Solubility Behavior and Thermodynamic Modelling of Inosine (Form β) in Four Cosolvency Systems at T = (278.15 to 323.15) K

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ABSTRACT: The *N,N*-dimethylformamide (DMF) as the main solvent with strong dissolving power was blended with four secondary solvents (ethanol, n-propanol, isopropanol, propylene glycol (PG)) with relatively weak dissolving power to form many new solvents. The dispersion index (Inosine (form β) mole fraction) in five organic solvents such as DMF and in the newly formed solvent was also obtained one by one with static method commonly used in solid-liquid equilibrium. The temperature environment is that the high temperature was set at 323.15 K, and the low temperature was set at 278.15 K and the interval between each temperature was 5 K. The pressure environment was the atmospheric pressure in the natural state and the usual value was 101.0 kPa. In a mixed system, temperature was a non-negligible influencing factor from beginning to end and its increase often leaded the solute to the trend of high solubility. In addition, the proportion of the main solvent also dominated the solubilization trend of the inosine (form β), the larger the proportion of DMF, the easier the dissolution process was. When both of the above factors were fixed at a certain point, the dispersing ability of the dispersing liquid composed of DMF and ethanol was undoubtedly the first. Three models (the Jouyban-Acree model, van't Hoff-Jouyban-Acree model and Modified Apelblat-Jouyban-Acree model) were used to correlate the solubility data. The largest *RAD* and *RMSD* were 4.66×10^{-2} and 7.27×10^{-4}. The dispersion data of inosine (form β) obtained through this experimental process and related thermodynamic parameters obtained through thermodynamic calculations have important application significance for its industrial production and further purification.

■ INTRODUCTION

From the history of the development of chemicals, there are many methods for the purification of drugs, such as membrane separation, supercritical fluid technology and so on, but the dissolution crystallization technology is undoubtedly the most efficient and cheapest one and the most widely used one.[1–5] Especially for poorly water-soluble chemicals, how to increase the solubility is a

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priority problem, because lack of good solubility will affect the development and design of its liquid

dosage form, bioavailability, and synthesis of downstream products.[6–10] There are many ways to

increase the solute dissolution, such as adding a cosolvent, grinding the solute particles, sonicating,

adjusting the pH of the solution, adding a surfactant and so on.[11–16] Among the various methods

mentioned above, the method of adding a non-toxic co-solvent to the solvent is currently widely

used in industry due to its low cost, convenient operation and good results. In addition to the

above-mentioned advantages, the in-depth study of the dissolution behavior of drugs in a new

solvent formed by mixing two solvents provides a solid theoretical basis for the interaction between

solvents and solutes.[13,17]

Inosine ($C_{10}H_{12}N_4O_5$, CAS No. 58-63-9, molecular weight 268.23 g·mol^{-1}, IUPAC name

9-((2~(R),3~(R),4~(S),5~(R))-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl)-3~(H)-purin-6-one,

molecular structure shown in Figure 1 of supporting information) is known as hypoxanthin or

hypoxanthine nucleoside that is a nucleoside deriving from a purine derivative antimetabolite,

containing both a polar furan ring and an apolar aromatic group.[18–24] As we know, nucleoside

derivatives have been extensively investigated due to their potential activity as antibiotics, enzyme

inhibitors, anticancer, antiviral agents and ATP generation.[25–28] It is an important component of

ribonucleic acids, with the hydrophilic–hydrophobic balance of the molecule contributing to their

conformational stability which has great impact role on a large number of various chemical and

biological reactions and other areas.[18,19,21]

Up to date, two anhydrous polymorphic crystal forms (the orthorhombic α form[29] and the

monoclinic β form[18]) and a dehydrate[30] of inosine have been reported in previous literature. Noting

that the dihydrate form of inosine is easily crushed to facilitate the extract preparations than other

polymorphs due to high solubility and dissolution rate in practical usage.[18] In view of the fact that

solid oral preparations may affect the drug solubility due to their different crystalline forms, thereby

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affecting the bioavailability and clinical efficacy of drugs. On the other hand, the β form shows the least soluble ability at room temperature leading to be the most stable thermodynamic product among the above. Suzuki[31,32] and Tewari et al.[19] reported aqua- and aqua-DMSO system solubility of inosine (the polymorphism) at different pH values. As well, some aqueous solubility is also seen in the ref (33). Hence, there is little studies on the solubility and thermodynamic cosolvency conditions of the β form inosine.

