

Solubility of Sodium Acetate in Binary Mixtures of Methanol, 1-Propanol, Acetonitrile, and Water at 298.2 K

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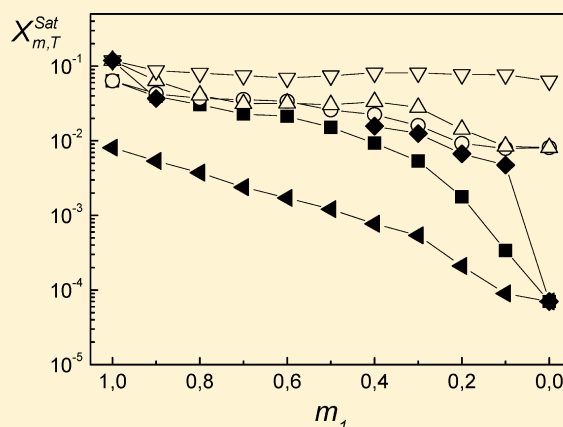
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ABSTRACT: The molar solubility of sodium acetate was measured in binary mixtures of methanol, 1-propanol, acetonitrile, and water along with the density of their saturated solutions at 298.2 K. The molar solubilities span a range of nearly 4 orders of magnitude from 5.53 mol·L⁻¹ in water to 0.0014 mol·L⁻¹ in acetonitrile, the according values for the mole fraction solubilities are 0.119 and 0.00007. For the calculation of the solubility and the density at any composition of the binary solvent mixture, a computational method is provided, based on the Jouyban–Acree model. The method uses the solubility data in the monosolvents and their density and model constants; the latter are derived by fitting the experimental data to the Jouyban–Acree model. Solubilities and densities were back-calculated, and the overall mean percentage deviations between experimental and calculated values were 9.8 % for the solubilities and 0.4 % for the densities of the saturated solutions.



INTRODUCTION

Solubility is the maximum amount of a solute dissolvable in a given volume of the solution. Knowledge of the solubility enables finding the most appropriate solvent system for solubilization or crystallization of a solute. Beside monosolvents, solvent mixtures provide systems with tunable polarity to alter the solubility of a given solute. As an example, the addition of an organic solvent to the aqueous solution usually decreases the solubility of electrolytes, thus facilitating the crystallization process of such compounds. Solvent mixtures are also used as mobile phases and/or solvents for the background electrolytes in analytical separation methods such as high-performance liquid chromatography (HPLC) or capillary electrophoresis (CE). In these methods the low solubility of electrolytes at higher concentrations of the organic solvent might be a limiting parameter on the one hand, but using a mixed solvent system is also the most effective tool to modify separation selectivity, on the other hand. Mixed solvents applied in this context may improve the solubility of the analyte or the resolution of the peaks of various analytes or determine other relevant analytical parameters like pK_a values, partition coefficients, or electrophoretic and electroosmotic mobilities.¹

A quick survey on the (507) published HPLC and CE methods for pharmaceutical analysis show that acetate buffer has been employed in the following solvent systems. The most frequently used mixed solvents are water + acetonitrile (ACN) (41%), followed by water + methanol (MeOH) (26%) and water + ACN + MeOH (21%). It is worth mentioning that the pK_a of acetic acid (4.78 in water) and thus the pH of acetate buffer with highest buffering capacity is shifted toward higher pK_a values upon addition of organic solvents. It is 9.7 in MeOH and is thus in the range of the pK_a values of aliphatic amines (which in fact do not show a pronounced pK_a difference in water and MeOH; they possess pK_a values around 9 or 10). This means that in MeOH acetate is a buffer of choice to the target-oriented adjustment of the degree of protonation of such amino groups typical, for example, for pharmaceuticals. Various aspects of the effects of organic solvents in electromigration methods were discussed in a most recent paper.¹

Due to this high practical importance, it was our intention to measure the solubilities of sodium acetate in a number of binary

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Table 1. Experimental Molar Solubilities, $C_{m,T}^{\text{sat}}$, of Sodium Acetate in Binary Mixtures of MeOH, PrOH, ACN, and Water at 298.2 K and at Atmospheric Pressure (0.1 MPa), Their Standard Deviations (SD), Mole Fraction Solubilities ($X_{m,T}^{\text{sat}}$) and Densities of the Saturated Solutions, and Volume (φ_1) and Mass (m_1) Fractions of Solvent Indicated by Equation 1^a

