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Ana Rute Duarte dos Santos

Bachelor of Science in Chemical and Biochemical Engineering

Study on solubility of pharmaceutical compounds in ionic liquids

Dissertation to obtain the degree of master in Chemical and Biochemical Engineering

Supervisor: Ewa Bogel-Łukasik, PhD, FCT/UNL

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March 2013

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À Klipa, a minha princesa, por se manter sempre fiel a si própria e por sempre me trazer de volta ao meu caminho.
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To my family, who I love dearly and always endured my temper.
To Rúben, that especially in this period of my life has always supported me, understood and never made me feel less than I really am.

I love you all, with all my heart.

Resumo

A solubilidade de N-acetyl-L-cysteine (NAC), Coumarin (COU) e 4-hydroxycoumarin (4HC) em solventes alternativos obtidos neste trabalho, pode abrir novas perspectivas no processamento farmacêutico. As medições do equilíbrio sólido-líquido (SLE) foram feitas utilizando um método dinâmico (sintético). O ponto de fusão e a entalpia de fusão dos compostos farmacêuticos foram obtidos utilizando *differential scanning calorimetry* (DSC). A solubilidade de N-acetyl-L-cysteine e 4-hydroxycoumarin em líquidos iónicos de trifluorometanossulfonato mostrou ser significativamente mais elevada do que nos líquidos iónicos de bis(trifluorometilsulfonil)imida estudados, e em comparação, Coumarin tem o comportamento oposto.

O melhor solvente entre os estudados para este antioxidante (NAC) e anticoagulantes (COU e 4HC) foi encontrado. O equilíbrio de fases sólido-líquido foi descrito utilizando seis equações diferentes de correlação que revelaram uma descrição relativamente boa com desvio padrão aceitável da gama de temperaturas.

Além disso, os dados de solubilidade foram usados para calcular os coeficientes de partição 1-octanol/água e os coeficientes de partição experimentais (logP) observaram-se negativos no caso de N-acetyl-L-cysteine e positivos no caso de Coumarin, em cinco temperaturas, sendo NAC uma molécula mais hidrofílica e COU mais hidrofóbica. Estes resultados são também uma prova da possibilidade de utilização destes compostos como produtos farmacêuticos.

Palavras-chave: Solubilidade, Equilíbrio Sólido-líquido, Líquido Iónico, Propriedades Termoquímicas, Coeficiente de Partição, Química Verde.

Abstract

The sufficient solubility of N-acetyl-L-cysteine (NAC), coumarin (COU) and 4-hydroxycoumarin (4HC) in alternative solvents obtained in this work can open new perspectives in pharmaceutical processing. Solid–liquid equilibrium (SLE) measurements have been made using a dynamic (synthetic) method. The melting point and the enthalpy of fusion of the pharmaceutical compounds were acquired using differential scanning calorimetry (DSC). The solubility of N-acetyl-L-cysteine and 4-hydroxycoumarin in trifluoromethanesulfonate ionic liquids was found to be significantly higher than in the studied bis(trifluoromethylsulfonyl)imide ionic liquids, and when compared, coumarin have the opposite behaviour.

The best solvent amongst studied for this antioxidant (NAC) and anticoagulants (COU and 4HC) was discovered. The solid–liquid phase equilibrium were described using six different correlation equations which revealed relatively good description with the acceptable standard deviation temperature range.

Moreover, the solubility data was used to calculate the 1-octanol/water partition coefficients and experimental partition coefficients (logP) was found to be negative in N-acetyl-L-cysteine and positive in the case of coumarin, at five temperatures with N-acetyl-L-cysteine being more hydrophilic and coumarin more hydrophobic; These results are also proof of the possibility of using these compounds as pharmaceutical products.

Keywords: Solubility, Solid–liquid equilibrium, Ionic Liquid, Thermochemical Properties, Partition Coefficient, Green Chemistry.

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List of symbols

NAC N-acetyl-l-cysteine

COU coumarin

4HC 4-hydroxycoumarin

[C_2mim] 1-ethyl-3-methylimidazolium

[C_4mim] 1-butyl-3-methylimidazolium

[C_6mim] 1-hexyl-3-methylimidazolium

[C_{10}mim] 1-decyl-3-methylimidazolium

[Ntf_2] bis(trifluoromethylsulfonyl)imide

[Otf] trifluoromethanesulfonate

DSC differential scanning calorimetry

$g_{12}-g_{22}$, $g_{21}-g_{11}$ adjustable parameters of Wilson

G^E Gibbs excess energy

K association constant

l_i bulk factor

n number of experimental points

q pure component surface parameter

P_1, P_2 model parameters resulting from the minimisation procedure

r pure component volume parameter

R ideal gas constant

SLE solid–liquid equilibrium

T temperature

$\mathbf{T}^{\mathbf{exp}}_{\mathbf{i}}$ experimental equilibrium temperature

$\mathbf{T}^{\mathbf{cal}}_{\mathbf{i}}$ calculated equilibrium temperature

$\mathbf{T_{fus,NAC}}$ melting temperature of N-acetyl-L-cysteine

$\mathbf{T_{fus,COU}}$ melting temperature of coumarin

$\mathbf{T_{fus,4HC}}$ melting temperature of 4-hydroxycoumarin

u standard uncertainty of measurement

$\mathbf{V_m}$ molar volume of pure compound i at 298.15 K

$\mathbf{x_1}$ mole fraction of drug

Z coordination number

α constant of the NRTL, NRTL 1 and NRTL 2 equations

$\boldsymbol{\gamma_1}$ activity coefficient

$\Delta_{\mathbf{fus}}\mathbf{Cp}$ heat capacity between the solid and liquid at the melting temperature

$\Delta\mathbf{g_{12}}$, $\Delta\mathbf{g_{21}}$ adjustable parameters of NRTL, NRTL 1 and NRTL 2 equations

$\Delta_{\mathbf{fus}}\mathbf{H_{NAC}}$ enthalpy of fusion of N-acetyl-L-cysteine

$\Delta_{\mathbf{fus}}\mathbf{H_{COU}}$ enthalpy of fusion of coumarin

$\Delta_{\mathbf{fus}}\mathbf{H_{4HC}}$ enthalpy of fusion of 4-hydroxycoumarin

$\Delta\mathbf{h_h}$ enthalpy of association

$\Delta\mathbf{u_{12}}$, $\Delta\mathbf{u_{21}}$ adjustable parameters of UNIQUAC and UNIQUAC ASM equations

$\boldsymbol{\sigma_T}$ root-mean-square deviation of temperature

Ω objective function

1. Introduction

There is a large variety of pharmaceutical substances used in the manufacture of drugs.[1] This type of manufacture generates high quantities of residues. Sheldon´s E-factor, defined as the mass ratio of waste to desired product, typically reaches E factors of 25-100[2] for the pharmaceutical industry, the highest among the oil refining, and the bulk or fine chemicals sectors. For this reason, attention is focused in the development of pharmaceutical processes in waste minimization and in assessing its current status in the broad context of green chemistry and sustainability. Particularly, the pharmaceutical industry is searching for solutions to the problem of waste generation in chemicals manufacture. Hazardous organic solvents may be replaced by green solvents, which are advantageous especially in terms of volatility and flammability. Ionic liquids have proven their sustainable applications in reactions[3,4] and separations[4,5] mostly due to their unique tuneable properties, and to their thermal stability [6,7] and solvent power[5,8,9,10,11,12,13]. In general, ILs with a short alkyl chain appended in the imidazolium cation and with hydrophilic anions have low toxicity[14,15]. The [C_4mim] and [C_6mim] cations are largely nontoxic towards Caco-2 cells[16], although a slightly higher toxicity was noticed for the surface active cation of [C_8mim]. Nevertheless, the toxicity of these ionic liquids should not prevent their use as pharmaceutical solvents as many pharmaceutical excipients such as the non-ionic surfactants (e.g. polysorbate 80) exhibit similar toxicities to many ILs[17]. Moreover, in operations such as granulation, blending, compounding and drying, volatile liquids are used, and thus flammable or explosive atmospheres can be created. The used flammable solvents has a direct impact on specific engineering designs, features of pharmaceutical facilities and process equipment[18]. Due to this it is desirable to improve manufacturing processes with solvents recognised as "safer"[18,19] and suitable in pharmaceutical processing[20,21,22].

In this work, N-acetyl-L-cysteine (NAC), coumarin and 4-hydroxycoumarin are used as examples of interesting pharmaceuticals. NAC may be used in preventing or treating the following conditions: acetaminophen poisoning, angina, chronic bronchitis and chronic obstructive pulmonary disease, influenza, Acute Respiratory Distress Syndrome, and HIV/AIDS[23].Animal and human studies showed NAC to be a powerful antioxidant and potential therapeutic agent in the treatment of cancer and myoclonus epilepsy[24]. Recently, NAC was reported to be used in the treatment of Parkinson's disease[25].

Coumarins (coumarin and 4-hydroxycoumarin) have biological activities and are used as pharmaceuticals. Their activity includes anti-HIV, anti-tumor, anti-hypertension, anti-

arrhythmia, anti-inflammatory, anti-osteoporosis, antiseptic, and analgesic[26]. Coumarin is also used in the treatment of asthma[26,] and lymphedema[27].

Coumarin derivatives are used widely as anticoagulants for the treatment of excessive or undesirable blood clotting due to their competitive binding to vitamin K reductase and vitamin K epoxide reductase, which are necessary for blood clotting[26]. 4-hydroxycoumarin has been used as useful intermediate for the synthesis of anticoagulants, herbicides, and anticancer agents[28].

This work is focused on screening of several ionic liquids as alternative solvents in the processing of those substances. Solubility data of coumarin, N-acetyl-L-cysteine and 4-hydroxycoumarin, in ionic liquids containing the anions bis(trifluoromethylsulfonyl)imide, also represented as Ntf_2, and trifluoromethanesulfonate, Otf. The reasons for this choice are the current popularity of these anions in the ionic liquid community as replacement for the fluorinated PF_6 and BF_4[29], and the distinctly different hydrophilicities of the two, with Otf much more hydrophilic than Ntf_2. We combined these anions with a series of imidazolium-based cations with growing alkyl chains. It is well known that the length of these alkyl chains control the size of the non-polar regions in this type of ionic liquids, leading to different solubility behaviours of many solutes.

To the best of our knowledge, until now there are no studies dedicated to ionic liquids and these drugs. In particular, the following ionic liquids were used: 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide $[C_2mim][Ntf_2]$, 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide $[C_4mim][Ntf_2]$, 1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide $[C_6mim][Ntf_2]$, 1-decyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide $[C_{10}mim][Ntf_2]$, 1-ethyl-3-methylimidazolium trifluoromethanesulfonate $[C_2mim][Otf]$, 1-butyl-3-methylimidazolium trifluoromethanesulfonate $[C_4mim][Otf]$ ionic liquids. Additionally, solubility in water and 1-octanol were sought to be measured for the following systems: coumarin and N-acetyl-L-cysteine.

Such data were needed to calculate 1-octanol/water partition coefficients for the investigated systems of the pharmaceutical compounds plus the mentioned solvents.

2. Methodology

2.1. Chemicals

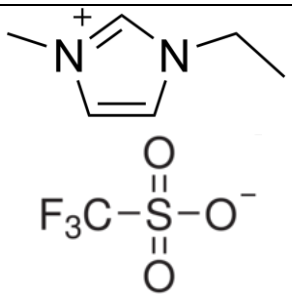
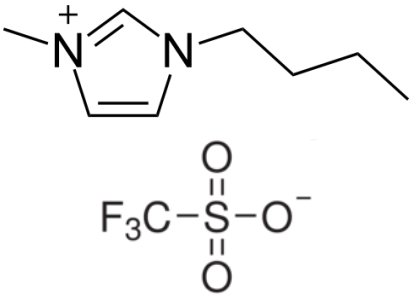
Coumarin with the stated purity of ≥99 mass% was purchased from Sigma Aldrich as well as N-acetyl-L-cysteine with stated purity of ≥99 mass% and 4-hydroxycoumarin with stated purity of 98 mass%.

1-octanol was purchased from Sigma Aldrich with stated purity of ≥99 mass%. Ionic liquids [$C_n$mim][Ntf_2] (n = 2, 4, 6, 10) and [C_2mim][Otf] were obtained from Solchemar with the purity of ≥98 mass% and [C_4mim][Otf] were obtained from Iolitec, Germany with the purity of ≥99 mass%.

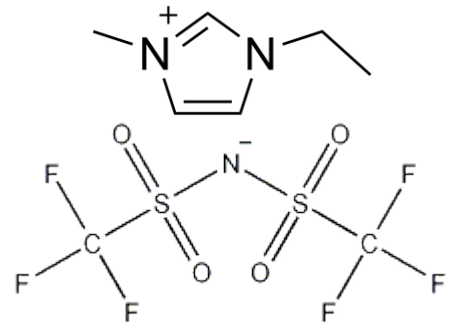
All ionic liquids were degassed, dried, and freed from residues of volatile compounds by applying a vacuum 0.1 Pa at a temperature of 60 ºC. All the drying techniques were carried out in the 48 h prior to the preparation of new solutions. The mass fraction of water remaining in the dried samples was analysed by coulometric Karl–Fischer titration and showed the following amount of water in the pure compounds: [C_2mim][Ntf_2], 120 ppm; [C_4mim][Ntf_2], 110 ppm; [C_6mim][Ntf_2], 130 ppm; [C_{10}mim][Ntf_2], 110 ppm; [C_2mim][Otf], 2100 ppm; [C_4mim][Otf], 3910 ppm.

The chemical structures of drugs and solvents used are illustrated in Table 2.1.

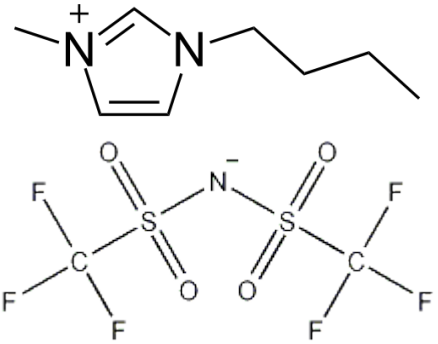
Table 2.1. Name, abbreviation and structure of used solvents and drugs.

Name, abbreviation	Structure
1-ethyl-3-methylimidazolium trifluoromethanesulfonate, [C_2mim][Otf]	
1-butyl-3-methylimidazolium trifluoromethanesulfonate, [C_4mim][Otf]	

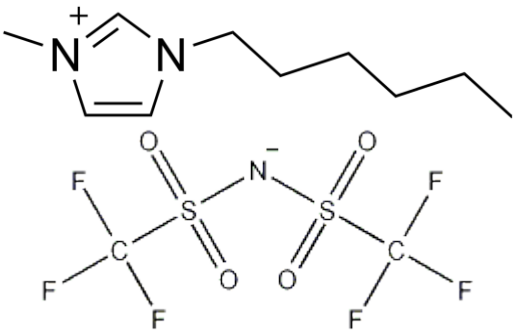
1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [C_2mim][Ntf_2]



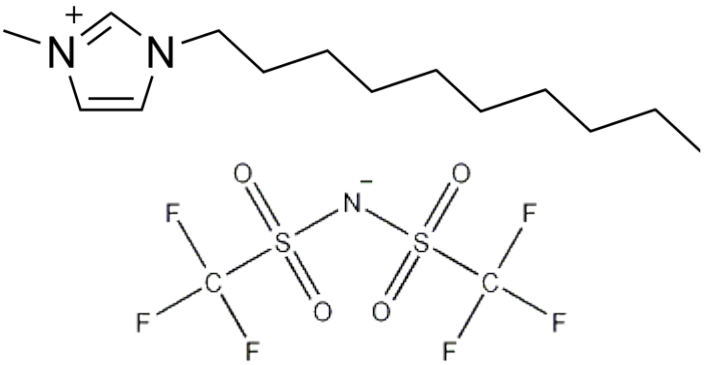
1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [C_4mim][Ntf_2]



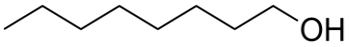
1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [C_6mim][Ntf_2]



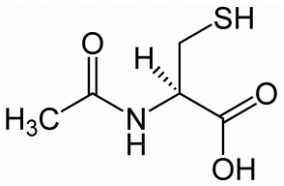
1-decyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [C_{10}mim][Ntf_2]



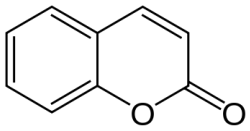
1-Octanol



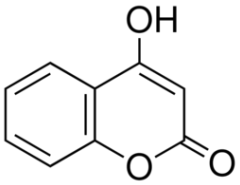
N-acetyl-L-cysteine, NAC



Coumarin, COU



4-hydroxycoumarin, 4HC



2.2. Experimental procedure for SLE measurement

Solid–liquid equilibria (SLE) of studied systems were obtained at the ambient pressure of 0.1 MPa and at temperature ranging from 257.58 K to 415.05 K using a dynamic (synthetic) method. Experiments were performed in a Pyrex glass cell that was equipped with stirring. The cell could be opened/closed by a Teflon valve at the end of a long, capillary-thin (inner diameter of 0.1 mm) neck, has shown in Figure 2.1. It allowed the cell to be deeply immersed in a temperature-controlled bath, while, at the same time, diminishing losses due to evaporation. The solutions were prepared in Pyrex conical 5 mL flasks (Supelco) by weighing the pure components with an accuracy of 10^{-4} g. The mixture of solute and solvent was heated very slowly (at less than 2 $K \cdot h^{-1}$ near the equilibrium temperature), with continuous stirring inside the Pyrex glass cell, placed in a thermostatic bath with ethanol (250–293 K), water (293–333 K) or silicon (333–416 K). The last crystal disappearance temperatures, detected visually, were measured with a calibrated DOSTMANN electronic P600 thermometer equipped in a Pt 100 probe totally immersed in the thermostatic liquid. The uncertainty of the temperature measurements was ±0.03 K and that of the mole fraction did not exceed ±0.0005.

Figure 2.1. Picture of cell used in SLE studies.

2.3. Differential scanning calorimetry

The melting temperatures and enthalpies of fusion of the used drugs were obtained by differential scanning calorimetry (DSC), according to the following procedure: a sample of up to 5 mg was encapsulated in a 40 μL aluminium crucible. The sample was scanned in a temperature range from 253 to 573 K. All scans were performed at the heating rate of 5 K/min. The results are the average of at least three scans.

The DSC instrument (Mettler Toledo DSC 822e) was calibrated with a sample of indium and zinc, both with 99.9999 mol% purity, before each scan. The indium and zinc samples were selected because zinc allows for the calibration in the range of temperatures corresponding to the expected range for high melting point compounds.

The calorimetric accuracy was ±1% and the precision was ±0.5%. In respect to melting points, the uncertainty was estimated at the level of ±0.5 K.

