

# Thermodynamic Study of Caffeine Solubility in Water in the Temperature Range of 10 TO 60°C

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## ABSTRACT

Caffeine in its anhydrous form is widely used in the pharmaceutical and food industries due to its stimulant action in the central nervous system, that improves reasoning, focus and physical performance. Knowing the behavior of caffeine in pure solvents is extremely important to develop new formulations of drugs, cosmetics, and energy drinks. Thus, this study contemplates the solubility of caffeine in water at temperatures ranging from 10°C to 60°C using intervals of 5°C in the analysis. The experiments were carried out in jacketed equilibrium cells. Known amounts of water and excess caffeine were added to the equilibrium cell, which operated at constant temperature. The analysis of the caffeine dissolved in water was performed in a spectrophotometer at 274 nm. The results showed that the solubility of caffeine in water increased with increasing temperature. Experimental data were fitted according to the Van't Hoff Equation and the Wilson model was used to model the solid-liquid equilibrium.

**Keywords:** Caffeine; Solid-liquid equilibrium; Solubility in Water; Thermodynamic modeling.

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## I. Introduction

Caffeine is an alkaloid the chemical formula  $C_8H_{10}N_4O_2$ . It belongs to the group of chemicals known as methylxanthines, which also includes the products theophylline and theobromine. In its pure form, caffeine occurs as fluffy, white, odorless mass of needles or shiny powders [1].

As well as all methylxanthines, caffeine has low water solubility and therefore is often combined with a wide variety of compounds to form complexes, such as double salt sodium benzoate, for increasing its solubility in consumer goods such as soft drinks [1]. The solubility of drugs in pure solvents and in mixtures of solvents is high interest area in pharmaceutical industries, as it involves the formulation of drugs and their bioavailability [2].

Thus, the objective of this work was to investigate the solubility of caffeine in water at temperatures ranging from 10 to 60°C using intervals of 5°C. In addition, the work aimed to correlate the experimental data using empirical equations and to model the solid-liquid equilibrium through the Wilson equation, also comparing these data with information from literature.

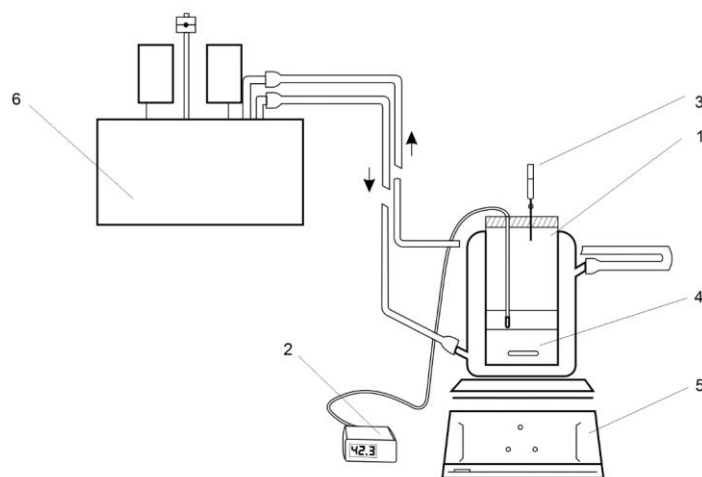
## II. Experimental section

### 2.1. Materials

Anhydrous caffeine was purchased from Sigma (> 99% purity) and was kept in an oven (Medicate MD 1.3) at 80°C to avoid the conversion into the hydrated form. Pure water was obtained by reverse osmosis (Gehaka, model OS20LX).

### 2.2. Experimental equipment

The experimental apparatus (Figure 1) was set up in a way that allowed the data collection on the solubility of caffeine in water. This unit was based on the experimental units proposed in several works [3-6].



**Figure 1** - Experimental apparatus scheme: 1- glass cell; 2-thermometer; 3-microburette 4-stir bar; 5-stirrer; 6-thermostatic bath.

The experimental apparatus consisted of a pyrex glass jacketed cell with an internal volume of 50 mL and equipped with a magnetic stirrer. This cell was connected to a Tecnal thermostated bath (model TE-184) with a temperature set resolution of 0.1°C. The function of this bath was to keep the temperature constant at each temperature case scenario. The outer jacket of the cell provided the thermostatization of the mixture.

