Solubility of Tris(hydroxymethyl)aminomethane in Water + Methanol +1-Propanol Mixtures at Various Temperatures

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ABSTRACT: The solubility of tris(hydroxymethyl)aminomethane (TRIS) in various mass fractions of ternary solvent mixtures of water + methanol +1-propanol at 293.2 K, 298.2 K, 303.2 K, 308.2 K, and 313.2 K was measured using a laser monitoring technique. The mole fractions of water in the ternary mixtures were between 0.90 and 0.17; the mole fraction solubility of TRIS ranged between 0.0150 and 0.1187. The generated data was mathematically represented by the combined models of Jouyban–Acree and van't Hoff, enabling the solubility to be expressed as a function of both ternary solvent compositions and temperatures. The back-calculated mole fraction solubilities agreed with the corresponding experimental values by an overall mean percentage deviation of 5.6%.
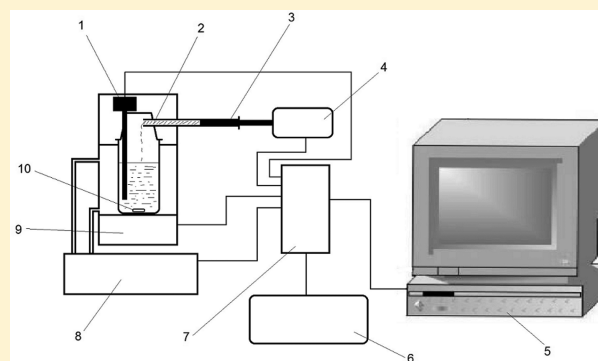
INTRODUCTION

It is evident that solubility data are of outstanding importance in nearly all areas of chemistry; as an example, they enable researchers to select the most appropriate solvent system for solubilization or crystallization of a solute. Mixed solvents provide tunable polarity solvents to alter the solubility of a given solute. Such mixtures are also used for mobile phases and for the background electrolytes in analytical separation methods such as high performance liquid chromatography (HPLC) or capillary electrophoresis (CE). In these methods, a low solubility of electrolytes used as background buffers at higher concentrations of the organic solvent is often a limiting parameter, whereas mixed solvents applied in this context may—as an advantage—increase the solubility of lipophilic analytes. The solvents determine other relevant analytical parameters like pK_a values, partition coefficients, retention factors or electrophoretic and electroosmotic mobilities and, thus, help in achieving the separation selectivity (and even the peak dispersion properties) for various analytes in HPLC or CE.[1]

In current HPLC and CE methods, selecting of the proper buffering agent can introduce favorable conditions for a given method where mineral buffers are utilized in wide variety ranges. For example, Kubalczyk et al. used phosphate buffer as background electrolyte for the analysis of hydrogen sulfide in hen tissues with CE, and Cunha et al. utilized a phosphate buffer for the analysis of paracetamol, caffeine, and ibuprofen in pharmaceutical formulations with both CE and HPLC.[2,3] Mineral buffers like phosphate are very helpful in water-rich media; however, their solubilities are decreased drastically with increasing percentage of organic solvent in the mixture. The solubility of these buffering agents is even lower in neat organic solvents. As an example, the solubility of potassium phosphate in methanol (MeOH) is less than 5×10^{-3} mol·L^{-1} which restricts it use in organic-rich aqueous mixtures.[4]

An organic buffering agent like TRIS (tris(hydroxymethyl)-aminomethane), with solubilities of 0.224 mol·L^{-1} (0.0092 in mole fraction) and 0.064 mol·L^{-1} (0.0050 in mole fraction) in MeOH and 1-propanol (1-PrOH)[5] and sodium acetate with solubilities of 1.58 and 0.0937 mol·L^{-1} in MeOH and 1-propanol, respectively,[6] is a favorable alternative buffering agent replacement for minerals. Moreover, organic buffers are sufficiently soluble in water (TRIS, 4.5 M, sodium acetate, 5.53 M) for use in both water- and organic-rich mixtures.