2.4. 1-Octanol/water partitioning

One of the most widely used parameters for assessing the environmental impact of a chemical specie is the octanol–water partition coefficient (P_{ow}), which is used to model blood/lipid partition, and is essential for understanding the tendency of a chemical to cross biological membranes.[30] 1-octanol is an amphiphilic solvent with dielectric properties similar to those of a generalized lipid phase.[31] This parameter is useful in the ecosystem risk analysis because partition coefficients in octanol–water systems display similarities to the partition of biological compounds between water and living organisms. The logarithm of the octanol/water partition coefficient (log $P_{o/w}$) is related to soil organic carbon partition coefficients, fish bioconcentration factors, as well as toxicities, for a wide variety of aquatic and mammalian species.[32] Correlations between environmental parameters for natural systems and P_{ow} have been successful because of the 1-octanol ability to mimic a lipid phase behaviour.

By definition, when equilibrium is reached, the activity of a compound, a_i, in both the water-rich and the octanol-rich phases must be the same ($a_i{}^w = a_i{}^o$). Since $a_i = \gamma_i x_i$ then:

$$\frac{x_i^o}{x_i^w} = \frac{\gamma_i^w}{\gamma_i^o} \quad (1)$$

where x_i is the mole fraction and γ_i is the activity coefficient in the water-rich (^{w}) and octanol-rich (^{o}) phases. At constant pressure and temperature, for sufficiently dilute solutions of the test compound, mole fractions and concentrations are proportional. Moreover, if the test

compound is sufficiently dilute in both phases that it can be considered at "infinite dilution", then the activity coefficients should not change with small variations in the concentrations. In this case, namely extremely dilute concentrations (C_i) of the test compound in both phases, the partition coefficient should be a constant, independent of composition.[33] This is also called the Nernst distribution law:

$$K_{ow} = \frac{C_i^o}{C_i^w} \quad (2)$$

Generally, hydrophobicity is favourable for bioaccumulation, or the bioconcentration of organic compounds.[34] Therefore, a low value of the 1-octanol/water partition coefficient is required for new pharmaceuticals to avoid bioaccumulation.

One must note that octanol and water are not completely immiscible. At 25 ºC, the solubility of water in octanol is quite large, 2.46 mol·dm^{-3}, 0.289 mole fraction, but the solubility of octanol in water is just 3.29x10^{-3} mol·dm^{-3}, 9.32x10^{-4} mole fraction.[35] These solubilities depend on the temperature of the solution and can affect the partitioning of the solute between the two solvents.

3. Results and Discussion

In this work, different types of results were obtained. In subchapter 3.1, we present the set of results that were the main objective of this work, the solubilities of the three above mentioned solid pharmaceutical compounds in the selected ionic liquids, that is, the solid-liquid phase diagrams of the systems studied. In subchapter 3.2, a brief discussion of the solubility trends uncovered by those results is presented. The auxiliary data obtained by differential scanning calorimetry are presented in subchapter 3.3. The solid–liquid phase equilibria were described using six different correlation equations as described in subchapter 3.4. Studies of partition coefficient of NAC and coumarin was performed, with the purpose to obtain knowledge about the absoption efficiency of these compounds, as presented in subchapter 3.5.

3.1. Solid–Liquid Equilibrium (SLE) experimental results

The aim of this work was to provide solubility data of N-acetyl-L-cysteine, an antioxidant drug, coumarin and 4-hydroxycoumarin, anticoagulant derivatives, in alternative solvents namely ionic liquids. The (solid + liquid) phase diagrams for N-acetyl-L-cysteine, coumarin and 4-hydroxycoumarin in a series of bis(trifluoromethylsulfonyl)imide and trifluoromethanesulfonate ionic liquids have been measured by a dynamic method from 257.58 K to 415.05 K.

The solubility data of the studied drugs in the aforementioned ionic liquids, water and 1-octanol, are presented in Tables 3.1.-3.3. The tables compile the direct SLE experimental results, temperatures, T_1, versus x_1 (mole fraction of drug in the saturated solution), for the investigated systems. All examined systems are described by the classical solid–liquid phase envelopes with the eutectic point below the detection limit. The phase envelopes of the systems containing each drug and the studied solvents are shown in Figs. 3.1.–3.3. As shown in the figures, the eutectic point is strongly shifted towards low values of the solute mole fraction, due to the high melting points and high enthalpies of fusion of the compounds studied.

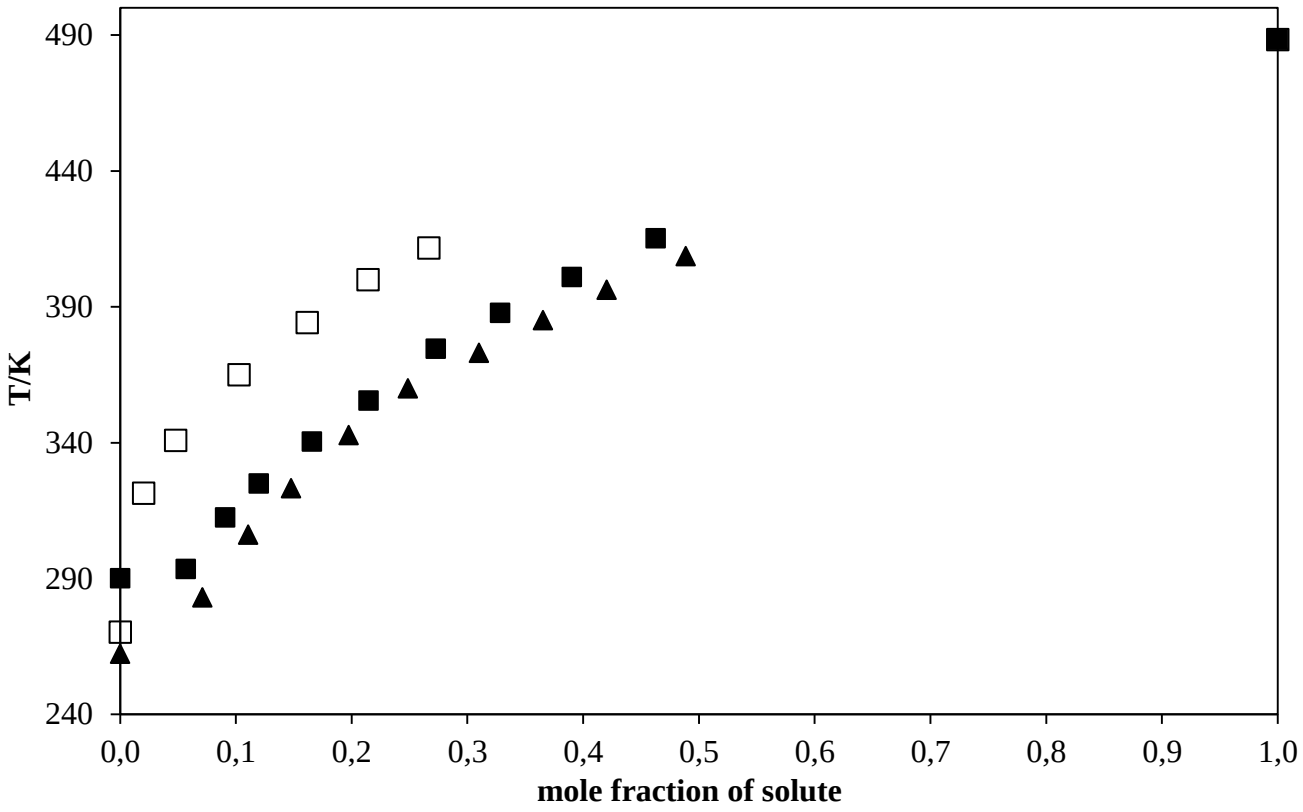


Figure 3.1. Solubilities of 4-hydroxycoumarin in [C_2mim][Otf] (▲), or [C_4mim][Otf] (■), or [C_4mim][Ntf2] (□).

Table 3.1. Experimental solubilities of 4-hydroxycoumarin (1) in the mentioned ionic liquids (2) at temperatures T[a] and ambient pressure. γ_1 is the activity coefficient of 4-hydroxycoumarin, calculated according to equation (1).

4-hydroxycoumarin								
[C_2mim][Otf]			[C_4mim][Otf]			[C_4mim][Ntf_2]		
x_1	T/K	γ_1	x_1	T/K	γ_1	x_1	T/K	γ_1
0.0000	262.23[b]		0.0000	290.10[c]		0.0000	270.22[d]	
0.0711	283.02	0.1769	0.0566	293.46	0.3222	0.0203	321.38	2.1513
0.1107	306.06	0.2490	0.0907	312.45	0.3698	0.0477	340.84	1.5420
0.1476	323.17	0.3107	0.1197	324.88	0.4019	0.1026	364.94	1.2686
0.1973	342.78	0.3915	0.1656	340.36	0.4389	0.1615	384.13	1.2060
0.2485	359.96	0.4684	0.2145	355.49	0.4897	0.2141	399.99	1.2333
0.3101	372.98	0.4995	0.2728	374.57	0.5872	0.2667	411.60	1.2186
0.3654	385.07	0.5432	0.3283	387.73	0.6372	1.0000	488.30	1.0000
0.4204	396.26	0.5860	0.3902	400.96	0.6887			
0.4887	408.56	0.6305	0.4625	415.20	0.7476			
1.0000	488.30	1.0000	1.0000	488.30	1.0000			

[a] Standard uncertainties u are u(T) = 0.03 K, $u_r(x)$ = 0.0005. [b] Reference 36. [c] Reference 37. [d] Reference 38.

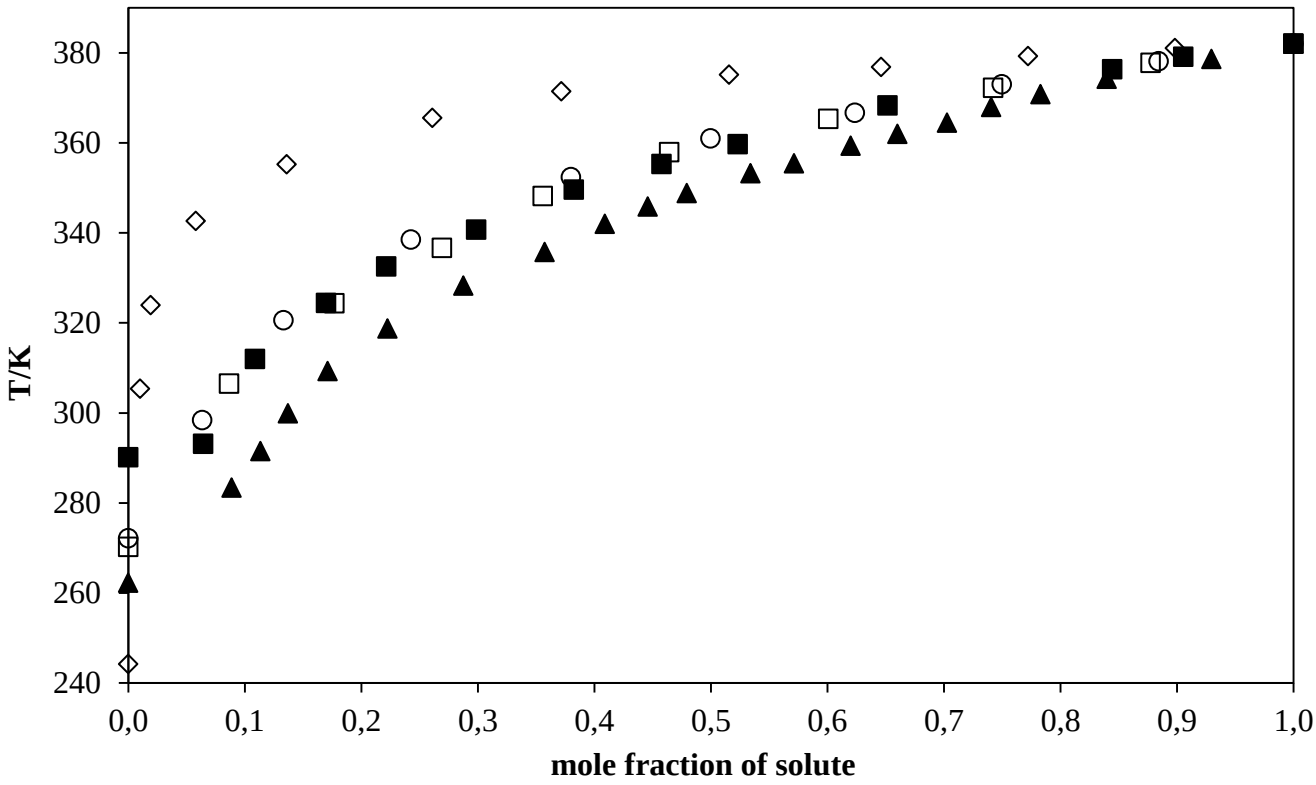


Figure 3.2. Solubilities of N-acetyl-L-cysteine in [C_2mim][Otf] (▲), or [C_4mim][Otf] (■), or [C_4mim][Ntf_2] (□), or [C_6mim][Ntf_2] (○), or [C_{10}mim][Ntf_2] (◊).

Table 3.2. Experimental solubility of N-acetyl-L-cysteine (1) in the mentioned ionic liquids (2) at Temperatures T[a] and ambient pressure. γ_1 is the activity coefficient of the solute , calculated according to equation (1).

N-acetyl-L-cysteine											
	Water			$[C_2mim][Otf]$			$[C_4mim][Otf]$			$[C_4mim][Ntf_2]$	
x_1	T/K	γ_1	x_1	T/K	γ_1	x_1	T/K	γ_1	x_1	T/K	γ_1
0.0000	273.15		0.0000	262.23[b]		0.0000	290.10[c]		0.0000	270.22[d]	
0.0110	286.16	3.0696	0.0889	283.34	0.3335	0.0644	293.11	0.7247	0.0866	306.47	0.9574
0.0142	291.91	3.1108	0.1135	291.49	0.3822	0.1088	311.94	0.9501	0.1769	324.32	0.9371
0.0173	295.44	2.9961	0.1372	299.83	0.4570	0.1699	324.38	0.9780	0.2692	336.64	0.9517
0.0212	299.07	2.8578	0.1711	309.26	0.5426	0.2214	332.53	1.0043	0.3559	348.19	1.0534
0.0287	305.85	2.8105	0.2226	318.74	0.6045	0.2985	340.68	0.9835	0.4642	357.91	1.0913
0.0405	310.31	2.3888	0.2876	328.22	0.6639	0.3824	349.56	1.0238	0.6006	365.28	1.0485
0.0498	313.04	2.1697	0.3574	335.74	0.6954	0.4576	355.28	1.0221	0.7422	372.23	1.0336
0.0627	315.31	1.8817	0.4091	341.94	0.7483	0.5230	359.70	1.0221	0.8775	377.79	1.0185
0.0856	320.72	1.6952	0.4457	345.81	0.7793	0.6515	368.28	1.0535	1.0000	381.99	1.0000
0.1128	324.69	1.4901	0.4794	348.83	0.7981	0.8445	376.34	1.0174			
0.1349	328.30	1.4194	0.5341	353.23	0.8222	0.9054	379.13	1.0234			
0.1638	331.91	1.3287	0.5715	355.39	0.8212	1.0000	381.99	1.0000			
0.1871	334.23	1.2607	0.6200	359.34	0.8530						
0.2192	337.75	1.2139	0.6602	361.93	0.8651						
0.2405	340.13	1.1984	0.7026	364.46	0.8753						
0.2607	342.48	1.1954	0.7406	367.93	0.9177						
0.2808	344.30	1.1780	0.7830	370.77	0.9406						
0.3281	348.77	1.1638	0.8398	374.17	0.9640						
0.3779	351.38	1.0971	0.9295	378.61	0.9830						
1.0000	381.99	1.0000	1.0000	381.99	1.0000						

[a] Standard uncertainties u are u(T) = 0.03 K, $u_r(x) = 0.0005$. [b] Reference 36. [c] Reference 37. [d] Reference 38.

Table 3.2. (Continuation)

N-acetyl-L-cysteine								
[C_6mim][Ntf_2]			[C_{10}mim][Ntf_2]			1-Octanol		
x_1	T/K	γ_1	x_1	T/K	γ_1	x_1	T/K	γ_1
0.0000	272.13[e]		0.0000	244.15[f]		0.0000	258.35[g]	
0.0635	298.36	0.9263	0.0102	305.35	7.7493	0.0160	288.30	2.3397
0.1333	320.58	1.0820	0.0193	323.88	8.4508	0.0321	311.93	3.2233
0.2424	338.52	1.1266	0.0580	342.61	5.3929	0.0703	330.50	2.9453
0.3799	352.37	1.1256	0.1360	355.24	3.4340	0.1078	341.24	2.7744
0.4996	360.96	1.1109	0.2610	365.51	2.4288	0.1756	352.39	2.4368
0.6236	366.65	1.0507	0.3717	371.43	2.0184	0.2546	360.41	2.1443
0.7497	372.99	1.0452	0.5157	375.09	1.6102	0.3721	367.69	1.8142
0.8843	378.10	1.0192	0.6461	376.83	1.3477	0.5052	372.30	1.5217
1.0000	381.99	1.0000	0.7722	379.26	1.2041	0.6598	376.12	1.2944
			0.8984	381.04	1.0854	0.8180	379.66	1.1490
			1.0000	381.99	1.0000	1.0000	381.99	1.0000

[a] Standard uncertainties u are u(T) = 0.03 K, $u_r(x) = 0.0005$. [e] Reference 39,40. [f] Reference 41. [g] Reference 42.

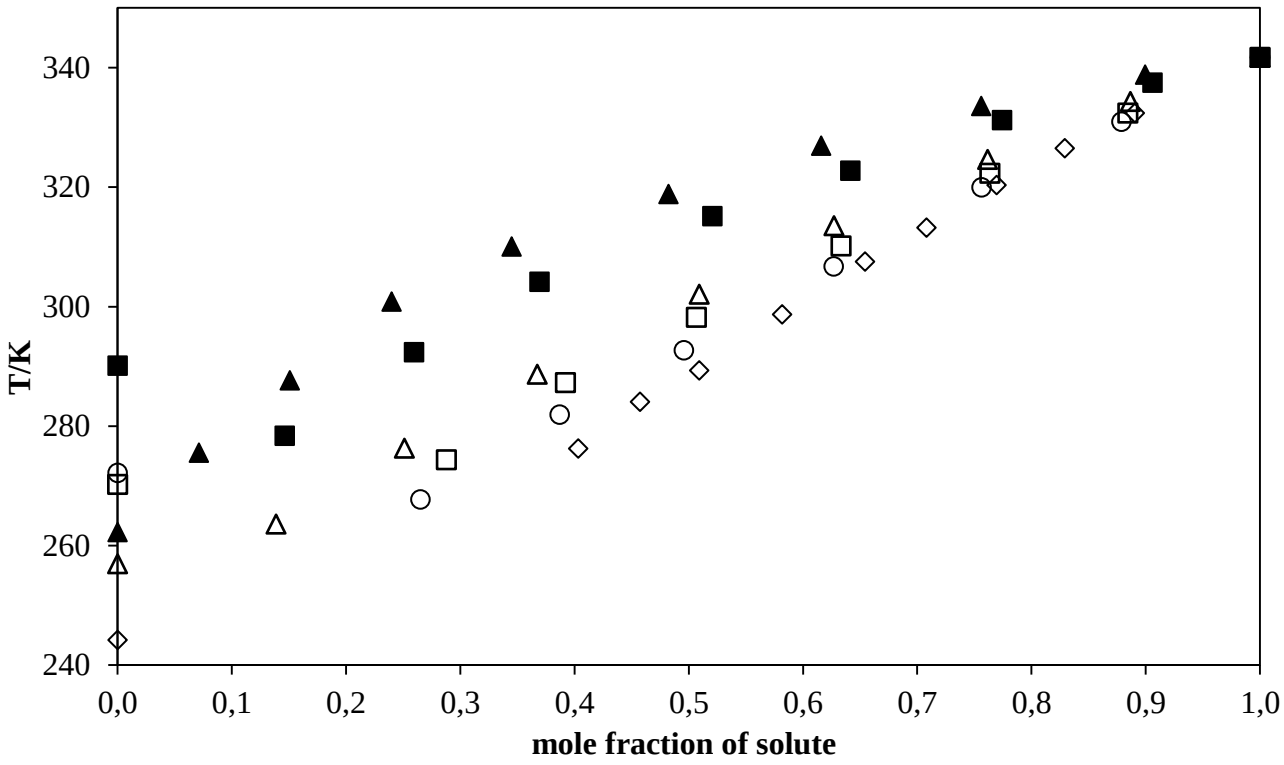


Figure 3.3. Solubilities of Coumarin in [C_2mim][Otf] (▲), or [C_4mim][Otf] (■),or [C_2mim][Ntf_2] (Δ), or [C_4mim][Ntf_2] (□), or [C_6mim][Ntf_2] (○), or [C_{10}mim][Ntf_2] (◊).

