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SOLUBILITY OF 1-ADAMANTANAMINE HYDROCHLORIDE IN SIX PURE SOLVENTS BETWEEN 283.15 K AND 333.15 K

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Abstract - The solubility of 1-adamantanamine hydrochloride (1-AH) in ethanol, acetic acid, distilled water, *N*-methylpyrrolidone (NMP), *N,N*-dimethylformamide (DMF) and dimethylacetamide (DMAC) between 283.15 K and 333.15 K was measured using a laser monitoring observation technique. Results of these measurements were correlated with the NRTL equation and a semi-empirical equation. For six solvents studied, the data are well fitted with the two equations, which can be used as a useful model in the production process of 1-AH.
Keywords: Solubility; 1-Adamantanamine hydrochloride; Modified Apelblat equation.

INTRODUCTION

1-Adamantanamine hydrochloride (abbreviated 1-AH CAS Registry No. 665-66-7, structural formula listed as Figure 1) (Schild and Sutton, 1965; Oxford and Schild, 1965), is a synthetic organic compound clinically used as an antiparkinsonism agent, as well as an antiviral drug (Davies *et al*., 1964; Van Voris *et al*., 1981; Bryson, 1982; Paci *et al*., 2001). Since 1-AH is highly soluble, relatively non-toxic and biologically stable (Schild and Sutton, 1965) it merited further extensive investigation.

As we know, the solubility of a drug is not only essential information in the drug discovery process, but also an important property in the recrystallization stage of solid drugs (Shayanfar *et al*., 2008; Nti-Gyabaah *et al*., 2008).

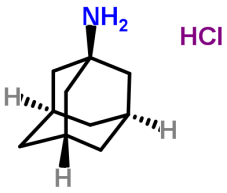

Figure 1: Structure of 1-Adamantanamine hydrochloride.

Crystallization processes are key steps that determine the quality of the final product. Crystal habit plays an important role in affecting the crystal product physicochemical properties, such as solubility, dissolution rate, compressibility, and bulk density, that have an effect on the product biological activity and production cost. The solubility of solid com-

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pounds in different solvents played a crucial role in the determination of proper solvents and the development and operation of the crystallization process (Wu *et al*., 2010; Pankaj and Murthy, 2010).

Therefore, the solubility of 1-AH in different solvents directly affects the size of crystal formation, crystal habit, yield, and cost of production. Hence, it is necessary to know the solubility of 1-AH in pure and mixed solvents. However, it was found that there were few reported experimental solubility data of 1-AH.

In recent research, the dynamic method is used as a common approach in solubility measurement (Liu *et al*., 2011), which incorporates laser techniques to monitor the dissolution process of the solid solute. Given the overwhelming advantages of the dynamic method (Jouyban-Guaramaleki *et al*., 2014; Qiao *et al*., 2014), it is also used in this research to measure the solubility of 1-AH in six pure organic solvents, including ethanol, acetic acid, distilled water, NMP, DMF and DMAC between 283.15 K and 333.15 K at atmospheric pressure. In addition, the experimental solubility results in pure solvents were correlated with the modified Apelblat equation and the NRTL equation, which proved good agreement with experimental data.

EXPERIMENTAL SECTION

Materials

ADA-NH_3Cl used during the solubility measurements had a mass purity of 0.998 and was purchased from China Langchem Inc. Its mass fraction purity was determined by HPLC and was purified through crystallization twice in distilled water before utilization. The X-ray diffraction (XRD) spectra of samples are shown in Figure 2. Other reagents were analytical research grade reagents from Shanghai Chemical Reagent Co.

The solubility of 1-AH was determined by a laser monitoring dynamic method. The experimental instrument and procedure were similar to those described in the previous literature[14-18]. A predetermined excess mass of solvent (about 30 g) and a known mass of solute were added to a jacketed glass vessel (about 200 mL) with the laser light adjusted accordingly. The solution in the vessel was maintained at a constant temperature by water circulating through the outer jacket from a thermostatic water bath (type MPG-10C, China). The temperature of the solution was determined by a mercury glass thermometer with an uncertainty of ± 0.05 K. The process of dissolution was facilitated by continuously stirring at a desired temperature. At the beginning of the experiment, the intensity of the laser beam dropped due to a large number of undissolved 1-AH particles suspended in the solution. As the solid particles dissolved, the intensity of the laser beam increased. When the solid particles dissolved completely, the laser beam intensity reached a maximum level, and the solution in the vessel was clear. Then additional solid solute of known mass (about 1 mg to 3 mg) was added to the solution in the vessel.

