

Thermodynamic Properties and Solvation of Uracil in Water + (Methanol, or Ethanol) Mixtures at Various Temperatures

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(Received 14 October 2025; Received in revised from 10 November 2025; Accepted 20 November 2025)

Abstract – The dissolution thermodynamics and preferential solvation of uracil (Ura) in aqueous mixtures of methanol and ethanol were systematically investigated over the temperature range 293.15–318.15 K. Experimental solubility data from the literature were analyzed using van't Hoff and Gibbs equations to evaluate the standard thermodynamic parameters of dissolution ($\Delta_{\text{sol}}H^\circ$, $\Delta_{\text{sol}}S^\circ$, $\Delta_{\text{sol}}G^\circ$). The results revealed that uracil dissolution was an endothermic and predominantly enthalpy-driven process across all solvent compositions, with solubility noticeably enhanced in intermediate alcohol-rich regions ($x_1 \approx 0.35$ – 0.45). The inverse Kirkwood–Buff integrals (IKBI) approach was employed to determine the preferential solvation parameter ($\delta x_{1,\text{Ura}}$), providing molecular-level insight into solute – solvent interactions. Positive $\delta x_{1,\text{Ura}}$ values in water-rich mixtures indicated preferential hydration, while negative values in alcohol-rich systems reflected the progressive replacement of water by alcohol in the cybotactic region around Ura. Temperature elevation reduced the magnitude of $\delta x_{1,\text{Ura}}$, suggesting a weakening of solvent structural heterogeneity and hydrogen-bond networks. Overall, this combined thermodynamic and molecular interpretation enhanced understanding of nucleobase solvation in mixed solvents and provided a quantitative framework for optimizing pharmaceutical formulation design and solubility prediction.

Key words: Uracil, Binary solvents, Solvent impact, Thermodynamic properties, IKBI approach, Preferential solvation

1. Introduction

Uracil ($\text{C}_4\text{H}_4\text{N}_2\text{O}_2$; 2,4(1H,3H)-pyrimidinedione is the chemical name that is also referred to as 2,4-dihydropyrimidine or 2,4-pyrimidinediol; CAS No. 66-22-8, Fig. 1) is a heterocyclic biologically based compound that makes up one of the main four nucleobases in ribonucleic acid (RNA). It is the central player in the transfer of genetic information, enzymatic regulation, and various biochemical pathways, which involve nucleotides and nucleosides [1,2]. After uracil is used in medicine, it can be used for other valuable purposes, such as being a precursor in the production of a variety of agrochemicals, herbicides, and fine chemicals [3,4], where the pyrimidine nature of the molecule imparts molecular stability and biological activity [2,4]. Becoming aware of its solvation characteristics in water and other solvent mixtures is extremely necessary because, in that case, these properties determine the stability, bioavailability, and reactivity of uracil in both biological and chemical contexts [5,6]. Besides, the practical utility drug solubility systematic in co-solvent systems opens the way to fundamental understanding of solute-solvent interactions, preferential solvation, and the thermodynamic driving forces of

dissolution, thus allowing for the rational design of advanced pharmaceutical formulations [7-9].

In recent years, considerable attention has been devoted to understanding the solubility and solvation phenomena of bioactive molecules in mixed solvent systems, as these parameters critically influence molecular stability, bioavailability, and formulation performance. Several studies have explored the thermodynamic behavior and preferential solvation of pharmaceutical and biologically relevant compounds using the inverse Kirkwood–Buff integrals (IKBI) method, including meloxicam [10], gallic acid [11], thiamphenicol [12], and various natural products [13,14]. These works have demonstrated the effectiveness of IKBI analysis in clarifying solute – solvent interactions and in differentiating between enthalpic and entropic contributions to solubility enhancement.

The current paper refers to experiments reported by Zhou *et al.* [15], who measured solubility of uracil in alcohol–water mixtures that contain methanol (MeOH) or ethanol (EtOH). Through combining thermodynamic and molecular analyses, the present study significantly extends the knowledge about uracil solvation in mixed solvents. Namely, thermodynamic investigation was realized through calculating main parameters such as solvation enthalpy, Gibbs free energy, and entropy which allowed deducing the energetic and entropic contributions to uracil dissolution in aqueous alcohol systems; (2) solubility mechanism was understood by means of the inverse Kirkwood–Buff integrals (IKBI) method that was used to quantify preferential solvation and to interpret solubility variations in different solvent compositions.

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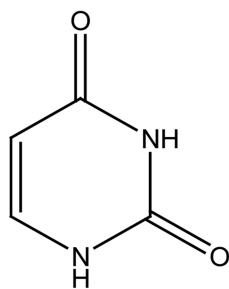


Fig. 1. Structure of Uracil (Ura) molecule.