Table 3.3. Experimental Solubility of coumarin (1) in the mentioned ionic liquids (2) at Temperatures T[a] and ambient pressure. γ_1 is the activity coefficient of the solute , calculated according to equation (1).

Coumarin											
	Water			$[C_2mim][Otf]$			$[C_4mim][Otf]$			$[C_2mim][Ntf_2]$	
x_1	T/K	γ_1	x_1	T/K	γ_1	x_1	T/K	γ_1	x_1	T/K	γ_1
0.0000	273.15		0.0000	262.23[b]		0.0000	290.10[c]		0.0000	256.91[d]	
0.00001	294.10		0.0714	275.51	2.6856	0.1463	278.38	1.4310	0.1387	263.58	0.9394
0.0001	306.28		0.1509	287.63	1.8198	0.2596	292.36	1.2073	0.2512	276.27	0.7813
0.0003	320.57		0.2400	300.83	1.6378	0.3693	304.12	1.1581	0.3673	288.66	0.7697
0.0007	326.93	1078.2493	0.3449	310.00	1.4354	0.5206	315.13	1.0761	0.5091	302.03	0.7962
0.0013	331.80	646.6660	0.4824	318.83	1.2662	0.6415	322.71	1.0404	0.6271	313.49	0.8591
0.0014	332.76	581.5529	0.6160	326.92	1.1901	0.7743	331.17	1.0382	0.7615	324.60	0.9144
0.0016	332.85	524.0316	0.7560	333.56	1.1188	0.9060	337.47	1.0131	0.8865	334.28	0.9687
0.0017	333.95	504.6247	0.8995	338.77	1.0479	1.0000	341.68	1.0000	1.0000	341.68	1.0000
0.0018	334.38	483.4655	1.0000	341.68	1.0000						
0.0020	334.74	429.2567									
0.0023	335.13	385.1154									
0.0029	336.13	306.7497									
0.0037	336.15	244.6611									
0.0044	336.15	205.2905									
0.0062	336.17	144.5606									
0.0078	336.59	115.3921									
0.0095	336.82	95.7208									
1.0000	341.68	1.0000									

[a] Standard uncertainties u are u(T) = 0.03 K, $u_r(x) = 0.0005$. [b] Reference 36. [c] Reference 37. [d] Reference 43.

Table 3.3. (Continuation)

Coumarin											
[C_4mim][Ntf_2]			[C_6mim][Ntf_2]			[C_{10}mim][Ntf_2]			1-Octanol		
x_1	T/K	γ_1	x_1	T/K	γ_1	x_1	T/K	γ_1	x_1	T/K	γ_1
0.0000	270.22[e]		0.0000	272.13[f]		0.0000	244.15[g]		0.0000	258.35[h]	
0.2879	274.32	0.6415	0.2651	267.71	0.5639	0.4034	276.24	0.4860	0.0107	274.28	17.2411
0.3920	287.27	0.6933	0.3870	281.91	0.6012	0.4573	284.02	0.5412	0.0272	290.80	11.0473
0.5068	298.16	0.7230	0.4958	292.67	0.6375	0.5092	289.27	0.5648	0.0593	301.93	6.8194
0.6332	310.12	0.7843	0.6269	306.70	0.7279	0.5818	298.69	0.6386	0.1043	311.81	4.9599
0.7637	322.28	0.8655	0.7563	319.94	0.8285	0.6544	307.49	0.7112	0.1704	319.89	3.6731
0.8844	332.38	0.9327	0.8788	330.92	0.9098	0.7081	313.21	0.7558	0.2338	323.72	2.9202
1.0000	341.68	1.0000	1.0000	341.68	1.0000	0.7695	320.32	0.8214	0.2904	326.04	2.4754
						0.8291	326.48	0.8757	0.4014	328.46	1.8890
						0.8906	332.36	0.9259	0.5376	332.22	1.5293
						1.0000	341.68	1.0000	0.6805	335.21	1.2867
									0.8344	338.70	1.1281
									1.0000	341.68	1.0000

[a] Standard uncertainties u are u(T) = 0.03 K, $u_r(x) = 0.0005$. [e] Reference 38.[f] Reference 39,40. [g] Reference 41. [h] Reference 42.

3.2. Discussion of SLE results

The main factor controlling the solubilities in this study is the melting temperature of the solutes. This is shown in the following Figures 3.4 to 3.6, where the solubility of the three solutes in one ionic liquid at a time is compared. Coumarin, with the lowest melting temperature, is more soluble than the others in all examined solvents. Its lower enthalpy of fusion also contributes to this behaviour, as it leads to a slower decrease of the solubility with decreasing temperature – see equation (1).

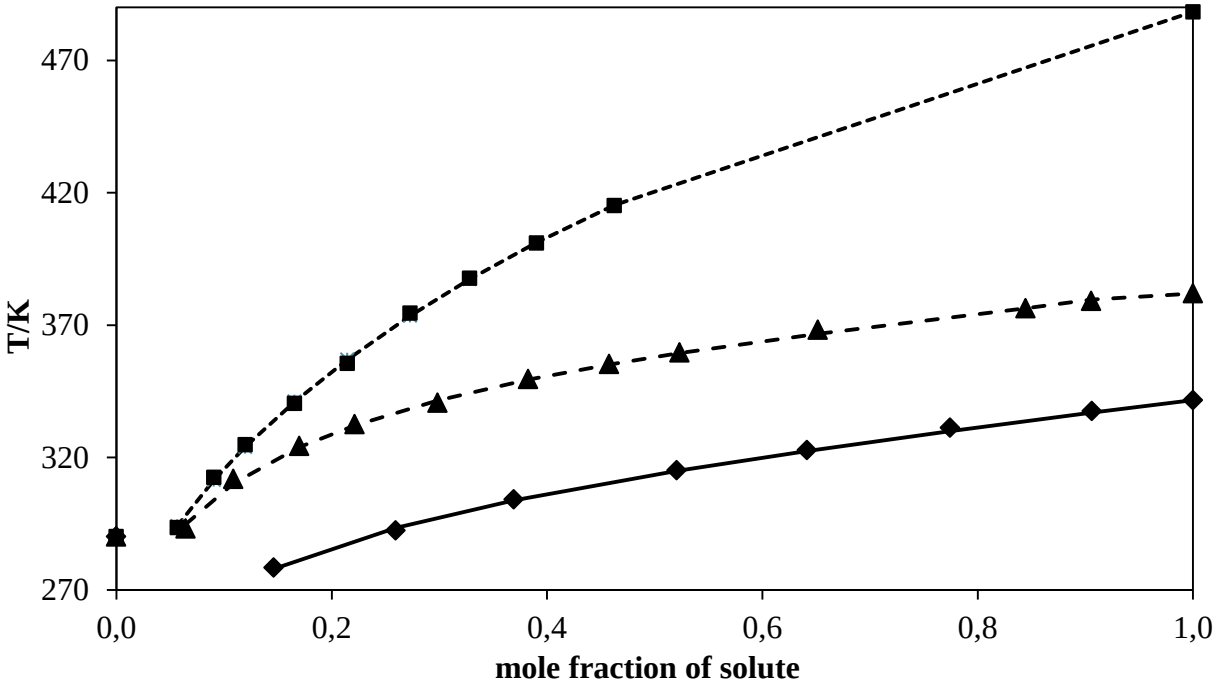


Figure 3.4. Comparison between the solubility of coumarin, 4-hydroxycoumarin and N-acetyl-L-cysteine, in [C_4mim][Otf]. Points, experimental results: (♦) coumarin; (▲) N-acetyl-L-cysteine; (■) 4-hydroxycoumarin. The solid line demonstrates the correlation by the Wilson equation. The dashed line illustrates the correlation by the NRTL 1 equation. The dotted line represents the correlation by the NRTL equation.

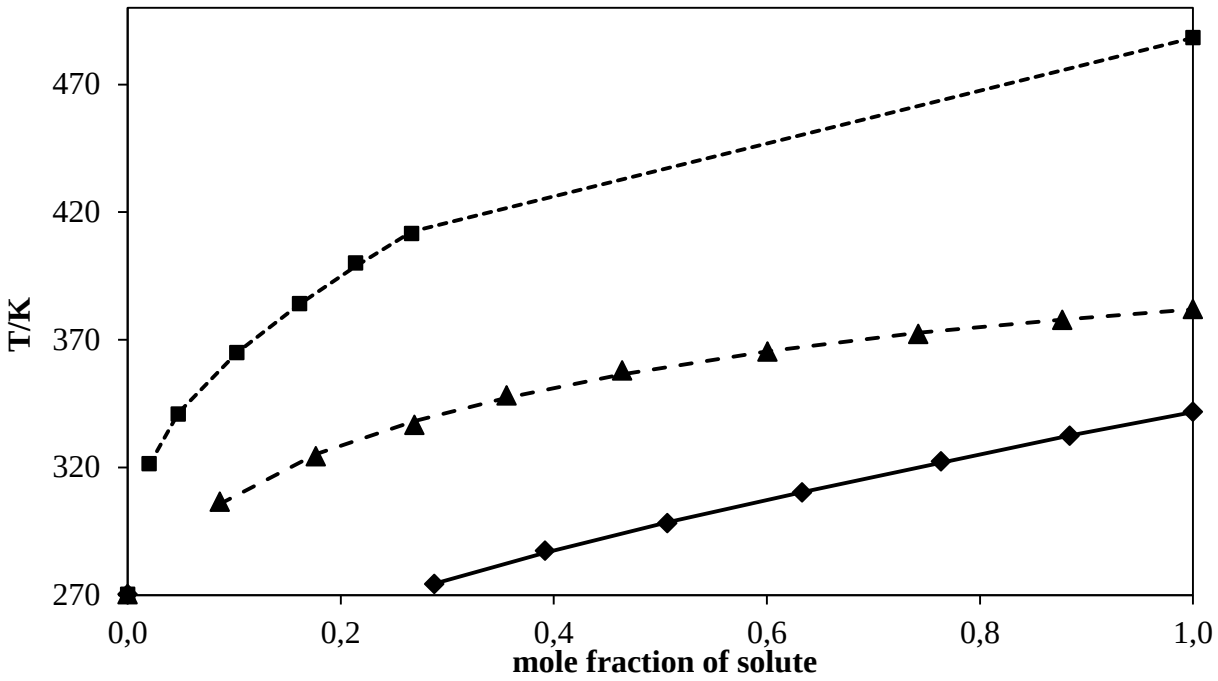


Figure 3.5. Comparison between the solubility of coumarin, 4-hydroxycoumarin and N-acetyl-L-cysteine, in [C_4mim][Ntf_2]. Points, experimental results: (♦) coumarin; (▲) N-acetyl-L-cysteine; (■) 4-hydroxycoumarin. Solid line correlation by the UNIQUAC ASM equation, dashed line UNIQUAC equation. The dotted line represents the correlation by the NRTL 1 equation.

The solvent properties of ionic liquids depend on the interactions of the solute with cation and anion. On the other hand, ionic liquids are usually stratified into polar regions, where the charged parts of the ions are located and interact with each other via Coulombic forces, and non-polar regions. The relative sizes of these different regions determine the hydrophobicity or hydrophilicity of the ionic liquids and consequently their characteristics as solvents.

In Figures 3.1 to 3.3, the behaviour of each of the three solutes studied in this work can be compared either in ionic liquids made of cations with alkyl substituents of different length, but the same anion, or in ionic liquids with the same cation, but two different anions. On the other hand, the three above mentioned solutes include: (i) two essentially planar, rigid, and very similar molecules, coumarin and 4-hydroxycoumarin, with a difference, the OH group, that confers higher hydrophilicity to 4-hydroxycoumarin; (ii) a structurally very different molecule, more flexible and polar, N-acetyl-L-cysteine.

When Figures 3.1 and 3.3 are compared, it becomes apparent that 4-hydroxycoumarin and coumarin have symmetric behaviours, that is, the factors that induce increase of the solubility of one of the substances in a series of ionic liquids lead to a decrease of similar magnitude in the solubility of the other one.

It may be observed in Figure 3.1 that the solubilities of 4-hydroxycoumarin decrease slightly with an increase in the cation alkyl chain for the ionic liquids with the same anion, trifluoromethanesulfonate. The opposite behaviour is shown in Figure 3.3 for coumarin, where solubilities are seen to grow slightly, but steadily with alkyl chain length, for the series with either the $[Otf]^-$ or the $[Ntf_2]^-$ anions. These effects of the cation series are however much smaller than the effect of changing anion, from the more polar $[Otf]^-$ to $[Ntf_2]^-$. In these cases, the solubility of 4-hydroxycoumarin markedly decreases, while it substantially increases for coumarin. It is interesting to note how a small structural change, the replacement of a hydrogen atom by a hydroxyl group, drastically inverts the solubility trends. On the other hand, the results seem to indicate that the interaction with the anions in the ionic liquids studied in this work is the dominant factor controlling solubility, although the shift in the polar to non-polar balance induced by the increase in length of the alkyl chains cannot be neglected.

As to N-acetyl-L-cysteine, its solubility presents yet another type of behaviour. Figure 3.3 shows that the solubility is practically insensitive to the swapping of the anions $[Otf]^-$ or the $[Ntf_2]^-$, in the ionic liquids with the cation $[C_4mim]^+$. On the contrary, it seems to be very sensitive to the size of the alkyl chain, markedly decreasing as alkyl chains grow longer.

Although these trends in solubility are generally consistent with the differences in polarity of the solute molecules, their diversity highlights the possibilities brought by the tuneability of solvent power in ionic liquids.

3.3 Differential scanning calorimetry results

Figures 3.6 to 3.8 show the thermographs obtained for 4-hydroxycoumarin, coumarin, and N-acetyl-L-cysteine. The thermophysical properties derived from these thermographs are given in Table 3.4.

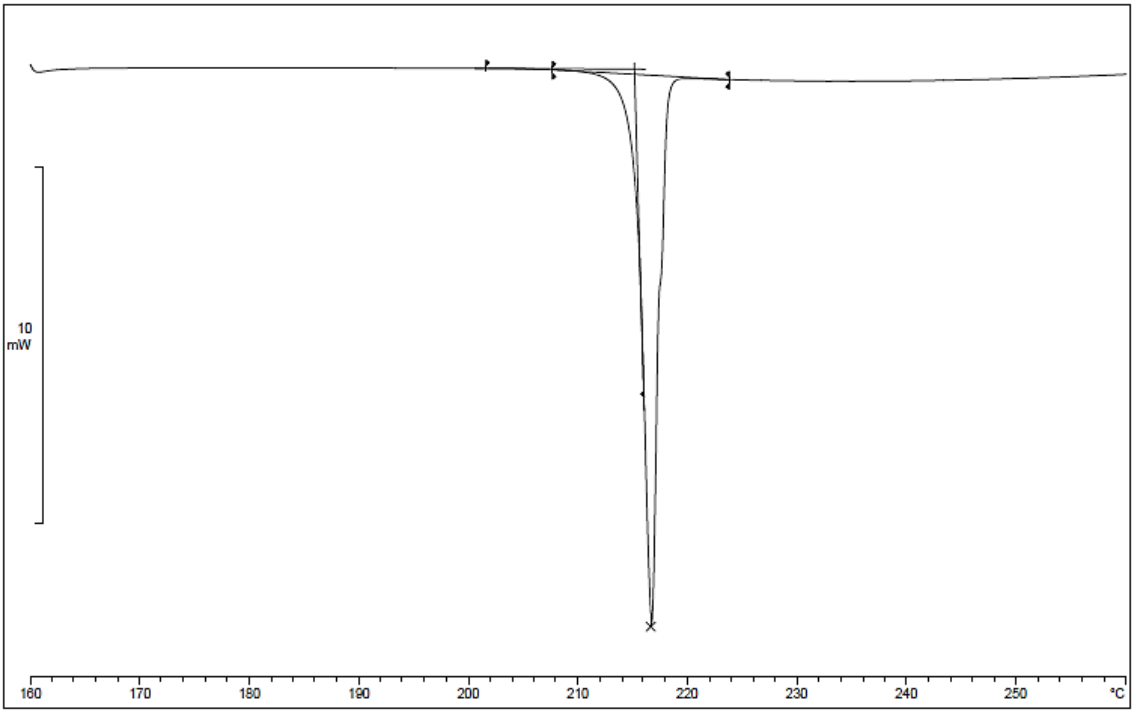


Figure 3.6. The thermograph of 4-hydroxycoumarin.

