Equilibrium Solubility of Triclocarban in (Cyclohexane + 1,4-Dioxane) Mixtures: Determination, Correlation, Thermodynamics and Preferential Solvation

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Abstract

Equilibrium solubility of triclocarban (TCC) expressed in mole fraction in 1,4-dioxane and cyclohexane, as well, as in 19 {cyclohexane (1) + 1,4-dioxane (2)} mixtures, was determined at seven temperatures from $T = (288.15$ to $318.15)$ K. Logarithmic TCC solubility in these cosolvent mixtures was adequately correlated with a lineal bivariate equation as function of both the mixtures composition and temperature. Apparent thermodynamic quantities for the dissolution and mixing processes were computed by means of the van't Hoff and Gibbs equations observing endothermal and entropy-driven dissolution processes in all cases. The enthalpy–entropy compensation plot of apparent enthalpy *vs.* apparent Gibbs energy was linear exhibiting positive slope implying enthalpy-driving for TCC transfer from cyclohexane to 1,4-dioxane. Ultimately, by using the inverse Kirkwood–Buff integrals it is observed that TCC is preferentially solvated by cyclohexane molecules in 1,4-dioxane-rich mixtures but preferentially solvated by 1,4-dioxane molecules in cyclohexane-rich mixtures.

1 Introduction

Triclocarban (TCC, $C_{13}H_9Cl_3N_2O$, molecular structure shown in Fig. 1, IUPAC name: 1-(4-chlorophenyl)-3-(3,4-dichlorophenyl)-urea, CAS number: 101-20-2, molar mass: 315.58 g·mol^{-1}) is a powerful antimicrobial agent, which affects fungi and bacteria, by inhibiting the enzymatic activity of enoyl-(acyl-carrier protein) (ACP) reductase [1, 2]. This step is essential for the production of fatty acids that are necessary for the development of cell membranes of these organisms [3].

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Fig. 1 Molecular structure of triclocarban
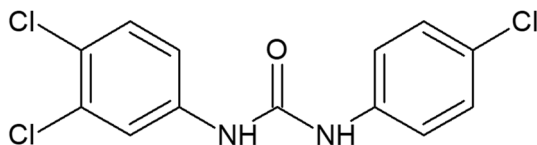
However, the increasing use of pharmaceutical and cosmetic products containing TCC [4] has been associated with environmental problems from the excessive dumping of these products into wastewater, which increases the presence of this drug in natural systems in such a way that organizations like the NORMAN Network have classified TCC as a "highly toxic emerging pollutant" [5–8]. In this way, the environmental problem generated by the presence of TCC in aquatic, benthic, sludge, sediment and biota environments has been recorded by many researchers [9–12].

In this regard, from an industrial viewpoint, one of the best strategies for reducing the volume of TCC dumping is the optimization of production processes and/or the design of clean methodologies for development of pharmaceutical or cosmetic products containing TCC [13, 14]. These interesting alternatives could be viable as long as every day there are more data about physicochemical properties involved directly with the development of pharmaceutical products, such as solubility in different media, product stability and partition coefficients, among others, which will allow design of rather than proposing production strategies with low environmental impact [15, 16]. Therefore, the availability of important data like TCC solubility in different neat solvents and cosolvent mixtures, could allow the development of more efficient processes, in terms of crystallization, purification, analysis and quality control, which are typical processes in the pharmaceutical industry that involve a significant amount of technical resources [17].

On the other hand, despite some reported studies intended for development of environment-friendly TCC-based products [18], the study of its dissolution physicochemical properties in neat or solvent mixtures is limited. Therefore, the main objective of this research work is to present the solubility and dissolution thermodynamics of TCC in some solvent mixtures, exhibiting mainly Lewis base behavior, involving cyclohexane and 1,4-dioxane owing the physicochemical importance of this cosolvent system [19]. Thus, it expands the available literature solubility data regarding solubility and dissolution thermodynamics of this controversial compound [20–25].

2 Experimental

2.1 Materials

In this physicochemical study, TCC (Sigma-Aldrich, USA; compound 3, purity at least 0.990 in mass fraction), cyclohexane (Merck A.R., Germany; solvent component 1, purity at least 0.997 in mass fraction), 1,4-dioxane (Merck A.R., Germany; solvent component 2, purity at least 0.998 in mass fraction), and ethanol (Merck A.R., Germany; used for dilutions previous to UV analyses, purity at least 0.995 in mass fraction) were

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]
Triclocarban	101-20-2	$C_{13}H_9Cl_3N_2O$	315.58	Sigma-Aldrich, USA	$\geq 0.990^b$	HPLC
Cyclohexane	110-82-7	C_6H_{12}	84.16	Merck, Germany	$\geq 0.997^b$	GC
1,4-Dioxane	123-91-1	$C_4H_8O_2$	88.11	Merck, Germany	$> 0.998^b$	GC
Ethanol	64-17-5	C_2H_6O	46.07	Merck, Germany	$\geq 0.995^b$	GC

[a]HPLC is high-performance liquid chromatography, GC is gas chromatography

[b]As indicated by the suppliers

used without further purification. Chemical suppliers, purities, and other select properties of the reagents are summarized in Table 1.

2.2 Preparation of Solvent Mixtures

All {cyclohexane (1) + 1,4-dioxane (2)} solvent mixtures were prepared gravimetrically using an (RADWAG AS 220.R2, Poland) analytical balance with sensitivity ± 0.1 mg, in quantities of 20.00 g. The mass fractions of cyclohexane of the 19 mixtures prepared, varied by 0.05 from $w_1 = 0.05$ to $w_1 = 0.95$.

2.3 Solubility Determinations

TCC solubility was determined using the shake-bottle method [26, 27], quantifying the dissolved drug by UV/Vis spectrophotometry. For these purposes, in 30 cm^3 amber bottles, TCC was added to 20 g of solvent mixture until excess of TCC does not dissolve, forming a solid phase at the bottom of the bottle. Subsequently, the flasks were transferred to refrigeration thermostats (Medingen K-22/T100, Germany), initially at 318.15 K for 48 h, with periodic shaking. Once equilibrium is attained (i.e., the composition of the solution remained constant) a liquid sample was taken from each flask and filtered under isothermal conditions through a 0.45 μm membrane (Millipore Corp. Swinnex®-13, USA). Then, each was diluted with absolute ethanol (to avoid TCC precipitation) and the absorbance of the sample was measured at 265 nm (UV/Vis EMC-11-UV spectrophotometer, Germany). Subsequently, the thermostat′s temperature was decreased to 313.15 K allowing the reaching of the new equilibrium for two days and performing the respective analysis procedures. This was repeated at 5-degree intervals (to complete 7 different temperatures) until reaching the lowest temperature, 288.15 K, All experiments were performed three times.

2.4 Calorimetric Study

To identify the nature of the TCC solid phases in equilibrium with the saturated solutions in both neat 1,4-dioxane and cyclohexane solvents and the mixture $w_1 = 0.50$, DSC analyses were performed (DSC 204 F1 Phoenix, Germany). Nearly 5.0 mg of TCC samples were analyzed. The equipment was calibrated using Indium as standard. The sample and

reference pans were heated to preserve the programmed temperature at a precise heating rate of 10 K·min^{-1} in a dynamic nitrogen atmosphere (10 cm^3·min^{-1}) at constant pressure.