2. Conceptual Section

2-1. Dissolution and transfer property

Information on the thermodynamic parameters that determine the dissolution of uracil (Ura) was extracted from the temperature dependence of solubility data by applying van't Hoff and Gibbs equations. These equations provide the estimates for standard enthalpy ($\Delta_{\text{sol}}H^\circ$), entropy ($\Delta_{\text{sol}}S^\circ$) and Gibbs free energy ($\Delta_{\text{sol}}G^\circ$) of dissolution which together characterize the energetic and molecular ones that accompany the process of solvation. In order to reduce the numerical deviation and to keep the values consistent across different temperature intervals, all thermodynamic quantities were in fact determined at the mean harmonic temperature (T_{mean}) which can be considered as the statistically weighted average temperature of the experimental range.

Mean harmonic temperature is extremely valuable when solubility measurements are done at certain discrete temperatures because mean harmonic temperature gives a representative reference temperature which is very close to the actual thermodynamic behavior of the system under near-equilibrium conditions. The mean harmonic temperature was calculated based on Eq. (1) [16]:

$$T_{\text{mean}} = n / \sum_{i=1}^n \frac{1}{T_i} \quad (1)$$

In this equation, n represented the number of temperature data points and T_{mean} was 305.41 K. The standard enthalpy change of dissolution ($\Delta H_{\text{sol}}^\circ$) was determined from Eq. (2)[17]:

$$\Delta H_{\text{sol}}^\circ = -R \left(\frac{\partial \ln(x_1)}{\partial (1/T - 1/T_{\text{mean}})} \right) = -R \times \text{slope} \quad (2)$$

The value of $\Delta H_{\text{sol}}^\circ$ was obtained from plotting $\ln(x)$ against reciprocal temperature ($1/T - 1/T_{\text{mean}}$), x represented the mole fraction solubility of Ura, and R was the general gas constant ($8.314 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$)

Standard Gibbs energy changes ($\Delta G_{\text{sol}}^\circ$) and entropic changes ($\Delta S_{\text{sol}}^\circ$) were calculated from Eq. (3) [18] and (4) [19] respectively:

$$\Delta G_{\text{sol}}^\circ = -RT_{\text{mean}} \times \text{intercept} \quad (3)$$

$$\Delta G_{\text{sol}}^\circ = \frac{\Delta H_{\text{sol}}^\circ - \Delta G_{\text{sol}}^\circ}{T_{\text{mean}}} \quad (4)$$

The relative contributions of enthalpy ($\% \xi_H$) and entropy ($\% \xi_{TS}$)

to the Gibbs energy of solution were quantified according to Eqs. (6) and (7) [10,20].

$$\% \xi_H = \frac{|\Delta H_{\text{sol}}^\circ|}{|\Delta H_{\text{sol}}^\circ| + |T \cdot \Delta S_{\text{sol}}^\circ|} \times 100 \quad (6)$$

$$\% \xi_{TS} = \frac{|T \cdot \Delta S_{\text{sol}}^\circ|}{|\Delta H_{\text{sol}}^\circ| + |T \cdot \Delta S_{\text{sol}}^\circ|} \times 100 \quad (7)$$

The solvation behavior of Ura was examined by calculating the standard Gibbs energy of transfer ($\Delta_{tr}G_{\text{Ura},2 \rightarrow 1+2}^\circ$) from neat water (2) to aqueous co-solvent mixtures (1 + 2) using Eq. (8) [21,22]. This approach provided a detailed evaluation of how co-solvent interactions, such as hydrogen bonding, hydrophobic effects, and solvation-shell restructuring, influenced Ura's solubility and stability, while also differentiating the enthalpic and entropic contributions governing solute – solvent compatibility.

$$\Delta_{tr}G_{\text{Ura},2 \rightarrow 1+2}^\circ = RT \ln \left(\frac{x_{\text{Ura},2}}{x_{\text{Ura},1+2}} \right) \quad (8)$$

2-2. Preferential solvation

The inverse Kirkwood–Buff integrals (IKBI) method is a highly effective statistical–thermodynamic technique used to describe preferential solvation in binary mixed solvents. The method essentially connects bulk thermodynamic data with the local solvent environment around solute molecules. IKBI provides the means to determine which solvent a solute prefers, thus, helping one to understand solute – solvent interactions, molecular arrangement, and the underlying forces of drug solvation and dissolution in complicated solvent systems. In particular, the parameter $\delta x_{1,\text{Ura}}$ signifies the improved solubility of Ura by organic solvents in such mixtures as MeOH – water, and EtOH – water [7,23-30].