### 2.3. Solubility measurements

The solubility of caffeine in water was analyzed in the temperature range from 10 to 60°C. For each experiment assay, a known mass of caffeine was added to a known mass of solvent on a sealed flask. Then, the equilibrium cell was heated to the required temperature with continuous stirring at around 1320 rpm. After 48 h, stirring was stopped, but the solution was kept in the assay temperature for other 48 h. After this time, an excess solid could be observed in the lower part of the equilibrium cell.

1 mL sample of the upper part of the solution was taken with a suitable warmed pipette and diluted in water in an 1 L volumetric flask for each temperature assay. For the spectrophotometric analysis, the standard solutions of caffeine were prepared by dissolving the accurately weighed standard drug into water. These saturated solutions were inserted in a spectrophotometric analyzer (Shimadzu UV - 1280) in which 274 nm wavelengths were used. All the solubility experiments were conducted three times to assure its repeatability.

### 2.4. Thermodynamic correlations for caffeine solubility in water

Two empirical equations obtained from the literature were used to correlate data of caffeine solubility in water as a function of temperature. Equation 1 was proposed by Shalmashi and Golmohammad [1], and the phenomenological Van't Hoff equation (Equation 2) that was previously used by Nagy et al. [7]:

$$\ln C = A + BT \quad (1)$$

$$\ln C = -\frac{\Delta H}{R} \frac{1}{T} + \frac{\Delta S}{R} \quad (2)$$

In Equations 1 and 2,  $C$  is the solubility in mass fraction (g of caffeine/g of H<sub>2</sub>O);  $T$  is the temperature (in Kelvin) of the solid-liquid mixture inside the equilibrium cell;  $A$  and  $B$  are the parameters of Equation 1;  $\Delta H$  is the enthalpy of dissolution, in Jmol<sup>-1</sup>;  $\Delta S$  is the entropy of dissolution, in Jmol<sup>-1</sup>K<sup>-1</sup>; and  $R$  is the universal gas constant, in Jmol<sup>-1</sup>K<sup>-1</sup>.

### 2.5. Thermodynamic models for the activity coefficient

To determine the thermodynamic activity coefficient of the caffeine-water mixture, the Wilson model was used (Equation 3). By using the activity coefficient, the solubility of caffeine was determined using the thermodynamic equations for solid-liquid equilibrium, which models are described in the work by Smith et al.

[8]. Wilson's model can directly predict the values of activity coefficients using experimental data. Its parameters can be adjusted once the solubility and temperature for the solution under analysis are known [9].

$$\ln \gamma_i = -\ln \left( \sum_j^N x_j \Lambda_{ij} \right) + 1 - \sum_k^N \frac{x_k \Lambda_{ki}}{\sum_j^N x_j \Lambda_{kj}} \quad (3)$$

In Equation 3,  $\gamma$  is the activity coefficient of the solute;  $x_1$  is the molar fraction of the solute; and  $\Lambda_{ij}$  are the parameters of the Wilson model.

Wilson's model for binary mixtures is represented in Equation (4) and Equation (5) presents the model parameters.

$$\ln \gamma_1 = -\ln(x_1 + \Lambda_{12}x_2) + x_2 \left( \frac{\Lambda_{12}}{x_1 + x_2\Lambda_{12}} - \frac{\Lambda_{21}}{x_2 + x_1\Lambda_{21}} \right) \quad (4)$$

$$\Lambda_{ij} = \frac{V_j}{V_i} \exp \left( \frac{c_{ij}}{RT} \right) \quad (5)$$

In Equations 4 and 5,  $\gamma_1$  is the solute activity coefficient;  $x_1$  is the molar fraction of the solute;  $x_2$  is the molar fraction of the solvent;  $\Lambda_{ij}$  are the parameters of the Wilson model;  $V_i$  is the molar volume of the solute;  $V_j$  is the molar volume of the solvent; and  $c_{ij}$  are the parameters of the Wilson model.

The solubility curves represent the equilibrium states of caffeine solutions at different temperatures, Equation 6 applies to the equilibrium states to determine the experimental activity coefficient.

$$\ln[x_1\gamma_1] = \frac{\Delta h_{fus,T_f}}{R} \left[ \frac{1}{T} - \frac{1}{T_f} \right] \quad (6)$$

In Equation 6,  $\gamma_1$  is the solute activity coefficient;  $x_1$  is the molar fraction of the solute;  $\Delta h_{fus,T_f}$  is the enthalpy of fusion;  $T$  is the temperature of the experiment; and  $T_f$  is the melting temperature of the solute.

