Solubility of Nicotinic Acid and Nicotinamide in Carbon Dioxide at $T = (313.15$ to $373.15)$ K and $p = (5$ to $30)$ MPa: Experimental Data and Correlation

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The solubilities of nicotinic acid and nicotinamide in supercritical CO_2 with a static-analytical method were determined at temperatures (313.15, 333.15, 353.15, and 373.15) K and over the pressure range from (5 to 30) MPa. Solid−liquid phase transitions were determined with a modified capillary method in order to verify the physical state of components under pressure of gas. Solubility increased with increasing pressure for both the investigated substances. The solubility of nicotinic acid was in the range from $(3.05 \cdot 10^{-7}$ to $1.04 \cdot 10^{-5})$ mole fraction. The solubility of nicotinamide was found to be much higher, in the order of 10^{-3} mole fraction. The solubility data were correlated using four different density-based models. The results showed good agreement between calculated and experimental data. Solubility measurements were also preformed for the ternary system nicotinic acid−nicotinamide−CO_2 with two different mass ratios of solid components in the system (w(nicotinic acid)−w(nicotinamide) = 1:1 and 2:1) in a pressure range from (10 to 30) MPa and temperatures of (333.15 and 353.15) K. It was discovered that the composition of the mixture influences the solubilities of both components in CO_2; the solubility of nicotinamide decreased 10-fold, and the solubility of nicotinic acid was up to 8 times higher than in the binary system.

Introduction

Phase equilibria represent an important factor in supercritical fluid extraction (SFE) design. Knowledge of phase transition and solubility data in SFE can provide efficiency and economy for the process. Many solid substances used in pharmaceutical, cosmetic, and food industries have already been investigated.[1−5]

B-group vitamins are used for the treatment and prevention of diabetes, cardiovascular diseases, and the lowering the blood cholesterol.[6] Niacin is one of the B-group vitamins and is common name for two vitamers, nicotinic acid (NA) and its amide derivate, nicotinamide (ND). Nicotinic acid is a water-soluble vitamin with a relatively simple organic molecular structure (Figure 1a), chemically pyridine-3-carboxylic acid, also named vitamin PP or B_3. Nicotinamide is chemically pyridine-3-carboxamide (Figure 1b). Niacin can be found in yeast, cereals, nuts, legumes, and in some vegetables,[7] and as with other vitamins from the B-group, it is needed for the activity of metabolism.

Vitamins are usually divided into water-soluble (e.g., B-group, folic acid, and C) and fat-soluble (e.g., A, D, E, and K) vitamins.[6] The behavior of fat-soluble vitamins in supercritical fluids has already been investigated.[5,8,9] The solubility of fat soluble vitamins A, D, E, and K was measured in supercritical CO_2 at (303, 313, 333, and 353) K and over a pressure range of (8 to 35) MPa.[5,8] The behavior of vitamins D_2, D_3, E, and K_3 was also investigated in system with propane at (303, 313, 333, and 353) K and over a pressure range of (5 to 11) MPa.[5] Recently, increased interest has been shown in the extraction and concentration of vitamins from vegetable oils,[10,11] where the knowledge of phase equilibria in dense gases is essential. Water-soluble vitamins have low solubility in supercritical fluids,[12] which can also be advantageous because they can be concentrated in natural materials (e.g., vitamin rich vegetables). The solubility of nicotinic acid in CO_2 has already been reported in the literature by Rehman et al.,[12] where the authors measured solubility using a dynamic flow system with online UV detection. The solubility of nicotinamide in CO_2, to the best of our knowledge, has not been reported in the literature until now.

(a) (b)

Figure 1. Chemical structure of nicotinic acid (a) and nicotinamide (b).

The aim of this work was to determine the solubility of nicotinic acid and nicotinamide in pure CO_2 in a pressure range from (5 to 30) MPa and at temperatures of (313.15, 333.15, 353.15, and 373.15) K using the static-analytical method. Furthermore, the solid−liquid phase transitions of both compounds in CO_2 were determined. Experimental solubility data were correlated using four models, which suggest that the solubility of solid solute is dependent on the density of the solvent. The solubility of NA and ND in a ternary system was determined in a pressure range from (10 to 30) MPa and temperatures of (353.15 and 373.15) K using different mass ratios of the solid components. The data obtained from the ternary system were compared with the solubilities in the binary system, under the same conditions.