$$\delta x_{1,\text{Ura}} = x_{1,\text{Ura}}^L - x_1 = -\delta x_{2,\text{Ura}} \quad (11)$$

In this expression, x_1 was alcohol mole fraction in the initial alcohol – water mixture before the addition of uracil (Ura), and $x_{1,\text{Ura}}^L$ was the local mole fraction of alcohol in the nearest solvation shell around Ura molecules. If the $\delta x_{1,\text{Ura}}$ value was negative, it mean that Ura was preferentially solvated by water molecules, and if $\delta x_{1,\text{Ura}}$ was positive, then dominant solvation by alcohol molecules prevailed. These parameters were calculated using equations based on the inverse Kirkwood–Buff integrals (IKBI) method [7,23,31-33].

$$\delta x_{1,\text{Ura}} = \frac{x_1 x_2 (G_{1,\text{Ura}} - G_{2,\text{Ura}})}{x_1 G_{1,\text{Ura}} + x_2 G_{2,\text{Ura}} + V_{\text{cor}}} \quad (12)$$

with,

$$G_{1,\text{Ura}} = RTk_T - V_{\text{Ura}} - x_2 V_2 D/Q \quad (13)$$

$$G_{2,\text{Ura}} = RTk_T - V_{\text{Ura}} + x_1 V_1 D/Q \quad (14)$$

$$V_{\text{cor}} = 2522.5 [r_{\text{Ura}} + 0.1363 (x_{1,\text{Ura}}^L \bar{V}_1 + x_{2,\text{Ura}}^L \bar{V}_2)^{1/3} - 0.085]^2 \quad (15)$$

The isothermal compressibility (k_T) of alcohol – water mixtures

was calculated from pure component values by mole fraction weighting. In such binary mixtures, the molar volume of uracil (Ura) was given as V_{Ura} , while V_1 and V_2 were the partial molar volumes of the cosolvent (alcohol) and water, respectively. The change of the standard molar Gibbs free energy of transfer of uracil, $\Delta_{tr}G^\circ_{Ura,2 \rightarrow 1+2}$ from pure water (solvent 2) to the mixed solvent system (1+2) versus solvent composition, was obtained by function D , which stood for the first derivative of $\Delta_{tr}G^\circ_{Ura,2 \rightarrow 1+2}$ with respect to solvent composition. The second derivative, denoted by function Q , points to the curvature of this Gibbs energy dependence and thus indicated the solvation energetics sensitivity to local composition changes. These connections were given by mathematical expressions in Eqs. (16) and (17), and they have been explained in detail in the papers referenced [7,9,34].

$$D = \left(\frac{\partial \Delta_{tr}G^\circ_{Ura,2 \rightarrow 1+2}}{\partial x_1} \right)_{T,P} \quad (16)$$

$$Q = RT + x_1 x_2 \left[\frac{\partial^2 G_{1+2}^{Exc}}{\partial x_2^2} \right]_{T,P} \quad (17)$$

$$r_{Ura} = \sqrt[3]{\frac{3 \times 10^{21} V_{Ura}}{4\pi N_{AV}}} \quad (18)$$

Avogadro's constant was represented by N_{AV} , and r_{Ura} denoted the molecular radius of uracil. In mixed solvent systems, the isothermal compressibility of the i pure component, $(k_{T,i}^\circ)$, can be estimated using Eq. (19). Since the RTk_T term exerted a negligible influence on the inverse Kirkwood–Buff integrals (IKBI) calculations, this approximation provided sufficient accuracy for evaluating preferential solvation parameters in such systems [7,23-27].

$$k_T = x_1 k_{T,1}^\circ + x_2 k_{T,2}^\circ \quad (19)$$

Due to the mutual dependence of $\delta x_{1,Ura}$ and V_{cor} established in Eqs. (12) and (15), their values were determined simultaneously using an iterative computational approach.