### III. Results and discussion

#### 3.1. Solubility of caffeine in water

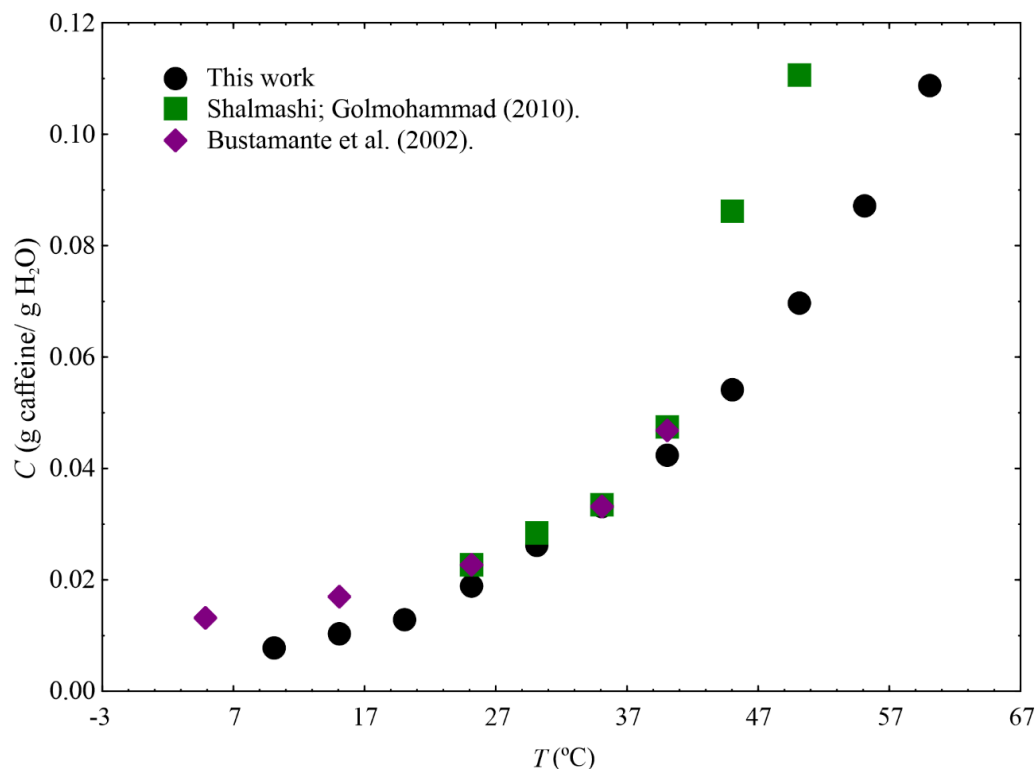
Table 1 presents the solubility data obtained experimentally for the caffeine/water system for each temperature with the standard deviations ( $\sigma$ ) for each estimation. Solubility values are expressed as mass fraction of caffeine per mass of the solution. Temperature is expressed in Celsius.

**Table 1** – Experimental data on the solubility of caffeine in water.

$T$ (°C)	$C$ (g caffeine / g water) $\pm \sigma$
10	0.0077 $\pm$ 0.0002
15	0.0100 $\pm$ 0.0002
20	0.0127 $\pm$ 0.0002
25	0.0187 $\pm$ 0.00005
30	0.0260 $\pm$ 0.0002
35	0.0329 $\pm$ 0.0006
40	0.0423 $\pm$ 0.0001
45	0.0541 $\pm$ 0.0009
50	0.0697 $\pm$ 0.0002
55	0.0870 $\pm$ 0.0001
60	0.1086 $\pm$ 0.0001

All presented experimental solubility mole fractions are the average of the replicates from three glass tubes under the same equilibrium conditions. As observed in Table 1 the solubility values increase with increasing temperature.

The comparison of experimental solubility data for caffeine in this work and the reported data from the literature (Shalmashi and Golmohammad [1] and by Bustamante et al. [2]) is graphically shown in Figure 2. As shown in the Figure 2, most of the solubility values are nearly close to each other. However, the measured values for the solubility of caffeine in water in this work are not in agreement with the literature values reported by Shalmashi and Golmohammad [1] at temperatures higher than 45°C. These deviations may be due to differences in purity source of compound, determination method, and the crystal forms of the solutes.



