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Mathematical representation of solubility of amino acids in binary aqueous-organic solvent mixtures at various temperatures using the Jouyban-Acree model

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Applicability of a solution model for calculating solubility of amino acids in binary aqueous-organic solvent mixtures at various temperatures was shown. The accuracy of the proposed model was evaluated by computing mean percentage deviation (MPD) employing available solubility data of amino acids in binary solvents at various temperatures from the literature. The overall MPD ($\pm$ SD) for correlation of solubility data was 16.5 $\pm$ 8.8%. In addition, the equations calculating solubility of amino acids in binary solvent mixtures at a fixed temperature was revisited.

1. Introduction

Amino acids are the monomers of the vital biological polymers, i.e. proteins, and their physico-chemical properties are an interesting information for the biological scientists and also pharmaceutical and nutraceutical industries where amino acids are used in many processes. Amino acids are characterized by the presence of hydrophilic groups (i.e. $-COO^-$ and $-NH_3^+$) and hydrophobic backbone (-R-) with a number of polar groups for some amino acids. Both hydrophilic and hydrophobic groups compete for solvent structure organization. When an amino acid dissolves in an aqueous-organic solvent mixture, the solvent structure is affected by amino acid – water, amino acid – organic solvent and water – organic solvent interactions. Therefore, the solubility of amino acids and also peptides could be altered using mixed solvent systems. Solubility alteration would be needed in design of a suitable solvent media for solid-to-solid peptide synthesis (Ulijn et al. 2002) or precipitation of proteins and peptides from biological fluids as part of sample pre-treatments for analytical methods like liquid chromatography, and also in solubilization and/or disaggregation process of peptides and proteins. For example, it was reported that polyglutamide peptides could be solubilized by exposing the peptide to 50 : 50 mixture of trifluoroacetic acid and hexafluoroisopropanol, followed by evaporating the solvents and adding in water to make its aqueous solution by eliminating seed aggregates from peptide (Chen and Wetzel 2001). Solubility of amino acids in binary solvents is temperature dependent, and the experimental variables of solubilization and/or desolubilization process could be fine tuned by the solvent composition and temperature. For pharmaceutical protein formulations, amino acids such as glycine have been used as a stabilizer and a bulking agent for lyophilized human growth hormone (Pikal-Cleland et al. 2002). For dry powder inhalation products, amino acids like leucine have been used to enhance both the physical stability and dispersibility of the powders (Chan 2002). These products are prepared by freeze drying and spray drying which subject the solution to temperature changes. Therefore, an understanding of the solubility of amino acids in mixed solvents at various temperatures is important to facilitate the formulation development.

The basic solution model, i.e. the Jouyban-Acree model, was used to correlate different physico-chemical properties in mixed solvent systems; including the solubility of polycyclic aromatic hydrocarbons in non-aqueous binary (Acree 1995), ternary (Deng et al. 1999a) and higher order multicomponent (Deng et al. 1999b) solvent mixtures, solubility of drugs in water-cosolvent mixtures (Jouyban-Gh et al. 1999), the electrophoretic mobility of analytes in mixed solvent electrolyte systems (Jouyban-Gh et al. 2000; Jouyban et al. 2003a, 2003b), the instability rate constants of solutes in binary solvent systems (Jouyban et al. 2002b), the acid dissociation constants in water-organic solvent mixtures (Jouyban et al. 2002a), the viscosity (Oswal and Desai 2003), the dielectric constant (Jouyban et al. 2004a), surface tension (Jouyban et al. 2004b), solvatochromic parameter (Habibi-Yanghjeh 2004) of solvent mixtures and solubility of solids in binary mixtures of supercritical fluids (Jouyban et al. 2005a). Theoretical basis of the model for describing the chemical potential of solutes dissolved in mixed solvents (Acree 1992) and acid dissociation constants in aqueous-organic mixtures (Jouyban et al. 2002a) have been provided earlier. The model constants of the Jouyban-Acree model represent differences in the various solute-solvent and solvent-solvent interactions in the mixture (Acree 1992). Therefore, it should be able to calculate any physico-chemical property (P) in mixed sol-

vents, which is a function of solute-solvent and/or solvent-solvent interactions. The general form of the Jouyban-Acree model for binary solvents is:

$$\ln P_m = f_1 \ln P_1 + f_2 \ln P_2 + f_1 f_2 \sum_{i=0}^{q} K_i (f_1 - f_2)^i \quad (1)$$

where P_m, P_1 and P_2 are the numerical values of the physico-chemical property of the mixture and solvents 1 and 2, respectively, f_1 and f_2 are the volume (weight or mole) fractions of solvents 1 and 2 in the mixture and K_i represent the model constants calculated using a no intercept least square method (Jouyban-Gh and Hanaee 1997). The adopted model for representing the solubility of amino acids in binary solvent mixtures at a fixed temperature is:

$$\ln S_m = f_1 \ln S_1 + f_2 \ln S_2 + f_1 f_2 \sum_{i=0}^{q} W_i (f_1 - f_2)^i \quad (2)$$

where S denotes the solubility of amino acid, subscripts m, 1 and 2 are the mixed solvent and neat solvents 1 and 2, respectively, and W_i is the model constant. The numerical values of $\ln S_1$ and $\ln S_2$ represent solute-solvent 1 and solute-solvent 2 interactions whereas W_i represents solute-mixed solvent interactions.

Solubility of amino acids in aqueous-alcoholic solutions at 25 °C was correlated using the three-suffix Margules, the Wilson and the NRTL equations by Orella and Kirwan (1991). The authors examined the accuracy of the equations employing solubility of five amino acids in aqueous mixtures of methanol, ethanol, 1-propanol and 2-propanol and found that the Wilson model was the best with an average deviation of 15% (Orella and Kirwan 1991). A combination of the Margules residual expression with a combinatorial term based on the Flory-Huggins theory was presented by Gude et al. (1996). The latter expression described the solubility of amino acids in water + methanol to within an average deviation of 28% (Gude et al. 1996). A polynomial function of f_1 derived from Eq. (2) has been recently used to represent the solubility of DL-p-hydroxyphenylglycine sulfate in water + acetone mixtures (Ren et al. 2004). The aforementioned models calculate the solubility at a fixed temperature; however, solubility of amino acids in mixed solvents at various temperatures is required since heating/cooling is one of the most common variables in process design. A single and simple model calculating the solubility with respect to both solvent composition and temperature could provide valuable information for researchers. To the best of our knowledge, there is no such a model in the literature. In the original derivation of the Jouyban-Acree model, the term RT in which R is the molar gas constant and T is the absolute temperature of the solution, is incorporated in W_i terms. In other words, it is possible to write Eq. (2) as:

$$RT \ln S_m = f_1 RT \ln S_1 + f_2 RT \ln S_2 + f_1 f_2 \sum_{i=0}^{q} A_i (f_1 - f_2)^i \quad (3)$$

in which $A_i = RT\ W_i$. By dividing both sides to the constant value of R, considering solubility variations in neat solvents 1 and 2 at T in $S_{1,T}$ and $S_{2,T}$ and defining K_i as $\frac{A_i}{R}$, the solubility in binary solvent mixtures at different temperatures could be presented by:

$$\ln S_{m,T} = f_1 \ln S_{1,T} + f_2 \ln S_{2,T} + f_1 f_2 \sum_{i=0}^{q} K_i \frac{(f_1 - f_2)^i}{T} \quad (4)$$

where $S_{m,T}$ is the solubility in mixed solvent at T, K_i terms could be computed via regressing $\ln S_{m,T} - f_1 \ln S_{1,T} - f_2 \ln S_{2,T}$ against $\frac{f_1 f_2}{T}$, $\frac{f_1 f_2 (f_1 - f_2)}{T}$, $\frac{f_1 f_2 (f_1 - f_2)^2}{T}$ etc. using a no intercept least squares analysis. By calculating K_i terms for a given amino acid dissolved in a binary solvent mixture and known values of the experimental solubility of amino acid in neat solvents at the temperature of interest, one can predict the solubility at all solvent compositions and temperatures using an interpolation technique. Other versions of Eq. (4) were used to represent the solubility of non-electrolytes (Jouyban and Acree 1998) and acid dissociation constants of analytes (Jouyban et al. 2005b) in binary solvent mixtures at various temperatures, the electrophoretic mobility of analytes in mixed solvent running buffers at various temperatures (Jouyban-Gh 2001), dielectric constant (Jouyban et al. 2004a), also surface tension (Jouyban et al. 2004b) and absolute viscosity (Jouyban et al. 2005c) of liquid mixtures at various temperatures. The aim of the present work is to show the applicability of the Jouyban-Acree model for calculating the solubility of amino acids in mixed solvents at a fixed and also various temperatures.