3. Results and Discussion

3-1. Dissolution and transfer properties

The data in Table 1 (at 305.41 K) showed that the dissolution process was non-spontaneous in all mixtures, as indicated by the positive standard molar Gibbs energy of dissolution (ΔG_{sol}°), which ranged from 18.147 to 21.832 kJ·mol⁻¹. The dissolution was endothermic across all compositions, with the standard molar enthalpy of dissolution (ΔH_{sol}°) always being positive (20.870 to 34.219 kJ·mol⁻¹). The maximum endothermicity was observed in the ethanol - water system at a mole fraction of $x_1 = 0.200$ (34.219 kJ·mol⁻¹), a typical effect called “maximum enthalpy” that was indicative of stronger solute-cosolvent interactions or the disruption of the water structure. The standard molar entropy of dissolution (ΔS_{sol}°) was positive in all the systems (2.381 to 52.302 J·mol⁻¹·K⁻¹), indicating an increase in disorder upon dissolution. The dissolution of Ura was clearly favored by the enthalpic contribution (which was greater than 50% in almost all

Table 2. Temperature-dependent standard Gibbs energy of transfer ($\Delta_{tr}G^\circ_{Ura,2 \rightarrow 1+2}$) of Ura from pure water to Cosolvent - water Mixtures at four temperatures (kJ·mol⁻¹)

MeOH (1) + water (2)			
^a x_1	293.15 K	303.15 K	318.15 K
0.000	0.000	0.000	0.000
0.200	-0.368	-0.479	-0.557
0.400	-0.763	-0.792	-0.955
0.600	-0.529	-0.484	-0.580
0.800	0.028	-0.042	0.163
1.000	0.605	0.790	0.931
EtOH (1) + water (2)			
^a x_1	293.15	303.15	318.15
0.000	0.000	0.000	0.000
0.200	-1.061	-1.062	-1.259
0.400	-1.427	-1.313	-1.607
0.600	-0.849	-0.591	-0.693
0.800	0.478	0.857	1.127
1.000	2.068	2.340	2.417

^a x_1 is the mole fraction of alcohol (1) in alcohol (1) + water (2) co-solvent mixtures free of Ura.

Table 1. Dissolution thermodynamics properties of Ura in alcohol - water binary solvent mixtures at 305.41 K and 101.3 kPa

^a x_1	$\Delta_{sol}H^\circ$ (kJ·mol ⁻¹)	$\Delta_{sol}G^\circ$ (kJ·mol ⁻¹)	$\Delta_{sol}S^\circ$ (J·mol ⁻¹ ·K ⁻¹)	% ζ_H	% ζ_{TS}
MeOH (1) + water (2)					
0.000	31.871	19.556	40.697	72.129	27.871
0.200	32.936	19.085	45.775	70.395	29.605
0.400	33.184	18.715	47.816	69.636	30.364
0.600	31.860	19.010	42.465	71.259	28.741
0.800	30.474	19.612	35.896	73.723	26.277
1.000	20.870	20.149	2.381	96.663	3.337
EtOH (1) + water (2)					
0.000	31.871	19.556	40.697	72.129	27.871
0.200	34.219	18.392	52.302	68.376	31.624
0.400	32.813	18.147	48.466	69.111	30.889
0.600	30.577	18.839	38.790	72.261	27.739
0.800	25.386	20.523	16.069	83.925	16.075
1.000	30.535	21.832	28.761	77.820	22.180

cases), with the highest enthalpy-driven percentage ($\% \xi_H$) reaching 96.663% in pure MeOH ($x_1=1.000$).

Table 2 displayed the standard Gibbs energy of transfer as a function of temperature ($\Delta_r G_{Ura,2 \rightarrow 1+2}^\circ$) of Ura from pure water to alcohol - water mixtures, thus describing Ura solvation in the binary mixtures relative to water. In the case of the MeOH - water mixture, $\Delta_r G_{Ura,2 \rightarrow 1+2}^\circ$ was lower than zero for x_1 ranging from 0.200 to 0.600, which mean that Ura was more soluble (favored) in these mixtures than in pure water. The transfer process became unfavorable (positive $\Delta_r G_{Ura,2 \rightarrow 1+2}^\circ$) at $x_1=0.800$ and 1.000, showing that Ura was less soluble in pure MeOH than in water. For the EtOH - water system, the transfer was strongly favorable (negative $\Delta_r G_{Ura,2 \rightarrow 1+2}^\circ$) across a wider range, from $x_1 = 0.200$ to 0.600, with the maximum stabilization (most negative $\Delta_r G_{Ura,2 \rightarrow 1+2}^\circ$) occurring at $x_1 = 0.400$ across all temperatures (e.g., $-1.607 \text{ kJ}\cdot\text{mol}^{-1}$ at 318.15 K). Similar to the MeOH system, the transfer became highly unfavorable (positive $\Delta_r G_{Ura,2 \rightarrow 1+2}^\circ$) in pure EtOH ($x_1 = 1.000$). Such behavior, in which $\Delta_r G_{Ura,2 \rightarrow 1+2}^\circ$ decreased, to a minimum, and then increased, was typical of co-solvency effects, thus the mixed solvent system providing a better solvation environment for Ura at intermediate compositions than either pure solvent.

