Extraction of Pyridine-3-carboxylic Acid Using 1-Dioctylphosphoryloctane (TOPO) with Different Diluents: Equilibrium Studies†

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Pyridine-3-carboxylic acid (also known as nicotinic acid) is widely used in food, pharmaceutical, and biochemical industries. The production of acid can be intensified by enzymatic conversion of 3-cyanopyridine or biosynthesis and by reactive extraction used as a separation step from a dilute fermentation broth. The extraction of pyridine-3-carboxylic acid by 1-dioctylphosphoryloctane, also known as tri-*n*-octylphosphine oxide (TOPO), with five different diluents (*n*-octane, methylbenzene, 4-methyl-2-pentanone (MIBK), decan-1-ol, and dichloromethane) is studied. The equilibrium experiments are carried out to investigate the effects of diluent, extractant (TOPO) composition, and initial acid concentration on extraction efficiency. The extraction efficiency is found to increase with increasing TOPO composition concentration, (0.10 to 0.60) mol·m^{-3}, and found to decrease with increasing initial acid concentration, (0.02 to 0.12) mol·m^{-3}. The number of TOPO molecules in the acid:TOPO complex is estimated through a proposed mathematical model using graphical methods as well as through an optimization route using the differential evolution algorithm and found to be 1:1 complexes in most of the cases. The extraction equilibrium constants are also determined. In all the tested diluents, methylbenzene containing the benzene ring in the structure is the best solvating agents for acid−TOPO complexation giving $K_{E1} = 5.04$.

Introduction

Pyridine-3-carboxylic acid (also called niacin or nicotinic acid) is an important carboxylic acid and a water-soluble vitamin (vitamin B3), which is used in animal feed supplementation and also in medicine.[1,2] Lack of this causes the deficiency disease pellagra. Pellagra prevention and treatment have been made by including pyridine-3-carboxylic acid in dietary intake. Since the human body does not have the ability to produce it, its intake by food and/or nutritional supplements represents the main way of avoiding deficiency.[2,3]

Pyridine-3-carboxylic acid (CAS#: 59-67-6) is mainly obtained by chemical synthesis, using 3-picoline (CAS#: 108-99-6) or 2-methyl-5-ethyl-pyridine (CAS#: 104-90-5) as starting-materials, at high temperature and pressure. Besides the technical aspects, other parameters such as desired quality, physical and chemical properties of the final product, and the ecological problems complicate the chemical synthesis methods. Due to these reasons, the chemical synthesis route for the acid production will become unattractive in the future. In recent years, the application of enzymes to organic chemical processing has attracted the attention of researchers.[4,5] Nitrilases enzymes are gaining popularity as biocatalysts for the mild and selective hydrolysis of nitriles.[6] The production of pyridine-3-carboxylic acid and pyridine-3-carboxamide (nicotinamide, CAS#: 98-92-0) can be intensified by enzymatic conversion of 3-cyanopyridine (CAS#: 100-54-9) or biosynthesis. Mathew et al.[7] made attempts for the microbial conversion of 3-cyanopyridine to pyridine-3-carboxylic acid by using resting *Rhodococcus rhodochrous* Jl cells containing high benzonitrilase activity. This process is promising for industrial production of this acid with attractive features such as total conversion (100 %) of 3-cyanopyridine under mild conditions and easy cultivation of the *R. rhodochrous* Jl cells. Very recently, amidase-catalyzed production of pyridine-3-carboxylic acid in batch and continuous stirred membrane reactors has been studied by Maria et al.[8] Amidase enzyme, operated under mild conditions, is suitable for the synthesis of labile organic molecules, and it is stable up to 50 °C. This fermentation process, because of various impurities and very low concentration of product in the fermentation broth, requires an economic separation method to compete with the synthetic process.[5]

Many separation processes in chemical industries have been employed to recover the organic acids from aqueous solution.[9,10] The classical recovery method includes the precipitation of calcium salt after the addition of calcium hydroxide (CAS#: 1305-62-0) to the aqueous fermentation broth. This precipitation method has disadvantages such as the substantial cost of chemicals, a low yield in crystallization, and product loss.[11] Many bioconversions, including fermentation, are highly inhibited by the product. A means to overcome this inhibition is In Situ Product Recovery (ISPR).[12,13] Among various alternate processes for the simultaneous removal of the product, extraction is often the most suitable option.[13−15] The combination of reaction with this extraction step may also be useful. So, a reactive extraction method has been proposed to be an effective primary separation step for the recovery of carboxylic acid from a dilute fermentation process.[16,17] Some of the advantages are increased reactor productivity and easy control of pH in reactor without requiring a base addition. This method may also allow the process to produce and recover the fermentation products in one continuous step and thereby reduce the downstream

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10.1021/je900205h CCC: $40.75
Published on Web 04/29/2009

Table 1. Characteristics of Diluents

reagents	purity (w = mass fraction)	mol. wt. / kg·mol^{-1}	specific gravity	dielectric constants	dipole moments / (debye)
n-octane (CAS#: 111-65-9)	0.997	114.23	0.701	1.94	0.02
dichloromethane (CAS#: 75-09-2)	0.990	84.93	1.326	9.08	1.80
4-methyl-2-pentanone (CAS#: 108-10-1)	0.998	100.16	0.801	13.1	2.81
methylbenzene (CAS#: 108-88-3)	0.997	92.14	0.867	2.38	0.39
decan-1-ol (CAS#: 112-30-1)	0.980	158.28	0.830	7.8	2.62

processing load and the recovery costs.[18] Three major factors have been found to influence the equilibrium characteristics of extraction of carboxylic acids from aqueous solutions, i.e., the nature of acid, concentrations of acid and extractant, and the type of diluent.[19−23]