φ_1	m_1	$C_{m,T}^{\text{sat}}$	SD	$X_{m,T}^{\text{sat}}$	density/g·cm ⁻³	SD
Water (1) + MeOH (2)						
1	1.00	5.53	0.29	0.119	1.1921	0.0040
0.9	0.92	4.12	0.112	0.0871	1.1664	0.0040
0.8	0.84	3.59	0.10	0.0810	1.1246	0.0040
0.7	0.75	3.17	0.14	0.0750	1.1025	0.0083
0.6	0.66	2.83	0.06	0.0694	1.1007	0.0068
0.5	0.56	2.834	0.16	0.0746	1.0834	0.0068
0.4	0.46	2.87	0.16	0.0816	1.0647	0.0040
0.3	0.35	2.69	0.17	0.0812	1.0467	0.0049
0.2	0.24	2.42	0.10	0.0773	1.0280	0.0049
0.1	0.12	2.13	0.14	0.0767	0.9502	0.0095
0	0.00	1.58	0.03	0.0637	0.8730	0.0049
Water (1) + PrOH (2)						
1	1.00	5.53	0.29	0.119	1.192	0.0040
0.9	0.92	2.81	0.10	0.0637	1.147	0.0011
0.8	0.83	1.59	0.05	0.0409	1.118	0.0030
0.7	0.74	1.03	0.06	0.0313	1.076	0.0273
0.6	0.65	0.902	0.06	0.0319	1.056	0.0286
0.5	0.55	0.702	0.03	0.0303	0.9734	0.0383
0.4	0.45	0.627	0.008	0.0334	0.8852	0.0040
0.3	0.35	0.471	0.017	0.0279	0.8820	0.0019
0.2	0.24	0.208	0.023	0.0142	0.8389	0.0097
0.1	0.12	0.109	0.005	0.00843	0.8183	0.0102
0	0.00	0.0937	0.0022	0.00807	0.8035	0.0030
Water (1) + ACN (2)						
1	1.00	5.53	0.29	0.119	1.1921	0.0040
0.9	0.92	1.89	0.04	0.0368	1.1393	0.0049
0.4	0.46	0.407	0.010	0.0157	0.8125	0.0019
0.3	0.36	0.302	0.015	0.0125	0.8106	0.0116
0.2	0.24	0.149	0.003	0.00668	0.7965	0.0011
0.1	0.12	0.0966	0.0039	0.00472	0.7849	0.0022
0	0.00	0.0014	<0.00005	0.00007	0.7675	0.0040
MeOH (1) + PrOH (2)						
1	1.00	1.58	0.03	0.0637	0.8730	0.0049
0.9	0.90	0.966	0.039	0.0427	0.8556	0.0030
0.8	0.80	0.761	0.024	0.0369	0.8479	0.0030
0.7	0.70	0.669	0.029	0.0358	0.8351	0.0011
0.6	0.60	0.576	0.029	0.0339	0.8196	0.0030
0.5	0.50	0.406	0.012	0.0260	0.8055	0.0011
0.4	0.40	0.327	0.007	0.0224	0.8016	0.0011
0.3	0.30	0.219	0.006	0.0160	0.8029	0.0019
0.2	0.20	0.120	0.006	0.00924	0.8016	0.0011
0.1	0.10	0.0961	0.0008	0.00786	0.8016	0.0030
0	0.00	0.0937	0.0022	0.00807	0.8035	0.0030
MeOH (1) + ACN (2)						
1	1.00	1.58	0.03	0.0637	0.8730	0.0049
0.9	0.90	0.960	0.039	0.0393	0.8524	0.0056
0.8	0.80	0.727	0.029	0.0306	0.8389	0.0011
0.7	0.70	0.528	0.021	0.0228	0.8293	0.0011
0.6	0.60	0.475	0.015	0.0213	0.8151	0.0022
0.5	0.50	0.326	0.010	0.0151	0.8022	0.0011
0.4	0.40	0.194	0.008	0.00928	0.7907	0.0022
0.3	0.30	0.109	0.007	0.00536	0.7823	0.0011
0.2	0.20	0.035	0.001	0.00178	0.7759	0.0019
0.1	0.10	0.0066	0.0003	0.00034	0.7707	0.0011
0	0.00	0.0014	<0.00005	0.00007	0.7675	0.0040
PrOH (1) + ACN (2)						
1	1.00	0.0937	0.0022	0.00807	0.8035	0.0029
0.9	0.90	0.0647	0.0055	0.00537	0.8010	0.0084