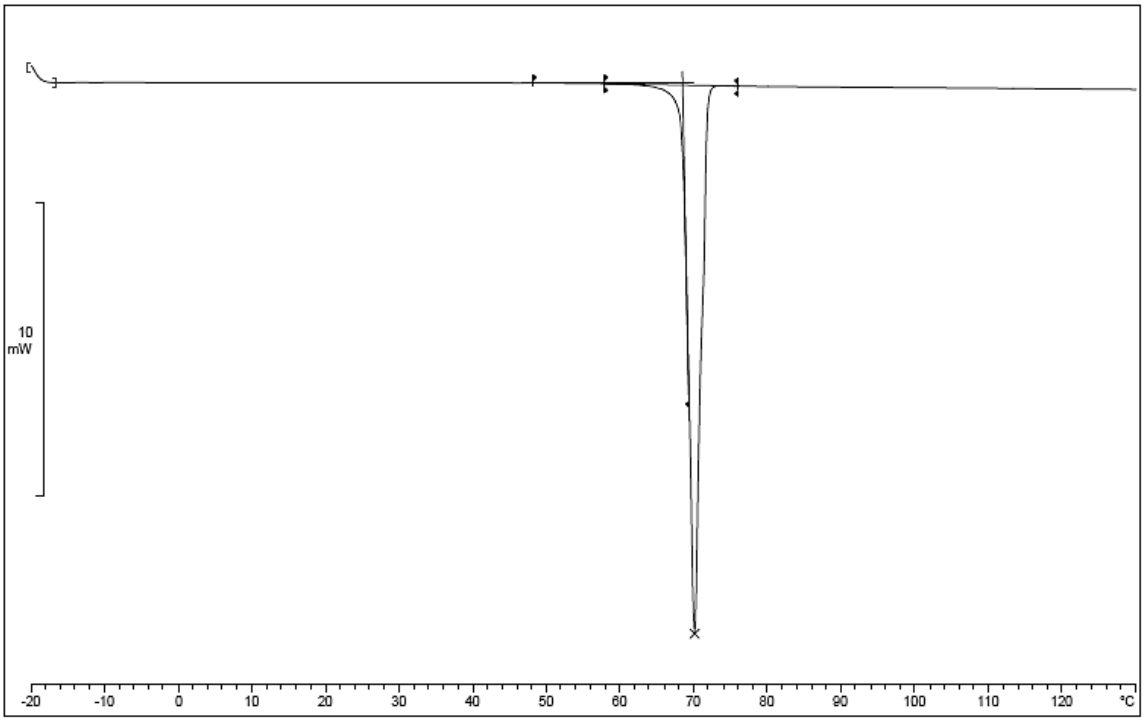


Figure 3.7. The thermograph of coumarin.

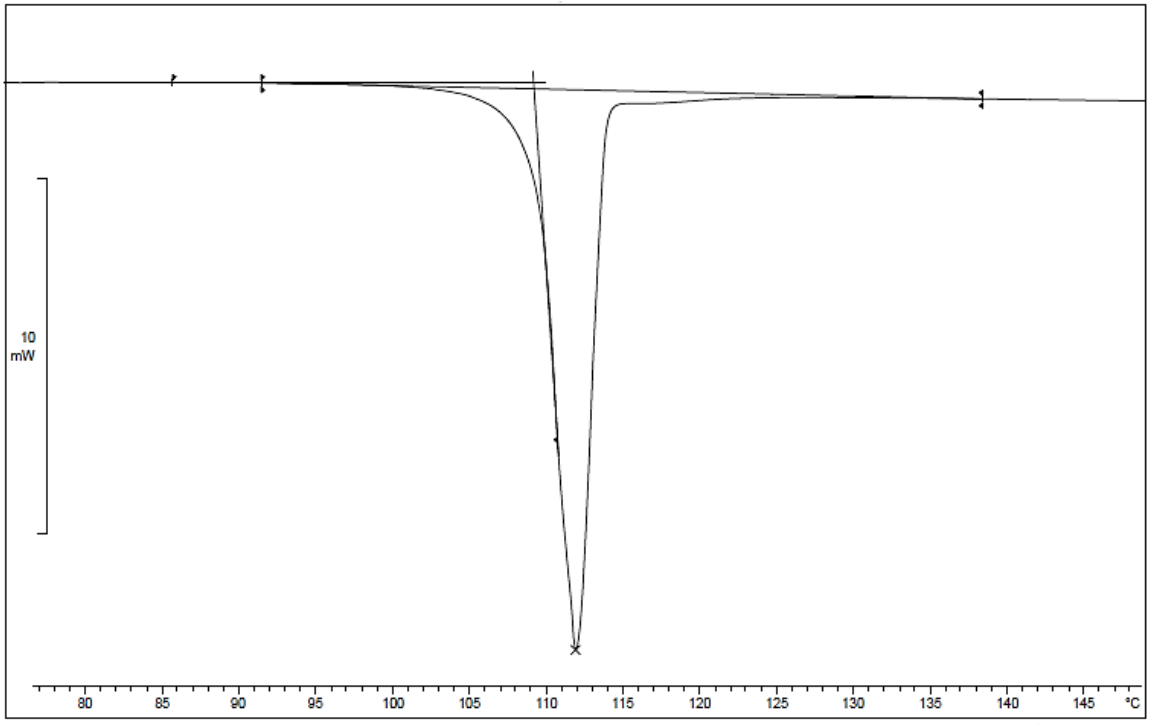


Figure 3.8. The thermograph of N-acetyl-L-cysteine.

Table 3.4. The thermophysical properties of drugs obtained by the differential scanning calorimetry.

	Parameter	Value	
		In this work[a]	Literature
NAC	Melting point, $T_{fus,NAC}$ (K)	381.99 ± 0.26	-
	Enthalpy of fusion, $\Delta_{fus}H_{NAC}$ (kJ·mol^{-1})	32.10 ± 0.06	-
COU	Melting point, $T_{fus,COU}$ (K)	341.68 ± 0.20	342.30 ± 0.04[44]b
	Enthalpy of fusion, $\Delta_{fus}H_{COU}$ (kJ·mol^{-1})	19.54 ± 0.06	18.63 ± 0.08[44]b
4HC	Melting point, $T_{fus,4HC}$ (K)	488.30 ± 0.06	483.62 ± 0.42[45]c
	Enthalpy of fusion, $\Delta_{fus}H_{4HC}$ (kJ·mol^{-1})	24.49 ± 0.24	23.17 ± 0.17[45]c

[a] Standard uncertainties u are $u(T_{fus,NAC}) = 0.26$ K, $u_r(\Delta_{fus}H_{NAC}) = 0.06$, $u(T_{fus,COU}) = 0.20$ K, $u_r(\Delta_{fus}H_{COU}) = 0.06$, $u(T_{fus,4HC}) = 0.06$ K, $u_r(\Delta_{fus}H_{4HC}) = 0.24$.
[b] Standard uncertainties u are $u(T_{fus,COU}) = 0.04$ K, $u_r(\Delta_{fus}H_{COU}) = 0.08$.
[c] Standard uncertainties u are $u(T_{fus,4HC}) = 0.42$ K, $u_r(\Delta_{fus}H_{4HC}) = 0.17$.

3.4. Correlation of (solid + liquid) equilibrium

The ideal solubility of a solid in a liquid can be calculated admitting that total miscibility (x=1) is obtained at the normal melting temperature of the solid, and that the chemical potential of the solute in the liquid solution at any lower temperature obeys the expression for an ideal solution. For a non-ideal solution, the solute concentration (mole fraction) is replaced by the activity a = γ x, and the solubility is given by equation (1).

$$-\ln x_1 = \frac{\Delta_{fus}H_1}{R}\left(\frac{1}{T_1}-\frac{1}{T_{fus,1}}\right) - \frac{\Delta_{fus}C_{p1}}{R}\ln\left(\frac{T_1}{T_{fus,1}}\right) + \frac{T_{fus,1}}{T_1} - 1 + \ln\gamma_1 \quad (1)$$

where x_1, γ_1, $\Delta_{fus}H_1$, $\Delta_{fus}C_{p1}$, $T_{fus,1}$ and T_1 stand for mole fraction, activity coefficient, enthalpy of fusion, difference in solute heat capacity between the solid and liquid at the melting temperature, melting temperature of the solute (1) and equilibrium temperature, respectively. If the solubility x is known, the activity coefficient γ can be calculated.

The second term of the right side of the equation is a usually small corrective term that accounts for the change of the enthalpy of fusion with temperature. As data on $\Delta_{fus}C_{p1}$ are not available for the solutes studied in this work, the equation was used in the calculations without the second term.

The equation may be used assuming the simple eutectic mixtures with a full miscibility in the liquid and immiscibility in the solid phases.

In this study, six methods were used to derive the solute activity coefficients γ_1 from the so-called correlation equations that describe the Gibbs excess energy (GE), the Wilson[46], UNIQUAC[47], UNIQUAC ASM[48], NRTL[49], NRTL 1[49] and NRTL 2[49].

The exact mathematical forms of the equations were presented elsewhere[50].

The two adjustable parameters of the equations were found by an optimisation technique using Marquardt's or Rosenbrock's maximum likelihood method of minimisation described by the equation:

$$\Omega = \sum_{i=1}^{n} \left(T_i^{exp} - T_i^{cal}\left(x_1, P_1, P_2\right)\right)^2 \quad (2)$$

where Ω is the objective function, n is the number of experimental points, T_i^{exp} and T_i^{cal} denotes respectively experimental and calculated equilibrium temperature corresponding to the concentration. The x_1, P_1 and P_2 are model parameters resulting from the minimisation procedure. The root-mean-square deviation of temperature was defined as follows:

$$\sigma_T = \sum_{i=1}^{n} \frac{T_i^{exp} - T_i^{cal}\ ^2}{n-2}^{1/2} \quad (3)$$

The pure component parameters r (volume parameter) and q (surface parameter) in the UNIQUAC ASM, NRTL, NRTL 1 and NRTL 2 equations were obtained by means of the following simple relationships[51]:

$$r_i = 0.029281 V_m \quad 4$$

$$q_i = \frac{Z-2}{Z}\ r_i + \frac{2}{Z}\ 1 - l_i \quad (5)$$

where V_m is the molar volume of pure compound i at 298.15 K. The molar volume of solute V_{m1} (298.15 K) was calculated by the group contribution method[52] and was assumed to be 156.3 $cm^3 \cdot mol^{-1}$ for coumarin, 112.13 $cm^3 \cdot mol^{-1}$ for 4-hydroxycoumarin and 126.11 $cm^3 \cdot mol^{-1}$ for N-acetyl-L-cysteine.

To the best of our knowledge, there are no association data for the studied drugs, thus the calculations to the data set of association were carried out by assuming that, at 323.15 K. Δh_h = 21 $kJ \cdot mol^{-1}$, Table 3.5. shows the optimized K, for each system.

Furthermore, the molar volumes of solvents needed for the correlation were taken from the literature in the following order: 187.2, 223.6 $cm^3 \cdot mol^{-1}$ for [C_2mim][Otf] and [C_4mim][Otf][53], 257.9, 292.4, 326.2, and 404.0 $cm^3 \cdot mol^{-1}$ for [C_2mim][Ntf_2], [C_4mim][Ntf_2], [C_6mim][Ntf_2], [C_{10}mim][Ntf_2], respectively[54].

The Kretschmer–Wiebe model of association for the developing of two adjustable parameters was used[55]. In this work, the value of parameter α, a proportionality constant similar to the nonrandomness constant of the UNIQUAC ASM, NRTL, NRTL 1 and NRTL 2 equations was used in calculations for different binary systems.

Values of model parameters obtained by fitting to the solubility results are presented in Tables 3.6.-3.8. together with the corresponding standard deviations.

Table 3.5. Optimized association constant K, for each system.

	K (323.15 K), Δh_h = 21 kJ·mol^{-1}		
	Solute		
Solvent	4-hydroxycoumarin	N-acetyl-L-cysteine	coumarin
[C_2mim][Otf]	245.44 (NRTL) 71.84 (NRTL 2)	4.93 (UNIQUAC ASM) 4.89 (NRTL) 4.90 (NRTL 1) 4.90 (NRTL 2)	1.65 (UNIQUAC ASM) 1.66 (NRTL) 1.66 (NRTL 1) 1.63 (NRTL 2)
[C_4mim][Otf]	32.03 (NRTL) 0.87 (NRTL 1)	4.68 (UNIQUAC ASM) 5.32 (NRTL) 5.20 (NRTL 1) 4.38 (NRTL 2)	1.76 (UNIQUAC ASM) 1.83 (NRTL) 1.92 (NRTL 1) 1.76 (NRTL 2)
[C_2mim][Ntf_2]	-	-	2.22 (UNIQUAC ASM) 2.25 (NRTL) 2.24 (NRTL 1) 2.23 (NRTL 2)
[C_4mim][Ntf_2]	3.73 (UNIQUAC ASM) 94.83 (NRTL) 298.00 (NRTL 1) 39.46 (NRTL 2)	5.77 (UNIQUAC ASM) 6.99 (NRTL) 7.51 (NRTL 1) 5.39 (NRTL 2)	2.71 (UNIQUAC ASM) 2.69 (NRTL) 2.70 (NRTL 1) 2.70 (NRTL 2)
[C_6mim][Ntf_2]	-	6.26 (UNIQUAC ASM) 8.19 (NRTL) 7.84 (NRTL 1) 5.93 (NRTL 2)	3.00 (UNIQUAC ASM) 3.06 (NRTL) 3.04 (NRTL 1) 3.01 (NRTL 2)
[C_{10}mim][Ntf_2]	-	8.96 (UNIQUAC ASM) 9.18 (NRTL) 8.82 (NRTL 1) 8.84 (NRTL 2)	3.60 (UNIQUAC ASM) 3.70 (NRTL) 3.74 (NRTL 1) 3.64 (NRTL 2)
1-Octanol	-	4.22 (UNIQUAC ASM) 3.66 (NRTL) 4.53 (NRTL 1) 3.75 (NRTL 2)	1.08 (UNIQUAC ASM) 1.24 (NRTL) 1.32 (NRTL 1) 1.08 (NRTL 2)
Water	-	0.40 (NRTL) 1.40 (NRTL 1) 0.28 (NRTL 2)	361.30 (UNIQUAC ASM) 871.89 (NRTL) 0.81 (NRTL 2)

Table 3.6. Correlation of the Solubility Data, SLE, of 4-hydroxycoumarin (1) + a solvent (2) by Wilson, UNIQUAC, UNIQUAC ASM, NRTL, NRTL 1, and NRTL 2 Equations: Values of Parameters and Deviations

	Parameters						Deviations					
	Wilson	UNIQUAC	UNIQUAC ASM	NRTL	NRTL 1	NRTL 2	Wilson	UNIQUAC	UNIQUAC ASM	NRTL	NRTL 1	NRTL 2
	$g_{12}-g_{22}$ $g_{21}-g_{11}$	Δu_{12} Δu_{21}	Δu_{12} Δu_{21}	Δg_{12} Δg_{21}	Δg_{12} Δg_{21}	Δg_{12} Δg_{21}	σ_T[b]	σ_T[b]	σ_T[a]	σ_T[a]	σ_T[a]	σ_T[a]
Solvent	$J \cdot mol^{-1}$	$J \cdot mol^{-1}$	$J \cdot mol^{-1}$	$J \cdot mol^{-1}$	$J \cdot mol^{-1}$	$J \cdot mol^{-1}$	K	K	K	K	K	K
[C_2mim][Otf]	-1061.22 -2796.54	-1463.73 448.87	223.94 -1548.27	-39252.79 35784.55	688.37 -3897.38	-3347.36 2501.31	2.71	2.97	6.08	1.15[b]	6.11[d]	1.06[g]
[C_4mim][Otf]	48.37 -2903.56	-1636.91 1315.89	-823.21 42.46	-32783.25 28523.06	-79711.31 -2059.93	-493.80 -338.22	1.38	1.38	2.45	0.94[b]	1.85[f]	2.33[i]
[C_4mim][Ntf_2]	2862.29 -1280.62	-566.64 1447.86	3988.52 -2281.42	23849.79 -8600.94	74133.03 -13200.76	16074.42 -2339.52	4.96	5.30	2.26	0.78[e]	0.78[c]	1.20[h]

[a]According to the equation

$$\sigma_T = \sum_{i=1}^{n} \frac{T_i^{exp} - T_i^{cal}\ ^2}{n-2}^{1/2}$$

[b]Calculated with the third non randomness parameter α =0.01. [c]Calculated with the third non randomness parameter α =0.05. [d]Calculated with the third non randomness parameter α =0.2. [e]Calculated with the third non randomness parameter α =0.25. [f]Calculated with the third non randomness parameter α =0.3. [g]Calculated with the third non randomness parameter α =0.45. [h]Calculated with the third non randomness parameter α =0.5. [i]Calculated with the third non randomness parameter α =0.7.

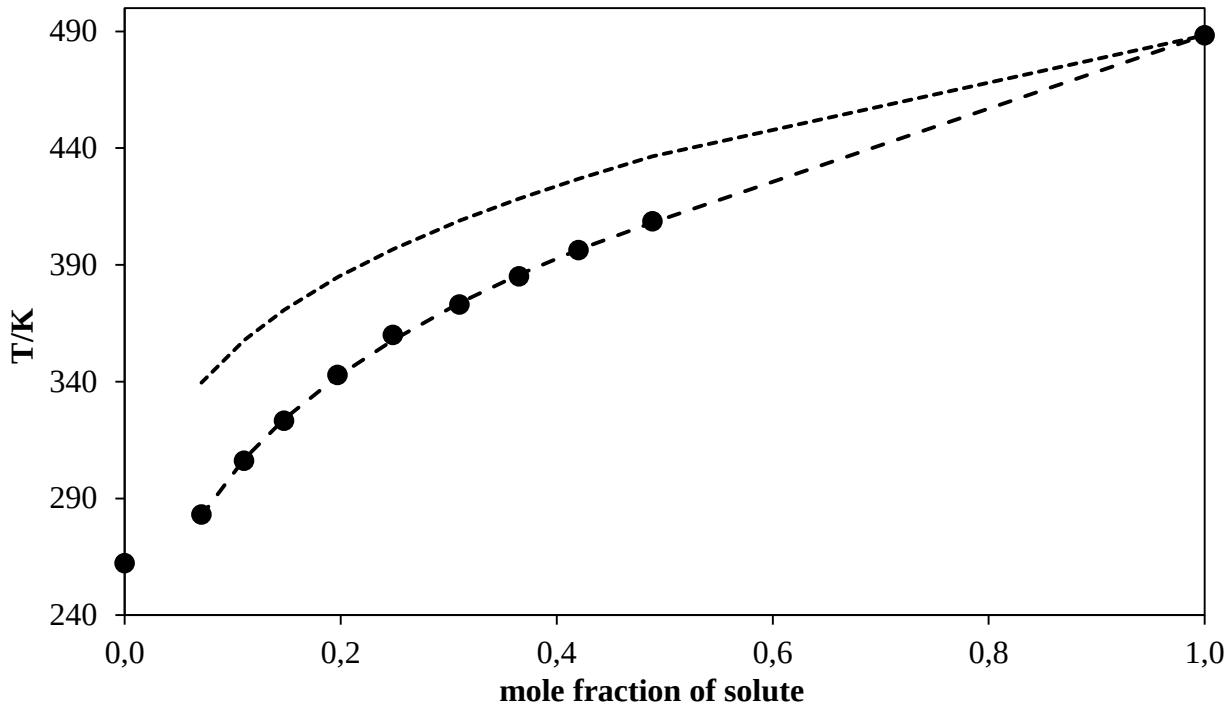


Figure 3.9. Solubility of 4-hydroxycoumarin in [C_2mim][Otf]. Points represent the experimental results. The dashed line demonstrates the correlation by the NTRL 2 equation. The dotted line represents the ideal solubility.

