Expanding the Equilibrium Solubility and Dissolution Thermodynamics of Benzoic Acid in Aqueous Alcoholic Mixtures

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Abstract: The equilibrium solubility of benzoic acid in water and ethanol, as well as in nine {ethanol (1) + water (2)} mixtures, was determined from T = (293.15 to 323.15) K. Benzoic acid mole fraction solubility in these aqueous-ethanolic mixtures was adequately correlated with some well-known correlation/prediction models, obtaining mean percentage deviations of 2.2 to 7.6%. Apparent thermodynamic quantities, namely, Gibbs energy, enthalpy, and entropy, for the dissolution, mixing and solvation processes, were computed by means of the van 't Hoff and Gibbs equations. The enthalpy–entropy compensation plot of apparent enthalpy vs. apparent Gibbs energy of dissolution was not linear, indicating enthalpy and entropy mechanisms for transfer. Ultimately, by using the inverse Kirkwood–Buff integrals, it is observed that benzoic acid is preferentially solvated by water molecules in water-rich mixtures but preferentially solvated by ethanol molecules in those {ethanol (1) + water (2)} mixtures of $0.24 < x_1 < 1.00$.

Keywords: benzoic acid; (ethanol + water) mixtures; solubility; solution thermodynamics; Jouyban-Acree model; preferential solvation

1. Introduction

The equilibrium solubility of compounds in chemical, food, pharmaceutical and material industries is of critical importance in selecting the most suitable solvent and operating temperature in separation techniques such as extraction, pollution prevention, purification and crystallization [1]. In addition, the dependence of the solubility on temperature allows the evaluation of the preferential dissolution analysis of the solute by types of co-solvents in the mixture, as well as the related thermodynamic analysis, which provides insight into the molecular mechanisms involved in the dissolution process [2–4].

Benzoic acid (Systematic IUPAC name: Benzenecarboxylic acid, molecular structure shown in Figure 1) is a colorless crystalline solid that is generally used as a significant intermediate in the production of a variety of chemical compounds [5–10]. Benzoic acid and its salts have a wide range of applications in different industries, especially in the chemical industry and pharmaceutical industry, such as resins, dyes, polymers, preservatives, cosmetics and pharmaceuticals [11,12]. In this regard, benzoic acid is widely used as an intermediate in the synthesis of phenol and caprolactam [8] as well as in the

preparation of resins, cosmetics, dyes, inks, plasticizers, pharmaceutical products and rust inhibitor [7,8,10,13–15]. Its salts are mainly used as intermediates in the preservation of foods, fruit juices, pickles and fats as well as in the production of synthetic flavors, perfumes and for the flavoring of tobacco. In addition, they are known to have very good antifungal activity [8,10,16]. Furthermore, the other end products of benzoic acid are also used as corrosion inhibitors [8,17].
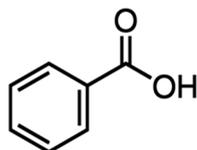
Figure 1. Molecular structure of benzoic acid.

Benzoic acid is sparingly soluble in water (0.3 g/100 g of water at 293 K) and the limited solubility of benzoic acid in water makes it difficult to use its application in products containing large amounts of water [10,18]. For this reason, it is necessary to increase its solubility in the aqueous phase. In this context, many researchers have reported temperature dependent solubility data of benzoic acid in both monosolvents and binary mixtures and have tried to understand the solubility and dissolution behavior of this excipient agent [6–10,12–17,19,20]. Thus, Chertkoff and Martin [21] measured the solubility of benzoic acid in binary mixtures of hexane, ethyl acetate, ethanol and water. Sahay et al. [22] examined the solubility of benzoic acid in distilled water and aqueous solutions of poly (vinyl alcohol) and poly (vinylpyrroildone) containing 0.5–6.0 wt% polymer at temperatures from 303.15 to 328.15 K. Li et al. [14] determined the solubility of benzoic acid in *N,N*-dimethylformamide as a function of temperature in the temperature range of 294.75–370.45 K using a laser monitoring observation technique. Oliveira et al. [19] performed benzoic acid solubility determinations in pure water and in mixtures of an organic solvent (DMF, ethanol, and 1,4 dioxane) with water within the temperature range of 303.65 to 355.65 K. Pires and Franco [20] investigated the solubility of benzoic acid in water-ethanol and water-n-propanol mixtures at temperatures between 303.5 and 333.7 K. Long et al. [6] carried out the solubility determination of benzoic acid in acetone, 2-propanol, acetic acid and cyclohexane over the temperature range of 277–346 K by using a gravimetric method. Thati et al. [16] conducted the solubility analysis of benzoic acid in monosolvents (ethanol, toluene, heptane, cyclohexane, pentane and chloroform) and binary solvent mixtures (ethanol + heptane and ethanol + toluene) at temperatures ranging from 278.15 to 323.15 K by the gravimetric method. Cheng et al. [15] measured the solubility values of benzoic acid in ethanol, benzene, acetic acid and ethyl acetate over the temperature range of 291.69–356.27 K. Wang et al. [12] investigated the solubility of benzoic acid in binary (benzyl alcohol + benzaldehyde) solvent mixtures at temperatures from 298.35 to 355.65 K under atmospheric pressure by a synthetic method. Kumari et al. [17] investigated the solubility of benzoic acid in (acetic acid + water) and (acetic acid + toluene) binary mixtures at different mass fractions of acetic acid ranging from 0.1 to 0.8 and at 299.15 K by the gravimetric method. Xue et al. [7] examined the solubility of benzoic acid in six alcohols (isobutanol, *n*-pentanol, isoamylol, 2-pentanol, tert-amyl alcohol and *n*-hexanol) at different temperatures from 288.15 K to 336.15 K by the dynamic method. Sandeepa et al. [8] performed the solubility study of benzoic acid in six monosolvents (tributyl phosphate, diacetone alcohol, methyl-n-propyl ketone, methyl acetate, amyl acetate and isooctane) at temperatures from (283.15 to 328.15) K and five binary systems, i.e., ethanol + hexane (288.15–328.15 K), isopropyl alcohol + hexane and chloroform + hexane (288.15–323.15 K), acetone + hexane (288.15–318.15 K), and acetone + water (288.15–318.15 K) at atmospheric pressure. AbouEllef et al. [9] determined the solubility of benzoic acid in binary mixtures of ethanol–water solvents at different temperatures by using the gravimetric method. Muhammad et al. [10] conducted the benzoic acid solubility study in the aqueous phase and various aqueous mixtures of methanol, ethanol and 2-propanol at temperatures ranging from 303 to

333 K by an analytical technique. Wang et al. [13] measured the solubility of benzoic acid in twelve organic solvents (1,2-ethanediol, 3,6-dioxa-1-decanol, octane, 3-oxa-1,5-pentanediol, *N,N*-dimethylacetamide, 1,4-dimethylbenzene, 1,3-dimethylbenzene, 1,2-dimethylbenzene, propanoic acid, cyclohexanone, decahydronaphthalene, thiacyclopentane dioxide) at temperature ranging from 286.15 to 354.15 K using the laser dynamic method. Mendez-Santiago and Teja [23] measured the solubility of benzoic acid in mixtures of CO_2 + hexane at temperatures ranging from (308 to 338) K, pressures ranging from 10 to 35 MPa, and cosolvent concentrations containing 0–7.0 mol% hexane. Sandeepa et al. [24] evaluated the solubility of benzoic acid in monosolvents (benzyl acetate and benzyl benzoate), in binary solvent systems (benzyl alcohol + toluene, benzyl acetate + toluene and benzyl benzoate + toluene) in the temperature range of 288.15–328.15 K, and in ternary solvent systems (benzoic acid + phthalic acid + benzyl alcohol/methanol) at two different temperatures (298.15 and 308.15) K. More recently, Zhang et al. [25] have carried out the solubility analysis of benzoic acid in seven pure solvents (water, methanol, ethanol, acetonitrile, dichloromethane, toluene, and ethyl acetate) within the temperature range of 273.15 to 323.15 K. Despite of all the benzoic acid solubility studies reported, there are limited experimental or modeling information about determination of the solubility of benzoic acid in binary solvent mixtures of {ethanol (1) + water (2)} at different temperatures and compositions.

Because of all of these reasons, the purposes of this study were to (1) measure the solubility of benzoic acid in solvent mixtures of {ethanol (1) + water (2)} in the temperature range of 293.15–323.15 K at constant pressure; (2) describe the determined experimental solubilities with various mathematical models; (3) evaluate the apparent thermodynamic parameters of dissolution, mixing and solvation of benzoic acid in binary solvent mixtures of {ethanol (1) + water (2)}; and (4) calculate the preferential solvation parameters of benzoic acid by ethanol in binary solvent combinations using the inverse Kirkwood–Buff integrals.

2. Materials and Methods

2.1. Materials

Benzoic acid was obtained from Sigma-Aldrich Chemical (Steinheim, Germany). Acetonitrile, ethanol and formic acid were of chromatographic grade and provided by Merck Chemical (Istanbul, Turkey). Ultra-pure water (18.2 MΩ·cm) was prepared by the MilliPore Milli-Q-Gradient water purification system (Billerica, MA, USA). More detailed information about these chemicals is listed in Table 1.

Table 1. Source and purities of the compounds used in this research.

Compound	CAS	Formula	Molar Mass/g·mol^{-1}	Source	Purity in Mass Fraction	Analytic Technique [a]
Benzoic acid	65-85-0	$C_7H_6O_2$	122.12	Sigma-Aldrich	≥0.995 [b]	HPLC
Ethanol	64-17-5	C_2H_6O	46.07	Merck	>0.995 [b]	GC
Acetonitrile	75-05-8	C_2H_3N	41.05	Merck	≥0.999 [b]	GC
Formic acid	64-18-6	CH_2O_2	46.03	Merck	≥0.999 [b]	GC
Water	7732-18-5	H_2O	18.02	Obtained by Millipore Milli-Q-Gradient water purification system	>0.999	-

[a] HPLC is high performance liquid chromatography, GC is gas chromatography. [b] As indicated by the suppliers.

2.2. Solubility Determinations

All {ethanol (1) + water (2)} binary solvent mixtures in mass fractions from 0.10 to 0.90, varying by 0.10, were prepared in 50.0 g dark glass flasks. All mass fractions were adjusted by using an analytical balance with an accuracy of ±0.1 mg (Kern ABJ 220-4NM, Balingen, Germany).

Solubility measurements of benzoic acid against the mass fraction of ethanol in {ethanol (1) + water (2)} binary solvent mixtures at temperatures ranging from 293.15 K to 323.15 K under atmospheric pressure were determined using the traditional shake-flask method [26] and are described in the following. Briefly, an excess amount of benzoic acid was added to the flask containing pure solvents and solvent mixtures in known mass ratios and capped tightly. Then, the suspensions were shaken for 18 h to saturation in a shaking thermostatic water bath ($\pm$0.1 K) at selected temperatures. After the 18 h equilibration period, all the saturated mixtures were centrifuged to remove fine solid particles and suitably diluted with the water$-$acetonitrile mixture (50:50% v/v) without observing solute precipitation. The solubility samples were then analyzed by high performance liquid chromatography (HPLC) for quantitative determination, described as follows.