Experimental Section

Materials. Nicotinic acid (catalog no. 72309, $w > 0.999$) and nicotinamide (catalog no. 72340, $w > 0.985$) were supplied by Fluka (Switzerland). Potassium dihydrogen phosphate (catalog no. 30407, $w = 0.99$, Sigma-Aldrich, Germany) was used for preparing the phosphatic buffer, and acetonitrile was supplied

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by Merck (Darmstadt, Germany). The CO_2 (purity 2.5) was supplied by Messer (Ruše, Slovenia). The reagents were used without further purification.

Determination of Solid−Liquid Transition under Pressure. The basic scheme and a detailed description of the experimental equipment used for determining solid−liquid−gas transition under pressure can be found in the literature.[5,13−15] The procedure for determining the melting-points of substances under pressure was based on the common method used at atmospheric pressure. The substance was loaded in a glass capillary and placed, together with the thermo element, into the high-pressure cell. The gas was introduced and the pressure measured by a high-pressure gauge (Digibar PE 200 Hottinger-Baldwin to ± 0.1 %). The cell was electrically thermostatted by a heating jacket within ± 0.5 K, and the temperature measured by a thermocouple with an accuracy of ± 0.1 K.

The melting process (solid−liquid transition) of the substance in the capillary was observed visually using a camera. Temperature and pressure were registered at the beginning and at the end of the melting process. The screening experiments checked whether the observed melting temperature range depended on the mode of operation (pressure/temperature increase-upward strategy or pressure/temperature decrease-downward strategy). No hysteresis was found within an experimental accuracy (± 0.2 K/± 0.05 MPa).

Determination of the Solubility of Solids in CO_2. A static-analytic method was used for measuring the solubilities of substances in the supercritical CO_2. A detailed description can be found in the literature.[3−5,13−15]

An equilibrium cell, i.e., a high-pressure autoclave (120 mL), was loaded with a sufficient amount (approximately 5 g) of the solid substance. A high-pressure pump was used to pump liquefied CO_2 into the autoclave. The solid and CO_2 phase were mixed at constant temperature and pressure using a magnetic stirrer until equilibrium was reached. The temperature in the high-pressure equilibrium cell was controlled by a thermocouple with an accuracy of ± 0.5 K, and the pressure measured by a Digibar gauge, Hottinger Baldwin Messtechnik (accuracy ± 0.1 %). The time for reaching phase equilibrium and for sedimentation of the solid particles was estimated to be 1 h for each, and a sample of substance−supercritical CO_2 solution was taken by means of a sampling valve into a solvent trap. The concentration of solute solubilized in the solvent (acetonitrile) was determined by HPLC. The amount of CO_2 released (approximately 10 mL of gas under atmospheric conditions) was measured with a disposal of water in a graduated cylinder. The drop in pressure observed while taking the sample was from (0.2 to 0.5) MPa, depending on the pressure in the cell. A temperature change was undetected. Further experiments could be performed as the quantity of the sample taken from the cell was sufficiently small compared to the volume of the equilibrium cell.

Analysis. The concentrations of nicotinic acid and nicotinamide in the solutions taken from the solvent trap were determined using HPLC apparatus. The chromatographic conditions were column, C18 Kromasil 250 × 4.6 mm, 5 μm particle size (Varian); mobile phase, 50 mM phosphatic buffer pH 4/acetonitrile (90/10 v/v); flow-rate of mobile phase, 1 mL/min; wavelength, 263 nm. The samples were analyzed immediately after the sampling process. Quantification was carried out using individual calibration curves for each substance. Each data point represents the average of at least three measurements, and the relative standard deviation between measurements was 0.5 %.

