

## Solution thermodynamics and preferential solvation of 3-chloro-N-phenyl-phthalimide in acetone + methanol mixtures

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### SUMMARY

The thermodynamic properties of the 3-chloro-N-phenyl-phthalimide in acetone + methanol cosolvent mixtures were obtained from solubility data report in literature. The solubility was higher in near acetone and lower in pure methanol at all temperatures studied. A non-linear plot of  $\Delta_{\text{soln}}H^\circ$  vs.  $\Delta_{\text{soln}}G^\circ$  shows a negative slope from pure acetone up to  $x_1 = 0.691$ . Beyond this composition, a variable positive slope is obtained with the exception of mixtures with  $x_1 = 0.121$ ,  $x_1 = 0.272$  and  $x_1 = 0.356$  which is a not common trend in these systems. The preferential solvation of 3-chloro-N-phenyl-phthalimide by the components of the solvents was estimated by means of the inverse Kirkwood–Buff integral method, showing the 3-chloro-N-phenyl-phthalimide is preferential solvated by methanol in more polar mixtures and by acetone in less polar ones.

**Keywords:** 3-Chloro-N-phenylphthalimide, solubility, solution thermodynamics, activity coefficients, preferential solvation.

## RESUMEN

## Termodinámica de soluciones y solvatación preferencial de 3-cloro-N-fenil-ftalimida en mezclas acetona + metanol

Las propiedades termodinámicas de 3-cloro-N-fenil-ftalimida en mezclas cosolventes acetona + metanol fueron obtenidas a partir de los datos de solubilidad reportados en la literatura. La mayor solubilidad se presentó en acetona y la menor en metanol puro en todas las temperaturas estudiadas. La grafica  $\Delta_{\text{soln}}H^\circ$  vs.  $\Delta_{\text{soln}}G^\circ$  presenta una tendencia no lineal, con una pendiente negativa desde la acetona pura hasta  $x_1 = 0,691$  a partir de esta composición hasta el metanol puro se obtiene una pendiente positiva variable con la excepción de las mezclas con  $x_1 = 0,121$ ,  $x_1 = 0,272$  y  $x_1 = 0,356$ , la cual es una tendencia poco común en estos sistemas. La solvatación preferencial de 3-cloro-N-fenil-ftalimida por cada uno de los solventes de la mezcla se estimó por medio del método de las integrales inversas de Kirkwood-Buff mostrando que la 3-cloro-N-fenil-ftalimida se solvata preferencialmente por metanol en las mezclas más polares y por acetona en las menos polares.

*Palabras clave:* 3-cloro-N-fenil-ftalimida, solubilidad, termodinámica de soluciones, coeficiente de actividad, solvatación preferencial.

## INTRODUCTION

3-chloro-N-phenyl-phthalimide (Fig. 1) (Synonyms: 4-chloro-2-phenyl-isoindolin-1,3-dione; 4-Chloro-2 phenyl-isoindolin-1,3-dion; 3-Chloro-N-phenyl-phthalimid; 4-chloro-2-phenyl-isoindole-1,3-dione; 3-chloro-N-phenyl-phthalimide) is an interesting compound because of its use in the synthesis of 3,3'-bis(N-phenylphthalimide) and 2,2',3,3'-diphenylthioether dianhydride, which are monomers for the preparation of polyimide, and those synthetic routes require a high purity 3-chloro-N-phenyl-phthalimide [1].

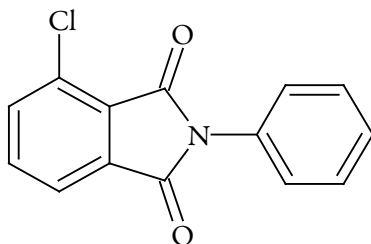


Figure 1. Molecular structure of 3-chloro-N-phenyl-phthalimide.

Knowledge of thermodynamic properties and preferential solvation is important in order to optimize synthesis processes like aforementioned [2]. For this reason, the purpose of this study is to evaluate the effect of the co-solvent composition on solubility, solution thermodynamics and preferential solvation of 3-chloro-N-phenyl-phthalimide in binary mixtures of acetone and methanol. The temperature dependence of the solubility allows a thermodynamic analysis that permits insight into the molecular mechanisms involved in the solution processes. The other hand, the estimate of the preferential solvation of the solute by the components of the solvent mixture, it is performed by the application of the inverse Kirkwood-Buff integral (IKBI) method [3-5].

## THEORETICAL

### Ideal solubility

The ideal solubility as a function of temperature can be calculated by using the following equation:

$$\ln x_3^{\text{id}} = -\frac{\Delta_{\text{fus}}H(T_{\text{fus}} - T)}{RT_{\text{fus}}T} + \left(\frac{\Delta C_p}{R}\right) \left[ \frac{(T_{\text{fus}} - T)}{T} + \ln\left(\frac{T}{T_{\text{fus}}}\right) \right] \quad (1),$$

here  $x_3^{\text{id}}$  is the ideal solubility of the solute as mole fraction,  $\Delta_{\text{fus}}H$  is the molar enthalpy of fusion of the pure solute (at the melting point),  $T_{\text{fus}}$  is the absolute melting point,  $T$  is the absolute solution temperature,  $R$  is the gas constant ( $8.314 \text{ J mol}^{-1} \text{ K}^{-1}$ ), and  $\Delta C_p$  is the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical super-cooled liquid form, both at the solution temperature [6]. Since  $\Delta C_p$  cannot be easily experimentally determined it is usual assuming that it may be approximated to the entropy of fusion,  $\Delta_{\text{fus}}S$  [7].