The quantification of benzoic acid in solubility samples was carried out in triplicate by using an Agilent 1200 HPLC (Santa Clara, CA, USA) coupled with an Agilent Zorbax SB Phenyl column (4.6 $\times$ 150 mm, 5 µm-Santa Clara, CA, USA). The chromatographic determination was conducted by using the mixture of acetonitrile:water:formic acid (20:79:1% $v/v/v$) as the mobile phase at a flow rate of 1.0 mL·min^{-1} and detected at 240 nm with a diode array detector. The volume of the injected sample was 10 µL.

Besides the solubility data, thermal and spectroscopic analyses such as differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD) were used to investigate the crystalline structure of crude and equilibrated benzoic acid samples before and after the solubility determination.

2.3. Solid Phase Characterization

2.3.1. Differential Scanning Calorimetry Analysis

Solid samples obtained after solubility determination were analyzed using a differential scanning calorimetric analyzer to determine the nature of the crude and equilibrated forms of benzoic acid. DSC analysis of samples was carried out using a METTLER TOLEDO STARe System DSC 3 series (Ohio, ABD). The instrument was calibrated by Indium as standard. About 5.0 mg of benzoic acid was placed in a crimped, sealed aluminum pan. Then, the sample was heated from 25 to 440 °C at a heating rate of 10 °C·min^{-1} under a dynamic nitrogen atmosphere (40 mL·min^{-1}).

2.3.2. X-ray Diffraction Analysis

The crystal form of benzoic acid, both crude and after equilibration in neat water, the mixture $w_1 = 0.50$, and neat ethanol were identified using XRD analyses. The powder XRD patterns of the solid benzoic acid were performed on Rigaku Smart Lab system (Tokyo, Japan) using CuKα radiation (1.5418 Å). The samples were scanned from ~10° to 90° (2θ°) to provide a degree of crystallinity and structural information.

3. Results and Discussion

3.1. Mole Fraction Solubility of Benzoic Acid

The mole fraction equilibrium solubilities of benzoic acid in aqueous–ethanol mixtures at seven temperatures from T = (293.15 to 323.15) K and an atmospheric pressure of 90 kPa as a function of the mass fraction of ethanol in the solvent mixtures are summarized in Table 2. Minimum and maximum benzoic acid solubilities are observed in neat water and in neat ethanol, respectively, at all temperatures studied. Benzoic acid solubility increases with temperature-arising, implying endothermic dissolution processes in all cases. Solubility in neat water is in agreement with data reported by Belhachemi et al. [27]. It is noteworthy that our solubility values in these binary mixtures at T = 298.15 K are in good agreement with those reported graphically by Chertkoff and Martin [21]. Although several authors have studied the solubility of benzoic acid in different solvent systems, no more direct comparisons are possible. For instance, Pal and Lahiri reported benzoic acid solubility values in {ethanol (1) + water (2)} mixtures determined at (288, 293 and 298) K but expressed in molarity scale [28].

Table 2. Experimental and ideal mole fraction solubility of benzoic acid (x_3) in {ethanol (1) + water (2)} mixtures at several temperatures and p = 90 kPa [a,c].

w_1 [b,c]	x_1 [b,c]	T/K [c]						
		293.15	298.15	303.15	308.15	313.15	318.15	323.15
0.00	0.0000	4.69×10^{-4}	5.61×10^{-4}	6.64×10^{-4}	7.87×10^{-4}	9.34×10^{-4}	1.12×10^{-3}	1.32×10^{-3}
0.10	0.0417	8.05×10^{-4}	9.51×10^{-4}	1.12×10^{-3}	1.26×10^{-3}	1.42×10^{-3}	1.58×10^{-3}	1.77×10^{-3}
0.20	0.0891	1.57×10^{-3}	1.75×10^{-3}	1.98×10^{-3}	2.22×10^{-3}	2.48×10^{-3}	2.81×10^{-3}	3.14×10^{-3}
0.30	0.1436	2.84×10^{-3}	3.19×10^{-3}	3.56×10^{-3}	4.02×10^{-3}	4.54×10^{-3}	5.07×10^{-3}	5.69×10^{-3}
0.40	0.2068	4.92×10^{-3}	5.61×10^{-3}	6.34×10^{-3}	7.09×10^{-3}	7.94×10^{-3}	8.98×10^{-3}	1.00×10^{-2}
0.50	0.2812	8.93×10^{-3}	1.04×10^{-2}	1.16×10^{-2}	1.31×10^{-2}	1.48×10^{-2}	1.65×10^{-2}	1.87×10^{-2}
0.60	0.3698	1.60×10^{-2}	1.88×10^{-2}	2.11×10^{-2}	2.38×10^{-2}	2.67×10^{-2}	3.01×10^{-2}	3.38×10^{-2}
0.70	0.4772	2.88×10^{-2}	3.37×10^{-2}	3.80×10^{-2}	4.30×10^{-2}	4.86×10^{-2}	5.44×10^{-2}	6.00×10^{-2}
0.80	0.6101	5.03×10^{-2}	5.67×10^{-2}	6.43×10^{-2}	7.16×10^{-2}	8.04×10^{-2}	9.03×10^{-2}	0.102
0.90	0.7788	8.56×10^{-2}	9.93×10^{-2}	0.112	0.126	0.139	0.153	0.167
1.00	1.0000	0.163	0.184	0.206	0.228	0.254	0.286	0.321
	Ideal	0.194	0.213	0.233	0.255	0.278	0.304	0.331

[a] p is the atmospheric pressure in Aksaray, Turkey. [b] w_1 and x_1 are the mass and mole fractions of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of benzoic acid (3), respectively. [c] Standard uncertainty in p is $u(p)$ = 3.0 kPa. Mean relative uncertainties in w_1 and x_1 were $u(w_1)$ = 0.0008 and $u(x_1)$ = 0.0008. Standard uncertainty in T is $u(T)$ = 0.10 K. Average relative uncertainty in x_3, $u_r(x_3)$ = 0.025.

On the other hand, Figure 2 depicts the benzoic acid solubility as a function of the Hildebrand solubility parameters of the aqueous-ethanol mixtures (δ_{1+2}). The Hildebrand solubility parameter is a polarity index widely used in pharmaceutical studies regarding cosolvency effects on the physical and chemical stabilities of drugs. Mixtures δ_{1+2} values were calculated from the corresponding δ values, i.e., δ_1 = 26.5 MPa$^{1/2}$ for ethanol and δ_2 = 47.8 MPa$^{1/2}$ for water [29,30] and volumetric solvent fractions as described in Equation (1) [31,32]. Volume fractions (f_i) were calculated assuming additive behavior.

$$\delta_{1+2} = \sum_{i=1}^{2} f_i \delta_i \tag{1}$$

Accordingly, it is expected that organic compounds reach their maximum solubilities in solvent systems exhibiting the same or similar Hildebrand solubility parameters, as them [33,34]. By keeping this in mind, the δ_3 value of benzoic acid would be lower than δ_1 value (i.e., neat ethanol δ value, 26.5 MPa$^{1/2}$) at T = 298.2 K, where the maximum benzoic acid solubilities are observed at all temperatures. Effectively, the calculated Fedors δ_3 value of benzoic acid is 24.4 MPa$^{1/2}$, as shown in Table 3 [35]. From this point, it would be very important to study the benzoic acid solubility in mixed solvent systems exhibiting lower polarities than that of neat ethanol. A very good option would be {ethyl acetate (1) + ethanol (2)} mixtures, with an interval of $19.8 \leq (\delta_{1+2}/\text{MPa}^{1/2}) \leq 26.5$, where most likely, a maximum benzoic acid solubility peak could be observed.

Table 3. Internal energy, molar volume, and Hildebrand solubility parameter of benzoic acid calculated according to the Fedors method.

Group	Number	$\Delta U^\circ/\text{kJ} \cdot \text{mol}^{-1}$	$V^\circ/\text{cm}^3 \cdot \text{mol}^{-1}$
Phenyl ring	1	31.9	71.4
–COOH	1	27.6	28.5
	Σ	59.5	99.9
		$\delta_3 = (59{,}500/99.9)^{1/2} = 24.4 \text{ MPa}^{1/2}$	
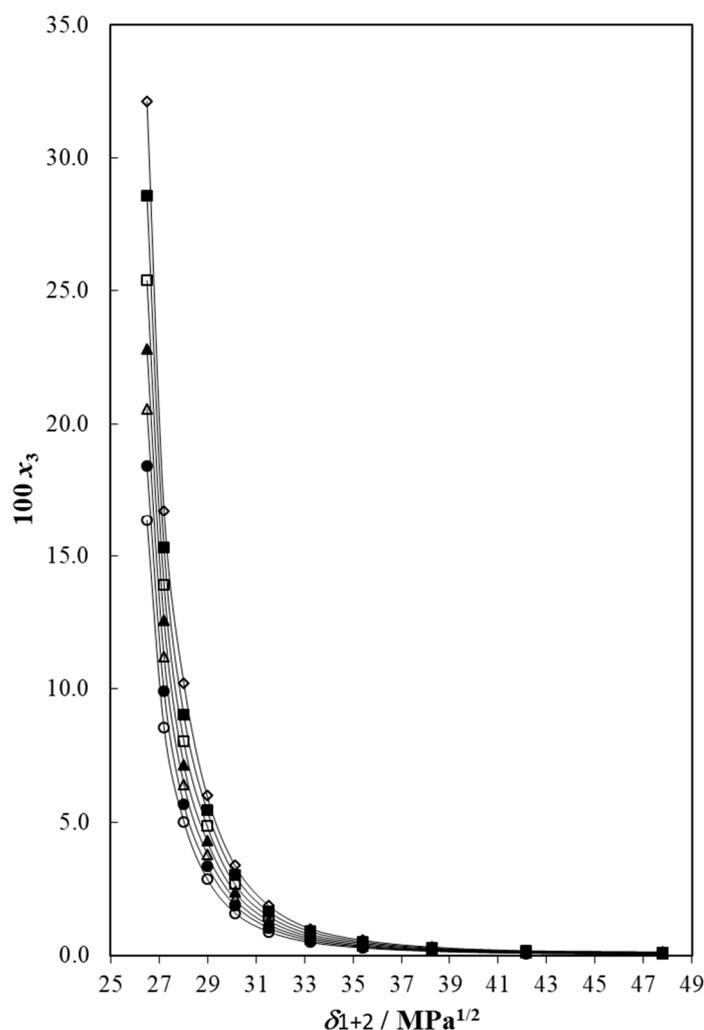
Figure 2. Mole fraction solubility of benzoic acid (x_3) as function of the Hildebrand solubility parameter in {ethanol (1) + water (2)} mixtures at different temperatures. ○: T = 293.15 K; •: T = 298.15 K, Δ: T = 303.15 K, ▲: T = 308.15 K, □: T = 313.15 K, ■: T = 318.15 K, ◊: T = 323.15 K.