Organophosphorus compounds and long-chain aliphatic amines are effective extractants for the separation of carboxylic acids from dilute aqueous solution. Phosphorus-bonded, oxygen-containing extractants have a phosphoryl group and a stronger Lewis basicity than those of carbon-bonded, oxygen-containing extractants. Phosphorus-bonded, oxygen-containing extractants can only coextract small amounts of water and show low solubilities in water. When organophosphorus extractants are used, the solvation has a higher specificity.[17]

Generally, organophosphorus-based and amine-based extractants are dissolved in a diluent such as ketone, alcohol, hydrocarbon, etc. to provide appropriate physical properties for use in the extraction process. For the removal and separation of organic acids, it is very important to understand the influence of different parameters on the overall distribution coefficient of each organic acid. Since the presence of hydroxyl and carboxylic groups increases the solubility of acids in the water phase, the strong interactions of solvent with solutes are necessary to extract carboxylic acids from dilute aqueous solutions. The extraction constant and the number of reacting molecules of extractant are estimated from the mass action law, but the obtained values are different according to the composition of the solvent for the same extractant and the organic acid.[24]

Extraction of organic acids has been studied using phosphorus bonded oxygen bearing extractants such as 1-dialkylphosphorylalkane, also known as tri-*n*-alkyl phosphine oxide (TRPO),[25−32] and phosphoric acid tributyl ester (CAS#: 126-73-8), also known as tri-*n*-butyl phosphate (TBP).[31−35] Very recently, the extraction equilibrium study of propanoic acid (CAS#: 79-09-4) using TBP in different diluents such as dodecan-1-ol (CAS#: 112-53-8), benzene (CAS#: 71-43-2), methylbenzene (CAS#: 108-88-3), heptane (CAS#: 142-82-5), hexane (CAS#: 110-54-3), and butyl ethanoate (CAS#: 123-86-4) has been performed by Keshav et al.[33] Equilibrium parameters such as the distribution coefficient, loading ratio, degree of extraction, and equilibrium complexation constant have been presented for the extraction of propanoic acid. Kumar et al.[31] studied reactive extraction of pyridine-3-carboxylic acid with TBP and TOPO at a fixed initial acid concentration to intensify the recovery from fermentation broth. The distribution of between water and *N*,*N*-dioctyl-1-octanamine (Alamine 300, CAS#: 1116-76-3) dissolved in polar and nonpolar diluents is studied at 298 K using a phase ratio of 1:1 (v/v) by Senol.[36] The comparative study of the reactive extraction of pyridine-3-carboxylic acid with lauryl-trialkyl-methylamine (Amberlite LA-2, CAS#: 11128-96-4) and di-(2-ethylhexyl)-phosphoric acid (D2EHPA, CAS#: 298-07-7) has been presented by Cascaval et al.[37] Compared to di-(2-ethylhexyl)-phosphoric acid, the use of lauryl-trialkyl-methylamine allows the possibility to reach higher extraction efficiency, the extraction degree being supplementarily increased by increasing the solvent polarity.

The aim of the present work is to study the reactive extraction of pyridine-3-carboxylic acid from aqueous solutions using 1-dioctylphosphoryloctane (TOPO) in different diluents covering wide range of categories (aliphatic hydrocarbon, chlorinated hydrocarbon, ketone, aromatic, and alcohol) to provide the extraction equilibrium data for intensification of pyridine-3-carboxylic acid production via an enzymatic route. Various diluents such as *n*-octane (CAS#: 111-65-9), methylbenzene (CAS#: 108-88-3), 4-methyl-2-pentanone (MIBK, CAS#: 108-10-1), decan-1-ol (CAS#: 112-30-1), and dichloromethane (CAS#: 75-09-2) are used for their abilities to improve the extractive efficiency of TOPO. The effects of initial acid concentration and composition of extractant (TOPO) are also studied. An equilibrium model based on mass action law is presented and used to determine the equilibrium extraction constant (K_E) and the number of extractant molecules per acid molecule (n) with a graphical method as well as an optimization procedure. The population-based search algorithm, differential evolution, is used as the optimization algorithm.