3 Results and Discussion

3.1 Mole Fraction Solubility of TCC

The mole fraction equilibrium solubilities of TCC in the neat solvents and the binary mixtures at seven temperatures from $T = (288.15$ to $318.15)$ K and atmospheric pressure of 96 kPa as functions of the mass fraction of 1,4-dioxane in the solvent mixtures are summarized in Table 2 and shown as logarithmic values in Figs. 2 and 3. Minimum and maximum TCC solubilities are observed in neat cyclohexane and neat 1,4-dioxane,

Table 2 Experimental and ideal mole fraction solubility of triclocarban (x_3) in {cyclohexane $(1) + 1,4$-dioxane (2)} mixtures at several temperatures and $p = 96$ kPa

$w_1^{a,b}$	$x_1^{a,b}$	T/K^b						
		288.15	293.15	298.15	303.15	308.15	313.15	318.15
0.00	0.0000	1.03×10^{-3}	1.76×10^{-3}	2.39×10^{-3}	4.03×10^{-3}	6.58×10^{-3}	9.31×10^{-3}	1.41×10^{-2}
0.05	0.0522	6.73×10^{-4}	1.07×10^{-3}	1.69×10^{-3}	2.66×10^{-3}	4.04×10^{-3}	6.10×10^{-3}	9.25×10^{-3}
0.10	0.1042	4.31×10^{-4}	6.97×10^{-4}	1.09×10^{-3}	1.70×10^{-3}	2.62×10^{-3}	3.98×10^{-3}	5.97×10^{-3}
0.15	0.1559	2.82×10^{-4}	4.43×10^{-4}	7.01×10^{-4}	1.13×10^{-3}	1.71×10^{-3}	2.59×10^{-3}	3.92×10^{-3}
0.20	0.2074	1.80×10^{-4}	2.90×10^{-4}	4.58×10^{-4}	7.21×10^{-4}	1.11×10^{-3}	1.68×10^{-3}	2.55×10^{-3}
0.25	0.2587	1.16×10^{-4}	1.87×10^{-4}	2.97×10^{-4}	4.69×10^{-4}	7.21×10^{-4}	1.10×10^{-3}	1.67×10^{-3}
0.30	0.3097	7.50×10^{-5}	1.22×10^{-4}	1.95×10^{-4}	3.01×10^{-4}	4.63×10^{-4}	7.09×10^{-4}	1.11×10^{-3}
0.35	0.3605	4.83×10^{-5}	7.78×10^{-5}	1.24×10^{-4}	1.98×10^{-4}	3.07×10^{-4}	4.68×10^{-4}	7.00×10^{-4}
0.40	0.4111	3.13×10^{-5}	5.03×10^{-5}	8.05×10^{-5}	1.28×10^{-4}	1.98×10^{-4}	3.02×10^{-4}	4.63×10^{-4}
0.45	0.4614	2.02×10^{-5}	3.25×10^{-5}	5.21×10^{-5}	8.33×10^{-5}	1.28×10^{-4}	1.97×10^{-4}	3.02×10^{-4}
0.50	0.5115	1.30×10^{-5}	2.12×10^{-5}	3.40×10^{-5}	5.37×10^{-5}	8.31×10^{-5}	1.28×10^{-4}	1.97×10^{-4}
0.55	0.5613	8.38×10^{-6}	1.37×10^{-5}	2.20×10^{-5}	3.47×10^{-5}	5.40×10^{-5}	8.31×10^{-5}	1.28×10^{-4}
0.60	0.6110	5.38×10^{-6}	8.88×10^{-6}	1.42×10^{-5}	2.25×10^{-5}	3.53×10^{-5}	5.43×10^{-5}	8.28×10^{-5}
0.65	0.6604	3.49×10^{-6}	5.71×10^{-6}	9.23×10^{-6}	1.47×10^{-5}	2.28×10^{-5}	3.52×10^{-5}	5.46×10^{-5}
0.70	0.7095	2.26×10^{-6}	3.65×10^{-6}	5.90×10^{-6}	9.65×10^{-6}	1.50×10^{-5}	2.31×10^{-5}	3.56×10^{-5}
0.75	0.7585	1.44×10^{-6}	2.38×10^{-6}	3.85×10^{-6}	6.13×10^{-6}	9.65×10^{-6}	1.49×10^{-5}	2.33×10^{-5}
0.80	0.8072	9.35×10^{-7}	1.54×10^{-6}	2.50×10^{-6}	3.97×10^{-6}	6.30×10^{-6}	9.76×10^{-6}	1.52×10^{-5}
0.85	0.8558	6.05×10^{-7}	9.92×10^{-7}	1.62×10^{-6}	2.63×10^{-6}	4.11×10^{-6}	6.42×10^{-6}	9.83×10^{-6}
0.90	0.9041	3.82×10^{-7}	6.38×10^{-7}	1.05×10^{-6}	1.66×10^{-6}	2.66×10^{-6}	4.11×10^{-6}	6.33×10^{-6}
0.95	0.9521	2.50×10^{-7}	4.18×10^{-7}	6.77×10^{-7}	1.09×10^{-6}	1.72×10^{-6}	2.69×10^{-6}	4.18×10^{-6}
1.00	1.0000	1.68×10^{-7}	2.73×10^{-7}	4.23×10^{-7}	7.31×10^{-7}	1.17×10^{-6}	1.82×10^{-6}	2.72×10^{-6}
	Ideal	3.07×10^{-3}	3.61×10^{-3}	4.25×10^{-3}	4.98×10^{-3}	5.82×10^{-3}	6.79×10^{-3}	7.90×10^{-3}

[a]p is the atmospheric pressure in Neiva, Huila, Colombia. w_1 and x_1 are the mass and mole fractions of cyclohexane (1) in the {cyclohexane $(1) + 1,4$-dioxane (2)} mixtures free of triclocarban (3), respectively

[b]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, $u_r(x_3) = 0.017$
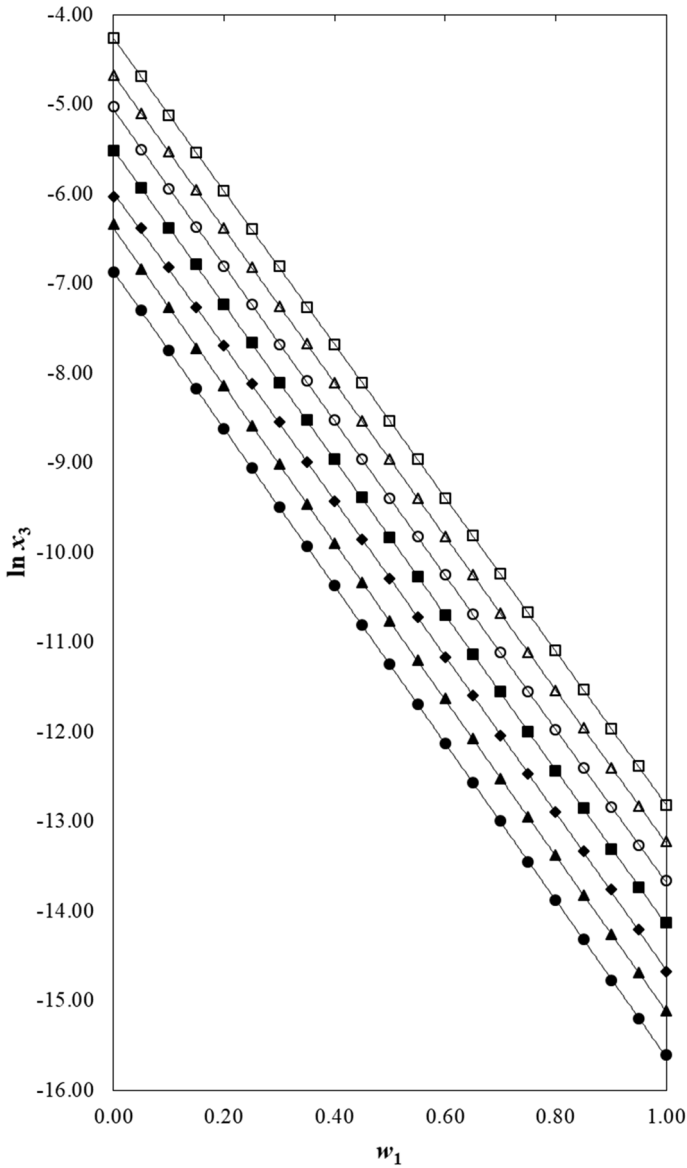
Fig. 2 Logarithmic mole fraction solubility of triclocarban (ln x_3) as function of the mass fraction of cyclohexane in {cyclohexane (1) + 1,4-dioxane (2)} mixtures at different temperatures. Black symbols, circles: $T = 288.15$ K; triangles: $T = 293.15$ K; diamonds: $T = 298.15$ K; squares: $T = 303.15$ K; White symbols, circles: $T = 308.15$ K; triangles: $T = 313.15$ K; squares: $T = 318.15$ K

