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# Preferential solvation of triclocarban in *N*-methyl-2-pyrrolidone + water cosolvent mixtures according to the Inverse Kirkwood-Buff Integrals (IKBI) method and correlation of solubility by means of some mathematical models

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## Summary

**Introduction:** Solubility is an important thermodynamic property due to its role in product development, as well as the understanding of biological processes. This research aims to evaluate the preferential solvation parameter ($\delta x_{1,3}$) of the triclocarban (TCC) solubility in *N*-methyl-2-pyrrolidone + water cosolvent mixtures and to assess some correlational and predictive mathematical models of concern to the pharmaceutical industry. **Calculations:** $\delta x_{1,3}$ was determined from

experimental data following the Inverse Kirkwood-Buff Integrals model (IKBI). The mathematical models were developed using Python, and functions for each model were fitted by non-linear least squares using the libraries scipy.optimize. curve_fit, and sklearn.model_selection. **Results:** According to the $\delta x_{1,3}$ heat, TCC has preferential solvation by water in water-rich mixtures, and preferential solvation by *N*-methyl-2-pyrrolidone in intermediate and *N*-methyl-2-pyrrolidone-rich mixtures. The models Yalkowsky–Roseman–van't Hoff, Wilson, Modified Wilson, NRTL, van't Hoff, Apelblat, and Buchowski–Ksiazaczak $\lambda$h were assessed, finding good correlations with all. Conclusions: The TCC solubility increase in *N*-methyl-2-pyrrolidone + water cosolvent mixtures with increasing *N*-methyl-2-pyrrolidone (NMP) concentration may be related to the rise in the local mole fraction ($x_{1,3}^{L}$) of NMP in the TCC solvation sphere. Regarding the mathematical models, the Yalkowsky–Roseman–van't Hoff model can be considered the most versatile due to its capability estimate solubility data as a function of both temperature and cosolvent composition, given a limited range of experimental data.

*Keywords:* Triclocarban, inverse Kirkwood-Buff integrals, IKBI, preferential solvation, mathematical assessment.

## Resumen

### Solvatación preferencial de triclocarbán en mezclas de cosolventes de *N*-metil-2-pirrolidona + agua según el método de la integrales inversas de Kirkwood-Buff y correlación de solubilidad mediante algunos modelos matemáticos

**Introducción:** La solubilidad es una de las propiedades termodinámicas de mayor importancia debido a su relación en desarrollo de productos como en la elucidación de procesos biológicos. El objetivo del presente trabajo de investigación es determinar y evaluar el parámetro de solvatación preferencial ($\delta x_{1,3}$) de la solubilidad del triclocarbán (TCC) en mezclas cosolventes *N*-metil-2-pirrolidona + agua, además de desafiar algunos modelos matemáticos de carácter correlacional y predictivo de interés para la industria farmacéutica. **Cálculos:** A partir de datos experimentales se determinó $\delta x_{1,3}$ de acuerdo con el modelo de integrales inversas de Kirkwood-Buff. Los modelos matemáticos fueron desarrollados con Python y las funciones de cada modelo se ajustaron mediante mínimos cuadrados no lineales utilizando las bibliotecas scipy.optimize.curve_fit y sklearn.model_selection. **Resultados:** De acuerdo con los calores del $\delta x_{1,3}$ el TCC se solvata preferencialmente por el agua en

mezclas ricas en agua y en mezclas intermedias y ricas en *N*-methyl-2-pyrrolidone es solvatado preferencialmente por la *N*-metil-2-pirrolidona. Se evaluaron los modelos de Yalkowsky–Roseman–van't Hoff, Wilson, Wilson Modificado, NRTL, van't Hoff, Apelblat y Buchowski–Ksiazaczak $\lambda$h, obteniendo buenas correlaciones con todos ellos. **Conclusiones:** El incremento de la solubilidad del TCC en mezclas cosolventes *N*-metil-2-pirrolidona + agua, al incrementar la concentración de *N*-metil-2-pirrolidona (NMP) puede estar relacionada con el incremento de la fracción molar local ($x_{1,3}^{L}$) de NMP en la esfera de solvatación del TCC, en cuanto a los modelos matemáticos el modelo de Yalkowsky–Roseman–van't Hoff, puede definirse como el modelo más versátil al tener la capacidad de calcular datos de solubilidad en función tanto de la temperatura como de la composición cosolventes con un excelente grado de precisión, el cual fue desarrollado a partir de un número limitado de datos experimentales.

*Palabras clave:* Triclocarbán, integrales inversas de Kirkwood-Buff, IKBI, solvatación preferencial, análisis matemático.

## Resumo

### Solvatação preferencial de triclocarban em misturas de *N*-metil-2-pirrolidona + água cosolvente de acordo com o método da integrais inversas da Kirkwood-Buff e correlação de solubilidade por meio de alguns modelos matemáticos

**Introdução:** A solubilidade é uma importante propriedade termodinâmica devido ao seu papel no desenvolvimento de produtos, bem como na compreensão de processos biológicos. Esta pesquisa tem como objetivo avaliar o parâmetro de solvatação preferencial ($\delta x_{1,3}$) da solubilidade do triclocarban (TCC) em misturas de co-solventes *N*-metil-2-pirrolidona + água e avaliar alguns modelos matemáticos correlacionais e preditivos de interesse para a indústria farmacêutica. **Cálculos:** $\delta x_{1,3}$ foi determinado a partir de dados experimentais seguindo o modelo da integrais inversas da Kirkwood-Buff. Os modelos matemáticos foram desenvolvidos em Python, e as funções de cada modelo foram ajustadas por mínimos quadrados não lineares usando as bibliotecas scipy.optimize.curve_fit e sklearn.model_selection. **Resultados:** De acordo com o calor $\delta x_{1,3}$, o TCC possui solvatação preferencial por água em misturas ricas em água, e solvatação preferencial por *N*-metil-2-pirrolidona em misturas intermediárias e ricas em *N*-metil-2-pirrolidona. Os modelos Yalkowsky–Roseman–van't Hoff, Wilson, Wilson modificado, NRTL, van't Hoff, Apelblat e