Experimental Section

Reagents and Solutions. 1-Dioctylphosphoryloctane (CAS#: 78-50-2), a phosphorus-bonded oxygen donor supplied by Sigma-Aldrich Co. USA, with purity of 0.99 (w = mass fraction) is a white powder with the molar mass of 386.65 kg·mol^{-1}. Pyridine-3-carboxylic acid (CAS#: 59-67-6), a white powdered material as analytical grade reagents (w = 0.995), is procured from HIMEDIA, India. Various diluents such as *n*-octane (CAS#: 111-65-9, supplied by S. D. Fine-Chem Ltd., India), 4-methyl-2-pentanone (CAS#: 108-10-1, supplied by SPECTROCHEM Pvt. Ltd. India), decan-1-ol (CAS#: 112-30-1, supplied by SPECTROCHEM Pvt. Ltd. India), methylbenzene (CAS#: 108-88-3, supplied by SISCO Res. Lab. Pvt. Ltd., India), and dichloromethane (CAS#: 75-09-2, supplied by S. D. Fine-Chem Ltd., India) of analytical reagent grade are used. Organic solutions are prepared using TOPO as extractant dissolved in diluents. The initial TOPO concentrations are varied in the range of (0.10 to 0.60) mol·m^{-3}. The various diluents with different characteristics as given in Table 1 are used with extractant (TOPO) to investigate the effect of diluent type. Deionized water is used to prepare the aqueous solutions of various concentrations of pyridine-3-carboxylic acid. Since acid concentration in the fermentation broth is found to be very low, the aqueous solutions of acid are prepared in the range of (0.02 to 0.12) mol·m^{-3}. Sodium hydroxide (CAS#: 1310-73-2) used for titration is of analytical grade (w = 0.98) and was supplied by Merck Pvt. Ltd., Germany. For the standardization of NaOH solution, ethanedioic acid (CAS#: 144-62-7) with w = 0.998 is obtained from S. D. Fine-Chem Ltd., India. 3,3-Bis(4-hydroxyphenyl)isobenzofuran-1(3H)-one, also known as phenolphthalein (CAS#: 77-09-8) solution (pH range of 8.2 to 10.0), used as an indicator for titration, is obtained from Ranbaxy, India. All chemicals are used without any pretreatment.

Table 2. Distribution Coefficients (K_D) of Pyridine-3-carboxylic Acid (Nicotinic Acid) between Water and Diluents by Physical Extraction at 298 K

diluents	K_D	refs
n-heptane (CAS#: 142-82-5)	0.012	37
kerosene (CAS#: 8008-20-6)	0.011	31
4-methyl-2-pentanone (CAS#: 108-10-1)	0.18	31
trichloromethane (CAS#: 67-66-3)	0.018	37
nitrobenzene (CAS#: 98-95-3)	0.011	37
cyclohexan-1-one (CAS#: 108-94-1)	0.59	37
cyclohexane (CAS#: 110-82-7)	0.015	37
octan-1-ol (CAS#: 111-87-5)	0.35	31
benzene (CAS#: 71-43-2)	0.014	31
methylbenzene (CAS#: 108-88-3)	0.015	31

Procedure. The extraction equilibrium experiments are carried out at constant temperature (298 K) with equal volumes (12 cm^3 of each phase) of the aqueous and organic solutions shaken at 100 rpm for 8 h in conical flasks of 100 mL on a temperature-controlled reciprocal shaking machine (HS 250 basic REMI laboratories). This mixing time could be considered as the appropriate time for attaining equilibrium based on our preliminary studies. After attaining equilibrium, the phases are brought into contact with each other for separation in a constant-temperature (298 K) bath operated at atmospheric pressure. After settling, organic and aqueous phases are separated. The concentration of acid in the aqueous phase is determined by potentiometric titration with fresh sodium hydroxide solution of 0.01 $mol \cdot m^{-3}$ concentration using 3,3-bis(4-hydroxyphenyl)-isobenzofuran-1(3*H*)-one as an indicator and also using a UV spectrophotometer (Systronics, 119 model, 262 nm). The acid concentration in the organic phase is calculated by mass balance. The initial and equilibrium pH values of aqueous solutions are measured using a digital pH-meter of ArmField Instruments (PCT 40, Basic Process Module) which varied in the range of (2.45 to 2.92) and (2.74 to 3.42), respectively. The reproducibility is checked by carrying out the experiments twice in some selected cases. The results are found to be reproducible within ± 5 %.

The extraction process was analyzed by means of the degree of extraction and distribution coefficient. The distribution coefficient, K_D, is calculated using eq 1.

$$K_D = \frac{\bar{C}_{HNc}}{C_{HNc}} \quad (1)$$

where $\bar{C}_{HNc}$ is the total (analytical) concentration of pyridine-3-carboxylic acid in the organic phase and C_{HNc} is the total (analytical) concentration (dissociated and undissociated) in the aqueous phase at equilibrium.

The degree of extraction is defined as the ratio of acid concentration in the extracted phase to the initial acid concentration in aqueous solution by assuming no change in volume at equilibrium as given by eq 2.

$$E = \frac{K_D}{1 + K_D} \cdot 100 \quad (2)$$

Results and Discussion

The physical solubility of pyridine-3-carboxylic acid in pure diluents alone is remarkably small with a maximum value of distribution coefficient of about 0.35 for octan-1-ol, 0.18 for 4-methyl-2-pentanone (MIBK), and ranges between 0.01 and 0.025 for other diluents such as hexane, heptane, benzene, trichloromethane (chloroform), and methylbenzene as given in Table 2. It is extracted by phosphorus-bonded oxygen-bearing extractants with a significantly higher distribution ratio than carbon-bonded oxygen-bearing extractants under comparable conditions. The chemical stability of the organophosphorous compound plays an important role in its use as an efficient extracting solution with good factors necessary for understanding the mechanism of extraction, the effect of diluents, and the role of additional reagents. 1-Dioctylphosphoryloctane (TOPO) is used as extractant to study the extraction equilibria of pyridine-3-carboxylic acid because of its excellent chemical stability, higher basicity, and low solubility in water. TOPO (as shown in Figure 1) contains a phosphoryl group (>P═O) which serves as a stronger Lewis base for its high polarity. In the case of TOPO, the alkoxy groups as found in TBP are substituted by alkyl groups. So, the Lewis basicity is increased through inductive effects. The degree of extraction increases markedly as the number of direct C−P linkages increases.