According to the survey, inosine is a slightly water soluble drug (0.001059 mole fraction, 283.15 K) with high permeability.[33] Whatever areas the inosine is applied in, the purity of inosine must be rather high in demand, in the meanwhile, to achieve the high-purity, stable and uniform particle size inosine product, it is necessary to select the best solvent or solvent mixtures to separate and purify. The solubility of some drugs strongly depends on the physiochemical properties of the drugs and composition of solvent medium.[3] In terms of the cosolvency method, non-aqueous solvent mixtures are commonly used in drug's crystallization or re-crystallization from synthetic reaction solutions.[17,34] There are also many requirements on how to choose a suitable solvent in the industry. First, the solvent to be selected must be non-toxic. Secondly, it must be chemically stable and cannot react chemically with the solute during the dissolution process. [13,17,35,36] It can be firmly believed that scientific and accurate dispersion of inosine in various solvents will definitely help it in industrial synthesis and will also help its clinical application.

■ THEORETICAL COSOLVENCY MODELS

The models used in this research process are scientifically reliable and have been verified by previous researchers.[13,17]

Jouyban-Acree Model. The Jouyban-Acree model is described as Eq. (1) Quantitatively measure the objective effects of temperature and the proportion of main solvent on the dispersion of solutes.[13,17,37]

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$$\ln x_{w,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + \frac{w_1 w_2}{T/K} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \qquad (1)$$

where $x_{w,T}$ is solubility of inosine at temperature T; w_1 and w_2 are proportion of primary solvent and secondary solvent; $x_{1,T}$ and $x_{2,T}$ inosine solubility in pure solvents; and J_i are model parameters.

Van't Hoff-Jouyban-Acree Model. The Van't Hoff equation is described as Eq. (2). The equation parameters are few and seem simple, but their role is significant in the field of thermodynamics.

$$\ln x_T = A + \frac{B}{T/K} \qquad (2)$$

Combining Eq. (1) and Eq. (2) to achieve the van't Hoff-Jouyban-Acree model (Eq. (3)).[13,17,38]

$$\ln x_{w,T} = w_1 (A_1 + \frac{B_1}{T/K}) + w_2 (A_2 + \frac{B_2}{T/K}) + \frac{w_1 w_2}{T/K} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \qquad (3)$$

A_1, B_1, A_2, B_2 and J_i are equation parameters.

Modified Apelblat-Jouyban-Acree Model. The expression of the modified Apelblat equation is described as[39,40]

$$\ln x_T = A + \frac{B}{T/K} + C \ln(T/K) \qquad (4)$$

Where A, B, and C are equation parameters; and also x_T is solubility of inosine at temperature T.

By substituting Eq. (4) into Eq. (1), the modified Apelblat-Jouyban-Acree model is obtained[13,17,39]

$$\ln x_{w,T} = w_1 [A_1 + \frac{B_1}{T/K} + C_1 \ln(T/K)] + w_2 [(A_2 + \frac{B_2}{T/K} + C_2 \ln(T/K)] + \frac{w_1 w_2}{T/K} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \qquad (5)$$

As usual, the specific value of the dispersion of inosine was calculated using a non-linear regression method. The basic basis of the non-linear regression method is the least square method, and its functional expression can be described as

$$F = \sum_{i=1}^{} \left(\ln x_i^e - \ln x_i^c \right)^2 \qquad (6)$$

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In addition, in order to scientifically compare experimental values with calculated values, the

relative average deviation (*RAD*) and root-mean-square deviation (*RMSD*) are introduced. They are

described as Eqs. (7) and (8).

$$RAD = \frac{1}{N} \sum \left(\frac{\left| x_{w,T}^{c} - x_{w,T}^{e} \right|}{x_{w,T}^{e}} \right) \qquad (7)$$

$$RMSD = \sqrt{\frac{\sum_{i=1}^{N} (x_{w,T}^{c} - x_{w,T}^{e})^{2}}{N}} \qquad (8)$$

where N is the number of experimental data points. $x_{w,T}^{e}$ is solubility determined in this work; and

$x_{w,T}^{c}$ is solubility calculated with the corresponding solubility model.

■ EXPERIMENTAL SECTION

Drug, Reagents and Apparatus. Synthesis of Inosine (form β, 0.98 mass fraction) and

transportation to the laboratory were completed by Meryer (Shanghai) Chemical Technology Co.,

Ltd. The crude drug purchased is dissolved in acetone and a higher purity drug is precipitated by

cooling the hot saturated solution until its mass fraction reached 0.996 confirmed by a

high-performance liquid phase chromatograph (HPLC, Shimadzu-6A). The brands of solvents such

as DMF, ethanol and so on used in the experiment are Aladdin. The minimum purity of the solvent

used is 0.994 determined by gas chromatography (GC, FULI 9790, China). More detailed

information of the above chemicals is shown in Table 1.

