Solubility of 3-Aminopyridine in Acetone + *n*-Butyl Acetate from (288.15 to 323.15) K

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The solubility of 3-aminopyridine in (acetone + *n*-butyl acetate) mixed solvents has been measured in the temperature range from (288.15 to 323.15) K by a static analytical method. The concentrations of 3-aminopyridine in saturated solution were analyzed by UV spectrometry. A semiempirical equation was proposed for correlating the experimental data.

Introduction

The chemical structure of 3-aminopyridine ($C_5H_6N_2$, CAS registry no. 462-08-8) involved in this study is shown in Figure 1. 3-Aminopyridine is widely used as an intermediate for pharmaceuticals, agrochemicals, and colorants.[1] Crystallization is the preferred method of purification in the pharmaceutical industry for both the final drug substance and the isolated intermediates in the synthesis. The solubility of solids in liquids is one of the most important crystallization process parameters and is of scientific interest for the development of the solution theory. However, only limited data are available on the solubility and temperature dependence of the solubility of 3-aminopyridine. It has been known that acetone added to *n*-butyl acetate can change the solubility of 3-aminopyridine. Therefore, also as a continuation of our earlier study,[2,3] the solubility of 3-aminopyridine in (acetone + *n*-butyl acetate) mixed solvents at different temperature was systematically measured by a static analytical method. The solubility data of 3-aminopyridine in (acetone + *n*-butyl acetate) mixed solvents have not been found in the literature.

Experimental Section

Chemicals. Analytically pure grade acetone and *n*-butyl acetate were purchased from Tianjin Kewei Chemical Reagent. Acetone and *n*-butyl acetate were refluxed over anhydrous $CaSO_4$ for 6 h and then fractionally distilled with precautions to exclude moisture. Liquids were stored over freshly activated molecular sieves of type 4A. Analysis, using the Karl Fischer technique, showed that the water content in each of the solvents was less than 0.02 mass %. The mass fraction purities of the solvents were determined in our laboratory by gas chromatography to be 99.95 % for acetone and 99.93 % for *n*-butyl acetate. 3-Aminopyridine, obtained from Kunshan Wilk Chemicals, was purified by recrystallization twice from the mixed solvent of benzene and petroleum ether in a volume ratio of 4:1 and dried at 40 °C under reduced pressure. The obtained sample was kept in a desiccator with dry silica gel. Its melting point was 64.5 °C, which agrees with the most reliable published data.[4−6]

Apparatus and Procedure. The experimental solubility of 3-aminopyridine in acetone + *n*-butyl acetate solvents has been measured at temperatures ranging from (288.15 to 313.15) K by a static analytical method that was described in our previous work[7,8] and is briefly explained here. The experimental saturated solutions were prepared by excess solute, 3-aminopyridine, in glass vessels containing the solvent. We determined solubilities 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. Attainment of equilibrium was verified by both repetitive measurement after a minimum of 2 additional days and 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 tubes can be exchanged by pressing or relaxing the gas bag at the top of the glass tube. Portions of 3-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 using spectrophotometric analysis (Shimadzu UV-160A). The mole fractions of the dilute solutions were determined from absorbance versus concentration calibration curves derived from the measured absorbance of solutions of known concentrations. The estimated uncertainty of the concentration

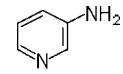

Figure 1. Structure of the 3-aminopyridine molecule.

Table 1. Solubility of 3-Aminopyridine in Acetone (w) + *n*-Butyl Acetate ($1 - w$) Solvents in the Temperature Range of (288.15 to 323.15) K[a]

	x_1					
T/K	$w = 0$	$w = 0.2$	$w = 0.4$	$w = 0.6$	$w = 0.8$	$w = 1.0$
288.15	0.1548	0.2088	0.2811	0.3252	0.3636	0.4325
293.15	0.1937	0.2501	0.3282	0.3755	0.4112	0.4806
298.15	0.2436	0.2993	0.3838	0.4305	0.4629	0.5375
303.15	0.3048	0.3575	0.4467	0.4909	0.5192	0.5910
308.15	0.3798	0.4265	0.5173	0.5551	0.5792	0.6499
313.15	0.4677	0.5046	0.5942	0.6244	0.6461	0.7115
318.15	0.5648	0.5930	0.6763	0.6975	0.7170	0.7704
323.15	0.6684	0.6898	0.7588	0.7735	0.7935	0.8349

[a] w: mass fraction.