**Figure 2** – Data of solubility of caffeine in water as a function of temperature obtained in this work compared with data from the works of Shalmashi and Golmohammad [1] and Bustamante et al. [2].

### 3.2. Empirical equations for solubility prediction

Equations 1 and 2 were used to correlate the experimental data on the solubility of caffeine in water. In this work, eleven (11) experimental points were obtained, making it possible to calculate the parameters of each Equation. To obtain the parameters, non-linear regression was performed on Statistica® 7.0 software. Table 2 shows the values of these adjusted parameters.

**Table 2** – Estimated parameters for Equations 1 and 2 for the solubility of caffeine in water.

Parameters of the Equation (1)		Parameters of the Equation (2)	
A	B (K <sup>-1</sup> )	ΔH (Jmol <sup>-1</sup> )	ΔS (Jmol <sup>-1</sup> K <sup>-1</sup> )
-18.5844	0.0492	41204.03	105.26
$r^2 = 0.9986$		$r^2 = 0.9998$	

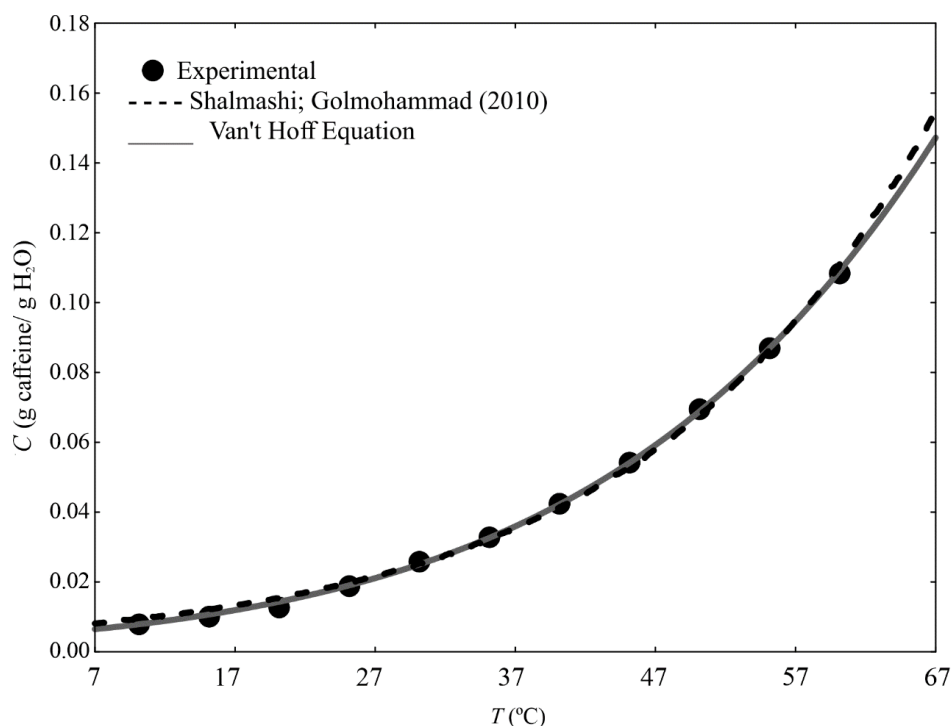
The solubility of caffeine in water was obtained inserting in Equations 1 and 2 the temperatures of each experiment assay and the parameters presented in Table 2. Table 3 compares the results obtained with Equations 1 and 2 with the results of the experimental data from this work by the relative deviations that were calculated according to Equations 7:

$$RD = \frac{|C_{exp} - C_{Eq}|}{C_{exp}} 100\% \quad (7)$$

In Equation 7, *RD* the relative deviation (%); *C<sub>exp</sub>* is the solubility obtained experimentally and *C<sub>Eq</sub>* is the solubility obtained using obtained using Equations 1 and 2. The solubilities obtained by the equation adjustments are very close to the solubilities obtained experimentally. This shows that, using Equations 1 and 2, and the parameters presented in Table 3, it is possible to predict the solubility of caffeine in water in the temperature range of 10 to 60°C. Figure 3 shows the fit adherence of each model to the experimental data.

**Table 3** – Results of the adjustments by Equations 1 and 2 and relative deviations comparing to the experimental data of caffeine solubility in water.

