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SOLUBILITY DIAGRAMS IN SOLVENT–ANTISOLVENT SYSTEMS BY TITRATION CALORIMETRY
Application to some pharmaceutical compounds in water–ethanol mixtures

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Isothermal titration calorimetry (ITC) has been used to develop a method to construct the solid-liquid equilibrium line in ternary systems containing the solute to precipitate and an aqueous mixed solvent. The method consists in measuring the heat of dissolution of a solid component (the solute) during successive additions of the liquid solvent. The cumulated heat, resulting from the successive heat peaks obtained for the different injections of known volumes of solvent, plotted *vs.* the ratio of the numbers of moles $n_{solvent}/n_{solute}$ is represented by two nearly straight lines. The intercept of the two lines gives the solubility limit and the corresponding enthalpy of dissolution of the solute in the solvent.

Solubility diagrams have been established at 303.15 K in binary mixed solvents ethanol–water over the whole concentration range for seven compounds of pharmaceutical interest, namely: urea, phenylurea, *l*-valine, *dl*-valine, *l*-valine ethyl ester hydrochloride, tris(hydroxymethyl)amino methane.

Keywords: *heat of dissolution, phenylurea, purine, solid–liquid equilibrium, solubility, ternary systems, titration calorimetry, tris(hydroxymethyl)amino methane, urea, valine*

Introduction

The present study takes place in the general approach regarding the design and the development of methods useful for the acquisition of thermodynamic data on phase equilibria in crystallization engineering. Crystallization is of particular interest since it constitutes the final step of purification of solids. Then appearance or disappearance that is precipitation or dissolution, of a crystalline form in a given solvent constitutes an accurate access to two important associated data, the solubility and the enthalpy of dissolution. Since a rigorous control of temperature is essential in solubility phenomena, isothermal experimental techniques have to be favored and construction of the phase diagram containing a solid solute and a liquid solvent is simply based on the determination of the solubility of the solid solute in the solvent. The solvent can be a pure liquid component or a liquid mixture for efficient solvent-antisolvent selective capability. The choice of optimal solvent-antisolvent systems in crystallization processes rests on the knowledge of the solid phase domain in the ternary concentration diagram of the product to precipitate in the presence of the solvent-antisolvent mixture. As a matter of fact, establishing the solubility limits of a solid compound in binary mixtures implies appropriate experimental determinations. The thermodynamic study of the whole system is focused on the determination of the maximum of solubility of the solid solute that is to say all along the solid-liquid line of the ternary system; in this way, this line which is the locus of the maximum solubility data points is readily obtained as of plot of those points. In this context we have developed a calorimetric method using isothermal titration calorimetry [1–3]. The solubility limit is determined by adding slowly (to remain at thermodynamic equilibrium) successive small increments of the binary solvent to a known (weighted) amount of the solid solute until the complete dissolution of the solid crystals. Experimental setup and associated methodology have been reported previously [1-3]. They have been used to establish ternary solid-liquid phase equilibria of vanillin, *o*-anisaldehyde and 1,3,5-trimethoxybenzene in water-alcohol binary mixtures. Phase diagrams have recently been established at 303.15 K over the whole concentration range for caffeine, nicotinamide, nicotinic acid and salicylic acid in water+ethanol binary mixtures [4].

In this work, the use of the above technique and methodology as a screening method to establish the solubility diagrams in solvent-antisolvent systems is illustrated in the case of some compounds of pharma-

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ceutical interest in water-alcohol mixtures. Solubility diagrams have been established at 303.15 K in binary ethanol-water over the whole concentration range for seven compounds, namely: urea, phenylurea, *l*-valine, *dl*-valine, *l*-valine ethylester hydrochloride, and tris(hydroxymethyl)amino methane.