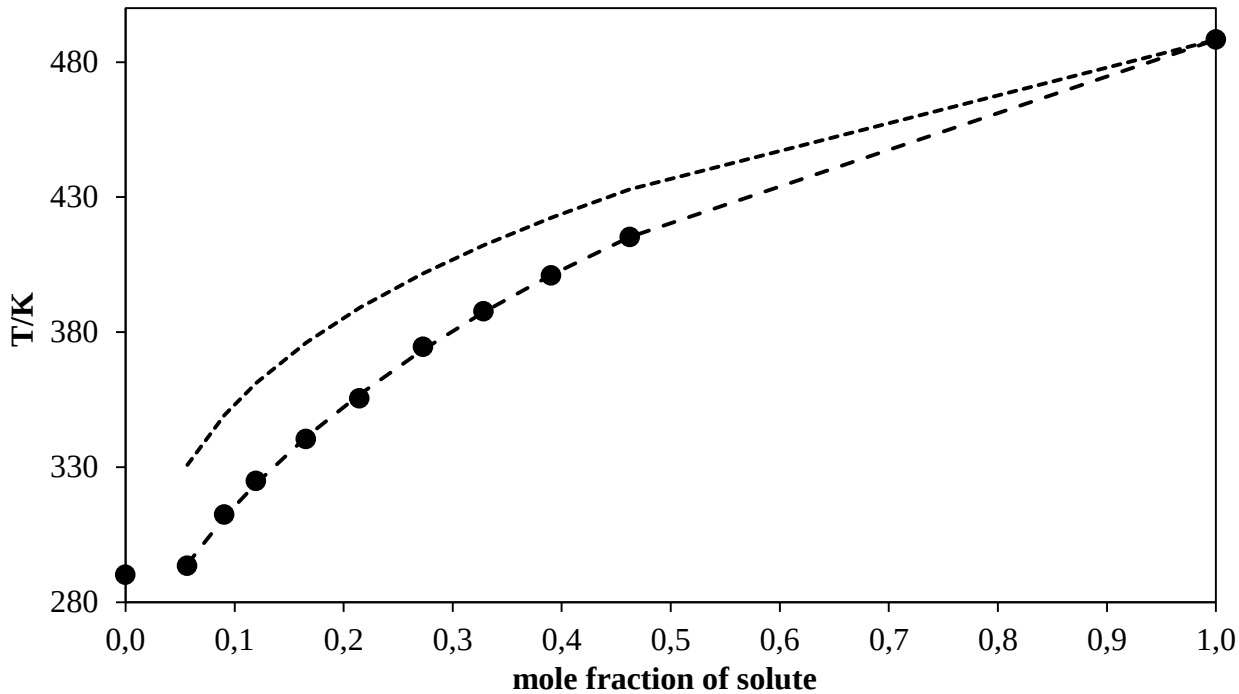


Figure 3.10. Solubility of 4-hydroxycoumarin in [C_4mim][Otf]. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL equation. The dotted line represents the ideal solubility.

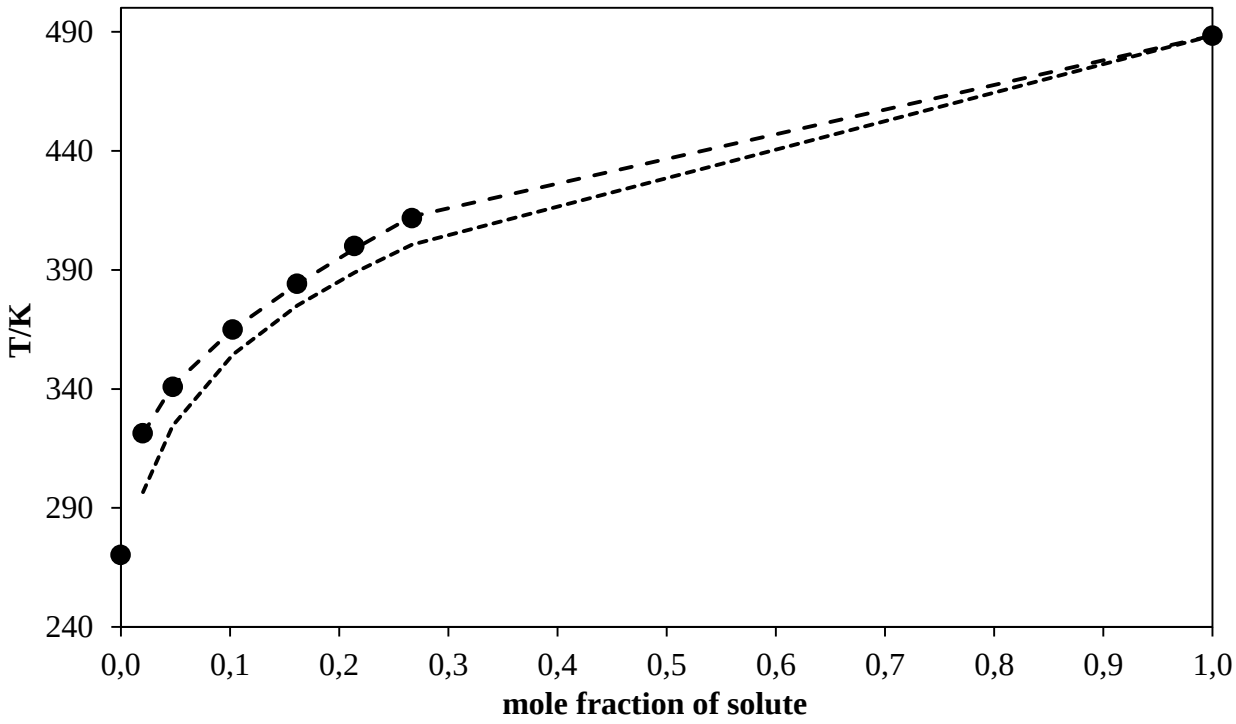


Figure 3.11. Solubility of 4-hydroxycoumarin in [C_4mim][Ntf_2]. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL 1 equation. The dotted line represents the ideal solubility.

Table 3.7. Correlation of the Solubility Data, SLE, of N-acetyl-L-cysteine (1) + a solvent (2) by Wilson, UNIQUAC, UNIQUAC ASM, NRTL, NRTL 1, and NRTL 2 Equations: Values of Parameters and Deviations

	Parameters						Deviations					
	Wilson	UNIQUAC	UNIQUAC ASM	NRTL	NRTL 1	NRTL 2	Wilson	UNIQUAC	UNIQUAC ASM	NRTL	NRTL 1	NRTL 2
	$g_{12}-g_{22}$ $g_{21}-g_{11}$	Δu_{12} Δu_{21}	Δu_{12} Δu_{21}	Δg_{12} Δg_{21}	Δg_{12} Δg_{21}	Δg_{12} Δg_{21}	σ_T[b]	σ_T[b]	σ_T[a]	σ_T[a]	σ_T[a]	σ_T[a]
Solvent	J·mol^{-1}	J·mol^{-1}	J·mol^{-1}	J·mol^{-1}	J·mol^{-1}	J·mol^{-1}	K	K	K	K	K	K
[C_2mim][Otf]	-3529.60	-1635.36	-3081.26	-2493.59	-2949.29	-1971.59	2.47	1.48	0.88	0.83[k]	0.85[k]	1.17[j]
	12964.09	1438.23	4190.92	1236.19	-696.94	1964.53						
[C_4mim][Otf]	-1346.74	-1137.41	-2369.01	-3831.80	-18073.63	-39930.85	1.58	2.21	3.90	1.21[h]	1.05[d]	2.65[b]
	6348.07	1459.61	2873.73	4283.32	18229.19	45810.46						
[C_4mim][Ntf_2]	-458.38	2033.80	-2202.60	-4351.38	-23216.98	-36011.58	1.07	1.01	3.85	0.93[e]	0.83[c]	3.34[b]
	5063.70	-1289.78	2606.01	1697.98	12897.76	40569.68						
[C_6,mim][Ntf_2]	116.80	1799.32	-2188.79	-6573.50	-8872.10	-39424.69	1.54	1.33	5.43	0.84[e]	0.34[g]	2.99[b]
	4715.67	-1038.19	2657.17	7390.78	8299.12	45160.96						
[C_{10}mim][Ntf_2]	6516.10	-1285.41	-866.76	24990.77	-7397.75	-5050.86	2.12	3.11	2.44	2.22[b]	2.18[f]	2.25[d]
	1400.61	3719.55	1664.11	-22103.74	7606.62	6708.47						
1-Octanol	1037.59	2501.96	6218.25	63704.08	28191.88	36375.25	2.53	2.36	5.38	2.60[b]	4.36[c]	2.34[b]
	7684.78	-684.96	-2369.51	-50293.27	-13684.80	-31734.25						
Water	-483.07	4533.14	4029.84	-1004.96	2735.66	4123.80	1.14	1.04	1.31	0.81[i]	0.91[g]	0.91[e]
	3714.95	1411.15	1542.11	4691.28	1324.25	683.08						

[a]According to the equation

$$\sigma_T = \sum_{i=1}^{n} \frac{T_i^{exp} - T_i^{cal}\ ^2}{n-2}^{1/2}$$

[b]Calculated with the third non randomness parameter α =0.01. [c]Calculated with the third non randomness parameter α =0.05. [d]Calculated with the third non randomness parameter α =0.1. [e]Calculated with the third non randomness parameter α =0.25. [f]Calculated with the third non randomness parameter α =0.3. [g]Calculated with the third non randomness parameter α =0.35. [h]Calculated with the third non randomness parameter α =0.6. [i]Calculated with the third non randomness parameter α =0.8. [j]Calculated with the third non randomness parameter α =0.9. [k]Calculated with the third non randomness parameter α =1.

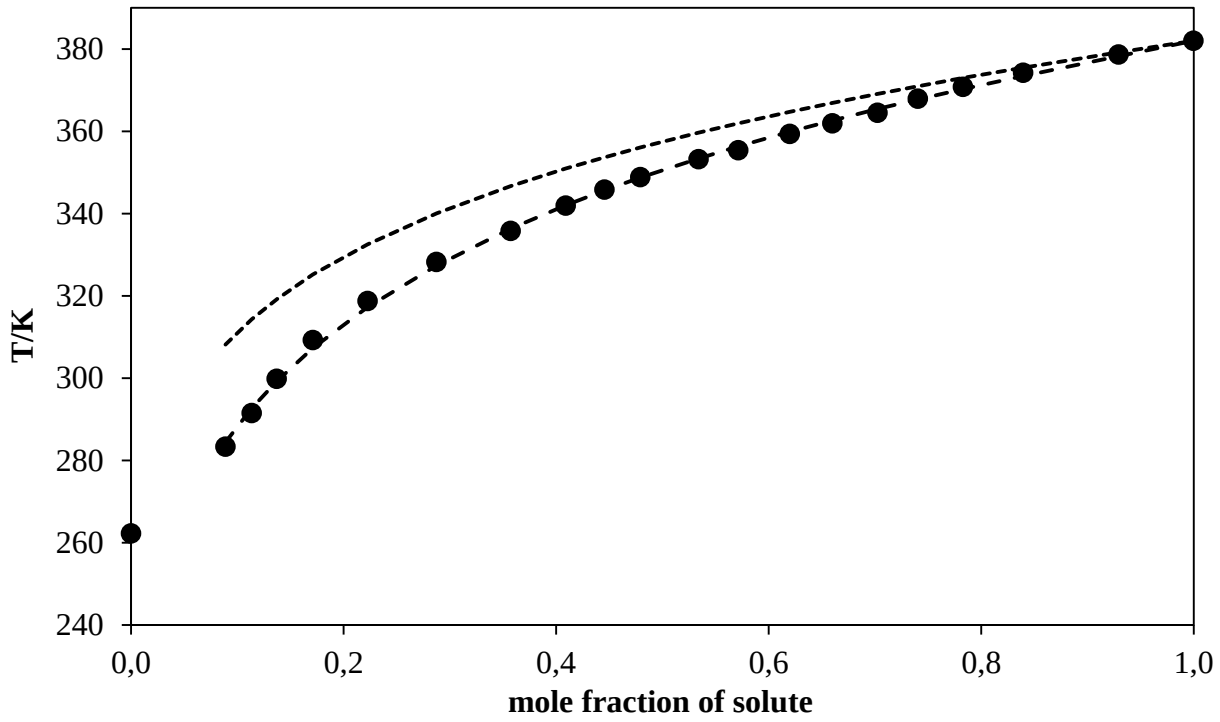


Figure 3.12. Solubility of N-acetyl-L-cysteine in [C_2mim][Otf]. Points represent the experimental results. The dashed line demonstrates the correlation by the UNIQUAC ASM equation. The dotted line represents the ideal solubility.

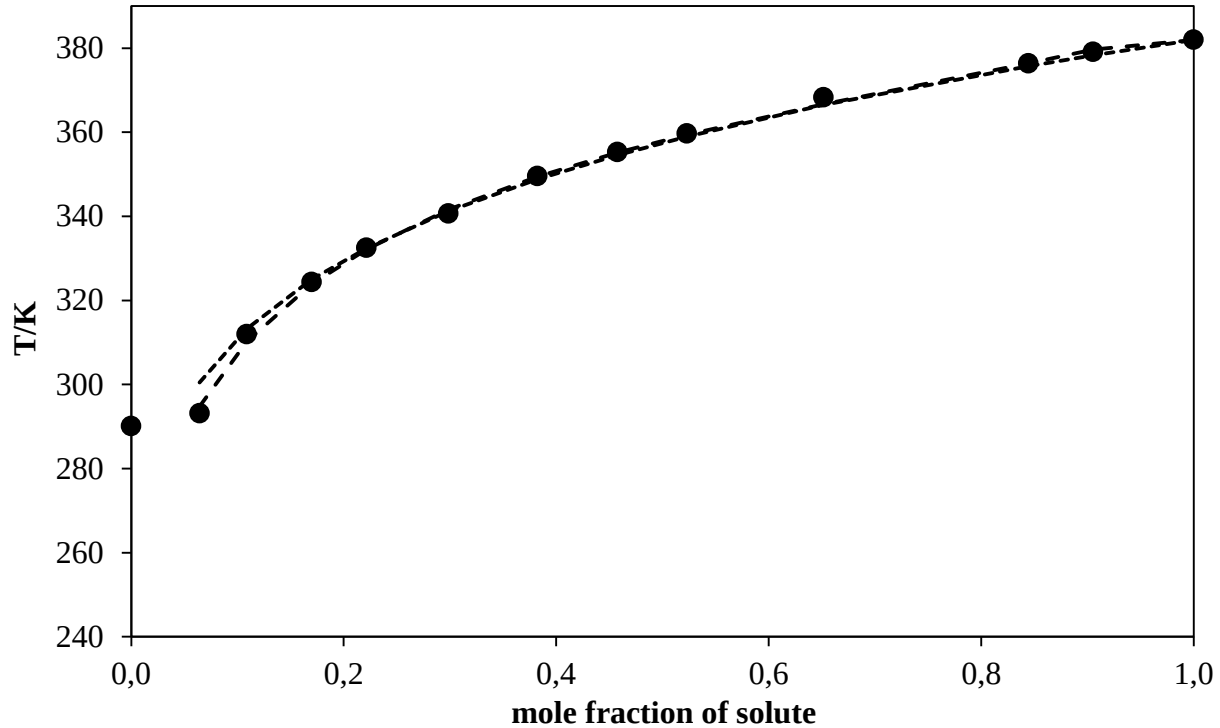


Figure 3.13. Solubility of N-acetyl-L-cysteine in [C_4mim][Otf]. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL 1 equation. The dotted line represents the ideal solubility.

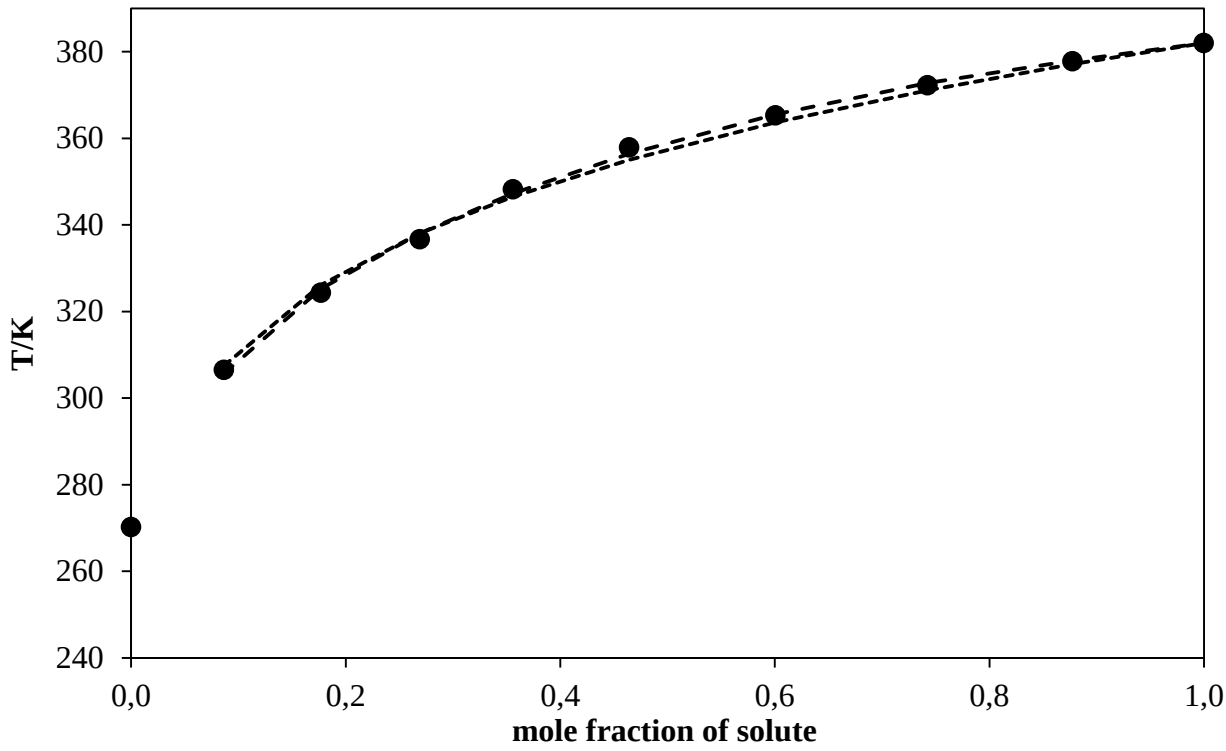


Figure 3.14. Solubility of N-acetyl-L-cysteine in [C_4mim][Ntf_2]. Points represent the experimental results. The dashed line demonstrates the correlation by the UNIQUAC equation. The dotted line represents the ideal solubility.