Table 1. continued

φ_1	m_1	$C_{m,T}^{\text{sat}}$	SD	$X_{m,T}^{\text{sat}}$	density/g·cm ⁻³	SD
PrOH (1) + ACN (2)						
0.8	0.80	0.0464	0.0013	0.00374	0.7900	0.0011
0.7	0.71	0.0305	0.0014	0.00238	0.7810	0.0011
0.6	0.61	0.0229	0.0011	0.00171	0.7752	0.0011
0.5	0.51	0.0169	0.0005	0.00121	0.7707	0.0022
0.4	0.41	0.0112	0.0004	0.00077	0.7701	0.0033
0.3	0.31	0.0084	0.0004	0.00054	0.7688	0.0029
0.2	0.20	0.0034	0.0002	0.00021	0.7701	0.0019
0.1	0.10	0.0015	0.0001	0.00009	0.7688	0.0011
0	0.00	0.0014	<0.00005	0.00007	0.7675	0.0040

^aData are the mean of three measurements. SD: standard deviation. The relative standard uncertainty for the solubilities is $u_r(x) = 0.10$. The relative standard uncertainty for the densities is $u_r(\text{density})$ is 0.005, and the standard uncertainty for temperature $u(T)$ is 0.2 K.

aqueous and nonaqueous solvent systems containing water, ACN, MeOH, or 1-propanol (PrOH) at 298.2 K at different compositions, extending in this way the available database of solubilities.² To enable the calculation of the solubility of sodium acetate at any composition of the binary solvent mixture, we fitted the data to the Jouyban–Acree model. This model—one of the most versatile models among similar algorithms³—relates the solubilities in solvent mixtures to the volume fractions of the solvent components, whereby the inherent model constants can be computed by regression analysis.³ The density of the saturated solutions is also provided to convert the molar solubilities into mole fraction solubilities.

EXPERIMENTAL SECTION

Materials. Sodium acetate (anhydrous, 0.995 mass fraction purity), MeOH (0.999 mass fraction purity), PrOH (0.999 mass fraction purity), and ACN (0.998 mass fraction purity) were purchased from Scharlau (Barcelona, Spain). Double-distilled water was used for the preparation of the solutions. All reagents were used as received from the company without further purification.

Apparatus and Procedures. The binary mixtures composed of the solvents with suitable volumes were prepared with the accuracy of 0.1 mL with a 100 mL end volume. From the different methods presented for determining the solubility of solutes,⁴ we used the saturation shake-flask method of Higuchi and Connors.⁵ Briefly, an excess amount of the solute was added to the solvent mixtures, and the resulting solutions were equilibrated for at least three days on a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature controlling system maintained at 298.2 (± 0.2) K. The saturated solutions were centrifuged at 13000 rpm for 10 min, and the obtained clear solutions were filtered through regenerated cellulose membrane filters (0.45 μm, Albet Lab Science, Spain) and diluted with water. Sodium concentrations of the diluted samples were assayed using a flame photometer (Fater Electronics, Tehran, Iran). The possible sodium contaminations from impurities or glassware were taken into account by adjusting the absorbance of the photometer to zero using a blank sample. Each experimental data point represents the average of at least three repetitive measurements with the measured mol·L⁻¹ (M) solubilities being reproducible within ± 3.9 % relative standard deviation. The densities of the saturated solutions were determined using a 5 mL calibrated pycnometer using a balance with the uncertainty of 0.001 g. The balance and required glassware were placed in an incubator equipped

with a temperature controlling system maintained at 298.2 (± 0.2) K.