The tools and instrumentation facilities involved in carrying out this scientific experiment are

simplified by simple drawing software and shown in Figure 2 of Supporting Information, there is no

doubt that the instrumentation equipment works and operates in exactly the same way as in previous

work. [41] In this experiment, first of all, make a glass container (100 mL) with double glass to ensure

that the interlayer of the container can pass the liquid. The original intention of choosing this design

was to enable constant temperature operation while using the magnetic stirrer. Of course, the next

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step is to prepare a suitable circulating liquid, which is usually a mixture of isopropanol and water. In order to ensure that the inosine (form β) dissolution process is performed in a constant temperature environment, the coordination of the circulating fluid and thermostatic bath (QYHX-1030, standard uncertainty: 0.05 K, Shanghai Joyn Electronic Co., Ltd., China) is the key. The detection of the system temperature is the key to the success of the experiment. There will inevitably be errors in the equipment during the production adjustment process. The introduction of a mercury glass micro thermometer (standard uncertainty: 0.02 K) can effectively eliminate the errors caused by the instrument measurement. Glass containers are generally open and organic solvents are volatile, choosing a suitable latex plug to seal the container can effectively avoid solvent loss. An analytical balance (model: BSA224S, standard uncertainty: 0.0001 g, Satorius Scientific Instrument (Beijing)) was used to determine the mass of the solute, solvent, and saturated solution.

Preparation of Cosolvency Mixture Systems. The use of gravimetric method throughout the preparation of new mixed solvents by an analytical balance. The amount of solvent added to the glass container is also required. It is generally considered that the amount of solvent added to account for half of the entire volume is most suitable, which is 50 g (standard uncertainty: 0.0001 g). The proportion of the main solvent DMF is added from 0 to 1 and the proportion of each increase is 0.1.

Solubility Measurement. The static method runs through the whole process of the inosine (form β) data measurement experiment,[42-47] and When the solute and the solvent reach a stable state with each other, HPLC is the preferred method of characterization. The double-layer glass container mentioned above is the main vessel that dissolves Inosine (form β) until it reaches saturation. How to saturate the solute is also a non-negligible operation step. There must be a surplus of solute added before the solute system can be considered to be saturated. While adding

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the solute, the full stirring process needs to be completed with the help of a magnetic stirrer. After one hour, 1 mL of the inosine solution was extracted by a heat-treated syringe (2 mL) with a pore syringe filter (PTFE 0.2 μm) in advance, the sample was diluted and other steps were processed, and then it was sent to HPLC for mapping. Repeat the above operation until there are almost no differences in the results obtained three times in a row. It can be considered that the dissolution has reached a dynamic equilibrium. Scientific operations are the basis for obtaining accurate data. In addition, two experimental operations are performed simultaneously to obtain a scientific and reliable saturated solution. A method called forward operation is to gradually add a solute to a solvent until a solid solute remains. The other method is called the reverse method, which is to gradually evaporate the solvent by heating until the solid crystals precipitate. Finally, two sets of control samples were placed in the same environment for one hour at the same time. According to the above sampling operation, transfer the sample to a 25mL volumetric flask, dilute to a constant volume and shake it for instrument analysis.

The solubility of inosine (form β) ($x_{w,T}$) is calculated with Eq. (9), and mass percent of primary and secondary solvents is calculated with Eqs. (10) and (11).

$$x_{w,T} = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \qquad (9)$$

$$w_1 = \frac{m_2}{m_2 + m_3} \qquad (10)$$

$$w_2 = \frac{m_3}{m_2 + m_3} \qquad (11)$$

Here, m_1 is the mass of inosine (form β), m_2 is mass of DMF, and m_3 is the mass of secondary solvents. M_1, M_2 and M_3 molar mass of them.

Analysis Method. The Agilent-1260 HPLC is equipped with a reverse phase column (Model: LB-C18 (250 mm × 4.6 mm)) and its usual operating temperature was set at 303 K. Before setting

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the ultraviolet absorption wavelength of inosine, a UV scanning operation is required. The result obtained is that the maximum absorption wavelength of UV-vis detector is set to 248 nm. The mobile phase was pure methanol with a flow rate of 0.8 ml·min^{-1}. Prepare three samples for each sample before injecting them and then analyze these samples to obtain three data. If the three data are not significantly different, take their average as the final result (relative standard uncertainty: 0.015).