respectively, at all temperatures studied. In all cases, TCC solubility increases with increasing temperature, which indicates endothermic dissolution processes. It is noteworthy that TCC logarithmic solubility decreases linearly with the cyclohexane proportion in the mixtures but increases linearly with the temperature. TCC solubility varied
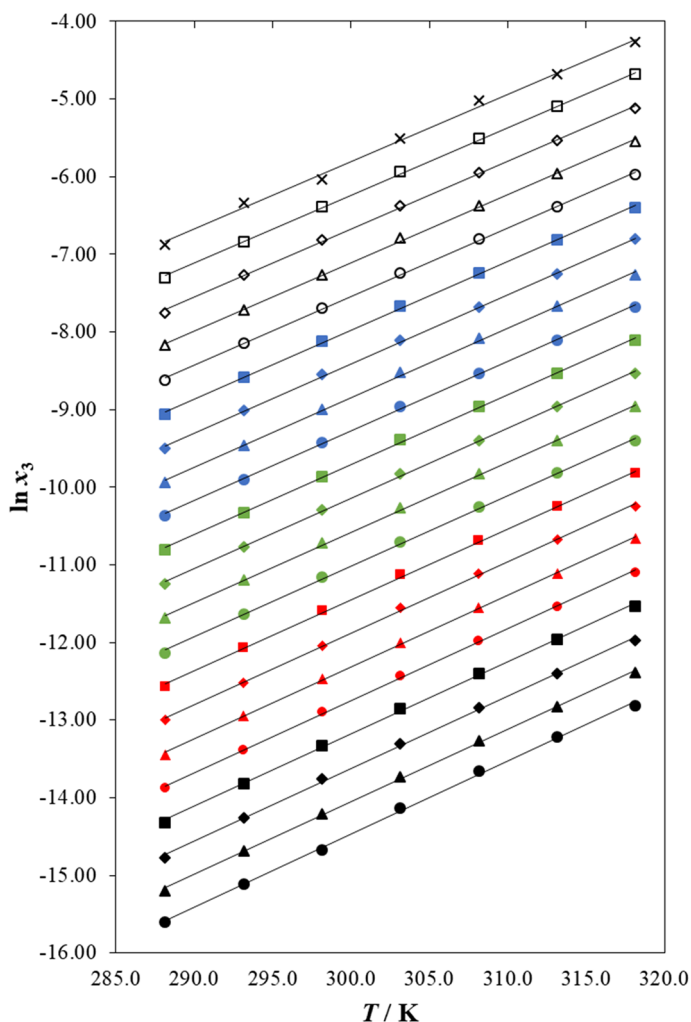
Fig. 3 Logarithmic mole fraction solubility of triclocarban (ln x_3) as function of temperature in {cyclohexane (1)+1,4-dioxane (2)} mixtures for different mixtures compositions. ×: w_1=0.00 (neat 1,4-dioxane); empty symbols, squares: w_1=0.05, diamonds: w_1=0.10, triangles: w_1=0.15, circles: w_1=0.20; blue symbols, squares: w_1=0.25, diamonds: w_1=0.30, triangles: w_1=0.35, circles: w_1=0.40; green symbols: squares: w_1=0.45, diamonds: w_1=0.50, triangles: w_1=0.55, circles: w_1=0.60; red symbols, squares: w_1=0.65, diamonds: w_1=0.70, triangles: w_1=0.75, circles: w_1=0.80; black symbols, squares: w_1=0.85, diamonds: w_1=0.90, triangles: w_1=0.95, circles: w_1=1.00 (neat cyclohexane) (Color figure online)

from 1.68×10^{-7} in neat cyclohexane at 288.15 K to 1.41×10^{-2} in neat 1,4-dioxane at 318.15 K. If $T = 298.15$ K is considered, TCC solubility is 5648 times higher in neat 1,4-dioxane than in neat cyclohexane. This is a consequence of the Lewis basic behavior of 1,4-dioxane owing the free electron pairs on its oxygen atoms, whereas, cyclohexane can only interact by weak London dispersion forces.
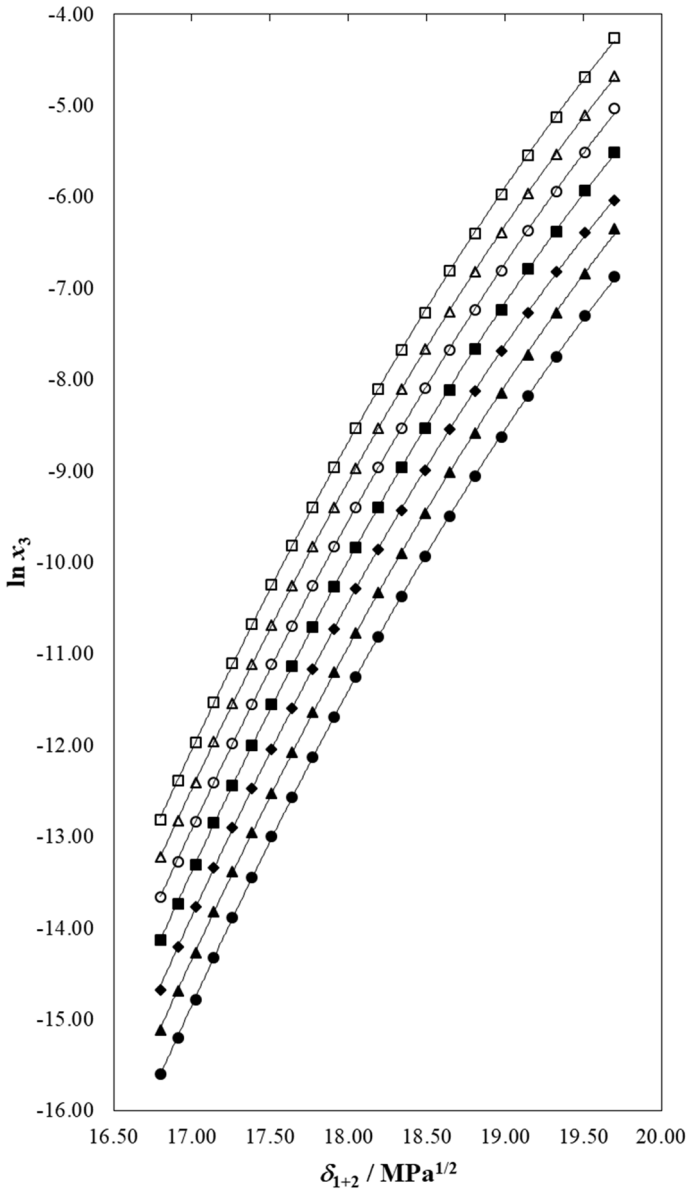
Fig. 4 Logarithmic mole fraction solubility of triclocarban (ln x_3) as function of the Hildebrand solubility parameter in {cyclohexane (1) + 1,4-dioxane (2)} mixtures at different temperatures. Black symbols, circles: $T = 288.15$ K; triangles: $T = 293.15$ K; diamonds: $T = 298.15$ K; squares: $T = 303.15$ K; White symbols, circles: $T = 308.15$ K; triangles: $T = 313.15$ K; squares: $T = 318.15$ K

Additionally, Fig. 4 shows the TCC logarithmic solubility as function of the Hildebrand solubility parameters of the {cyclohexane (1) + 1,4-dioxane (2)} mixtures (δ_{1+2}). As is well-known, the Hildebrand solubility parameter is a polarity index widely used in pharmaceutical studies regarding cosolvency effects on physical and chemical stabilities of drugs. Mixtures δ_{1+2} values were calculated from the corresponding δ values, i.e., $\delta_1 = 16.8$ MPa$^{1/2}$ for cyclohexane and $\delta_2 = 19.7$ MPa$^{1/2}$ for 1,4-dioxane [28, 29] and volumetric solvent proportions as described in Eq. 1. Volume fractions (f_i) were considered assuming additive behavior [30, 31]:

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

Accordingly, it is expected that TCC reaches its maximum solubilities in solvent systems with the same or similar Hildebrand solubility parameters [32, 33]. By keeping this in mind, the δ_3 value of TCC would be higher than the δ_1 value (i.e., neat 1,4-dioxane δ value, 19.7 MPa$^{1/2}$) at $T = 298.15$ K, where the maximum TCC solubilities are observed at all temperatures. Effectively, the calculated Fedors–van Krevelen δ_3 value of TCC is 26.5 MPa$^{1/2}$ as reported in the literature [22]. Hence, it would be important to study the TCC solubility in mixed solvent systems exhibiting higher polarities than that of neat 1,4-dioxane, like {1,4-dioxane (1) + propylene glycol (2)} mixtures (obtaining an interval of $19.7 \leq \delta_{1+2}/\text{MPa}^{1/2} \leq 30.2$), where maximum drug solubility peaks could be observed as they were observed in {1,4-dioxane (1) + water (2)} mixtures [23].