Calculation Procedures. Evaluation of the accuracy of the calculated data was carried out by comparing the mean percentage deviations (MPD) between calculated and experimental solubilities or densities according to:

$$\text{MPD} = \frac{100}{N} \sum \left[\frac{|\text{calculated} - \text{experimental}|}{\text{experimental}} \right] \quad (1)$$

where N is the number of data points in each set. All calculations were performed using SPSS (version 11.5) and Excel software.

RESULTS AND DISCUSSION

Experimental Data of Solubility and Density. Table 1 lists the experimental molar and mole fraction solubilities of sodium acetate in the investigated binary solvent mixtures expressed in volume and mass fractions, the measured density of the saturated solution together with their standard deviations. There is a possibility of solid phase transformation in the saturated solutions, so one should consider the reported data as apparent solubility of sodium acetate. As expected, the solubility of sodium acetate in the monosolvents decreases in the sequence water > MeOH > PrOH > ACN; the molar solubility covers nearly 4 orders of magnitude from 5.53 mol·L⁻¹ in water to 0.0014 mol·L⁻¹ in ACN. Upon addition of a small amount of the less polar to the more polar solvent a marked reduction of the solubility (the difference of the molar concentrations at saturation) is observed in the range of the volume ratio between 1 and 0.9 to 0.8 of the more polar solvent, independent of the kind of the binary system. Although this decrease is largest by addition of ACN to water (the molar solubility drops from 5.53 mol·L⁻¹ in pure water to 1.89 mol·L⁻¹ when the volume fraction of ACN is 0.1), it is also observed when ACN is added to PrOH (whereas at a much lower molar solubility level; here the decrease is from 0.0937 to 0.0647 mol·L⁻¹ for 1.00 to 0.90 mass fraction PrOH). However, if we consider the relative effect, ACN-rich binary mixtures show the most pronounced change in solubility. For better visualization of this effect the solubility data are plotted in a logarithmic scale as function of the composition of the binary solvent mixture in Figure 1 (here we depict the mole fraction solubility as function of the mass fraction). It can be seen that if water is added at mass fraction of 0.1 to the pure apolar diprotic solvent ACN the mole fraction solubility is increased (whereas at a very low level) very markedly by 3 orders of magnitude from 1.19 ×

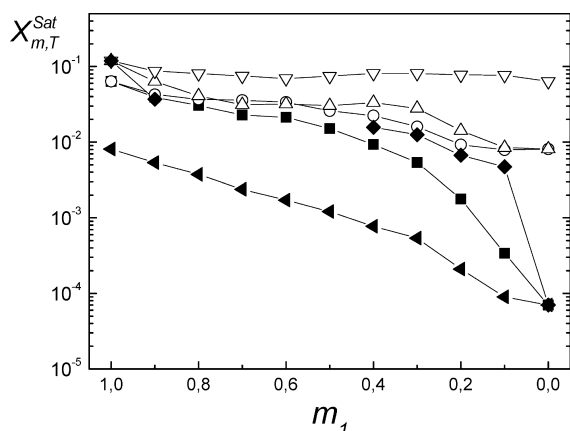


Figure 1. Mole fraction solubility, $X_{m,T}^{\text{sat}}$, of sodium acetate in binary solvent mixtures as function of the mass fraction, m_1 , of solvent (1), ▽, water (1) + MeOH (2); △, water (1) + PrOH (2); ◆, water (1) + ACN (2); ○, MeOH (1) + PrOH (2); ■, MeOH (1) + ACN (2); ◀, PrOH (1) + ACN (2).

10^{-1} to about 7×10^{-5} . A similar, but less pronounced effect can be observed for the MeOH + ACN mixtures.

The strong increase in solubility upon addition of water to ACN is explainable by the extremely differing solvation abilities of these two solvents for ions: whereas water is an excellent solvator for both cations and anions, ions are hardly stabilized in ACN due to its low solvation ability; the consequence is the low solubility of salts in this solvent. If water is added to ACN, the water molecules solvate the ions and stabilize them in the solution: even small amounts of water added to ACN result in a drastic increase in solubility.