Table 1. Physico-Chemical Properties of Nicotinic Acid and Nicotinamide

properties			nicotinic acid	nicotinamide
molecular weight	$M/g \cdot mol^{-1}$	FORMULA[a]	123.11	122.12
melting temperature	T_m/K	literature[b]	509.75	403.15
		measured[c]	510.26	404.15
boiling temperature	T_b/K	JOBACK[a]	sublimes	543.46
critical temperature	T_c/K	LYDERSEN[a]	529.42	828.19
critical pressure	p_c/MPa	LYDERSEN[a]	4.544	5.649
critical volume	$V_c/cm^3 \cdot mol^{-1}$	LYDERSEN[a]	0.372	0.326
acentric factor	ω	DEFINITION[a]	0.121	0.227

[a] ASPEN software.[22] [b] Data from literature.[21] [c] Measured with DSC (Thermoanalitical system Mettler TA 3000).

Solubility Data Correlations. The solubility data for the binary mixtures were correlated with four density-based models. All constants in the applied models were estimated by regression of the experimental solubility data to obtain a minimum value of an absolute average relative deviation (AARD/%), which was calculated as

$$\mathrm{AARD}/\% = \frac{1}{N}\sum_{1}^{N}\frac{|y_{\mathrm{calc}} - y_{\mathrm{exp}}|}{y_{\mathrm{exp}}} \cdot 100 \qquad (1)$$

where y_{calc} is the mole fraction of the compound solubilized in CO_2, calculated by the model, y_{exp} is the mole fraction of the compound determined experimentally, and N is the number of measurements.

Correlation Model by Kumar and Johnston: ln(y) vs ln(ρ_r). The expression relating the solubility of a solid solute in a supercritical fluid as a function of solvent density was proposed by Kumar and Johnston.[16]

Correlation Model by Chrastil. The model proposed by Chrastil[17] relates the solubility of a solute to the density of the supercritical solvent. It is based on the assumption that the molecule of a solute associates with the molecules of gas by the formation of a solvato complex, which is in equilibrium with the gas.

Correlation Model by Mendez.[18] The authors suggest that a linear expression, which is valid for diluted solutions, also can be used for the calculation of solid solubility data. They improved the equation proposed by Harvey.[19] Because sublimation pressure is unavailable for all solids, the Clausius−Clapeyron-type expression for sublimation pressure was added to the equation suggested by Harvey.[19]

Correlation Model by Miller.[20] Correlation of the solubility data using the model proposed by Miller[20] is based on the concept of solubility enhancement.

Results and Discussion

The physicochemical properties of the substances investigated are presented in Table 1. The normal melting points were obtained from the literature[21] and were measured using a differential scanning calorimeter (DSC) at atmospheric pressure. The boiling point, critical temperature, critical pressure, critical volume, and acentric factor were estimated by the group contribution method, using ASPEN software.[22]

Phase Transitions under the Pressure of CO_2. The S−L transitions of nicotinic acid and nicotinamide under the pressure of CO_2 are presented in Table 2 and Figure 2. Each value was measured at least twice, and the relative standard deviation was 3.5 %. The S−L transitions for both substances were observed

Table 2. Experimental Phase Equilibrium of Nicotinic Acid and Nicotinamide

nicotinic acid		nicotinamide	
p/MPa	T/K	p/MPa	T/K
0.2	510.1	0.1	402.3
5.1	506.6	4.3	401.5
10.2	503.8	7.4	400.7
15.2	505.4	11.2	399.3
27.3	503.7	16.9	397.8
34.6	503.8	22.0	398.1
		28.4	401.1
		36.2	400.8

at pressures ranging from (0 to 35) MPa and the corresponding temperatures (Table 2).

The melting-point of nicotinic acid under the pressure of CO_2 decreases with increasing pressure from 510.3 K at atmospheric pressure to 503.8 K at 10.2 MPa, after which it remains constant regarding any further increase in pressure. The melting-point of nicotinamide in CO_2 decreases with increasing pressure from 404.2 K at atmospheric pressure to 397.8 K at 16.9 MPa. With a further increase of pressure from (16.9 to 36.2) MPa, the melting point increases again, by approximately 3 K.