X-ray Powder Diffraction. Exploring the crystal structure of solid medicine inosine (form β), the X-ray Powder Diffraction (XPRD, Bruker AXS D8 Advance) is a more direct and efficient choice. It is equipped with Cu Ka radiation (λ=1.54184 nm) and the tube voltage is 40 kV and current is 30 mA. Set the diffraction angle (2-Theta) with 5° as the starting point and 80° as the end point at a scan speed of 5°·min^{-1} under room temperature and 101.0 kPa.

■ RESULTS AND DISCUSSION

XPRD Results. The inosine (form β) sample without any treatment and the sample spectrum after dissolving out are plotted in Figure 3 of supporting information. Vertically, the positions of characteristic peaks are basically at the same diffraction angle, and the size and shape of the characteristic peaks are basically similar. It can be explained that the crystal form of the drug that has undergone dissolution is basically the same as that of the untreated raw material sample, and there is no change.

Equilibrium Solubility. The mole fraction of inosine (form β) obtained in experiments in various mixed solvents with different proportions of DMF are listed in Tables 2, 3, 4 and 5. The relationship between the measured solubility and temperature and solvent composition are demonstrated graphically in Figures 1-4. That can be also seen from Tables 2-5 that decrease and increase in temperature are decisive for the direction of the dissolution process. Not to mention, as the proportion of DMF changes, the solubility of solvents to solutes varies widely.

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The Mathcad software as a commonly used mathematical calculation software is also used for the calculation of this data. First enter the corresponding formula (Eqs. (1) to (5)) into it, and then enter the experimental value to get the calculated value and related model parameters with *RAD* and *RMSD*, which are listed in Table 6.

■ CONCLUSION

The equilibrium solubility of inosine (form β) was obtained one by one with static method commonly used in solid-liquid equilibrium. The *N,N*-dimethylformamide (DMF) as the main solvent with strong dissolving power was blended with four secondary solvents (ethanol, n-propanol, isopropanol, propylene glycol (PG)) with relatively weak dissolving power to form many new solvents. The temperature environment is that the high temperature was set at 323.15 K, and the low temperature was set at 278.15 K and the interval between each temperature was 5 K. The pressure environment was the atmospheric pressure in the natural state and the usual value was 101.0 kPa. A solvent combination of DMF and ethanol has unparalleled advantages in dissolving inosine (form β). The inosine (form β) solubility was calculated a with three models, the largest *RAD* and *RMSD* were 4.66×10^{-2} and 7.27×10^{-4}. The dispersion data of inosine (form β) obtained through this experimental process and related thermodynamic parameters obtained through thermodynamic calculations have important application significance for its industrial production and further purification.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Supporting Information Available: Chemical structure of inosine (Figure S1), experimental apparatus (Figure S2), XRD patterns (Figure S3).

■ AUTHOR INFORMATION

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Figure 1. Mole fraction solubility (x) of inosine in DMF (w) + ethanol ($1-w$) solutions with various mass fractions at different temperatures: w, mass fraction of DMF; ☆, $w=1$; ▲, $w=0.9009$; ○, $w=0.7985$; ■, $w=0.6998$; ★, $w=0.6012$; ◆, $w=0.4993$; ◇, $w=0.3997$; ▼, $w=0.3013$; △, $w=0.2001$; ●, $w=0.1007$; □, $w=0$; —, calculated curves by the Jouyban−Acree model.

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Figure 2. Mole fraction solubility (x) of inosine in DMF (w) + n-propanol (1-w) solutions with various mass fractions at different temperatures: w, mass fraction of DMF; ☆, w=1; ▲, w=0.9005; ○, w=0.8015; ■, w=0.7021; ★, w=0.6003; ◆, w=0.5000; ◇, w=0.3986; ▼, w=0.2978; △, w=0.2003; ●, w=0.0997; □, w=0; —, calculated curves by the Jouyban−Acree model.

