J. Chem. Eng. Data **2009,** *54,* 1129–1130

Solubility of 2-Aminopyridine in Ethanol + *n*-Butyl Acetate from (288.15 to 318.15) K

Dongwei Wei* and Limei Chen

Research and Development Center for Petrochemical Technology, Tianjin University, Tianjin 300072, China

The solubility of 2-aminopyridine in (ethanol + *n*-butyl acetate) mixed solvents has been measured in the temperature range from (288.15 to 318.15) 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 proposed to correlate the experimental data.

Introduction

The chemical structure of 2-aminopyridine ($C_5H_6N_2$, CAS Registry No. 504-29-0) involved in this study is shown in Figure 1. 2-Aminopyridine is widely used as an intermediate in the synthesis of pharmaceuticals especially for antihistamines, antinflammatories, and other drugs.[1,2] Crystallization is the preferred method of purification in the pharmaceutical industry for both the final drug substance and the isolated intermediates in the synthesis. Accordingly, knowledge of solubility is of clear importance for the design of the separation and purification process.

The solubility of solutes of all kinds in mixed solvents is of great practical importance since many industrial processes as well as laboratory procedures call for the use of solvent mixtures. The reasons for the preference for the use of solvent mixtures are manifold, including the amelioration of certain physical properties, such as the density, viscosity, volatility, etc., or of their chemical properties, such as stability, inflammability, and not least, their ability to dissolve certain substances. It has been known that ethanol added to *n*-butyl acetate can change the solubility of 2-aminopyridine. Therefore, also as a continuation of our earlier study,[3] the solubility of 2-aminopyridine in (ethanol + *n*-butyl acetate) mixed solvents at different temperature was systematically measured by a static analytical method. The solubility data of 2-aminopyridine in (ethanol + *n*-butyl acetate) mixed solvents have not been found in the literature.

Experimental Section

Chemicals. Analytically pure grade ethanol and *n*-butyl acetate were purchased from Tianjin Kewei Chemical Reagent. Ethanol and *n*-butyl acetate were refluxed over freshly activated CaO and anhydrous $CaSO_4$ for 6 h, respectively, 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 for ethanol, 99.95 %, and for *n*-butyl acetate, 99.93 %. 2-Aminopyridine, obtained from Kunshan Wilk Chemicals, was purified by recrystallization twice from the mixed solvent of chloroform 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 57.8 °C, which agrees with the most reliable published data.[4−6]

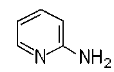

Figure 1. Structure of the 2-aminopyridine molecule.

Apparatus and Procedure. The experimental solubility of 2-aminopyridine in ethanol + *n*-butyl acetate solvents has been measured at temperatures ranging from (288.15 to 313.15) K by a static analytical method described in our previous work[7,8] and explained briefly here. The experimental saturated solutions were prepared by adding 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. Attainment of equilibrium was verified both by repetitive measurement after a minimum of two additional days and by 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 can 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 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.

Results and Discussion

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

The solubilities of 2-aminopyridine in ethanol (w) + *n*-butyl acetate ($1 - w$) solvents reported in Table 1 represent an average of three measurements with reproducibility better than 97 %. From the results, we can see that the solubilities of 2-aminopyridine in solvents increase as the temperature increases.

* Corresponding author. E-mail: weidwei@tju.edu.cn.

10.1021/je800841v CCC: $40.75
Published on Web 02/03/2009

Table 1. Solubility of 2-Aminopyridine in Ethanol (w) + n-Butyl Acetate ($1 - w$) Solvents in the Temperature Range (288.15 to 318.15) K (w = Mass Fraction)

	x_1					
T/K	$w = 0$	$w = 0.2$	$w = 0.4$	$w = 0.6$	$w = 0.8$	$w = 1.0$
288.15	0.1979	0.3097	0.3757	0.4125	0.4492	0.4955
293.15	0.2490	0.3562	0.4235	0.4575	0.4978	0.5410
298.15	0.3088	0.4095	0.4745	0.5056	0.5458	0.5929
303.15	0.3775	0.4699	0.5313	0.5613	0.6023	0.6506
308.15	0.4575	0.5394	0.5932	0.6250	0.6645	0.7133
313.15	0.5483	0.6190	0.6611	0.6964	0.7319	0.7783
318.15	0.6545	0.7095	0.7420	0.7649	0.8042	0.8445

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

w	A	B	10^3rmsd	R^2_{adj}
0	11.0410	−3644.80	2.97	0.9996
0.2	7.6059	−2532.18	3.57	0.9993
0.4	6.1872	−2066.14	2.96	0.9995
0.6	5.7053	−1901.88	3.69	0.9967
0.8	5.3625	−1777.40	3.10	0.9992
1.0	4.9996	−1644.90	2.20	0.9995

A semiempirical equation as follows was proposed to correlate the experimental data[3]

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

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^2_{adj}, ranging from 0.9967 to 0.9996.