In water (1) + ACN (2) mixtures between volume fraction (φ_2) of 0.5 and $\varphi_2 = 0.8$ saturated with sodium acetate phase separation was observed. This behavior is in contrast to that of the pure solvents, but in agreement with results reported for other saturated solutions of nonelectrolytes^{6–12} and electrolytes^{13,14} in mixed solvents. Paruta observed phase separation in the presence of salicylic acid and parabens (ethyl, propyl, and butyl) for water + dioxane mixtures,¹² and in presence of butyl paraben for water + ethanol mixtures.¹⁵ Pena and co-workers¹⁶ reported the phase separation of water + dioxane mixtures caused by dissolved benzocaine and salicylic acid at various temperatures.

Densities of the saturated solutions are given in Table 1, too. They are all in the relatively small range between $1.192 \text{ g}\cdot\text{cm}^{-3}$ for water and $0.7675 \text{ g}\cdot\text{cm}^{-3}$ for ACN. As expected, they are higher than those of the solute-free binary solvent mixtures.^{17–21} In both cases, the densities are uniformly continuous and nonlinear functions of the volume fraction without maxima.

Application of the Jouyban–Acree Model. Solubility. The Jouyban–Acree model provides mathematical descriptions for the solubility of solutes with respect to solvent composition and temperature as:³

$$\ln C_{m,T}^{\text{sat}} = m_1 \ln C_{1,T}^{\text{sat}} + m_2 \ln C_{2,T}^{\text{sat}} + \left[\frac{m_1 m_2}{T} \sum_{i=0}^2 J_i (m_1 - m_2)^i \right] \quad (2)$$

where $C_{m,T}^{\text{sat}}$ is the molar solute solubility in the solvent mixtures at absolute temperature T , m_1 and m_2 are the mass fractions of

the solvents 1 and 2 in the absence of the solute, $C_{1,T}^{\text{sat}}$ and $C_{2,T}^{\text{sat}}$ denote the molar solubility of the solute in the monosolvents 1 and 2, respectively, and J_i are the constants (expressed in K unit) of the model computed by regression analysis.

Equation 2 was used to fit the solubility data sets of sodium acetate in the present binary solvent mixtures as given in Table 1. The resulting model constants are computed and shown in Table 2. By the use of these constants, it is possible to predict

Table 2. Constants of the Jouyban–Acree Model for the Back-Calculation of Solubility of Sodium Acetate in Binary Solvent Mixtures According to Equation 2, N : Number of Binary Solvent Mixtures, MPD: Mean Percentage Deviation

solvent system	N	J_0	J_1	J_2	MPD
water + MeOH	11	−142	−652	−235	2.4
water + PrOH	11	−233	−1008	a	18.9
water + ACN	7	1766	−6291	a^a	24.0
MeOH + PrOH	11	277	81	−1581	3.2
MeOH + ACN	11	2344	−1801	−634	6.4
PrOH + ACN	11	382	a	a	12.9
overall:					11.3

^aNot statistically significant ($p > 0.10$).

the solubility of sodium acetate in all composition ranges of the solvents at various temperatures employing the experimental solubility in the monosolvents, that is, the values for $C_{1,T}^{\text{sat}}$ and $C_{2,T}^{\text{sat}}$ (the data for $m_1 = 1.000$ and $m_1 = 0.000$).

For the evaluation of the quality of the calculated solubility data upon application of the Jouyban–Acree model, these constant were used to back-calculate the data by eq 2. The agreement between calculated and experimental data was expressed by the MPD values as defined in the Introduction. As a result, the best agreement, indicated by the lowest MPD value, is observed for water + MeOH mixtures with 2.4 %, and the highest MPD value is found for water + ACN mixtures with 24.0 %. The relatively large MPD value for the water + ACN system is a consequence of the smaller number of obtainable solubility data (7 vs 11 for the other solvent systems) due to phase separation between 0.5 and 0.8 volume fractions of ACN. The overall MPD (OMPD) value (the mean of all values) is 11.3 %.

In Figure 2, the experimentally measured solubilities were plotted vs those recalculated by the aid of the Jouyban–Acree model. Because the solubilities vary over nearly 4 orders of magnitude, a bilogarithmic scale was chosen. A linear relation with a slight scatter around the line with slope 1 (the ideal relation between calculated and experimental data) can be observed, most pronounced for the solubilities in the water + ACN mixture. However, the generally only slight scatter reflects the agreement between the two data sets, which by far suffices for the purpose to forecast the solubility of sodium acetate in the binary solvents often used in practice.