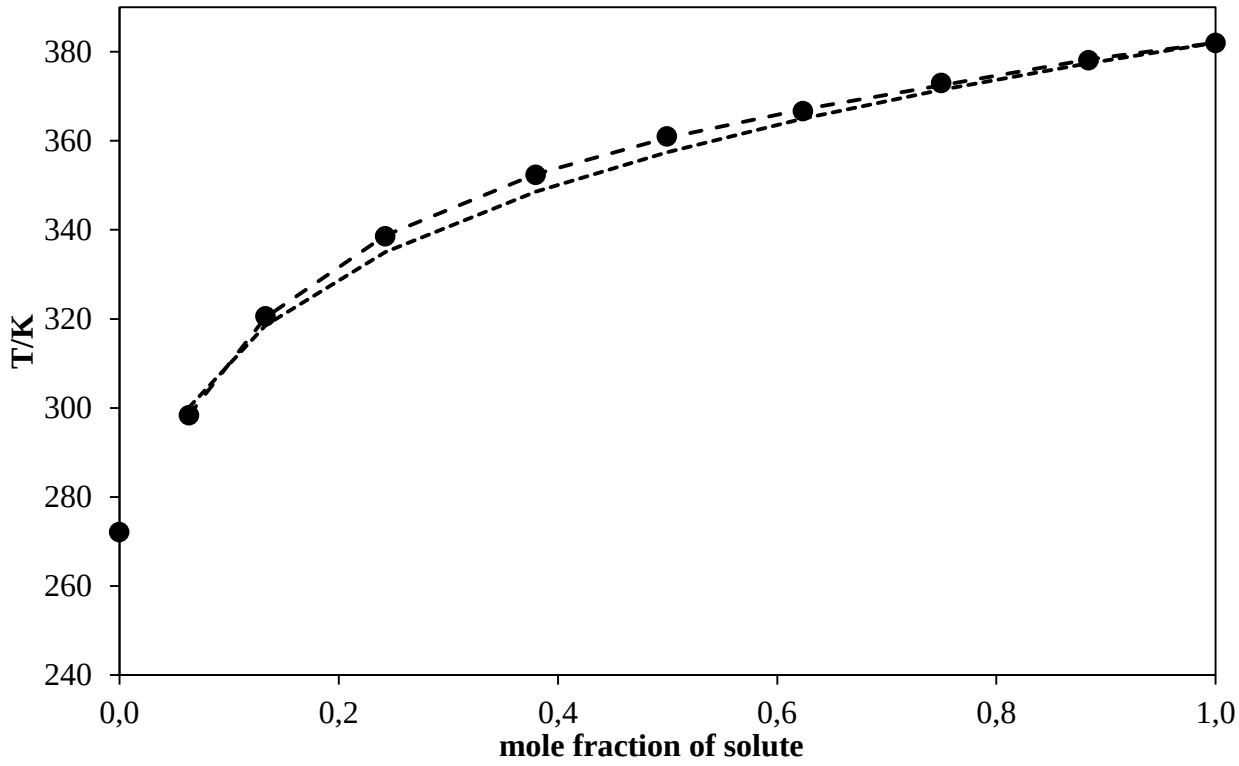


Figure 3.15. Solubility of N-acetyl-L-cysteine in [C_6mim][Ntf_2]. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL 1 equation. The dotted line represents the ideal solubility.

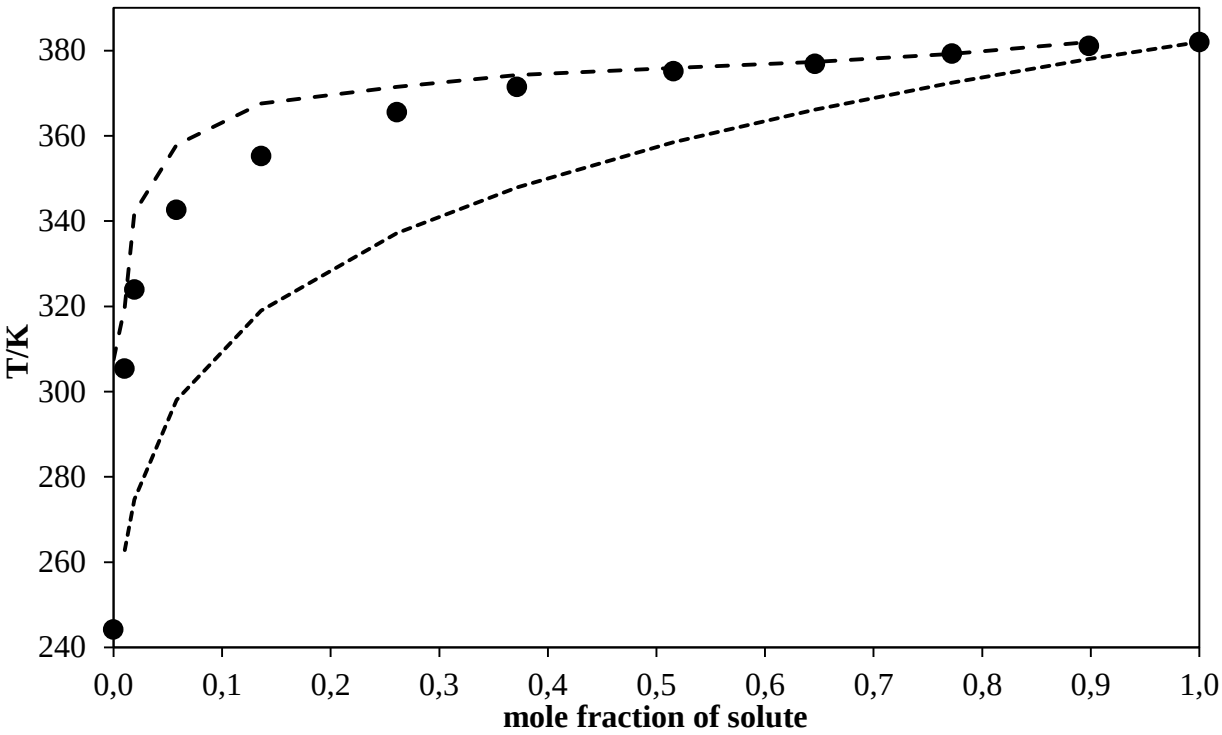


Figure 3.16. Solubility of N-acetyl-L-cysteine in [C_{10}mim][Ntf_2]. Points represent the experimental results. The dashed line demonstrates the correlation by the Wilson equation. The dotted line represents the ideal solubility.

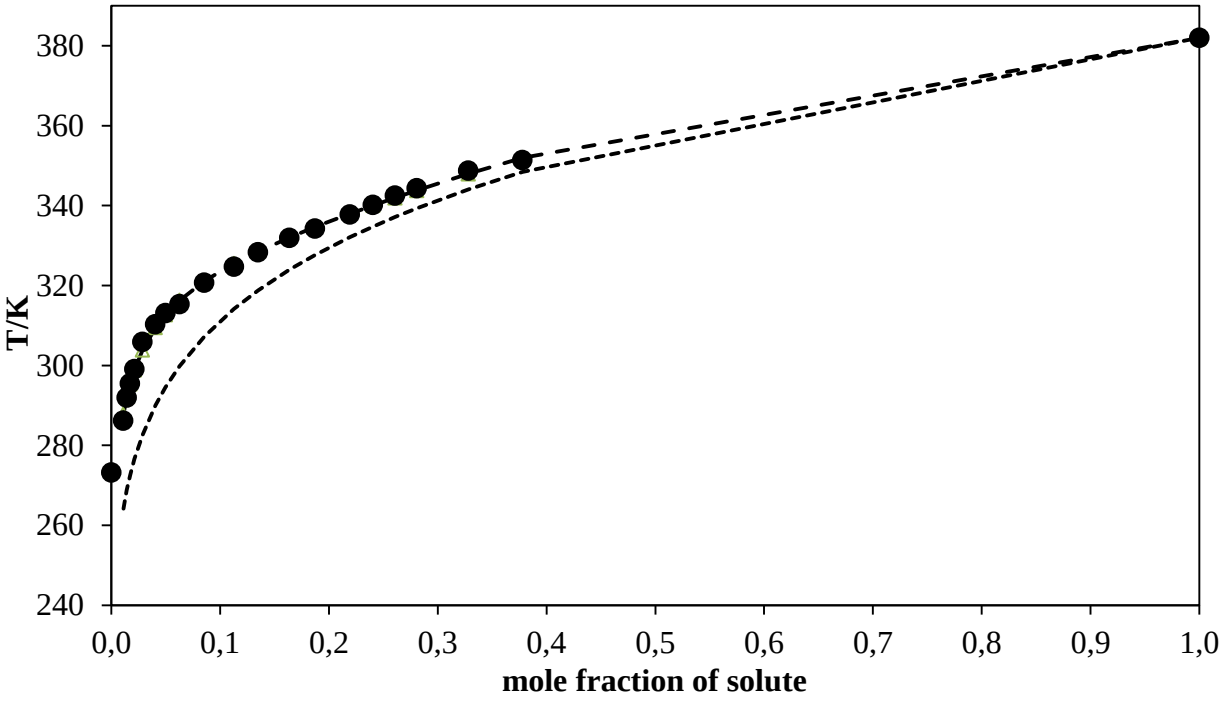


Figure 3.17. Solubility of N-acetyl-L-cysteine in water. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL equation. The dotted line represents the ideal solubility.

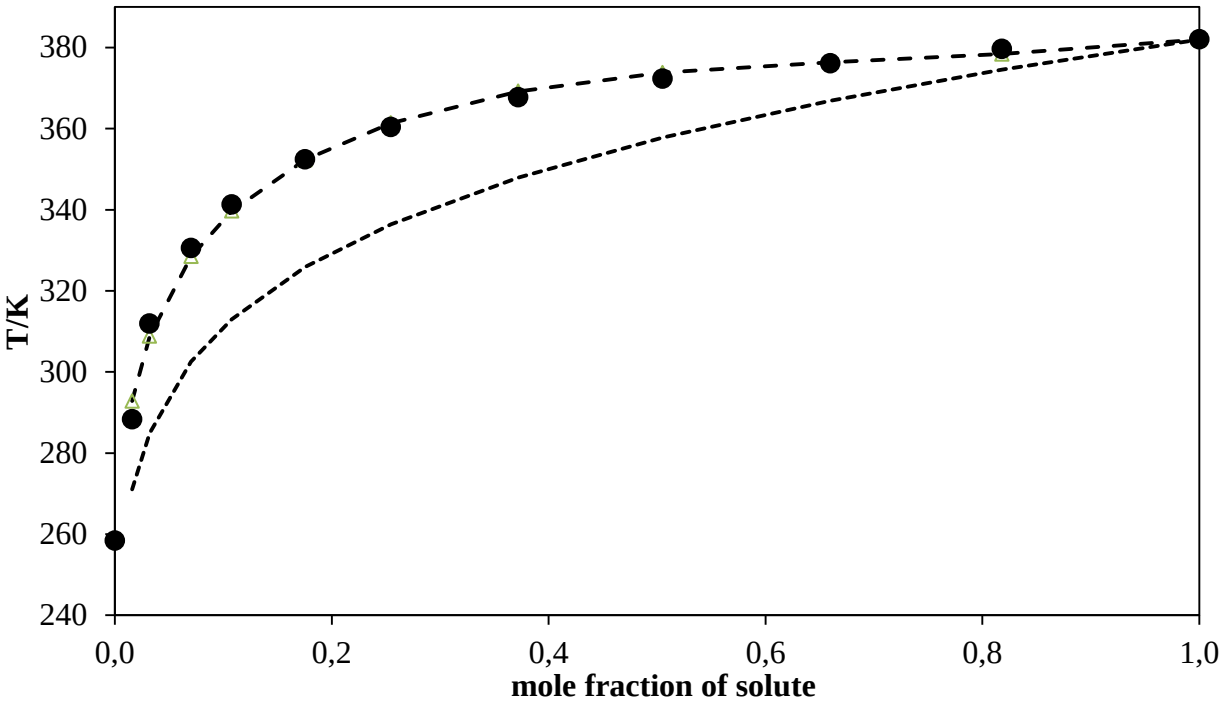


Figure 3.18. Solubility of N-acetyl-L-cysteine in 1-Octanol. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL 2 equation. The dotted line represents the ideal solubility.

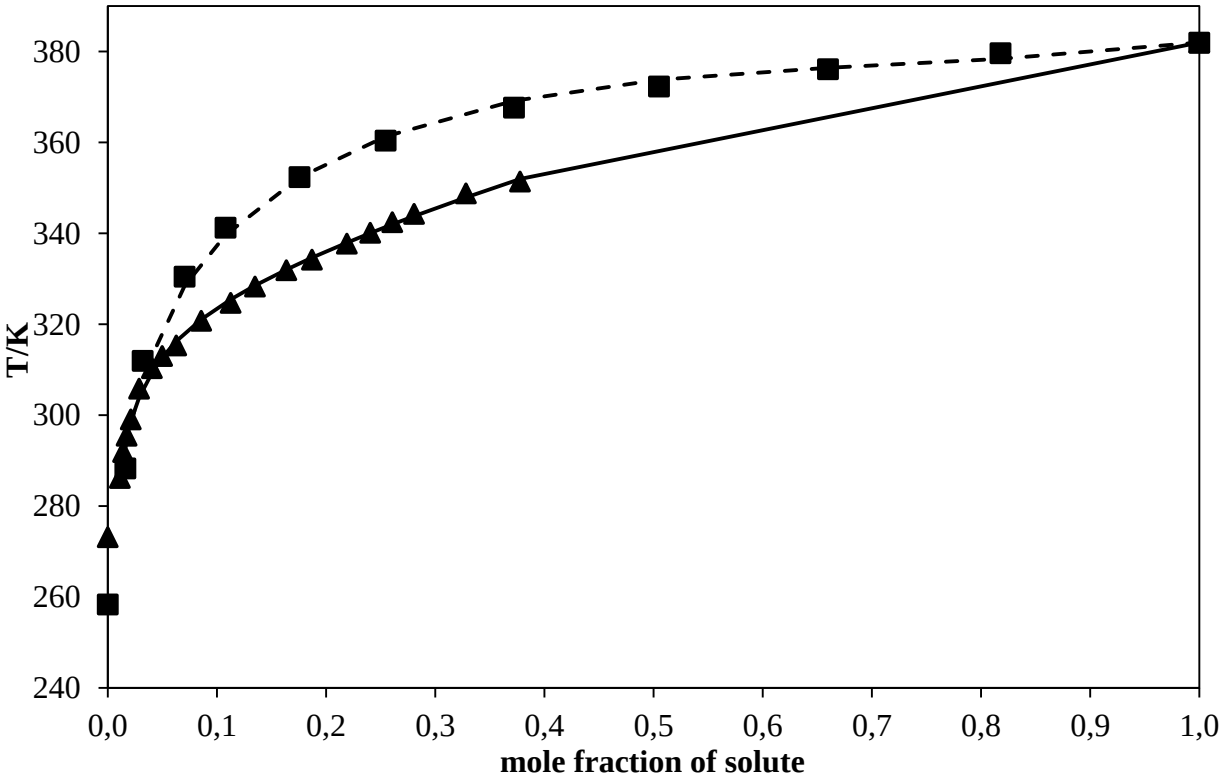


Figure 3.19. Comparison of solubilities of N-acetyl-L-cysteine in water (▲), or 1-octanol (■). Points represent the experimental results. The solid line demonstrates the correlation by the NRTL equation. The dashed line demonstrates the correlation by the NRTL 2 equation.

Table 3.8. Correlation of the Solubility Data, SLE, of coumarin (1) + a solvent (2) by Wilson, UNIQUAC, UNIQUAC ASM, NRTL, NRTL 1, and NRTL 2 Equations: Values of Parameters and Deviations

	Parameters						Deviations					
	Wilson	UNIQUAC	UNIQUAC ASM	NRTL	NRTL 1	NRTL 2	Wilson	UNIQUAC	UNIQUAC ASM	NRTL	NRTL 1	NRTL 2
	$g_{12}-g_{22}$ $g_{21}-g_{11}$	Δu_{12} Δu_{21}	Δu_{12} Δu_{21}	Δg_{12} Δg_{21}	Δg_{12} Δg_{21}	Δg_{12} Δg_{21}	σ_T[b]	σ_T[b]	σ_T[a]	σ_T[a]	σ_T[a]	σ_T[a]
Solvent	$J\cdot mol^{-1}$	$J\cdot mol^{-1}$	$J\cdot mol^{-1}$	$J\cdot mol^{-1}$	$J\cdot mol^{-1}$	$J\cdot mol^{-1}$	K	K	K	K	K	K
[C_2mim][Otf]	1958.47	-216.61	3362.09	5692.83	6855.70	1933.67	2.34	2.41	0.95	0.89[i]	0.90[g]	0.93[m]
	677.20	875.92	-1841.76	-1776.32	-2299.86	-915.02						
[C_4mim][Otf]	3126.28	-1156.88	-1331.74	-1611.97	-38470.10	-24409.99	0.73	0.81	2.84	1.68[m]	0.91[b]	2.37[b]
	-1558.86	1906.39	1532.69	1256.50	30165.90	26883.45						
[C_2mim][Ntf_2]	-870.16	339.23	-1140.19	1571.21	-24232.78	-862.53	3.79	3.87	0.94	0.75[c]	0.84[b]	0.90[l]
	632.38	-460.54	675.46	-4733.684	13448.83	361.21						
[C_4,mim][Ntf_2]	-1710.34	801.28	-1568.23	-1712.62	-3516.09	-2145.49	1.65	1.91	0.45	0.44[k]	0.45[h]	0.44[h]
	1355.52	-1005.23	1166.90	-1972.18	-444.60	2268.27						
[C_6mim][Ntf_2]	-1899.38	28.57	-1355.86	833.00	-30063.77	-1117.48	1.84	2.22	0.56	0.43[e]	0.48[b]	0.53[j]
	1426.80	-1087.89	707.20	-5302.60	12392.19	436.82						
[C_{10}mim][Ntf_2]	-1366.84	268.03	-2150.18	1985.03	-43290.45	-1307.54	0.46	0.48	0.54	0.41[d]	0.39[b]	0.48[m]
	-965.61	-739.59	2042.09	-7753.08	15146.32	777.31						
1-Octanol	4854.84	-279.77	493.17	3823.20	4424.74	405.40	2.56	3.91	1.20	0.71[j]	0.67[k]	1.19[b]
	3002.29	1945.67	531.08	2383.94	2491.81	571.00						
Water			14211.18	168.07		1422.69			4.01	3.23[f]		3.29[k]
			2862.34	8741.23		5176.03						

[a]According to the equation

$$\sigma_T = \sum_{i=1}^{n} \frac{T_i^{exp} - T_i^{cal}\ ^2}{n-2}^{1/2}$$

[b]Calculated with the third non randomness parameter α =0.01. [c]Calculated with the third non randomness parameter α =0.05. [d]Calculated with the third non randomness parameter α =0.1. [e]Calculated with the third non randomness parameter α =0.15. [f]Calculated with the third non randomness parameter α =0.2. [g]Calculated with the third non randomness parameter α =0.35. [h]Calculated with the third non randomness parameter α =0.45. [i]Calculated with the third non randomness parameter α =0.55. [j]Calculated with the third non randomness parameter α =0.7. [k]Calculated with the third non randomness parameter α =0.75. [l]Calculated with the third non randomness parameter α =0.8. [m]Calculated with the third non randomness parameter α =1.