Buchowski–Ksiazaczak $\lambda$h foram avaliados, encontrando boas correlações com todos. Conclusões: O aumento da solubilidade do TCC em misturas de cosolventes de *N*-metil-2-pirrolidona + água com o aumento da concentração de N-metil-2-pirrolidona (NMP) pode estar relacionado ao aumento na fração molar local ($x_{1,3}^{L}$) de NMP em a esfera de solvatação do TCC. Em relação aos modelos matemáticos, o modelo Yalkowsky–Roseman–van't Hoff pode ser considerado o mais versátil devido à sua capacidade de estimar dados de solubilidade em função da temperatura e da composição do cosolvente, dada uma gama limitada de dados experimentais.

*Palavras-chave:* Triclocarban, integrais inversas de Kirkwood-Buff, IKBI, solvatação preferencial, avaliação matemática.

## Introduction

Triclocarban (5-Chloro-2-(2,4-dichlorophenoxy)phenol; abbreviated TCC hereafter; Figure 1) is a broad-spectrum antimicrobial agent [1]. Although TCC was initially developed exclusively for medical use due to its antimicrobial properties, it is currently included in more than 2000 commodities, from soaps, toothpaste, detergents, and textiles to construction products and plastics [2]. Due to the potential endocrine-disrupting effect and bacterial resistance associated with this drug, the US Food and Drug Administration (FDA) banned the use of the drug in personal care products and over-the-counter medicines. Despite restrictions, many products still incorporate TCC [3, 4], and consequently, it is discharged into the environment mostly through wastewater, affecting a variety of ecosystems and becoming a public health issue as it generates antimicrobial resistance, among other significant environmental problems [5, 6].

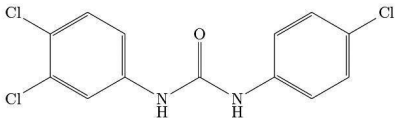


**Figure 1.** Molecular structure of triclocarban.

Solubility is one of the main physicochemical properties, as it is crucial in industrial processes such as crystallization, purification, pre-formulation, formulation, and quantification [7, 8]; pharmacological processes such as pharmacokinetics and pharmacodynamics; and environmental processes such as biotoxicity assessment, bioadsorption, bioaccumulation, among others [9-11].

The TCC solubility has been studied in different organic solvents [12, 13], and some cosolvent mixtures such as (1,4-dioxane + water) [14, 15], (ethanol + propylene glycol) [16], (cyclohexane + 1,4-dioxane) [17] and (ethylene glycol + water) [18].

Thermodynamic analyses of the solution process are valuable to rationalizing the solubility results since they allow the understanding of the possible molecular phenomena occurring in the process [19, 20]. As a complement, preferential solvation studies permit the analysis of the local cosolvent composition of the solvation sphere [21-25]. Another field related to solubility studies is mathematical modeling, which is especially interesting for the industry since it offers computational tools that allow reducing experimental tests or calculating solubility data under other than experimental conditions [26-29].

In this context, this research aims to evaluate the preferential solvation of TCC in *N*-methyl-2-pyrrolidone + water mixtures ({NMP (1) + W (2)}) and to assess some predictive and correlational mathematical models.

## Results and discussion

The preferential solvation parameter and the mathematical models were computed from the solubility data reported by Caviedes-Rubio *et al.* [30], the preferential solvation parameter and some mathematical models were calculated or challenged. Figure 2 plots the solubility of TCC as a function of the NMP mass fraction, where is observed a positive cosolvent effect of the NMP, especially in NMP-rich mixtures.

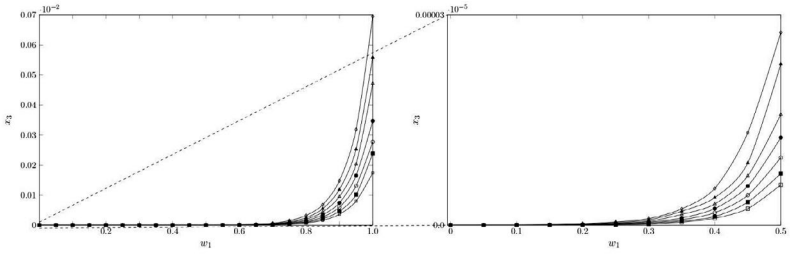


**Figure 2.** Mole fraction of TCC depending on the mass fraction of NMP in the {NMP (1) + W (2)} mixtures free of TCC. ●: 288.15 K; ○: 293.15 K; △: 298.15 K; ▲: 303.15 K; □: 308.15 K; ■: 313.15 K; ⧈: 318.15 K.