Density. The density data of the saturated solutions are required in some process design computations and are also needed to convert the molar solubility to the mole fraction solubility or vice versa. The measured data for the density of the saturated solutions ($\rho_{m,T}^{\text{sat}}$) of binary solvent mixtures (see Table 1) were fitted to eq 3:

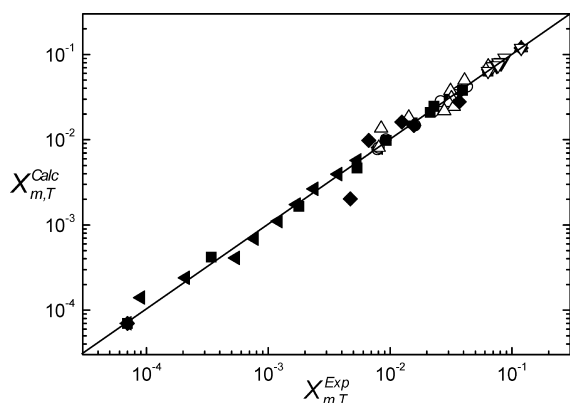


Figure 2. Calculated mole fraction solubility ($X_{m,T}^{\text{calc}}$) of sodium acetate versus experimental ($X_{m,T}^{\text{exp}}$) values: ∇ , water (1) + MeOH (2); $\triangle$, water (1) + PrOH (2); $\diamond$, water (1) + ACN (2); $\circ$, MeOH (1) + PrOH (2); $\blacksquare$, MeOH (1) + ACN (2); $\blacktriangleleft$, PrOH (1) + ACN (2).

$$\ln \rho_{m,T}^{\text{sat}} = m_1 \ln \rho_{1,T}^{\text{sat}} + m_2 \ln \rho_{2,T}^{\text{sat}} + \left[\frac{m_1 m_2}{T} \sum_{i=0}^2 A_i (m_1 - m_2)^i \right] \quad (3)$$

where $\rho_{1,T}^{\text{sat}}$ and $\rho_{2,T}^{\text{sat}}$ are the densities of the solute saturated solution of the monosolvents 1 and 2, respectively, at temperature T , A_i terms are the model constants.²² They are listed in Table 3 for all data sets (after excluding the constants

Table 3. Model Constants of the Jouyban–Acree Model for the Back-Calculation of (eq 3) of Density of Saturated Solutions of Sodium Acetate in Binary Solvent Mixtures According to Equation 3, MPD: Mean Percentage Deviation; N: Number of Binary Solvent Mixtures

solvent system	N	A_0	A_1	A_2	MPD
water + MeOH	11	70	−126	60	0.5
water + PrOH	11	−13	92	<i>a</i>	1.0
water + ACN	7	−141	28	173	0.3
MeOH + PrOH	11	−41	8	24	0.2
MeOH + ACN	11	−23	4	−11	0.1
PrOH + ACN	11	−18	<i>a</i>	<i>a</i>	0.2
overall:					0.4

^aNot statistically significant ($p > 0.10$).

with $p > 0.10$). Employing these model constants, the densities of the saturated solutions could be interpolated in solvent mixtures at all possible compositions.²²

It can be seen that the MPD values are 1 order of magnitude lower for the density than for the solubility: they range between 0.1 and 1.0. In other words, the predictions of the density of the saturated solution in the binary solvent mixtures are much better. This is clear considering the precision of the measurement of these two properties: whereas the RSD of the flame photometric determination of the salt concentration is in the range of 4 %, that of the pycnometric determination of the density is 1 order of magnitude lower. At a first view, the scatter of the data when the experimental and the calculated densities are plotted (see Figure 3) seems to differ from that of the solubility data (compare with Figure 2), but this is caused by the different scaling.