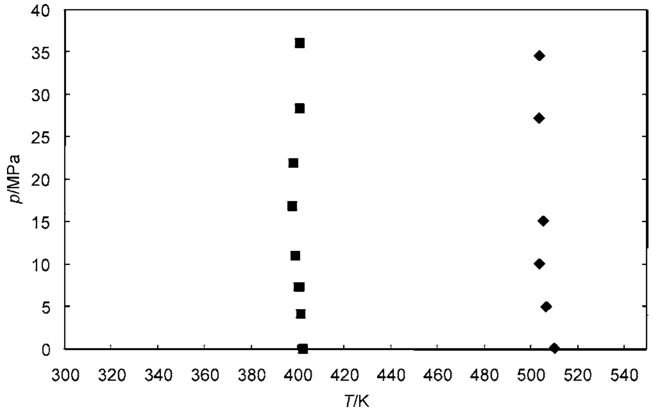

Figure 2. $p-T$ diagram for nicotinic acid−CO_2 and nicotinamide−CO_2 systems: ■, nicotinamide; ♦, nicotinic acid.

Table 3. Equilibrium Mole Fraction y_2 of Nicotinic Acid in Carbon Dioxide from T = (313.15 to 373.15) K

p/MPa	$y_2 \cdot 10^6$
T/K=313.15	
5.2	0.31 ± 0.05
11.1	0.99 ± 0.10
14.2	1.03 ± 0.10
19.6	1.29 ± 0.13
25.0	1.80 ± 0.15
29.7	1.95 ± 0.21
T/K= 333.15	
5.4	0.91 ± 0.05
15.4	1.18 ± 0.12
20.2	1.40 ± 0.15
25.7	2.69 ± 0.24
29.8	2.87 ± 0.28
T/K = 353.15	
4.5	0.69 ± 0.05
11.4	1.10 ± 0.10
15.5	1.39 ± 0.15
20.3	2.80 ± 0.30
25.4	3.67 ± 0.35
30.2	4.22 ± 0.39
T/K = 373.15	
5.6	0.66 ± 0.10
10.8	1.68 ± 0.13
19.7	4.07 ± 0.37
25.7	5.89 ± 0.41
30.1	10.41 ± 0.83

Table 4. Equilibrium Mole Fraction y_2 of Nicotinamide in Carbon Dioxide from T = (313.15 to 373.15) K

p/MPa	$y_2 \cdot 10^3$
T/K= 313.15	
5.4	0.26 ± 0.02
9.8	0.31 ± 0.03
15.3	0.67 ± 0.05
20.0	0.75 ± 0.05
23.7	1.37 ± 0.05
29.3	1.86 ± 0.08
T/K= 333.15	
5.9	0.18 ± 0.02
11.4	0.16 ± 0.02
15.2	0.69 ± 0.03
20.5	1.09 ± 0.03
25.3	1.66 ± 0.06
29.8	2.65 ± 0.15
T/K = 353.15	
5.5	0.04 ± 0.02
11.8	0.22 ± 0.02
15.9	0.83 ± 0.03
19.9	2.25 ± 0.09
24.4	2.68 ± 0.14
30.5	3.02 ± 0.20
T/K = 373.15	
5.5	$0.01 \pm 9 \cdot 10^{-3}$
11.6	0.12 ± 0.02
16.0	0.57 ± 0.03
20.2	1.67 ± 0.06
25.2	2.77 ± 0.16
30.2	3.14 ± 0.27

Experimental Solubility Data in the Binary System. The results of solubility measurements for NA and ND in the CO_2 obtained during this work are listed in Tables 3 and 4. These solubilities were determined at temperatures of (313.15, 333.15, 353.15, and 373.15) K, in pressure range from (5 to 30) MPa. Each value from the solubility data reported in this work was taken from an average from triplicate measurements. The uncertainty of the mole fraction for nicotinic acid and nicotinamide was estimated as being generally less than 11 % and 9 %, respectively.