Experimental

Chemicals

The chemicals belong to four different groups and it was interesting to relate their thermodynamic and solubility behavior to their individual chemical structures. The first group includes urea [carbamide, $(NH_2)_2CO$] and phenyl urea [phenyl carbamide, $C_6H_5NHCONH_2$]. Urea is known for its capacity to strongly modify the structure of water [5] and is used in numerous applications in dermatology to enhance rehydration, or in bacteriology to make specific tests for the detection of bacteria species. Phenyl urea derivatives are used among other applications as herbicides to inhibit photosynthesis [6]. The second group includes *l*-valine [*l*-2-amino-3-methylbutyric acid, $(CH_2)CHCH(NH_2)CO_2H$], *dl*-valine [*dl*-2-amino-3-methylbutyric acid, $(CH_2)CHCH(NH_2)CO_2H$] and *l*-valine ethylester hydrochloride [*l*-$(CH_3)_2CHCH(NH_2)COOCH_3{\cdot}HCl$]. *l*-valine is a very important amino acid used in human nutrition with applications to favor muscle growth or tissue repair. *dl*-valine is an anti-inflammatory also known as creatine used in different pharmaceutical applications [7, 8]. *l*-valine ethylester hydrochloride is a chemical derivative more water soluble than *l*-valine for pharmaceutical formulations. Purine [a crystalline organic base, $C_5H_4N_4$] is a significant biochemical component of DNA and RNA which belongs to the family of double-ring {6 atoms+ 5 atoms} combining N and C atoms where the rings interconnection is a C–C bond; this series includes caffeine investigated previously [4]. Tris(hydroxymethyl)amino methane [$(HOCH_2)_3CNH_2$] also known as TRIS is mostly used to prepare buffer solutions for applications is biological applications.

Urea with purity >99.5%, *l*-valine with 99% purity, *dl*-valine with 99% purity, *l*-valine ethylester hydrochloride with 99%, purine with 99% purity and tris(hydroxymethyl)aminomethane, biochemical grade p.a. with >99.8% purity respectively were provided by (Fine Chemicals) Acros Organics France. Ethyl alcohol absolute RE was provided by Carlo Erba France. All chemicals were used without further purification. Solutions were prepared by mass using freshly bidistilled water.

Method

The titration calorimeter, Titrys model, commercialized by Setaram was used to perform the solubility measurements [1–3]. The calorimeter is built according to the Calvet principle. The calorimetric block whose temperature can be regulated to ±20 mK houses two thermopiles in which are placed the measuring and reference cells respectively. The differential detection allows detecting heat effects with 0.1 μW sensitivity. The instrument can be operated in the temperature range from 303.15 to 353.15 K. In each cell an active volume from 1 up to 12 cm^3 can be used and the content of each cell can be stirred by means of a small magnetic bar activated by a single small motor which ensures the same (adjustable) stirring speed in both cells. The calorimeter can be fed with an injection system Dual Syringe Pump Model 33 from Harvard, composed of two identical syringe pumps mounted on a dual carriage in such a way that identical volumes delivered by stainless capillaries can be injected simultaneously at exactly the same rate in both cells; during each injection the corresponding heat effect is recorded. The injection system is entirely programmable and computer controlled. In order to ensure a better control of the volumes delivered by the pumps, the whole assembly, syringe pumps and their carriage/holder, were placed in a small air bath thermostated to ±50 mK. Before injection in the calorimetric cells, liquids coming from the pumps are further thermostated as the feeding capillaries are coiled in two small thermostats placed inside the calorimetric block on top of each cell.