3.2. The Cosolvency Models

Among all the reported cosolvency models used to calculate drug solubilities in mixed solvents at ambient or any other temperature [36,37], the log-linear model proposed by Yalkowsky is the simplest one [38], which requires only two experimental solubility determinations (in neat solvents) to predict the solubility at other solvent compositions. The Yalkowsky model is commonly represented as:

$$\ln x_{3(1+2)} = w_1 \ln x_{3(1)} + w_2 \ln x_{3(2)} \qquad (2)$$

where $x_{3(1+2)}$ is the mole fraction solubility of benzoic acid in the solvent mixtures, $x_{3(1)}$ is the mole fraction solubility in neat ethanol (component 1), $x_{3(2)}$ is the mole fraction solubility in neat water (component 2), and w_1 and w_2 are the mass fractions of ethanol (1) and water (2) in the solvent mixtures in the absence of benzoic acid (3). Thus, the obtained mean percentage deviation (MPD) values for calculating the solubility of benzoic acid in {ethanol (1) + water (2)} mixtures at T = (293.15, 298.15, 303.15, 308.15, 313.15, 318.15 and

323.15) K by using this model are (2.4, 2.2, 2.7, 4.2, 6.1, 9.0 and 5.5) %, respectively, with an overall MPD of 5.5%. It is important to note that the MPD is computed using:

$$MPD = \frac{100}{N} \sum \frac{\left| x_3^{cal} - x_3 \right|}{x_3} \tag{3}$$

where N is the number of experimental data points.

As mentioned above, Equation (2) is capable of estimating drug solubilities using only solubility data in the mono-solvents. However, it could be extended as:

$$\ln x_{3(1+2),T} = w_1 \left(A_1 + \frac{B_1}{T} \right) + w_2 \left(A_2 + \frac{B_2}{T} \right) \tag{4}$$

to be applied at various temperatures ($x_{3(1+2),T}$) using a single equation. In Equation (4), A and B terms are the model constants [39]. In particular, the obtained constants for equilibrium solubility of benzoic acid in {ethanol (1) + water (2)} mixtures are $A_1 = 5.392$, $B_1 = -2113.628$, $A_2 = 3.466$ and $B_2 = -3266.275$, which resulted in the MPD of 5.7%.

In addition to above mentioned simple and extended models, the Jouyban–Acree model is the most accurate model to describe the drug solubility in binary solvent mixtures at various temperatures and it is expressed as [36]:

$$\ln x_{3(1+2),T} = w_1 \ln x_{3(1),T} + w_2 \ln x_{3(2),T} + \left(\frac{w_1 w_2}{T} \right) \sum_{i=0}^{2} J_i (w_1 - w_2)^i \tag{5}$$

where J_i terms are the model constants that are computed using a no intercept least square analysis [34]. Accordingly, the generated solubility values of benzoic acid in {ethanol (1) + water (2)} was fitted to Equation (5) and the trained model is:

$$\ln x_{3(1+2),T} = w_1 \ln x_{3(1),T} + w_2 \ln x_{3(2),T} + \left(\frac{w_1 w_2}{T} \right) \left[-65.289 + 144.997(w_1 - w_2) \right] \tag{6}$$

The F value of Equation (6) was 23, and the correlation and the model constants were significant with $p < 0.0005$. Equation (6) is valid for calculating the solubility of benzoic acid in {ethanol (1) + water (2)} mixtures at various temperatures by employing the solubility data of benzoic acid in ethanol and water at each temperature or mixture-composition of interest. The obtained MPD for the back-calculated solubility data of benzoic acid using Equation (6) was 4.6%.

Although Equation (6) provided accurate correlation for solubility of benzoic acid in {ethanol (1) + water (2)} mixtures, it requires the experimental solubility data in neat ethanol and water at any temperature of interest (i.e., $x_{3(1),T}$ and $x_{3(2),T}$) to calculate the solubility of benzoic acid in binary mixtures. However, one may combine the trained version of Equation (4) with Equation (6) to provide a full predictive model as:

$$\begin{aligned} \ln x_{3(1+2),T} &= w_1 \left(5.392 - \frac{2113.628}{T} \right) + w_2 \left(3.466 - \frac{3266.275}{T} \right) \\ &+ \left(\frac{w_1 w_2}{T} \right) \left[-65.882 + 144.819(w_1 - w_2) \right] \end{aligned} \tag{7}$$

Equation (7) calculates the solubilities of benzoic acid in these binary mixtures at various temperatures with an MPD of 4.6% and does not require any experimental input data. It should be noted that the J_2 term in both Equations (6) and (7) was not statistically significant ($p > 0.05$) and was excluded from the equation. In practical applications of Equation (7), one may train the model using a minimum number of seven experimental data points and then predict the rest of the required data in any solvent composition and temperature of interest, as has been exemplified in a previous communication [40]. When the model was trained with the solubility data in ethanol and water at $T = (293.15$ and 323.15) K (the lowest and highest temperatures) and in $w_1 = 0.3$, 0.5 and 0.7 at $T = 298.15$ (totally, 7 data points), the rest of data points were predicted with the MPD of 7.6% ($N = 70$).

All produced MPD values rely on experimental relative standard deviation values (usually < 10.0%) and could be considered as an acceptable error level.

3.3. Solid Phases' Analyses

The DSC thermograms of benzoic acid as the original untreated sample and after saturating it in neat water, in the aqueous mixture of $w_1 = 0.50$, and in neat ethanol, are depicted in Figures A1–A4 (Appendix A). There are two endothermic peaks corresponding to the melting and thermal degradation of benzoic acid. Observed on-set temperatures of melting varied from (394.8 to 395.1) K; whereas, enthalpies of melting varied from (20.49 to 21.04) kJ·mol^{-1}, which are in agreement with those reported earlier [41]. The X-ray diffraction spectra for benzoic acid without any treatment and after dissolving it in neat water, in the aqueous mixture of $w_1 = 0.50$, and in neat ethanol, are shown in Figures A5–A8 (Appendix B). As observed, the positions of the characteristic peaks are comparable in each of the samples analyzed and also are in agreement with those reported earlier [42]. Thus, it is observable that benzoic acid did not suffer crystal polymorphic transitions or solvate formation after dissolution and saturation in these solvent systems.

3.4. Ideal Solubility and Activity Coefficients of Benzoic Acid in Mixed Solvents

Ideal solubilities of benzoic acid (x_3^{id}) at the temperatures of interest were calculated by means of:

$$\ln x_3^{\mathrm{id}} = -\frac{\Delta_{\mathrm{fus}}H(T_{\mathrm{fus}} - T)}{RT_{\mathrm{fus}}T} + \left(\frac{\Delta C_p}{R}\right)\left[\frac{(T_{\mathrm{fus}} - T)}{T} + \ln\left(\frac{T}{T_{\mathrm{fus}}}\right)\right] \tag{8}$$

Here, $\Delta_{\mathrm{fus}}H$ is the molar enthalpy of melting of the pure benzoic acid (obtained at the melting point, i.e., 18.01 kJ·mol^{-1} [39]), T_{fus} is the absolute melting point (i.e., 395.2 K [39]), T is the absolute dissolution temperature, R is the universal gas constant (8.3145 J·mol^{-1}·K^{-1}), and ΔC_p is the difference between the molar heat capacities of benzoic acid as crystalline form and its hypothetical super-cooled liquid form at the dissolution temperature [43]. However, due to the difficulty in ΔC_p determination, this value has been considered in this research as the same as the one of the entropy of fusion ($\Delta_{\mathrm{fus}}S = \Delta_{\mathrm{fus}}H/T_{\mathrm{fus}}$, i.e., 45.7 J·mol^{-1}·K^{-1}). Table 2 shows that the ideal solubilities of benzoic acid are higher than the experimental solubilities at all the temperatures studied.

On the other hand, Table 4 summarizes the asymmetrical activity coefficients of benzoic acid (γ_3) in neat solvents and in {ethanol (1) + water (2)} mixtures at all temperatures. The γ_3 values were calculated as the quotient: x_3^{id}/x_3 from the experimental and ideal benzoic acid solubilities summarized in Table 2. As observed, at $T = 298.15$ K γ_3 values vary from 379 in neat water (where the minimum benzoic acid solubility is obtained) to 1.15 in neat ethanol (where the maximum benzoic acid solubility is achieved). In all solvent systems, the γ_3 values decrease with the temperature-arising. All the obtained γ_3 values are higher than the unit because the experimental solubilities in all the solvent systems are lower than x_3^{id} at all temperatures tested. However, in neat ethanol, the γ_3 values are near unit, indicating nearly-ideal behavior of benzoic acid in this solvent. Furthermore, a rough estimate of the respective solute-solvent intermolecular interactions was performed from the γ_3 values, based on [44]:

$$\ln \gamma_3 = (e_{ss} + e_{33} - 2e_{s3})\frac{V_3 \varphi_s^2}{RT} \tag{9}$$

Here, subscript s stands for the solvent system (which corresponds to neat solvents or aqueous–ethanol binary mixtures), e_{ss}, e_{33} and e_{s3} represent the solvent–solvent, solute–solute and solvent–solute interaction energies, respectively. However, it is important to note that in multicomponent systems like ethanol–water–benzoic acid, some water–cosolvent interactions are present, which could also play an important role in the magnitudes of equilibrium solubility and dissolution rate of drugs. V_3 is the molar volume of the super-cooled

liquid benzoic acid and φ_s is the volume fraction of the solvent system in every saturated solution. It is noteworthy that when low x_3 values are obtained, the term $(V_3\varphi_s{}^2/RT)$ can be considered as almost constant regardless of the solvent system composition because φ_s is almost invariant and near to 1.0. Thus, the γ_3 values would depend mainly on the terms e_{ss}, e_{33} and e_{s3} [44]. As well-known, e_{ss} and e_{33} are unfavorable for drug dissolution and equilibrium solubility, but e_{s3} favors the respective drug dissolution processes. The contribution of e_{33} towards the equilibrium solubility and dissolution rate of benzoic acid was considered to be almost constant regardless of the solvent system studied.