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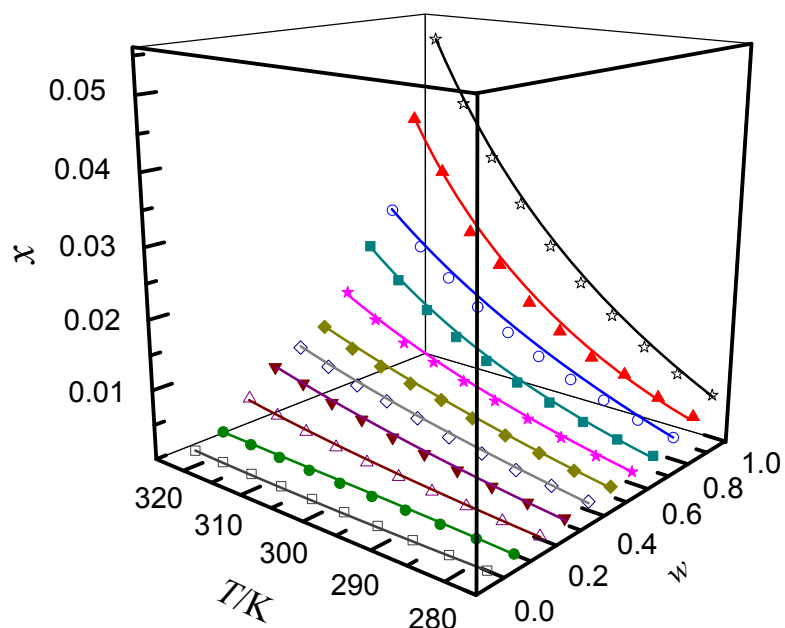
Figure 3. Mole fraction solubility (*x*) of inosine in DMF (*w*) + isopropanol (1-*w*) solutions with various mass

fractions at different temperatures: *w*, mass fraction of DMF; ☆, *w*=1; ▲, *w*=0.9011; ○, *w*=0.7996; ■, *w*=0.7002;

★, *w*=0.5993; ◆, *w*=0.5001; ◇, *w*=0.4011; ▼, *w*=0.3009; ▵, *w*=0.2005; ●, *w*=0.0997; □, *w*=0; —, calculated

curves by the Jouyban−Acree model.
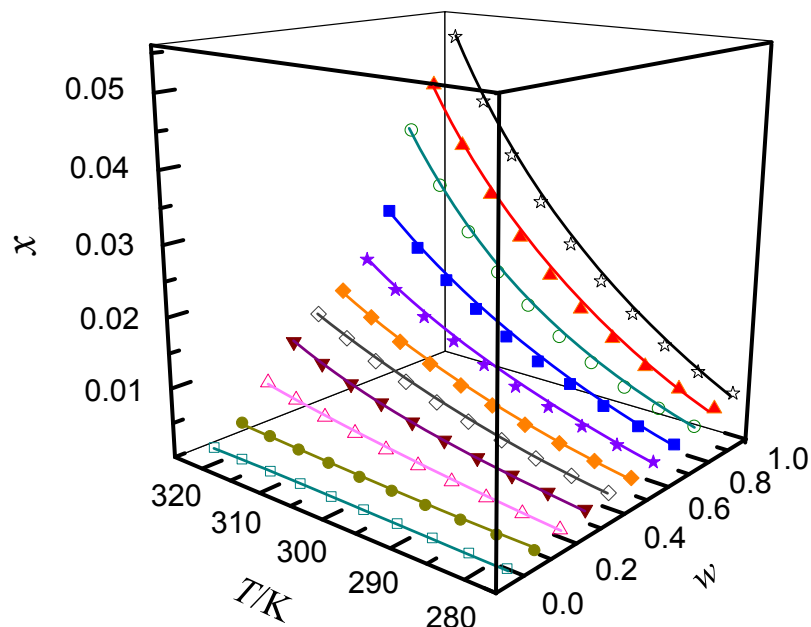
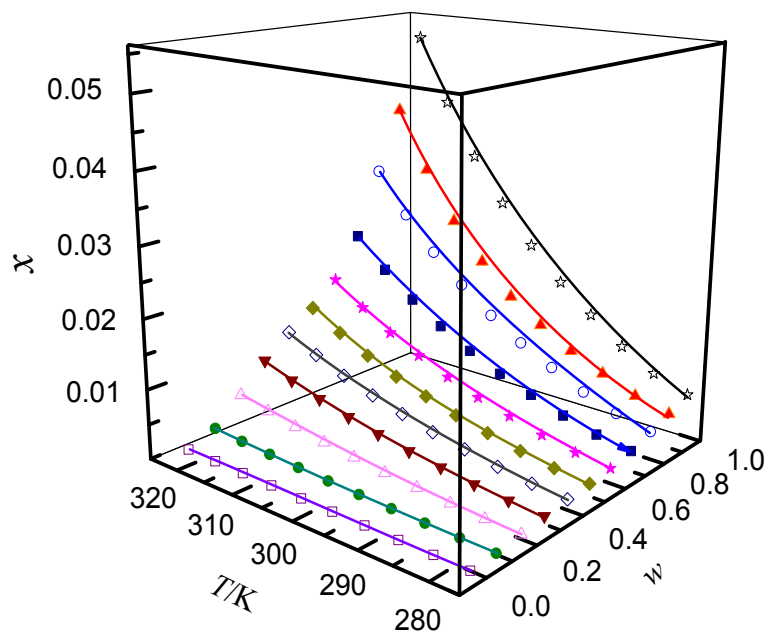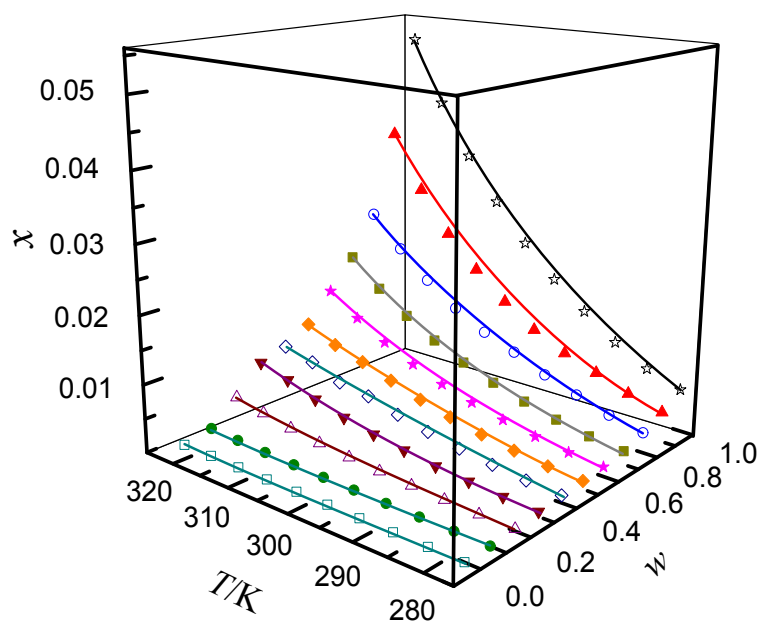**Figure 4.** Mole fraction solubility (*x*) of inosine in DMF (*w*) + PG (1-*w*) solutions with various mass fractions at different temperatures: *w*, mass fraction of DMF; ☆, *w*=1; ▲, *w*=0.9012; ○, *w*=0.8000; ■, *w*=0.7001; ★, *w*=0.5986; ◆, *w*=0.5003; ◇, *w*=0.4015; ▼, *w*=0.2998; △, *w*=0.2003; ●, *w*=0.1000; □, *w*=0; —, calculated curves by the Jouyban−Acree model