Owing to the practical importance of calculating the TCC solubility at different temperatures or {cyclohexane (1) + 1,4-dioxane (2)} mixtures compositions regarding those experimentally determined, the equilibrium solubilities reported in Table 2 were logarithmically correlated as function of both temperature and mixtures composition to obtain the multivariate model shown as Eq. 2:

$$\ln x_{3,1+2} = -32.95 - 8.654 w_1 + 9.044 \cdot 10^{-2} T \tag{2}$$

With adj. $r^2 = 0.9998$, typical error $= 0.0345$, and $F = 475{,}593$. Mean percentage deviations (MPD) obtained with Eq. 2 were calculated by means of Eq. 3, where $x_{3,1+2}^{\text{exptl}}$ and $x_{3,1+2}^{\text{calcd}}$ are experimental and calculated solubilities, respectively. The following results were obtained: for logarithmic solubility, MPD = 0.31% (minimum PD = 0.006% in $w_1 = 0.55$ at $T = 293.15$ K, maximum PD = 1.98% in neat 1,4-dioxane at $T = 318.15$ K), for linear solubility, MPD = 2.72% (minimum PD = 0.068% in $w_1 = 0.55$ at $T = 293.15$ K, maximum PD = 10.32% in $w_1 = 0.90$ at $T = 288.15$ K) [34–36].

$$\text{MPD} = \frac{100}{N} \sum \frac{\left| x_{3,1+2}^{\text{exptl}} - x_{3,1+2}^{\text{calcd}} \right|}{x_{3,1+2}^{\text{exptl}}} \tag{3}$$

3.2 TCC Solid Phases' DSC Analyses

DSC thermograms of TCC corresponding to original untreated sample and after equilibrating it in neat 1,4-dioxane, in the mixture of $w_1 = 0.50$, and in neat cyclohexane, are shown in Fig. 5. There are two endothermic peaks corresponding to the melting and thermal

Fig. 5 DSC thermograms of the triclocarban solid phases in equilibrium with the saturated solutions. From top to bottom: neat 1,4-dioxane, mixture $w_1 = 0.50$, neat cyclohexane, and original untreated sample
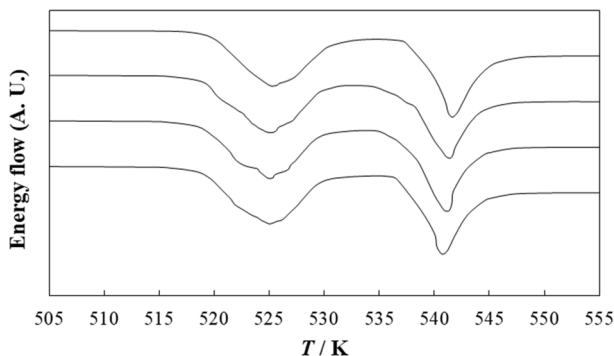
degradation of TCC. These peaks are almost coincident with those reported earlier in the literature for TCC in aqueous mixtures of 1,4-dioxane [23]. Thus, based on DSC results it is observable that TCC did not suffer crystal polymorphic transitions or solvate formation after dissolution and saturation in these organic solvent systems. Therefore, for ideal solubility calculations the following reported values were considered: 41.9 kJ·mol^{-1} for molar enthalpy of melting and 528.2 K for the temperature of melting [18].

3.3 Ideal Solubility and Activity Coefficients of TCC in Neat and Mixed Solvents

Ideal solubilities of TCC (x_3^{id}) at the temperatures of interest from 288.15 to 318.15 K were calculated by means of the well-known equation:

$$\ln x_3^{id} = -\frac{\Delta_{fus}H(T_{fus} - T)}{RT_{fus}T} + \left(\frac{\Delta C_p}{R}\right)\left[\frac{(T_{fus} - T)}{T} + \ln\left(\frac{T}{T_{fus}}\right)\right] \tag{4}$$

Here, $\Delta_{fus}H$ is the molar enthalpy of melting of the pure TCC (obtained at the melting point, i.e., 41.9 kJ·mol^{-1} [18]), T_{fus} is the absolute melting point (i.e., 528.2 K), 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 TCC in its crystalline form and its hypothetical super-cooled liquid form at every dissolution temperature [37]. However, owing the experimental difficulty in ΔC_p determination, this value has been considered in this research as the same as the one of the entropy of fusion ($\Delta_{fus}S = \Delta_{fus}H/T_{fus}$, i.e., 79.4 J·mol^{-1}·K^{-1}). Table 2 shows that the ideal solubilities of TCC are higher than the experimental solubilities at almost all the temperatures studied, except in the case of neat 1,4-dioxane at temperatures of (308.15, 313.15 and 318.15) K.

On the other hand, Table 3 summarizes the asymmetrical activity coefficients of TCC (γ_3) in neat solvents and in {cyclohexane (1) + 1,4-dioxane (2)} mixtures at all temperatures. These γ_3 values were calculated as the quotient: x_3^{id}/x_3 from the experimental and ideal solubilities summarized in Table 2. As observed, at $T = 298.15$ K γ_3 values vary from 1.777 in neat 1,4-dioxane (where the maximum TCC solubility is obtained) to 10,039 in neat cyclohexane (where the minimum TCC solubility is achieved). In all solvent systems, γ_3 values decrease with the temperature arising. All obtained γ_3 values are higher than the unity because the experimental solubilities in all the solvent systems are lower than x_3^{id} at all temperatures tested, except in neat 1,4-dioxane at temperatures of (308.15, 313.15 and 318.15) K. Furthermore, a rough estimate of the respective solute–solvent intermolecular interactions present in the solutions was performed from the γ_3 values, based on Eq. 5 [38]:

Table 3 Activity coefficients of triclocarban (γ_3) in {cyclohexane (1) + 1,4-dioxane (2)} mixtures at several temperatures and $p = 96$ kPa

w_1 [a,b]	x_1 [a,b]	T/K [b]						
		288.15	293.15	298.15	303.15	308.15	313.15	318.15
0.00	0.0000	2.971	2.054	1.777	1.234	0.885	0.730	0.560
0.05	0.0522	4.554	3.386	2.520	1.875	1.441	1.112	0.854
0.10	0.1042	7.114	5.186	3.888	2.927	2.219	1.707	1.323
0.15	0.1559	10.87	8.159	6.057	4.408	3.401	2.623	2.014
0.20	0.2074	17.03	12.47	9.271	6.908	5.251	4.029	3.097
0.25	0.2587	26.34	19.33	14.32	10.61	8.077	6.189	4.738
0.30	0.3097	40.87	29.64	21.84	16.55	12.56	9.58	7.121
0.35	0.3605	63.47	46.45	34.21	25.14	18.94	14.52	11.28
0.40	0.4111	97.9	71.83	52.76	38.77	29.45	22.46	17.05
0.45	0.4614	151.8	111.1	81.46	59.75	45.31	34.50	26.15
0.50	0.5115	235.6	170.8	125.0	92.77	70.07	53.17	40.12
0.55	0.5613	365.9	263.6	193.0	143.4	107.8	81.65	61.69
0.60	0.6110	569.6	407.1	299.7	221.6	165.1	124.9	95.3
0.65	0.6604	877.5	632.5	460.2	339.7	255.3	192.7	144.7
0.70	0.7095	1355	991	720.3	516.2	389.2	294.4	221.8
0.75	0.7585	2123	1522	1103	812.5	603.2	456.3	338.8
0.80	0.8072	3279	2342	1697	1253	924.4	695.5	520.2
0.85	0.8558	5066	3643	2629	1890	1416	1057	803.3
0.90	0.9041	8025	5663	4031	2999	2191	1651	1248
0.95	0.9521	12,247	8640	6277	4585	3375	2524	1888
1.00	1.0000	18,293	13,245	10,039	6809	4995	3739	2907

[a] p is the atmospheric pressure in Neiva, Huila, Colombia. w_1 and x_1 are the mass and mole fractions of cyclohexane (1) in the {cyclohexane (1) + 1,4-dioxane (2)} mixtures free of triclocarban (3), respectively

[b] Standard uncertainty in T is $u(\text{Thm}) = 0.10$ 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 $u_r(\gamma_3) = 0.026$

$$\ln \gamma_3 = (e_{ss} + e_{33} - 2e_{s3}) \frac{V_3 \varphi_s^2}{RT} \tag{5}$$

Here subscript s stands for the solvent system (which corresponds to neat solvents or cyclohexane-1,4-dioxane 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 keep in mind that in multicomponent systems like cyclohexane-1,4-dioxane-TCC, some cosolvent–cosolvent interactions would be present, which could also play an important role in the magnitudes of dissolution and equilibrium solubility of this antibacterial agent. V_3 is the molar volume of the super-cooled liquid TCC 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 constant regardless the solvent system because φ_s is almost 1.0. Thus, the γ_3 values would depend mainly on the terms e_{ss}, e_{33} and e_{s3} [38]. As well-known, e_{ss} and e_{33} are not favorable for drug dissolution processes and equilibrium solubilities but e_{s3} favors the respective drug dissolution processes and

solubilities. Moreover, the contribution of e_{33} toward the dissolution rate and equilibrium solubility of TCC was considered as constant regardless the solvent system studied.