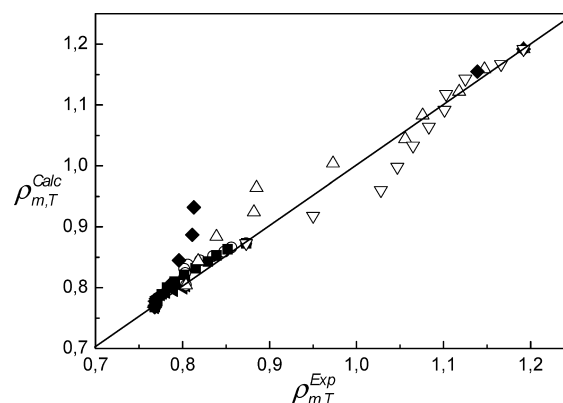


Figure 3. Calculated density ($\rho_{m,T}^{\text{calc}}$) of saturated solutions of sodium acetate versus experimental values ($\rho_{m,T}^{\text{exp}}$), both in $\text{g}\cdot\text{cm}^{-3}$; ∇ , water (1) + MeOH (2); $\triangle$, water (1) + PrOH (2); $\diamond$, water (1) + ACN (2); $\circ$, MeOH (1) + PrOH (2); $\blacksquare$, MeOH (1) + ACN (2); $\blacktriangleleft$, PrOH (1) + ACN (2).

CONCLUSIONS

We have reported the experimental apparent solubilities of sodium acetate in binary mixtures of MeOH, PrOH, ACN, and water and applied the Jouyban–Acree model to calculate the solubilities and the densities at any composition of the binary mixtures. This not only extends the available solubility database of solutes in mixed solvents² but demonstrates the relevance of these data for practical purposes, for example, for crystallization procedures in the chemical industry or for methods like liquid chromatography or capillary electrophoresis. Acetate buffers play an important role in these high-performance separation techniques. From our data it can be seen that the solubility ranges over nearly 4 orders of magnitude in the particular solvents, facts that have to be taken into account for their positive and negative aspects. Reducing solubility is an important task for purification by crystallization. It might have crucial consequences for example, in liquid chromatography when solvent gradients are applied for the mobile phase from water-rich compositions of the binary mixtures especially with MeOH or ACN to mixtures consisting of a high fraction of the organic solvent. Buffer constituents dissolved in the mobile phase may precipitate thus leading to a clogging of the separation column. Addition of organic solvents to the aqueous background electrolyte often used in capillary electrophoresis in order to increase analyte solubility or to change separation selectivity by changing the pK_a values of the acidic and basic constituents can also lead to partial precipitation of the buffer constituents; even if not explicitly visible, the microcrystalline precipitate results in unwanted and nonreproducible spikes in the recorded electropherograms and must be avoided.

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Notes

The authors declare no competing financial interest.

REFERENCES

- Jouyban, A.; Kenndler, E. Capillary Electrophoresis with Organic Solvents in Pharmaceutical Analysis: A Systematic Guide Through the Background. *Curr. Anal. Chem.* **2013**, in press.