The experiments showed that the dissolution and solvation of uracil in water - alcohol mixtures were significantly affected by the interplay of the molecular structure, solvent polarity, and hydrogen-bonding dynamics. The positive enthalpy values signify that the dissolution process was endothermic, thus implying that it was necessary to break the hydrogen-bond network of water in order to fit uracil molecules. At the same time, the positive entropy values signified overall an increase in molecular disorder, which was due to the rearrangement of solvent molecules around uracil during .

3-2. Preferential solvation

The $\Delta_r G_{Ura,2 \rightarrow 1+2}^\circ$ of transfer of Ura from pure water (2) to MeOH (1) + water (2), EtOH (1) + water (2) mixtures was computed by using Eq. (8) and correlated to regular quartic polynomials from the solubility values by using Eq. (20).

$$\Delta_r G_{Ura,2 \rightarrow 1+2}^\circ = a + bx_1 + cx_1^2 + dx_1^3 + ex_1^4 \quad (20)$$

Values for the standard Gibbs energy of transfer ($\Delta_r G_{Ura,2 \rightarrow 1+2}^\circ$) were derived from Eq. (20) and were compiled in Table 2. The temperature dependence of this parameter at 293.15, 303.15, and 318.15 K was depicted in Fig. S1, with the coefficients for the associated regression equation listed in Table S1. In addition, the computation of parameter D in Eq (21), denoting the molar proportion of the organic solvent, was carried out by employing a constant alcohol mole fraction of 0.05 for all the experiments, which was the main point in Table S2.

$$D = b + 2cx_1 + 3dx_1^2 + 4ex_1^3 \quad (21)$$

To evaluate the Q values, the excess molar Gibbs energies of mixing ($G_{1,2}^{Exc}$) at all investigated temperatures were required. For

the MeOH (1) + water (2) and EtOH (1) + water (2) co-solvent mixtures, $G_{1,2}^{Exc}$ values at 298.15 K were calculated using Eqs. (22) and (23), respectively, as reported by Marcus [7]. The corresponding $G_{1,2}^{Exc}$ values at other temperatures were obtained from Eq. (24), which related the temperature dependence of excess Gibbs energy to the excess molar enthalpy of mixing ($H_{1,2}^{Exc}$), using $T_1 = 298.15 \text{ K}$ and T_2 as the target temperature under consideration [7]. The $H_{1,2}^{Exc}$ values utilized in this computation were derived from Eqs. (25) and (26) for the MeOH (1) + water (2) and EtOH (1) + water (2) mixtures, respectively, both at 298.15 K.

$$G_{1,2}^{Exc} = x_1(1-x_1)[1200 - 87(1-2x_1) + 330(1-2x_1)^2] \quad (22)$$

$$G_{1,2}^{Exc} = x_1(1-x_1)[2907 - 777(1-2x_1) + 494(1-2x_1)^2] \quad (23)$$

$$G_{1,2}^{Exc}(T_2) = G_{1,2}^{Exc}(T_1) - T_1 \int_{T_1}^{T_2} \frac{H_{1,2}^{Exc}}{T^2} d\left(\frac{1}{T}\right) \approx \frac{T_2}{T_1} G_{1,2}^{Exc} + H_{1,2}^{Exc} \left(1 - \frac{T_2}{T_1}\right) \quad (24)$$

$$H_{1,2}^{Exc} = x_1(1-x_1)[-3102 + 2040(1-2x_1) - 2213(1-2x_1)^2] \quad (25)$$

$$H_{1,2}^{Exc} = x_1(1-x_1)[-1300 + 3567(1-2x_1) - 4971(1-2x_1)^2] \quad (26)$$

The calculated Q values across different temperatures were provided in Supplementary Tables S3 and S4. The isothermal compressibility, k_T , and corresponding RTk_T values at 298.15 K, 1.248 GPa^{-1} (MeOH), 1.153 GPa^{-1} (EtOH), and 0.457 GPa^{-1} (water), were taken from the literature [35]. The densities of the solvent mixtures that were necessary for the calculation of partial molar volumes were measured by literature methods [35]. The partial molar volume of the mixture, V , was computed as $V = (x_1M_1 + x_2M_2)/\rho$, where M_1 and M_2 referred to the molar masses of the alcohol (MeOH: 32.06 $\text{g}\cdot\text{mol}^{-1}$; EtOH: 46.07 $\text{g}\cdot\text{mol}^{-1}$) and water (18.02 $\text{g}\cdot\text{mol}^{-1}$) correspondingly. Subsequently, the partial molar volumes of the individual components, \bar{V}_1 (co-solvent) and \bar{V}_2 (water), were obtained by means of Eqs. (27) and (28), with the MeOH + water and EtOH + water systems results regrouped in Supplementary Tables S5 and S6, respectively.

