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General treatment of pH solubility profiles of weak acids and bases. II. Evaluation of thermodynamic parameters from the temperature dependence of solubility profiles applied to a zwitterionic compound

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Summary

The solubility of a zwitterionic compound has been determined as a function of pH and temperature. The data were used to determine the pK_a, intrinsic solubility of the uncharged species and the thermodynamic quantities ΔG, ΔH, ΔS and ΔCp as a function of temperature. It was found that with an increase in temperature from 4°C to 45°C, pKa_1 decreased from 3.42 to 3.19 while pKa_2 decreased from 10.20 to 9.29. Over this same increase in temperature, the intrinsic solubility of the uncharged species increased from 1.28 to 3.40 mg/ml. The thermodynamic quantities calculated were consistent with values found in the literature for similar compounds where ΔH for the equilibria are endothermic and the ΔS values indicate an increase in solution structure with dissociation. The intrinsic solubility of the uncharged species was found to decrease with the introduction of NaCl to the solution. This decrease is consistent with reported solubility effects of electrolytes upon non-electrolytes.

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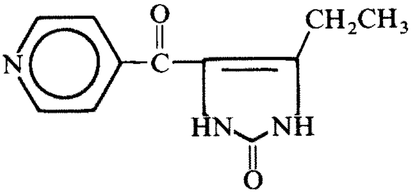
Introduction

The solubilities of weak acids and bases are dependent upon the pH of the solution as well as the base or acid used to adjust the pH. Since this dependency is related to the solubility product (pK_{sp}), ionization constant (pK_a) and uncharged species intrinsic solubility, there should be a change in the solubility profiles with temperature.

The manner in which the pK_as and uncharged species intrinsic solubility of Compound (I) change with temperature has been investigated and the data used to calculate the thermodynamic quantities ΔH, ΔG, ΔS, and ΔCp.



4-Ethyl-1,3-dihydro-5(4-pyridinylcarbonyl)-2H-imidizol-2-one (I)

This compound can either gain or lose a proton and, as such, is in the zwitterionic class of compounds where the nitrogen in the pyridine ring can gain the proton, causing the molecule to be positively charged, and one of the protons on the nitrogens in the imidizole ring can be lost, resulting in a negative charge on the molecule. Since the pK_a of pyridine compounds are generally in the 3–5-range as described previously (Perrin, 1965; Suppl., 1972) and imidizoles having substitutions similar to this compound are usually in the 8–10-range as described previously (Kortum et al., 1961; Serjeant and Dempsey, 1979), it would be expected that the compound would be primarily uncharged in the intermediate pH range. Therefore, the solubility profiles of I should go through a minimum as the solution pH increases from 2 to 11. Furthermore, because pK_1 and pK_2 should differ by 3–7 units, it will be possible to separate the data into two independent pH regions. The lower pH range, 2–7, will be associated with the basic properties of the compound and the higher pH range, 7–11, with the acidic properties.

Theoretical

It has previously been shown (Streng et al., 1984) that the pH–solubility profile of a monoprotic weak base is divided into two regions and can be described by Eqns. 1 and 2.

$$S_{1,0} = \frac{-\left([M] + \frac{\{H\}}{Y_H} - \frac{K_w}{\{H\}Y_{OH}}\right) + \left(\left[[M] + \frac{\{H\}}{Y_H} - \frac{K_w}{\{H\}Y_{OH}}\right]^2 + \frac{4K_{sp}}{Y_{HD}Y_X}\right)^{1/2}}{2\left(\frac{\{H\}Y_D}{KY_{HD} + \{H\}Y_D}\right)} \quad (1)$$

$$S_{1,1} = \left(\frac{1}{Y_D} + \frac{\{H\}}{KY_{HD}} \right) \cdot \{D\} \tag{2}$$

Similarly, the equations which describe the solubility of a monoprotic weak acid are given in Eqns. 3 and 4.