Table 4. Activity coefficients of benzoic acid (γ_3) in {ethanol (1) + water (2)} mixtures at several temperatures and p = 90 kPa. [a,c.]

w_1 [b,c]	x_1 [b,c]	*T*/K [c]						
		293.15	298.15	303.15	308.15	313.15	318.15	323.15
0.00	0.0000	413	379	351	324	298	272	251
0.10	0.0417	241	223	209	202	197	192	186
0.20	0.0891	123	121	117	115	112	108	106
0.30	0.1436	68.2	66.5	65.4	63.3	61.2	59.9	58.2
0.40	0.2068	39.4	37.9	36.7	36.0	35.1	33.8	32.9
0.50	0.2812	21.7	20.4	20.1	19.4	18.9	18.4	17.6
0.60	0.3698	12.1	11.3	11.0	10.7	10.4	10.1	9.78
0.70	0.4772	6.73	6.31	6.12	5.92	5.72	5.58	5.52
0.80	0.6101	3.85	3.75	3.62	3.56	3.46	3.36	3.24
0.90	0.7788	2.26	2.14	2.07	2.02	2.00	1.98	1.98
1.00	1.0000	1.18	1.15	1.13	1.12	1.10	1.06	1.03

[a] p is the atmospheric pressure in Aksaray, Turkey. [b] w_1 and x_1 are the mass and mole fractions of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of benzoic acid (3), respectively. [c] Standard uncertainty in T is $u(T_{hm}) = 0.10$ K. Standard uncertainty in p is $u(p) = 3.0$ kPa. Mean relative uncertainties in w_1 and x_1 were $u(w_1) = 0.0008$ and $u(x_1) = 0.0008$. Standard uncertainty in T is $u(T) = 0.10$ K. Average relative uncertainty in γ_3 is $u_r(\gamma_3) = 0.028$.

As indicated above, a qualitative approach to intermolecular interactions was made based on the e_{ss}, e_{33} and e_{s3} energetic terms of Equation (9). Hence, based on polarities, it follows that e_{ss} is highest in neat water ($\delta = 47.8$ MPa$^{1/2}$) and lowest in neat ethanol ($\delta = 26.5$ MPa$^{1/2}$) [27,28]. Neat water and water-rich mixtures, exhibiting γ_3 values higher than 250, would imply high e_{ss} and low e_{s3} values. Otherwise, in ethanol-rich mixtures exhibiting γ_3 values lower than 2.5, the e_{ss} values are relatively low and the e_{s3} values would be comparatively high regarding water-rich mixtures.

3.5. Apparent Thermodynamic Functions of Dissolution

All the apparent thermodynamic quantities of dissolution of benzoic acid in neat solvents and in {ethanol (1) + water (2)} mixtures were estimated at $T = 298.15$ K. In this way, the apparent standard enthalpic changes for benzoic acid dissolution processes ($\Delta_{soln}H°$) were obtained by means of the modified van 't Hoff equation, as [45,46]:

$$\left(\frac{\partial \ln x_3}{\partial (1/(T/\text{K}) - 1/298.15\,\text{K})}\right)_P = -\frac{(\Delta_{soln}H°/\text{J}\cdot\text{mol}^{-1})}{R} \tag{10}$$

The apparent standard Gibbs energy changes for the benzoic acid dissolution processes ($\Delta_{soln}G°$) were calculated by means of:

$$\Delta_{soln}G° = -R \cdot 298.15\,\text{K} \cdot \text{intercept} \tag{11}$$

Here, the intercepts used are those obtained in the respective linear regressions of ln x_3 vs. $(1/T - 1/298.15\,\text{K})$. As visual help, Figure 3 depicts the solubility van 't Hoff plots obtained in the neat solvents, water and ethanol, and in the nine {ethanol (1) + water (2)} mixtures. Linear regressions with determination coefficients higher than 0.99 were obtained

in all cases [47–49]. Standard apparent entropic changes for benzoic acid dissolution processes ($\Delta_{\text{soln}}S°$) were obtained from the respective $\Delta_{\text{soln}}H°$ and $\Delta_{\text{soln}}G°$ values by using Equation (12) [50]:

$$\Delta_{\text{soln}}S°/\text{J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1} = \frac{\left(\Delta_{\text{soln}}H°/\text{J} \cdot \text{mol}^{-1} - \Delta_{\text{soln}}G°/\text{J} \cdot \text{mol}^{-1}\right)}{298.15\text{K}} \quad (12)$$
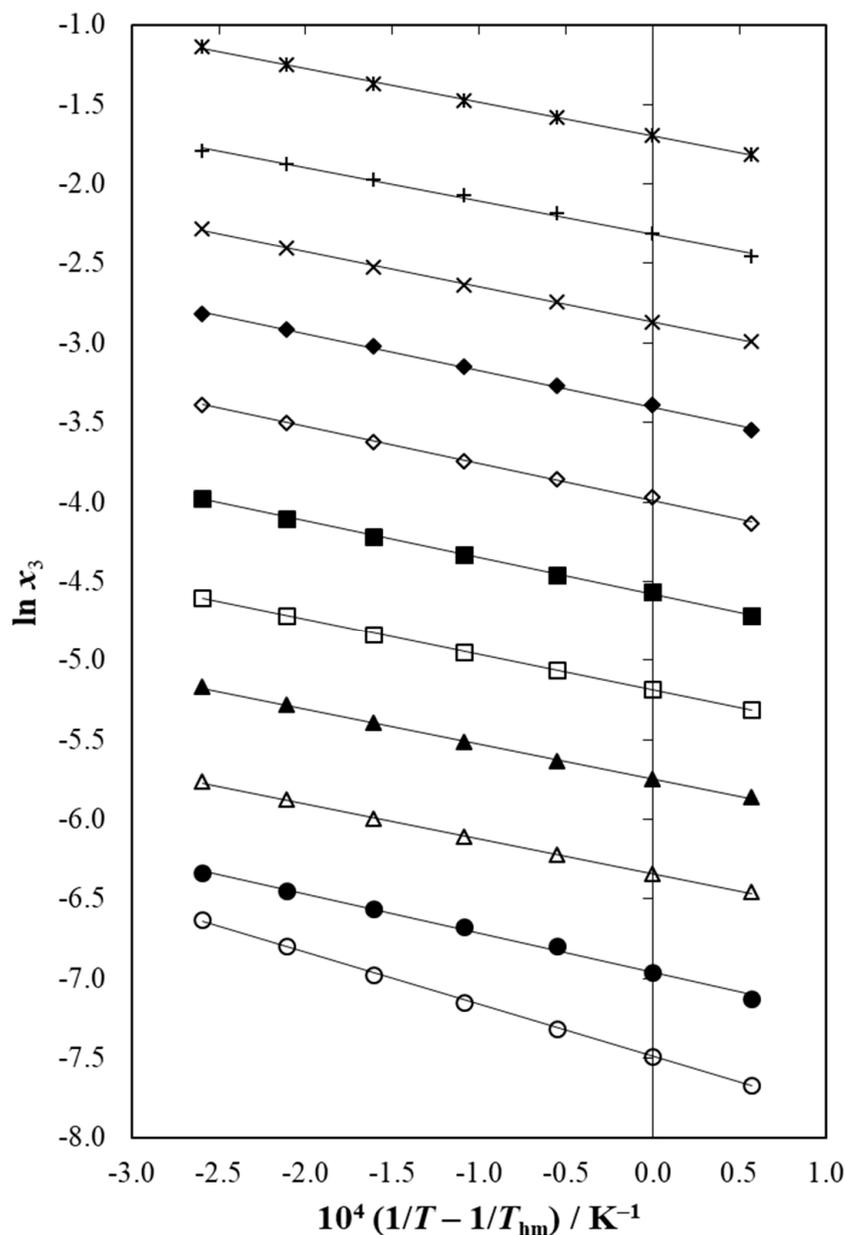
Figure 3. van 't Hoff plot of the solubility of benzoic acid (3) in some {ethanol (1) + water (2)} solvent systems. ○: $w_1 = 0.00$ (neat water), ●: $w_1 = 0.10$, △: $w_1 = 0.20$, ▲: $w_1 = 0.30$, □: $w_1 = 0.40$, ■: $w_1 = 0.50$, ◇: $w_1 = 0.60$, ◆: $w_1 = 0.70$, ×: $w_1 = 0.80$, +: $w_1 = 0.90$, ✳: $w_1 = 1.00$ (neat ethanol).

Table 5 summarizes the standard apparent molar thermodynamic functions for dissolution processes of benzoic acid (3) in neat solvents and in all the {ethanol (1) + water (2)} mixtures at $T = 298.15$ K.

Table 5. Apparent thermodynamic functions relative to dissolution processes of benzoic acid (3) in {ethanol (1) + water (2)} mixtures at T = 298.15 K and p = 90 kPa. [a,c]

w_1 [b,c]	x_1 [b,c]	$\Delta_{\text{soln}}G°$/kJ·mol^{-1} [c]	$\Delta_{\text{soln}}H°$/kJ·mol^{-1} [c]	$\Delta_{\text{soln}}S°$/J·mol^{-1}·K^{-1} [c]	$T\Delta_{\text{soln}}S°$/kJ·mol^{-1} [c]	ζ_H [d]	ζ_{TS} [d]
0.00	0.0000	18.57	27.15	28.79	8.58	0.760	0.240
0.10	0.0417	17.25	20.45	10.72	3.20	0.865	0.135
0.20	0.0891	15.72	18.19	8.30	2.48	0.880	0.120
0.30	0.1436	14.25	18.29	13.57	4.04	0.819	0.181
0.40	0.2068	12.86	18.60	19.26	5.74	0.764	0.236
0.50	0.2812	11.35	19.07	25.89	7.72	0.712	0.288
0.60	0.3698	9.89	19.30	31.55	9.41	0.672	0.328
0.70	0.4772	8.43	19.19	36.09	10.76	0.641	0.359
0.80	0.6101	7.11	18.46	38.06	11.35	0.619	0.381
0.90	0.7788	5.74	17.41	39.15	11.67	0.599	0.401
1.00	1.0000	4.21	17.53	44.70	13.33	0.568	0.432
	Ideal	3.84	14.06	34.28	10.22	0.579	0.421

[a] p is the atmospheric pressure in Aksaray, Turkey. [b] w_1 and x_1 are the mass and mole fractions of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of benzoic acid (3), respectively. [c] Standard uncertainty in T is $u(T)$ = 0.1 K. Standard uncertainty in p is $u(p)$ = 3.0 kPa. Mean relative uncertainties in w_1 and x_1 were $u(w_1)$ = 0.0008 and $u(x_1)$ = 0.0008. Average relative standard uncertainty in apparent thermodynamic quantities of real dissolution processes are $u_r(\Delta_{\text{soln}}G°)$ = 0.027, $u_r(\Delta_{\text{soln}}H°)$ = 0.035, $u_r(\Delta_{\text{soln}}S°)$ = 0.044, $u_r(T\Delta_{\text{soln}}S°)$ = 0.044. [d] ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward apparent Gibbs energy of dissolution.