Tris(hydroxymethyl)aminomethane (TRIS) is a common buffering agent, used in many areas of applications; its acid dissociation constant (pK_a) is 8.1. The solubility of TRIS in a

Table 1. List of the Used Materials

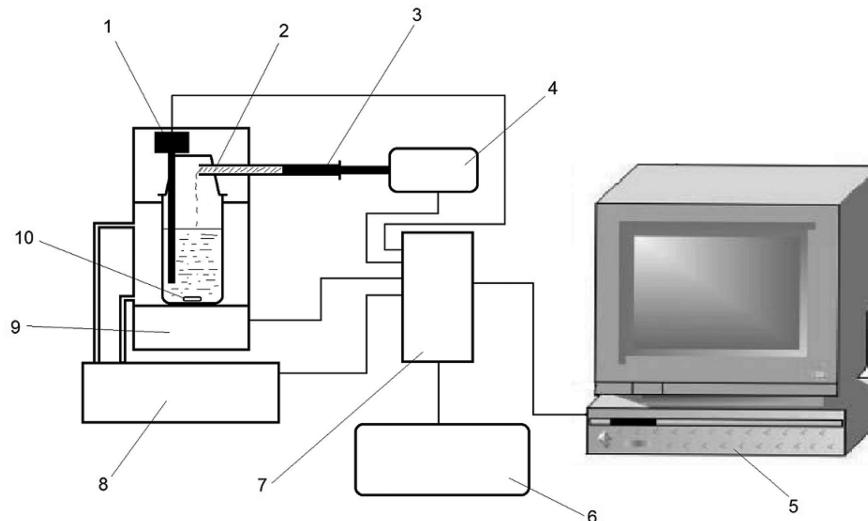|	country	company	purity in mass fraction	material
TRIS: tris(hydroxymethyl)aminomethane (CAS no. of 77-86-1)	Merck	0.999	Germany	
MeOH	0.999	Scharlau	Spain	
water	conductivity < 1.5 μS·cm^{-1}	lab made		
1-PrOH	0.999	Merck	Germany	

Figure 1. Schematic representation of the set up: 1, laser generator and photoelectronic convertor; 2, drug powder; 3, dispensing syringe; 4, syringe actuator; 5, display system; 6, power supply; 7, data processor and controller; 8, thermostate system; 9, magnetic stirrer; and 10, stir bar.

number of mixed solvent systems has been reported in binary mixtures of water + 2-methoxyethanol at 288.15 K, 298.15 K, and 308.15 K (measured by acidimetric titration of the saturated solutions),[7] in mixtures of water + 1,4-dioxane at 298 K,[8] in mixtures of water + ethanol at 298 K,[9] in mixtures of MeOH + propylene glycol at 298 K,[10] in mixtures of ethylene glycol + water at 298 K,[11] in mixtures of N-methylpropionamide + water at 298 K,[12] in mixtures of acetonitrile + ethylene glycol at 298.15 K,[13] in mixtures of water +2-ethoxyethanol,[14] and in mixtures of water + sulfolane.[15,7]

TRIS is used by biochemists as a quality control buffer of blood pH (or other physiological samples) due to its large temperature coefficient (−0.026 pH °C).[16] Phosphate buffers on the other hand cause undesirable side reactions with the biological substances in their test samples. Moreover, TRIS does not precipitate calcium salts. TRIS is also applied as an excipient in pharmaceutical and cosmetics formulations[17−19] and has been used in polymer technology, preparation of surface active agents, metal working fluid, surfactant manufacturing, and as an additive in inks and chemical intermediates (e.g., in the production of nitroparaffin).[20,21]

In the present work, we measured the solubility of TRIS in ternary solvent mixtures containing water, MeOH, and 1-PrOH (1-propanol) at temperatures between 293.2 K and 313.2 K in 5.0 K steps using an automated solubility determination system.[22] This ternary solvent system might be used when binary solvent mixtures were not able to solve analytical problem in HPLC or CE methods.[23−25] For the purpose of predicting the solubility of TRIS as a function of both solvent composition and temperature, we developed a new model by combining the concepts of Jouyban−Acree and van't Hoff model.