$$S_{1,0} = \left(\frac{1}{Y_{HD}} + \frac{K}{Y_D\{H\}} \right) \cdot \{HD\} \tag{3}$$

$$S_{1,1} = \frac{-\left([X] + \frac{\{H\}}{Y_H} - \frac{K_w}{\{H\}Y_{OH}} \right) + \left(\left[[X] + \frac{\{H\}}{Y_H} - \frac{K_w}{\{H\}Y_{OH}} \right]^2 + \frac{4K_{sp}}{Y_M Y_D} \right)^{1/2}}{2\left(\frac{KY_{HD}}{\{H\}Y_D + KY_{HD}} \right)} \tag{4}$$

where [M] and [X] are the concentrations of the cation and anion forming the salt; Y_i is the activity coefficient of the species i; {D} and {HD} are the intrinsic solubilities (activities) of the uncharged species.

Therefore, for Compound I, Eqns. 1 and 2 can be used to represent the solubility through the lower pH range while Eqns. 3 and 4 can be used for the higher pH range.

Knowing the equilibrium constants as a function of temperature, the Gibbs free energy (ΔG), enthalpy (ΔH), entropy (ΔS) and heat capacity (ΔC_p) can be determined. Using the experimental procedure to be described, the equilibrium constants are determined on a molar scale. In order to obtain the correct values for the thermodynamic quantities, either the K_a values need to be converted to the molal scale or an additional term needs to be added to each of the thermodynamic quantities.

It can be shown (Robinson and Stokes, 1970a) that the equilibrium constant on a molal scale is related to that on the molar scale through the solvent density at the temperature of interest according to:

$$K_m = K_c/d_0^{\nu-1} \tag{5}$$

where d_0 = solvent density; ν = number of ions the compound dissociates into; K_m = equilibrium constant on molal scale; and K_c = equilibrium constant on molar scale.

The Gibbs free energy is given by the expression:

$$\Delta G_m = -RT \ln K_m \tag{6}$$

where R = gas law constant, 8.315 J/deg · mol (1.987 cal/deg · mol); and T = temperature (K).

The enthalpy can be determined from the temperature derivative of the equilibrium constant as given by the van't Hoff equation:

$$R\left(\frac{\partial \ln K_m}{\partial(1/T)}\right)_p = -\Delta H_m \tag{7}$$

When the equilibrium constant is on a molar scale, then Eqn. 7 needs to have an additional term as described previously (MacDonald and Barton, 1976).

$$R\left(\frac{\partial \ln K_c}{\partial(1/T)}\right) = -\Delta H_m + RT^2(\nu - 1)\alpha_s \tag{8}$$

where

$$\alpha_s = \left(\frac{\partial \ln V_s}{\partial T}\right)_p$$

which is the coefficient of thermal expansion of the solvent.

The entropy is determined using the thermodynamic relationship:

$$\Delta S_m = \frac{\Delta H_m - \Delta G_m}{T} \tag{9}$$

It has been shown (Robinson and Stokes, 1970b) that the equilibrium constant can be expressed as a function of temperature as given in Eqn. 10.

$$-RT \ln K_m = a + bT + cT^2 \tag{10}$$

where a, b, c = constants.
Substituting Eqn. 10 into Eqns. 6, 7 and 9 results in

$$\Delta G_m = a + bT + cT^2 \tag{11}$$

$$\Delta H_m = a - cT^2 \tag{12}$$

$$\Delta S_m = -b - 2cT \tag{13}$$

These thermodynamic quantities can therefore be determined from knowledge of the temperature dependence of the equilibrium constant.

The heat capacity, C_p, can also be determined using the temperature derivative of the enthalpy, Eqn. 14, or the temperature derivative of the entropy as described previously (Lewis and Randall, 1961), Eqn. 15.

$$\Delta C_p = \left(\frac{\partial \Delta H_m}{\partial T}\right)_p \tag{14}$$

$$\Delta C_p = \left(\frac{\partial \Delta S_m}{\partial \ln T}\right)_p \tag{15}$$

