Solubility of 5-Amino Salicylic Acid in Different Solvents at Various Temperatures

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The solubility data of 5-amino salicylic acid in methanol, ethanol, carbon tetrachloride, and tetrahydrofuran (THF) at various temperatures were measured by gravimetrical method from (293.15 to 313.15) K under atmospheric pressure, and the solubility data were correlated as a function of temperature. The order of solubility is THF > carbon tetrachloride > ethanol > methanol. Further, some thermodynamic parameters such as enthalpy, Gibb's energy, and entropy have also been evaluated for the dissolution process. It is observed that enthalpy and entropy are positive, whereas the Gibb's energy of activation is negative for all of the four solvents. The negative Gibb's energy suggests the spontaneous nature of dissolution process, whereas positive enthalpy indicates endothermic dissolution of compounds. The positive entropy is due to favorable dissolution in the studied solvents.

Introduction

The solubility of a drug is essential information in drug discovery and is important in the preparation of liquid drug formulation stages in the pharmaceutical industry.[1,2] Various methods for the solubilization of drugs including cosolvency, surface active agents, salt information, complexation, hydrotropism, crystal engineering, and preparation of a soluble prodrug have been reported.[3–5]

5-Aminosalicylic acid (5-ASA) is an important intermediate drug for the synthesis of some azodrugs in pharmaceutical industry. It is useful for localized chemotherapy of inflammatory bowl disease[6] and is likely to be absorbed or degraded in the stomach and small intestine before reaching the colon sites.[7] It is useful in ulcerative colitis[8] and anti-inflammatory[9] diseases.

Thus, the study of the solubility of 5-ASA in different solvents will help to select a better solvent.

In the present work, the solubility of this compound was studied in methanol, ethanol, carbon tetrachloride, and tetrahydrofuran (THF) at different temperatures of (293.15 to 313.15 K). Further, enthalpy, Gibb's energy, and entropy of solution have also been evaluated.

Experimental Section

Materials. 5-ASA (CAS Registry No. 89-57-6), with a mass fraction purity of 99.50 %, was purchased from Hiran Orgochem Ltd. (Ankleshwar, India). All of the solvents were analytical grade reagents, which were purified by fractional distillation. Their purities were checked by Shimadzu gas chromatography/mass spectrometry (GC-MS; model no. QP-2010) and were found to be greater than 99.65 %.

The drug was recrystallized, and its melting point was determined by differential scanning calorimetry (DSC). The observed value was found to be 554.15 K, which is in good agreement with the reported value (553.15 K).[10]

Solubility Measurement. The solubilities were measured by a gravimetric method.[11] For each measurement, an excess number of moles of 5-ASA was added to a known mass of solvent. Then, the equilibrium cell was heated to a constant temperature with continuous stirring. After at least 3 h (the temperature of the water bath approached constant value, and then the actual value of the temperature was recorded), the stirring was stopped, and the solution was kept still for 2 h. The uncertainty of temperature was ± 0.01 K. A portion of this solution was filtered, and by a preheated injector, 2 mL of this clear solution was taken in another weighted measuring vial (m_0). The vial was quickly and tightly closed and weighted (m_1) to determine the mass of the sample ($m_1 - m_0$). Then, the vial was covered with a piece of filter paper to prevent dust contamination. After the solvent in the vial had completely evaporated at room temperature, the vial was dried and reweighed (m_2) to determine the mass of the constant residue solid ($m_2 - m_0$). All of the masses were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ± 0.0001 g. Thus, the mole fraction of the solid sample in the solution, x, could be determined from eq 1.

$$x = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad (1)$$

where M_1 is the molar mass of compound and M_2 is the molar mass of the solvent.

At each temperature, the measurement was repeated three times, and an average value is given in Table 1 along with the uncertainty.

Results and Discussion

The mole fraction solubilities x of 5-ASA in methanol, ethanol, carbon tetrachloride, and THF at different temperatures of (293.15 to 313.15) K are summarized in Table 1. It is evident from Table 1 that the solubility is at a minimum in methanol and maximum in THF.