The mole fraction of NA in CO_2 phase rises with increasing pressure from $3.1 \cdot 10^{-7}$ (5.2 MPa) at 313.15 K to $1.041 \cdot 10^{-5}$ (30.12 MPa) at 373.15 K. At constant temperature, the solubility of NA increased with increasing pressure, as expected. The obtained results were compared with the literature data published

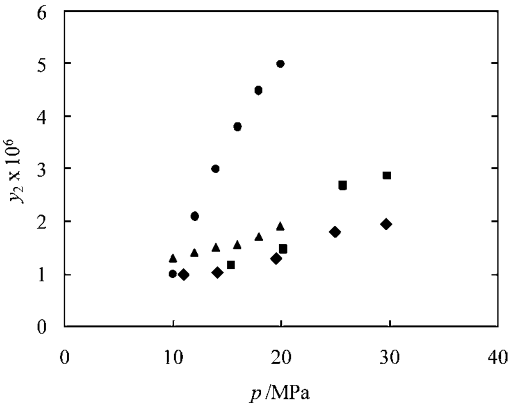

Figure 3. Solubility of nicotinic acid y_2 in CO_2 in the binary system, comparison of measured and reference data: ♦, 313.15 K this work; ■, 333.15 K this work; ▲, 308.15 K Rehman et al.;[12] ●, 328.15 K Rehman et al.[12]

Table 5. Constants Obtained from Data Correlation

$\ln(y) - \ln(\rho_r)$	T range/K	p range/MPa	Θ	C_0		AARD/%
nicotinic acid	313.15−373.15	10−30	2.0365	−13.6933		14.76
nicotinamide	313.15−373.15	10−30	3.4729	−7.8259		15.06
Chrastil model	T range/K	p range/MPa	K	a	b	AARD/%
nicotinic acid	313.15−373.15	10−30	3.0365	−1601.26	−6.2480	19.51
nicotinamide	313.15−373.15	10−30	4.3770	−1962.34	−6.1734	18.82
Mendez model	T range/K	p range/MPa	A'/K	$B'/\mathrm{m^3 \cdot K \cdot kg^{-1}}$	C'/−	AARD/%
nicotinic acid	313.15−373.15	10−30	−8207.3	2.1493	12.195	16.02
nicotinamide	313.15−373.15	10−30	−8497.0	3.0487	17.559	22.47
Miller model	T range/K	p range/MPa	a/−	b/K	$c/\mathrm{m^3 \cdot kg^{-1}}$	AARD/%
nicotinic acid	313.15−373.15	10−30	10.156	−5916.9	0.006 775	36.66
nicotinamide	313.15−373.15	10−30	17.182	−6223.9	0.008 675	20.68

by Rehman et al.,[12] where the solubility of NA in CO_2 was measured in the pressure range from (10 to 20) MPa and temperatures (308.15 and 328.15) K. The high-pressure solubility data obtained during this work at a lower temperature of 313.15 K are in good agreement with literature data at 308.15 K (Rehman et al.[12]). On the other hand, at 328.15 K and pressures above 12 MPa, the solubilities measured by Rehman et al.[12] are much higher than data from the presented research. The difference could be a consequence of different measurement techniques. Authors[12] have used the dynamic method with continuous-flow over the bed of the substance while in our case static apparatus was used. The high-pressure autoclave was loaded with the substance and then CO_2 from a gas cylinder was cooled to a liquid state and compressed into the autoclave using a high-pressure pump. The content of the cell was mixed with a stirrer under constant operating conditions (temperature and pressure) until equilibrium was reached. Afterward, the two phases were left to separate for 1 h before samples from the upper phase were taken, as described in the Experimental Section. Comparisons between measurements obtained during this work and literature data[12] are shown in Figure 3.

ND was more soluble in CO_2 because of the amino group in the structure. The solubility is approximately 10^3 times higher than the solubility of NA; however, the solubility trends are similar. The mole fraction of ND in the CO_2 phase rises when increasing the pressure, from $2.6 \cdot 10^{-4}$ (5.4 MPa) at 313.15 K to $3.14 \cdot 10^{-3}$ (30.2 MPa) at 373.15 K.