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Table 1. Detailed information of all used the drug and reagents.

Materials	CAS No.	Molar mass (g·mol^{-1})	Source	Mass fraction purity	Purification method	Analytical method
Inosine (form β)	58-63-9	268.23	Meryer (Shanghai) Chem. Tech. Co. Ltd.	0.996	Recrystallization	HPLC[a]
Ethanol	64-17-5	46.07		0.998	None	GC[b]
n-Propanol	71-23-8	60.10	Aladdin Reagent Co., Ltd.	0.996	None	GC
Isopropanol	67-63-0	60.10		0.996	None	GC
Propylene glycol	57-55-6	76.09		0.995	None	GC
N,N-Dimethyl formamide	68-12-2	73.10		0.994	None	GC

[a] High-performance liquid chromatography.

[b] Gas chromatography.

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Table 2. Experimental solubility ($x_{T,w}^{e} \times 10^{3}$) of inosine in DMF ($w$) + ethanol (1-$w$) mixture with T = (278.15 to 323.15) K at p = 101.0 kPa.[a]

T/K	w										
	0	0.1007	0.2001	0.3013	0.3997	0.4993	0.6012	0.6998	0.7985	0.9009	1
278.15	0.03160	0.3086	1.007	1.727	2.112	2.359	2.777	3.597	4.575	5.550	6.309
283.15	0.04282	0.4034	1.294	2.209	2.703	3.025	3.566	4.617	5.700	7.000	8.121
288.15	0.05672	0.5191	1.648	2.816	3.468	3.912	4.646	6.048	7.375	9.000	10.85
293.15	0.07401	0.6594	2.075	3.551	4.405	5.013	6.001	7.861	9.650	11.925	14.43
298.15	0.09594	0.8296	2.578	4.402	5.477	6.261	7.525	9.877	12.29	15.21	18.31
303.15	0.1237	1.039	3.188	5.429	6.771	7.772	9.371	12.32	15.86	19.28	23.04
308.15	0.1602	1.306	3.952	6.703	8.367	9.625	11.62	15.28	19.80	24.19	28.67
313.15	0.2000	1.586	4.748	8.036	10.058	11.62	14.08	18.54	25.03	29.90	35.10
318.15	0.2527	1.949	5.761	9.716	12.17	14.09	17.11	22.54	31.33	36.69	42.83
323.15	0.3150	2.368	6.923	11.65	14.63	17.00	20.70	27.32	39.08	45.41	52.32