2. Investigations, results and discussion

The solubilities of amino acids in binary aqueous-organic solvent mixtures at each temperature were fitted to Eq. (2 with $q = 2$) and the back calculated solubilities were used to compute the MPD values. The best fit result was shown for DL-alanine in water + ethanol mixture at 60 °C with MPD of 0.1%. The worst MPD was 41.5% for L-valine in water + methanol mixture at 25 °C. The overall MPD (± SD) for 42 data sets at a fixed temperature (for the references of data sets see Table) was 11.4 ± 11.4%. Ren et al. (2004) correlated the solubility data DL-p-hydroxyphenylglycine in water + acetone at five various temperatures using a previously reported general single model (GSM) derived by Barzegar-Jalali and Jouyban-Gh (1997). The overall MPD (± SD) of the GSM for the above mentioned 42 data sets was 14.1 ± 11.2%. The overall MPD difference between GSM and the Jouyban-Acree model was statistically significant (paired t-test, $p < 0.0005$). One should keep in mind that the model constants of Eq. (2) can be calculated by two procedures:

1. regressing $(\ln S_m - f_1 \ln S_1 - f_2 \ln S_2)/f_1 f_2$ against $f_1 - f_2$ and $(f_1 - f_2)^2$ by a classical least squares analysis (Acree et al. 1991)
2. regressing $(\ln S_m - f_1 \ln S_1 - f_2 \ln S_2)$ against $f_1 f_2$, $f_1 f_2 (f_1 - f_2)$ and $f_1 f_2 (f_1 - f_2)^2$ by a no intercept least squares analysis (Jouyban-Gh and Hanaee 1997).

The latter produced more accurate correlations than the first one for the solubility of non-electrolytes in aqueous binary solvent mixtures (Jouyban-Gh and Hanaee 1997). This is also the case for the solubility of amino acids in binary solvent mixtures in which the overall MPD (± SD) of the Jouyban-Acree model (with $q = 2$) using classical least squares analysis was 13.7 ± 10.4%. The mean differences of overall MPD for two numerical methods, i.e. no intercept and classical least squares analyses, was statistically significant (paired t-test, $p < 0.004$).

The solubilities of amino acids in binary aqueous solvent mixtures at various temperatures were fitted to Eq. (4) and the back calculated solubilities were used to compute the MPD values. The best fit result was shown for L-asparagine in water + methanol mixture with MPD of 6.8%.

Table: Details of solubility data, the references, number of data points in each set (N), and the mean percentage deviation (MPD) of calculated solubilities using Eq. (4 with q = 2) and experimental values

No.	Solute	Organic solvent	Reference	N	MPD
1	DL-Alanine	Ethanol	Ferreira et al. 2004	18	12.9
2	DL-Alanine	Propanol	Ferreira et al. 2004	18	8.4
3	DL-Alanine	Isopropanol	Ferreira et al. 2004	18	13.2
4	Glycine	Ethanol	Ferreira et al. 2004	32	17.9
5	DL-p-Hydroxyophenylglycine	Acetone	Ren et al. 2004	65	10.2
6	Glycine	Methanol	Dey and Lahiri 1998	33	23.8
7	α-Alanine	Methanol	Dey and Lahiri 1998	33	18.2
8	L-Valine	Methanol	Dey and Lahiri 1998	33	41.3
9	L-Leucine	Methanol	Dey and Lahiri 1998	33	15.7
10	L-Asparagine	Methanol	Dey and Lahiri 1998	33	9.0
11	L-Phenylalanine	Methanol	Dey and Lahiri 1998	33	17.6
12	L-Serine	Methanol	Dey and Lahiri 1998	33	8.2
13	L-Histidine	Methanol	Dey and Lahiri 1998	33	18.6
				Overall	16.5
				SD	8.8

