Solubility of Phenacetinum in Methanol, Ethanol, 1-Propanol, 1-Butanol, 1-Pentanol, Tetrahydrofuran, Ethyl Acetate, and Benzene between 282.65 K and 333.70 K

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The solubility of phenacetinum in methanol, ethanol, 1-propanol, 1-butanol, 1-pentanol, tetrahydrofuran, ethyl acetate, and benzene was measured using a laser technique with a temperature range from 282.65 K to 333.70 K. The results of these measurements were correlated with a semiempirical equation.

Introduction

Phenacetinum ($C_2H_5ONHCOCH_3$, molecular weight 179.218, CAS Registry No. 62-44-2) is a kind of white crystalline powder. As an intermediate, phenacetinum has been widely used in synthesis of medicament for antifebrile anodyne and other antibiotics for combination drugs. In the present study, the solubility of phenacetinum was meaned in the temperature range from 282.65 K to 333.70 K in various organic solvents using a laser monitoring observation technique. The method employed in this work was classed as a synthetic method, which was much faster and more readily available than the analytical method.[1,2]

Experimental Sections

Materials. A white crystalline powder of phenacetinum was purified by recrystallization from methanol solution. Its mass fraction purity determined by HPLC was higher than 99.4 %. All solvents used for experiments were analytical research grade reagents from Beijing Chemical Reagent Co.

Methods and Apparatus

The apparatus for the solubility measurement is the same as that described in the literature[1,2] and described briefly here. A 250 mL jacketed vessel was used to determine the solubility; the temperature was controlled to ± 0.05 K through a thermostat water bath. The dissolution of the solute was examined by a laser beam penetrating the vessel. To prevent evaporation of the solvent, a condenser vessel was introduced. The masses of the samples and solvents were measured using an analytical balance (Sartorius CP124S, Germany) with an uncertainty of ± 0.0001 g.

The solubility of phenacetinum was measured by the laser technique.[3−8] During the experiments, a known mass of phenacetinum was added to a known mass of solvent. Continuous stirring was achieved with a magnetic stir bar. A mercury-in-glass thermometer was inserted into the inner chambers of the vessel for the measurement of the temperature. During the dissolution of the particles of the solute, the intensity of the laser beam increased gradually. When the solute dissolved completely, the solution was clear; the laser intensity reached its maximum; and an additional amount of solute of known mass (about 1 mg to 5 mg) was introduced into the vessel. This procedure was repeated until the laser intensity did not return to maximum or, in other words, the last addition of solute was not dissolved completely. The interval of the addition was 60 min. The same solubility experiment was conducted three times, and the mole fraction solubility x_1 in different pure solvents was obtained as follows

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{1}$$

where m_1, m_2, and m_3 represent the mass of the solute, methanol, and isopropanol, respectively, and M_1, M_2, and M_3 are the molecular weight of the solute, methanol, and isopropanol, respectively. The uncertainty in the solubility was estimated to be 0.5 %, whereas the uncertainty in temperature was estimated to be 0.05 K.

Results and Discussion

The measured solubilities of phenacetinum in methanol, ethanol, 1-propanol, 1-butanol, 1-pentanol, tetrahydrofuran, ethyl acetate, and benzene are presented in Table 1 and more visually given in Figure 1.

The solubility of a solid in a liquid may be expressed in a very general manner by eq 2

$$\ln x_1 = a + \frac{b}{(T/\mathrm{K})} + c \ln(T/\mathrm{K}) \tag{2}$$

where T is the absolute temperature, and a, b, and c are empirical constants. The difference between experimental and calculated results is also presented in Table 1. The values of the three parameters a, b, and c together with the root-mean-square deviations (rmsd) are listed in Table 2. The rmsd is defined as follows[4]

$$\mathrm{rmsd} = \left[\frac{\sum_{i=1}^{N} (x_{1,i} - x_{1,i}^{\mathrm{calcd}})^2}{N-1}\right]^{1/2} \tag{3}$$

where N is the number of experimental points; $x_{1,j}^{\mathrm{calcd}}$ is the

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Table 1. Mole Fraction Solubility x_1 of Phenacetinum in Different Pure Solvents from 282.65 K to 333.70 K