Solubility Correlations. Solubility data were correlated using four density-based models: Kumar and Johnston, the Chrastil model, the Mendez model, and the model of Miller. Generally, the models are valid for densities ranging from half to twice the critical density of CO_2 ($\rho_c/\mathrm{kg \cdot m^{-3}} = 467.6$). In all four models, measurements at low solvent densities (below ($\rho/\mathrm{kg \cdot m^{-3}} = 230$) were excluded from the calculation because of high AARD value (over 150 %). In this way, low values of AARD were generally obtained, which suggests that the experimental data and calculated data are in good agreement (Table 5). Comparison between the measured and calculated data for the better fitting models are shown in Figures 4 and 5.

The AARD values for the both substances in the Kumar and Johnson and Chrastil models were approximately (15 and 19) %, respectively. Within the same pressure and temperature ranges, the AARD values in the Mendez model were (16.02 and 22.47) % for NA and ND, respectively. When the Miller model was used, the AARD of the calculated and experimental data were somewhat higher, 36.66 % and 20.68 % for NA and ND, respectively.

Solubility Data in the Ternary System. A comparison of the solubility data for compounds in the binary and ternary systems is presented in Figures 6 and 7 for NA and ND, respectively. Each value of solubility data reported in this work was taken from the average of triplicate measurements. The uncertainty for the mole fraction of nicotinic acid and nicotinamide in the ternary system was generally estimated to be less than (10 and 12) %, respectively.

According to the phase transition measurements under the pressure of CO_2 (Figure 2), the substances were solid at the temperatures and pressures investigated. In Figure 6, it can be seen that the solubility of NA in CO_2 is generally higher in the case of the ternary system than in the binary system. At mass

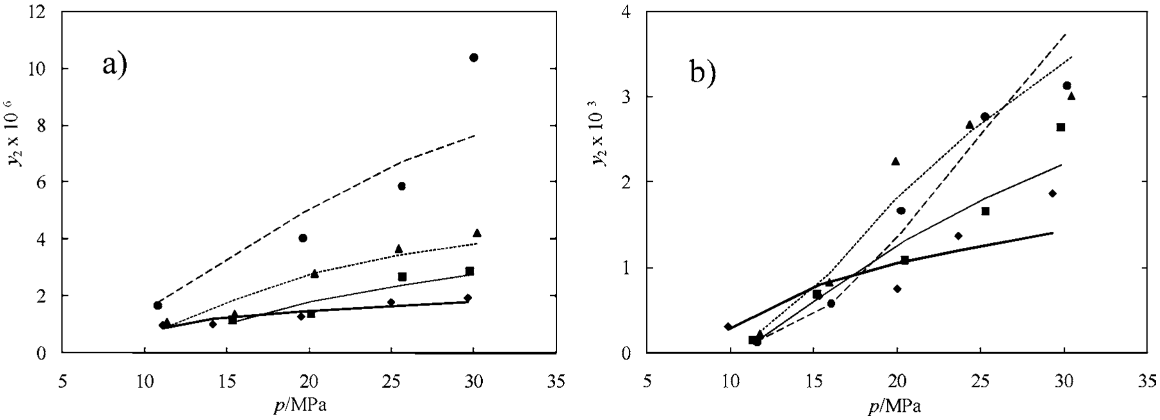

Figure 4. Solubility of (a) nicotinic acid and (b) nicotinamide in CO_2, comparison of measured (exp) and calculated (calc) data with the Kumar and Johnston correlation: ◆, 313.15 K exp; thick —, 313.15 K calc; ■, 333.15 K exp, —, 333.15 K calc; ▲, 353.15 K exp; •••, 353.15 K calc; ●, 373.15 K exp; ---, 373.15 K calc.