The experimental procedures and data handling were the same as in previous publications [1–3]. An initial mass, 0.05–2.50 g depending on the type of solid, of finely hand-ground (in a mortar) crystallized powder was placed in the measuring cell. The two syringe pumps were filled with the same water-alcohol solution of known composition. A dissolution run consists in adding the same volume of the solution simultaneously in both cells. The heat repeatedly evolved during each addition, due to the heat of dissolution of part of the solid in the small amount of added solution, was recorded. Typically, at each injection 0.20 cm^3 of solution was added at the rate of 0.10 cm^3 min^{-1} and a complete run was achieved after an average of 10 successive additions. The volume for an injection may vary from 0.04 to 2.00 cm^3 of solution at the rate between 0.02 and 0.70 cm^3 min^{-1}. Each run produces a series of heat peaks *vs.* time. The cumulative sums ΔH of heat effects (the actual total peak areas) divided by n_1 ($n_1=n_{solute}$, initial number of moles of solute) were plotted *vs.* $\alpha=n_{solvent}/n_{solute}$ which represents the ratio

of the number of moles of solvent to the number of moles of the solute. Each dissolution/dilution run yields a plot of $\Delta H/n_1$ *vs.* α. Typically this type of plot is composed of two parts, an initial linear part associated to the dissolution of the solute and corresponding to $\Delta H/n_1=A_1\alpha$; then, when the entire solid has been completely solubilized, the second part which is only related to the heat of dilution of the medium is generally well represented by a polynomial of the form:

$$\Delta H/n_1 = A_0' + A_1'\alpha + A_2'\alpha^2 \quad (1)$$

The coefficients A_1, A_0', A_1', A_2' were determined by linear regression. The intercept of the two parts gives the enthalpy of dissolution for the ratio α_s at saturation, according to Eq. (2):

$$A_1\alpha_s = A_0' + A_1'\alpha_S + A_2'\alpha_S^2 \quad (2)$$

From α_s at saturation, the composition of the ternary system at saturation can be determined. Remarkably, when $\alpha=\alpha_S$ the heat of dissolution in the mixed binary solvent, that is the enthalpy of solution at saturation, is given by the ordinate of the intercept in the plot of $\Delta H/n_1$ *vs.* α [1].

The dissolution/dilution runs were made in such a way as to cover the whole concentration of the binary aqueous mixture. Then a ternary plot (x_1, x_2, x_3) can be constructed where the three mole fractions are the actual experimental mole fractions corresponding to the individual coordinates of the different intercepts.

Results and discussion

For the different investigated systems the experimental mole fractions x_1, x_2 and x_3, representing component 1, the solid solute, component 2, water (H_2O), and component 3, ethanol (EtOH), respectively are listed in Table 1. Graphical representations of the measured data are shown in Figs 1–4. In these figures the smoothed curves have been obtained through the procedure described previously [1, 2].

Firstly, a plot of x_1 *vs.* x_2 was fitted with the following polynomial y:

$$y = x_1 = f(x_2) = \sum_{i=0}^{n} a_i (1 - x_2)^i \quad (3)$$

Coefficients a_1 were adjusted to give the best fit. Secondly, using polynomial y a table of numerical values X_3 was generated as a function of X_2, $X_3=f(X_2)$, at rounded values of X_2 (e.g. $0\le X_2\le 1$ at 0.05 increments) using the relation: $X_3=1-x_1-X_2$, where $x_1=y=f(X_2)$ as given by Eq. (3) and $x_1+X_2+X_3=1$.

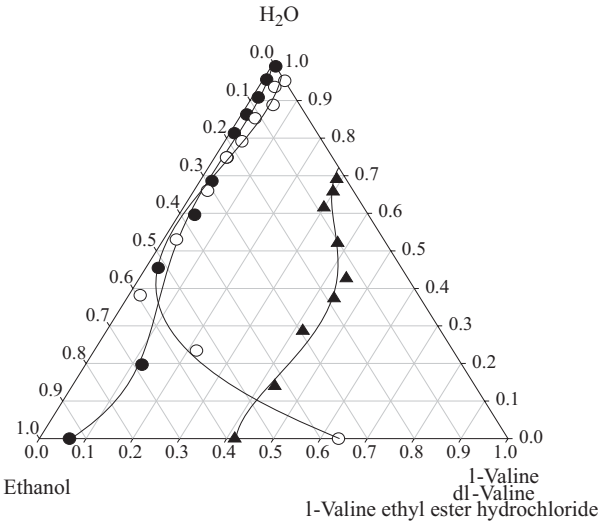

Fig. 1 Ternary plots for the three systems valine (1)+ water (2)+ethanol (3) at 303.15 K: • – *l*-valine; ○ – *dl*-valine; ▲ – *l*-valine ethyl ester hydrochloride. The fitting curves represent Eq. (4), with coefficients of Table 2