Apparent standard Gibbs energies, enthalpies and entropies relative to the benzoic acid dissolution processes are positive in all cases, as shown in Table 5. This implies endothermic and entropy-driven dissolution processes. Moreover, $\Delta_{\text{soln}}G°$ values decrease continuously from neat water to neat ethanol indicating more affinity of benzoic acid by semipolar solvent media like the one corresponding to neat ethanol or even by less polar solvents if they were analyzed. Relative contributions by enthalpy (ζ_H) and entropy (ζ_{TS}) toward the benzoic acid dissolution processes were calculated by means of [51]:

$$\zeta_H = \frac{|\Delta_{\text{soln}}H°|}{|\Delta_{\text{soln}}H°| + |T\Delta_{\text{soln}}S°|} \tag{13}$$

$$\zeta_{TS} = \frac{|T\Delta_{\text{soln}}S°|}{|\Delta_{\text{soln}}H°| + |T\Delta_{\text{soln}}S°|} \tag{14}$$

As shown in Table 5, the main contributor to the positive standard apparent molar Gibbs energies of dissolution of benzoic acid was the positive enthalpy, with ζ_H values higher than 0.56, which demonstrates the energetic predominance in all these benzoic acid dissolution processes.

3.6. Apparent Thermodynamic Quantities of Mixing

Global dissolution processes of benzoic acid in {ethanol (1) + water (2)} mixtures may be represented by means of the following hypothetical process:

Solute$_{\text{(Solid)}}$ at $T \rightarrow$ Solute$_{\text{(Solid)}}$ at $T_{\text{fus}} \rightarrow$ Solute$_{\text{(Liquid)}}$ at $T_{\text{fus}} \rightarrow$ Solute$_{\text{(Liquid)}}$ at $T \rightarrow$ Solute$_{\text{(Solution)}}$ at T

Here, the hypothetical stages are as follows: (i) the heating and melting of benzoic acid at T_{fus} = 395.2 K [41], (ii) the cooling of the liquid benzoic acid to the considered temperature (T = 298.15 K), and (iii) the subsequent mixing of both the hypothetical benzoic acid super-cooled liquid and the solvent system under consideration at T = 298.15 K [52]. This allowed the calculation of the individual thermodynamic contributions by fusion and mixing toward the overall benzoic acid dissolution processes, by means of:

$$\Delta_{\text{soln}}H° = \Delta_{\text{fus}}H^{298.15} + \Delta_{\text{mix}}H° \tag{15}$$

$$\Delta_{\text{soln}}S° = \Delta_{\text{fus}}S^{298.15} + \Delta_{\text{mix}}S° \tag{16}$$

where $\Delta_{\text{fus}}H^{298.15}$ and $\Delta_{\text{fus}}S^{298.15}$ indicate the thermodynamic quantities of benzoic acid fusion and its cooling at $T = 298.15$ K. In turn, these two functions were calculated by means of Equations (17) and (18), respectively [53]:

$$\Delta_{\text{fus}}H^{298.15} = \Delta_{\text{fus}}H^{T_{\text{fus}}} - \Delta C_p(T_{\text{fus}} - 298.15\text{ K}) \tag{17}$$

$$\Delta_{\text{fus}}H^{298.15} = \Delta_{\text{fus}}H^{T_{\text{fus}}} - \Delta C_p(T_{\text{fus}} - 298.15\text{ K}) \tag{18}$$

Table 6 summarizes the apparent thermodynamic quantities of mixing of the hypothetical benzoic acid as a super-cooled liquid with all the aqueous–ethanol mixtures and the neat solvents at $T = 298.15$ K. The apparent Gibbs energies of mixing are positive because the experimental solubilities of benzoic acid are lower than the ideal ones at all temperatures, as indicated above. Otherwise, $\Delta_{\text{mix}}H°$ are positive in all cases, but $\Delta_{\text{mix}}S°$ are negative from neat water to the mixture of $w_1 = 0.60$, but positive from the mixture of $w_1 = 0.70$ to neat ethanol. In this way, non-enthalpy-nor entropy driving is observed for benzoic acid mixing processes in the composition interval $0.0 \leq w_1 \leq 0.6$ (where $\Delta_{\text{mix}}H°$ > 0 and $\Delta_{\text{mix}}S°$ < 0); whereas, in the interval $0.7 \leq w_1 \leq 1.0$, the mixing processes are entropy-driven (where $\Delta_{\text{mix}}H°$ > 0 and $\Delta_{\text{mix}}S°$ > 0). Moreover, to compare the relative contributions of enthalpy (ζ_H) and entropy (ζ_{TS}) to the mixing processes, two equations analogous to Equations (13) and (14) were also employed. Thus, in almost all cases the main contributor to apparent Gibbs energy of mixing is the apparent mixing enthalpy, except in the interval $0.1 \leq w_1 \leq 0.3$, where the apparent mixing entropy is the dominant thermodynamic function.

Table 6. Apparent thermodynamic functions relative to mixing processes of benzoic acid (3) in {ethanol (1) + water (2)} mixtures at $T = 298.15$ K and $p = 90$ kPa. [a,c.]

w_1 [b,c]	x_1 [b,c]	$\Delta_{\text{mix}}G°$/kJ·mol^{-1} [c]	$\Delta_{\text{mix}}H°$/kJ·mol^{-1} [c]	$\Delta_{\text{mix}}S°$/J·mol^{-1}·K^{-1} [c]	$T\Delta_{\text{mix}}S°$/kJ·mol^{-1} [c]	ζ_H [d]	ζ_{TS} [d]
0.00	0.0000	14.73	13.09	−5.49	−1.64	0.889	0.111
0.10	0.0417	13.41	6.39	−23.56	−7.02	0.476	0.524
0.20	0.0891	11.88	4.14	−25.98	−7.74	0.348	0.652
0.30	0.1436	10.41	4.23	−20.71	−6.18	0.407	0.593
0.40	0.2068	9.02	4.54	−15.01	−4.48	0.504	0.496
0.50	0.2812	7.51	5.01	−8.39	−2.50	0.667	0.333
0.60	0.3698	6.05	5.24	−2.73	−0.81	0.866	0.134
0.70	0.4772	4.59	5.13	1.82	0.54	0.905	0.095
0.80	0.6101	3.27	4.40	3.78	1.13	0.796	0.204
0.90	0.7788	1.90	3.35	4.87	1.45	0.698	0.302
1.00	1.0000	0.37	3.47	10.42	3.11	0.528	0.472

[a] p is the atmospheric pressure in Aksaray, Turkey. [b] w_1 and x_1 are the mass and mole fraction of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of benzoic acid (3). [c] Standard uncertainty in T is $u(T) = 0.1$ K. Standard uncertainty in p is $u(p) = 3.0$ kPa. Mean relative uncertainties in w_1 and x_1 were $u(w_1) = 0.0008$ and $u(x_1) = 0.0008$. Average relative standard uncertainty in apparent thermodynamic quantities of mixing processes are $u_r(\Delta_{\text{mix}}G°)$ = 0.029, $u_r(\Delta_{\text{mix}}H°) = 0.038$, $u_r(\Delta_{\text{mix}}S°) = 0.048$, $u_r(T\Delta_{\text{mix}}S°) = 0.048$. [d] ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward apparent Gibbs energy of mixing.

3.7. Thermodynamic Quantities of Solvation

Furthermore, in addition to the previous fusion-mixing subprocesses, the overall dissolution process may also be represented by the hypothetic stages: Solute$_{\text{(Solid)}}$ → Solute$_{\text{(Vapor)}}$ → Solute$_{\text{(Solution)}}$; where, the respective partial processes toward the dissolution process are sublimation and solvation of benzoic acid [54]. This treatment allowed the calculation of the partial thermodynamic contributions to the dissolution process by means of Equations (19) and (20), respectively, while the Gibbs energy of solvation was calculated by means of Equation (21):

$$\Delta_{\text{soln}}H° = \Delta_{\text{subl}}H° + \Delta_{\text{solv}}H° \tag{19}$$

$$\Delta_{\text{soln}}S° = \Delta_{\text{subl}}S° + \Delta_{\text{solv}}S° \tag{20}$$

$$\Delta_{\text{soln}}G^\circ = \Delta_{\text{subl}}G^\circ + \Delta_{\text{solv}}G^\circ \tag{21}$$

where, $\Delta_{\text{subl}}G^\circ = 5.58 \text{ kJ·mol}^{-1}$ and $\Delta_{\text{subl}}H^\circ = 92.11 \text{ kJ·mol}^{-1}$ at 298.15 K as reported by Kruif and Blok [55]. Thermodynamic functions of solvation are summarized in Table 7, where negative enthalpies and entropies of solvation were obtained. On the other hand, with the aim of comparing the relative contributions of enthalpy (ζ_H) and entropy (ζ_{TS}) toward the solvation process, two equations analogous to Equations (13) and (14) were employed again.

Table 7. Apparent thermodynamic functions relative to solvation processes of benzoic acid (3) in {ethanol (1) + water (2)} mixtures at T = 298.15 K and p = 90 kPa. [a,c]

w_1 [b,c]	x_1 [b,c]	$\Delta_{\text{solv}}G^\circ$/kJ·mol^{-1} [c]	$\Delta_{\text{solv}}H^\circ$/kJ·mol^{-1} [c]	$\Delta_{\text{solv}}S^\circ$/J·mol^{-1}·K^{-1} [c]	$T\Delta_{\text{solv}}S^\circ$/kJ·mol^{-1} [c]	ζ_H [d]	ζ_{TS} [d]	ε_H [e]	ε_S [e]
0.00	0.0000	12.99	−64.96	−261.43	−77.94	0.455	0.545	0.666	0.795
0.10	0.0417	11.67	−71.66	−279.49	−83.33	0.462	0.538	0.838	0.924
0.20	0.0891	10.14	−73.91	−281.91	−84.05	0.468	0.532	0.896	0.941
0.30	0.1436	8.67	−73.81	−276.65	−82.48	0.472	0.528	0.893	0.903
0.40	0.2068	7.28	−73.50	−270.95	−80.78	0.476	0.524	0.885	0.863
0.50	0.2812	5.77	−73.03	−264.32	−78.81	0.481	0.519	0.873	0.816
0.60	0.3698	4.31	−72.81	−258.66	−77.12	0.486	0.514	0.868	0.775
0.70	0.4772	2.85	−72.91	−254.12	−75.77	0.490	0.510	0.870	0.743
0.80	0.6101	1.53	−73.65	−252.15	−75.18	0.495	0.505	0.889	0.729
0.90	0.7788	0.16	−74.69	−251.06	−74.85	0.499	0.501	0.916	0.721
1.00	1.0000	−1.37	−74.57	−245.51	−73.20	0.505	0.495	0.913	0.682

[a] p is the atmospheric pressure in Aksaray, Turkey. [b] w_1 and x_1 are the mass and mole fraction of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of benzoic acid (3). [c] Standard uncertainty in T is $u(T)$ = 0.1 K. Standard uncertainty in p is $u(p)$ = 3.0 kPa. Mean relative uncertainties in w_1 and x_1 were $u(w_1)$ = 0.0008 and $u(x_1)$ = 0.0008. Average relative standard uncertainty in apparent thermodynamic quantities of mixing processes are $u_r(\Delta_{\text{solv}}G^\circ)$ = 0.032, $u_r(\Delta_{\text{solv}}H^\circ)$ = 0.042, $u_r(\Delta_{\text{solv}}S^\circ)$ = 0.053, $u_r(T\Delta_{\text{solv}}S^\circ)$ = 0.053. [d] ζ_H and ζ_{TS} are the relative contributions of enthalpy and entropy toward the apparent Gibbs energy of mixing. [e] ε_H and ε_S are the relative ratios of specific and non-specific solute–solvent interactions expressed in terms of enthalpy and entropy.