EXPERIMENTAL SECTION

Materials. TRIS and 1-PrOH (with the stated purity of 0.999 in mass fraction) were purchased from Merck (Germany) and MeOH (0.999 mass fraction purity) from Scharlau (Barcelona, Spain). Solutions were prepared with double distilled water. All reagents were used as received from the company without further purification. Table 1 listed details of chemicals used in this work.

Instrumentation. For the measurement of the thermodynamic solubility of a solute, the well-established so-called synthetic method[26,27] was employed. The method is an automated version of the shake-flask method of Higuchi and Connors, which is the most widely applied method.[28] The laser monitoring technique determines the point of the disappearance of the solid solute. In the present paper, a lab-made set up (see Figure 1 for schematic representation) has been applied. Details of this setup have already been described in a previous paper.[22] The setup was validated by measuring the solubility of acetaminophen in water, ethanol, and propylene glycol at various temperatures and by comparing the measured values with available data from the literature. Our measured values differed from literature data by an overall mean percentage of 14%.[22]

The syringe filled with solute powder (the maximum and minimum amount of TRIS added are 6.27 and 96.35 g, respectively) was weighed on an electronic balance (Sartorius, Germany) with an uncertainty of weighing of 0.01 g before and after saturation of the solution. The resulting mass difference determines the mass of solute added to saturate the solution. In this setup, 120 g are the total masses of the mixed solvent; those of the solute + syringe varied between 0.10 and 4.00 g. Measurements were performed at least in triplicate.

Calculations of Solubility. The mole fractions x_1^0, x_2^0, and x_3^0 of the solvents 1 (water), 2 (MeOH), and 3 (1-PrOH) with

Table 2. Experimental Mole Fraction Solubility^b of Tris(hydroxymethyl)aminomethane in Ternary Solvent Mixtures at Various Temperatures and Atmospheric Pressure of 0.1 MPa^a

x_1^0	x_2^0	x_3^0	293.2 K	SD	298.2 K	SD	303.2 K	SD	308.2 K	SD	313.3 K	SD
0.90	0.06	0.03	0.0773	0.0012	0.0856	0.0012	0.0928	0.0010	0.1073	0.0014	0.1187	0.0015
0.74	0.08	0.18	0.0555	0.0015	0.0677	0.0015	0.0750	0.0003	0.0858	0.0016	0.0986	0.0008
0.66	0.30	0.04	0.0516	0.0011	0.0619	0.0005	0.0709	0.0009	0.0816	0.0013	0.0928	0.0003
0.66	0.09	0.25	0.0492	0.0011	0.0580	0.0017	0.0688	0.0006	0.0755	0.0030	0.0853	0.0008
0.63	0.18	0.19	0.0486	0.0004	0.0584	0.0026	0.0699	0.0003	0.0752	0.0015	0.0865	0.0003
0.61	0.26	0.14	0.0474	0.0003	0.0571	0.0003	0.0681	0.0002	0.0745	0.0002	0.0854	0.0009
0.58	0.33	0.09	0.0465	0.0001	0.0554	0.0005	0.0659	0.0008	0.0728	0.0004	0.0830	0.0009
0.56	0.40	0.04	0.0452	0.0005	0.0543	0.0000	0.0652	0.0013	0.0725	0.0012	0.0838	0.0015
0.51	0.29	0.20	0.0373	0.0007	0.0404	0.0016	0.0501	0.0010	0.0589	0.0007	0.0690	0.0007
0.37	0.41	0.22	0.0250	0.0011	0.0301	0.0004	0.0352	0.0013	0.0442	0.0004	0.0509	0.0001
0.25	0.14	0.61	0.0192	0.0007	0.0225	0.0004	0.0260	0.0010	0.0292	0.0012	0.0320	0.0015
0.21	0.47	0.32	0.0173	0.0001	0.0192	0.0009	0.0239	0.0004	0.0272	0.0010	0.0319	0.0007
0.20	0.56	0.24	0.0169	0.0001	0.0192	0.0002	0.0228	0.0006	0.0262	0.0012	0.0313	0.0006
0.17	0.78	0.05	0.0150	0.0007	0.0171	0.0008	0.0200	0.0006	0.0239	0.0006	0.0277	0.0008