[a] Standard uncertainties u are $u(T)$ = 0.02 K, $u(p)$ = 0.15 KPa; Relative standard uncertainty u_r is $u_r(x)$ = 0.015. $u_r(w)$ = 0.0002. w represents the mass fraction of DMF.

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Table 3. Experimental solubility ($x_{T,w}^e \times 10^3$) of inosine in DMF (w) + n-propanol (1-w) mixture with $T = (278.15$ to $323.15)$ K at $p = 101.0$ kPa.[a]

T/K	w										
	0	0.0997	0.2003	0.2978	0.3986	0.5000	0.6003	0.7021	0.8015	0.9005	1
278.15	0.02079	0.1839	0.6228	1.125	1.496	1.772	2.146	2.843	4.005	4.988	6.309
283.15	0.02697	0.2317	0.7752	1.398	1.867	2.227	2.713	3.609	5.102	6.188	8.121
288.15	0.03835	0.3186	1.048	1.877	2.504	2.988	3.641	4.838	6.824	8.141	10.85
293.15	0.05388	0.4335	1.403	2.498	3.330	3.978	4.851	6.442	9.070	10.224	14.43
298.15	0.07126	0.5565	1.775	3.147	4.196	5.025	6.140	8.159	11.48	12.93	18.31
303.15	0.09500	0.7195	2.259	3.980	5.301	6.350	7.759	10.30	14.46	16.14	23.04
308.15	0.1233	0.9080	2.812	4.931	6.567	7.882	9.645	12.80	17.96	20.51	28.67
313.15	0.1595	1.141	3.482	6.071	8.075	9.696	11.86	15.73	22.02	25.86	35.10
318.15	0.2045	1.424	4.284	7.429	9.872	11.86	14.52	19.23	26.87	33.05	42.83
323.15	0.2607	1.768	5.252	9.066	12.04	14.49	17.75	23.50	32.80	41.59	52.32

[a] Standard uncertainties u are $u(T) = 0.02$ K, $u(p) = 0.15$ KPa; Relative standard uncertainty u_r is $u_r(x) = 0.015$. $u_r(w) = 0.0002$. w represents the mass fraction of DMF .

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Table 4. Experimental solubility ($x_{T,w}^e \times 10^3$) of inosine in DMF (w) + isopropanol (1-w) mixture T = (278.15 to 323.15) K at p = 101.0 kPa.[a]

T/K	w										
	0	0.0997	0.2005	0.3009	0.4011	0.5001	0.5993	0.7002	0.7996	0.9011	1
278.15	0.005500	0.07522	0.3459	0.7790	1.130	1.380	1.675	2.214	3.195	4.605	6.309
283.15	0.008500	0.1104	0.4911	1.084	1.553	1.879	2.260	2.954	4.212	5.996	8.121
288.15	0.012550	0.1562	0.6784	1.517	2.029	2.742	3.326	3.994	5.670	8.038	10.85
293.15	0.018400	0.2197	0.9325	2.061	2.742	3.691	4.513	5.374	7.361	9.283	14.43
298.15	0.026150	0.2995	1.241	2.705	3.454	4.640	5.699	6.936	9.515	12.04	18.31
303.15	0.03655	0.4022	1.628	3.505	4.695	5.882	7.197	8.861	11.91	15.27	23.04
308.15	0.05135	0.5426	2.143	4.550	5.718	6.904	8.712	11.25	14.66	20.12	28.67
313.15	0.07310	0.7402	2.846	5.510	6.667	8.091	10.37	14.20	18.08	24.27	35.10
318.15	0.1012	0.9852	3.698	7.007	8.091	9.515	12.75	17.73	22.02	32.89	42.83
323.15	0.1387	1.301	4.773	8.089	9.735	11.63	15.87	22.09	26.82	40.43	52.32

[a] Standard uncertainties u are $u(T)$ = 0.02 K, $u(p)$ = 0.15 KPa; Relative standard uncertainty u_r is $u_r(x)$ = 0.015. $u_r(w)$ = 0.0002. w represents the mass fraction of DMF.