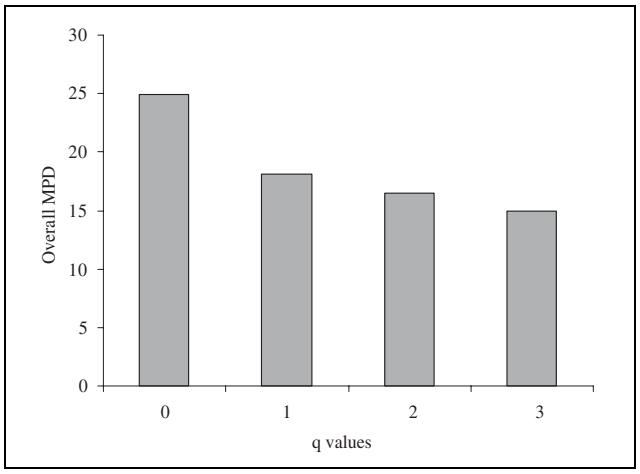

Fig.: The overall mean percentage deviation (MPD) of Eq. (4) vs. different number of curve-fitting parameters (q values)

The worst MPD was 29.5% for L-valine in water + methanol mixture. The overall MPD (± SD) was 15.0 ± 6.4%. The accuracy of Eq. (4) could be altered using different q values as it has been shown in the Figure. However, it reaches to the plateau when q = 3.

In conclusion, the proposed model produced accurate calculations and could be used to represent the solubility of amino acids in binary solvent mixtures at various temperatures using a single equation.

3. Experimental

To assess the accuracy of the model, available experimental solubility of amino acids in aqueous organic solvent mixtures at various temperatures were collected from the literature. Because of the existence of curve-fitting parameters of the model, it correlates the solubility in mole fraction (mass/volume fractions), gram and/or mol per liter of solutes to the solute free mole fractions (volume or mass fractions) of the solvents in the mixture.

To assess the accuracy of the proposed equation, the experimental X_m values were fitted into the equations and the mean percentage deviation (MPD) between experimental and calculated X_m values is considered as an accuracy criterion. The MPD is defined as:

$$\mathrm{MPD} = \left(\frac{100}{N}\right)\sum\left|\frac{X_m^{\mathrm{calculated}} - X_m^{\mathrm{observed}}}{x_m^{\mathrm{observed}}}\right| \qquad (5)$$

where N is the number of experimental data points in each set.

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References

Acree WE Jr (1992) Mathematical representation of thermodynamic properties. Part II. Derivation of the combined nearly ideal binary solvent (NIBS)/Redlich-Kister mathematical representation from a two-body and three-body interactional mixing model. Thermochim Acta 198: 71–79.

Acree WE Jr (1995) Polycyclic aromatic hydrocarbons: binary nonaqueous systems. Part 1 (Solutes A–E), IUPAC Solubility Data Series, vol. 58, Oxford University Press, Oxford.

Acree WE Jr, Zvaigzne AI (1991) Thermodynamic properties of nonelectrolyte solution. 4. Estimation and mathematical representation of solute activity coefficient and solubilities in binary solvents using the NIBS and modified Wilson equations. Thermochim Acta 178: 151–167.

Chan H-K (2002) Formulation challenges: protein powders for inhalation, In: Rathbone, MJ, Hadgraft, J, Roberts, MS (eds.) Modified-Release Drug Delivery Systems, Marcel Dekker, Inc., New York, pp. 879–890.

Chen S, Wetzel R (2001) Solubilization and disaggregation of polyglutamine peptides. Protein Sci 10: 887–891.

Deng T, Childress SD, De Fina KM, Hernández CE, Roy LE, Sharp TL, Acree WE Jr (1999a) Solubility of anthracene in ternary 2-alkoxyethanol + cyclohexane + heptane and 2-alkoxyethanol + cyclohexane + 2,2,4-trimethylpentane solvent mixtures. J Chem Eng Data 44: 357–359.

Deng T, Horiuchi S, De Fina KM, Hernández CE, Acree WE Jr (1999b) Solubility of anthracene in multicomponent solvent mixtures containing propanol, butanol, and alkanes. J Chem Eng Data 44: 798–802.

Dey BP, Lahiri SC (1988) Solubilities of amino acids in methanol + water mixtures at different temperatures. Indian J Chem 27A: 297–302.

Ferreira LA, Macedo EA, Pinho SP (2004) Solubility of amino acids and diglycine in aqueous-alkanol solutions. Chem Eng Sci 59: 3117–3124.