As shown in Figure 1, the mole fraction solubility x of 5-ASA in methanol, ethanol, and carbon tetrachloride was correlated as a function of temperature using the modified Apelblat equation[12,13]

$$\ln x = A + B/(T/\mathrm{K}) \quad (2)$$

where x is the mole fraction solubility of 5-ASA, T is the absolute temperature, and A and B are the parameters. The values

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10.1021/je900646u
Published on Web 01/26/2010

Table 1. Observed Mole Fraction Solubilities (x) and Relative Deviations (RDs) of 5-ASA in Methanol, Ethanol, Carbon Tetrachloride, and THF

T/K	$10^2\,x$	100 RD
	Methanol	
293.15	0.1408 ± 0.002	0.76
295.15	0.1551 ± 0.001	0.51
297.15	0.1705 ± 0.003	0.28
299.15	0.1876 ± 0.009	0.04
301.15	0.2018 ± 0.007	0.15
303.15	0.2154 ± 0.006	0.39
305.15	0.2401 ± 0.001	−0.07
307.15	0.2642 ± 0.001	−0.34
309.15	0.2837 ± 0.004	−0.20
311.15	0.3021 ± 0.008	0.08
313.15	0.3162 ± 0.004	0.68
	Ethanol	
293.15	0.1765 ± 0.005	0.57
295.15	0.1931 ± 0.005	0.14
297.15	0.2117 ± 0.009	−0.33
299.15	0.2254 ± 0.001	−0.33
301.15	0.2334 ± 0.003	0.11
303.15	0.2491 ± 0.007	0.07
305.15	0.2738 ± 0.002	−0.46
307.15	0.2946 ± 0.002	−0.65
309.15	0.3087 ± 0.002	−0.38
311.15	0.3227 ± 0.007	−0.06
313.15	0.3454 ± 0.001	−0.16
	Carbon Tetrachloride	
293.15	0.2902 ± 0.004	−0.11
295.15	0.3027 ± 0.009	−0.43
297.15	0.3098 ± 0.002	−0.42
299.15	0.3116 ± 0.010	−0.12
301.15	0.3159 ± 0.004	0.05
303.15	0.3187 ± 0.006	0.30
305.15	0.3313 ± 0.004	0.04
307.15	0.3446 ± 0.009	−0.23
309.15	0.3619 ± 0.008	−0.68
311.15	0.3705 ± 0.008	−0.68
313.15	0.3827 ± 0.002	−0.84
	THF	
293.15	81.5521 ± 0.110	−2.57
295.15	81.9627 ± 0.824	−2.74
297.15	82.3619 ± 0.521	−2.85
299.15	82.7622 ± 0.630	−2.96
301.15	83.1734 ± 0.511	−3.11
303.15	83.5734 ± 0.410	−3.21
305.15	83.9720 ± 0.100	−3.30
307.15	84.3804 ± 0.315	−3.45
309.15	84.7909 ± 0.233	−3.59
311.15	85.2012 ± 0.508	−3.73
313.15	85.6024 ± 0.714	−3.80

Table 2. Constants A and B of Equation 2, Relative Average Deviations (ARDs), and Root-Mean-Square Deviations (rmsd's) of 5-ASA in Methanol, Ethanol, Carbon Tetrachloride, and THF

solvent	A	B	C	10^6 rmsd	100 ARD
methanol	−18.053	0.0399		0.1036	2.80
ethanol	−15.354	0.0313		0.0613	1.95
carbon tetrachloride	−9.3301	0.0118		0.2812	−0.14
THF	−0.9140	0.0024	−0.1237	17.9244	−3.86

of these parameters are given in Table 2. For THF, mole fraction solubility increases nonlinearly with temperature, so the following Apelblat equation[12] is used:

$$\ln x = A + B/(T/\mathrm{K}) + C\ln(T/\mathrm{K}) \tag{3}$$

where A, B, and C are the parameters and are reported in Table 2. Figure 2 shows the variation of the mole fraction solubility x of 5-ASA in THF.

Further, relative average deviations (ARDs) and root-mean-square deviations (rmsd's), calculated by eqs 4 and 5, are listed in Table 2.

$$\mathrm{ARD} = \frac{1}{N}\sum_{i}^{N}\frac{x - x_c}{x} \tag{4}$$

$$\mathrm{rmsd} = \left[\sum_{i=1}^{N}\frac{(x_c - x)^2}{N-1}\right]^{1/2} \tag{5}$$

where N is the number of experimental points and x_{ci} is the solubility calculated by eq 2.

The relative deviations (RDs) between the experimental and the calculated values of the solubilities are also calculated by eq 6 and are given in Table 1.

$$\mathrm{RD} = \left(\frac{x - x_c}{x}\right) \tag{6}$$

The enthalpy of solution ($\Delta_{sol}H$) was calculated by modified van't Hoff equation[14,15]

$$\frac{\partial \ln x}{\partial\left(\frac{1}{T} - \frac{1}{T_{hm}}\right)^P} = -\frac{\Delta_{sol}H}{R} \tag{7}$$

where T is the experimental temperature and R is the gas constant. T_{hm} is the mean harmonic temperature which is given as

$$T_{hm} = \frac{n}{\sum_{i}^{n}(1/T)} \tag{8}$$

where n is the number of experimental temperatures.[13] In the present case, the T_{hm} value obtained is only 303 K. The slope of the plot of ln x versus ($1/T - 1/303$) gives the value of $\Delta_{sol}H$.