### Activity coefficients

The activity coefficients  $\gamma_3$ , were calculated as  $x_3^{\text{id}}/x_3$  where  $x_3$  is the experimental solubility. From  $\gamma_3$  values a rough estimate of solute-solvent intermolecular interactions can be made by considering the following expression [8]:

$$\ln \gamma_3 = (e_{11} + e_{33} - 2e_{13}) \frac{V_3 \phi_1^2}{RT} \quad (3),$$

where  $e_{11}$ ,  $e_{33}$  and  $e_{13}$  represent the solvent-solvent, solute-solute and solvent-solute interaction energies, respectively, the first two terms are unfavorable for solubility and the third term favors the solution process;  $V_3$  is the molar volume of the super-cooled liquid solute and  $\phi_1$  is the volume fraction of the solvent. As reported in the literature,

for relatively low solubilities  $x_3$ , the term  $V_3\phi_1^2/RT$  may be considered constant; thus,  $\gamma_3$  depends mainly on  $e_{11}$ ,  $e_{33}$  and  $e_{13}$  [9]. The contribution of the  $e_{33}$  term could be considered as constant in all mixtures [10].

### Thermodynamic functions of solution

Apparent standard enthalpy change of solution is obtained from the Eq. (4) by using the mean harmonic temperature ( $T_{hm}$ ) [calculated as:  $T_{hm} = n / \sum_{i=1}^n (1/T)$ ], where  $n$  is the number of temperatures studied [4].

$$\left( \frac{\partial \ln x_3}{\partial (1/T - 1/T_{hm})} \right)_p = - \frac{\Delta_{\text{soln}} H^\circ}{R} \quad (4)$$

The apparent standard Gibbs energy change for the solution process ( $\Delta_{\text{soln}} G^\circ$ ), considering the approach proposed by Krug *et al.* [11], is calculated at  $T_{hm}$  by means of:

$$\Delta_{\text{soln}} G^\circ = -R \times T_{hm} \times \text{intercept} \quad (5)$$

where the intercept is obtained from the treatment of  $\ln x_3$  as a function of  $1/T - 1/T_{hm}$ . Finally, the standard apparent entropy change for solution process ( $\Delta_{\text{soln}} S^\circ$ ) is obtained from the respective  $\Delta_{\text{soln}} H^\circ$  and  $\Delta_{\text{soln}} G^\circ$  values at  $T_{hm}$  by using:

$$\Delta_{\text{soln}} S^\circ = \frac{(\Delta_{\text{soln}} H^\circ - \Delta_{\text{soln}} G^\circ)}{T_{hm}} \quad (6)$$

the relative contributions by enthalpy ( $\zeta_H$ ) and entropy ( $\zeta_{TS}$ ) toward the solution process are given by equations 7 and 8 [12-13].

$$\zeta_H = \frac{|\Delta_{\text{soln}} H^\circ|}{|\Delta_{\text{soln}} H^\circ| + |T \Delta_{\text{soln}} S^\circ|} \quad (7)$$

$$\zeta_{TS} = \frac{|T \Delta_{\text{soln}} S^\circ|}{|\Delta_{\text{soln}} H^\circ| + |T \Delta_{\text{soln}} S^\circ|} \quad (8)$$

## Preferential solvation

*The KBIs are given by the following expressions:*

$$G_{1,3} = \int_0^{r_{cor}} (g_{1,3} - 1) 4\pi r^2 dr \quad (9),$$

here  $g_{1,3}$  is the pair correlation function for molecules of solvent 1 in the 1 + 2 mixtures around the solute 3,  $r$  is the distance between the centers of molecules 3 and 1, and  $r_{cor}$  is a correlation distance for which  $g_{1,3}(r > r_{cor}) \approx 1$ . Thus, for all distances  $r > r_{cor}$  up to infinite, the value of the integral is essentially zero. So, the results are expressed in terms of the preferential solvation parameter,  $\delta x_{1,3}$ , for the solute 3 by the component solvents 1 and 2 [5, 14].

$$\delta x_{1,3} = x_{1,3}^L - x_1 = -\delta x_{2,3} \quad (10)$$

Where  $x_1$  is the mole fraction of 1 in the bulk solvent mixture and  $x_{1,3}^L$  is the difference between the local mole fraction of 1 in the near environment of the solute. If  $\delta x_{1,3} > 0$  then 3 is preferentially solvated by 1, else by 2, within the correlation volume  $V_{cor} = (4\pi/3)r_{cor}^3$ , and the bulk mole fraction of 1,  $x_1$ . Values of  $\delta x_{1,3}$  are obtainable from those of  $G_{1,3}$ , and these, in turn from thermodynamic data for the solvent mixture with the solute in it as shown below [6, 15].