**Preferential solvation**

The solvation sphere of the TCC molecule in each of the cosolvent mixtures can be evaluated from the equations of the IKBI model [21, 22, 31, 32].

$$\delta x_{1,3} = x_1 x_2 (G_{1,3} - G_{2,3}) [x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}]^{-1} \quad (1)$$

$$G_{1,3} = RT\kappa_T - V_3 + x_2 V_2 DQ^{-1} \quad (2)$$

$$G_{1,3} = RT\kappa_T - V_3 + x_2 V_2 DQ^{-1} \quad (3)$$

$$\kappa_{T(1+2)} = x_1 \kappa_1 + x_2 \kappa_2 \quad (4)$$

$$V_1 = V + x_2 \frac{\partial V}{\partial x_1} \quad (5)$$

$$V_2 = V + x_1 \frac{\partial V}{\partial x_2} \quad (6)$$

$$V_{cor} = 2522.5 \left[ r_3 + 0.1363 \sqrt[3]{x_1^L V_1 + x_2^L V_2} - 0.085 \right]^3 \quad (7)$$

$$x_1^L = \delta x_{1,3} + x_1 \quad (8)$$

$$D = \frac{\partial \Delta_{tr} G^o_{3 2 \rightarrow 1+2}}{\partial x_1} \quad (9)$$

$$Q = RT + x_1 x_2 \left( \frac{\partial^2 G^E_{1,2}}{\partial x_2^2} \right) \quad (10)$$

Here $G_{1,3}$ and $G_{2.3}$ are the Kirkwood–Buff integrals (in cm$^3$·mol) obtained from the thermodynamic data in equations 2 and 3, and $V_{cor}$ is the correlation volume around TCC where preferential solvation occurs. In equations 2 and 3 $\varkappa T$ is the isothermal compressibility of the mixtures (in GPa$^{-1}$), $V_3$ is the partial molar volume of the solute (206.26 cm$^3$·mol [13]), and $V_1$ and $V_2$ are the partial molar volume of the solvents (in cm$^3$·mol), while $D$ and $Q$ (in kJ·mol$^{-1}$, as is $RT$) are given in equations 9 and 10. The

compressibility is given to sufficient approximation as the linear expression equation 4 and the partial molar volumes are calculated from the experimental data of the density of the mixtures free of solute through equations 5 and 6. Eq. 7 requires iteration since it depends on the local mole fractions given by equations 1 and 8.

Parameter *D* is calculated from the TCC Gibbs energy of transfer from the water to each of the cosolvent and neat organic solvent mixtures (Figure 3).

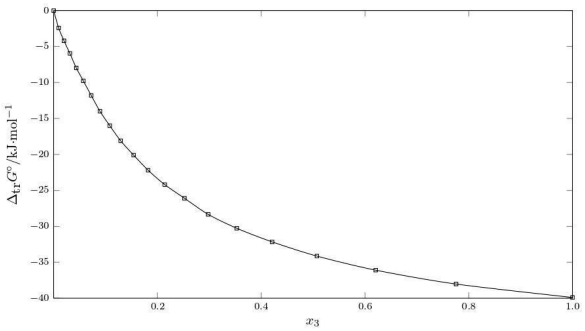


**Figure 3.** Gibbs energy of transfer of TCC (3) from neat water (2) to {NMP (1) + W (2)} mixtures at 298.15 K

Equation 11 describes the trends of the TCC Gibbs energy of transfer in each of the cosolvent mixtures, from where *D* is calculated as the first polynomial derivative, with $r^2$=1.0.

$$\Delta G^o_{3,2\rightarrow 1+2} = RT\ln(x_{3,2}/x_{3,1+2}) = -253.9x_1^5 + 758.2x_1^4 - 889.3x_1^3 + 538.3x_1^2 - 192.9x_1 - 0.409 \quad (11)$$

Some data necessary for the model development were taken from the literature to calculate the preferential solvation parameter (Eq. 1). The isothermal compressibility of the mixtures was calculated from the compressibility of the neat solvents (Eq. 4) by using $\varkappa T$ of NMP as 0.620 GPa$^{-1}$, and $\varkappa T$ of water as 0.457 GPa$^{-1}$ [33]; $V_3$ = 206.26 cm$^3$·mol$^{-1}$ [14]. The partial molar volume of both solvents (water and NMP), necessary for the calculation of the inverse Kirkwood-Buff integrals (Equations 2 and 3), were taken from literature [34]. $r_3$, necessary to compute $V_{cor}$ (Eq. 7) was assumed as 0.434 nm [14]; the excess Gibbs energy for the {NMP (1) + water (2)} mixtures free of TCC, necessary for the calculation of *Q* (Eq. 10), was calculated from the equation and coefficients reported by Marcus [35]. Other values, such as *D,* were calculated from the experimental solubility data according to Eq. (9). Table 1 presents the data of the solvation parameters and some other parameters required to develop the IKBI model.

**Table 1.** Some properties associated with preferential solvation of TCC (3) in {NMP (1) + W (2)} mixtures at 298.15 K.