The accuracy of the values obtained for ΔC_p when calculated from equilibrium constant data is usually uncertain because of the need to take the second derivative of the experimental data. Furthermore, the temperature dependence of the heat capacity is often found to be a quadratic or cubic function of the temperature as described previously (Glasstone and Lewis, 1960; Lewis and Randall, 1961) while the second derivative of Eqn. 10 will result in the linear function given by Eqn. 16:

$$\Delta C_p = -2cT \tag{16}$$

Experimental procedure

Into fourteen 10 ml ampules, 150 mg of I were weighed. From 1 to 10 ml of 0.069 N hydrochloric acid were added to six ampules and 1 to 10 ml of 0.069 N sodium hydroxide were added to six additional ampules. The total volume was adjusted to 10 ml in each ampule with water. Into one ampule 10 ml water was placed and into one ampule 10 ml of sodium chloride solution (8.5 mg/ml) was added. The ampules were sealed, placed in a water bath and subjected to vibration[1] for 3–5 days. The temperature of the water bath was set at 5, 10, 15, 20, 25, 30, 40 and 45° ± 0.05°C.

Following equilibration, the ampules were removed and the samples filtered through a 0.22 μm filter [2].

One ml aliquots of the solutions were taken for assay and approximately 5 ml placed in centrifuge tubes for pH measurement [3]. The centrifuge tubes were returned to the water bath in order to determine the pH of the saturated solutions at the experimental temperature.

The aliquots removed for assay were placed in 50 ml volumetric flasks and brought to volume with water. A second dilution, in the range 5/10 to 2/25, was made with the mobile phase used in the HPLC assay. Average values for the solubilities were obtained from either duplicate or triplicated assays of the aliquots. The following are the HPLC conditions used for the assay:
Column: Zorbax C-8 [4]
Mobile phase: 0.05 M phosphate buffer/methanol (60 : 40) pH 3.2
Flow rate: 55 ml/h
Sample size: 10 μl (0.2–0.5 μg)
Wavelength: 322 nm [5]

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[1] Vibro Mixer, Chemapac, Hoboken, NJ or Ultrasonic Cleaner, Branson Equipment, Shelton, CT.

[2] Millipore Filter, Millipore Filter Corporation.

[3] Beckman Instrument Model 4500 with a Radiometer GK2321C Combination Electrode.

[4] E.I. DuPont DeNemours, Wilmington, DE.

[5] LDC SpectroMonitor III.

Results and Discussion

Representative results of this study are plotted in Fig. 1. Since the solutions were never saturated in one of the charged species (the solubility profile obtained was only dependent upon the uncharged species solubility) only Eqn. 2 was used for the lower pH range while Eqn. 3 was used for the higher pH range. The solid curves in the figures were calculated using the values for pK_1, pK_2 and the uncharged species intrinsic solubility given in Table 1. It can be seen that there is excellent agreement between the experimental data and the calculated curves. The calculated values for pK_1 and pK_2 agree with the expected values as pK_1 was expected to be in the 3–5-range (Perrin, 1965; Suppl., 1972) while pK_2 was expected to be in the 8 to 10 range as described previously (Kortum et al., 1961; Serjeant and Dempsey, 1979) at 25°C.

The data for 25°C is from two independent sets of data and shows good reproducibility. Inspection of these data indicate differences of 2–5% in the solubility values. It has been found that when the intrinsic solubility of the uncharged species can be accurately determined, as in this investigation, the values calculated for the pK are very reproducible, usually within ±0.01 units. This is, however, a