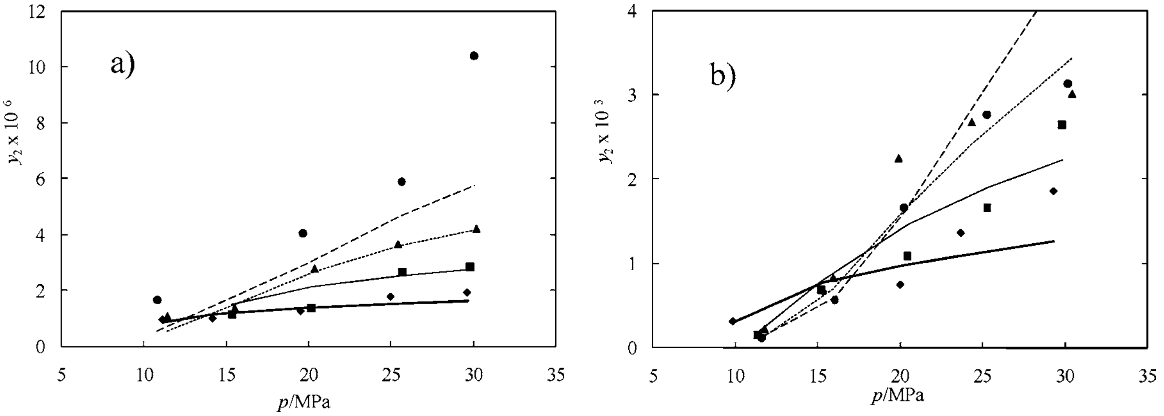

Figure 5. Solubility of (a) nicotinic acid and (b) nicotinamide in CO_2, comparison of measured (exp) and calculated (calc) data with the Chrastil correlation: ◆, 313.15 K exp; thick —, 313.15 K calc; ■, 333.15 K exp; —, 333.15 K calc; ▲, 353.15 K exp; •••, 353.15 K calc; ●, 373.15 K exp; ---, 373.15 K calc.

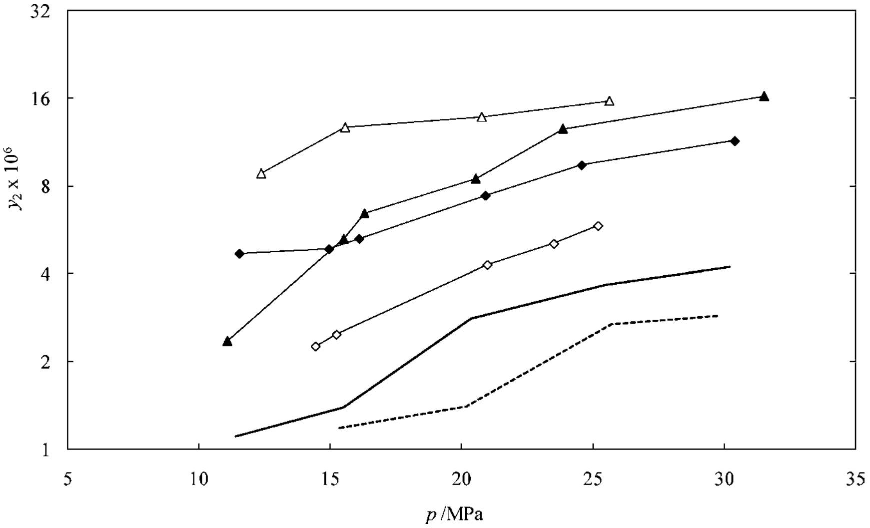

Figure 6. Experimental solubility data of nicotinic acid in CO_2 in binary and in ternary system with nicotinamide at different mass ratios of solid components: -◇-, ternary w(NA)−w(ND) = 1:1 at 333.15 K; -Δ-, ternary w(NA)−w(ND) = 1:1 at 353.15 K; -◆-, ternary w(NA)−w(ND) = 2:1 at 333.15 K; -▲-, ternary w(NA)−w(ND) = 2:1 at 353.15 K; ---, binary at 333.15 K; —, binary at 353.15 K.