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Table 5. Experimental solubility ($x^e_{T,w} \times 10^3$) of inosine in DMF (w) + PG (1-w) mixture with T = (278.15 to 323.15) K at p = 101.0 kPa.[a]

T/K	w										
	0	0.1000	0.2003	0.2998	0.4015	0.5003	0.5986	0.7001	0.8000	0.9012	1
278.15	0.001787	0.04573	0.2809	0.6810	0.9988	1.188	1.422	1.925	2.979	4.403	6.309
283.15	0.002532	0.06149	0.3676	0.881	1.290	1.537	1.843	2.494	4.056	5.718	8.121
288.15	0.004043	0.0926	0.5343	1.257	1.821	2.155	2.565	3.441	5.608	7.507	10.85
293.15	0.006050	0.1315	0.7381	1.714	2.472	2.921	3.473	4.643	7.270	9.169	14.43
298.15	0.009185	0.1887	1.024	2.333	3.327	3.902	4.603	6.093	9.406	11.54	18.31
303.15	0.01321	0.2580	1.360	3.054	4.327	5.057	5.945	7.827	11.23	14.79	23.04
308.15	0.01892	0.3514	1.800	3.981	5.598	6.513	7.622	9.970	13.79	18.77	28.67
313.15	0.02739	0.4830	2.398	5.212	6.251	7.997	9.727	12.60	17.11	23.52	35.10
318.15	0.03876	0.6511	3.141	6.719	8.003	9.364	12.29	15.80	21.15	29.69	42.83
323.15	0.05421	0.8693	4.082	8.008	9.118	11.35	15.47	19.76	25.75	37.85	52.32

[a] Standard uncertainties u are $u(T)$ = 0.02 K, $u(p)$ = 0.15 KPa; Relative standard uncertainty u_r is $u_r(x)$ = 0.015. $u_r(w)$ = 0.0002. w represents the mass fraction of DMF.

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Table 6. Values of parameters obtained from the selected thermodynamic models.

	Jouyban−Acree model		Van't Hoff−Jouyban−Acree model		Modified Apelblat−Jouyban−Acree model	
	parameter	value	parameter	value	parameter	value
	J_0	1875.84	A_1	9.77173	A_1	109.026
	J_1	-2401.51	B_1	-4109.96	B_1	-8641.56
	J_2	2314.39	A_2	6.07107	C_1	-14.7520
			B_2	-4567.14	A_2	18.9671
DMF + Ethanol			J_0	1868.07	B_2	-5157.28
			J_1	-2412.44	C_2	-1.91596
			J_2	2294.89	J_0	1874.88
					J_1	-2403.29
					J_2	2311.98
$RAD·10^2$	2.53		3.04		2.69	
$RMSD·10^4$	6.80		7.00		6.85	
	J_0	1786.70	A_1	9.77173	A_1	109.026
	J_1	-2343.26	B_1	-4109.96	B_1	-8641.56
	J_2	1961.21	A_2	7.27348	C_1	-14.7520
			B_2	-5016.46	A_2	69.9696
DMF + n-Propanol			J_0	1773.94	B_2	-7891.84
			J_1	-2345.11	C_2	-9.31129
			J_2	1929.24	J_0	1784.97
					J_1	-2343.64
					J_2	1956.87
$RAD·10^2$	2.39		3.41		2.83	
$RMSD·10^4$	6.44		6.31		6.45	

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DMF + Isopropanol	J_0	2193.10	A_1	9.77173	A_1	109.026
	J_1	-2937.50	B_1	-4109.96	B_1	-8641.56
	J_2	2107.75	A_2	11.1605	C_1	-14.7520
			B_2	-6477.45	A_2	-52.3493
			J_0	2192.63	B_2	-3546.09
			J_1	-2961.84	C_2	9.42189
			J_2	2106.48	J_0	2191.18
					J_1	-2937.55
					J_2	2102.91
$RAD \cdot 10^2$		4.26		4.66		4.46
$RMSD \cdot 10^4$		7.27		7.10		7.19
DMF + PG	J_0	2671.29	A_1	9.77173	A_1	109.026
	J_1	-3730.04	B_1	-4109.96	B_1	-8641.56
	J_2	2794.31	A_2	11.5909	C_1	-14.7520
			B_2	-6919.78	A_2	-1.11098
			J_0	2666.15	B_2	-6332.47
			J_1	-3745.87	C_2	1.88379
			J_2	2781.38	J_0	2670.45
					J_1	-3732.10
					J_2	2792.26
$RAD \cdot 10^2$		3.26		3.92		3.74
$RMSD \cdot 10^4$		7.10		6.73		7.06

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