This work		Equation 1		Equation 2	
<i>T</i> (°C)	<i>C</i> (g caf/ g H <sub>2</sub> O)	<i>C<sub>Eq1</sub></i>	<i>RD<sub>1</sub></i>	<i>C<sub>Eq,2</sub></i>	<i>RD<sub>2</sub></i>
10	0.0077	0.0095	-22.1690	0.0079	-1.8914
15	0.0100	0.0121	-20.5260	0.0107	-6.5054
20	0.0127	0.0155	-21.8150	0.0143	-12.8830
25	0.0187	0.0198	-6.0415	0.0190	-2.0361
30	0.0260	0.0253	2.7959	0.0250	3.7837
35	0.0329	0.0323	1.7052	0.0326	0.7994
40	0.0423	0.0414	2.2388	0.0422	0.2553
45	0.0541	0.0529	2.3292	0.0541	0.0609
50	0.0697	0.0676	2.9857	0.0689	1.2138
55	0.0870	0.0865	0.6138	0.0870	0.0241
60	0.1086	0.1106	-1.8486	0.1092	-0.5140



**Figure 3** – Adjustment of experimental data for the solubility of caffeine in water by Shalmashi and Golmohammad (2010) and by the Van't Hoff Equation.

Figure 3 shows high adherence of Shalmashi and Golmohammad [1] and the Van't Hoff Equation models to the experimental data for the solubility of caffeine in water. Considering a significance level of 95% for this system, it was possible to verify that the parameters of Equations 1 and 2 were all significant in a p-test. The correlation coefficient ( $r^2$ ) was close to 1 for both models. When analyzing the relative deviations of Table 3, it is observed that the Van't Hoff equation (Equation 2), presented the less significative relative deviations. Therefore, we suggest that all solubility calculations in crystallization assays for the solubility of caffeine in water must be performed with this equation.

The Van't Hoff equation also allows correlation between the concentration of caffeine ( $\ln C$ ) as a function of  $1/T$  (Figure 4). The curve and the intercept of the linear graph result in  $\Delta H = 41204 \text{ Jmol}^{-1}$  and  $\Delta S = 105.26 \text{ Jmol}^{-1}\text{K}^{-1}$ , which represent the model parameters: enthalpy and entropy of dissolution, respectively.

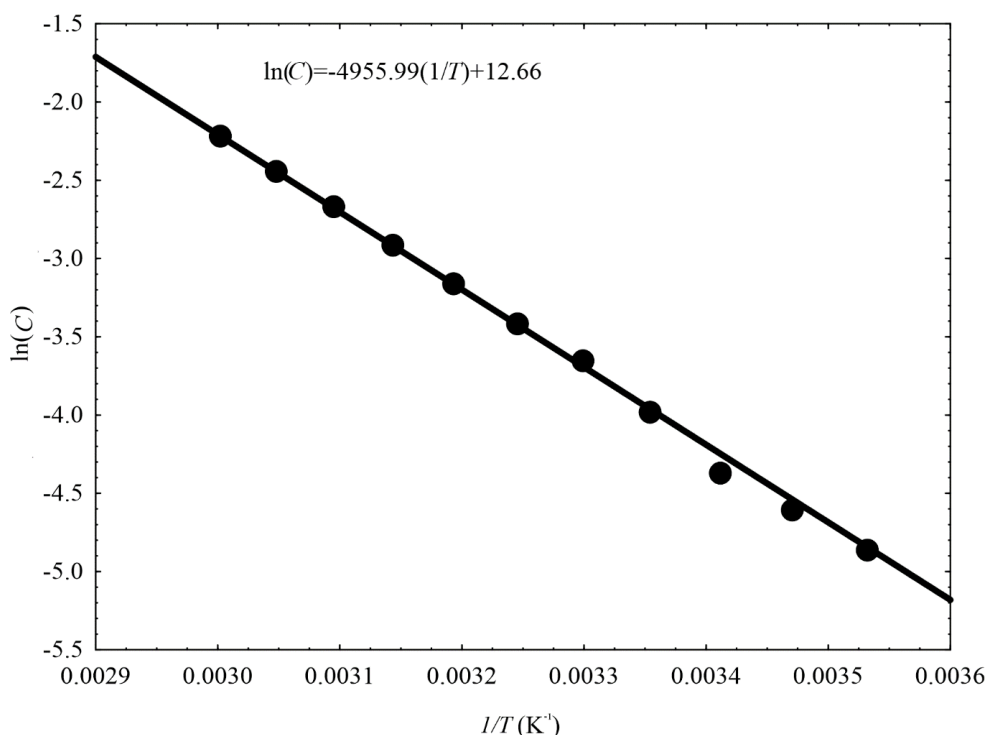


Figure 4 – Van't Hoff solubility curve for caffeine in water.