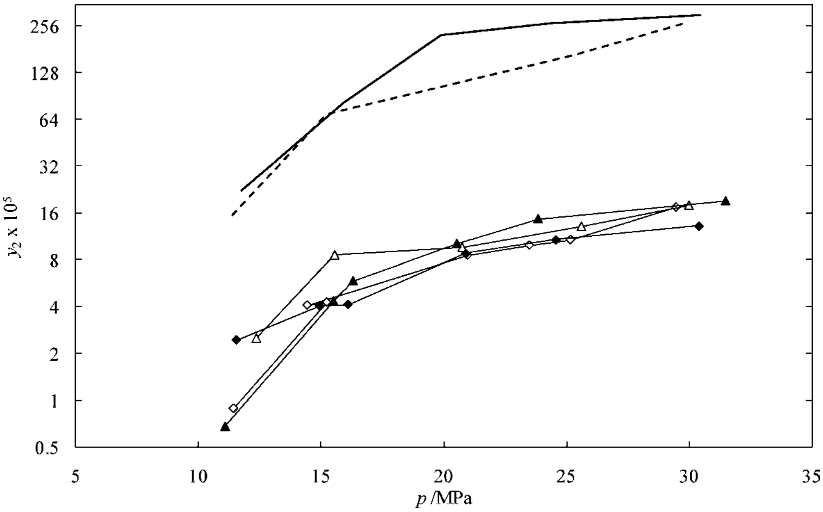

Figure 7. Experimental solubility data of nicotinamide in CO_2 in binary and in ternary system with nicotinic acid at different mass ratios of solid components: -◇-, ternary w(NA)−w(ND) = 1:1 at 333.15 K; -Δ-, ternary w(NA)−w(ND) = 1:1 at 353.15 K; -◆-, ternary w(NA)−w(ND) = 2:1 at 333.15 K; -▲-, ternary, w(NA)−w(ND) = 2:1 at 353.15 K; ---, binary at 333.15 K; —, binary at 353.15 K.

ratio w(NA)−w(ND) = 1:1 and 333.15 K the solubility increased for factor 2 at all investigated pressures, and at 353.15 K for factor 8 at 10 MPa and for factor 4 at 30 MPa. At mass ratio w(NA)−w(ND) = 2:1, the same solubility trends were observed and the solubilities of NA were 4 times higher. Oppositely, the solubility of ND in CO_2 in the presence of NA was lower than in the binary system. The solubility isotherms of ND in CO_2 in the ternary and binary systems are shown in Figure 7. The solubility of ND in CO_2 decreased in the presence of NA for factor 6 at 10 MPa and 333.15 K up to factor 33 at

10 MPa and 353.15 K (mass ratio $w(\mathrm{NA})-w(\mathrm{ND}) = 2{:}1$). At mass ratio $w(\mathrm{NA})-w(\mathrm{ND}) = 1{:}1$, the solubility of ND in CO_2 was lower for factor 15 at all investigated pressures and temperatures.

In the mixture of two polar solid substances under the pressure of CO_2, strong solute−solute interactions exist due to the presence of hydrogen bonding sites. It was observed that the ND has a greater entraining effect on the solubility enhancement of NA. This result supports Dobbs and Johnston's[23] postulate that a more soluble solute causes a significant increase in the solubility of the less soluble solute rather than vice versa. Furthermore, the decrease in solubility of ND in the presence of NA in the ternary system could be a consequence of strong interactions between carboxyl- (NA) and amino- (ND) groups. One possible explanation is that the ND molecule is protonated and becomes more polar and less soluble in CO_2. The second reason could be the change in pH. More detailed investigation on this type of effect should be done in the future.

Conclusions

The solubility of NA and ND in binary and ternary systems with CO_2 was determined in the pressure range from (5 to 30) MPa and in the temperature range from (313.15 to 373.15) K using the static-analytical method. The solubilities of both compounds in CO_2 increased with increasing pressure for both investigated substances. In the binary system, the solubility of ND in CO_2 was higher by 3 orders of magnitude than the solubility of NA. The solubility of NA and ND in supercritical CO_2 was correlated with models based on solvent density. Four different models were tested and satisfactory results were obtained for all four.

The solubilities of single compounds in SCF in the ternary system NA−ND−CO_2 are different than in the binary systems and depend on the composition of the ternary mixture. In the case of NA, the solubility in CO_2 in the ternary system was up to 8 times higher while in the case of ND, it was up to 33 times lower. The solubility enhancement observed in this system confirms the entrainer effect.

Investigations of solubility measurements in ternary systems are vital, since in nature real systems are multicomponent and the entrainer effect in these systems offers new possibilities in SCF technology. Future investigations should involve more detailed solubility studies of polar substances in ternary systems.

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