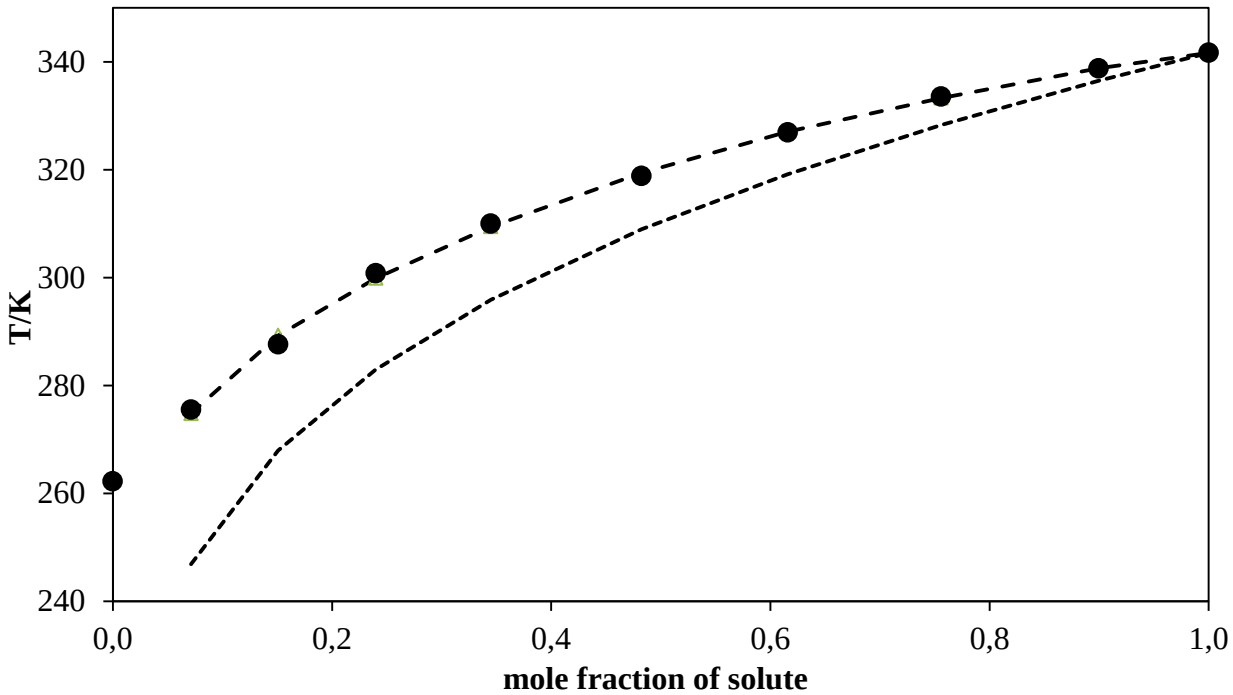


Figure 3.20. Solubility of coumarin in [C_2mim][Otf]. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL equation. The dotted line represents the ideal solubility.

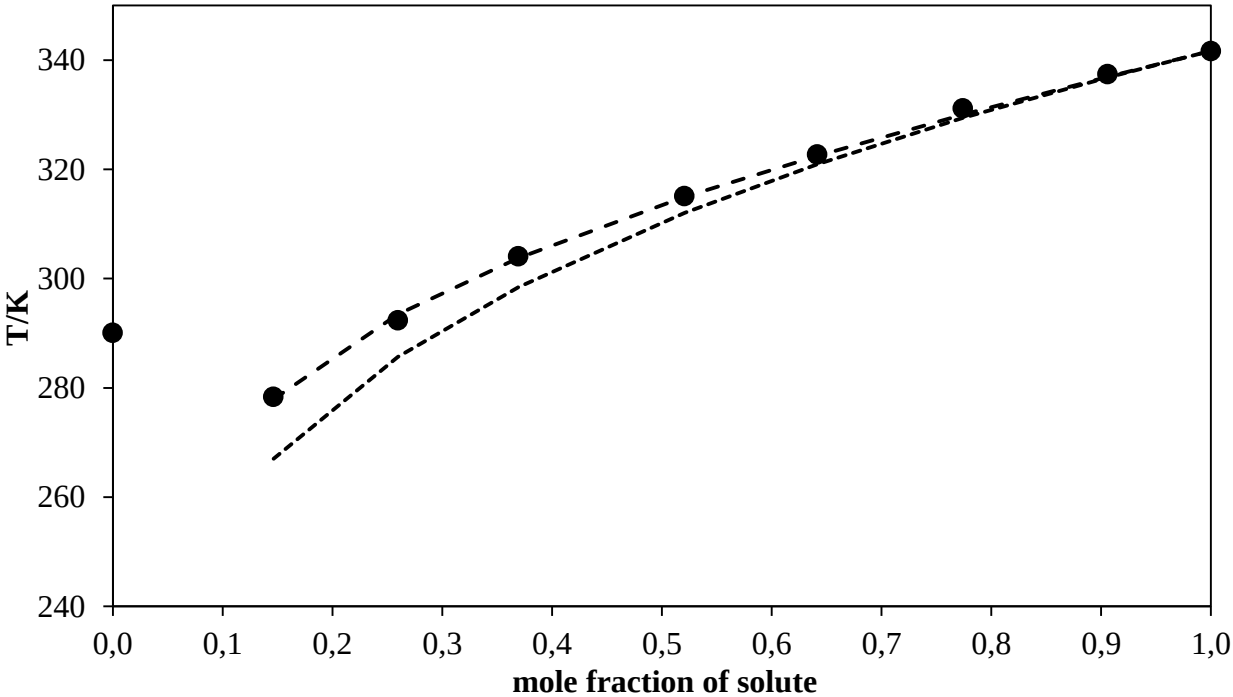


Figure 3.21. Solubility of coumarin in [C_4mim][Otf]. Points represent the experimental results. The dashed line demonstrates the correlation by the Wilson equation. The dotted line represents the ideal solubility.

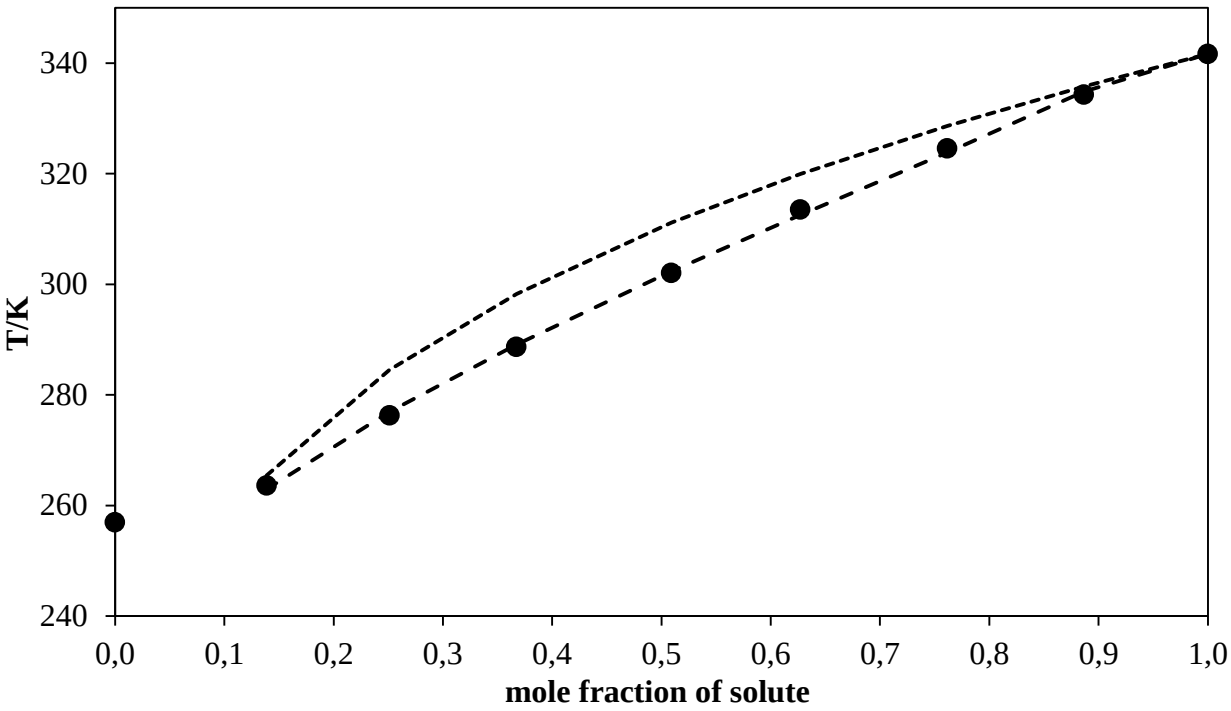


Figure 3.22. Solubility of coumarin in [C_2mim][Ntf_2]. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL equation. The dotted line represents the ideal solubility.

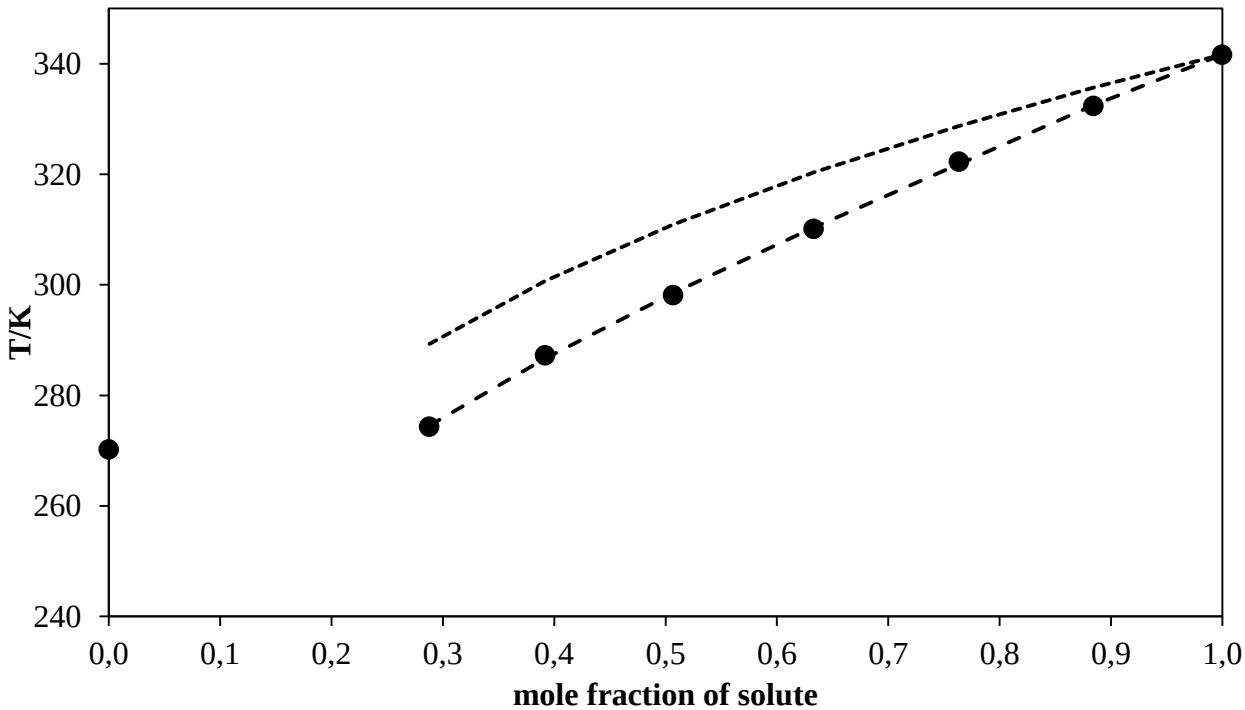


Figure 3.23. Solubility of coumarin in [C_4mim][Ntf_2]. Points represent the experimental results. The dashed line demonstrates the correlation by the UNIQUAC ASM equation. The dotted line represents the ideal solubility.

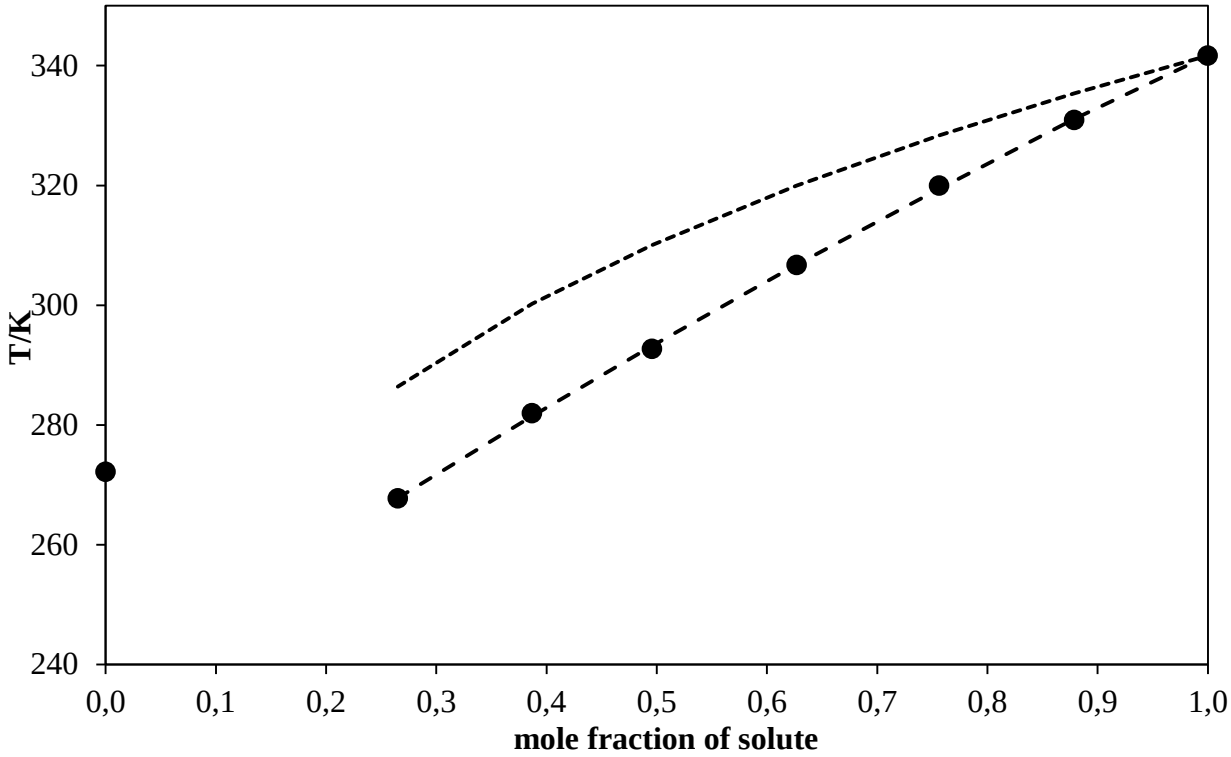


Figure 3.24. Solubility of coumarin in [C_6mim][Ntf_2]. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL equation. The dotted line represents the ideal solubility.

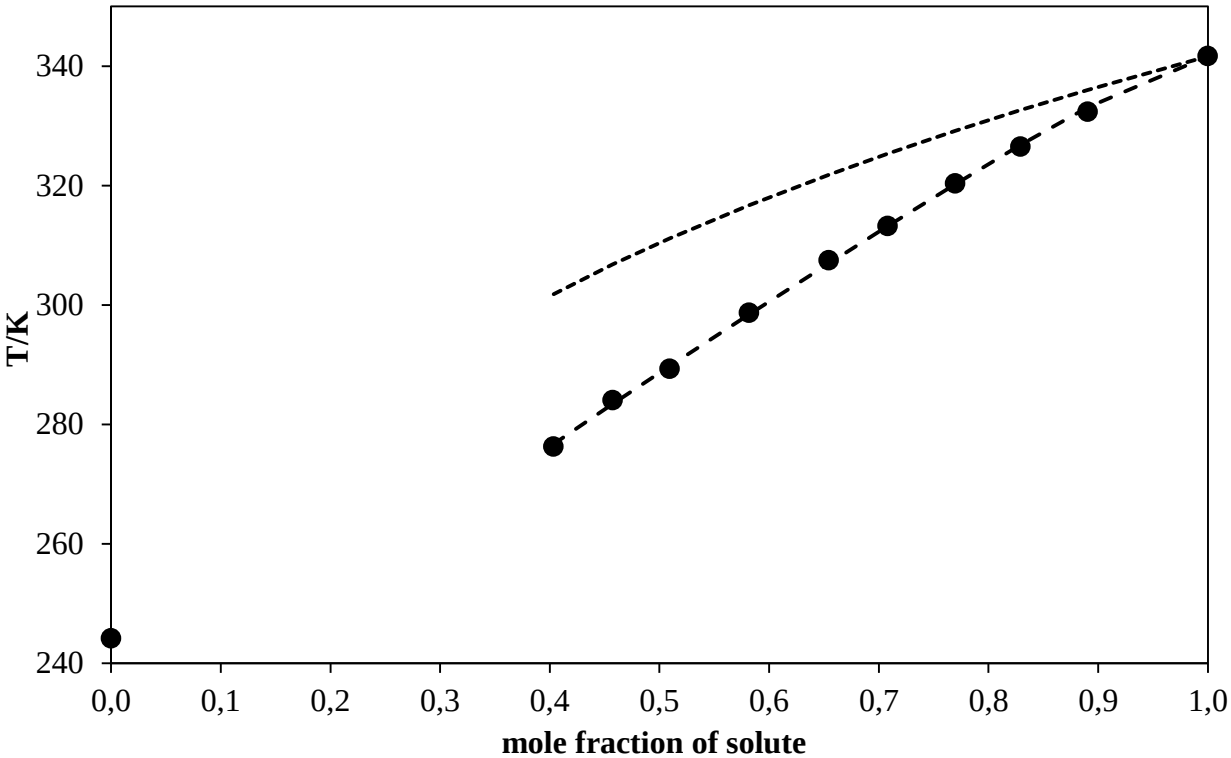


Figure 3.25. Solubility of coumarin in [C_{10}mim][Ntf_2]. Points represent the experimental results. The dashed line demonstrates the correlation by the UNIQUAC equation. The dotted line represents the ideal solubility.