As indicated above, a qualitative approach to intermolecular interactions was made based on the e_{ss}, e_{33} and e_{s3} energetic terms of Eq. 5. Hence, based on polarities it follows that e_{ss} is highest in neat 1,4-dioxane ($\delta = 19.7$ MPa$^{1/2}$) and lowest in neat cyclohexane ($\delta = 16.8$ MPa$^{1/2}$) [28, 29]. Neat cyclohexane and cyclohexane-rich mixtures, exhibiting γ_3 values higher than 1600 at $T = 298.15$ K, would imply high e_{33} and low e_{s3} values. Otherwise, in 1,4-dioxane-rich mixtures, exhibiting γ_3 values lower than 10, the e_{ss} values are also relatively low but the e_{s3} values would be comparatively higher regarding cyclohexane-rich mixtures.

3.4 Apparent Thermodynamic Functions of TCC Dissolution

All the apparent thermodynamic quantities of dissolution of TCC in neat solvents and in {cyclohexane (1) + 1,4-dioxane (2)} mixtures were estimated at the harmonic mean temperature (T_{hm}), which in turn was calculated by using Eq. 6 [39, 40]:

$$T_{hm} = n \left/ \sum_{i=1}^{n} (1/T) \right. \tag{6}$$

where $n = 7$ is the number of temperatures studied. Thus, from $T = (218.15$ to $318.15)$ K, the obtained T_{hm} value is 302.8 K. In this way, the apparent standard enthalpic changes for TCC dissolution processes ($\Delta_{soln}H°$) were obtained by means of the modified van't Hoff equation, as [40, 41]:

$$\left(\frac{\partial \ln x_3}{\partial (1/T - 1/T_{hm})} \right)_P = -\frac{\Delta_{soln}H°}{R} \tag{7}$$

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

$$\Delta_{soln}G° = -R \cdot T_{hm} \cdot \text{intercept} \tag{8}$$

Here, the intercepts used are those obtained in the respective linear regressions of ln x_3 vs. $(1/T - 1/T_{hm})$. As visual help, Fig. 6 shows the solubility van't Hoff plots obtained in the neat solvents and in the 19 {cyclohexane (1) + 1,4-dioxane (2)} mixtures. Linear regressions with determination coefficients higher than 0.997 were obtained in all cases [34–36]. Standard apparent entropic changes for TCC dissolution processes ($\Delta_{soln}S°$) were obtained from the respective $\Delta_{soln}H°$ and $\Delta_{soln}G°$ values by using Eq. 9 [41]:

$$\Delta_{soln}S° = \frac{(\Delta_{soln}H° - \Delta_{soln}G°)}{T_{hm}} \tag{9}$$

Table 4 summarizes the standard apparent molar thermodynamic functions of the dissolution processes of TCC (3) in neat solvents and in all the {cyclohexane (1) + 1,4-dioxane (2)} mixtures at $T_{hm} = 302.8$ K.

Apparent standard Gibbs energies, enthalpies and entropies relative to the TCC dissolution processes are positive in all cases as shown in Table 4. This implies
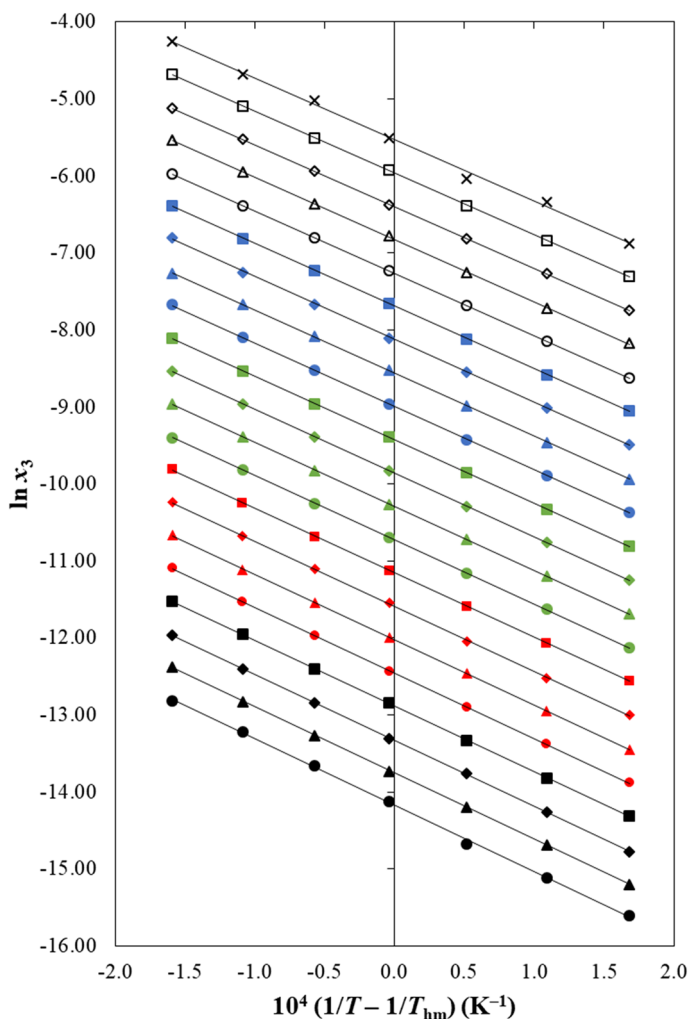
Fig. 6 van't Hoff plot of the solubility of triclocarban (3) in some {cyclohexane (1) + 1,4-dioxane (2)} solvent systems. ×: $w_1 = 0.00$ (neat 1,4-dioxane); empty symbols, squares: $w_1 = 0.05$, diamonds: $w_1 = 0.10$, triangles: $w_1 = 0.15$, circles: $w_1 = 0.20$; blue symbols, squares: $w_1 = 0.25$, diamonds: $w_1 = 0.30$, triangles: $w_1 = 0.35$, circles: $w_1 = 0.40$; green symbols: squares: $w_1 = 0.45$, diamonds: $w_1 = 0.50$, triangles: $w_1 = 0.55$, circles: $w_1 = 0.60$; red symbols, squares: $w_1 = 0.65$, diamonds: $w_1 = 0.70$, triangles: $w_1 = 0.75$, circles: $w_1 = 0.80$; black symbols, squares: $w_1 = 0.85$, diamonds: $w_1 = 0.90$, triangles: $w_1 = 0.95$, circles: $w_1 = 1.00$ (neat cyclohexane) (Color figure online)

endothermic and entropy-driven dissolution processes in all cases. Moreover, $\Delta_{soln}G°$ values increase continuously from neat 1,4-dioxane (13.93 kJ·mol^{-1}) to neat cyclohexane (35.69 kJ·mol^{-1}) indicating more affinity of TCC by 1,4-dioxane-rich media. As observed, $\Delta_{soln}H°$ values increase continuously from neat 1,4-dioxane (66.37 kJ·mol^{-1}) to reach the maximum value in neat cyclohexane (71.67 kJ·mol^{-1}) but on the contrary, $\Delta_{soln}S°$ values decrease from neat 1,4-dioxane (173.2 J·mol^{-1}·K^{-1}) to reach the minimum