| $x_1$ [a] | $D$ / kJ·mol$^{-1}$ | $Q$ [b] / kJ·mol$^{-1}$ | $RT \cdot \varkappa T$ [b] / kJ·mol$^{-1}$ | $V_1$ [b] / cm$^3$·mol$^{-1}$ | $V_2$ [b] / cm$^3$·mol$^{-1}$ | $G_{1,3}$ / cm$^3$·mol$^{-1}$ | $G_{2,3}$ / cm$^3$·mol$^{-1}$ | $V_{cor}$ / cm$^3$·mol$^{-1}$ | $x^L_{1,3}$ | 100·$\delta x_{1,3}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.00 | −192.87 | 2.479 | 1.133 | 89.90 | 18.09 | −1612.6 | −205.1 | 890.8 | 0.000 | 0.00 |
| 0.05 | −145.34 | 2.263 | 1.153 | 90.89 | 18.07 | −1307.6 | −497.0 | --- | --- | --- |
| 0.10 | −108.98 | 2.252 | 1.173 | 91.77 | 18.00 | −989.0 | −649.2 | --- | --- | --- |
| 0.15 | −81.81 | 2.357 | 1.193 | 92.55 | 17.89 | −732.9 | −686.9 | 1121.6 | 0.136 | −1.37 |
| 0.20 | −62.03 | 2.513 | 1.214 | 93.25 | 17.74 | −555.3 | −665.4 | 1266.4 | 0.228 | 2.83 |
| 0.25 | −48.02 | 2.670 | 1.234 | 93.85 | 17.56 | −441.9 | −627.0 | 1366.5 | 0.294 | 4.42 |
| 0.30 | −38.38 | 2.800 | 1.254 | 94.38 | 17.37 | −371.7 | −593.1 | 1450.2 | 0.350 | 5.04 |
| 0.35 | −31.88 | 2.887 | 1.274 | 94.82 | 17.15 | −328.1 | −571.4 | 1527.2 | 0.403 | 5.32 |
| 0.40 | −27.47 | 2.925 | 1.295 | 95.20 | 16.92 | −300.3 | −562.5 | 1601.8 | 0.455 | 5.50 |
| 0.45 | −24.31 | 2.919 | 1.315 | 95.52 | 16.69 | −281.4 | −562.9 | 1674.6 | 0.506 | 5.63 |
| 0.50 | −21.74 | 2.881 | 1.335 | 95.78 | 16.46 | −267.0 | −566.3 | 1744.8 | 0.556 | 5.63 |
| 0.55 | −19.30 | 2.826 | 1.355 | 95.98 | 16.23 | −254.8 | −565.5 | 1811.0 | 0.604 | 5.43 |
| 0.60 | −16.72 | 2.769 | 1.375 | 96.14 | 16.01 | −243.6 | −553.2 | 1872.7 | 0.649 | 4.94 |
| 0.65 | −13.90 | 2.725 | 1.396 | 96.26 | 15.82 | −233.1 | −524.1 | 1929.9 | 0.692 | 4.15 |
| 0.70 | −10.96 | 2.704 | 1.416 | 96.35 | 15.64 | −223.9 | −478.2 | 1983.9 | 0.732 | 3.17 |
| 0.75 | −8.18 | 2.710 | 1.436 | 96.40 | 15.49 | −216.5 | −423.2 | 2037.3 | 0.772 | 2.19 |
| 0.80 | −6.06 | 2.737 | 1.456 | 96.44 | 15.38 | −211.6 | −375.7 | 2093.1 | 0.814 | 1.42 |
| 0.85 | −5.27 | 2.769 | 1.476 | 96.45 | 15.31 | −209.2 | −360.9 | 2152.8 | 0.860 | 1.01 |
| 0.90 | −6.68 | 2.773 | 1.497 | 96.46 | 15.29 | −208.4 | −413.9 | 2216.5 | 0.909 | 0.93 |
| 0.95 | −11.34 | 2.699 | 1.517 | 96.45 | 15.32 | −208.0 | −589.9 | 2279.6 | 0.959 | 0.88 |
| 1.00 | −20.51 | 2.479 | 1.537 | 96.45 | 15.40 | −204.7 | −1002.7 | 2331.6 | 1.000 | 0.00 |

[a] $x_1$ is the mole fraction of NMP (1) in the {NMP (1) + W (2)} mixtures free of TCC (3).
[b] From Nozohouri *et al.* [34].

According to the $\delta x_{1,3}$ analysis (Figure 4), from neat water to $x_1 = 0.15$, the correlation volume calculations are not possible by iteration because the equations do not converge, yielding inconsistent data since  takes negative values (Figure 5) when limited only to values between 0 and 1, even if a trend can be identified. Therefore, it can be inferred that TCC has preferential solvation by water within this range of cosolvent composition. The hydrophobic hydration around the non-polar groups of TCC may contribute to lowering the net $\delta x_{1,3}$ to negative values in these water-rich mixtures [36-40]. From this cosolvent composition ($x_1 = 0.15$) up to neat NMP, $\delta x_{1,3}$ exhibits positive values indicating preferential solvation by NMP.

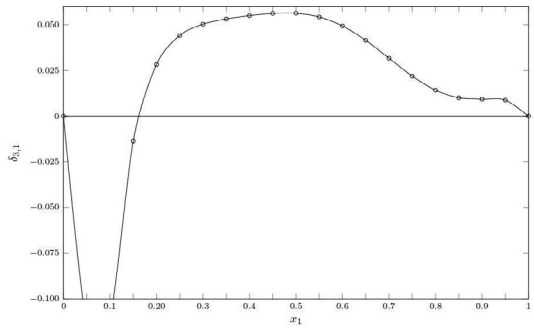


**Figure 4.** Preferential solvation parameters of TCC in {NMP (1) + W (2)} mixtures at 298.15 K.

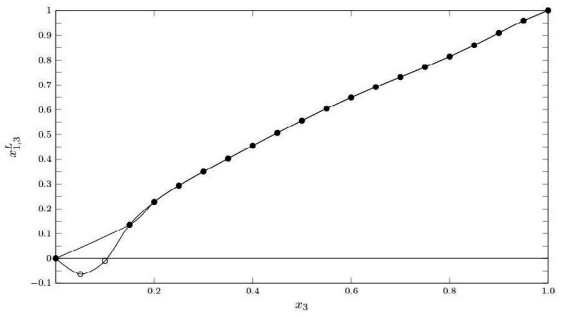


**Figure 5.** Local mole fraction of NMP (1) in the environment near to TCC in {NMP (1) + W (2)} mixtures at 298.15 K.

In water-rich cosolvent mixtures, the TCC behaves as a Lewis base against water since the Kamlet-Taft parameter $\beta$ is 0.14 for water and 0.754 ± 0.019 for the NMP [41]. On the other hand, in intermediate and NMP-rich cosolvent mixtures, where the TCC is preferentially solvated by NMP, the TCC act as a Lewis acid due to the acid hydrogen of the -NH- groups.

### Mathematical Assessment of Solubility

One of the most versatile tools for process optimization is mathematical modeling, which allows making approximations under different conditions than experimental ones [42, 43].