### 3.3. Thermodynamic modeling for predicting solid-liquid equilibrium data

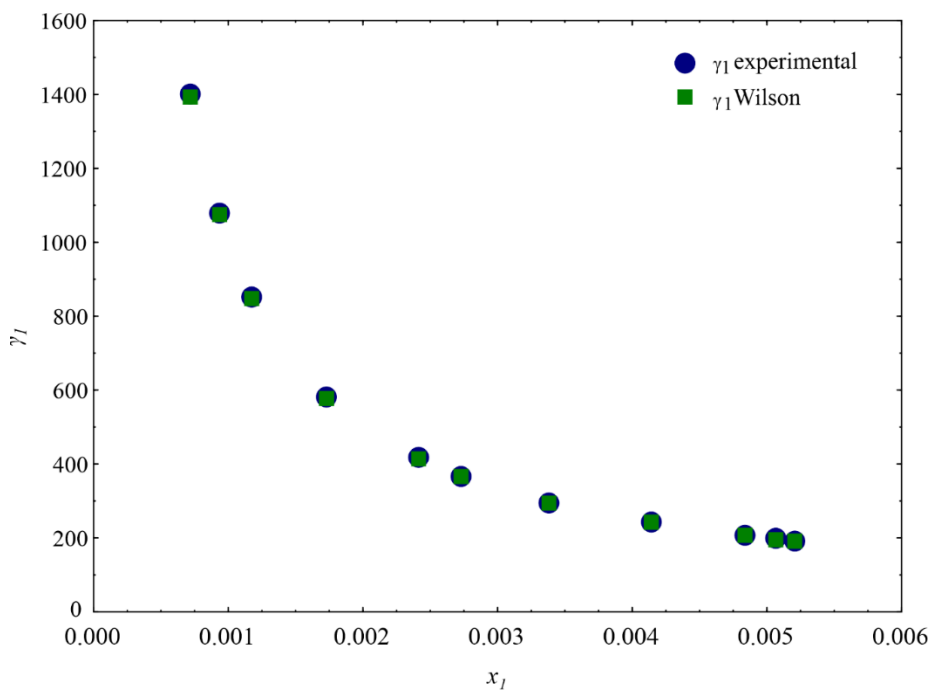
Wilson's thermodynamic model was used to determine the activity coefficient of the caffeine (1) and water (2) binary system. Calculations were performed in Microsoft Excel® software using the Solver tool.

Table 4 shows the molar volumes of the studied species caffeine and water. Such data is necessary to calculate the parameters of the Wilson model [8].

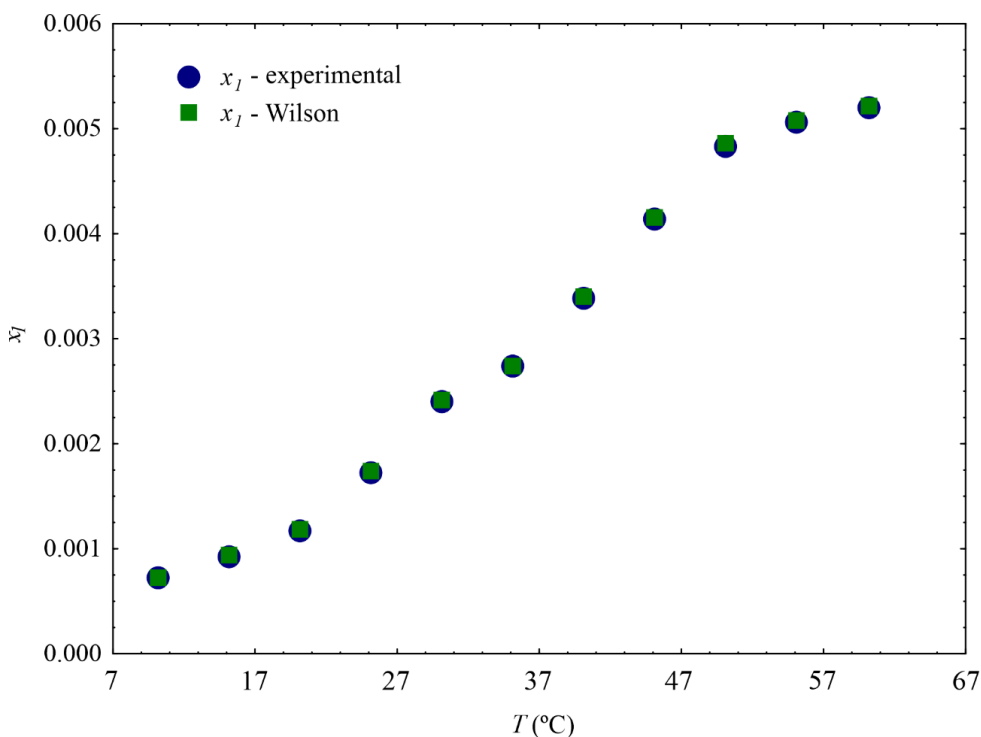
Table 4 – Molar volume of the compounds studied.