Table 4 Apparent thermodynamic functions relative to dissolution processes of triclocarban (3) in {cyclohexane (1) + 1,4-dioxane (2)} mixtures at $T_{hm} = 302.8$ K and $p = 96$ kPa

w_1[a,b]	x_1[a,b]	$\Delta_{soln}G°$ /kJ·mol^{-1}[b]	$\Delta_{soln}H°$ /kJ·mol^{-1}[b]	$\Delta_{soln}S°$ /J·mol^{-1}·K^{-1}[b]	$T\Delta_{soln}S°$ / kJ·mol^{-1}[b]	ζ_H[c]	ζ_{TS}[c]
0.00	0.0000	13.93	66.37	173.2	52.4	0.559	0.441
0.05	0.0522	15.02	66.56	170.2	51.5	0.564	0.436
0.10	0.1042	16.12	66.68	167.0	50.6	0.569	0.431
0.15	0.1559	17.20	67.09	164.8	49.9	0.574	0.426
0.20	0.2074	18.29	67.29	161.8	49.0	0.579	0.421
0.25	0.2587	19.38	67.60	159.2	48.2	0.584	0.416
0.30	0.3097	20.46	67.90	156.7	47.4	0.589	0.411
0.35	0.3605	21.56	68.16	153.9	46.6	0.594	0.406
0.40	0.4111	22.65	68.44	151.2	45.8	0.599	0.401
0.45	0.4614	23.74	68.71	148.5	45.0	0.604	0.396
0.50	0.5115	24.83	68.83	145.3	44.0	0.610	0.390
0.55	0.5613	25.92	69.07	142.5	43.1	0.615	0.385
0.60	0.6110	27.01	69.37	139.9	42.4	0.621	0.379
0.65	0.6604	28.10	69.64	137.2	41.5	0.626	0.374
0.70	0.7095	29.19	70.19	135.4	41.0	0.631	0.369
0.75	0.7585	30.28	70.43	132.6	40.1	0.637	0.363
0.80	0.8072	31.37	70.66	129.8	39.3	0.643	0.357
0.85	0.8558	32.45	70.98	127.2	38.5	0.648	0.352
0.90	0.9041	33.57	71.20	124.3	37.6	0.654	0.346
0.95	0.9521	34.64	71.38	121.3	36.7	0.660	0.340
1.00	1.0000	35.69	71.67	118.8	36.0	0.666	0.334
	Ideal	13.36	24.03	35.2	10.7	0.693	0.307

[a] p is the atmospheric pressure in Neiva, Huila, Colombia. w_1 and x_1 are the mass and mole fractions of cyclohexane (1) in the {cyclohexane (1) + 1,4-dioxane (2)} mixtures free of triclocarban (3), respectively

[b] Standard uncertainty in T is $u(T) = 0.13$ 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 $u_r(\Delta_{soln}G°) = 0.019$, $u_r(\Delta_{soln}H°) = 0.024$, $u_r(\Delta_{soln}S°) = 0.031$, $u_r(T\Delta_{soln}S°) = 0.031$

[c] ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward apparent Gibbs energy of dissolution

value in neat cyclohexane (118.8 J·mol^{-1}·K^{-1}). Additionally, the relative contributions by enthalpy (ζ_H) and entropy (ζ_{TS}) toward the TCC dissolution processes were calculated by means of the following equations [42]:

$$\zeta_H = \frac{|\Delta_{soln}H°|}{|\Delta_{soln}H°| + |T\Delta_{soln}S°|} \tag{10}$$

$$\zeta_{TS} = \frac{|T\Delta_{\text{soln}}S^\circ|}{|\Delta_{\text{soln}}H^\circ| + |T\Delta_{\text{soln}}S^\circ|} \tag{11}$$

As shown in Table 4, the main contributor to the positive standard apparent molar Gibbs energies of dissolution of TCC was the positive enthalpy, which demonstrates the energetic predominance in all these TCC dissolution processes.

3.5 Apparent Thermodynamic Quantities of Mixing

Global dissolution processes of TCC in {cyclohexane (1)+1,4-dioxane (2)} mixtures may also 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 TCC at $T_{\text{fus}} = 528.2$ K, (*ii*) the cooling of the liquid TCC to the considered temperature ($T_{\text{hm}} = 302.8$ K), and (*iii*) the subsequent mixing of both the hypothetical TCC super-cooled liquid and the {cyclohexane (1)+1,4-dioxane (2)} solvent system under consideration at $T_{\text{hm}} = 302.8$ K [43]. This allowed us the calculation of the individual thermodynamic contributions by fusion and mixing toward the overall TCC dissolution processes, by means of the following equations:

$$\Delta_{\text{soln}}H^\circ = \Delta_{\text{fus}}H^{T_{\text{hm}}} + \Delta_{\text{mix}}H^\circ \tag{12}$$

$$\Delta_{\text{soln}}S^\circ = \Delta_{\text{fus}}S^{T_{\text{hm}}} + \Delta_{\text{mix}}S^\circ \tag{13}$$

where $\Delta_{\text{fus}}H^{T_{\text{hm}}}$ and $\Delta_{\text{fus}}S^{T_{\text{hm}}}$ indicate the thermodynamic quantities of TCC fusion and its cooling at $T_{\text{hm}} = 302.8$ K. In turn, these two functions were calculated by means of Eqs. 14 and 15, respectively [44]:

$$\Delta_{\text{fus}}H^{T_{\text{hm}}} = \Delta_{\text{fus}}H^{T_{\text{fus}}} - \Delta C_p(T_{\text{fus}} - T_{\text{hm}}) \tag{14}$$

$$\Delta_{\text{fus}}S^{T_{\text{hm}}} = \Delta_{\text{fus}}S^{T_{\text{fus}}} - \Delta C_p \ln\left(\frac{T_{\text{fus}}}{T_{\text{hm}}}\right) \tag{15}$$

Table 5 summarizes the apparent thermodynamic quantities of mixing of the hypothetical TCC as super-cooled liquid with all the {1,4-dioxane (1)+cyclohexane (2)} mixtures and the neat solvents, at $T_{\text{hm}} = 302.8$ K. Apparent Gibbs energies of mixing are positive because the experimental solubilities of TCC in all these solvent systems are lower than the ideal solubilities at almost all temperatures, except in neat 1,4-dioxane at $T \geq 308.15$ K and the mixture of $w_1 = 0.05$ at 318.15 K, as indicated above. As observed, the contributions by the mixing thermodynamic quantities, $\Delta_{\text{mix}}H^\circ$ and $\Delta_{\text{mix}}S^\circ$, to the overall dissolution processes of TCC in neat solvents and {1,4-dioxane (1)+cyclohexane (2)} mixtures, are positive in all the systems, indicating endothermic and entropy-driven mixing processes. Moreover, to compare the relative contributions by enthalpy (ζ_H) and entropy (ζ_{TS}) to the mixing processes, two equations analogous to Eqs. 10 and 11 were also employed. As shown in Table 5, the main contributor to the positive standard apparent molar Gibbs energies of mixing of TCC was the positive enthalpy, which demonstrates the energetic predominance

Table 5 Apparent thermodynamic functions relative to mixing processes of triclocarban (3) in {cyclohexane (1) + 1,4-dioxane (2)} mixtures at $T_{hm} = 302.8$ K and $p = 96$ kPa

w_1 [a,b]	x_1 [a,b]	$\Delta_{mix}G°$ /kJ·mol^{-1} [b]	$\Delta_{mix}H°$ /kJ·mol^{-1} [b]	$\Delta_{mix}S°$ /J·mol^{-1}·K^{-1} [b]	$T\Delta_{mix}S°$ / kJ·mol^{-1} [b]	ζ_H [c]	ζ_{TS} [c]
0.00	0.0000	0.57	42.34	137.94	41.77	0.503	0.497
0.05	0.0522	1.66	42.53	134.98	40.88	0.510	0.490
0.10	0.1042	2.75	42.65	131.76	39.90	0.517	0.483
0.15	0.1559	3.83	43.06	129.53	39.22	0.523	0.477
0.20	0.2074	4.93	43.26	126.60	38.34	0.530	0.470
0.25	0.2587	6.02	43.57	124.02	37.55	0.537	0.463
0.30	0.3097	7.10	43.87	121.43	36.77	0.544	0.456
0.35	0.3605	8.20	44.13	118.66	35.93	0.551	0.449
0.40	0.4111	9.28	44.41	116.00	35.13	0.558	0.442
0.45	0.4614	10.37	44.68	113.29	34.31	0.566	0.434
0.50	0.5115	11.47	44.80	110.09	33.34	0.573	0.427
0.55	0.5613	12.56	45.04	107.26	32.48	0.581	0.419
0.60	0.6110	13.65	45.34	104.65	31.69	0.589	0.411
0.65	0.6604	14.73	45.61	101.96	30.88	0.596	0.404
0.70	0.7095	15.82	46.16	100.17	30.33	0.603	0.397
0.75	0.7585	16.92	46.40	97.36	29.48	0.611	0.389
0.80	0.8072	18.00	46.63	94.53	28.63	0.620	0.380
0.85	0.8558	19.08	46.95	92.02	27.87	0.628	0.372
0.90	0.9041	20.20	47.17	89.05	26.97	0.636	0.364
0.95	0.9521	21.28	47.35	86.09	26.07	0.645	0.355
1.00	1.0000	22.32	47.64	83.61	25.32	0.653	0.347