Algebraic manipulation of expressions presented by Newman [16] leads to expressions for the Kirkwood-Buff integrals (in  $\text{cm}^3 \text{mol}^{-1}$ ) for the individual solvent components 1 and 2 in terms of thermodynamic quantities [3, 6-7]:

$$G_{1,3} = RT\kappa_T - V_3 + \frac{x_2 V_2 D}{Q} \quad (11)$$

$$G_{2,3} = RT\kappa_T - V_3 + \frac{x_1 V_1 D}{Q} \quad (12)$$

Where  $\kappa_T$  is the isothermal compressibility of the solvent mixtures 1+2 (in  $\text{GPa}^{-1}$ ),  $V_1$  and  $V_2$  are the partial molar solvent volumes in the mixture, and  $V_3$  is the standard partial molar volume of solute in this mixture (in  $\text{cm}^3 \text{mol}^{-1}$ ). The function  $D$  is the derivative of the standard molar transfer Gibbs energies of 3 with respect to the solvent composition and the function  $Q$  involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents,  $G_{1,2}^E$ , with respect to the solvent composition (in  $\text{kJ mol}^{-1}$ , as is  $RT$ ) [17]:

$$D = \frac{\partial \Delta_r G_{(3,2 \rightarrow 1+2)}^o}{\partial x_2} \quad (13)$$

$$Q = RT + x_1 x_2 \left[ \frac{\partial^2 G_{1+2}^E}{\partial x_2^2} \right]_{T,p} \quad (14)$$

Because of the dependence of  $\kappa_T$  on composition this term is not known for all the systems investigated. Moreover, due to the small contribution of  $RT \kappa_T$  to the IKBI, the dependence of  $\kappa_T$  on composition will be approximated by [18-19]:

$$\kappa_T = x_1 \kappa_{T,1}^o + x_2 \kappa_{T,2}^o \quad (15),$$

where  $x_i$  is the volume fraction of component  $i$  in solution and  $\kappa_{T,i}^o$  is the isothermal compressibility of the pure component  $i$ .

Ben-Naim [20] showed that the preferential solvation parameter can be calculated from the Kirkwood-Buff integrals as follows:

$$\delta x_{1,3} = \frac{x_1 x_2 (G_{1,3} - G_{2,3})}{x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}} \quad (16)$$

The correlation volume,  $V_{cor}$ , is obtained by means of the following expression proposed by Marcus [21]:

$$V_{cor} = 2522.5 \left[ r_3 + 0.1363 (x_{2,3}^L V_2 + x_{1,3}^L V_1)^{1/3} - 0.085 \right]^3 \quad (17)$$

Where  $r_3$  is the radius of the solute (in nm), calculated as

$$r_3 = \sqrt[3]{\frac{3 \times 10^{21} V_3}{4\pi N_A}} \quad (18)$$

However, the correlation volume requires iteration, because it depends on the local mole fractions [14].

## RESULTS AND DISCUSSION

The solubility of 3-chloro-N-phenyl-phthalimide (3) in acetone (1) + methanol (2) mixtures (Fig. 2) was taken from the literature [1].

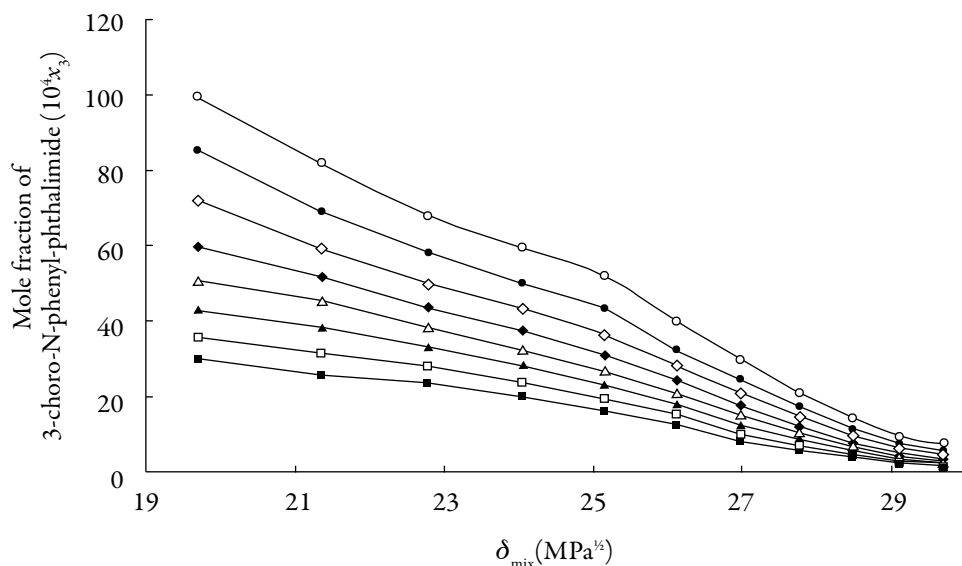


Figure 2. Experimental molar solubility of 3-chloro-N-phenyl-phthalimide in acetone + methanol mixtures at different temperatures; (■ = 288.15 K; □ = 293.15 K; ▲ = 298.15 K; △ = 303.15 K; ◆ = 308.15 K; ◇ = 313.15 K; ● = 318.15 K; and ○ = 323.15 K). Data taken from Xie *et al.* [1].

The solubility increases with temperature in all cases indicating that the dissolution process is endothermic. The highest solubility of 3-chloro-N-phenyl-phthalimide expressed as a mole fraction were obtained in near acetone at  $T = 323.15$  K, whereas the lowest values were found in pure methanol (2) at 288.15 K (Fig. 2).

Table 1 shows the ideal solubilities expressed as a mole fraction of the solutes ( $x_3^{id}$ ) calculated by using Eq. (1) with the temperature and heat of fusion of 3-chloro-N-phenyl-phthalimide taken from literature, i.e.  $T_{fus} = 466.05$  K and  $\Delta_{fus}H = 29.14$  kJ mol<sup>-1</sup> [22].