- (2) Jouyban, A. *Handbook of Solubility Data for Pharmaceuticals*; CRC Press: Boca Raton, FL, 2009.
- (3) Jouyban, A. Review of the Cosolvency Models for Predicting Solubility of Drugs in Water-Cosolvent Mixtures. *J. Pharm. Pharmaceut. Sci.* **2008**, *11*, 32–58.
- (4) Jouyban, A.; Fakhree, M. A. A. Experimental and Computational Methods Pertaining to Drug Solubility. In *Toxicity and Drug Testing*; Acree, W. E., Jr., Ed.; InTech Publisher: New York, 2012.
- (5) Higuchi, T.; Connors, K. A. Phase Solubility Diagram. *Adv. Anal. Chem. Instrum.* **1965**, *4*, 117–212.
- (6) Soltanpour, S.; Jouyban, A. Solubility of Acetaminophen and Ibuprofen in Polyethylene Glycol 600, N-methyl Pyrrolidone and Water mixtures. *J. Solution Chem.* **2011**, *40*, 2032–2045.
- (7) Soltanpour, S.; Jouyban, A. Solubility of Pioglitazone Hydrochloride in Binary Mixtures of Polyethylene Glycol 400 with Ethanol, Propylene Glycol, N-Methyl-2-Pyrrolidone, and Water at 25 °C. *Chem. Pharm. Bull.* **2010**, *58*, 1132–1135.
- (8) Armitage, D. A.; Blandamer, J.; Foster, J.; Hidden, N. J.; Morcom, K. W.; Symons, M. C. R.; Wootten, M. J. Thermodynamic, Ultrasonic, Spectroscopic and Miscibility Studies of Water-Methyl Cyanide Solutions. *Trans. Faraday Soc.* **1968**, *64*, 1193–1200.
- (9) Pence, D. N.; Gu, T. Liquid-Liquid Equilibrium of the Acetonitrile Water System for Protein Purification. *Sep. Technol.* **1996**, *6*, 261–264.
- (10) Paruta, A. N.; Sciarrone, B. J.; Lordi, N. G. Solubility of Salicylic Acid as a Function of Dielectric Constant. *J. Pharm. Sci.* **1964**, *53*, 1349–1353.
- (11) Paruta, A. N.; Sciarrone, B. J.; Lordi, N. G. Solubility Profiles for the Xanthines in Dioxane - Water Mixtures. *J. Pharm. Sci.* **1965**, *54*, 838–841.
- (12) Paruta, A. N. Solubility of the Parabens in Dioxane-Water Mixtures. *J. Pharm. Sci.* **1969**, *58*, 204–206.
- (13) Takamuku, T.; Yamaguchi, A.; Matsuo, D.; Tabata, M.; Kumamoto, M.; Nishimoto, J.; Yoshida, K.; Yamaguchi, T.; Nagao, M.; Otomo, T.; Adachi, T. Large-Angle X-ray Scattering and Small-Angle Neutron Scattering Study on Phase Separation of Acetonitrile-Water Mixtures by Addition of NaCl. *J. Phys. Chem. B* **2001**, *105*, 6236–6245.
- (14) Nagaosa, Y. Salting Out of Polar Solvents from Aqueous Solution and its Application to Ion-Pair Extractions. *Anal. Chim. Acta* **1980**, *120*, 279–287.
- (15) Paruta, A. N. Solubility of the Parabens in Ethanol-Water Mixtures. *J. Pharm. Sci.* **1969**, *58*, 364–366.
- (16) Pena, M. A.; Bustamante, P.; Escalera, B.; Reillo, A.; Bosque-Sendra, J. M. Solubility and Phase Separation of Benzocaine and Salicylic Acid in 1,4-Dioxane-Water Mixtures at Several Temperatures. *J. Pharm. Biomed. Anal.* **2004**, *36*, 571–578.
- (17) Mikhail, S. Z.; Kimel, W. R. Densities and Viscosities of Methanol-Water Mixtures. *J. Chem. Eng. Data* **1961**, *6*, 533–537.
- (18) Fong-Meng, P.; Chye-Eng, S.; Tjoon-Tow, T.; Ibrahim, M. H. Densities and Viscosities of Aqueous Solutions of 1-Propanol and 2-Propanol at Temperatures from 293.15 K to 333.15 K. *J. Mol. Liq.* **2007**, *136*, 71–78.
- (19) Hickey, K.; Waghorne, W. E. Viscosities and Volumes of Dilute Solutions of Formamide in Water + Acetonitrile and for Formamide and N,N-Dimethyl formamide in Methanol + Acetonitrile Mixed Solvents: Viscosity B-Coefficients, Activation Free Energies for Viscous Flow, and Partial Molar Volumes. *J. Chem. Eng. Data* **2001**, *46*, 851–857.
- (20) Iglesias, M.; Orge, B.; Tojo, J. Densities and Refractive Indices for Acetone + Methanol + 1-Propanol at 298.15 K. *J. Chem. Eng. Data* **1996**, *41*, 218–221.
- (21) Nikam, P. S.; Shirsat, L. N.; Hasan, M. Density and Viscosity Studies of Binary Mixtures of Acetonitrile with Methanol, Ethanol, Propan-1-ol, Propan-2-ol, Butan-1-ol, 2-Methylpropan-1-ol, and 2-Methylpropan-2-ol at (298.15, 303.15, 308.15, and 313.15) K. *J. Chem. Eng. Data* **1998**, *43*, 732–737.
- (22) Jouyban, A.; Fathi-Azarbayjani, A.; Khoubnasabjafari, M.; Acree, W. E. Mathematical Representation of the Density of Liquid Mixtures at Various Temperatures using Jouyban-Acree Model. *Indian J. Chem. A* **2005**, *44*, 1553–1560.