Mathematical models to correlate drug solubility in cosolvent systems can be classified into two groups: the models that work as a function of the cosolvent composition and the models that work as a function of temperature. In the former, the most used models

are Yalkowsky–Roseman-van't Hoff [44, 45], Wilson [46], Modified Wilson [47], NRTL [46], and Extended Hildebrand [28, 48, 49]. In the latter, the most used models are [26, 50], Apelblat [51], Buchowski–Ksiazaczak $\lambda h$ [52, 53] and van't Hoff–Yaws model [54]. The latter models have a significant predictive potential whenever the data to predict are to interpolate.

Hence, the experimental solubility data [30] were correlated with the models Yalkowsky-Roseman-van't Hoff (Eq. 12), van't Hoff (Eq. 13), Apelblat (Eq. 14), Buchowski–Ksiazaczak $\lambda h$ (Eq. 15), van't Hoff–Yaws (Eq. 16), NRTL (Eq. 17), Wilson (Eq. 18), and Modified Wilson (Eq. 19).

$$\ln x_{3,1+2} = \left[w_1\left(A+\frac{B}{T}\right)+w_2\left(C+\frac{D}{T}\right)\right] \tag{12}$$

$$\ln x_{3,1+2} = A + BT^{-1} \tag{13}$$

$$\ln x_{3,1+2} = A + BT^{-1} + C\ln T \tag{14}$$

$$\ln\left[1+\lambda(1-x_3)x_3\right] = \lambda h(T^{-1}-T_m^{-1}) \tag{15}$$

$$\ln x_{3,1+2} = A + BT^{-1} + CT^{-2} \tag{16}$$

$$\ln x_{3,1+2} = 1 - w_1(1+\ln x_{3,1})(w_1+w_2\lambda_{12})^{-1} - w_2(1+\ln x_{3,2})(w_2+w_1\lambda_{21})^{-1} \tag{17}$$

Here, the parameters $A$, $B$, $C$, $D$, $\lambda$, and $h$ are coefficients for each of the models; $T$ is the temperature (in K); $x_{3,1+2}$ is the solubility of TCC in the cosolvent mixture; $x_{3,1}$ is the TCC solubility in NMP; $x_{3,2}$ is the solubility of TCC in water; and $w_1$ is the mass fraction of NMP in the solvent mixture {NMP (1) + W (2)} free of solute (3).

$$\begin{aligned}\ln\gamma_3 = {} & (x_2\tau_{23}G_{23}+x_1\tau_{13}G_{13})(x_3+x_2G_{23}+x_3G_{13})^{-1} - x_3(x_2\tau_{23}G_{23}+x_1\tau_{13}G_{13})(x_3+\\ & x_2G_{23}+x_3G_{13})^{-2} + x_2G_{32}(x_3G_{32}+x_2+x_1G_{12})^{-1}[\tau_{32}-(x_3\tau_{32}G_{32}+x_1\tau_{12}G_{12})(x_3G_{32}+\\ & x_2+x_1G_{12})^{-1}] + x_1G_{31}(x_3G_{31}+x_2G_{21}+x_1)^{-1}[\tau_{31}-(x_3\tau_{31}G_{31}+x_2\tau_{21}G_{21})(x_3G_{31}+\\ & x_2G_{31}+x_1)^{-1}]\end{aligned} \tag{18}$$

$$\ln \gamma_3 = 1 - ln\, ln\,(x_3 + x_2\Lambda_{32} + x_1\Lambda_{31}) - [(x_3(x_3 + x_2\Lambda_{32} + x_1\Lambda_{31})^{-1}) + (x_2\Lambda_{23}(x_3\Lambda_{23} + x_2 + x_1\Lambda_{21})^{-1}) + (x_1\Lambda_{13}(x_3\Lambda_{13} + x_2\Lambda_{12} + x_1)^{-1})] \quad (19)$$

Where $\gamma_3$ is the activity parameter of TCC; and $\tau$, $G$ and $\Lambda$ are model parameters.

Regarding the NRTL model, $G$ is a dimensionless interaction parameter, which depends on the energy interaction parameter, $g$, and the nonrandomness factor, $\alpha$. The NRTL model contains three parameters, but the reduction of experimental data for several binary systems indicates that $\alpha$ varies from 0.20 up to 0.47; when experimental data are few, $\alpha$ value is usually settled arbitrarily as $\alpha = 0.3$. Therefore:

$$G_{ij} = e^{(-\alpha_{ij}\tau_{ij})};\ \alpha_{ij} = \alpha_{ji} = 0.3 \quad (20)$$

The mathematical models were developed using Python, and functions for each model were fitted through non-linear least squares using the scipy.optimize.curve_fit library [55]. To validate the fit of the models the experimental data were randomly sorted into training and test data using the sklearn.model_selection library [56, 57]. The fit was conducted with 60% of the experimental data, while the remaining 40% was used for validation. An exception to this approach was the Yalkowsky-Roseman-van't Hoff model since the data corresponds to pure solvents at the lowest and highest study temperatures, i.e., TCC solubility in neat water at 278.15 K and 318.15 K, and TCC solubility in neat NMP at the same temperatures. Tables 2-9 present the parameters of each of the models and their Mean Relative Difference (MRD) (Eq. 21).

$$MRD = \frac{100}{N}\Sigma\frac{|x_3^e - x_3^c|}{x_3^e} \quad (21)$$

Here, $N$ is the number of solubility data points, while $x_3^e$ and $x_3^c$ represent the experimentally measured and calculated solubility.