On the other hand, Fig. 2 shows the solubility profiles as a function of the polarity of the mixtures, expressed by their solubility parameters ( $\delta_{mix}$ ). For a binary mixture  $\delta_{mix}$

is calculated from the solubility parameters of the pure solvents ( $\delta_1 = 19.6 \text{ MPa}^{1/2}$  and  $\delta_2 = 29.78 \text{ MPa}^{1/2}$  [23]).

The solubility parameter of solute, estimated according to the groups contribution method proposed by Fedors [24], is  $\delta_3 = 27.08 \text{ MPa}^{1/2}$  (Table 2), which is higher than the experimental value obtained ( $\delta_3 \leq 27.08 \text{ MPa}^{1/2}$ ). This indicates that the actual polarity of solute is lower than the expected from the additive contribution of its groups, which is lower than the experimental value [25].

Table 1. 3-chloro-N-phenyl-phthalimide activity coefficients as natural logarithms ( $\ln \gamma_3$ ) in ethanol (1) + water (2) cosolvent mixtures at several temperatures.

$\delta_{\text{mix}}$	Temperatures (K)							
	288.15	293.15	298.15	303.15	308.15	313.15	318.15	323.15
29.70	0.601	0.458	0.333	0.247	0.156	0.051	-0.040	-0.157
29.12	0.143	0.024	-0.066	-0.121	-0.174	-0.249	-0.329	-0.388
28.49	-0.396	-0.466	-0.520	-0.543	-0.579	-0.642	-0.719	-0.802
27.77	-0.731	-0.847	-0.926	-0.982	-1.017	-1.067	-1.117	-1.183
26.98	-1.116	-1.188	-1.272	-1.342	-1.383	-1.430	-1.472	-1.541
26.12	-1.555	-1.609	-1.644	-1.673	-1.700	-1.724	-1.747	-1.832
25.15	-1.800	-1.847	-1.900	-1.910	-1.943	-1.979	-2.035	-2.100
24.05	-2.002	-2.048	-2.089	-2.103	-2.130	-2.156	-2.179	-2.234
22.79	-2.172	-2.221	-2.256	-2.274	-2.279	-2.293	-2.329	-2.365
21.36	-2.257	-2.334	-2.396	-2.437	-2.452	-2.465	-2.500	-2.555
19.70	-2.405	-2.460	-2.513	-2.550	-2.595	-2.659	-2.709	-2.749
Ideal solubility	2.69 $\times 10^{-4}$	3.06 $\times 10^{-4}$	3.48 $\times 10^{-4}$	3.94 $\times 10^{-4}$	4.45 $\times 10^{-4}$	5.03 $\times 10^{-4}$	5.66 $\times 10^{-4}$	6.37 $\times 10^{-4}$



The activity coefficients of 3-chloro-N-phenyl-phthalimide expressed as natural logarithms are also shown in Table 1. These values were calculated from experimental solubility was taken from Xie *et al.* (2016) [1]) and ideal solubility data (table 1). In the vast majority of cases,  $\gamma_3$  values were lower than unit (negative logarithmic values) due to the experimental solubilities are greater than the ideal ones in those cosolvent systems (acetone-rich mixtures).

As a qualitative approach, the following analysis could be made based on the energetic quantities and magnitudes described in the Eq. (2): The term  $e_{11}$  is highest in neat methanol and methanol-rich mixtures having larger  $\gamma_3$  values (0.855-1.825) which implies higher  $e_{11}$  and lower  $e_{13}$  values. On the other hand, in intermediate composition mixtures and acetone-rich mixtures (having  $\gamma_3$  values  $<1$ ), the  $e_{11}$  values are relatively low but the  $e_{13}$  values could not to be so high. Accordingly, the solvation of 3-chloro-N-phenyl-phthalimide could be just a little higher in acetone-rich mixtures.

Table 2. Application of the Fedors' method to estimate internal energy, molar volume, and Hildebrand solubility parameter of 3-chloro-N-phenyl-phthalimide (3).

Group	Group number	$V$ (cm <sup>3</sup> mol <sup>-1</sup> )	$U$ (kJ mol <sup>-1</sup> )
> N -	1	1 × -9.0	1 × 4.2
> C = O	2	2 × 10.8	2 × 17.4
- Cl	1	1 × 24.0	1 × 11.55
Phenyl	1	1 × 71.4	1 × 31.9
Phenyl (trisubstitute)	1	1 × 33.4	1 × 31.9
Ring closure	1	1 × 16.00	1 × 1.05
	Total	157.4	115.4
	Solubility parameter	$(115400/157.4)^{1/2}$	27.08 MPa <sup>1/2</sup>

### Thermodynamic functions of solution

From the solubility data, the thermodynamic functions in solution are calculated (Table 3). Over the range of temperatures studied (288.15 to 323.15 K) the heat capacity change of solution may be assumed to be constant, hence  $\Delta_{\text{soln}}H^\circ$  should be valid for the mean harmonic temperature,  $T_{hm} = 305.27$  K.

Table 3. Apparent thermodynamic functions relative to solution process of 3-chloro-N-phenyl-phthalimide in acetone + methanol cosolvent mixtures at 305.27 K.