[a] p is the atmospheric pressure in Neiva, Huila, Colombia. w_1 and x_1 are the mass and mole fraction of cyclohexane (1) in the {cyclohexane (1) + 1,4-dioxane (2)} mixtures free of triclocarban (3), respectively

[b] Standard uncertainty in T_{hm} is $u(T_{hm}) = 0.13$ 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 $u_r(\Delta_{mix}G°) = 0.028$, $u_r(\Delta_{mix}H°) = 0.033$, $u_r(\Delta_{mix}S°) = 0.043$, $u_r(T\Delta_{mix}S°) = 0.043$

[c] ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward apparent Gibbs energy of mixing

in all these TCC mixing processes, although in neat 1,4-dioxane and 1,4-dioxane-rich mixtures the contributions are similar.

3.6 Enthalpy–Entropy Compensation Analysis

As well-known, the extra-thermodynamic studies, which includes enthalpy–entropy compensation analysis, provide powerful tools to inquiry into the main molecular mechanisms implicated in a lot of physical and chemical processes involving several organic compounds like a variety of drugs [45, 46]. These physicochemical studies have been performed in order to identify the main mechanisms involved in the cosolvent action to
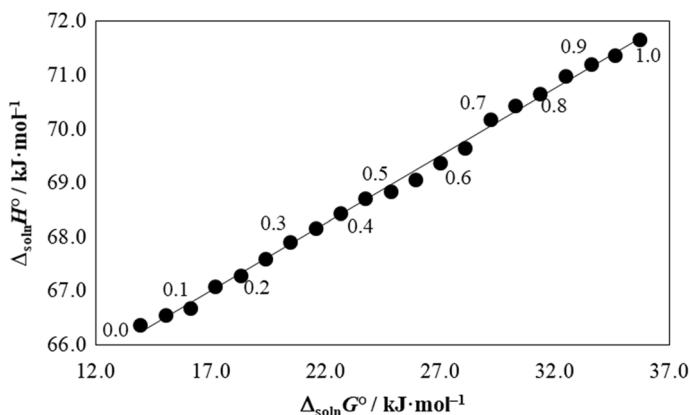
Fig. 7 $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$ enthalpy–entropy compensation plot for the dissolution processes of triclocarban (3) in {cyclohexane (1) + 1,4-dioxane (2)} mixtures at $T_{hm} = 302.8$ K

increase or decrease the drugs solubility depending on the solvent mixtures compositions. Normally, weighted plots of $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$ and/or $\Delta_{mix}H°$ vs. $\Delta_{mix}G°$ have been used for performing these analyses [47–49]. In particular, Fig. 7 clearly shows that TCC exhibits a linear $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$ trend in the studied organic mixtures, adjusted to $\Delta_{soln}H°/kJ\cdot mol^{-1} = 0.250 \cdot \Delta_{soln}G°/kJ\cdot mol^{-1} + 62.75/kJ\cdot mol^{-1}$ [34–36]. The positive slope indicates that the transfer processes of TCC from neat cyclohexane to neat 1,4-dioxane is enthalpy-driven, probably owing the better drug solvation by 1,4-dioxane molecules.

3.7 Preferential Solvation of TCC

The preferential solvation parameters of TCC (indicated as compound 3) by cyclohexane (indicated as compound 1) molecules in the different {cyclohexane (1) + 1,4-dioxane (2)} mixtures ($\delta x_{1,3}$) are defined as [50–52]:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \qquad (16)$$

where $x_{1,3}^{L}$ is the local mole fraction of cyclohexane in the molecular environment of TCC and x_1 is the bulk mole fraction of cyclohexane in the initial {cyclohexane (1) + 1,4-dioxane (2)} binary solvent mixture free of TCC. Thus, if $\delta x_{1,3}$ value is positive TCC molecules are preferentially solvated by cyclohexane molecules in the solutions. In contrast, TCC molecules are preferentially solvated by 1,4-dioxane 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 [50–52], based on the following expressions:

$$\delta x_{1,3} = \frac{x_1 x_2 \left(G_{1,3} - G_{2,3}\right)}{x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}} \qquad (17)$$

with

$$G_{1,3} = RT\kappa_T - \overline{V}_3 + x_2 \overline{V}_2 D/Q \qquad (18)$$

$$G_{2,3} = RT\kappa_T - \overline{V}_3 + x_1\overline{V}_1 D/Q \tag{19}$$

$$V_{\text{cor}} = 2522.5 \left(r_3 + 0.1363 \left(x_{1,3}^L \overline{V}_1 + x_{2,3}^L \overline{V}_2 \right)^{1/3} - 0.085 \right)^3 \tag{20}$$

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 cyclohexane, 1,4-dioxane, and TCC in the dissolutions. The function D, defined in Eq. 21, corresponds to the first derivative of the standard molar Gibbs energies of transfer of TCC from neat 1,4-dioxane to every {cyclohexane (1) + 1,4-dioxane (2)} mixture regarding the mole fraction of cyclohexane. The function Q, defined in Eq. 22, involves the second derivative of the excess molar Gibbs energy of mixing of cyclohexane and 1,4-dioxane (G_{1+2}^{Exc}) regarding the mole fraction of 1,4-dioxane. V_{cor} and r_3 are, respectively, the correlation volume and the molecular radius of TCC. Here, r_3 was roughly calculated by means of Eq. 23, where N_{Av} is the number of Avogadro.

$$D = \left(\frac{\partial \Delta_{\text{tr}} G_{3,2\to1+2}^{\text{o}}}{\partial x_1} \right)_{T,p} \tag{21}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G_{1+2}^{\text{Exc}}}{\partial x_2^2} \right)_{T,p} \tag{22}$$

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{\text{Av}}} \right)^{1/3} \tag{23}$$

To obtain definitive V_{cor} values, iteration processes are required because they depend on the local mole fractions of cyclohexane and 1,4-dioxane around the TCC molecules in the respective solutions. Thus, these iteration processes were performed by replacing $\delta x_{1,3}$ and
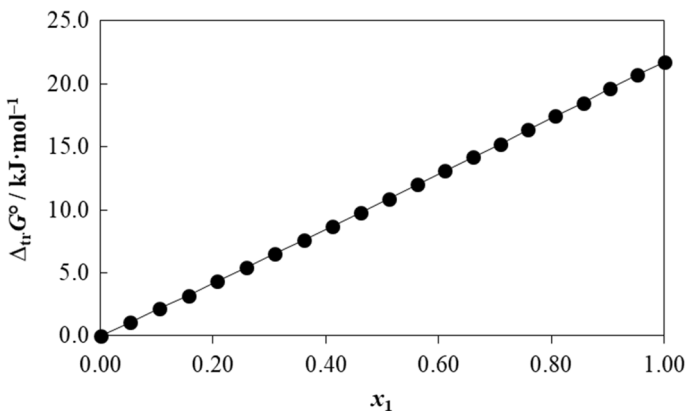

Fig. 8 Gibbs energy of transfer of triclocarban (3) from neat 1,4-dioxane (2) to {cyclohexane (1) + 1,4-dioxane (2)} mixtures at $T = 303.15$ K

V_{cor} in Eqs. 17, 18 and 20 to recalculate the $x_{1,3}^L$ values until obtaining non-variant values of V_{cor}.