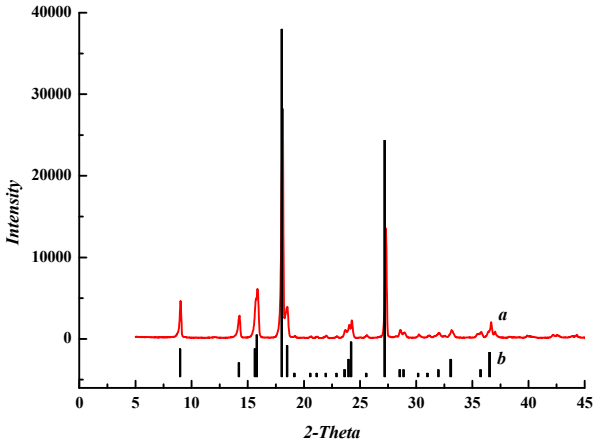

Figure 2: XRD pattern of 1-Adamantanamine hydrochloride: *a*, samples; *b*, standard XRD pattern.

Apparatus and Procedure.

This process was repeated several times until the maximum intensity of the laser beam started to decline after the last addition of solute. The time interval depended on the dissolution speed of 1-AH, usually more than 60 min. When the intensity of the laser beam could no longer reach 90% of the maximum, the mixture was considered to be in phase equilibrium. The total amount of the solute added to the vessel was recorded. Then the undissolved solute was separated and identified to be 1-AH by X-ray diffraction (XRD). Through all of the experiments in this work, polymorphic transformation was not found.

The weight of all the chemicals was measured by an electronic analytical balance (Sartorius CP124S, Germany) with the precision of ± 0.0001 g. In order to ensure the accuracy of the experimental data, all of the above processes were repeated more than three times, and the average value was taken as the final experimental value. The standard uncertainty of the measured solubility values was estimated to be less than 2%. The uncertainty in the solubility values can be due to uncertainties in the weighing procedure, temperature measurements, excess addition of solute, and instabilities of the water bath.

THERMODYNAMIC MODELS

Modified Apelblat Equation

The Apelblat equation is the commonly used (Hefter and Tomkins, 2003; Wang *et al*., 2005; Li *et al*., 2010; Apelblat and Manzurola, 1997; Kondepudi and Prigogine, 2002) semi-empirical expression which is used to correlate experimental solubilities with calculated ones and to evaluate the influence of temperature on the mole fraction solubility of the solute.

According to the solid-liquid phase equilibrium theory, the relationship between solubility and temperature is generally modeled by (Apelblat and Manzurola, 1997):

$$\ln x_1 = -\frac{\Delta H_{f,1}}{RT_{f,1}}\left(\frac{T_{f,1}}{T}-1\right)-\frac{\Delta C_{pf,1}}{R}\left(\frac{T_{f,1}}{T}-1\right) + \frac{\Delta C_{pf,1}}{R}\ln\frac{T_{f,1}}{T}-\ln\gamma_1 \tag{1}$$

where $x_1, \gamma_1, \Delta H_{f,1}, \Delta C_{pf,1}, T_{f,1}, R$ and T stand for the mole fraction of the solute, activity coefficient, enthalpy of fusion, difference in the solute heat capacity between the solid and liquid at the melting temperature, melting temperature of the solute, gas constant, and equilibrium temperature in the saturated solution, respectively. The values of ΔH_f, ΔC_{pf}, T_f were estimated by ASPEN PLUS software version 8.4 (ΔH_f =-1.3673×10^8 J/kmol, ΔC_{pf}=23.0446 kJ/(kmol·K), T_f = 300 ℃).

Equation (2) can be written as

$$\ln x_1 = A + \frac{B}{T} + C\ln T \tag{2}$$

where x_1 is the mole fraction solubility of 1-AH, T stands for the absolute temperature (K), A、B and C are the dimensionless parameters.

NRTL Model

In the binary system, the activity coefficient can be calculated by the following formula (Domanska and Marciniak, 2003):

$$\ln\gamma_1 = x_2^2\left[\frac{\tau_{21}G_{21}^{\ 2}}{\left(x_1+G_{21}x_2\right)^2}+\frac{\tau_{12}G_{12}^{\ 2}}{\left(x_2+G_{12}x_1\right)^2}\right] \tag{3}$$

where,

$$G_{12}=\exp(-\alpha_{12}\tau_{12}) \qquad G_{21}=\exp(-\alpha_{21}\tau_{21}) \tag{4}$$

$$\tau_{12}=\frac{g_{12}-g_{22}}{RT} \qquad \tau_{21}=\frac{g_{21}-g_{11}}{RT} \tag{5}$$

where $\Delta g_{12}\ (=g_{12}-g_{22})$ and $\Delta g_{21}\ (=g_{21}-g_{11})$ are cross interaction energy parameters, independent of temperature and composition. In addition, α_{12} is a constant that reflects the non-randomness of the mixture and its value generally varies between 0.20 and 0.47 (Wei and Pei, 2008). Different values of α_{12} were chosen to correlate the solubility data of 1-AH. It turns out that α_{12} = 0.30 is the most suitable value because of the smallest relative deviation for the measurement system.