$^a x_1^0, x_2^0, x_3^0$: solute-free mole fraction of water (1), MeOH (2) and 1- PrOH (3). The relative standard uncertainty for the solubilities is 1.9% or ur(x) = 0.019, the standard uncertainty for temperature is 0.1 K and the measurements were made at atmospheric pressure. Solvent mixtures were prepared by mixing different masses of the solvents with uncertainty of 0.01 g. ^{b}Data are the mean of three measurements. SD: standard deviation.

masses m_1, m_2, and m_3 weighed with uncertainty of 0.01 g in the absence of the solute were computed as

$$x_i^0 = \frac{m_i/\mathrm{MW}_i}{((m_1/\mathrm{MW}_1) + (m_2/\mathrm{MW}_2) + (m_3/\mathrm{MW}_3))} \quad (1)$$

where MW_1, MW_2, and MW_3; are the molar masses of the solvents 1–3. The saturated mole fraction solubility of TRIS $(x_{m,T})$ in different compositions of the ternary solvents at various temperatures was calculated as

$$x_{m,T} = \frac{m_{\mathrm{TRIS}}/\mathrm{MW}_{\mathrm{TRIS}}}{(m_{\mathrm{TRIS}}/\mathrm{MW}_{\mathrm{TRIS}}) + (m_1/\mathrm{MW}_1) + (m_2/\mathrm{MW}_2) + (m_3/\mathrm{MW}_3)} \quad (2)$$

where m_{TRIS} is he the mass of TRIS added to the solution upon saturation; ($\mathrm{MW}_{\mathrm{TRIS}}$, the molar mass of TRIS, is 121.14 g·mol^{-1}).

The accuracy of the model was evaluated using the mean percentage deviations (MPD)

$$\mathrm{MPD} = \frac{100}{N} \sum \left[\frac{x_{m,T}^{\mathrm{calculated}} - x_{m,T}^{\mathrm{experimental}}}{x_{m,T}^{\mathrm{experimental}}} \right] \quad (3)$$

which measures the difference between the experimental and calculated solubilities. In eq 3, N is the number of data points in each set.

■ RESULTS AND DISCUSSION

Experimental Solubility Data. Table 2 lists the observed mole fraction solubilities of TRIS (with the corresponding standard deviations) in ternary mixtures of water + MeOH + 1-PrOH at mole fraction compositions corresponding to decreasing water content. Solubilities were measured at 293.2 K, 298.2 K, 303.2 K, 308.2 K, and 313.2 K. The chosen mole fractions of water, x_1^0, were in the range between 0.90 and 0.17. As expected the maximum mole fraction solubility (0.1178 at 313.2 K) is observed in the water-rich solution at solvent mole compositions x_1^0, x_2^0, and x_3^0 of 0.90, 0.06, and 0.03. The minimum solubility (0.0150 at 293.2 K) is found at x_1^0, x_2^0, and x_3^0 of 0.17, 0.78, and 0.05. In all cases the increase of x_1^0 leads to an increase in solubility at a given temperature. The solubility of TRIS is increased roughly 4- to 5-fold as one goes from the solvent mixture having the lowest water content to the mixture with the highest water

composition. The measured data are in accord with the published data at sub-binary mixtures of water + MeOH + 1-PrOH ternary mixture.[5,29,30]