**Table 2.** Parameters of the Yalkowsky–Roseman-van't Hoff model parameter and its corresponding MRD.

| Parameter | Values |
|---|---|
| *A* | 10.63 |
| *B* | -4230.53 |
| *C* | -3.56 |
| *D* | -4751.56 |
| | 8.13 |

**Table 3.** Parameters of the van't Hoff model and its corresponding MRD.

| $W_1$ | *A* | *B* | *MRD%* |
|---|---|---|---|
| 0.00 | -5127.8 | -2.38 | 6.00 |
| 0.05 | -5127.6 | -1.53 | 3.34 |
| 0.10 | -5152.5 | -0.72 | 3.60 |
| 0.15 | -5211.7 | 0.20 | 0.94 |
| 0.20 | -5322.0 | 1.38 | 2.51 |
| 0.25 | -5410.2 | 2.43 | 3.69 |
| 0.30 | -5347.2 | 2.98 | 2.28 |
| 0.35 | -5222.7 | 3.49 | 3.36 |
| 0.40 | -5174.9 | 4.10 | 2.09 |
| 0.45 | -5047.1 | 4.56 | 3.71 |
| 0.50 | -4969.8 | 5.13 | 2.69 |
| 0.55 | -4862.8 | 5.55 | 2.72 |
| 0.60 | -4749.2 | 6.01 | 1.00 |
| 0.65 | -4736.2 | 6.80 | 2.79 |
| 0.70 | -4550.8 | 6.99 | 1.32 |
| 0.75 | -4496.5 | 7.62 | 1.62 |
| 0.80 | -4410.2 | 8.10 | 0.68 |
| 0.85 | -4321.3 | 8.59 | 0.35 |
| 0.90 | -4262.2 | 9.17 | 0.00 |
| 0.95 | -4235.0 | 9.86 | 0.00 |
| 1.00 | -4188.1 | 10.49 | 2.53 |
| Overall *MRD* | | | 2.25 |

**Table 4.** Parameters of the Buchowski–Ksiazczak $\lambda$h model and its corresponding MRD.

| $W_1$ | *A* | *B* | *MRD%* |
|---|---|---|---|
| 0.00 | 0.00001 | 913568649 | 6.00 |
| 0.05 | 0.00001 | 390972442 | 3.33 |
| 0.10 | 0.00003 | 183266236 | 3.59 |
| 0.15 | 0.00006 | 82730914 | 0.94 |
| 0.20 | 0.00017 | 32041877 | 2.50 |
| 0.25 | 0.00040 | 13431986 | 3.69 |
| 0.30 | 0.00078 | 6817187 | 2.29 |

*(Continued)*

| $W_1$ | $A$ | $B$ | $MRD\%$ |
|---|---|---|---|
| 0.35 | 0.00166 | 3141589 | 3.36 |
| 0.40 | 0.00334 | 1549812 | 2.09 |
| 0.45 | 0.00670 | 752882 | 3.71 |
| 0.50 | 0.01380 | 359683 | 2.69 |
| 0.55 | 0.02570 | 188971 | 2.72 |
| 0.60 | 0.05003 | 94801 | 1.00 |
| 0.65 | 0.11326 | 41762 | 2.78 |
| 0.70 | 0.19494 | 23312 | 1.32 |
| 0.75 | 0.40503 | 11087 | 1.60 |
| 0.80 | 0.77909 | 5658 | 0.68 |
| 0.85 | 1.51958 | 2847 | 0.36 |
| 0.90 | 3.13912 | 1365 | 0.04 |
| 0.95 | 7.02004 | 612 | 0.11 |
| 1.00 | 16.85140 | 258 | 2.58 |
| Overall *MRD* | | | 2.26 |

**Table 5.** Parameters of the Apelblat model and its corresponding MRD.

| $W_1$ | $A$ | $B$ | $C$ | $MRD\%$ |
|---|---|---|---|---|
| 0.00 | -80.6 | -1665.3 | 11.7 | 6.16 |
| 0.05 | -731.3 | 27925.3 | 108.6 | 4.02 |
| 0.10 | -314.3 | 9066.0 | 46.7 | 3.07 |
| 0.15 | 3.9 | -5353.7 | -0.56 | 0.87 |
| 0.20 | -274.9 | 7160.8 | 41.1 | 2.02 |
| 0.25 | 176.0 | -13292.9 | -25.8 | 3.82 |
| 0.30 | 327.6 | -19994.6 | -48.3 | 1.38 |
| 0.35 | 612.4 | -32827.0 | -90.6 | 4.80 |
| 0.40 | -52.9 | -2583.7 | 8.47 | 1.94 |
| 0.45 | -762.6 | 29706.7 | 114.2 | 4.66 |
| 0.50 | -81.7 | -1081.0 | 12.9 | 2.70 |
| 0.55 | -16.4 | -3852.3 | 3.25 | 2.64 |
| 0.60 | 23.4 | -5527.5 | -2.60 | 1.04 |
| 0.65 | -261.3 | 7378.9 | 39.9 | 2.22 |
| 0.70 | 18.4 | -5035.1 | -1.72 | 1.44 |
| 0.75 | -338.2 | 11147.6 | 51.5 | 1.40 |
| 0.80 | -132.1 | 1936.6 | 20.9 | 0.81 |
| 0.85 | -65.4 | -973.1 | 11.0 | 0.30 |

*(Continued)*

| $W_1$ | $A$ | $B$ | $C$ | $MRD\%$ |
|---|---|---|---|---|
| 0.90 | 9.2 | -4263.9 | 0.01 | 0.00 |
| 0.95 | 10.4 | -4260.6 | -0.08 | 0.00 |
| 1.00 | -21.0 | -2758.6 | 4.68 | 2.55 |
| Overall MRD | | | | 2.28 |