$$\bar{V}_1 = V + x_2 \frac{dV}{dx_1} \quad (27)$$

$$\bar{V}_2 = V - x_1 \frac{dV}{dx_1} \quad (28)$$

The molar volume of the solute, Ura, was assumed to be independent of co-solvent composition and temperature. As no experimental partial molar volume data for Ura were available, the molar volume of the pure solid was used as a reasonable approximation [11,23,28,36-38]. Using the molar mass (112.09 $\text{g}\cdot\text{mol}^{-1}$) and density (1.32 $\text{g}\cdot\text{cm}^{-3}$) of Ura, its molar volume was calculated to be 84.916 $\text{cm}^3\cdot\text{mol}^{-1}$. Subsequently, by modeling the solute as a sphere, its radius was estimated from this volume using Eq. (18), yielding a value of 0.323 nm.

The Kirkwood-Buff integrals, $G_{1,Ura}$ and $G_{2,Ura}$, were calculated for the mixtures using Eqs. (13) and (14) at co-solvent mole fraction intervals of 0.05. As presented in Tables S7 and S8, all $G_{1,Ura}$ values were negative, with maxima occurring at $x_1=0.65$ for the MeOH/water system and at $x_1=0.70$ for the EtOH/water systems. The consistently

Table 3. Corrected volumes and solvation parameter of Uracil in MeOH (1) + Water (2) Binary mixtures as a function of temperature

$^a x_1$	V_{cor} (cm ³ ·mol ⁻¹)			$100 \delta x_{1,Ura}$		
	293.15 K	303.15 K	318.15 K	293.15K	303.15K	318.15 K
0	533	534	536	0.000	0.000	0.000
0.05	550	551	554	0.123	0.212	0.201
0.1	567	569	571	0.317	0.379	0.423
0.15	585	586	590	0.524	0.497	0.614
0.2	602	603	607	0.700	0.559	0.735
0.25	620	620	625	0.805	0.556	0.755
0.3	637	638	643	0.800	0.477	0.657
0.35	653	655	660	0.658	0.314	0.435
0.4	670	671	677	0.369	0.071	0.104
0.45	686	688	694	-0.049	-0.239	-0.301
0.5	702	705	711	-0.541	-0.583	-0.732
0.55	718	722	728	-1.023	-0.916	-1.134
0.6	734	739	745	-1.410	-1.194	-1.452
0.65	751	757	763	-1.637	-1.379	-1.646
0.7	769	775	782	-1.678	-1.453	-1.694
0.75	788	794	802	-1.547	-1.413	-1.594
0.8	808	813	822	-1.282	-1.272	-1.363
0.85	827	833	843	-0.932	-1.046	-1.033
0.9	848	853	864	-0.556	-0.752	-0.650
0.95	868	874	885	-0.218	-0.401	-0.277
1	888	895	906	0.000	0.000	0.000

^a x_1 is the mole fraction of MeOH (1) in MeOH (1) + water (2) co-solvent mixtures free of Ura.

Table 4. Corrected volumes and solvation parameter of Uracil in EtOH (1) + Water (2) Binary mixtures as a function of temperature

$^a x_1$	V_{cor} (cm ³ ·mol ⁻¹)			$100 \delta x_{1,Ura}$		
	293.15 K	303.15 K	318.15 K	293.15 K	303.15 K	318.15 K
0	533	534	537	0.000	0.000	0.000
0.05	566	568	572	0.476	0.489	0.550
0.1	599	601	607	0.912	0.942	1.177
0.15	631	634	641	1.235	1.257	1.683
0.2	663	666	674	1.388	1.354	1.892
0.25	693	695	704	1.328	1.188	1.708
0.3	722	723	732	1.027	0.747	1.126
0.35	749	750	757	0.461	0.035	0.185
0.4	775	775	780	-0.389	-0.937	-1.062
0.45	799	798	801	-1.546	-2.162	-2.574
0.5	820	819	821	-3.024	-3.633	-4.318
0.55	840	839	840	-4.810	-5.322	-6.251
0.6	858	857	857	-6.803	-7.138	-8.278
0.65	876	877	876	-8.701	-8.839	-10.155
0.7	898	900	898	-9.912	-9.932	-11.365
0.75	929	930	930	-9.741	-9.757	-11.125
0.8	969	971	974	-8.018	-8.027	-8.967
0.85	1014	1017	1027	-5.443	-5.359	-5.608
0.9	1059	1064	1078	-2.973	-2.805	-2.544
0.95	1100	1106	1123	-1.134	-0.996	-0.677
1	1137	1145	1162	0.000	0.000	0.000

^a x_1 is the mole fraction of EtOH (1) in EtOH (1) + water (2) co-solvent mixtures free of Ura.

negative $G_{2,Ura}$ values indicated a net attraction between uracil and both water and co-solvents. However, $G_{2,Ura}$ became positive in alcohol-rich mixtures across the studied temperature range (293.15–

318.15 K). This sign change suggested that water molecules were preferentially solvated by the solutes in alcohol-rich environments.