The Jouyban−Acree model. With the Jouyban−Acree model (the modified version of the combined nearly ideal binary solvent/Redlich−Kister equation),[31] the solubility of TRIS at temperature, T, of the binary solvent mixtures could be calculated as[32]

$$\ln x_{m,T} = x_1^0 \ln x_{1,T} + x_2^0 \ln x_{2,T} + \left[\frac{x_1^0 x_2^0}{T} \sum_{i=0}^{2} J_i (x_1^0 - x_2^0)^i \right] \quad (4)$$

The extended version of the model for describing the solubility of a solute in ternary solvent mixtures is

$$\begin{aligned}
\ln x_{m,T} = & \, x_1^0 \ln x_{1,T} + x_2^0 \ln x_{2,T} + x_3^0 \ln x_{3,T} \\
& + \left[\frac{x_1^0 x_2^0}{T} \sum_{i=0}^{2} J_i (x_1^0 - x_2^0)^i \right] + \left[\frac{x_1^0 x_3^0}{T} \sum_{i=0}^{2} J_i' (x_1^0 - x_3^0)^i \right] \\
& + \left[\frac{x_2^0 x_3^0}{T} \sum_{i=0}^{2} J_i'' (x_2^0 - x_3^0)^i \right]
\end{aligned} \quad (5)$$

where $x_{m,T}$ is the mole fraction solute solubility in the solvent mixtures at absolute temperature T. Note that $x_{1,T}$, $x_{2,T}$, and $x_{3,T}$ is the mole fraction solubility of the solute in the monosolvents 1, 2, and 3 respectively. J_i' and J_i'' are the constants of the model and represent the two-body and three-body interactions between solvent−solvent and solvent−solute molecules. Numerical values of the constants were computed by a regression analysis and are collected in Table 3 for the three sub-binary solvent systems. The solubility data of TRIS in water (1) + MeOH (2) + 1-PrOH (3) mixtures at various temperature

Table 3. Model Constants for Jouyban−Acree Equation for Sub-Binary Mixtures of Water, MeOH, and 1-PrOH

solvent mixture	J_0	J_1	J_2	reference
water + MeOH	540.8	133.6		29
water +1-PrOH	624.3	37.8		30
MeOH + 1-PrOH	−257.8	−93.7	169.5	5

was predicted by eq 5. The observed and predicted values differed by an overall MPD of 11.8%. It should be noted that no solubility data in ternary solvent mixture was used to train the model; therefore, eq 5 could be considered as a predictive model. By including ternary solvent interactions terms in eq 5, it is possible to improve the model's predictive ability. The numerical values of these terms could be calculated by regressing

$$
\ln x_{m,T} - x_1^0 \ln x_{1,T} - x_2^0 \ln x_{2,T} - x_3^0 \ln x_{3,T}
$$
$$
- \left[540.8 \frac{x_1^0 x_2^0}{T} + 133.6 \frac{x_1^0 x_2^0 (x_1^0 - x_2^0)}{T} \right]
$$
$$
- \left[624.3 \frac{x_1^0 x_3^0}{T} + 37.8 \frac{x_1^0 x_3^0 (x_1^0 - x_3^0)}{T} \right]
$$
$$
- \left[-257.8 \frac{x_2^0 x_3^0}{T} - 93.7 \frac{x_2^0 x_3^0 (x_2^0 - x_3^0)}{T} \right.
$$
$$
\left. + 169.5 \frac{x_2^0 x_3^0 (x_2^0 - x_3^0)^2}{T} \right]
$$

against $(x_1^0 x_2^0 x_3^0 / T)$, $(x_1^0 x_2^0 x_3^0 (x_1^0 - x_2^0 - x_3^0)/T)$ and $(x_1^0 x_2^0 x_3^0 (x_1^0 - x_2^0 - x_3^0)^2/T)$ using a no-intercept least-square analysis. Using this extended version of the model, the overal MPD was reduced from 11.8% to 5.6%. The computed J_0 for ternary solvent mixture was 1774.5, the J_1 was −1528.8, and the J_2 was zero.