From the data listed in Table 2 for eq 1, the regressed value of A decreases, whereas B increases with the increase of ethanol concentration as shown in Figure 3. The empirical formulas of

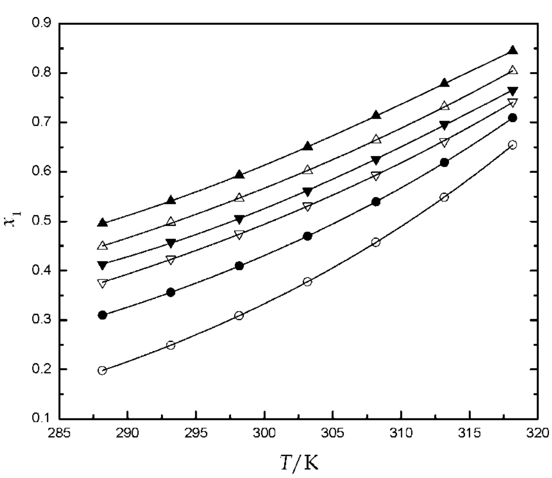

Figure 2. Solubility of 2-aminopyridine in ethanol (w) + n-butyl acetate ($1 - w$) solvents: ○, $w = 0$; ●, $w = 0.2$; ▽, $w = 0.4$; ▼, $w = 0.6$; △, $w = 0.8$; ▲, $w = 1.0$. The line is the best fit of the experimental data calculated with the semiempirical eq 1.

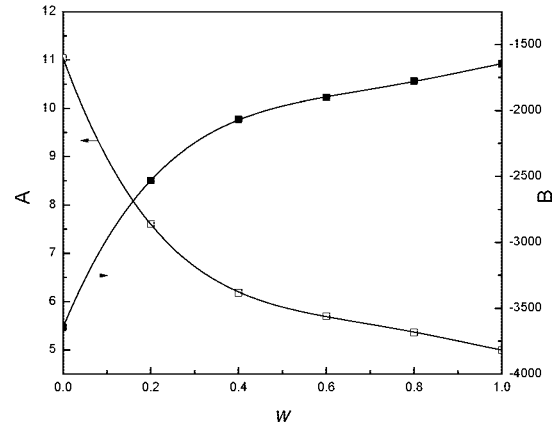

Figure 3. Variation of parameters A and B in eq 1 with ethanol concentration w. The lines are the best fit with the polynomial eqs 3 and 4.

the parameters A and B as a function of the concentration of ethanol, w, are as follows

$$A = 11.0424 - 24.8397w + 45.3343w^2 - 38.5226w^3 + 11.9837w^4 \quad (3)$$

$$B = -3645.33 + 8031.58w - 14595.88w^2 + 12432.51w^3 - 3867.27w^4 \quad (4)$$

with the adjusted coefficient of determination (R^2_{adj}) of 0.99990 and 0.99988, respectively. Using the relational expressions in eqs 1, 3, and 4, the solubility of 2-aminopyridine at any temperature and ethanol concentration can be evaluated by interpolation.

Conclusion

The solubility of 2-aminopyridine in ethanol + n-butyl acetate solvents has been measured, respectively, at temperatures ranging from (288.15 to 313.15) K by a static analytical method. The solubilities of 2-aminopyridine increase significantly as the temperature and the concentration of ethanol in solvents increase. According to the theory of "similarity and intermiscibility", it is reasonable that higher polar 2-aminopyridine is easily dissolved in the higher polar solvents. A semiempirical equation was employed to correlate the experimental data with good agreement.

Literature Cited

(1) Carlucci, G.; Colanzi, A.; Mazzeo, P.; Quaglia, M. G. Determination of 2-aminopyridine in piroxicam by derivative UV-spectrophotometry. *Int. J. Pharm.* **1989**, *53*, 257–259.
(2) Acker, R.-D.; Hamprecht, G. Preparation of 2-aminopyridine derivatives, U. S. Patent 4,395,555, 1981.
(3) Wei, D.; Chen, L. Solubility of 2-Aminopyridine in Acetone, Chloroform, and Ethyl Acetate. *J. Chem. Eng. Data* **2009**, in press.
(4) Lide, D. R. *CRC Handbook of Chemistry and Physics: a Ready-reference Book of Chemical and Physical Data*, 86th ed.; CRC Press: Boca Raton, 2005.
(5) Gokel, G. W. *Dean's Handbook of Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 2004.
(6) Speight, J. G. *Lange's Handbook of Chemistry*, 16th ed.; McGraw-Hill: New York, 2005.
(7) Wei, D.; Jiang, H.; Jing, X.; Yuan, J. Measurement and correlation of solubilities of 4-hydroxybenzaldehyde and its bromo-derivatives in chloroform. *J. Chem. Ind. Eng. (China, Chin. Ed.)* **2004**, *55*, 1192–1195.
(8) Wei, D.; Pei, Y. Measurement and correlation of solubility of diphenyl carbonate in alkanols. *Ind. Eng. Chem. Res.* **2008**, *47*, 8953–8956.

Received for review November 10, 2008. Accepted January 10, 2009.

JE800841V