The evaluation of Tables 3 and 4 and Fig. 2 representing the

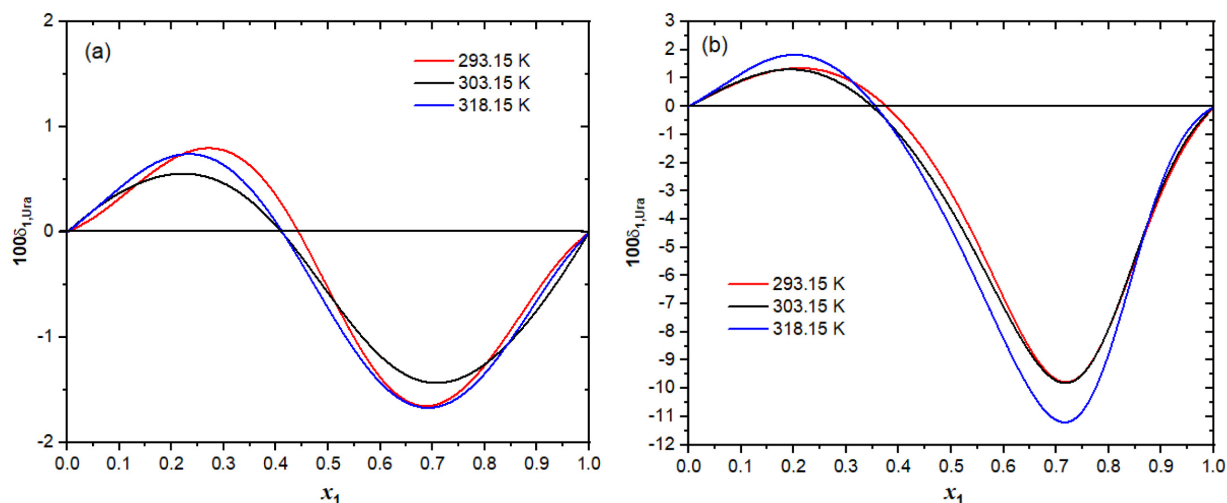


Fig. 2. Solvation parameter ($\delta x_{1,Ura}$) of Uracil in (a) MeOH - water and (b) EtOH - water mixtures at various temperatures.

solvation parameter ($\delta x_{1,Ura}$) of Ura in (a) MeOH + Water and (b) EtOH + Water mixtures distinctly showed the non-linearity and intricacy of preferential solvation of Ura. Positive $\delta x_{1,Ura}$ values indicated preferential solvation by the alcohol (1), while negative values indicated preferential solvation by water (2). In both mixtures, the plots showed a characteristic S-shaped curve. In the water-rich region ($x_1 < 0.40$ for MeOH and $x_1 < 0.45$ for EtOH), $\delta x_{1,Ura}$ was positive, meaning Ura was preferentially solvated by the alcohol even at low compositions, which was typical for a non-electrolyte. Conversely, in the alcohol-rich region, $\delta x_{1,Ura}$ became negative, reaching a significant minimum (strongest water preference) around $x_1 \approx 0.70$ for MeOH and for EtOH. The magnitude of negative $\delta x_{1,Ura}$ much larger in EtOH + Water (minimum ≈ -10 to -11) than in MeOH + Water (minimum ≈ -1.5), demonstrating that water was much more strongly preferred by Ura in the EtOH-rich mixtures. It was important to note that, when $|\delta x_{1,Ura}| < 1.0 \times 10^{-2}$, the result was not considered evidence of preferential solvation but was interpreted as a consequence of propagated experimental uncertainties [39,40].

The solvation of Ura was largely determined by its amphiprotic nature, which means that it can act as both a Lewis acid (by N-H hydrogen-bond donation) and a Lewis base (by C=O electron-pair donation) (Fig. 1). In mixtures rich in water, preferential hydration was a consequence of the hydrophobic effect that acted on the Ura structure. Due to this, there was an alcohol-dominated solvation shell, which led to a net decrease in the measurable solute-solvent interaction values. On the other hand, in mixtures rich in alcohol, Ura showed a dominant Lewis base character, and thus, interacted preferentially with the leftover water molecules. This was because of much stronger hydrogen bond donor capacity of water ($\alpha=1.017$) than the co-solvents methanol ($\alpha=0.99$) or ethanol ($\alpha=0.86$) [35, 41], which made the Ura - water hydrogen-bonding interaction more favorable from a thermodynamic point of view than the Ura - alcohol interaction in these circumstances.