**Table 6.** Parameters of the van't Hoff-Yaws model and its corresponding MRD.

| $W_1$ | $A$ | $B$ | $C$ | $MRD\%$ |
|---|---|---|---|---|
| 0.00 | 4.91 | -9476.6 | 647836.2 | 6.10 |
| 0.05 | 52.3 | -37892.0 | 4981229.3 | 4.08 |
| 0.10 | 22.3 | -19169.8 | 2134242.9 | 3.07 |
| 0.15 | -0.30 | -4933.1 | -38098.8 | 0.87 |
| 0.20 | 22.2 | -17993.5 | 1921841.5 | 2.04 |
| 0.25 | -10.1 | 2234.9 | -1165925.7 | 3.83 |
| 0.30 | -21.6 | 9532.8 | -2252899.8 | 1.40 |
| 0.35 | -41.1 | 21943.8 | -4135104.1 | 4.82 |
| 0.40 | 8.17 | -7664.5 | 380483.3 | 1.95 |
| 0.45 | 61.0 | -39409.7 | 5225825.2 | 4.72 |
| 0.50 | 12.3 | -9266.2 | 645959.9 | 2.66 |
| 0.55 | 7.05 | -5792.6 | 144533.9 | 2.64 |
| 0.60 | 4.56 | -3883.7 | -129734.7 | 1.04 |
| 0.65 | 26.9 | -16942.5 | 1851319.2 | 2.21 |
| 0.70 | 5.73 | -3818.6 | -105450.2 | 1.42 |
| 0.75 | 33.2 | -20055.3 | 2362329.4 | 1.42 |
| 0.80 | 18.4 | -10686.3 | 953561.0 | 0.82 |
| 0.85 | 14.1 | -7651.3 | 505463.1 | 0.30 |
| 0.90 | 9.17 | -4260.5 | -258.6 | 0.00 |
| 0.95 | 9.82 | -4209.2 | -3906.0 | 0.00 |
| 1.00 | 13.0 | -5689.7 | 228991.6 | 2.56 |
| Overall *MRD* | | | | 2.28 |

**Table 7.** Parameters of the NRTL model and its corresponding MRD.

| $T$ | $\tau(1.2)$ | $\tau(1.3)$ | $\tau(2.1)$ | $\tau(2.3)$ | $\tau(3.1)$ | $\tau(3.2)$ | MRD |
|---|---|---|---|---|---|---|---|
| 288.15 | -7.38 | 7.73 | 4.09 | 17.15 | -3.12 | -1.72 | 0.06 |
| 293.15 | -7.77 | 7.48 | 4.03 | 17.59 | -3.07 | -1.91 | 0.14 |
| 298.15 | -8.10 | 7.37 | 4.08 | 18.14 | -3.02 | -2.10 | 0.04 |
| 303.15 | -8.07 | 7.14 | 4.11 | 17.80 | -2.97 | -2.02 | 0.02 |
| 308.15 | -6.28 | 6.61 | 4.15 | 13.32 | -2.93 | 0.58 | 0.06 |
| 313.15 | -6.25 | 6.52 | 4.24 | 13.23 | -2.89 | 0.58 | 0.09 |
| 318.15 | -0.09 | 5.96 | 3.44 | 12.47 | -2.89 | 3.40 | 0.75 |
| Overall *MRD* | | | | | | | 0.17 |

**Table 8.** Parameters of the Wilson model and its corresponding MRD

| $T$ | $\Lambda(1.2)$ | $\Lambda(1.3)$ | $\Lambda(2.1)$ | $\Lambda(2.3)$ | $\Lambda(3.1)$ | $\Lambda(3.2)$ | MRD |
|---|---|---|---|---|---|---|---|
| 288.15 | 0.000 | 0.000 | 5.789 | 0.683 | 6.438 | 1.675 | 0.000 |
| 293.15 | 0.000 | 0.000 | 5.625 | 0.636 | 6.488 | 1.875 | 0.000 |
| 298.15 | 0.000 | 0.000 | 5.466 | 0.695 | 6.437 | 1.769 | 0.001 |
| 303.15 | 0.000 | 0.000 | 5.308 | 0.696 | 6.499 | 1.852 | 0.001 |
| 308.15 | 0.000 | 0.000 | 5.151 | 0.630 | 6.780 | 2.217 | 0.001 |
| 313.15 | 0.000 | 0.000 | 4.999 | 0.657 | 6.916 | 2.261 | 0.001 |
| 318.15 | 0.000 | 0.000 | 4.849 | 0.637 | 7.287 | 2.553 | 0.001 |
| Overall MRD | | | | | | | 0.001 |

**Table 9.** Parameters of the Modified Wilson model and its corresponding MRD.

| $T$ | $\lambda_{12}$ | $\lambda_{21}$ | MRD |
|---|---|---|---|
| 288.15 | 0.98 | 1.02 | 13.35 |
| 293.15 | 1.03 | 0.97 | 7.93 |
| 298.15 | 1.98 | 0.93 | 3.53 |
| 303.15 | -0.03 | 1.24 | 34.25 |
| 308.15 | 1.02 | 0.98 | 5.75 |
| 313.15 | 0.98 | 1.02 | 6.47 |
| 318.15 | 0.98 | 1.02 | 5.25 |
| Overall *MRD* | | | 10.93 |

The two models with higher deviations from the experimental data are the Modified Wilson and Yalkowsky-Roseman-van't Hoff (YRvH) models with MRD of 10% and 8%, respectively. However, based on the modeling principle of using the least number of experimental data, the best model was the YRvH. The YRvH model parameters were calculated from only four experimental data and would allow maximum reduction of tests for a wide range of temperatures and cosolvent compositions. Regarding the MRD results, the best models were Wilson (MRD%=0.001%) and NRTL (MRD%=0.17%).