Gude MT, Wielen LAM, Luyben KChAM (1996) Phase behavior of α-amino acids in multicomponent alkanol solutions. Fluid Phase Equilib 116: 110–117.

Habibi-Yanghjeh A (2004) A model for correlation of various solvatochromic parameters with composition in aqueous and organic binary solvent systems. Bull Korean Chem Soc 25: 1165–1170.

Jouyban A, Chan HK, Clark BJ, Acree WE Jr (2002a) Mathematical representation of apparent acid dissociation constants in aqueous-organic solvent mixtures. Int J Pharm 246: 135–142.

Jouyban A, Chan HK, Barzegar-Jalali M, Acree WE Jr (2002b) A model to represent solvent effects on the chemical stability of solutes in mixed solvent systems. Int J Pharm 243: 167–172.

Jouyban A, Grosse SC, Chan HK, Coleman MW, Clark BJ (2003a) Mathematical representation of electrophoretic mobility of basic drugs in ternary solvent buffers in capillary zone electrophoresis. J Chromatogr A 994: 191–198.

Jouyban A, Khoubnasabjafari M, Chan HK, Altria KD, Clark BJ (2003b) Predicting electrophoretic mobility of beta-blockers in water-methanol mixed electrolyte system. Chromatographia 57: 191–196.

Jouyban A, Soltanpour Sh, Chan HK (2004a) A simple relationship between dielectric constant of mixed solvents with solvent composition and temperature. Int J Pharm 269: 353–360.

Jouyban A, Fathi-Azarbayjani A, Barzegar-Jalali M, Acree WE Jr (2004b) Correlation of surface tension of mixed solvents with solvent composition. Pharmazie 59: 937–941.

Jouyban A, Fathi-Azarbayjani A, Acree WE Jr (2004c) Surface tension calculation of mixed solvents with respect to solvent composition and temperature by using Jouyban-Acree model. Chem Pharm Bull 52: 1219–1222.

Jouyban A, Khoubnasabjafari M, Acree WE Jr (2005a) Mathematical representation of solute solubility in binary mixture of supercritical fluids by using Jouyban-Acree model. Pharmazie 60: 527–529.

Jouyban A, Soltani S, Chan HK, Acree WE Jr (2005b) Modeling acid dissociation constant of analytes in binary solvents at various temperatures using Jouyban-Acree model. Thermochim Acta 428: 119–123.

Jouyban A, Khoubnasabjafari M, Vaez-Gharamaleki Z, Fekari Z, Acree WE Jr (2005c) Calculation of the viscosity of binary liquids at various temperatures using Jouyban-Acree model. Chem Pharm Bull 53: 519–523.

Jouyban-Gh A, Hanaee J (1997) A novel method for improvement of predictability of the CNIBS/R-K equation. Int J Pharm 154: 245–247.

Jouyban-Gh A, Khaledi MG, Clark BJ (2000) Calculation of electrophoretic mobilities in water-organic modifier mixtures in capillary electrophoresis. J Chromatogr A 868: 277–284.

Jouyban-Gh A, Valaee L, Barzegar-Jalali M, Clark BJ, Acree WE Jr (1999) Comparison of various cosolvency models for calculating solute solubility in water-cosolvent mixtures. Int J Pharm 177: 93–101.

Pikal-Cleland KA, Cleland JL, Anchordoquy TJ, Carpenter JF (2002) Effect of glycine on pH changes and protein stability during freeze-thawing in phosphate buffer systems. J Pharm Sci 91: 1969–1979.

Orella CJ, Kirwan DJ (1991) Correlation of amino acid solubilities in aqueous aliphatic alcohol solutions. Ind Eng Chem Res 30: 1040–1045.

Oswal SL, Desai HS (2003) Studies of viscosity and excess molar volume of binary mixtures: 4. 1-Alkanol + tri-n-butylamine mixtures at 303.15 and 313.15 K. Fluid Phase Equilib 204: 281–194.

Ren G-B, Wang J-K, Yin Q-X, Zhang M-J (2004) Solubility of DL-p-hydroxyphenylglycine sulfate in binary acetone + water solvent mixtures. J Chem Eng Data 49: 1376–1378.

Ulijin RV, De Martin L, Gardossi L, Janssen AEM, Moore BD, Halling PJ (2002) Solvent selection for solid-to-solid synthesis. Biotech Bioeng 80: 509–515.