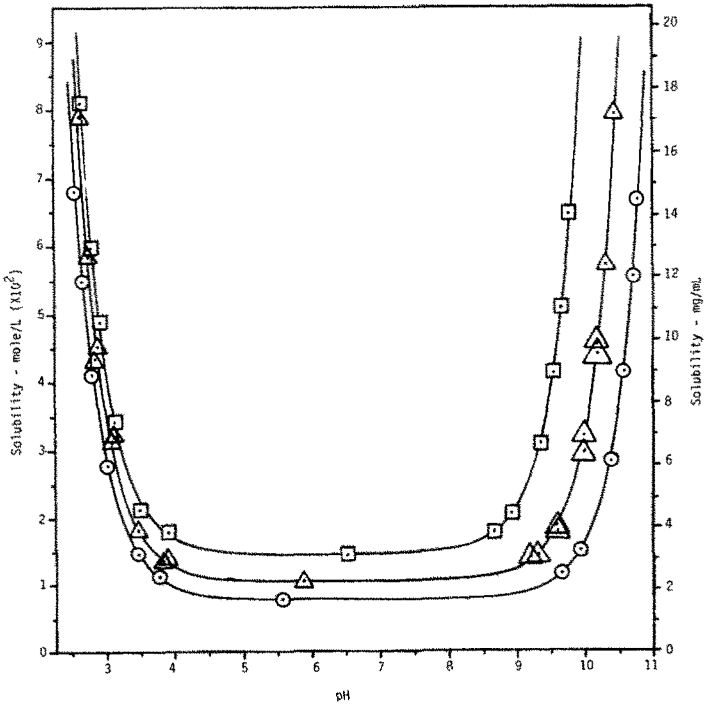

Fig. 1. pH–solubility profiles at: 10°C (⊙); 25°C (△); and 40°C (⊡). The data at 25°C represent two independent determinations.

TABLE 1

EXPERIMENTAL MOLAR EQUILIBRIUM CONSTANTS AND UNCHARGED SPECIES INTRINSIC SOLUBILITIES OF COMPOUND I

T (°C)	pK_{1c}	pK_{2c}	S (mol/l)×10^2	S (mg/ml)
45	3.19	9.32	1.77	3.84
40	3.22	9.36	1.45	3.15
30	3.26	9.53	1.19	2.58
25	3.30	9.73	1.03	2.24
20	3.32	9.84	0.92	2.00
15	3.34	9.92	0.80	1.74
10	3.37	10.02	0.78	1.69
5	3.42	–	0.65	1.41

function of the temperature dependence of the pK. If the pK has a high temperature dependence, then the reproducibility will not be as small.

In Fig. 2, log K_{1m} and log K_{2m} are plotted vs 1/T, respectively. The solid curves in this figure are the fit of the data to Eqn. 10. In Table 2 the predicted pK values, indicated by the symbol "^", are listed along with their differences from the observed values. The regression equations used, Eqn. 10, are given in the legend to

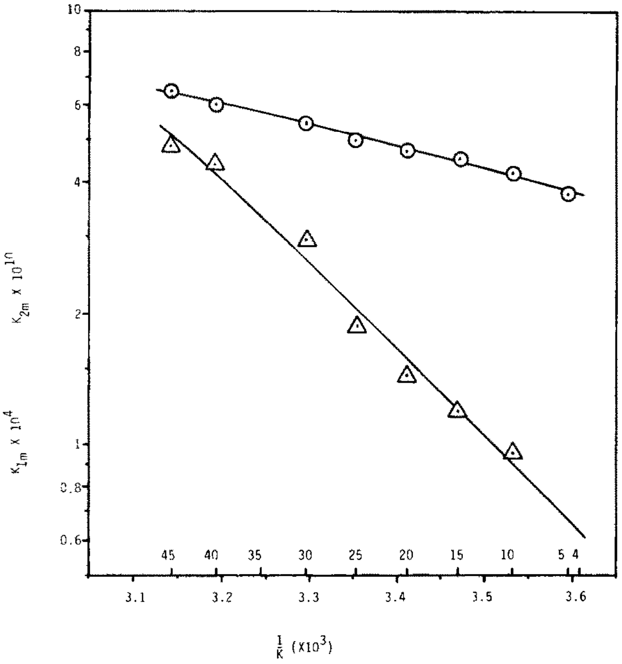

Fig. 2. Temperature dependence of the equilibrium constants: K_{1m} (⊙); K_{2m} (▲).