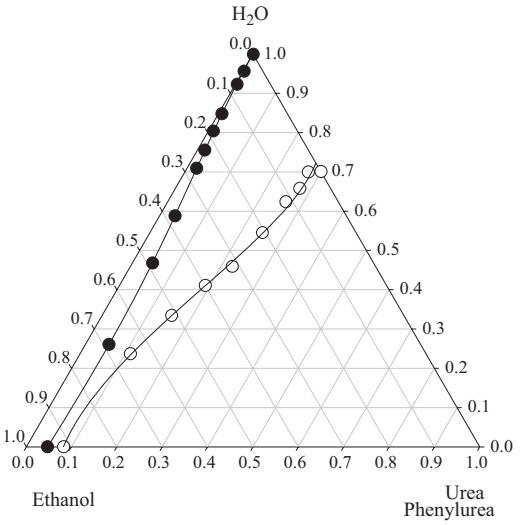

Fig. 2 Ternary plots for the two systems urea (1)+water (2)+ ethanol (3) at 303.15 K: ○ – urea; • – phenylurea. The fitting curves represent Eq. (4), with coefficients of Table 2

This 'normalization' step allows then to draw the smoothed curves in Figs 1–4. Equation (3) is the actual fitting equation of the experimental data points. Coefficients a_1 and corresponding standard deviations σ are listed in Table 2. The best fit has been obtained using a SigmaPlot software which gives the solubility maximum of the solid in the optimal composition of the aqueous mixture as listed Table 3.

As expected from their chemical structures urea and phenylurea exhibit different solubility behavior in water-ethanol mixtures; urea more water

Table 1 Experimental mole fractions at 303.15 K of the different components in the ternary systems corresponding to the data points in Figs 1 to 4

Urea (1)+H_2O (2)+EtOH (3)			Phenylurea (1)+H_2O (2)+EtOH (3)		
x_1	x_2	x_3	x_1	x_2	x_3
0.2994	0.7006	0.0000	0.0011_4	0.9989	0.0000
0.2721	0.6995	0.0284	0.0019_4	0.9562	0.0419
0.2741	0.6578	0.0681	0.0033_5	0.9232	0.0737
0.2602	0.6237	0.1161	0.0072_7	0.8479	0.1448
0.2479	0.5451	0.2070	0.0106	0.8038	0.1856
0.2247	0.4592	0.3161	0.0162	0.7552	0.2286
0.1892	0.4107	0.4002	0.0210	0.7094	0.2696
0.1532	0.3346	0.5122	0.0338	0.5881	0.3782
0.1114	0.2368	0.6519	0.0448	0.4679	0.4873
0.0823	0.0000	0.9177	0.0521	0.2607	0.6872
			0.0494	0.0000	1.0000
Purine (1)+H_2O (2)+EtOH (3)			*l*-Valine (1)+H_2O (2)+EtOH (3)		
0.0744	0.9526	0.0000	0.0088_9	0.9911	0.0000
0.0660	0.8410	0.0930	0.0073_5	0.9557	0.0369
0.0686	0.7599	0.1715	0.0128	0.9085	0.0787
0.0590	0.6730	0.2680	0.0112	0.8627	0.1260
0.0600	0.5800	0.3600	0.0267	0.4544	0.5189
0.0640	0.3240	0.6120	0.0098_5	0.8130	0.1771
0.0440	0.0000	0.9560	0.0265	0.7485	0.2250
			0.0257	0.6856	0.2888
			0.0336	0.5956	0.3707
			0.1211	0.1965	0.6823
			0.0645	0.0000	0.9355
dl-Valine (1)+H_2O (2)+EtOH (3)			*l*-Valine ethyl ester hydrochloride (1)+H_2O (2)+EtOH (3)		
0.0474	0.9526	0.0000	0.2889	0.6911	0.0200
0.0344	0.9361	0.0295	0.2982	0.6574	0.0444
0.0547	0.8885	0.0568	0.2998	0.6154	0.0848
0.0341	0.8527	0.1132	0.3763	0.5206	0.1031
0.0365	0.7916	0.1720	0.4418	0.4266	0.1316
0.0255	0.7483	0.2262	0.4421	0.3732	0.1847
0.0290	0.6600	0.3110	0.4191	0.2865	0.2943
0.6384	0.0000	0.3616	0.4326	0.1398	0.4276
0.0276	0.5302	0.4422	0.4169	0.0000	0.5831
0.2180	0.2340	0.5470			
0.0247	0.3814	0.5939			
Tris(hydroxymethyl)aminomethane (1)+H_2O (2)+EtOH (3)					
0.1000	0.9000	0.0000			
0.1220	0.7940	0.0840			
0.1350	0.6910	0.1740			
0.1350	0.6050	0.2600			
0.1470	0.3850	0.4680			
0.2400	0.0000	0.7600			