T/K	10^3x_1	$10^3(x_1 - x_1^{calcd})$	T/K	$10x_1$	$10^3(x_1 - x_1^{calcd})$	T/K	$10x_1$	$10^3(x_1 - x_1^{calcd})$
				Methanol				
283.74	10.460 ± 0.0012	0.078	303.18	25.574 ± 0.0012	−0.197	323.25	63.176 ± 0.0012	0.386
288.15	12.790 ± 0.0020	−0.025	308.05	32.072 ± 0.0016	−0.053	328.15	77.480 ± 0.0011	−0.025
293.83	16.571 ± 0.0010	−0.172	313.25	40.701 ± 0.0020	0.179	333.45	95.735 ± 0.0015	−1.309
298.18	20.259 ± 0.0021	−0.232	318.10	50.556 ± 0.0012	0.373			
				Ethanol				
282.65	9.6408 ± 0.0039	−0.0637	303.31	22.580 ± 0.0009	−0.126	323.25	53.061 ± 0.0012	0.375
289.25	12.861 ± 0.0030	0.171	307.85	27.324 ± 0.0030	−0.141	328.65	66.650 ± 0.0015	0.338
293.41	15.170 ± 0.0039	0.116	313.30	34.532 ± 0.0028	−0.022	333.70	82.236 ± 0.0015	−0.032
298.25	18.376 ± 0.0026	−0.015	318.25	42.789 ± 0.0025	0.183			
				1-Propanol				
282.65	8.9512 ± 0.0005	−0.1406	303.31	22.224 ± 0.0005	−0.132	323.25	54.049 ± 0.0005	0.337
289.25	12.371 ± 0.0006	0.272	307.85	27.068 ± 0.0006	−0.216	328.45	67.999 ± 0.0006	0.476
293.45	14.756 ± 0.0005	0.230	313.30	34.520 ± 0.0049	−0.148	333.70	85.175 ± 0.0006	0.114
298.25	17.969 ± 0.0005	0.056	318.15	42.973 ± 0.0045	0.059			
				1-Butanol				
283.37	16.433 ± 0.0027	0.119	303.18	35.331 ± 0.0020	−0.211	323.25	80.964 ± 0.0027	0.686
288.15	19.652 ± 0.0030	0.026	308.05	43.203 ± 0.0022	−0.027	328.15	98.408 ± 0.0013	0.212
293.73	24.265 ± 0.0009	−0.151	313.23	53.612 ± 0.0018	0.294	333.27	119.91 ± 0.0027	−1.385
298.20	28.897 ± 0.0015	−0.241	318.43	66.512 ± 0.0020	0.612			
				1-Pentanol				
282.95	11.414 ± 0.0030	−0.111	303.15	24.323 ± 0.0036	−0.132	323.17	55.923 ± 0.0032	0.620
288.23	13.629 ± 0.0049	0.016	307.95	29.741 ± 0.0031	0.021	328.30	68.482 ± 0.0035	0.699
293.27	16.382 ± 0.0037	−0.551	312.95	36.708 ± 0.0039	0.026	333.27	82.759 ± 0.0049	−1.836
298.20	19.863 ± 0.0049	−0.205	317.87	45.061 ± 0.0032	0.336			
				Tetrahydrofuran				
283.03	18.830 ± 0.0022	−0.064	303.15	39.546 ± 0.0031	−0.161	323.45	84.863 ± 0.0031	0.274
288.35	23.073 ± 0.0036	0.106	307.95	47.304 ± 0.0028	−0.163	328.33	101.65 ± 0.0034	0.176
293.88	27.588 ± 0.0030	0.054	313.15	57.561 ± 0.0035	−0.050	333.55	122.77 ± 0.0032	−0.500
298.17	32.940 ± 0.0031	−0.067	318.15	69.547 ± 0.0027	0.131			
				Ethyl Acetate				
282.65	5.9313 ± 0.0017	−0.4994	303.17	13.683 ± 0.0022	−0.110	323.25	30.650 ± 0.0018	−0.170
289.45	8.2669 ± 0.0020	0.6355	308.03	16.438 ± 0.0019	−0.308	328.15	37.683 ± 0.0021	0.129
293.30	9.5839 ± 0.0019	0.0528	313.05	20.055 ± 0.0023	−0.563	333.15	46.424 ± 0.0028	−0.096
298.35	11.494 ± 0.0022	0.180	318.25	24.842 ± 0.0025	−0.208			
				Benzene				
283.10	0.7884 ± 0.0024	−0.1233	303.25	2.4537 ± 0.0029	−0.0487	322.85	7.2153 ± 0.0035	−1.676
288.15	1.2485 ± 0.0039	0.1071	308.23	3.1283 ± 0.0032	−0.1158	328.35	9.9350 ± 0.0031	0.2809
293.10	1.6052 ± 0.0030	0.0751	313.15	4.0896 ± 0.0031	−2.003	333.15	13.028 ± 0.0036	0.108
297.90	1.9537 ± 0.0033	0.0320	318.15	5.4662 ± 0.0028	−1.113			

