(7) Chudzicki, M., Laboratory MicroSystems, Inc., P.O. Box 336, Troy, NY 12180, unpublished work, 1980.
(8) "Selected Values of Chemical Thermodynamic Properties"; National Bureau of Standards, U.S. Department of Commerce: Washington, DC, 1960; Circular 500.
(9) Janz, G. J. *J. Phys. Chem. Ref. Data* **1980**, *9*, 791.
(10) Clark, R. P. *J. Chem. Eng. Data* **1973**, *20*, 18.
(11) Rogers, D. J.; Janz, G. J. *J. Chem. Eng. Data* **1982**, *27*, 424.
(12) Rogers, D. J.; Yoko, T.; Janz, G. J. *J. Chem. Eng. Data* **1982**, *27*, 366.
(13) Feher, F.; Berthold, H. J.; Fresenius *Z. Anal. Chem.* **1953**, *138*, 245.
(14) Janz, G. J.; Coutts, J. W.; Downey, J. R.; Roduner, E. *Inorg. Chem.* **1976**, *15*, 1755.
(15) Cleaver, B.; Davies, A. J.; Hames, M. D. *Electrochem. Acta* **1973**, *18*, 719.

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# Acidic Dissociation of Amantadine Hydrochloride

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**The acidic dissociation constants of aqueous amantadine hydrochloride have been determined by acid/base colorimetry between 25 and 50 °C using thymol blue indicator. The temperature variations of the equilibrium constants yield standard enthalpies and entropies for the acid dissociation ($\Delta H° = 14.15$ kcal mol$^{-1}$; $\Delta S° = -0.9$ cal mol$^{-1}$ K$^{-1}$) and for the second indicator dissociation ($\Delta H° = 2.55$ kcal mol$^{-1}$; $\Delta S° = -33.2$ cal mol$^{-1}$ K$^{-1}$).**

Amantadine (adamantanamine or tricyclo[3.3.1.1$^{3,7}$]decan-1-amine, which will be referred to as A) has been the subject of many researches including especially its biological and medicinal uses (*1*). However, this unusual compound, which features a large rigid hydrocarbon skeleton, also affords an opportunity to study aqueous solvation phenomena with a so-called "hydrophobic species". Presumably information regarding solvation properties of A could be surmised from its acid/base properties but these have not appeared in the chemical literature. Therefore, we have undertaken to measure the thermodynamic properties of A basicity as detailed below.

## Methodology

The presence of a suitable acid/base indicator in a solution allows a simple means of estimating the pH value from measurements of the absorbance. Such measurements with A, AH$^+$ solutions would yield estimates of acidity constants of AH$^+$ (or, equivalently, basicity constants of A). In order to relate the solution absorbance to pH, however, it is first necessary to "calibrate" the indicator by determining the indicator absorbance in solutions of known pH. We determined that a thymol blue indicator (thymolsulfonephthalein) and glycine buffer would be appropriate for these calibration measurements. We will abbreviate the thymol blue acid-base pair as HIn$^-$, In$^{2-}$ and the glycine pair as HGly, Gly$^-$. Thus, we made measurements with six or seven mixtures of HGly, NaOH, and thymol blue added as NaHIn at each temperature which would be employed in later experiments with A. Absorbances were determined with 1.000-cm cells at an irradiating wavelength of 596 nm, where only the blue In$^{2-}$ species absorbs. The data were analyzed as follows.

In each calibrating solution, the relevant equilibria are

$$K_{\mathrm{Gly}} = \frac{a_{\mathrm{H^+}} a_{\mathrm{Gly^-}}}{a_{\mathrm{HGly}}} = \frac{\gamma_{\mathrm{H}} \gamma_{\mathrm{Gly}}}{\gamma_{\mathrm{HGly}}} \frac{[\mathrm{H^+}][\mathrm{Gly^-}]}{[\mathrm{HGly}]} \tag{1}$$

$$K_{\mathrm{In}} = \frac{a_{\mathrm{H^+}} a_{\mathrm{In^{2-}}}}{a_{\mathrm{HIn^-}}} = \frac{\gamma_{\mathrm{H}} \gamma_{\mathrm{In}}}{\gamma_{\mathrm{HIn}}} \frac{[\mathrm{H^+}][\mathrm{In^{2-}}]}{[\mathrm{HIn^-}]} \tag{2}$$