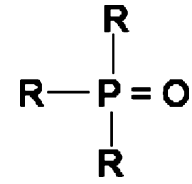

Figure 1. Molecular structure of 1-dioctylphosphoryloctane, also known as tri-*n*-octyl phosphine oxide (TOPO), with R = C_8H_{17}.

Table 3. Equilibrium Results for the Extraction of Pyridine-3-carboxylic Acid Using TOPO Dissolved in *n*-Octane at 298 K with Various Concentrations of TOPO and Acid

C_{in}	$[P_{org}]_{in}$	$10^2 \cdot C_{HNc}$	$10^2 \cdot \bar{C}_{HNc}$				
$mol \cdot m^{-3}$	$mol \cdot m^{-3}$	$mol \cdot m^{-3}$	$mol \cdot m^{-3}$	K_D	E	Z	pH_{eq}
0.02	0.10	1.53	0.47	0.31	23.63	0.05	3.84
	0.25	1.24	0.76	0.62	38.25	0.03	3.88
	0.40	0.99	1.01	1.02	50.44	0.03	3.92
	0.60	0.81	1.19	1.46	59.38	0.02	3.96
0.05	0.10	3.90	1.10	0.28	22.00	0.11	3.70
	0.25	3.15	1.85	0.59	36.95	0.07	3.72
	0.40	2.50	2.50	1.00	49.95	0.06	3.75
	0.60	2.08	2.92	1.40	58.4	0.05	3.76
0.08	0.10	6.44	1.56	0.24	19.56	0.16	3.58
	0.25	5.12	2.88	0.56	36.06	0.12	3.65
	0.40	4.37	3.63	0.83	45.34	0.09	3.67
	0.60	3.59	4.41	1.23	55.14	0.07	3.70
0.10	0.10	8.17	1.83	0.22	18.33	0.18	3.53
	0.25	6.52	3.48	0.53	34.83	0.14	3.58
	0.40	5.49	4.51	0.82	45.14	0.11	3.63
	0.60	4.54	5.46	1.20	54.63	0.09	3.67
0.12	0.10	9.90	2.10	0.21	17.50	0.21	3.48
	0.25	8.00	4.00	0.50	33.31	0.16	3.54
	0.40	6.60	5.40	0.82	45	0.14	3.58
	0.60	5.53	6.47	1.17	53.94	0.11	3.63

The chemical extraction data for pyridine-3-carboxylic acid extraction using TOPO with different diluents are presented in Tables 3 to 7. The data clearly show that chemical extraction using the organophosphorus compound (TOPO) is far better than physical extraction as indicated by higher K_D values. The isotherms for the acid are determined from five aqueous solution concentrations, four concentrations of TOPO dissolved in various diluents as shown in Figures 2 to 6. The concentration of components is expressed in molar units ($mol \cdot m^{-3}$). For a higher range of TOPO concentration, there is a linear relationship between acid concentration in the two phases and a slightly nonlinear relationship for lower concentrations of TOPO. It may be noted that for low concentrations of acid with respect to a higher range of TOPO concentration, Henry's law is valid, whereas at low concentrations of TOPO, nonideal behavior can prevail causing this deviation.

Table 4. Equilibrium Results for the Extraction of Pyridine-3-carboxylic Acid Using TOPO Dissolved in Methylbenzene at 298 K with Various Concentrations of TOPO and Acid

C_{in}	$[P_{org}]_{in}$	$10^2 \cdot C_{HNc}$	$10^2 \cdot \bar{C}_{HNc}$				
mol·m^{-3}	mol·m^{-3}	mol·m^{-3}	mol·m^{-3}	K_D	E	Z	pH_{eq}
0.02	0.10	1.27	0.73	0.57	36.50	0.07	3.87
	0.25	0.89	1.11	1.25	55.50	0.04	3.94
	0.40	0.72	1.28	1.78	64.00	0.03	4.0
	0.60	0.59	1.41	2.39	70.50	0.02	4.02
0.05	0.10	3.38	1.62	0.48	32.40	0.16	3.69
	0.25	2.34	2.66	1.14	53.20	0.11	3.74
	0.40	1.85	3.15	1.70	63.00	0.08	3.75
	0.60	1.53	3.47	2.27	69.40	0.06	3.78
0.08	0.10	5.69	2.31	0.41	28.88	0.23	3.58
	0.25	3.96	4.04	1.02	50.50	0.16	3.65
	0.40	3.26	4.74	1.45	59.25	0.12	3.69
	0.60	2.56	5.44	2.13	68.00	0.09	3.72
0.10	0.10	7.26	2.74	0.38	27.40	0.27	3.53
	0.25	5.03	4.97	0.99	49.70	0.20	3.58
	0.40	4.21	5.79	1.38	57.90	0.15	3.63
	0.60	3.30	6.70	2.03	67.00	0.11	3.69
0.12	0.10	8.91	3.09	0.35	25.75	0.31	3.48
	0.25	6.19	5.81	0.94	48.42	0.23	3.54
	0.40	5.45	6.55	1.20	54.58	0.16	3.58
	0.60	4.04	7.96	1.97	66.33	0.13	3.63