When evaluating the performance of the models (Table 10), it was observed that all correlation coefficients are approximately 1.0 (Figure 6), -values are high, the $F_{\text{Critical}}$-values are low, and $p$-values are below 0.001. This statistical analysis indicates that the correlation and model constants are meaningful, and the increase in the number of parameters in the models does not represent a significant advantage when predicting solubility. As mentioned before, one of the most versatile models due to the reduced number of experimental data required to calculate its parameters and its great predictive power is the Yalkowsky-Roseman-van't Hoff model. In addition, this model allows the calculation of solubility as a function of both cosolvent composition and temperature, unlike the other models evaluated.

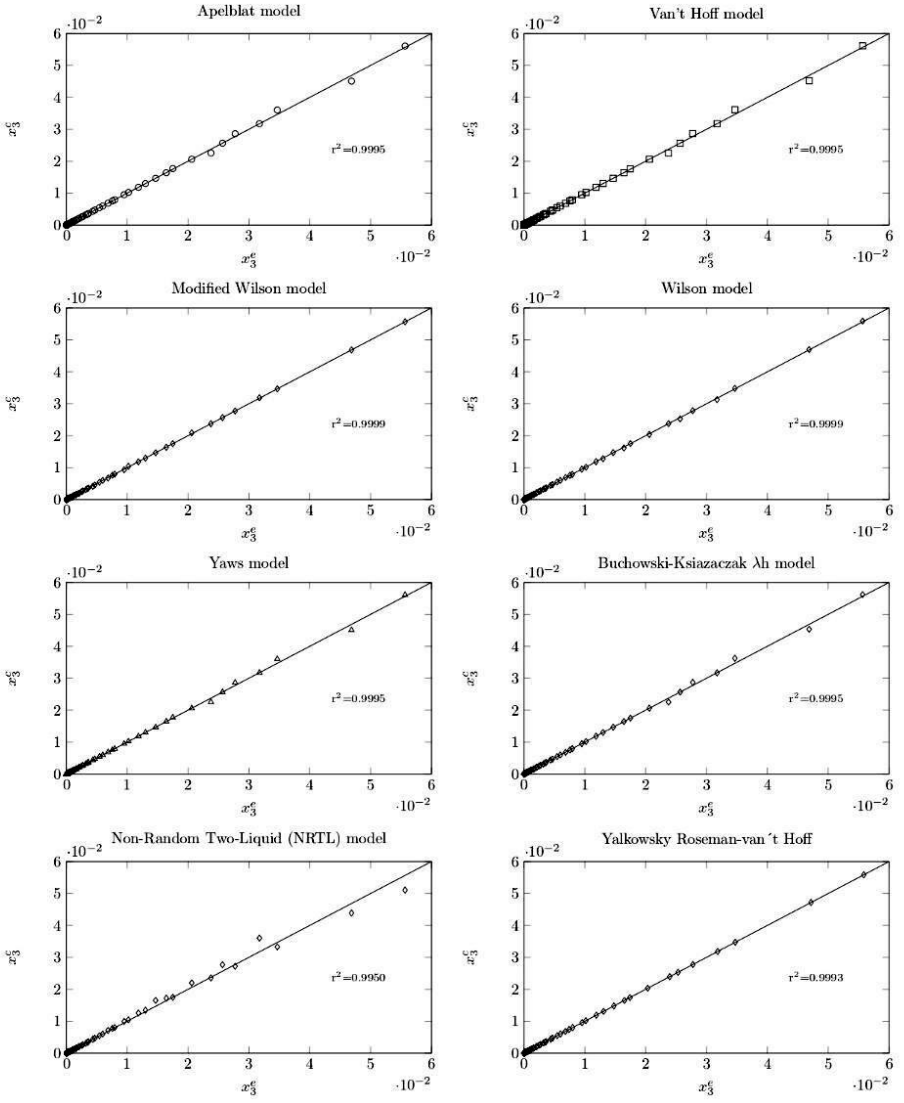


**Figure 6.** Experimental solubility data versus predicted solubility of TCC (3) in {NMP (1) + W (2)} and cosolvent mixtures.

**Table 10.** Statistical analysis of the correlation for all mathematical models.

| Model | Correlation coefficient | $F$ | $F_{critical}$ | $p$ |
|---|---|---|---|---|
| Apelblat | 0.9995 | 283485.9 | $4.2 \cdot 10^{-239}$ | $\ll 0.001$ |
| Modified Wilson | 1.0000 | 6416467.2 | 0.00 | $\ll 0.001$ |
| NRTL | 0.9950 | 28907.9 | $7.5 \cdot 10^{-168}$ | $\ll 0.001$ |
| van't Hoff | 0.9995 | 281565.6 | $6.9 \cdot 10^{-239}$ | $\ll 0.001$ |
| Wilson | 1.0000 | 3048266.1 | 0.00 | $\ll 0.001$ |
| Yaws | 0.9995 | 283653.0 | $4.1 \cdot 10^{-239}$ | $\ll 0.001$ |
| Buchowski–Ksiazczak | 0.9995 | 272478.9 | $7.3 \cdot 10^{-238}$ | $\ll 0.001$ |
| Yalkowsky–Roseman–van't Hoff | 0.9993 | 216725.5 | $1.0 \cdot 10^{-230}$ | $\ll 0.001$ |

## Conclusions

The TCC solubility in cosolvent mixtures {NMP (1) + W (2)} is strongly controlled by the cosolvent composition. According to the solvation parameter, this increase in the solubility of TCC when increasing the NMP concentration is due to a higher affinity between TCC and NMP. Furthermore, the low solubility of TCC in neat water and water-rich mixtures may be due to a hydrophobic hydration effect around the nonpolar groups of TCC, which could also lead to free water structuring.

According to the statistical analysis, all the mathematical models implemented achieved satisfactory results. However, the Yalkowsky-Roseman-van't Hoff model was the most versatile due to its simplicity and ability to use a limited number of experimental data for its development.

## Conflicts of interest

The authors declare no conflict of interest.

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