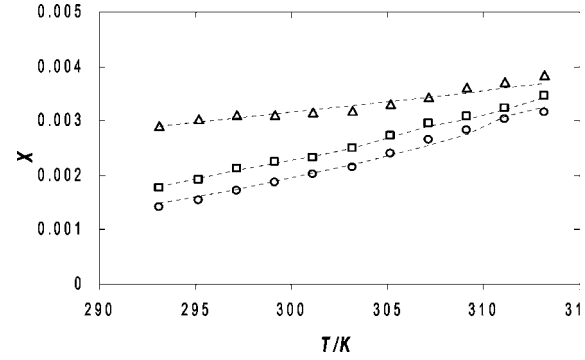

Figure 1. Variation of mole fraction solubilities (x) with temperature (T) for 5-ASA in methanol, ethanol, and carbon tetrachloride. ○, methanol; □, ethanol; △, carbon tetrachloride. Dotted line shows the calculated solubility data.

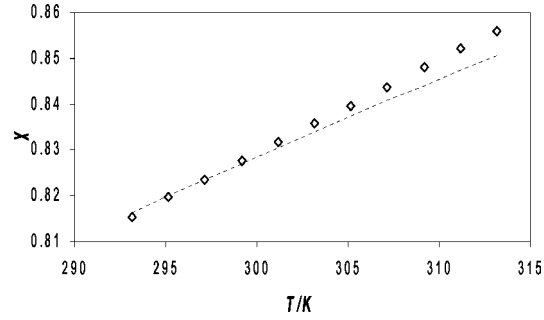

Figure 2. Variation of mole fraction solubilities (x) with temperature (T) for 5-ASA in ◇, THF. Dotted line shows the calculated solubility data.

Table 3. Thermodynamic Parameters, Gibb's Energy ($\Delta_{sol}G$), Enthalpy ($\Delta_{sol}H$), and Entropy ($\Delta_{sol}S$), of Dissolution of 5-ASA in Methanol, Ethanol, Carbon Tetrachloride, and THF

	ΔG	ΔH	ΔS
solvent	kJ·mol^{-1}	kJ·mol^{-1}	J·mol^{-1}·K^{-1}
methanol	−5.9	69.2	0.2
ethanol	−6.6	63.5	0.2
carbon tetrachloride	−8.4	33.6	0.1
THF	−2138.5	1545.1	11.8

The Gibbs energy change for the solubility process was then evaluated from the slope of above plot using the following relation[14]

$$\Delta_{sol}G = -RT\,\text{intercept} \quad (9)$$

Using these evaluated $\Delta_{sol}H$ and $\Delta_{sol}G$ values, the entropy of solution $\Delta_{sol}S$ was obtained from the equation[17]

$$\Delta_{sol}S = \frac{\Delta_{sol}H - \Delta_{sol}G}{T_{hm}} \quad (10)$$

All of these thermodynamic parameters are given in Table 3.

It is evident from Table 3 that, for all of the studied solvents, $\Delta_{sol}H$ and $\Delta_{sol}S$ values are positive, whereas $\Delta_{sol}G$ values are negative. When stronger bonds are broken and weaker bonds are formed, energy is consumed. So, $\Delta_{sol}H$ becomes positive.[16] This indicates endothermic dissolution of the compounds. The positive $\Delta_{sol}S$ values suggest that the dissolution process is entropically favorable.[17] This is further confirmed by negative $\Delta_{sol}G$ which suggests the spontaneous nature of the dissolution process. For THF, both $\Delta_{sol}H$ and $\Delta_{sol}S$ values are highly positive, whereas $\Delta_{sol}G$ value is highly negative.

Conclusions

The solubility of 5-ASA in the four solvents (methanol, ethanol, carbon tetrachloride, and THF) increased with an increase in temperature. The maximum solubility of 5-ASA is found to be in THF. The solubility data calculated by the modified Apelblat equation are in good agreement with the experimental values. The negative $\Delta_{sol}G$ suggests the spontaneous nature of the dissolution process, whereas positive $\Delta_{sol}H$ values indicate endothermic dissolution of the compounds in all of the studied solvents.

Acknowledgment

Authors are thankful to Head of Department of Chemistry, Saurashtra University, Rajkot, India, for providing necessary facilities.

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Received for review July 29, 2009. Accepted January 4, 2010.

JE900646U