Table 5. Equilibrium Results for the Extraction of Pyridine-3-carboxylic Acid Using TOPO Dissolved in 4-Methyl-2-pentanone at 298 K with Various Concentrations of TOPO and Acid

C_{in}	$[P_{org}]_{in}$	$10^2 \cdot C_{HNc}$	$10^2 \cdot \bar{C}_{HNc}$				
mol·m^{-3}	mol·m^{-3}	mol·m^{-3}	mol·m^{-3}	K_D	E	Z	pH_{eq}
0.02	0.10	1.38	0.62	0.45	31.00	0.06	3.84
	0.25	1.10	0.90	0.82	45.00	0.04	3.89
	0.40	0.92	1.08	1.17	54.00	0.03	3.93
	0.60	0.75	1.25	1.67	62.50	0.02	3.96
0.05	0.10	3.48	1.52	0.44	30.40	0.15	3.71
	0.25	2.76	2.24	0.81	44.80	0.09	3.74
	0.40	2.31	2.69	1.16	53.80	0.07	3.78
	0.60	1.89	3.11	1.65	62.20	0.05	3.82
0.08	0.10	5.63	2.37	0.42	29.63	0.24	3.59
	0.25	4.50	3.50	0.78	43.75	0.14	3.65
	0.40	3.75	4.25	1.13	53.13	0.11	3.71
	0.60	3.08	4.92	1.60	61.50	0.08	3.72
0.10	0.10	7.13	2.87	0.40	28.70	0.29	3.57
	0.25	5.70	4.30	0.75	43.00	0.17	3.61
	0.40	4.76	5.24	1.10	52.40	0.13	3.66
	0.60	3.90	6.10	1.56	61.00	0.10	3.68
0.12	0.10	8.63	3.37	0.39	28.08	0.34	3.53
	0.25	6.90	5.10	0.74	42.50	0.20	3.58
	0.40	5.78	6.22	1.08	51.83	0.16	3.61
	0.60	4.73	7.27	1.54	60.58	0.12	3.66

Table 6. Equilibrium Results for the Extraction of Pyridine-3-carboxylic Acid TOPO Dissolved in Dichloromethane at 298 K with Various Concentrations of TOPO and Acid

C_{in}	$[P_{org}]_{in}$	$10^2 \cdot C_{HNc}$	$10^2 \cdot \bar{C}_{HNc}$				
mol·m^{-3}	mol·m^{-3}	mol·m^{-3}	mol·m^{-3}	K_D	E	Z	pH_{eq}
0.02	0.10	1.50	0.50	0.33	25.00	0.05	3.84
	0.25	1.17	0.83	0.71	41.50	0.03	3.89
	0.40	0.98	1.02	1.04	51.00	0.03	2.91
	0.60	0.84	1.16	1.38	58.00	0.02	3.94
0.05	0.10	3.94	1.06	0.27	21.20	0.11	3.68
	0.25	3.01	1.99	0.66	39.80	0.08	3.77
	0.40	2.47	2.53	1.02	50.60	0.06	3.77
	0.60	2.12	2.88	1.36	57.60	0.05	3.80
0.08	0.10	6.37	1.63	0.26	20.38	0.16	3.60
	0.25	4.90	3.10	0.63	38.75	0.12	3.65
	0.40	4.11	3.89	0.95	48.63	0.10	3.68
	0.60	3.53	4.47	1.27	55.88	0.08	3.70
0.10	0.10	8.01	1.99	0.25	19.90	0.20	3.55
	0.25	6.17	3.83	0.62	38.30	0.15	3.60
	0.40	5.21	4.79	0.92	47.90	0.12	3.64
	0.60	4.38	5.62	1.28	56.20	0.09	3.66
0.12	0.10	9.73	2.27	0.23	18.92	0.23	3.48
	0.25	7.47	4.53	0.61	37.75	0.18	3.56
	0.40	6.30	5.70	0.90	47.50	0.14	3.60
	0.60	5.34	6.66	1.25	55.50	0.11	3.64

Table 7. Equilibrium Results for the Extraction of Pyridine-3-carboxylic Acid Using TOPO Dissolved in Decan-1-ol at 298 K with Various Concentrations of TOPO and Acid

C_{in}	$[P_{org}]_{in}$	$10^2 \cdot C_{HNc}$	$10^2 \cdot \bar{C}_{HNc}$				
mol·m^{-3}	mol·m^{-3}	mol·m^{-3}	mol·m^{-3}	K_D	E	Z	pH_{eq}
0.02	0.10	1.56	0.44	0.28	22.00	0.04	3.84
	0.25	1.53	0.47	0.31	23.50	0.02	3.84
	0.40	1.50	0.50	0.33	25.00	0.01	3.85
	0.60	1.47	0.53	0.36	26.50	0.01	3.85
0.05	0.10	3.99	1.01	0.25	20.20	0.10	3.68
	0.25	3.93	1.07	0.27	21.40	0.04	3.70
	0.40	3.84	1.16	0.30	23.20	0.03	3.71
	0.60	3.72	1.28	0.34	25.60	0.02	3.72
0.08	0.10	6.68	1.32	0.20	16.50	0.13	3.58
	0.25	6.53	1.47	0.23	18.38	0.06	3.59
	0.40	6.30	1.70	0.27	21.25	0.04	3.59
	0.60	6.00	2.00	0.33	25.00	0.03	3.60
0.10	0.10	8.55	1.45	0.17	14.50	0.16	3.53
	0.25	8.25	1.75	0.21	17.50	0.07	3.54
	0.40	7.95	2.05	0.26	20.50	0.05	3.54
	0.60	7.54	2.46	0.33	24.60	0.04	3.55
0.12	0.10	10.43	1.57	0.15	13.08	0.16	3.46
	0.25	10.20	1.80	0.18	15.00	0.07	3.47
	0.40	9.68	2.32	0.24	19.33	0.06	3.49
	0.60	9.08	2.92	0.32	24.33	0.05	3.51