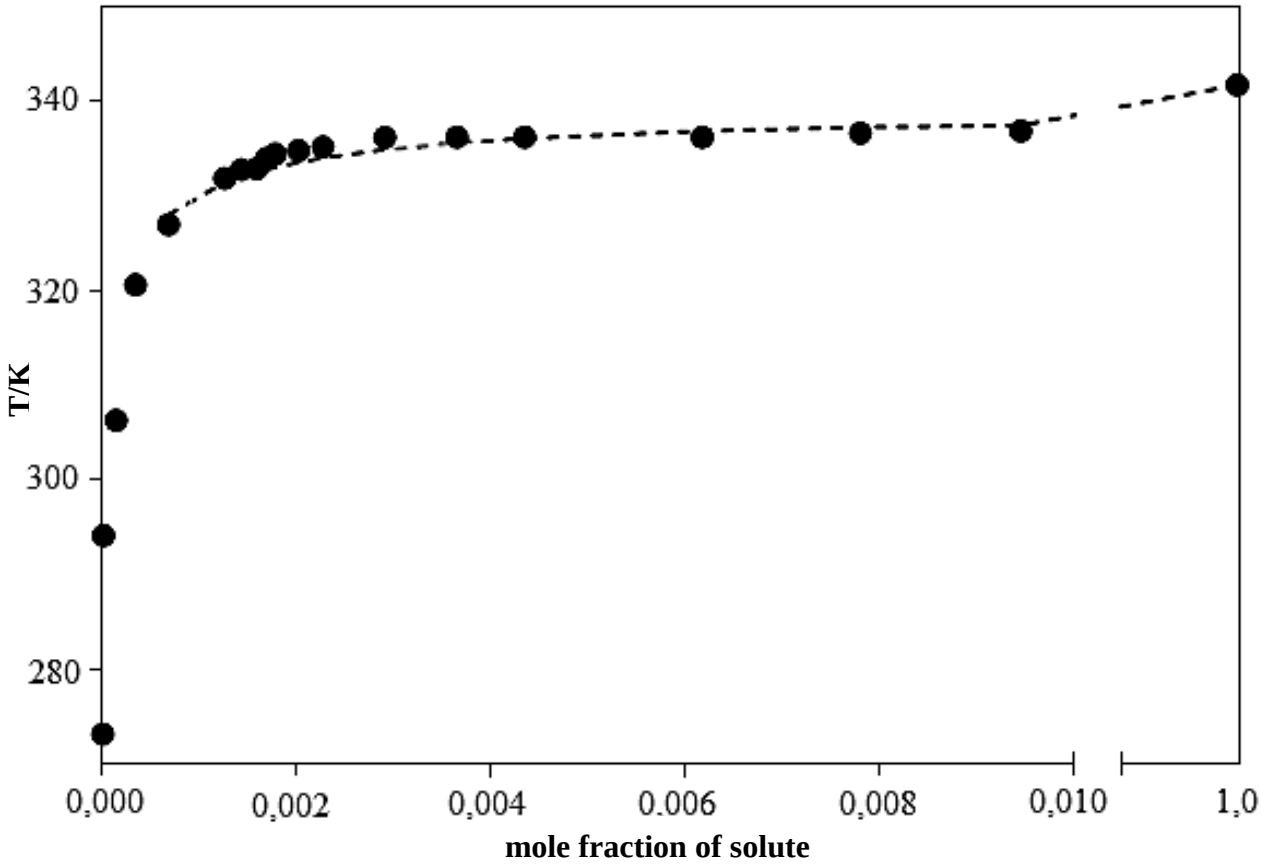


Figure 3.26. Solubility of coumarin in water. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL equation.

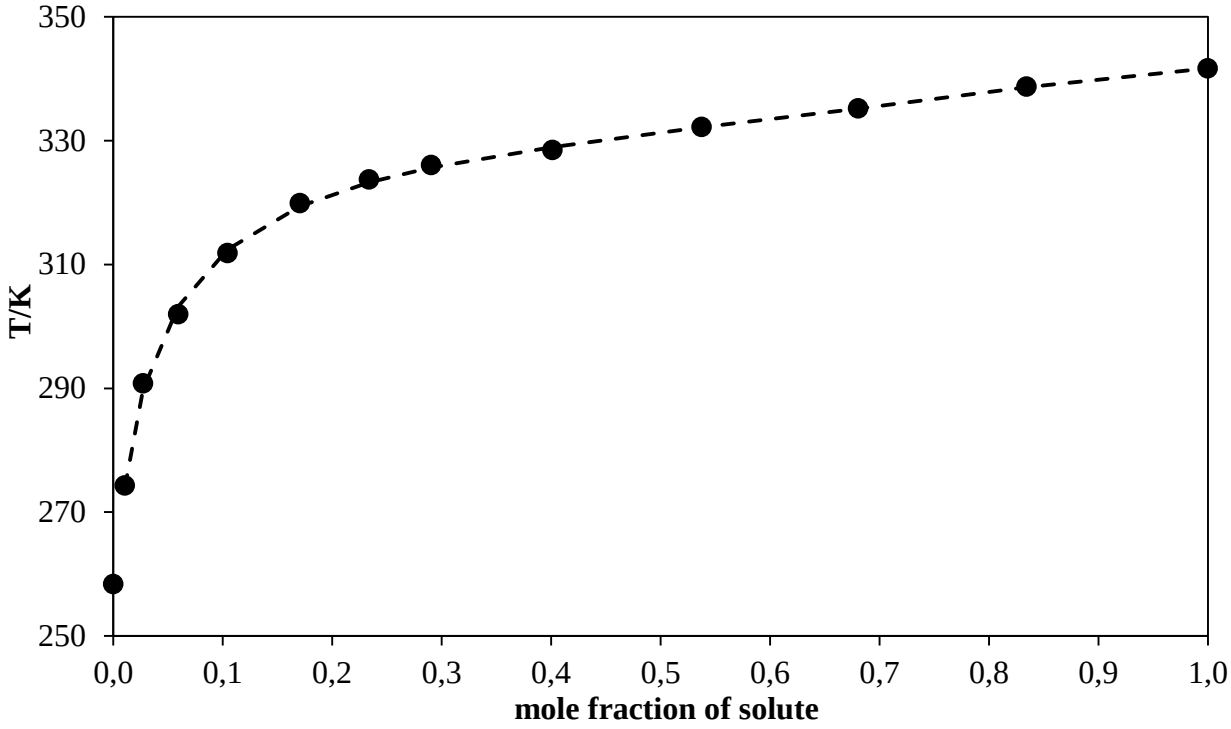


Figure 3.27. Solubility of coumarin in 1-Octanol. Points represent the experimental results. The dashed line demonstrates the correlation by the NRTL 1 equation.

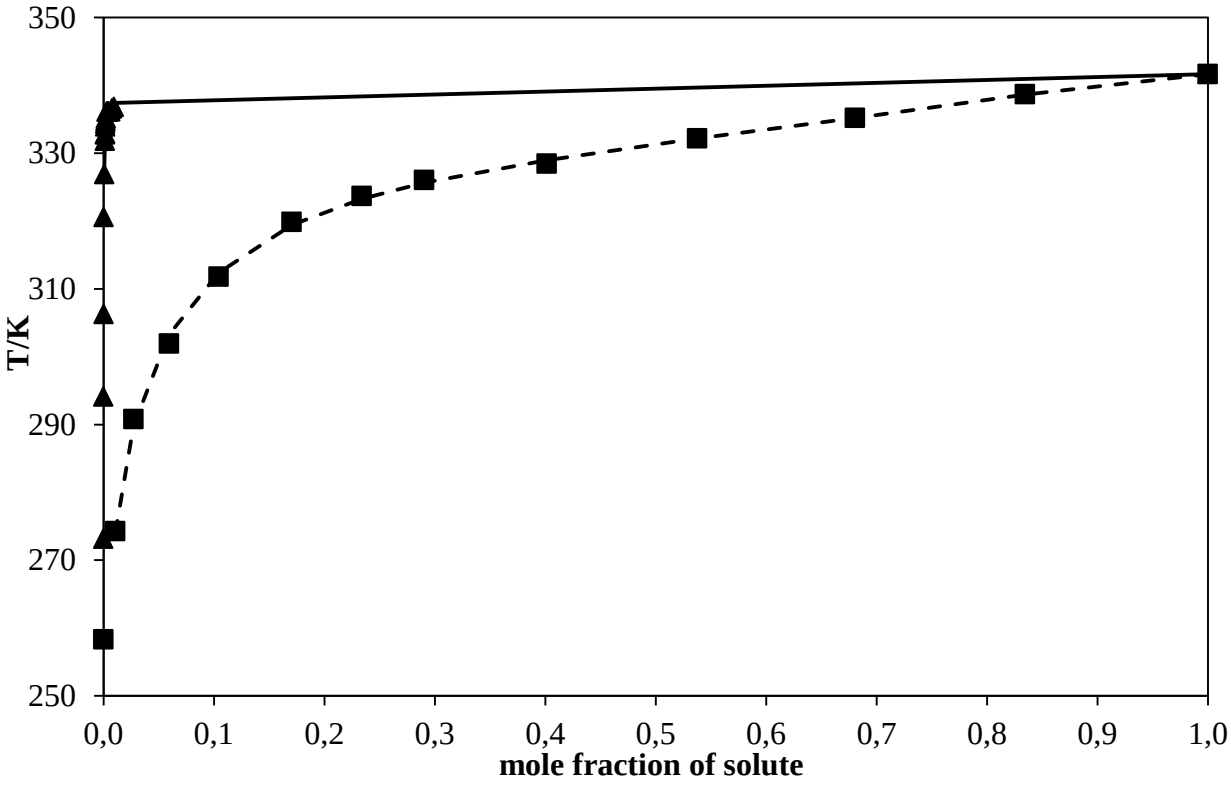


Figure 3.28. Comparison of solubilities of coumarin in water (▲), or 1-octanol (■). Points represent the experimental results. The solid line demonstrates the correlation by the NRTL equation. The dashed line demonstrates the correlation by the NRTL 1 equation.

4-hydroxycoumarin and N-acetyl-L-cysteine are hydrophilic drugs, with NAC being the most hydrophilic one. As expected, positive deviations from ideality (γ>1) were found for systems with [Ntf_2] ionic liquids, where the activity coefficients of solutes are very high (even higher than 8). The values of activity coefficients of solutes for [Otf] ionic liquids are significantly lower than for [Ntf_2] ionic liquids, but in some cases for NAC are still above 1. This can be explained by the fact that the interaction between the solute and solvent are stronger resulting in a higher solubility of NAC in the studied ionic liquid.

As predicted, coumarin exhibits the opposite behaviour due to its hydrophobic character. Negative deviations from ideality were found for systems with [Ntf_2] ionic liquids and the activity coefficient of solute, γ_1 is lower than 1.

Considering the correlation of the experimental results, the average standard deviation (σ_T) ranged from 0.34 to 6.11 K. Taking into account the complexity of systems studied here and the assumption related to the association constants of the examined drugs, the correlation equations gave acceptable σ_T.

3.5. 1-Octanol/water partition coefficient

The experimental results for five temperatures are reported in Table 3.9.

Table 3.9. Solubilities and experimental data for the partition coefficient at 288.15, 298.15, 308.15, 318.15 and 328.15 K.

Substance	x_1^o	x_1^w	c_1^{o*} [mol·dm^{-3}][a]	c_1^{w*} [mol·dm^{-3}][b]	P	$logP$
			288.15 K			
NAC	0.0150	0.0124	0.0950	0.6484	0.1465	-0.8342
COU	0.0146	0.000029	0.0923	0.0016	57.1220	1.7568
			298.15 K			
NAC	0.0183	0.0184	0.1165	0.9327	0.1249	-0.9034
COU	0.0353	0.000098	0.2234	0.0054	41.4015	1.6170
			308.15 K			
NAC	0.0291	0.0364	0.1847	1.6966	0.1089	-0.9630
COU	0.0559	0.0002	0.3518	0.0130	27.0679	1.4325
			318.15 K			
NAC	0.0496	0.0729	0.3127	2.9259	0.1069	-0.9712
COU	0.1076	0.0004	0.6704	0.0233	28.7164	1.4581
			328.15 K			
NAC	0.0829	0.1341	0.5240	4.3804	0.1196	-0.9222
COU	0.2616	0.0011	1.6260	0.0613	26.5463	1.4240

[a]Calculated with the density of 1-octanol equal to 0.8226 (288.15 K), 0.8226 (298.15 K), 0.8193 (308.15 K), 0.8085 (318.15 K) and 0.8013 (328.15 K)[56]. [b]Calculated with the density of water equal to 0.9991 (288.15 K), 0.997 (298.15 K), 0.994 (308.15 K), 0.9902 (318.15 K) and 0.9857 (328.15 K)[57]. The densities of subcooled solutes at 298.15 K (molar volumes in the text) were assumed to be constant at three temperatures.

It is evident that the low aqueous solubility of 1-octanol has a negligible influence on the aqueous solubility of drugs. On the other hand, the rather large amount of water present in the 1-octanol phase ("solute-free"), changes considerably the drugs solubility in the 1-octanol phase even if a simple linear dependence of solubility for binary "solute free" solvent was assumed. Corresponding values of the drugs solubilities in mutually saturated solvent as a molar concentration in water-saturated 1-octanol, are given in Table 3.9. The solute partition coefficient of drugs was shown to be less than one in N-acetyl-L-cysteine, and higher than one in coumarin.

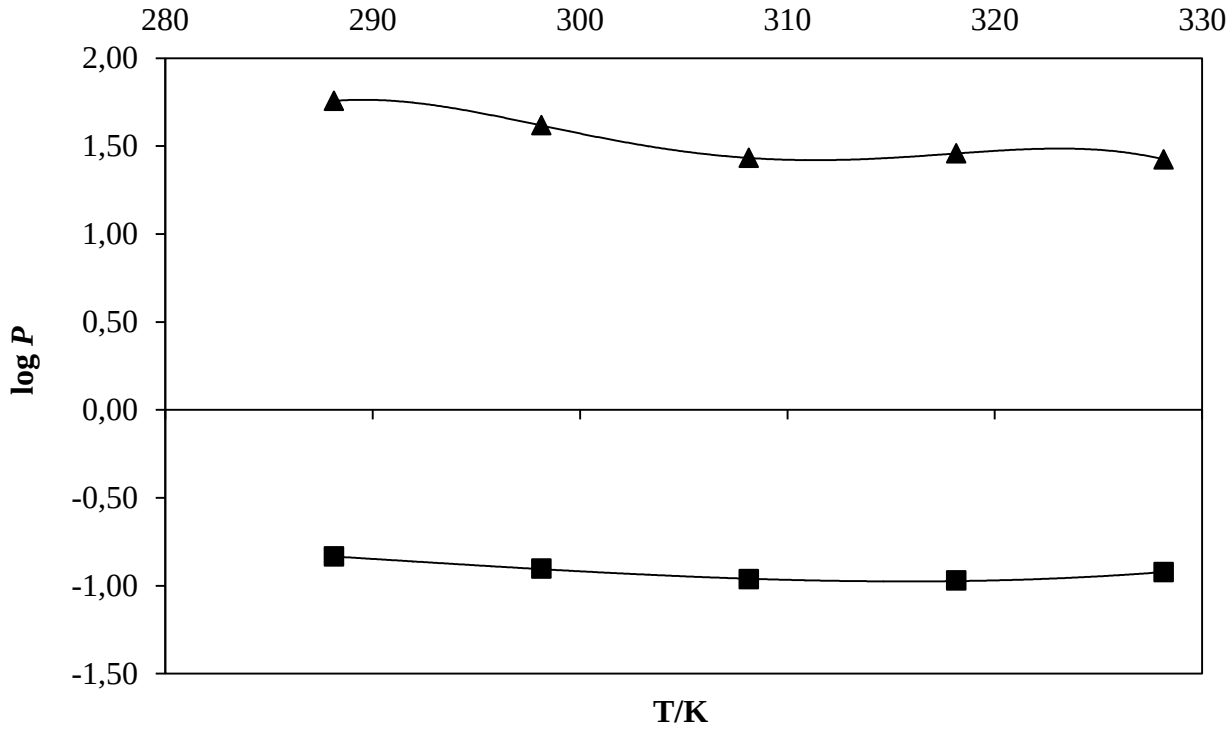


Figure 3.29. Log P as a function of the temperature for (♦)Coumarin and (▲)N-acetyl-L-cysteine. The solid lines are calculated by means of polynomials.

While hydrophilic molecules tend to remain in the aqueous phases and hydrophobic molecules tend to go into the lipid bilayer, for efficient transport, the drug must be hydrophobic enough to partition into the lipid bilayer, but not so hydrophobic, that once it is in the bilayer, it will not partition out again (optimal hydrophilic-lipophilic balance).[58]

Hydrophobic molecules tend to present high octanol/water partition coefficient, while hydrophilic molecules have low octanol/water partition coefficient, which can be seen in Figure 3.29.

Coumarin have high partition coefficient, which is considered favourable for the rapid absorption of compounds once they are in aqueous solution. This coupled with the fact that coumarin is non-polar, suggests that in theory coumarin should cross lipid bilayers easily by passive diffusion.[59]

On the other hand, the solvents used should not have high partition coefficient (in order not to be retained in the lipid bilayer). Several studies in bioaccumulation of ionic liquid have been performed, and many present high partition coefficient[60,61,62] but not all[61,63]. This means that

special care must be taken to design ionic liquids with increased biodegradabilities and so still propose compounds that can be viewed as sustainable.

Table 3.10. Properties of used drugs and solvents.

	Melting Point T_{fus} (T/K)	Enthalpy of fusion $\Delta_{fus}H$ (kJ·mol^{-1})	Molar Volume V_m (cm^3·mol^{-1})	Molar Mass MM (g·mol^{-1})
4-hydroxycoumarin	488.30	24.49	112.13	162.14
N-acetyl-L-cysteine	381.99	32.10	126.11	163.19
Coumarin	341.68	19.54	156.30	146.14
[C_2mim][Otf]	262.23	-	187.20	260.23
[C_4mim][Otf]	290.10	-	223.58	288.29
[C_2mim][Ntf_2]	256.91	-	257.90	391.31
[C_4mim][Ntf_2]	270.22	-	292.40	419.36
[C_6mim][Ntf_2]	272.13	-	326.20	447.42
[C_{10}mim][Ntf_2]	244.15	-	404.00	503.53
1-Octanol	258.35	-	158.31	130.23
Water	273.15	-	18.07	18.02

4. Conclusions

Data on solubilities of N-acetyl-L-cysteine (antioxidant), coumarin, and 4-hydroxycoumarin (anticoagulants) in ionic liquids: four with the bis(trifluoromethylsulfonyl)imide anion and two with trifluoromethanesulfonate, are collected in this work. The provided solubility data are in the satisfactory range of solubilities[64] permitting to conclude that: (1) the studied ionic liquids are appropriate solvents for drug manufacturing and (2) such solvents can be suitable for pharmaceutical processing.[20,21,64,65] The binary systems composed of drugs and an ionic liquid yield solid–liquid phase equilibrium with the eutectic point shifted towards ionic liquid-rich solutions. We sought to discover the best solvent amongst the analysed ionic liquids. The trifluoromethanesulfonate ionic liquid [C_2mim][Otf] was found to be the best solvent for the hydrophilic drugs, N-acetyl-L-cysteine and 4-hydroxycoumarin. And in the case of Coumarin, the best solvent was [C_{10}mim][Ntf_2].

Analysing solubilities obtained in the case of the bis(trifluoromethylsulfonyl)imide ionic liquids, it can be noticed that the solubility of the studied drugs decreases with an increase of the alkyl chain in the cation of the ionic liquid for N-acetyl-L-cysteine and 4-hydroxycoumarin, but have the opposite behaviour in Coumarin. Solid–liquid phase equilibrium were described using six different correlation equations (Wilson, UNIQUAC, UNIQUAC ASM, NRTL, NRTL 1 and NRTL 2), which allowed for a good description, with the standard deviation of temperature in the range of 0.34-6.11K for the examined systems. Thermophysical properties of the studied drugs determined by the differential scanning calorimetry technique are in good agreement with the literature data.

The favourable solubilities in alternative solvents obtained within this study for the investigated drugs, accompanied by the above mentioned beneficial properties of ionic liquids, can allow ionic liquids compete in a “safer” mode than with solvents routinely used in pharmaceutical industry.

Studies of partition coefficient of the present compounds (NAC and coumarin) were performed and showed that molecules tend to go into the lipid bilayer, therefore considered favourable for the rapid absorption of compounds.

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