$$K_{\mathrm{W}} = a_{\mathrm{H}} a_{\mathrm{OH}} = \gamma_{\mathrm{H}} \gamma_{\mathrm{OH}} [\mathrm{H^+}][\mathrm{OH^-}] \tag{3}$$

and mass and charge balances are

$$F_{\mathrm{Gly}} = [\mathrm{Gly^-}] + [\mathrm{HGly}] \tag{4}$$

$$F_{\mathrm{In}} = [\mathrm{In^{2-}}] + [\mathrm{HIn^-}] \tag{5}$$

$$[\mathrm{Na^+}] + [\mathrm{H^+}] = [\mathrm{Gly^-}] + [\mathrm{HIn^-}] + 2[\mathrm{In^{2-}}] + [\mathrm{OH^-}] \tag{6}$$

In these equations $a$'s and $\gamma$'s denote activities and activity coefficients, respectively, of species denoted by subscripts and $F_{\mathrm{Gly}}$ (0.010 F throughout) and $F_{\mathrm{In}}$ (0.06 mF throughout) denote formal (analytical) concentrations of glycine and thymol blue. The pH value in our solutions was always high enough so that protonated $H_2Gly^+$ and $H_2In$ species were negligible. The absorbance at 596 nm is related to solution concentrations by

$$A_{596} = \mathrm{ab}F_{\mathrm{In}}([\mathrm{In^{2-}}]/F_{\mathrm{In}}) \tag{7}$$

These equations involve a number of assumptions and primary among these is the absence of any specific interaction between glycine species and thymol blue species. We were able to verify directly that no measurable interaction occurs between neutral glycine and HIn$^-$ present as the dominant indicator species at pH 6 by noting that the indicator spectrum over the visible range from 400 to 700 nm is unaffected by the presence of glycine at this pH. Similar experiments at very high pH precluded interactions between In$^{2-}$ and Gly$^-$ species. Remaining possible interactions are excluded by inference from the data analysis. These interactions would presumably cause deviations from the model equations 1-7, which make no provision for them. The deviations would lead to unsatisfactorily large uncertainties in calculated parameters but these uncertainties were not observed.

In our analysis of absorbance vs. composition data we regarded $K_{\mathrm{W}}$ and $K_{\mathrm{Gly}}$ as known parameters whose values were obtained from ref *2* and *3*, respectively. Activity coefficients were estimated from the Debye–Hückel equation and employed the temperature-dependent parameter values given by Robinson and Stokes (*4*). Ion-size parameters of 0.35, 0.4, 0.6, and 0.9 nm were used for OH$^-$, Gly$^-$, AH$^+$, and H$^+$ ions and 0.9 nm was used for both indicator forms. Species concentrations are expressed in units of mol kg$^{-1}$.

The quantities that we seek in these experiments are $K_{\mathrm{In}}$ and ab$F_{\mathrm{In}}$. We proceeded interatively by first estimating $K_{\mathrm{In}}$ which then yielded direct solution of eq 1-7 for $a_{\mathrm{H}}$ in each measurement solution. Then, combining eq 3, 5, and 7 yields

$$1/A_{596} = (\gamma_{\mathrm{H_{In}}})(K_{\mathrm{In}}/\mathrm{ab}F_{\mathrm{In}})a_{\mathrm{H}} + 1/\mathrm{ab}F_{\mathrm{In}} \tag{8}$$

A plot of $1/A_{596}$ vs. $a_{\mathrm{H}}$ yields values of $K_{\mathrm{In}}/\mathrm{ab}F_{\mathrm{In}}$ and $1/\mathrm{ab}F_{\mathrm{In}}$

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Table I. Values of $K_{In}$ and $abF_{In}$ for Thymol Blue at Various Temperatures

| $T$, °C | $10^9 K_{In}$ | $abF_{In}$ |
|---|---|---|
| 25.1 | 0.719 ± 0.004[a] | 1.875 ± 0.004[a] |
| 29.6 | 0.815 ± 0.004 | 1.849 ± 0.003 |
| 37.0 | 0.913 ± 0.010 | 1.813 ± 0.010 |
| 44.3 | 0.964 ± 0.003 | 1.785 ± 0.003 |
| 50.4 | 1.029 ± 0.010 | 1.750 ± 0.008 |

[a] Uncertainties are standard error estimates derived by propogation-of-variance analysis from least-squares estimates of slope and intercept values in eq 8.