The distribution coefficients (K_D) and degree of extraction (E) are found to increase with an increase in TOPO concentration in different diluents. However, TOPO (solid white powder) is used only in the range of (0.10 to 0.60) mol·m^{-3} in different diluents. Higher range concentrations of TOPO in diluents may form highly viscous solution that may take a longer time to reach equilibrium. The initial concentration of acid also affects the extraction efficiency as shown in Tables 3 to 7. The distribution coefficients (K_D) and degree of extraction (E) decrease when the concentration of acid is increased from (0.02 to 0.12) mol·m^{-3}. Different concentrations of extractant (TOPO) have been used to derive the effect of initial acid concentration on extraction efficiency. The trends in experimental results of this study on equilibrium concentrations of pyridine-3-carboxylic acid in the aqueous phase are in good agreement with the results reported by Kertes and King.[17] For the estimation of equilibrium extraction constant (K_E) and the number of extractant (TOPO) molecules per acid molecule (n) with different diluents, the following theoretical study has been performed.[17,31] The values of K_E and n with different types of diluents are used to find the effect of diluent on the extraction efficiency of the extractant (TOPO).

Reactive Extraction Mechanism. The extraction of pyridine-3-carboxylic acid occurs by means of a successful competition of the solvating phosphoryl group in TOPO against water molecules at the interface between the aqueous and organic phase. Apparent equilibrium extraction constants, expressed in terms of species concentrations, are used. The physical extraction of acid, the acid dimerization, and the water coextraction are neglected due to strong interactions between acid and extractant (TOPO) molecules. The extraction mechanism of pyridine-3-carboxylic acid (HNc) using TOPO as an extractant with various diluents is described by eq 3, showing interfacial equilibrium in the formation of complexes between acid and extractant

$$HNc_{aq} + nP_{org} \leftrightarrow \overline{HNcP}_{n(org)} \quad (3)$$

The extraction equilibrium constant, K_E, can be calculated using eq 4

$$K_E = \frac{[\overline{HNcP}_{n(org)}]}{[HNc_{aq}][P_{org}]^n} \quad (4)$$

Acid also dissociates under equilibrium in the aqueous phase as given by eq 5

$$HNc \leftrightarrows Nc^- + H^+ \quad (5)$$

The corresponding dissociation constant, K_H, is determined with the relationship as given by eq 6

$$K_H = \frac{[Nc^-_{aq}][H^+]}{[HNc_{aq}]} \quad (6)$$

The experimentally accessible distribution coefficient, K_D, is calculated with eq 7.

$$K_D = \frac{\bar{C}_{HNc}}{C_{HNc}} = \frac{[\overline{HNcP}_{n(org)}]}{[HNc_{aq}] + [Nc_{aq}]^-} \quad (7)$$

where $[\overline{HNcP}_{n(org)}]$ refers to the concentration of pyridine-3-carboxylic acid in the organic phase; and $[HNc_{aq}]$ and $[Nc_{aq}]^-$ symbolize nondissociated and dissociated concentrations of pyridine-3-carboxylic acid in the aqueous phase, respectively, at the equilibrium state.

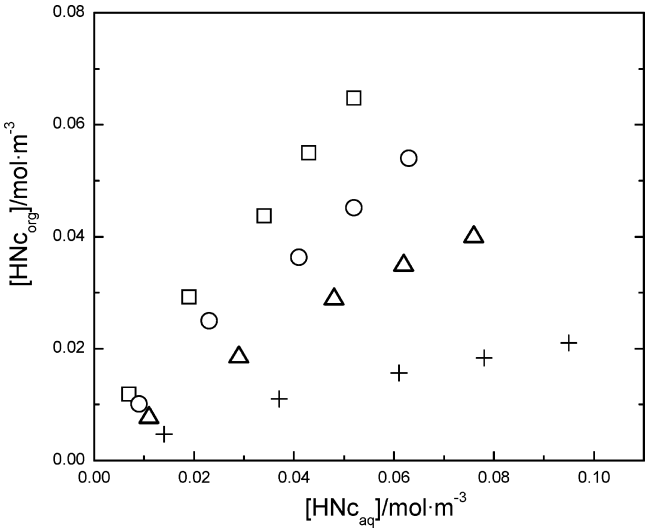

Figure 2. Equilibrium isotherms of pyridine-3-carboxylic acid for TOPO dissolved in *n*-octane. Symbol: □, 0.60 mol·m^{-3}; ○, 0.40 mol·m^{-3}; △, 0.25 mol·m^{-3}; +, 0.10 mol·m^{-3}.