From the ζ_H and ζ_{TS} values presented in Table 7, it follows that enthalpy is the main contributing force to the standard Gibbs energy of the solvation process of benzoic acid in every solvent mixture (ζ_H values are higher than 0.66 in all solvent systems). Moreover, because the balance between specific and non-specific solute–solvent interactions are also important, some parameters describing the relative ratio of specific and non-specific solute-solvent interaction in terms of enthalpies (ε_H) and entropies (ε_S) were also calculated, according to the following definitions [51]:

$$\varepsilon_H = \left| \frac{\Delta_{\text{spec}}H^\circ}{\Delta_{\text{non-spec}}H^\circ} \right| \tag{22}$$

$$\varepsilon_S = \left| \frac{\Delta_{\text{spec}}S^\circ}{\Delta_{\text{non-spec}}S^\circ} \right| \tag{23}$$

where, $\Delta_{\text{spec}}H^\circ = \Delta_{\text{soln(solvent-i)}}H^\circ - \Delta_{\text{soln(CH)}}H^\circ = \Delta_{\text{soln(CH} \rightarrow \text{solvent-i)}}H^\circ$, $\Delta_{\text{non-spec}}H^\circ = \Delta_{\text{soln(CH)}}H^\circ - \Delta_{\text{subl}}H^\circ = \Delta_{\text{solv(CH)}}H^\circ$, $\Delta_{\text{spec}}S^\circ = \Delta_{\text{soln(solvent-i)}}S^\circ - \Delta_{\text{soln(CH)}}S^\circ = \Delta_{\text{soln(CH} \rightarrow \text{solvent-i)}}S^\circ$, and $\Delta_{\text{non-spec}}S^\circ = \Delta_{\text{soln(CH)}}S^\circ$.

Cyclohexane (CH) was chosen as an "inert" solvent because it interacts with benzoic acid molecules mainly by non-specific interactions like London dispersion forces, while the cosolvent mixtures studied here interact with benzoic acid by specific interactions such as hydrogen bonding. Dissolution thermodynamics quantities of benzoic acid in CH were calculated by means of the modified van 't Hoff and Gibbs equations from solubility values taken from the literature [6]. The respective values for apparent dissolution thermodynamic functions are: $\Delta_{\text{soln(CH)}}G^\circ = 11.25 \text{ kJ·mol}^{-1}$, $\Delta_{\text{soln(CH)}}H^\circ = 53.12 \text{ kJ·mol}^{-1}$,

and $\Delta_{\text{soln(CH)}}S° = 140.43$ J·mol^{-1}·K^{-1}. In this way, the ε_H and ε_S values for benzoic acid solvation are also presented in Table 7. These values indicate that during the dissolution process of this chemical in all solvent systems, the specific solute-solvent interactions (hydrogen bonding, mainly) effectively affect the entropic term of Gibbs energy with respect to non-specific interactions.

3.8. Enthalpy-Entropy Compensation Analysis

Extra-thermodynamic studies, which include enthalpy–entropy compensation analysis, provide powerful tools to inquire into the main molecular mechanisms implicated in several physical and chemical processes that involve organic compounds like a variety of drugs [56,57]. Hence, non-enthalpy-entropy compensation effects have been associated to the dissolution processes of several organic compounds in {ethanol (1) + water (2)} mixtures as has been summarized earlier [58]. These physicochemical studies were performed in order to identify the main mechanisms involved in the cosolvent action of ethanol for increasing or decreasing the solubility depending on the solvent mixtures composition. Normally, weighted plots of $\Delta_{\text{soln}}H°$ vs. $\Delta_{\text{soln}}G°$ have been used for performing these analyses [59–61]. In particular, Figure 4 clearly shows that benzoic acid exhibits a non-linear $\Delta_{\text{soln}}H°$ vs. $\Delta_{\text{soln}}G°$ trend defined by the quotient polynomial shown as Equation (24), where the obtained statistical parameters were as follows: adjusted $r^2 = 0.982$, typical error = 0.335, and $F = 161.3$. Thus, variant-positive slopes are observed from neat water to the mixture of $w_1 = 0.20$ and the composition interval of $0.60 < w_1 < 0.90$, whereas variant-negative slopes are observed in the composition interval of $0.20 < w_1 < 0.60$ and from the mixture of $w_1 = 0.90$ to neat ethanol. Accordingly, in the first cases, the benzoic acid transfer processes are entropy-driven, whereas, in the other cases, the driving mechanism for the transfer processes of benzoic acid from the more polar to the less polar solvent systems is entropy.

$$\Delta_{\text{soln}}H° = 37.40 - 10.69 \cdot (\Delta_{\text{soln}}G°) + 1.96 \cdot (\Delta_{\text{soln}}G°)^2 - 0.142 \cdot (\Delta_{\text{soln}}G°)^3 + 3.56 \cdot 10^{-3} \cdot (\Delta_{\text{soln}}G°)^4 \tag{24}$$
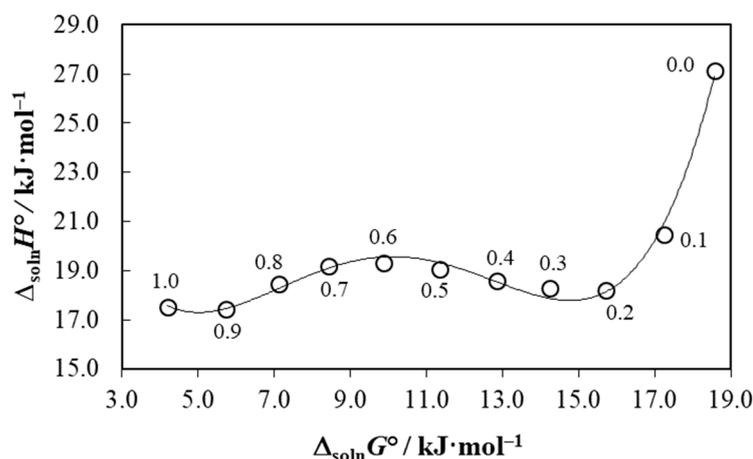
Figure 4. $\Delta_{\text{soln}}H°$ vs. $\Delta_{\text{soln}}G°$ enthalpy–entropy compensation plot for dissolution processes of benzoic acid (3) in {ethanol (1) + water (2)} mixtures at $T = 298.15$ K.

3.9. Preferential Solvation of Benzoic Acid

The preferential solvation parameters of benzoic acid (identified as compound 3) by ethanol (identified as compound 1) molecules in the different {ethanol (1) + water (2)} mixtures ($\delta x_{1,3}$), are defined as [2–4]:

$$\delta x_{1,3} = x_{1,3}^L - x_1 = -\delta x_{2,3} \tag{25}$$

where $x_{1,3}^L$ is the local mole fraction of ethanol in the molecular environment of benzoic acid and x_1 is the bulk mole fraction of ethanol in the initial {ethanol (1) + water (2)} binary solvent mixture free of benzoic acid. Thus, if the $\delta x_{1,3}$ value is positive, benzoic acid molecules are preferentially solvated by ethanol molecules in the solutions. In contrast, benzoic acid molecules are preferentially solvated by water molecules if this $\delta x_{1,3}$ parameter is negative. The values of $\delta x_{1,3}$ were obtained from the inverse Kirkwood-Buff integrals (IKBI) as described earlier [2–4]:

$$\delta x_{1,3} = \frac{x_1 x_2 (G_{1,3} - G_{2,3})}{x_1 G_{1,3} + x_2 G_{2,3} + V_{\text{cor}}} \tag{26}$$

with,

$$G_{1,3} = RT\kappa_T - \overline{V}_3 + x_2 \overline{V}_2 D/Q \tag{27}$$

$$G_{2,3} = RT\kappa_T - \overline{V}_3 + x_1 \overline{V}_1 D/Q \tag{28}$$

$$V_{\text{cor}} = 2522.5 \left(r_3 + 0.1363 \left(x_{1,3}^L \overline{V}_1 + x_{2,3}^L \overline{V}_2 \right)^{1/3} - 0.085 \right)^3 \tag{29}$$

Here, κ_T denotes the isothermal compressibility of the aqueous-ethanol mixtures. $\overline{V}_1$, $\overline{V}_2$ and $\overline{V}_3$ are respectively the partial molar volumes of ethanol, water, and benzoic acid in the dissolutions. The function D, defined in Equation (30), corresponds to the first derivative of the standard molar Gibbs energies of transfer of benzoic acid from neat water to every aqueous-ethanol mixture regarding the mole fraction of ethanol. The function Q, defined in Equation (31), involves the second derivative of the excess molar Gibbs energy of mixing of ethanol and water (G_{1+2}^{Exc}) regarding the mole fraction of water [2–4]. V_{cor} and r_3 are, respectively, the correlation volume and the molecular radius of benzoic acid. Here, r_3 was roughly calculated by means of Equation (32), where N_{Av} is the number of Avogadro.

$$D = \left(\frac{\partial \Delta_{\text{tr}} G_{3,2 \to 1+2}^{\text{o}}}{\partial x_1} \right)_{T,p} \tag{30}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G_{1+2}^{Exc}}{\partial x_2^2} \right)_{T,p} \tag{31}$$

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{\text{Av}}} \right)^{1/3} \tag{32}$$

To obtain definitive V_{cor} values, iteration processes are required because they depend on the local mole fractions of ethanol and water around the benzoic acid molecules in the respective solutions. Thus, these iteration processes were performed by replacing $\delta x_{1,3}$ and V_{cor} in the Equations (25), (26) and (29) to recalculate the $x_{1,3}^L$ values until obtaining non-variant values of V_{cor}.