$x_1^a$	$\Delta_{\text{soln}}G^\circ$ (kJ mol <sup>-1</sup> )	$\Delta_{\text{soln}}H^\circ$ (kJ mol <sup>-1</sup> )	$\Delta_{\text{soln}}S^\circ$ (J mol <sup>-1</sup> K <sup>-1</sup> )	$T\Delta_{\text{soln}}S^\circ$ (kJ mol <sup>-1</sup> )	$\zeta_H$	$\zeta_{TS}$
0.000	20.3	34.9	48.0	14.6	0.704	0.296
0.058	19.4	30.1	35.1	10.7	0.738	0.262
0.121	18.3	27.1	29.0	8.8	0.754	0.246
0.193	17.2	28.0	35.2	10.7	0.723	0.277
0.272	16.3	28.0	38.2	11.6	0.706	0.294
0.358	15.5	24.2	28.5	8.7	0.735	0.265
0.455	14.8	25.0	33.4	10.2	0.711	0.289
0.565	14.4	23.4	29.7	9.1	0.721	0.279
0.691	14.0	22.6	28.4	8.7	0.723	0.277
0.834	13.6	24.6	36.1	11.0	0.691	0.309
1.000	13.2	26.7	44.2	13.5	0.664	0.336

<sup>a</sup>  $x_1$  is the molar fraction of acetone in the cosolvent mixture free of solute.

The standard Gibbs free energy of solution is positive in all cases as is the enthalpy of solution; therefore the process is always endothermic. Figure 3 shows the change of enthalpy versus the mole fraction of acetone. The decreasing enthalpy between pure methanol up to the mixture with  $x_1 = 0.121$  indicates that solubility is favored for enthalpy in these mixtures. Besides, from the mixture with  $x_1 = 0.121$  up to the mixture with  $x_1 = 0.565$  the enthalpy of solution tends to increase and then decrease, for this reason it is not possible to identify the thermodynamics properties driving the solution process. Finally, between the mixture  $x_1 = 0.691$  and the pure acetone, the enthalpy increases.

The main contributor to the (positive) standard molar Gibbs energy of solution of 3-chloro-N-phenyl-phthalimide, in all cases, is the (positive) enthalpy ( $\zeta_H > 0.754$ ). The experimental data of thermodynamic functions of solution are collected in Fig. 4. The regions where ( $\Delta_{\text{tr}}H^\circ > T\Delta_{\text{tr}}S^\circ > 0$ )  $\equiv$  sector I; corresponds to enthalpy determined processes [4, 26-27], which is proposed by the equations 7 and 8.

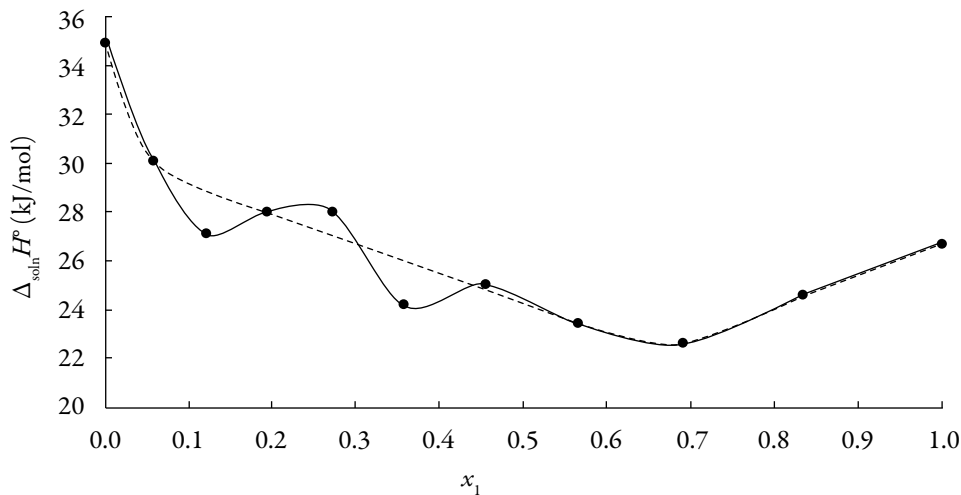


Figure 3. Enthalpy of solution of 3-chloro-N-phenyl-phthalimide in acetone (1) + methanol (2) mixtures at 305.27 K. The dotted lines not consider the mixture with 0.193, 0.272 and 0.455 mole fractions.