TABLE 2

MEASURED AND PREDICTED VALUES OF THE EQUILIBRIUM CONSTANTS OF COMPOUND I

T (°C)	pK_{1m}	$p\hat{K}_{1m}$	ΔpK_m *	pK_{2m}	$p\hat{K}_{2m}$	ΔpK_{2m} *
45	3.18	3.19	−0.01	9.32	9.29	0.03
40	3.22	3.21	0.01	9.36	9.38	−0.02
30	3.26	3.26	0.00	9.53	9.58	−0.05
25	3.30	3.29	0.01	9.73	9.69	0.04
20	3.32	3.32	0.00	9.83	9.80	0.03
15	3.34	3.35	−0.01	9.92	9.92	0.00
10	3.37	3.38	−0.01	10.02	10.04	−0.02
5	3.42	3.41	0.01	–	–	

* $\Delta pK_m = pK_m - p\hat{K}_m$; where the symbol "$\hat{}$" indicates the predicted value
$-RT \ln \hat{K}_{1m} = 3.3838 \times 10^3 - 0.1235T + 1.2820 \times 10^{-2}T^2$
$-RT \ln \hat{K}_{2m} = 12.0100 \times 10^3 - 6.3596T + 3.4955 \times 10^{-2}T^2$

Table 2. There is excellent agreement between the observed and calculated values for K_1 and good agreement for K_2.

In Table 3, the measured, calculated and difference in the uncharged species intrinsic solubilities as a function of temperature are given. As described previously (Lewis and Randall, 1961), the heat of solution is related to the solubility according to Eqn. 17. The data were fitted, using linear regression analysis, to Eqn. 17 with the resulting equation given in the legend to Table 3. From this analysis, the heat of solution was determined to be endothermic with a value of 4.19, kcal/mol. The predicted values calculated are indicated by the symbol "$\hat{}$" in Table 3.

$$\left(\frac{\partial \ln m}{\partial(1/T)}\right)_p = -\frac{\Delta H_s}{R} \tag{17}$$

where ΔH_s = heat of solution.

Utilizing the regression equations in the legend of Table 2, values for ΔG_m, ΔH_m, ΔS_m and ΔC_{pm} were calculated using Eqns. 11, 13 and 16. These results are given in Table 4. The positive value for the enthalpy indicates the dissociation reaction is endothermic. The entropy values found for the K_1 equilibria are in the −7 to −8 cal/deg · mol range which compares favorably with the entropy values of pyridine and similar 4-substituted pyridine compounds which are in the −6 to −8 cal/deg · mol range as described previously (Martell and Smith, 1974a). The ΔS_m values associated with the imidizole equilibria (K_2) are reasonable when compared to those compounds reported (Martell and Smith, 1974a and b); however, none of these compounds had closely similar structures. The negative entropy values found for both equilibria indicate there is a net increase in the solution structure when proceeding from the protonated species to the unprotonated species.

As mentioned, the values obtained for the heat capacities are questionable due to the necessity of having to take the second derivative of the experimental data. The

TABLE 3

UNCHARGED SPECIES INTRINSIC SOLUBILITY OF COMPOUND I AS A FUNCTION OF TEMPERATURE

T°C	S (mol/l)$\times 10^2$	Ŝ (mol/l)$\times 10^2$	$\Delta S \times 10^2$ *
45	1.77	1.66	0.11
40	1.45	1.50	−0.05
30	1.19	1.20	−0.01
25	1.03	1.06	−0.03
20	0.92	0.94	−0.02
15	0.80	0.83	−0.03
10	0.78	0.73	0.05
5	0.65	0.64	0.01
4		0.62	

*$\Delta S = S - \hat{S}$; where the symbol "^" indicates the predicted value.

Linear Regression Equation: $\ln \hat{S} = 2107(\frac{1}{T}) + 2.5261$

heat capacities associated with the first equilibria of carboxyl acids have been reported (Lewis and Randall, 1961) to be in the range −34 to −50 cal/deg · mol which are slightly more negative than their respective entropy values. if the pyridine and tetrazole structures behave similarly, it would be expected that the heat capacity values would be slightly more negative than the entropy. According to Table 4, the calculated heat capacity values for each structure are slightly more negative than the entropy values.