Table 2. Regression Curve Coefficients in Equation 1 for 3-Aminopyridine Solubility in Acetone (w) + *n*-Butyl Acetate ($1 - w$) Solvents

w	A	B	10^3rmsd	R^2_{adj}
0	11.8195	−3943.66	5.32	0.9995
0.2	9.5326	−3200.15	1.35	0.9999
0.4	7.9958	−2669.16	3.93	0.9996
0.6	6.8989	−2309.17	3.52	0.9995
0.8	6.1894	−2075.05	0.38	0.9999
1.0	5.2563	−1754.27	3.76	0.9992

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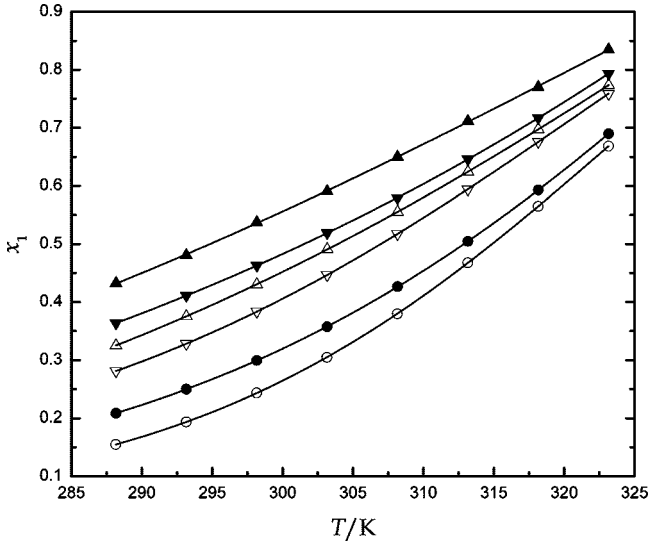

Figure 2. Solubility of 3-aminopyridine in acetone (w) + n-butyl acetate ($1 - w$) solvents: ○, $w = 0$; ●, $w = 0.2$; ▽, $w = 0.4$; ▼, $w = 0.6$; △, $w = 0.8$; ▲, $w = 1.0$. The line is the best fit of the experimental data calculated with the semiempirical eq 1.

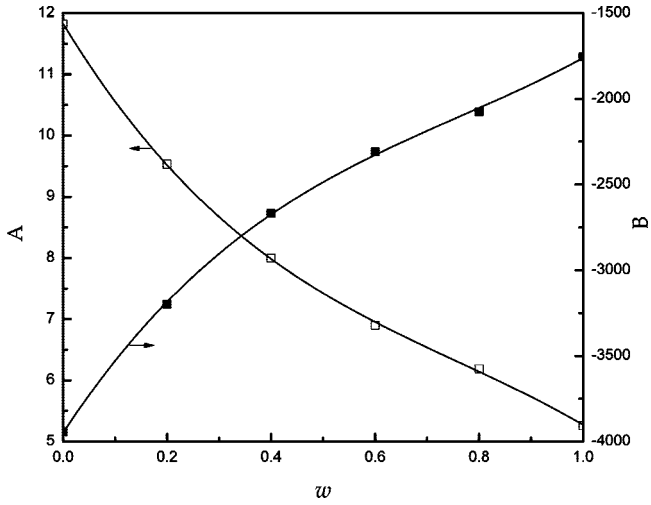

Figure 3. Variation of parameters A and B in eq 1 with acetone concentration, w. The lines are the best fit with the polynomial eqs 3 and 4.

from the calibration curve based on error analysis and repeated observations was within 2 %.

Results and Discussion

UV spectrometry was chosen to determine the concentration of a saturated solution of 3-aminopyridine in the solvents. To check the reliability of the experimental method, known masses of 3-aminopyridine were completely dissolved in acetone, and the concentrations of solution were measured by a spectrometer (Shimadzu UV-160A). The average relative uncertainty was 2.8 % ($n = 5$).

The solubilities of 3-aminopyridine in acetone (w) + n-butyl acetate ($1 - w$) solvents 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 3-aminopyridine in solvents increase as the temperature increases.

A semiempirical equation as follows was proposed to correlate the experimental data

$$\ln x_1 = A + B/(T/\mathrm{K}) \quad (1)$$

where x_1 and T are the mole fraction of the solute and absolute temperature, respectively, and A and B are empirical constants. The parameter values of A and B are given in Table 2 with the root-mean-square deviation of solubility (rmsd). The rmsd is defined as the following

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

where n is the number of experimental points, $x_{1,j}^{\mathrm{calcd}}$ is the solubility calculated from eq 1, and $x_{1,j}$ is the experimental value of solubility. Figure 2 shows that the experimental data follow the semiempirical equation with an adjusted coefficient of determination, R_{adj}^2, ranging from 0.9967 to 0.9996.

From Table 2 for eq 1, the regressed values of A decrease, whereas B increases with the increase in acetone concentration, as shown in Figure 3. The empirical formulas of the parameters A and B as a function of the concentration of acetone, w, are as follows

$$A = 11.8270 - 13.9645w + 13.2249w^2 - 5.8171w^3 \quad (3)$$

$$B = -3949.12 + 4605.84w - 4305.82w^2 + 1888.07w^3 \quad (4)$$

with the adjusted coefficient of determination (R_{adj}^2) 0.9995 and 0.9991, respectively. Using the relational expressions in eqs 1, 3, and 4, the solubility of 3-aminopyridine at any temperature and acetone concentration can be evaluated by interpolation.

Conclusions

The solubility of 3-aminopyridine in acetone + n-butyl acetate solvents has been measured at temperatures ranging from (288.15 to 313.15) K by a static analytical method. The solubilities of 3-aminopyridine significantly increase as the temperature and the concentration of acetone in solvents increase. A semiempirical equation was employed to correlate the experimental data with good agreement.

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