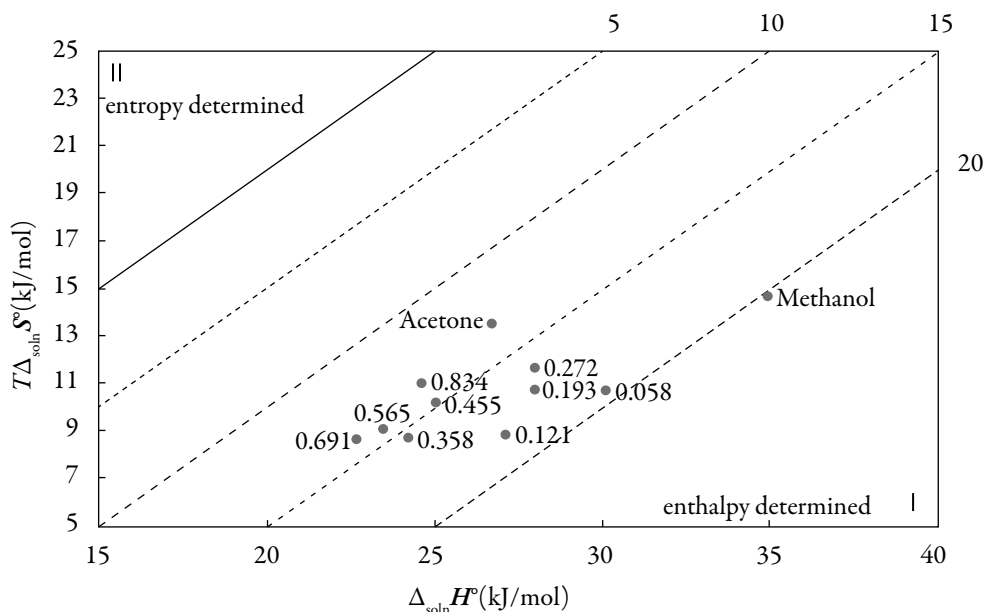


Figure 4. Relationship between the enthalpic and entropic terms of solution of 3-chloro-N-phenyl-phthalimide in acetone (1) + methanol (2) mixtures at 305.27 K. The isoenergetic curves of  $\Delta_{\text{soln}}G^\circ$  function are marked by dotted lines.

### Thermodynamic functions of transfer

In order to verify the effect of co-solvent composition on the thermodynamic function driving the solution process, Fig. 5 collects the thermodynamic functions of transfer of 3-chloro-N-phenyl-phthalimide (3) from the more polar solvents to the less polar ones. These new functions were calculated as the differences between the thermodynamic quantities of solution obtained in the less polar mixtures and the more polar ones, by means of:

$$\Delta_{tr}F^\circ = \Delta_{soln}F^\circ_{\text{less polar}} - \Delta_{soln}F^\circ_{\text{more polar}} \quad (19)$$

Where  $\Delta_{soln}F^\circ$  represents the thermodynamic functions ( $\Delta_{soln}G^\circ$ ,  $\Delta_{soln}H^\circ$  or  $\Delta_{soln}S^\circ$ ). This procedure is the same followed previously in other studies reported by Holguín *et al.* and Delgado *et al.* [28-29].

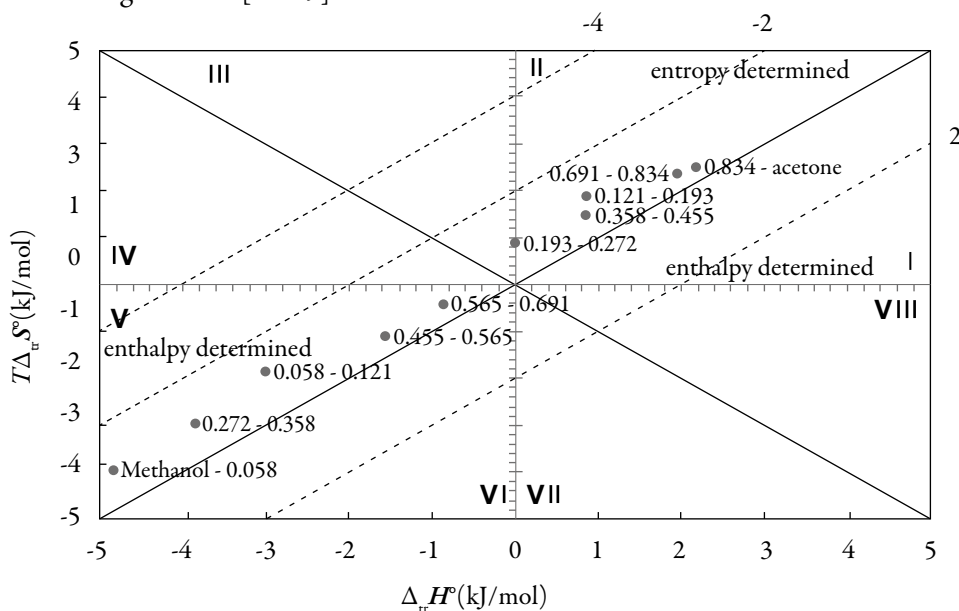


Figure 5. Relationship between the enthalpy and entropic terms of transfer functions of 3-chloro-N-phenyl-phthalimide from more polar solvents to less polar solvents at 305.27 K. The isoenergetic curves of  $\Delta_{tr}G^\circ$  function are marked by dotted lines.

Theregions where  $(\Delta_{tr}H^\circ > T\Delta_{tr}S^\circ > 0) \equiv$  sector I;  $(\Delta_{tr}H^\circ < 0; T\Delta_{tr}S^\circ > 0; |\Delta_{tr}H^\circ| > |T\Delta_{tr}S^\circ|) \equiv$  sector IV and  $(\Delta_{tr}H^\circ < 0; T\Delta_{tr}S^\circ < 0; |\Delta_{tr}H^\circ| > |T\Delta_{tr}S^\circ|) \equiv$  sector V corresponds to enthalpy determined processes. The regions of the diagram where  $(T\Delta_{tr}S^\circ > \Delta_{tr}H^\circ > 0) \equiv$  sector II correspond to entropy determined processes [4, 26-27]. A schematic depiction of these relationships is given in figure 5.

So, the process of transfer in acetone-rich mixtures may indicate that the 3-chloro-N-phenyl-phthalimide molecule interacts more strongly with the acetone, however in all cases, the behavior is very random.