In Table 5, the values obtained for the solubility of Compound I in 8.5 mg/ml sodium chloride solution is listed along with the pH. These values parallel the intrinsic solubilities of the uncharged species except for those at 10 and 5°C. The reason for this is that the higher pH for the latter data resulted in the deprotonation

TABLE 4

CALCULATED THERMODYNAMIC CONSTANTS* FOR COMPOUND I

T (°C)	K_1—pyridine					K_2—imidizole				
	pK_m	ΔG_m	ΔH_m	$-\Delta S_m$	$-\Delta C_{pm}$	pK_m	ΔG_m	ΔH_m	$-\Delta S_m$	$-\Delta C_{pm}$
45	3.19	4.64	2.09	8.03	8.16	9.29	13.52	8.47	15.9	22.2
40	3.21	4.60	2.13	7.90	8.03	9.38	13.45	8.58	15.5	21.9
35	3.24	4.56	2.17	7.78	7.90	9.48	13.37	8.69	15.2	21.5
30	3.26	4.52	2.21	7.65	7.77	9.58	13.29	8.80	14.8	21.2
25	3.29	4.49	2.24	7.52	7.64	9.69	13.22	8.90	14.5	20.8
20	3.32	4.45	2.28	7.39	7.52	9.80	13.15	9.01	14.1	20.5
15	3.35	4.41	2.32	7.26	7.39	9.92	13.08	9.11	13.8	20.1
10	3.38	4.38	2.36	7.14	7.26	10.04	13.01	9.21	13.4	19.8
5	3.41	4.34	2.39	7.01	7.13	10.17	12.95	9.30	13.1	19.4
4	3.42	4.33	2.40	6.98	7.11	10.20	12.93	9.32	13.0	19.4

* Units on ΔG_m and ΔH_m: kcal/mol; units on ΔS_m and ΔC_{pm}: cal/deg · mol.

TABLE 5

EXPERIMENTAL AND CALCULATED INTRINSIC SOLUBILITIES OF THE UNCHARGED SPECIES OF COMPOUND I IN THE PRESENCE OF 8.5 mg/ml NaCl

T (°C)	S (mol/l)×10^2	pH	Ŝ (mol/l)×10^2 *
45	1.71	5.763	1.58
40	1.375	6.434	1.42
35	–	–	1.27
30	1.139	6.253	1.14
25	0.982	7.689	1.01
20	0.864	6.478	0.90
15	0.754	6.053	0.79
10	0.799	8.584	0.70
5	0.726	8.998	0.61
4	–	–	0.59

* Ŝ are the predicted values using Eqn. 18 and the calculated intrinsic solutions from Table 3.

of some of the compound resulting in an increase in the solubility. The change in solubility of a non-electrolyte in the presence of a salt has been reviewed (Lewis and Randall, 1961). Setchenow (1892) proposed an empirical equation which is useful in obtaining good first approximations to the change in solubility, Eqn. 18.

$$\log Y = \log \frac{S_0}{S} = km \tag{18}$$

Where Y = activity coefficient of non-electrolyte; S_0 = solubility of non-electrolyte with no salt present; S = solubility of non-electrolyte in the presence of salt; k = Setchenow parameter; and m = concentration of salt.

Using the experimental data from 45 to 15°C, the value 0.159 for k was obtained. Values of k in the range 0.14–0.19 have been reported (Lewis and Randall, 1961) for organic compounds in the presence of NaCl. It can, therefore, be concluded that the solubilities measured in the presence of NaCl are reasonable. In Table 5, calculated values for the intrinsic solubility of the uncharged species in the presence of 8.5 mg/ml NaCl solution are given. The calculated values for S_0 used in these calculations were taken from Table 3. Although k should be a function of temperature, the effect of its change is probably within the experimental error of this study.

Conclusion

The results of this study show the temperature behavior of the various thermodynamic parameters. They are consistent with reported values of similar compounds and indicate the dissociation equilibria to be endothermic reactions and that with dissociation there is an increase in solution structure. The effect of the salt upon the intrinsic solubility of the uncharged species also agrees with reported effects.

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