Figure 5 shows the apparent Gibbs energies of transfer of benzoic acid from neat water to all aqueous-ethanol mixtures ($\Delta_{\text{tr}} G_{3,2 \to 1+2}^{\text{o}}$) at $T = 298.15$ K. These $\Delta_{\text{tr}} G_{3,2 \to 1+2}^{\text{o}}$ values were calculated from the experimental mole fraction solubility values reported in Table 2 by using:

$$\Delta_{\text{tr}} G_{3,2 \to 1+2}^{\text{o}} = RT \ln \left(\frac{x_{3,2}}{x_{3,1+2}} \right) \tag{33}$$

Obtained $\Delta_{\text{tr}} G_{3,2 \to 1+2}^{\text{o}}$ values were correlated by means of the regular polynomial shown as Equation (34), where the obtained statistical parameters were as follows: adjusted $r^2 = 0.9999$, typical error = 0.0421, and $F = 32{,}256$.
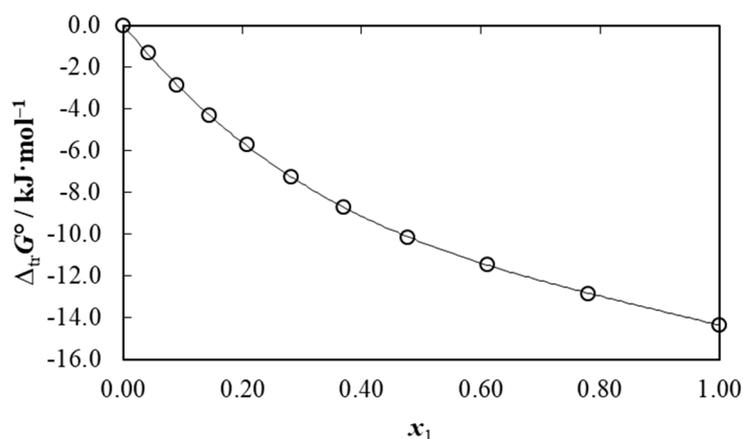
Figure 5. Gibbs energy of transfer of benzoic acid (3) from neat water (2) to {ethanol (1) + water (2)} mixtures at T = 298.15 K.

$$\Delta_{tr}G^o_{3,2\rightarrow1+2} = 0.02 - 34.92x_1 + 38.11x_1^2 - 21.95x_1^3 + 4.37x_1^4 \tag{34}$$

The D values summarized in Table 8 were calculated as the first derivative of Equation (34) solved in mixture composition steps of x_1 = 0.05. For the studied aqueous-ethanol mixtures, the Q, $RT\kappa_T$, $\overline{V}_1$ and $\overline{V}_2$ values at T = 298.15 K were taken from the literature [62,63]. In this research, the $\overline{V}_3$ value was considered the same as the one calculated by using the Fedors method (i.e., 99.9 cm^3·mol^{-1}, Table 3). Table 8 also shows that the $G_{1,3}$ and $G_{2,3}$ values are negative in all the mixed-solvent systems. The benzoic acid r_3 value was calculated as 0.341 nm. As indicated above, the V_{cor} values shown in Table 8 were obtained after three iterations. V_{cor} values increase with the ethanol-proportion in the mixtures because the $\overline{V}_1$ values are higher than the $\overline{V}_2$ values in all cases. Moreover, Table 8 also summarizes the preferential solvation parameters of benzoic acid by ethanol molecules ($\delta x_{1,3}$) in all the aqueous-ethanol mixtures at T = 298.15 K.

Table 8. Some properties associated to preferential solvation of benzoic acid (3) in {ethanol (1) + water (2)} mixtures at T = 298.15 K.

x_1 [a]	D/kJ·mol^{-1}	$G_{1,3}$/cm^3·mol^{-1}	$G_{2,3}$/cm^3·mol^{-1}	V_{cor}/cm^3·mol^{-1}	$100\ \delta x_{1,3}$
0.00	−34.92	−353.4	−98.8	583	0.00
0.05	−31.28	−340.2	−136.4	601	−2.13
0.10	−27.94	−320.5	−173.1	628	−3.01
0.15	−24.91	−297.0	−206.3	663	−2.61
0.20	−22.17	−272.3	−234.6	704	−1.31
0.25	−19.71	−248.6	−258.1	748	0.36
0.30	−17.51	−227.2	−277.8	791	2.01
0.35	−15.56	−208.7	−295.1	832	3.46
0.40	−13.85	−193.3	−311.9	873	4.68
0.45	−12.36	−180.6	−329.7	911	5.69
0.50	−11.09	−170.3	−350.3	949	6.54
0.55	−10.01	−161.8	−375.1	985	7.26
0.60	−9.12	−154.4	−404.3	1021	7.83
0.65	−8.40	−147.5	−436.3	1055	8.15
0.70	−7.83	−140.0	−464.3	1085	8.03
0.75	−7.42	−131.2	−476.7	1112	7.24
0.80	−7.13	−121.4	−461.8	1134	5.76
0.85	−6.97	−112.2	−419.6	1154	3.94
0.90	−6.91	−104.9	−363.8	1174	2.23
0.95	−6.94	−100.0	−309.4	1197	0.92
1.00	−7.05	−97.0	−264.0	1222	0.00

[a] x_1 is the mole fraction of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of benzoic acid (3).

Figure 6 shows a non-linear variation of benzoic acid $\delta x_{1,3}$ values regarding the ethanol proportion in the solvent mixtures as expressed by their mole fractions before solute adding. Initially, the addition of ethanol to neat water as solvent makes negative the $\delta x_{1,3}$ values of benzoic acid in the composition interval of $0.00 < x_1 < 0.24$. The maximum negative $\delta x_{1,3}$ value is obtained in the mixture of $x_1 = 0.10$ (i.e., $\delta x_{1,3} = -3.01 \times 10^{-2}$), which is higher than $|1.0 \times 10^{-2}|$. Hence, this result could be considered as a consequence of real preferential solvation effects of benzoic acid by water molecules, rather than a consequence of merely the uncertainties propagation associated to IKBI calculations [64,65]. Possibly the structuring of water molecules around the phenyl ring of this compound by hydrophobic hydration contributes to the lowering of the net $\delta x_{1,3}$ to negative values in these water-rich mixtures.
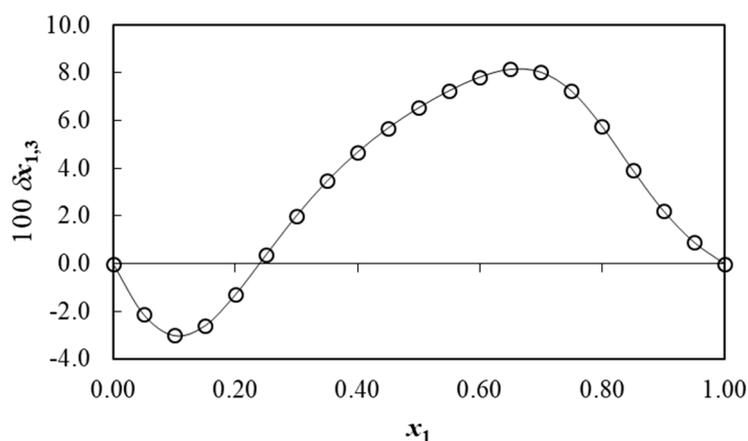
Figure 6. Preferential solvation parameters ($\delta x_{1,3}$) of benzoic acid ($\bigcirc$) by ethanol in {ethanol (1) + water (2)} mixtures at $T = 298.15$ K.

In the mixtures' composition interval of $0.24 < x_1 < 1.00$ the local mole fractions of ethanol around benzoic acid molecules are higher than those in the bulk aqueous-ethanol mixtures free of this drug. The maximum positive $\delta x_{1,3}$ value is obtained in the mixture of $x_1 = 0.65$ (i.e., $\delta x_{1,3} = 8.15 \times 10^{-2}$), which is also higher than $|1.0 \times 10^{-2}|$. Thus, it could be considered as a consequence of preferential solvation effects of this drug by ethanol molecules [64,65]. In this composition interval, benzoic acid could be acting as a Lewis acid with ethanol molecules by means of its carboxylic hydroxyl group that would be interacting with the unshared electron pairs of the oxygen atoms of ethanol. It is noteworthy that ethanol exhibits higher Lewis base behavior compared with water [30].