Substance	Molar volume ( $\text{cm}^3 \text{mol}^{-1}$ )	Temperature (K)	Reference
Caffeine	134.200	298.3	Cesaro and Starec [10]
Water	18.069	298.2	Harr <i>et al.</i> [11]

With the experimentally obtained data on the solubility of caffeine in water, the Wilson's Equation binary parameters of interaction were determined. In Figure 5, the Wilson's model adjustment for the activity coefficient is compared with the experimental activity coefficient obtained with Equation 4. Figure 6 illustrates the comparison between the experimental data and those predicted by the model as a function of water temperature.



**Figure 5** –Comparison of activity coefficients obtained experimentally and by using the Wilson model for the solubility of caffeine in water.



**Figure 6** – Comparison between the experimental solubility of caffeine in water and that predicted by the Wilson model.

Table 5 presents the parameters found for the Wilson model and the correlation coefficient. Table 6 presents the values used to determine the parameters and solubility values predicted by the Wilson model for caffeine in water.

**Table 5** – Wilson’s model obtained parameters.

	Parameters	Model	r <sup>2</sup>
c <sub>12</sub>	85658.32	Wilson	0.9999
c <sub>21</sub>	629145.60		

**Table 6** – Values for determining the binary parameters, solubility values predicted by the Wilson model, residuals, and mean deviation for water.

T (K)	x <sub>1</sub> (exp)	(1-x <sub>1</sub> )	γ <sub>1</sub> (exp)	γ <sub>1</sub> (Wilson)	x <sub>1</sub> (Wilson)	Residuals □10 <sup>6</sup>	Mean deviation
10	0.0007	0.9993	1399.71	1393.20	0.0007	-3.35	
15	0.0009	0.9991	1079.96	1075.14	0.0009	-4.17	
20	0.0012	0.9988	853.66	850.00	0.0012	-5.07	
25	0.0017	0.9983	581.36	578.96	0.0017	-7.15	
30	0.0024	0.9976	416.96	415.31	0.0024	-9.56	
35	0.0027	0.9973	367.16	365.76	0.0027	-0.10	4.22
40	0.0034	0.9966	296.50	295.42	0.0034	-0.12	
45	0.0041	0.9959	242.24	241.39	0.0042	-0.15	
50	0.0048	0.9952	207.31	206.62	0.0047	-0.16	
55	0.0051	0.9949	198.08	197.45	0.0051	-0.16	
60	0.0052	0.9948	192.65	192.05	0.0052	-0.16	

Wilson's model adjusted well to the experimental data and managed to provide accurate values of the activity coefficient for calculating the solubility of caffeine in water in the solid-liquid equilibrium equation (Equation 4) for the temperature range of this work, presenting low standard deviations and a high correlation coefficient.

#### IV. Conclusion

The solubility of caffeine in water was analyzed in temperatures ranging from 10 to 60°C. The obtained results are in accordance with data reported in the literature, assuring the efficiency of the experimental unit. Temperature had a positive effect on the solubility of caffeine in water.

The two empirical equations employed in this work presented high adherence with the experimental data, but the Van't Hoff equation stood out, as it presented the smallest relative deviations and the highest correlation coefficient. In this way, Van't Hoff equation is proposed for solubility calculations for tests crystallization and other applications.

Wilson's model was used to the obtain activity coefficient data for the components for the caffeine-water mixture. This model was effective in predicting the solubility of caffeine in water, also being effective to predict the values of solid-liquid equilibrium with small deviations.

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