Table 2 Coefficients of the fitting Eq. (3) and corresponding standard deviations σ used to represent the smoothed curves in Figs 1 to 4

Systems	a_0	a_1	a_2	a_3	a_4	σ
Urea+H_2O+EtOH		2.1141	–5.0395	3.9457	–0.9384	0.0115
Phenylurea+H_2O+EtOH		0.0038	0.3759	–0.5353	0.2026	0.0009
Purine+H_2O+EtOH	0.772	–0.0362	–0.1785	0.5487	–0.3671	0.0039
l-Valine+H_2O+EtOH	–0.0014	0.3310	–1.8003	3.6295	–2.0922	0.0129
dl-Valine+H_2O+EtOH	0.0201	0.5010	–2.7341	3.9716	–1.1179	0.0206
l-Valine ethyl ester hydrochloride+H_2O+EtOH	0.8168	–5.0322	15.6111	–18.0971	7.1210	0.0201
Tris(hydr)am.meth+H_2O+EtOH	0.0572	0.5530	–1.4257	1.5386	–0.4831	0.0027

Table 3 Mole fractions of the 3 components in each ternary system corresponding to the maximum of solubility at 303.15 K of the solid solute in the optimal composition of the binary aqueous mixture

Systems	x_1 (max)	X_2 (H_2O)	X_3 (EtOH)
Urea+H_2O+EtOH	0.2799	0.6800	0.0401
Phenylurea+H_2O+EtOH	0.0526	0.2200	0.7274
Purine+H_2O+EtOH	0.0734	0.9200	0.0066_0
l-Valine+H_2O+EtOH	0.1165	0.1600	0.7235
dl-Valine+H_2O+EtOH	0.6407	0.0000	0.3593
l-Valine ethyl ester hydrochloride+ H_2O+EtOH	0.4155	0.4461	0.3000
Tris(hydr)am.meth+H_2O+EtOH	0.2400	0.0000	0.7600

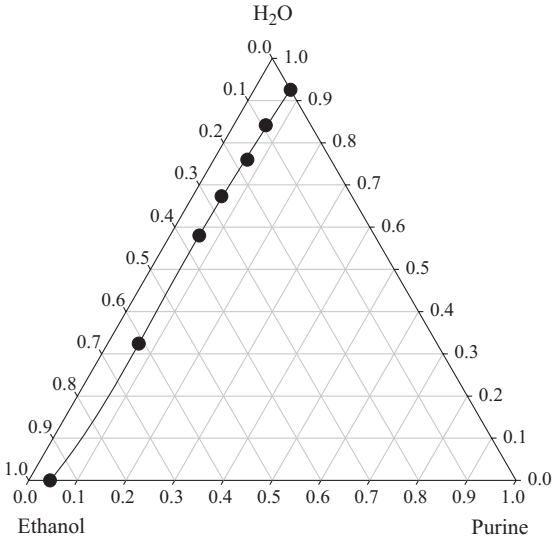

Fig. 3 Ternary plot for the system purine (1)+water (2)+ ethanol (3) at 303.15 K, • – The fitting curve represents Eq. (4), with coefficients of Table 2