solubility calculated from eq 2; and $x_{1,i}$ is the experimental value of solubility.

Conclusions

From Table 1, it can be seen that tetrahydrofuran is a better solvent than other solvents for phenacetinum. The solubility of the title compound depends on the polarity of the solvents to some degree. The solubility in strongly polar tetrahydrofuran is obviously higher than in weakly polar solvents. In fact, a carbonyl and an amido are in the molecule of phenacetinum, which bring it some polarity. The solubility behavior just reflected the empirical rule that "like dissolves like".

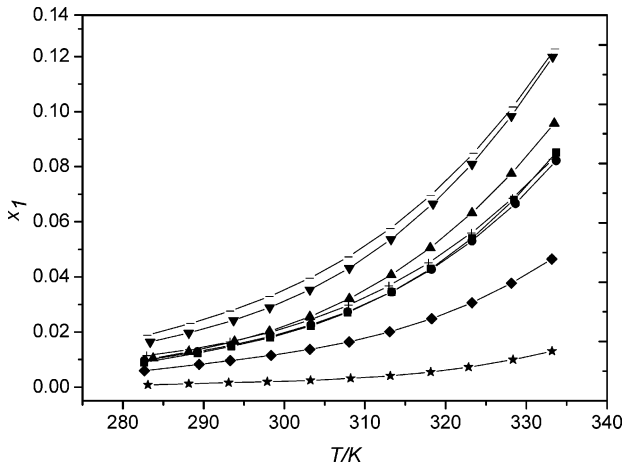

Figure 1. Mole fraction solubility x_1 of phenacetinum in different solvents: ●, methanol; ▲, ethanol; ■, 1-propanol; ▼, 1-butanol; ◆, ethyl acetate; ★, benzene; +, 1-pentanol; −, tetrahydrofuran.

Table 2. Parameters of Equation 5 for Phenacetinum in Different Pure Solvents

solvent	a	b	c	10^4rmsd
methanol	−100.528	810.8610	16.484	4.438
ethanol	−192.953	5272.242	30.060	1.841
1-propanol	−180.920	4567.938	28.358	2.320
1-butanol	−193.722	5462.699	30.164	5.252
1-pentanol	−214.371	6398.446	33.172	6.561
tetrahydrofuran	−153.333	3871.533	24.034	2.022
ethyl acetate	−178.853	4773.699	27.794	3.318
benzene	−266.820	7626.045	41.243	1.415

From Table 1, Table 2, and Figure 1, we can elicit the following conclusions: (1) For all selected pure solvent systems, solubility is a function of temperature, and it increases with temperature. (2) The solubility of phenacetinum in these eight organic solvents decreases in the order tetrahydrofuran > 1-butanol > methanol > 1-pentanol > 1-propanol > ethanol > ethyl acetate > benzene. (3) Results were regressed by eq 2 for each solvent. The experimental solubility and correlation equation in this work can be used as essential data and models in the purification process of phenacetinum.

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