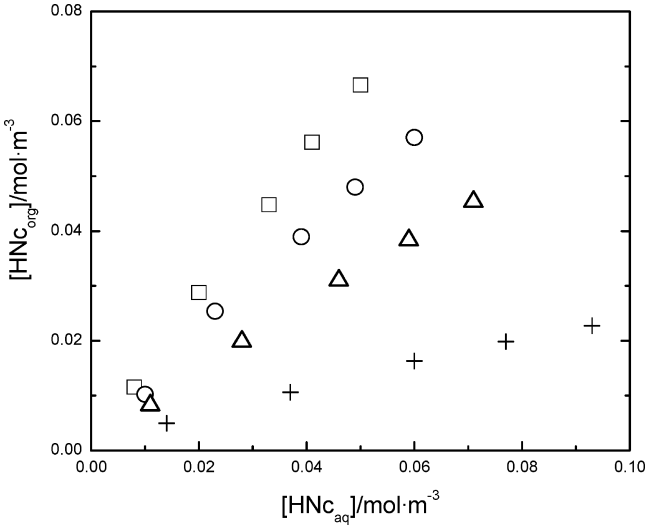

Figure 3. Equilibrium isotherms of pyridine-3-carboxylic acid for TOPO dissolved in dichloromethane (DCM). Symbol: □, 0.60 mol·m^{-3}; ○, 0.40 mol·m^{-3}; △, 0.25 mol·m^{-3}; +, 0.10 mol·m^{-3}.

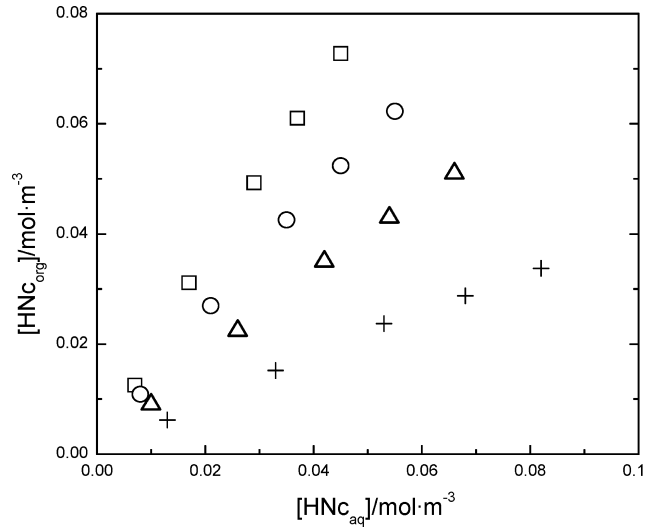

Figure 4. Equilibrium isotherms of pyridine-3-carboxylic acid for TOPO dissolved in 4-methyl-2-pentanone. Symbol: □, 0.60 mol·m^{-3}; ○, 0.40 mol·m^{-3}; △, 0.25 mol·m^{-3}; +, 0.10 mol·m^{-3}.

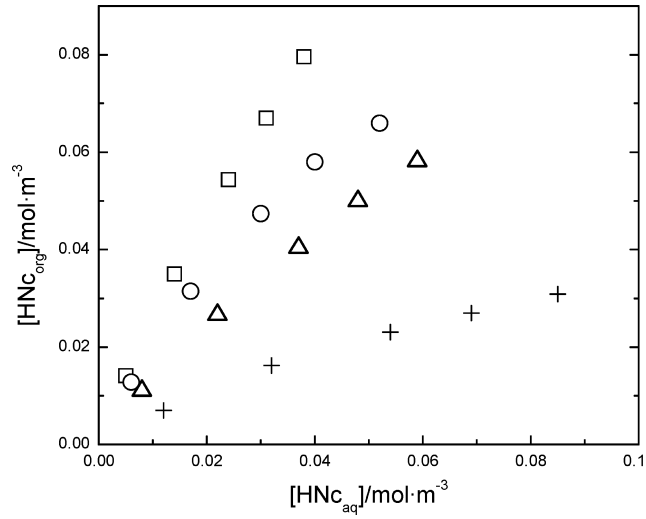

Figure 5. Equilibrium isotherms of pyridine-3-carboxylic acid for TOPO dissolved in methylbenzene. Symbol: □, 0.60 mol·m^{-3}; ○, 0.40 mol·m^{-3}; △, 0.25 mol·m^{-3}; +, 0.10 mol·m^{-3}.

Putting the values of $[\overline{HNcP}_{n(org)}]$ and $[Nc_{aq}]^-$ from eqs 4 and 6, respectively, in eq 7 results in eq 8

$$K_D = \frac{K_E[P_{org}]^n}{\left(1 + \frac{K_H}{[H^+]}\right)} \quad (8)$$

Linearizing eq 8 by taking the logarithm on both sides of the equation, we get eq 9.

$$\log K_D + \log\left(1 + \frac{K_H}{[H^+]}\right) = \log K_E + n \log[P_{org}] \quad (9)$$

A plot of the above equation by taking $\log K_D + \log(1 + (K_H/[H^+]))$ on the *y*-axis and $\log[P_{org}]$ on the *x*-axis yields a straight line with a slope of *n* and an intercept of $\log K_E$.

$[P_{org}]$is the free TOPO concentration in the organic phase, represented as

$$[P_{org}] = [P_{org}]_{in} - n[\overline{HNcP}_{n(org)}] \quad (10)$$

Putting the value of $[P_{org}]$ from eq 10 in eq 9 results in eq 11

$$\log K_D + \log\left(1 + \frac{K_H}{[H^+]}\right) = \log K_E + n \log([P_{org}]_{in} - n[\overline{HNcP}_{n(org)}]) \quad (11)$$

Due to apparition of n under logarithm, an optimization route for the estimation of n and K_E is applied. If $[P_{org}]_{in} \gg n[\overline{HNcP}_{n(org)}]$, the initial extractant concentration $[P_{org}]_{in}$ can also be used to determine n and K_E in eq 9.