Table II. Thermodynamic Acidic Dissociation Constants of Amantadine Hydrochloride at Various Temperatures

| $I$ | $10^{11} K_{AH^+}$ | | | | |
|---|---|---|---|---|---|
| | 25.1 °C | 29.6 °C | 37.0 °C | 44.3 °C | 50.4 °C |
| 0.010 | 2.88 | 3.85 | 7.03 | 11.9 | 18.7 |
| 0.010 | 2.85 | 3.83 | 7.06 | 11.5 | 18.8 |
| 0.010 | 2.91 | 3.64 | 6.90 | 11.1 | 17.9 |
| 0.025 | 2.72 | 3.69 | 6.76 | 11.2 | 17.7 |
| 0.025 | 2.81 | 3.80 | 6.72 | 11.1 | 17.2 |
| | 2.83 ± 0.07[a] | 3.76 ± 0.09 | 6.89 ± 0.15 | 11.4 ± 0.3 | 18.1 ± 0.7 |

[a] Mean and standard deviations of five entries above.

as the slope and the intercept. These values yield a new estimate of $K_{In}$ and the calculation is repeated until $K_{In}$ remains unchanged. The results of this analysis appear in Table I. The uncertainties given in the table represent standard error estimates and are derived from the least-squares estimates of standard errors of the slope and intercept values. These are propogated into $K_{In}$ and $abF_{In}$ by propogation-of-variance techniques.

Calculated values of $abF_{In}$ represent absorbances of thymol blue solutions at very high pH where $In^{2-}$ is the dominant indicator species. These agree with measured values determined in separate experiments with 0.02 F NaOH solutions to within the estimated uncertainties and to within our a priori estimate of ±0.006 absorbance unit. This agreement leads us to conclude that our values of $K_{In}$ and $abF_{In}$ are reliable and free from systematic errors of any significance.

Having established $K_{In}$ and $abF_{In}$ values, we prepared solutions of A·HCl at different concentrations and with varying quantities of added NaOH but the same concentration of thymol blue used throughout the earlier experiments. Absorbance measurements with the same cuvette along with an estimate of the ionic strength allowed direct calculation of $a_H$ via eq 8. This value along with eq 2, 3, and 9–11 yielded $K_{AH^+}$ from each

$$K_{AH^+} = a_H a_A / a_{AH^+} = \gamma_H \gamma_A [H^+][A]/(\gamma_{AH^+}[AH^+]) \quad (9)$$

$$[Na^+] + [H^+] + [AH^+] = [Cl^-] + [OH^-] + [HIn^-] + 2[In^{2-}] \quad (10)$$

$$F_{AHCl} = [AH^+] + [A] \quad (11)$$

absorbance measurement. The results are in Table II. These data correspond to $[AH^+]/[A]$ ratios ranging from 10:1 to about 2:1 but smaller proportions of $[AH^+]/[A]$ could not be employed because the pH values encountered would be higher than the effective range of the thymol blue color change.

In these experiments we verified that no specific interactions were present between $HIn^-$ and $AH^+$ by independent spectral measurements at pH 6 and that the $In^{2-}$ spectrum was unaffected by the presence of A in strongly alkaline solutions. These observations along with the apparently high precision obtained for $K_{AH^+}$ warranted a further data analysis via the van't Hoff equation to determine $\Delta H°$ and $\Delta S°$ for the acidic dissociation reaction. The values obtained for $AH^+$ are given in Table III and compared there with other ammonium acid dissociations.