RESULTS AND DISCUSSION

The mean values were used to calculate the mole fraction solubility x_1 based on

$$x_1=\frac{m_1/M_1}{m_1/M_1+m_2/M_2} \tag{6}$$

where m_1 and m_2 are the mass of the solute and solvent respectively, M_1 and M_2 the molecular weight of the solute and solvent respectively. The solubility data of 1-AH in distilled water, acetic acid, ethanol, DMF, NMP and DMAC between 283.15 K and 333.15 K are listed in Table 1.

To evaluate the correlation results and select the most suitable model for 1-AH solubility in pure solvents, the relative deviation (*RD* %) and the average relative deviation (*ARD* %) were calculated. The relative deviation and the average relative deviation are defined as

$$RD\% = \frac{x_{1,i}^{\exp}-x_{1,i}^{cal}}{x_{1,i}^{\exp}} \tag{7}$$

$$ARD\% = \frac{100}{N}\sum_{i=1}^{N}\left|\frac{x_{1,i}^{\exp}-x_{1,i}^{cal}}{x_{1,i}^{\exp}}\right| \tag{8}$$

The parameters of the mentioned equations and the root mean square deviations (*RMSD*) are listed in Table 2. The *RMSD* is defined as (Douglas, 1997):

$$RMSD=\left[\frac{\sum_{i=1}^{N}\left(x_{1,i}^{\exp}-x_{1,i}^{cal}\right)^2}{N-1}\right]^{1/2} \tag{9}$$

Table 1: Mole fraction solubility (x_1) of 1-adamantanamine hydrochloride in selected solvents with the temperature range from 278.15 to 333.15 K and pressure p = 0.1 MPa[a].

T (K)	$100x_1^{exp}$	$100x_1^{calc}$		T (K)	$100x_1^{exp}$	$100x_1^{calc}$	
		Apelblat	*NRTL*			Apelblat	*NRTL*
DMAC							
278.35	1.863	1.873	1.815	307.95	2.700	2.730	2.678
282.75	2.007	2.029	2.033	313.15	2.803	2.818	2.805
288.05	2.213	2.207	2.292	318.15	2.857	2.881	2.888
292.45	2.405	2.345	2.406	322.85	2.898	2.922	2.934
298.65	2.536	2.519	2.499	328.95	2.961	2.949	2.985
302.65	2.620	2.618	2.575	333.15	2.979	2.950	2.932
DMF							
278.35	1.414	1.436	1.430	307.95	1.829	1.835	1.859
282.75	1.503	1.502	1.501	313.15	1.873	1.892	1.887
288.25	1.602	1.582	1.577	318.15	1.905	1.943	1.859
292.45	1.662	1.641	1.641	322.85	1.975	1.986	1.973
298.65	1.731	1.723	1.737	328.95	2.047	2.037	2.050
302.65	1.784	1.773	1.806	333.15	2.094	2.068	2.099
NMP							
283.45	1.849	1.854	1.928	312.85	4.178	4.118	4.250
288.15	2.226	2.225	2.310	318.15	4.399	4.403	4.467
293.25	2.643	2.644	2.728	323.15	4.525	4.606	4.590
298.45	3.075	3.073	3.158	328.15	4.690	4.738	4.752
303.25	3.467	3.453	3.546	333.35	4.874	4.800	4.932
308.25	3.809	3.820	3.885				
Acetic acid							
293.35	1.132	1.125	1.138	318.15	2.999	2.943	3.003
298.05	1.377	1.353	1.386	323.25	3.601	3.573	3.596
303.35	1.606	1.664	1.617	328.15	4.339	4.299	4.327
308.15	1.978	2.005	1.990	333.15	5.097	5.184	5.081
313.25	2.456	2.440	2.465				
Water							
278.05	2.660	2.660	2.771	308.15	6.399	6.331	6.414
282.95	3.193	3.193	3.284	313.25	6.928	6.953	6.937
288.45	3.833	3.838	3.902	318.65	7.481	7.572	7.485
293.05	4.356	4.407	4.410	323.35	7.986	8.064	7.987
298.35	5.128	5.082	5.165	328.05	8.485	8.504	8.484
303.35	5.777	5.723	5.801	333.12	9.013	8.914	9.014
Ethanol							
283.55	4.126	4.201	4.040	313.25	6.452	6.461	6.390
287.85	4.651	4.590	4.759	318.15	6.700	6.692	6.661
293.35	5.162	5.069	5.219	323.25	6.884	6.878	6.889
298.05	5.466	5.453	5.478	328.15	7.012	7.004	7.047
303.35	5.822	5.850	5.792	333.15	7.094	7.079	7.126
308.15	6.081	6.169	6.047				

[a] The standard uncertainties u are $u(T)$ = 0.1 K, $u_r(p)$ = 0.05, $u_r(x)$ =0.03

Table 2: Parameters of Equation (2) for 1-adamantanamine hydrochloride in Different Solvents.