4. Conclusions

Dissolution physicochemical properties of benzoic acid in aqueous-ethanol binary mixtures depend strongly on the ethanol proportion in the cosolvent mixtures. The experimental mole fraction solubility values of benzoic acid in these mixtures were adequately correlated with the classical Jouyban–Acree model and other well-known correlation models. The apparent thermodynamic quantities of dissolution, mixing and solvation of benzoic acid in aqueous-ethanol mixtures were calculated based on the van 't Hoff and Gibbs equations. Non-linear enthalpy-entropy compensation was found for benzoic acid in these aqueous-ethanol mixtures, indicating different mechanisms for the drug transfer depending on the solvent mixture composition. Moreover, based on IKBI calculations, it was stated that benzoic acid is preferentially solvated by water molecules in water-rich mixtures but preferentially solvated by ethanol molecules in the composition interval of $0.24 < x_1 < 1.00$. Finally, the thermodynamic results presented in this communication could be useful in optimizing different physical and chemical processes involving benzoic acid in mixed aqueous–ethanol media at the industrial level.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A. DSC Thermograms
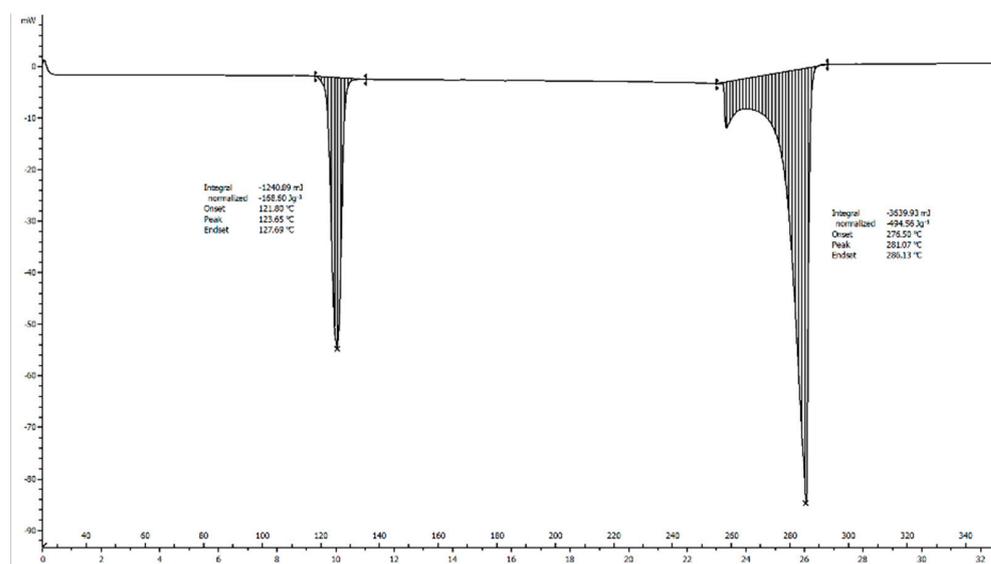
Figure A1. DSC thermogram of benzoic acid as original sample.
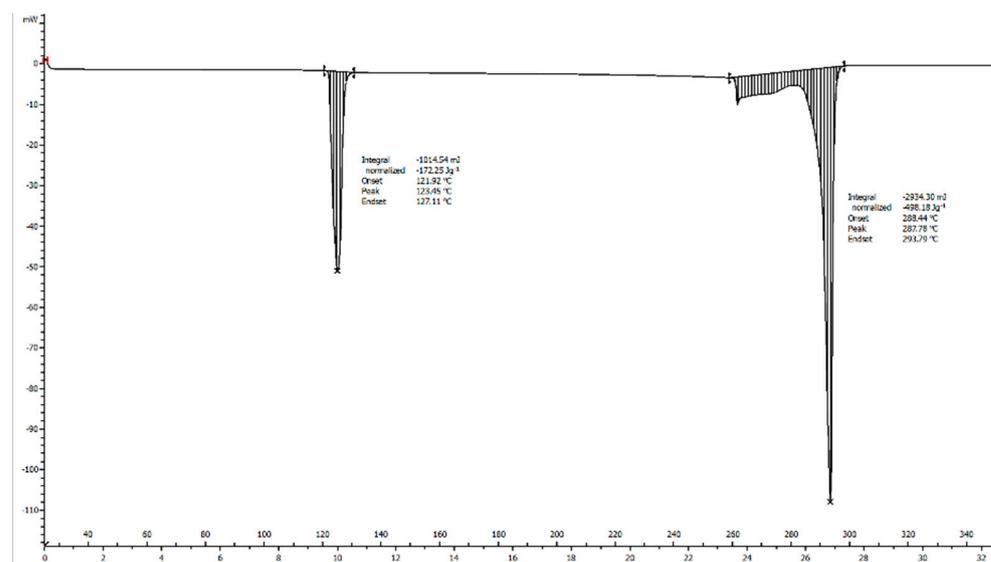
Figure A2. DSC thermogram of benzoic acid crystallized in neat water.
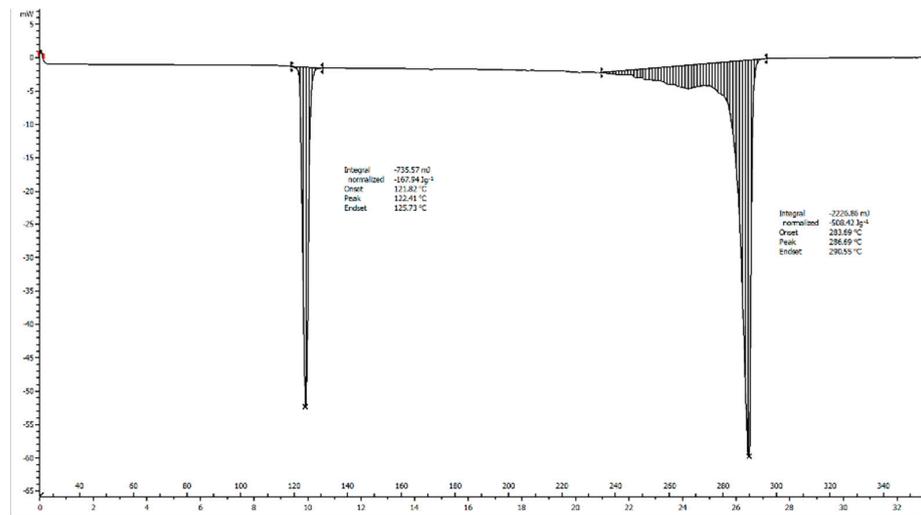
Figure A3. DSC thermogram of benzoic acid crystallized in {ethanol (1) + water (2)} (w_1 = 0.50) mixture.
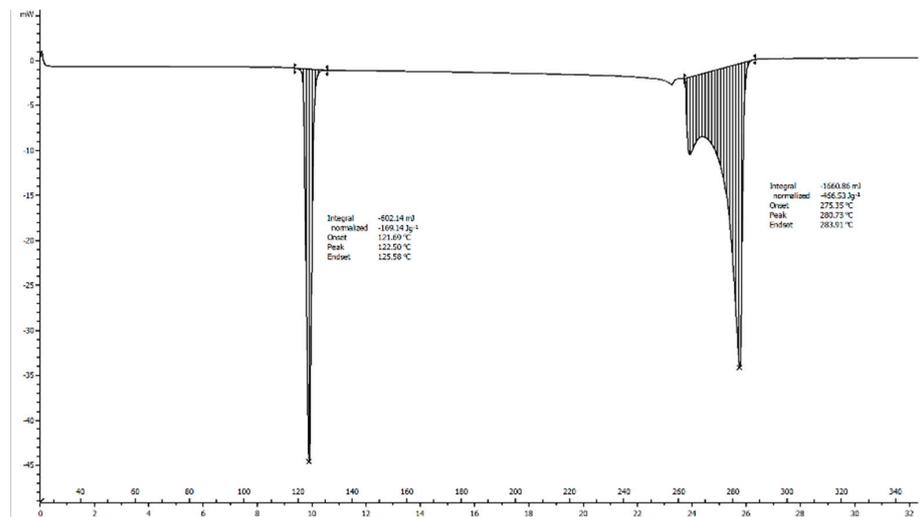
Figure A4. DSC thermogram of benzoic acid crystallized in neat ethanol.

Appendix B. X-ray Diffraction Spectra
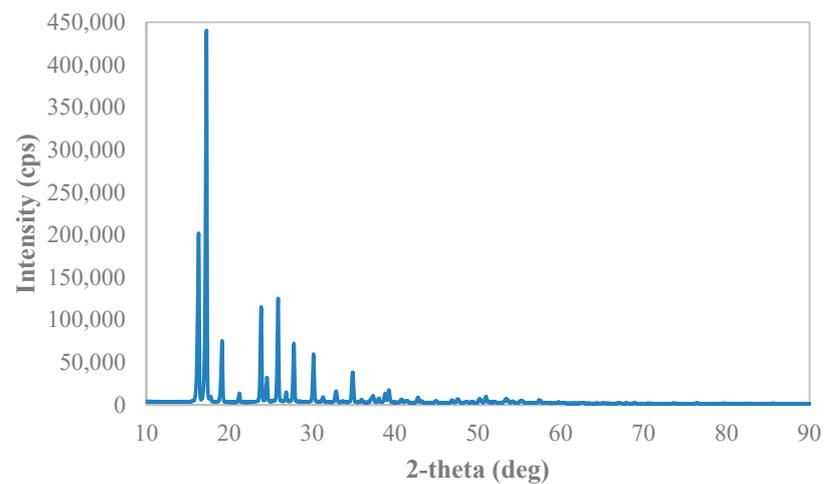
Figure A5. X-ray diffraction spectra of benzoic acid as original sample.
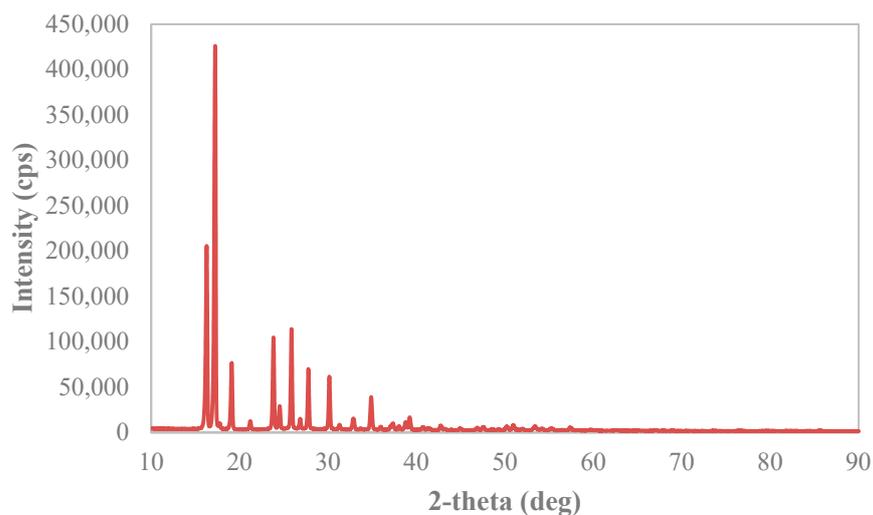
Figure A6. X-ray diffraction spectra of benzoic acid crystallized in neat water.
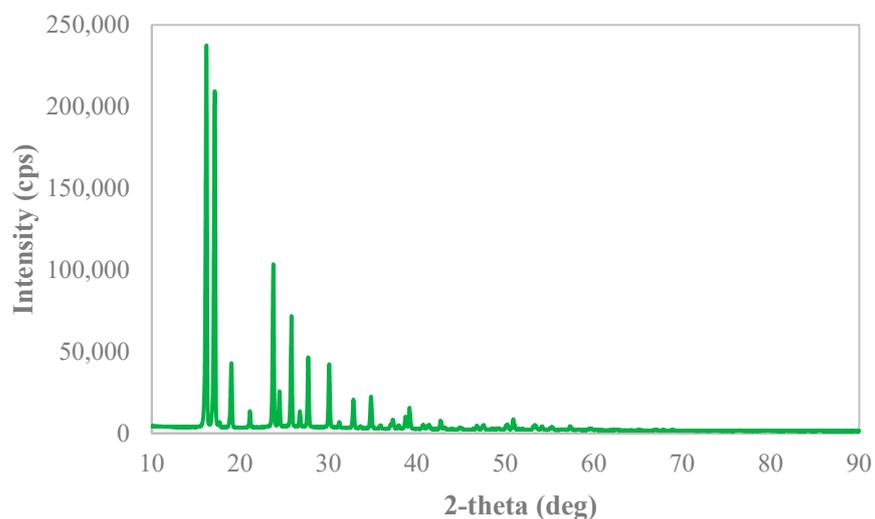
Figure A7. X-ray diffraction spectra of benzoic acid crystallized in {ethanol (1) + water (2)} ($x_1 = 0.50$) mixture.
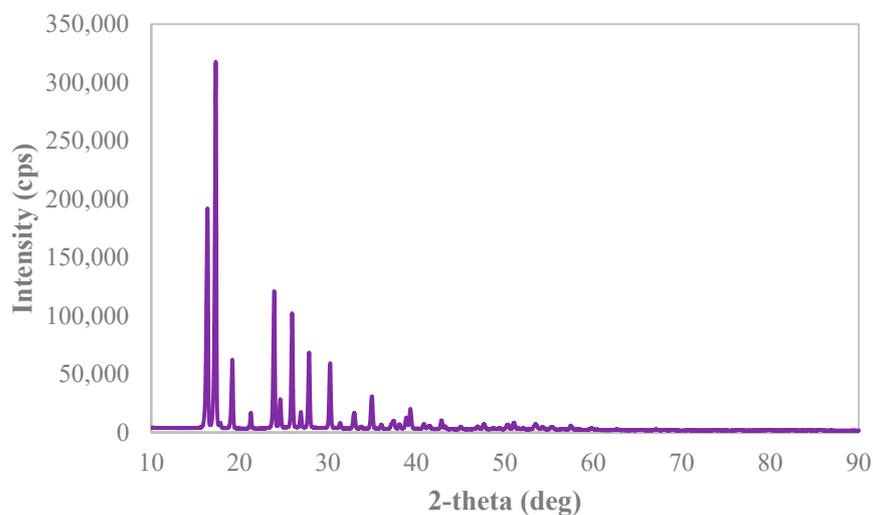
Figure A8. X-ray diffraction spectra of benzoic acid crystallized in neat ethanol.

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