### Enthalpy-entropy compensation of 3-chloro-N-phenyl-phthalimide

There are several reports in the literature that have demonstrated enthalpy-entropy compensation effects for the solubility of drugs in aqueous co-solvent mixtures. This analysis has been used in order to identify the mechanism of the co-solvent action. Weighted graphs of  $\Delta_{\text{soln}}H^\circ$  as a function of  $\Delta_{\text{soln}}G^\circ$  at the mean temperature allow such an analysis [30-31].

Figure 6 shows that 3-chloro-N-phenyl-phthalimide (3) in the acetone (1) + methanol (2) solvent system presents a non-linear behavior of  $\Delta_{\text{soln}}H^\circ$  vs.  $\Delta_{\text{soln}}G^\circ$  with a variable negative slope from pure acetone up to  $x_1 = 0.691$ . Beyond this composition a variable positive slope is obtained with exception of mixtures with  $x_1 = 0.12$ ,  $x_1 = 0.272$  and  $x_1 = 0.36$ , showing a non-common trend in these systems. Accordingly, the driving mechanism for solubility is the entropy in the former case, whereas in the latter case the driving mechanism is the enthalpy, probably due to better solvation of the 3-chloro-N-phenyl-phthalimide by acetone molecules.

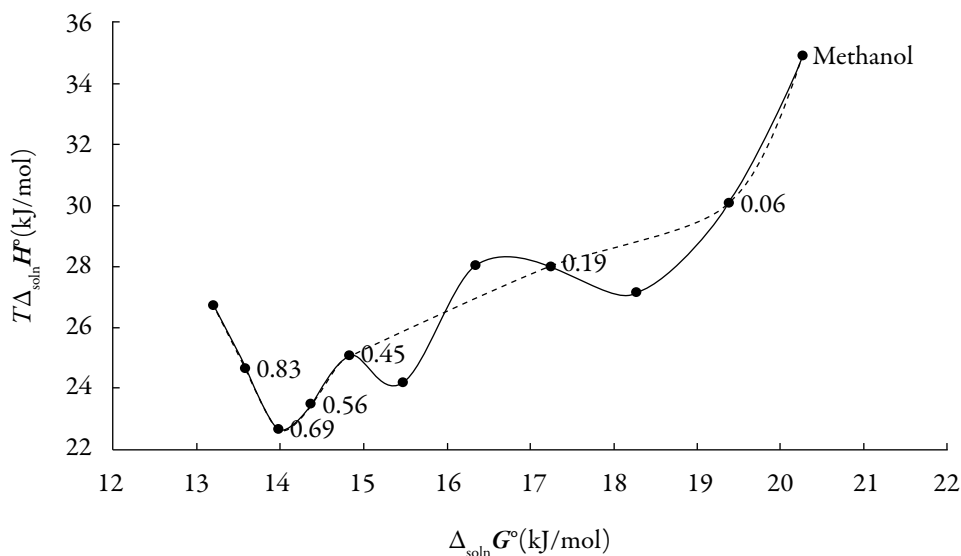


Figure 6.  $\Delta_{\text{soln}}H^\circ$  vs.  $\Delta_{\text{soln}}G^\circ$  enthalpy-entropy compensation plot for solubility of 3-chloro-N-phenyl-phthalimide in acetone + methanol cosolvent mixtures at 305.27 K. The dotted lines represent a behavior without considering the mixtures with 0.193, 0.272 and 0.455 mole fractions of acetone.

### Preferential solvation

Standard molar Gibbs energy of transfer of 3-chloro-N-phenyl-phthalimide from neat methanol to acetone + methanol mixtures is calculated and correlated to a third grade polynomial from the drug solubility data by using equation (13). Figure 7 shows the Gibbs energy of transfer behavior at 323.15 K.

$$\Delta_{tr}G_{3,2 \rightarrow 1+2}^0 = RT \ln \left( \frac{x_{3,2}}{x_{3,1+2}} \right) = 0.217 - 19.307x_1 + 20.778x_1^2 - 8.6271x_1^3 \quad (20)$$

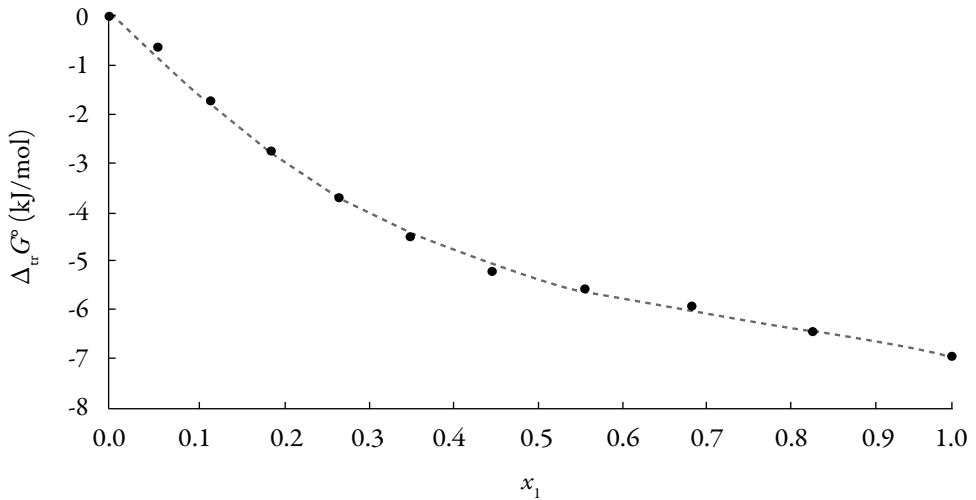


Figure 7. Gibbs energy of transfer of 3-chloro-N-phenyl-phthalimide from neat methanol to acetone + methanol co-solvent mixtures at 323.15 K.