Table III. Standard Enthalpies and Entropies for the Acidic Dissociation of Amantadine Hydrochloride and Various Substituted Ammonium Acids[5]

| ammonium acid | $\Delta H°$, kcal mol$^{-1}$ | $\Delta S°$, cal mol$^{-1}$ K$^{-1}$ |
|---|---|---|
| amantadine hydrochloride | 14.15 ± 0.16[a] | −0.9 ± 0.5[a] |
| ammonium | 12.48 | −0.44 |
| methylammonium | 13.09 | −4.7 |
| ethylammonium | 13.58 | −3.1 |
| *tert*-butylammonium | 14.36 | −0.7 |
| dimethylammonium | 11.86 | −9.5 |
| trimethylammonium | 8.82 | −15.2 |

[a] Uncertainties represent standard error estimates derived from the scatter of points about the van't Hoff regression lines of ln $K$ vs. $1/T$ for $\Delta H°$ and $T$ ln $K$ vs. $T$ for $\Delta S°$.

We also note here for the sake of completeness that a van't Hoff analysis of the data in Table I yields values of 2.55 ± 0.31 kcal mol$^{-1}$ and −33.2 ± 1.0 cal mol$^{-1}$ K$^{-1}$ for $\Delta H°$ and $\Delta S°$ for the second acidic dissociation of thymol blue. While these data are not of particular interest here, they seem not to have been reported previously.

## Discussion

In the following discussion we will associate $\Delta S°$ for ammonium acid dissociations primarily with differential solvent ordering around ammonium ions as compared with the hydronium ion products of these reactions (*5*). Thus, the very small $\Delta S°$ values for dissociation of primary ammonium acids such as methyl-, ethyl-, *tert*-butyl-, and adamantanylammonium are indicative of similar extents of solvent restriction in the neighborhood of each of these ions and the presumably extensive solvent ordering near a solvated hydronium ion. $\Delta S°$ values for these dissociation reactions are in sharp contrast to those observed in $NH_4^+$, $CH_3NH_3^+$, $(CH_3)_2NH_2^+$, and $(CH_3)_3NH^+$ where the direct addition of even rather small substituents on the nitrogen atom seems to effectively hinder ordering of water molecules near the ammonium species. $\Delta S°$ for these dissociations decreases from −0.44 cal mol$^{-1}$ K$^{-1}$ for the unsubstituted ammonium ion to a value of −15.2 cal mol$^{-1}$ K$^{-1}$ for $(CH_3)_3NH^+$ dissociation. It appears likely, therefore, that the most important solvent ordering effects are direct hydrogen bonding between $H_2O$ and hydrogen atoms bonded directly to N in these systems. Apparently, longer range interactions between the dipolar solvent molecules and the ionic site play a much less important role.

The present results for $AH^+$ dissociation also afford an opportunity to examine the so-called "hydrophobic" interaction of hydrocarbon with water. Presumably this interaction involves substantial ordering of water molecules around bulky hydrocarbon groups like adamantyl and furthermore would be influenced in some way by the presence of a charged species. The very small magnitude of $\Delta S°$ of dissociation seems to indicate either that such hydrophobic ordering does not occur to any appreciable extent at all or that it is unaffected by the solvation changes occurring upon ammonium dissociation.

## Experimental Section

Amantadine hydrochloride (Gold Label) was obtained from Aldrich Chemical Co. and was used without further purification. Titration of weighed samples of the salt with $AgNO_3$ yielded values of percentage Cl within 0.3% of theoretical. All other chemicals were reagent grade.

Spectrophotometric measurements employed a Beckman Acta CIII UV–visible spectrophotometer equipped with a thermostated cell compartment and 1.00-cm matched quartz cuvettes. Distilled water was used as the blank for all measurements and absorbance measurements were always made at 596 nm with a spectral band-pass of 0.3 nm. Special care was taken to assure that thermal equilibration and readings were made only after absorbances were stable for at least 3 min.

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**Registry No.** Amantadine hydrochloride, 665-66-7.

### Literature Cited

(1) Whitley, R. J.; Alford, C. A. *Annu. Rev. Microbiol.* **1978**, *32*, 285–300.
(2) Harned, H. S.; Robinson, R. A. *Trans. Faraday Soc.* **1940**, *36*, 973.
(3) King, E. J. *J. Am. Chem. Soc.* **1951**, *73*, 155.
(4) Robinson, R. A.; Stokes, R. H. "Electrolyte Solutions", 2nd ed.; Butterworths: London, 1965.
(5) Larson, J. W.; Hepler, L. G. In "Solute–Solvent Interactions"; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969.