Solubility As a Function of Ternary Solvent Composition and Temperature: Combined Jouyban−Acree and van't Hoff Equations. The solubility data of TRIS in each solvent system at various temperatures (x_T) could be mathematically represented using the van't Hoff equation[33]

$$
\ln x_T = A + \frac{B}{T} \tag{6}
$$

where A and B are the model constants calculated using a least-square method.

In our previosly published papers,[5,29,30] we presented a combined model based on the Jouyban−Acree and van't Hoff equations to predict the solubility of TRIS in binary mixtures at various temperatures. The model was expressed by

$$
\ln x_{m,T} = x_1^0 \left(A_1 + \frac{B_1}{T} \right) + x_2^0 \left(A_2 + \frac{B_2}{T} \right)
$$
$$
+ \left[\frac{x_1^0 x_2^0}{T} \sum_{i=0}^{2} J_i (x_1^0 - x_2^0)^i \right] \tag{7}
$$

which is an extension of eq 4. By an alternative calculation method, the measured data (Table 2) were fitted to the combined form of the Jouyban−Acree and van't Hoff equations to train an equation for ternary mixtures, which is given by eq 8

$$
\ln x_{m,T} = x_1^0 \left(A_1 + \frac{B_1}{T} \right) + x_2^0 \left(A_2 + \frac{B_2}{T} \right) + x_3^0 \left(A_3 + \frac{B_3}{T} \right)
$$
$$
+ \left[\frac{x_1^0 x_2^0}{T} \sum_{i=0}^{2} J_i (x_1^0 - x_2^0)^i \right] + \left[\frac{x_1^0 x_3^0}{T} \sum_{i=0}^{2} J_i' (x_1^0 - x_3^0)^i \right]
$$
$$
+ \left[\frac{x_2^0 x_3^0}{T} \sum_{i=0}^{2} J_i'' (x_2^0 - x_3^0)^i \right] \tag{8}
$$

Table 4. Model Constants for van't Hoff Equation for Sub-Binary Mixtures of Water + MeOH + 1-PrOH

solvent	A	B	reference
water	3.520	−1760.0	29
1-PrOH	7.224	−3740.0	30
MeOH	6.070	−3211.7	5

The model constants of eq 8 have been reported in earlier works and are summarized in Tables 3 and 4. By employing these constants, the solubility of TRIS in the investigated ternary solvent mixtures at various temperatures could be predicted with the MPD of 11.8%. Addition of ternary solvent interaction terms to eq 8 improves its predictive ability. The trained version of the model for estimating the solubility in the monosolvents, binary and ternary solvents of water + MeOH + 1-PrOH mixtures at various temperatures is

$$
\ln x_{m,T} = x_1^0 \left(3.520 - \frac{1760.0}{T} \right) + x_2^0 \left(7.224 - \frac{3740.1}{T} \right)
$$
$$
+ x_3^0 \left(6.070 - \frac{3211.7}{T} \right)
$$
$$
+ \frac{x_1^0 x_2^0}{T} [540.8 + 133.6(x_1^0 - x_2^0)]
$$
$$
+ \frac{x_1^0 x_3^0}{T} [624.3 + 37.8(x_1^0 - x_3^0)]
$$
$$
+ \frac{x_2^0 x_3^0}{T} [-257.8 - 93.7(x_2^0 - x_3^0)
$$
$$
+ 169.5(x_2^0 - x_3^0)^2]
$$
$$
+ \frac{x_1^0 x_2^0 x_3^0}{T} [-3583.9 - 6722.4(x_1^0 - x_2^0 - x_3^0)] \tag{9}
$$