Thus,  $D$  values are calculated from the first derivative of polynomial models (Eq. 20) solved according to the co-solvent mixtures composition. This procedure was done varying by 0.05 in mole fraction of methanol but in the following tables the respective values are reported varying only by 0.10.

$$D = \left( \frac{\partial \Delta_{tr}G_{(3,2 \rightarrow 1+2)}^0}{\partial x_2} \right)_{T,p} = -19.307 + 41.556x_1 - 25.881x_1^2 \quad (21)$$

In order to calculate the  $Q$  values the excess molar Gibbs energies of mixing  $G_{1,2}^{Exc}$  at 323.15 K were used as is reported by Marcus [18], the isothermal compressibility ( $\kappa_T$ ) is given, as a good approximation, by the linear expression:  $x_1 \kappa_{T1} + x_2 \kappa_{T2}$  ( $\kappa_{T1} = 1,324 \text{ GPa}^{-1}$ ;

( $\kappa_{T_2} = 1.248 \text{ GPa}^{-1}$ ) [21] and the partial molar volumes can be replaced by the molar volumes of the pure substances [32-34].

$$G_{1,2}^{Exc} = x_1 x_2 (1725 - 37(1 - 2x_1)) \quad (22)$$

The application of the IKBI method with the gyration radius  $r = 0.397 \text{ nm}$  leads to the preferential solvation parameter,  $\delta x_{1,3}$  for acetone around 3-chloro-N-phenyl-phthalimide which is shown in Fig. 8 at 323.15 K. The values of  $\delta x_{1,3}$  vary non-linearly with the proportion of acetone in the alcoholic mixtures (figure 8). The addition of acetone to methanol causes a negative change in  $\delta x_{1,3}$  from pure methanol up to the 0.35 in molar fraction of acetone reaching minimum values near to  $-0.018$  at 0.15 in molar fraction of acetone at 323.15 K. In this composition, methanol is preferred over acetone around the 3-chloro-N-phenyl-phthalimide.

The local mole fractions of methanol are greater than those of acetone from pure methanol up to 0.35 mole fractions of acetone and minors beyond this up to pure acetone. From the preferential solvation results, it may be conjectured that, in intermediate compositions and in acetone-rich mixtures, 3-chloro-N-phenyl-phthalimide is acting as a Lewis base with acetone molecules because it is more acid than methanol (the Kamlet-Taft hydrogen bond acceptor parameters are  $\beta = 0.66$  for methanol and 0.507 for acetone [35]).

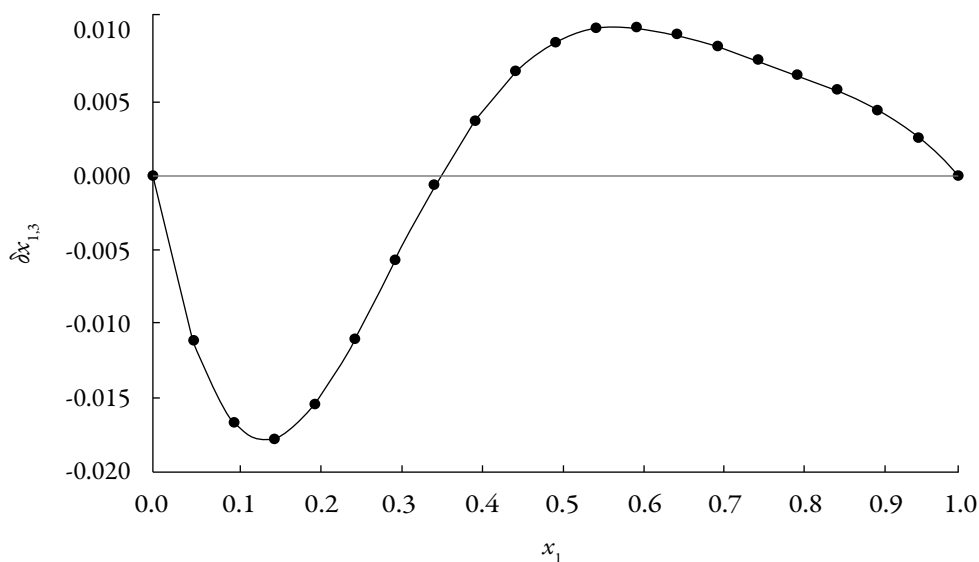


Figure 8.  $\delta x_{1,3}$  values 3-chloro-N-phenyl-phthalimide in acetone + methanol co-solvent mixtures at 323.15 K.

## CONCLUSIONS

From this work it can be concluded that the solution process of 3-chloro-N-phenylphthalimide (3) in acetone (1) + methanol (2) mixtures is endothermic. A nonlinear enthalpy–entropy compensation was found for this solute in this solvent system. In this context, entropy-driving was found for the solution process in rich-acetone mixtures, whereas, for mixtures methanol-rich enthalpy-driving was found. On the other hand, 3-chloro-N-phenyl-phthalimide is preferentially solvated for methanol in mixtures more polar and preferentially solvated for acetone in minus polar ones.

## DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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