Solubility of 2-Aminopyridine in Acetone, Chloroform, and Ethyl Acetate

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The solubility of 2-aminopyridine in acetone, chloroform, and ethyl acetate has been measured, respectively, at temperatures ranging from (288.15 to 313.15) K, (288.15 to 318.15) K, and (288.15 to 323.15) K by a static analytical method. The concentrations of the 2-aminopyridine in the saturated solution were analyzed by UV spectrometry. A semiempirical equation was used to correlate the experimental data.

Introduction

The chemical structure of 2-aminopyridine ($C_5H_6N_2$, CAS registry no. 504-29-0) is shown in Figure 1. 2-Aminopyridine is widely used in the synthesis of pharmaceuticals, especially for antihistamines, anti-inflammatories, and other drugs.[1,2] The solubility of solids in liquids is one of the most important process parameters and is of scientific interest for the development of the solution theory. However, limited data are available on the solubility and temperature dependence of the solubility of 2-aminopyridine.[3] In this article, the solubility of 2-aminopyridine in acetone, chloroform, and ethyl acetate was systematically measured by a static analytical method.

Experimental Section

Chemicals. Analytically pure grade acetone, chloroform and ethyl acetate were purchased from Tianjin Kewei Chemical Reagent. All above solvents were refluxed over anhydrous $CaSO_4$ for 6 h and then fractionally distilled. Distillates were stored over freshly activated 4Å molecular sieves before use. Analysis, using the Karl Fischer technique, showed that the water mass fraction in each of the solvents was less than 0.02 %. The mass fraction purities of the solvents were determined in our laboratory by gas chromatography: 99.95 % for acetone, 99.93 % for chloroform, and 99.95 % for ethyl acetate. 2-Aminopyridine, obtained from Kunshan Wilk Chemicals, was purified by recrystallization twice from a mixed solvent of chloroform and petroleum ether in a volume ratio of 4:1 and dried at 30 °C under reduced pressure. The obtained sample was kept in a desiccator with dry silica gel. Its melting temperature was determined to be 57.8 °C by a differential scanning calorimeter (Mettler DSC30),[4] which agrees with the literature data, respectively, Mod and Skau[3] to 58 °C and Arbuzov et al.[5] to 57 °C.

Apparatus and Procedure. The experimental solubility of 2-aminopyridine in acetone, chloroform, and ethyl acetate has been measured, respectively, at temperatures ranging from (288.15 to 313.15) K, (288.15 to 318.15) K, and (288.15 to 323.15) K by a static analytical method that was described in our previous work[6,7] and is briefly explained here. The experimental saturated solutions were prepared by the addition of an excess solute, 2-aminopyridine, to glass vessels containing the solvent. Solubilities were determined by equilibrating the solute with solvent in a water jacketed vessel with magnetic stirring in a constant temperature water bath (± 0.05 K) for at least 2 days. The attainment of equilibrium was verified by both the repetitive measurement of 2-aminopyridine after a minimum of 2 additional days and the approaching equilibrium from supersaturation by pre-equilibrating the solutions at a higher temperature. The actual temperature in the glass vessel was monitored by a mercury thermometer with an uncertainty of 0.05 K. The fluid between the internal and external glass tube could be exchanged by pressing or relaxing the gas bag at the top of the glass tube. Portions of 2-aminopyridine-saturated solutions were transferred from the internal glass tube to the volumetric flasks to determine the amounts of samples diluted quantitatively with solvent mixtures at 287 nm using spectrophotometric analysis (Shimadzu UV-160A). The mole fractions of the dilute solutions were determined from a Beer−Lambert law absorbance versus concentration working curves derived from the measured absorbances of standard solutions of known molar concentrations.

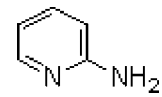

Figure 1. Structure of the 2-aminopyridine molecule.

Results and Discussion

UV spectrometry was chosen to determine the composition of a saturated solution of 2-aminopyridine in the solvents. To check the reliability of the experimental method, known masses of 2-aminopyridine were completely dissolved in chloroform, and the concentrations of solution were measured by a spectrometer (Shimadzu UV-160A). The estimated uncertainty of the solubility values on the basis of error analysis and repeated observations was within 2.8 %.

The solubilities of 2-aminopyridine in acetone, chloroform, and ethyl acetate reported in Table 1 represent an average of three measurements with a reproducibility of better than 97 %. From the results, we can see that the solubilities of 2-aminopyridine in solvents increase as the temperature increases.