Figure 8 shows the apparent Gibbs energies of transfer of TCC from neat 1,4-dioxane to all {cyclohexane (1) + 1,4-dioxane (2)} mixtures ($\Delta_{\text{tr}} G^{\text{o}}_{3,2\to1+2}$) at $T = 303.15$ K. These $\Delta_{\text{tr}} G^{\text{o}}_{3,2\to1+2}$ values were calculated from the experimental mole fraction solubility values reported in Table 2 by using:

$$\Delta_{\text{tr}} G^{\text{o}}_{3,2\to1+2} = RT \ln \left(\frac{x_{3,2}}{x_{3,1+2}} \right) \tag{24}$$

Obtained $\Delta_{\text{tr}} G^{\text{o}}_{3,2\to1+2}$ values were correlated by means of the lineal function shown as Eq. 25, where the obtained statistical parameters were as follows: adjusted $r^2 = 0.9998$, typical error $= 0.0871$, and $F = 120{,}539$ [34–36].

$$\Delta_{\text{tr}} G^{\text{o}}_{3,2\to1+2} = 21.81(\pm0.06)x_1 - 0.18(\pm0.04) \tag{25}$$

The constant D value shown in Table 6 was determined as the slope of Eq. 25. Required Q, $\overline{V}_1$ and $\overline{V}_2$ values at $T = 303.15$ K were calculated from some thermodynamic quantities reported by Deshpande and Oswal that include excess Gibbs energies of mixing and excess volumes [53], whereas $RT\kappa_T$ values were calculated from κ_T reported by Marcus [29]. All these values are also summarized in Table 6. Moreover, as-before in the analysis of TCC in {1,4-dioxane (1) + water (2)} mixtures, the $\overline{V}_3$ value was considered the same as the one calculated by considering molar mass and density (1.53 g·cm^{-3} [1]), i.e., 206.26 cm^3·mol^{-1}, despite the solvent mixtures composition.

Table 6 shows that the $G_{1,3}$ and $G_{2,3}$ values are positive in almost all the solvent systems, except for $G_{1,3}$ in the interval $0.85 \leq x_1 \leq 1.00$ and for $G_{2,3}$ in the interval $0.00 \leq x_1 \leq 0.10$. TCC r_3 value was calculated as 0.434 nm. It is noteworthy that V_{cor} values shown in Table 6 were obtained after three iterations. V_{cor} values increase with the cyclohexane proportion in the mixtures because $\overline{V}_1$ values are higher than $\overline{V}_2$ values. Additionally, Table 6 also summarizes the preferential solvation parameters of TCC by cyclohexane molecules ($\delta x_{1,3}$) in the mixtures at $T = 303.15$ K.

Figure 9 shows a nonlinear variation $\delta x_{1,3}$ values for TCC regarding the cyclohexane proportion in the mixtures as expressed by their mole fractions before TCC adding. Initially, the addition of cyclohexane to neat 1,4-dioxane makes positive the $\delta x_{1,3}$ values of TCC in the composition interval of $0.00 < x_1 < 0.44$. The maximum positive $\delta x_{1,3}$ value is obtained in the mixture of $x_1 = 0.25$ (i.e., $\delta x_{1,3} = 5.92 \times 10^{-2}$), which is higher than $|1.0 \times 10^{-2}|$. Hence, this result is a consequence of real preferential solvation effects of TCC by cyclohexane molecules, rather than a consequence of uncertainties propagation in the IKBI calculations [54, 55].

Based on the negative $\delta x_{1,3}$ values observed in the composition interval of $0.44 < x_1 < 1.00$, it follows that the local mole fractions of 1,4-dioxane around TCC molecules are higher than those in the bulk mixtures in the absence of TCC. The maximum negative $\delta x_{1,3}$ value is obtained in the mixture of $x_1 = 0.70$ (i.e., $\delta x_{1,3} = -7.63 \times 10^{-2}$), which is also higher than $|1.0 \times 10^{-2}|$. Preferential solvation by cyclohexane in 1,4-dioxane could be a consequence of polarization effects, whereas, preferential solvation by 1,4-dioxane in cyclohexane-rich mixtures could be a consequence of acidic Lewis behavior of hydrogen amide groups interacting with the basic Lewis oxygen atoms of this solvent [29].

Table 6 Some properties associated to preferential solvation of triclocarban (3) in {cyclohexane (1) + 1,4-dioxane (2)} mixtures at T = 313.15 K

x_1^a	D/kJ·mol^{-1}	Q/kJ·mol^{-1}	$RT\,\kappa_T$/kJ·mol^{-1}	V_1/cm^3·mol^{-1}	V_2/cm^3·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	21.81	2.521	1.860	111.40	85.71	537.1	−204.4	2163	0.00
0.05	21.81	2.000	1.911	111.33	85.71	683.5	−143.7	2191	1.88
0.10	21.81	1.584	1.961	111.24	85.72	857.5	−51.2	2218	3.62
0.15	21.81	1.259	2.012	111.12	85.74	1057.6	84.4	2244	5.02
0.20	21.81	1.012	2.063	110.99	85.76	1274.4	274.2	2267	5.84
0.25	21.81	0.830	2.113	110.83	85.81	1486.0	523.5	2286	5.92
0.30	21.81	0.705	2.164	110.67	85.87	1656.3	823.4	2303	5.18
0.35	21.81	0.626	2.215	110.49	85.96	1742.5	1143.2	2316	3.72
0.40	21.81	0.587	2.265	110.31	86.07	1714.2	1434.9	2327	1.73
0.45	21.81	0.582	2.316	110.12	86.21	1572.1	1652.2	2338	−0.50
0.50	21.81	0.607	2.367	109.93	86.38	1348.3	1771.4	2348	−2.71
0.55	21.81	0.658	2.417	109.74	86.59	1087.6	1796.8	2359	−4.66
0.60	21.81	0.734	2.468	109.56	86.83	828.2	1749.3	2372	−6.20
0.65	21.81	0.835	2.519	109.39	87.12	592.8	1653.7	2386	−7.20
0.70	21.81	0.962	2.569	109.23	87.45	391.2	1530.2	2402	−7.63
0.75	21.81	1.117	2.620	109.09	87.83	224.9	1393.3	2420	−7.46
0.80	21.81	1.306	2.671	108.96	88.26	91.2	1252.3	2439	−6.72
0.85	21.81	1.533	2.721	108.86	88.75	−14.1	1113.1	2459	−5.50
0.90	21.81	1.805	2.772	108.78	89.29	−95.6	979.4	2479	−3.88
0.95	21.81	2.131	2.823	108.73	89.90	−157.4	853.7	2499	−2.01
1.00	21.81	2.521	2.873	108.71	90.56	−203.4	737.2	2519	0.00

$^a x_1$ is the mole fraction of cyclohexane (1) in the {cyclohexane (1) + 1,4-dioxane (2)} mixtures free of triclocarban (3)
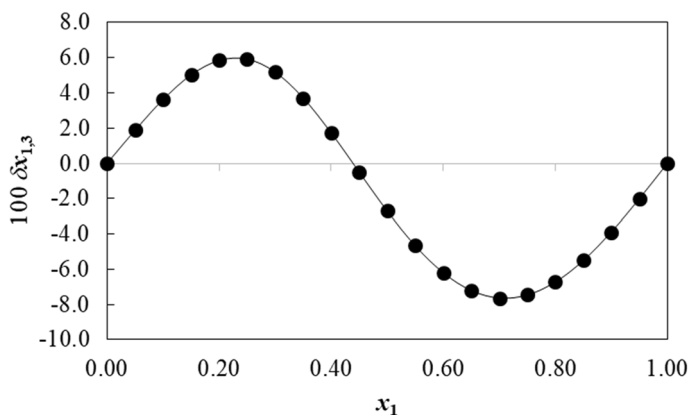
Fig. 9 Preferential solvation parameters ($\delta x_{1,3}$) of triclocarban (3) by cyclohexane (1) in {cyclohexane (1) + 1,4-dioxane (2)} mixtures at $T = 303.15$ K

4 Conclusions

Based on all previously discussed, it is demonstrated that all dissolution physicochemical properties of TCC in the {cyclohexane (1) + 1,4-dioxane (2)} mixtures depend strongly on the mixtures composition. Logarithmic mole fraction solubilities of TCC vary linearly with temperature and cyclohexane proportion. The apparent thermodynamic quantities of dissolution and mixing of TCC in these mixtures were calculated based on van't Hoff and Gibbs equations. Linear enthalpy–entropy compensation was found for TCC indicating the same mechanism for the drug transfer. Moreover, based on IKBI calculations it was stated that TCC is preferentially solvated by cyclohexane molecules in 1,4-dioxane-rich mixtures but preferentially solvated by 1,4-dioxane molecules in cyclohexane-rich mixtures.

Declarations

Conflict of interest The authors report no conflict of interest related with this manuscript.

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