in which the constant values for ternary solvents were calculated by regression of

$$
\ln x_{m,T} - x_1^0 \left(3.520 - \frac{1760.0}{T} \right) - x_2^0 \left(7.224 - \frac{3740.1}{T} \right)
$$
$$
- x_3^0 \left(6.070 - \frac{3211.7}{T} \right)
$$
$$
- \frac{x_1^0 x_2^0}{T} [540.8 + 133.6(x_1^0 - x_2^0)]
$$
$$
- \frac{x_1^0 x_3^0}{T} [624.3 + 37.8(x_1^0 - x_3^0)]
$$
$$
- \frac{x_2^0 x_3^0}{T} [-257.8 - 93.7(x_2^0 - x_3^0)
$$
$$
+ 169.5(x_2^0 - x_3^0)^2]
$$

against. $(x_1^0 x_2^0 x_3^0 / T)$, $(x_1^0 x_2^0 x_3^0 (x_1^0 - x_2^0 - x_3^0)/T)$ and $(x_1^0 x_2^0 x_3^0 (x_1^0 - x_2^0 - x_3^0)^2/T)$.

Equation 9 is able to predict the solubility of TRIS in ternary solvent mixture of in water (1) + MeOH (2) + 1-PrOH (3) with an overall MPD of 10.2%.

Figure 2 graphically compares the experimental TRIS solubilites and calculated values based on eq 9. Careful examination of
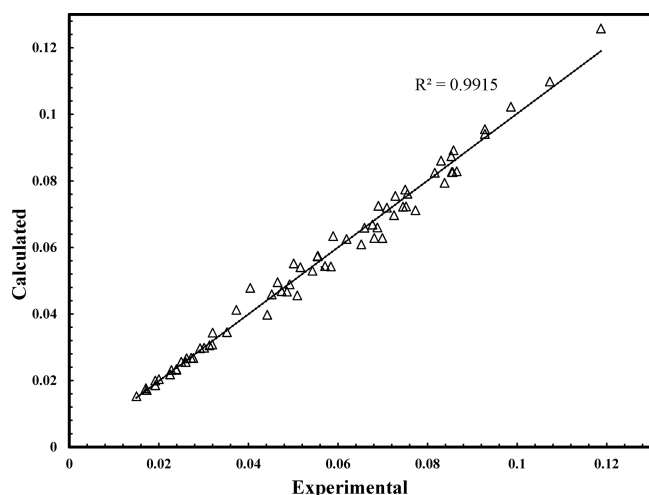
Figure 2. Plot of calculated mole fraction solubilities of TRIS versus the corresponding experimental values.

the figure reveals that the scatter around the regression line (R^2 is 0.9915) is more pronounced at solubilities higher than 0.035.

CONCLUSIONS

In the present work, we reported the solubility of TRIS in ternary solvent mixtures of water, MeOH, and 1-PrOH at temperatures of 293.2 K, 298.3, 303.2 K, 308.2 K, and 313.2 K. As expected the highest and lowest solubility were observed at 313.2 K in the water-rich fraction of 0.9/0.06/0.03 and at 293.2 K in the organic solvent-rich fraction of 0.17/0.78/0.05 mole fraction of water, MeOH, and 1-PrOH solvents, respectively. The data were correlated with the combined form of the Jouyban−Acree and the van't Hoff equations. The resulting mathematically was found to describe the observed solubility data to within a MPD of 11.8%. In addition, sub-binary mixtures of water, MeOH, and 1-PrOH were used to predict the solubility data of the solute in the ternary solvent mixtures studied in the present communication. Although the combined form of the model produced larger MPD when compared with the model needing measured solubility data of TRIS with monosolvents, we recommend it for practical applications because it requires less measured input values to predict TRIS solubility in water + MeOH + 1-PrOH mixtures at any temperature of interest.

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Notes
The authors declare no competing financial interest.

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