958).
(17) R. G. Bates and H. B. Hetzeer, *J. Res. Nat. Bur. Stand., Sect. A*, **64**, 427 (1960).
(18) L. Sacconi, P. Paoletti, and M. Ciampolini, *J. Amer. Chem. Soc.*, **82**, 3831 (1960).
(19) E. J. King, "Acid–Base Equilibria," Macmillan, New York, N.Y., 1965, p 211.
(20) P. D. Bolton and L. G. Hepler, *Quart. Rev., Chem. Soc.*, **25**, 521 (1971).
(21) L. G. Hepler, *Can. J. Chem.*, **49**, 2803 (1971).
(22) L. G. Hepler and E. M. Woolley, "Water—A Comprehensive Treatise," F. Frands, Ed., Plenum Press, New York, N.Y., 1973.
(23) P. D. Bolton and F. M. Hall, *J. Chem. Soc. B*, 259 (1969).
(24) D. T. Ives and P. D. Marsden, *J. Chem. Soc.*, 649 (1965).
(25) A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).
(26) S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1461 (1952).
(27) M. L. Bender and Y. L. Chow, *J. Amer. Chem. Soc.*, **81**, 3929 (1959).
(28) K. S. Pitzer, "Quantum Chemistry," Prentice-Hall, Englewood Cliffs, N.J., 1953.
(29) R. W. Gurney, "Ionic Processes in Solution," McGraw-Hill, New York, N.Y., 1953, Chapter 10.