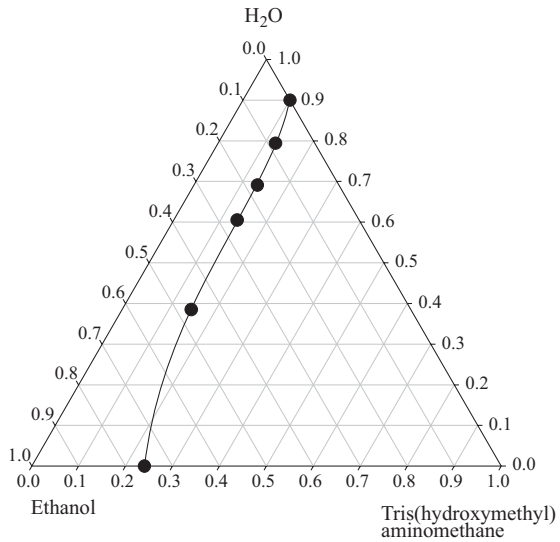

Fig. 4 Ternary plot for the system tris(hydroxymethyl) aminometane (1)+water (2)+ethanol (3) at 303.15 K, • – The fitting curve represents Eq. (4), with coefficients of Table 2

compatible is easily solubilized in the mixed solvent in which the ethanol concentration is rather small, whereas the aromatic ring of phenylurea significantly lowers its solubility and much alcohol is then necessary. Interestingly, molecular conformation plays an important role in solubilization/crystallization of valine; the racemic *dl*-form is much more (c.a. six times) soluble than the *l*-form in ethanol. Understandably, the active *l*-form must be considered in its ethylester hydrochloride derivative which is more soluble for practical applications. As indicated before, purine and caffeine belong to the same structural (double-ring) molecular series; evidently

the two carbonyl groups of caffeine render this compound less soluble in water [4] whereas purine requires very small amounts of ethanol to be solubilized. Obviously as regards tris(hydroxymethyl) aminomethane, although it is slightly more soluble in ethanol than in water, it can be used for buffer solutions in water-ethanol binary mixtures over the entire concentration range including pure components (Fig. 4).

As previously quoted [4], isothermal titration calorimetry appears as a convenient technique to obtain not only a qualitative description of solid–liquid phase diagrams in ternary systems, but also precise concentrations of the components along the solid–liquid line; the fitting equations being useful analytical tools for engineering calculations.

References

1 M. H. Hamedi, B. Laurent and J.-P. E. Grolier, Thermochim. Acta, 445 (2006) 70.
2 F. Dan, M. H. Hamedi and J.-P.E. Grolier, J. Therm. Anal. Cal., 85 (2006) 531.
3 M. H. Hamedi and J.-P.E. Grolier, Scientific Study and Research, VII (2006) 833.
4 M. H. Hamedi, L. Pison and J.-P.E. Grolier, J. Therm. Anal. Cal., (2007) (in press).
5 M. D'Alagni and B. Pispisa, J. Biol. Chem., 244 (1969) 5843.
6 V. Librando, S. R. Sarpietro, C. Cascone, Z. Minniti and F. Castelli, Environ. Chem., 2 (2005) 63.
7 N. K. Khanna and B. R. Madam, Arch. Int. Pharmacodyn. Ther., 231 (1978) 340.
8 S. B. Macedo, L. R. Ferreira, F. F. Perazzo and J. C. Carvalho, Homeopathy, 93 (2004) 84.

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