It was observed in Figure 2 that the absolute value of the negative

decreased with increasing temperature, which indicated that the preferential solvation of water was diminishing. With the rising temperature, the hydrogen-bond network was getting weaker, and the solvent structure was partially breaking; therefore, both changes lead to a more uniform and less selective solvent environment around uracil molecules.

Analyzing Figure 3, which depicted the solvation parameter ($\delta x_{1,Ura}$) of Ura in MeOH + Water and EtOH + Water mixtures at a single temperature (318.15 K), revealed that the difference in the preferential solvation behavior of Ura between the two alcohol systems was very significant. The Figure 3 also exhibited the same trend of favored dissolution of Ura by water in the alcohol-water mixtures for all binary mixed solvents, with the EtOH mixture showing the greatest extent, followed by the MeOH mixture. The points at which maxima occur depend on the cosolvent ratios: for MeOH (1) + Water (2), $x_1 = 0.70$, $|\delta x_{1,Ura}| = -1.694 \times 10^{-2}$; and for EtOH

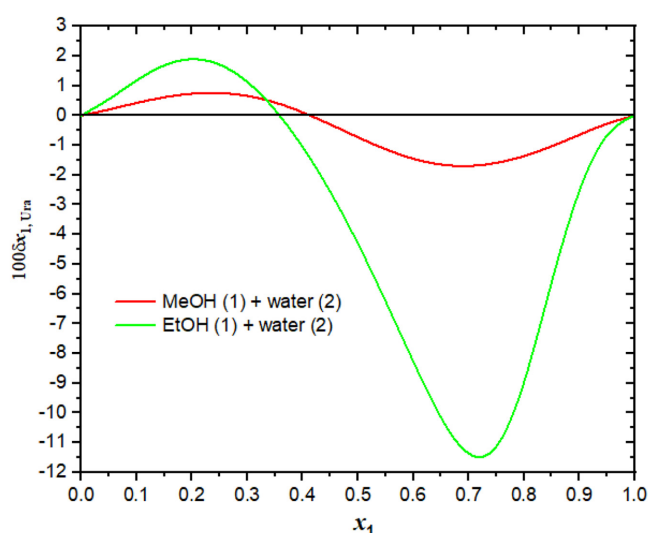


Fig. 3. Plot of $\delta x_{1,Ura}$ values of Uracil in alcohol (1) + water (2) mixtures at 318.15 K.

(1) + Water (2), $= 0.70$, $|\delta x_{1,Ura}| = -11.365 \times 10^{-2}$.

The increase in solubility that was measured for intermediate alcohol mole fractions was essentially the co-solvency effect, by which the partial substitution of water with alcohol reduced the total polarity of the medium and resulting improved compatibility of solute – solvent. Besides that, the preferential solvation analysis indicated that alcohol molecules have stronger interactions with the hydrophobic parts of uracil, whereas water was the preferred partner for the hydrophilic sites. The equilibrium of these interactions accounted for the non-linear solubility trends at different compositions and it also explained that both enthalpic and entropic factors were involved in determining uracil's thermodynamic behavior in mixed solvents.

Conclusions

The study examined the thermodynamic properties and preferential solvation of Ura in binary mixtures of MeOH + Water and EtOH + Water in a temperature range of 293.15–313.15 K. The dissolution was endothermic and mainly enthalpy-driven, as indicated by $\Delta_{sol}H^\circ$ values of 20.9–34.2 kJ·mol⁻¹ and $\Delta_{sol}G^\circ$ ranging from 18.1 to 21.8 kJ·mol⁻¹. The highest solubility was observed at intermediate alcohol mole fractions ($x_1 \approx 0.35$ – 0.40), thus a strong co-solvency effect was confirmed. The IKBI analysis showed preferential hydration (negative) at most compositions, with the effect weakening at higher temperatures due to hydrogen-bond disruption. In sum, these findings deepen the knowledge of solute – solvent interactions and preferential solvation processes, which are helpful in drug solubility optimization and formulation design in mixed solvent environments.

Notes: The authors declare no competing financial interest.

Acknowledgments

The authors extend their appreciation to Northern Border University, Saudi Arabia, for supporting this work through project number (NBU-CRP-2025-1497).

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