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# Transference Number Measurements in Aqueous Solutions at 25 °C. 1. Sodium Iodide

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**Cation and anion transference numbers for aqueous solutions of NaI at different ionic concentrations are determined by using the moving-boundary method. The values of the ionic transference numbers at each concentration of NaI are verified through the value of their sum. The small variation with the NaI concentration of the transference number obtained is attributed mainly to the variation of the electrophoretic effect, in accord with the Debye–Hückel picture. The limiting cation transference number, $T_+^\circ$, is calculated by employing the various Fuoss–Onsager (FO) and Pitts (P) equations. Limiting ionic conductances, $\lambda_\pm^\circ$, are also reported.**

## Introduction

Ionic transference numbers can be used to understand the ion–solvent interactions in electrolytic solutions. Nevertheless, only a few experimental data of such parameters have been reported, even in water, it being necessary to resort to the utilization of limiting ionic conductances for their calculation.

This paper reports the transference numbers for NaI in water at 25 °C, obtained by measuring both the cation and the anion transference numbers at different concentrations of salt to contribute to a better knowledge of electrolytic aqueous solutions.

## Experimental Section

***Chemicals and Solutions.*** NaI (Merck Suprapur) was dried in vacuo at 150 °C for 72 h before use. Merck analytical-reagent-grade $NaOOCCH_3$ was recrystallized twice from a saturated aqueous solution. $(C_2H_5)_4NClO_4$, for polarography, was supplied by Carlo Erba and recrystallized once from a methanol–water mixture. All the chemicals were stored in a desiccator over $P_2O_5$.

Conductivity-grade water with a specific conductivity $\kappa_0 = 5 \times 10^{-7}\ \Omega^{-1}\ \mathrm{cm}^{-1}$ was used as solvent. The solutions were prepared by weighing and correcting to vacuo each of the components.

***Apparatus.*** The apparatus to detect and follow the moving boundary has been described in a previous paper from this laboratory (*1*) as well as the falling-boundary cell employed. In the cation runs a silver electrode was used as the anode in the closed compartment whereas an electrolytic cadmium electrode was the closed anode in the anion runs. In all runs, a platinum wire was used as the cathode in the open compartment.

## Results and Discussion

The transference numbers observed are presented in Table I together with the current interval employed.

The volume correction at each concentration studied was calculated from (*2*, *3*)

$$\Delta T_{\mathrm{vol}} = C \cdot \Delta V \qquad (1)$$

where $\Delta V$ is the volume change per faraday between the closed electrode compartment and a point in the leading solution. These corrections are given in Table I and are added to the values observed in the anion runs but subtracted from those in the cation runs.

In the cation runs $(C_2H_5)_4NClO_4$ was used as following electrolyte and their volume increases per faraday were calculated from

$$\Delta V_+ \simeq \phi^0(\mathrm{AgClO_4}) - \bar{V}(\mathrm{Ag}) + \phi^0(\mathrm{Et_4NI}) - \phi^0(\mathrm{Et_4NClO_4}) - T_+(\mathrm{NaI})\,\phi(\mathrm{NaI}) \qquad (2)$$

where $\phi(\mathrm{Et_4NI})$ and $\phi(\mathrm{Et_4NClO_4})$ have been replaced by their $\phi^0$ values.

In the anion runs $NaOOCCH_3$ was used as the following electrolyte. The volume increase per faraday for these runs was given by

$$\Delta V_- \simeq \tfrac{1}{2}\phi^0(\mathrm{CdI_2}) - \tfrac{1}{2}\bar{V}(\mathrm{Cd}) - T_+(\mathrm{NaI})\,\phi(\mathrm{NaI}) \qquad (3)$$

where $\phi(\mathrm{CdI_2})$ has been approximated to its $\phi^0$ value. The values used for $\bar{V}(\mathrm{Ag})$ and $\bar{V}(\mathrm{Cd})$ were 10.3 and 13.0 cm$^3$ mol$^{-1}$, respectively (*4*), and the apparent partial molar volumes, $\phi(\mathrm{NaI})$, were determined at each concentration from

$$\phi = 35.10 + 1.346C^{1/2} \qquad (4)$$

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