According to the solid−liquid phase equilibrium theory, the relationship between the solubility of a solid (1) in a liquid and temperature is described as[8]

$$\ln\left(\frac{1}{\gamma_1 x_1}\right) = \frac{\Delta_{fus}H_1}{RT_{t,1}}\left(\frac{T_{t,1}}{T} - 1\right) + \frac{\Delta c_{p,1}}{R}\left(\ln\frac{T_{t,1}}{T} - \frac{T_{t,1}}{T} + 1\right) \quad (1)$$

where x_1 is the solubility and γ_1 is the solute activity coefficient. $T_{t,1}$, T, $\Delta_{fus}H_1$, and $\Delta c_{p,1}$ are the triple-point temperature, the

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Table 1. Solubility of 2-Aminopyridine in Acetone, Chloroform, and Ethyl Acetate

	x_1		
T/K	acetone	chloroform	ethyl acetate
288.15	0.4205	0.3092	0.3444
290.15	0.4387	0.3245	0.3633
292.15	0.4624	0.3496	0.3835
294.15	0.4839	0.3705	0.4048
296.15	0.5048	0.3921	0.4265
298.15	0.5277	0.4155	0.4497
300.15	0.5501	0.4392	0.4745
302.15	0.5740	0.4649	0.4994
304.15	0.5981	0.4908	0.5252
306.15	0.6232	0.5198	0.5529
308.15	0.6489	0.5485	0.5809
310.15	0.6761	0.5796	0.6110
312.15	0.7028	0.6112	0.6419
313.15	0.7166		
314.15		0.6452	0.6744
316.15		0.6810	0.7082
318.15		0.7182	0.7432
320.15			0.7801
323.15			0.8383

absolute temperature, the enthalpy of fusion, and the difference between the molar heat capacity of the solute in the solid and liquid states, respectively, and R is the gas constant.

In addition, in eq 1, the last term in the right-hand side containing the $\Delta c_{p,1}$ term almost cancels each other and is of less importance than the remaining term. Therefore, a simplified form of this equation can be used

$$\ln\left(\frac{1}{\gamma_1 x_1}\right) = \frac{\Delta_{\text{fus}}H_1}{RT_{\text{t},1}}\left(\frac{T_{\text{t},1}}{T} - 1\right) \tag{2}$$

The activity coefficient, γ_1, may be approximately given by[9]

$$\ln \gamma_1 = A + \frac{B}{T/\text{K}} \tag{3}$$

where A and B are constants. Introducing γ_1 from eq 3 into eq 2 and subsequent rearrangement results in

$$\ln x_1 = \left(\frac{\Delta_{\text{fus}}H_1}{RT_{\text{t},1}} - A\right) - \left(\frac{\Delta_{\text{fus}}H_1}{R} + B\right)\frac{1}{T/\text{K}} \tag{4}$$

Equation 4 can be written as

$$\ln x_1 = a + \frac{b}{T/\text{K}} \tag{5}$$

where x_1 and T are the mole fraction of the solute and absolute temperature, respectively, and a and b are empirical constants.

The experimental data of mole fraction solubility in Table 1 were correlated with eq 1 and plotted, as shown in Figure 2, whereas the parameter values of a and b and the root-mean-square deviation (rmsd) are given in Table 2. The rmsd is defined as

$$\text{rmsd} = \left[\frac{1}{n}\sum_{j}^{n}\left(x_{1,j} - x_{1,j}^{\text{calcd}}\right)^2\right]^{1/2} \tag{6}$$

where n is the number of experimental points, $x_{1,j}^{\text{calcd}}$ is the solubility calculated from eq 1, and $x_{1,j}$ is the experimental value of solubility.

Conclusions

The experimental solubility of 2-aminopyridine in acetone, chloroform, and ethyl acetate has been measured, respectively, at temperatures ranging from (288.15 to 313.15) K, (288.15 to 318.15) K, and (288.15 to 323.15) K by a static analytical method. From Table 1 and Figure 2, it was found that solubilities of 2-aminopyridine in solvents increase as the temperature increases and decrease in the order acetone > ethyl acetate > chloroform. The semiempirical equation, $\ln x_1 = a + b/(T/\text{K})$, was employed in correlating the experimental data with good agreement.

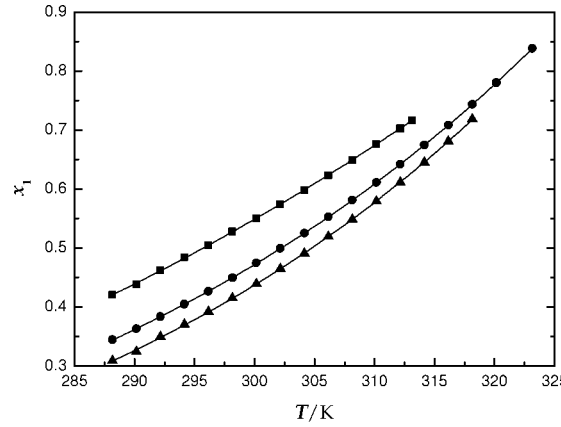

Figure 2. Solubility of 2-aminopyridine in various solvents: ■, acetone; ▲, chloroform; ●, ethyl acetate. The line is the best fit of the experimental data calculated with the semiempirical equation.

Table 2. Regression Curve Coefficients in Equation *5* for 2-Aminopyridine Solubility in Acetone, Chloroform, and Ethyl Acetate

solvent	a	b	10^3·rmsd
acetone	5.8073	−1922.60	0.88
chloroform	7.7651	−2577.15	1.47
ethyl acetate	7.1356	−2365.09	1.92

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