Solvent	Apelblat				NRTL		
	A	*B*	*C*	*RMSD* %	Δg_{12} (J·mol^{-1})	Δg_{21} (J·mol^{-1})	*RMSD* %
DMAC	187.88	-9324.5	-28.133	0.027	2725.3	14731.3	0.039
DMF	52.886	-3102.2	-8.1694	0.02	-3524.8	22243.5	0.02
NMP	437.00	-21630	-64.578	0.043	1626.3	11973.3	0.20
acetic acid	-118.93	2139.7	18.859	0.048	-1061.8	3247.6	0.47
water	261.07	-13673	-38.297	0.058	1377.1	7453.6	1.61
ethanol	217.28	-10890	-32.235	0.05	9692.3	9193.3	0.05

Table 3 lists the ARD % of different correlation models. The average relative deviations of the two models are 0.86% (Apelblat) and 1.13% (NRTL). Therefore, the Apelblat model fits well with the experimental solubility data of 1-AH in pure solvents.

Table 3: ARD% of different models in pure solvents.

Solvent	Water	DMF	DMAC	NMP	Acetic acid	Ethanol
Apelblat	0.6750	0.8992	0.7742	0.6316	1.4729	0.7050
NRTL	0.9688	0.9081	1.3524	2.3161	0.4149	0.8532

We can conclude from Figure 3 that: (1) Solubility of 1-AH is the lowest in DMF and the highest in water when the temperature is higher than 310 K; this may be because of the intermolecular interaction between solvent and solute molecules. 1-AH is a salt and most salts can be dissolvent in water, especially in hot water. In addition, the structure of 1-AH is much more complicated and is harder to disperse in organic solvents. Hence, solvents which have complicated structures such as DMF show a lower solubility value than in water. (2) Solubility increases with temperature in all the selected solvents; (3) the solubility curves of 1-AH in NMP and ethanol show almost the same curvature, which may mean that both solubilities have the same sensitivity to temperature though their solubility values are different. The reason for this phenomenon needs to be studied further.

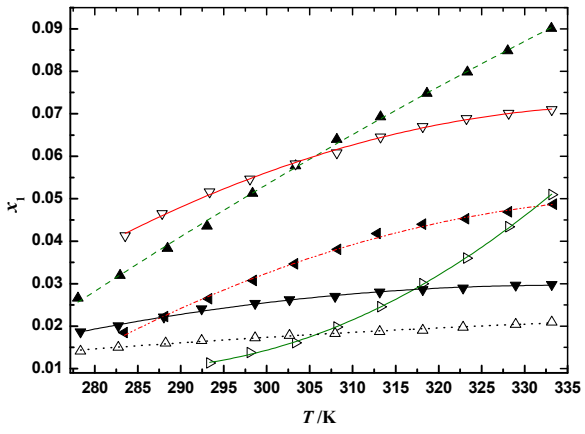

Figure 3: Mole fraction solubility of 1-Adamantanamine hydrochloride (x_1) in different solvents between 278 K and 333 K: ◂, NMP; ▹ acetic acid; ▾, DMAC; ▲, water; ▵, DMF; ▽, ethanol.

The solid line solubility curve was calculated by the modified Apelblat equation.

CONCLUSIONS

The solubility of 1-adamantanamine hydrochloride (1-AH) in ethanol, acetic acid, distilled water, *N*-methylpyrrolidone (NMP), *N,N*-dimethylformamide (DMF) and dimethylacetamide (DMAC) between 283.15 K and 333.15 K were measured using a laser monitoring observation technique. The solubilities in all selected solvents are functions of temperature and increase with the rise of temperature.

The modified Apelblat equation based on solid-liquid phase equilibrium principles and the NRTL equation were used to correlate the solubility data of 1-AH in these solvent systems. The RDs of the modified Apelblat Equation among all of these values does not exceed 1.82%. The average relative deviation of the two models are 0.86% (Apelblat) and 1.13% (NRTL). Therefore, the modified Apelblat equation fits well with the experimental solubility data of 1-AH in pure solvents.

The solubility values calculated by the modified Apelblat equation and NRTL equation show good agreement with experimental values. Both the experimental solubility and correlation equation can be used as essential data in the purification process of 1-AH, as well as good support for further development of solubility models for 1-AH.

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