The extent to which the organic phase (extractant and diluents) may be loaded with nicotinic acid is expressed by the loading ratio, Z (ratio of total acid concentration in the organic phase to the total TOPO concentration), as given by eq 12

$$Z = \frac{\bar{C}_{HNc}}{[\overline{P}_{org}]_{in}} \quad (12)$$

The stoichiometry of the overall extraction equilibrium is dependent on the loading ratio in the organic phase, Z. If the organic phase is not highly concentrated by acid, i.e., at very low loading ratios ($Z < 0.5$), a 1:1 complex of acid and extractant (TOPO) is formed. A plot of $Z/(1 - Z)$ versus [HNc] yields a straight line with a slope of complexation constant (K_{E1}) as given by eq 13

$$\frac{Z}{1 - Z} = K_{E1}[HNc] \quad (13)$$

A plot of eq 9 by taking $\log K_D + \log(1 + (K_H/[H^+]))$ on the y-axis and $\log[P_{org}]$ on the x-axis yields the straight line with a slope of n and intercept of $\log K_E$ as shown in Figures 7 to 9. For the extraction equilibrium of pyridine-3-carboxylic acid with TOPO, the slopes of the straight lines suggest the formation of a complex between one molecule each of both the reactants in all cases of acid concentration. The slope, n, and the values of equilibrium constants K_E for different diluents and different initial acid concentrations using TOPO in the range of (0.10 to 0.60) mol·m^{-3} are given in Table 8. The results indicate a stoichiometric association between the individual phosphoryl group and the individual acid group and display the effect of acid concentration on the experimentally determined distribution ratio. From Figures 7 and 8, it can be seen that there is not a significant difference between the slopes and intercepts for different initial acid concentrations with higher TOPO concentrations as compared to initial acid concentrations. However, there is a significant difference between the slopes and intercepts for diluents used with TOPO depending upon diluent characteristics as shown in Figure 9.

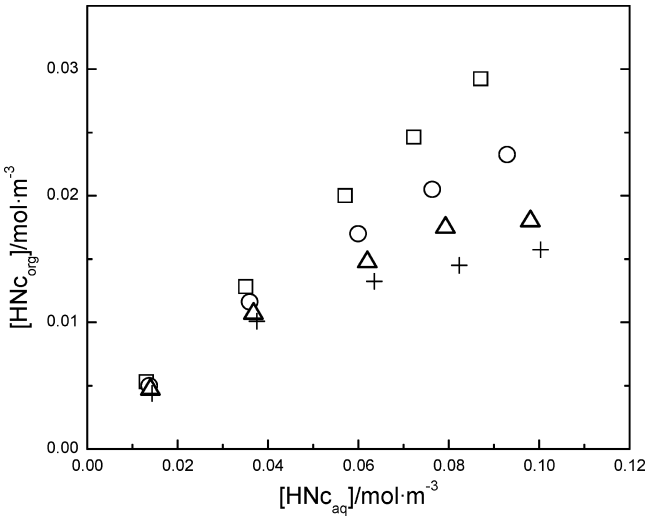

Figure 6. Equilibrium isotherms of pyridine-3-carboxylic acid for TOPO dissolved in decan-1-ol. Symbol: □, 0.60 mol·m^{-3}; ○, 0.40 mol·m^{-3}; △, 0.25 mol·m^{-3}; +, 0.10 mol·m^{-3}.

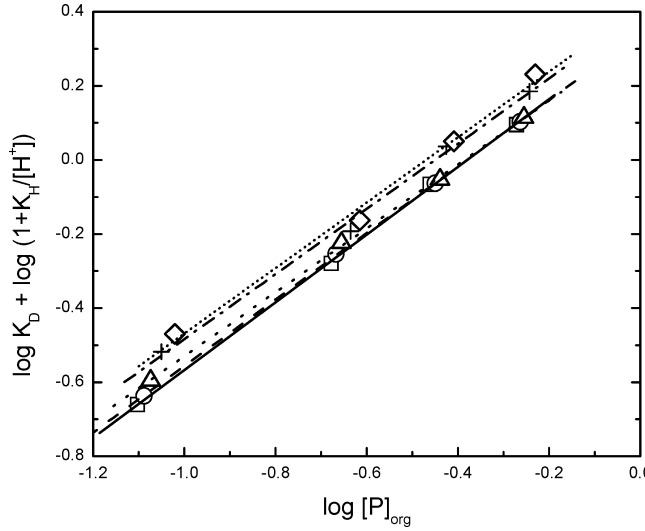

Figure 7. Determination of extraction constants (K_E) and apparent number of reacting molecules (n) using TOPO dissolved in n-octane with different initial acid concentration. Symbol: □, data, —, linear fit for 0.12 mol·m^{-3}; ○, data, - - -, linear fit for 0.10 mol·m^{-3}; Δ, data, •••, linear fit for 0.08 mol·m^{-3}; +, data, -•-•-, linear fit for 0.05 mol·m^{-3}; ◇, data, ••••, for 0.02 mol·m^{-3}.

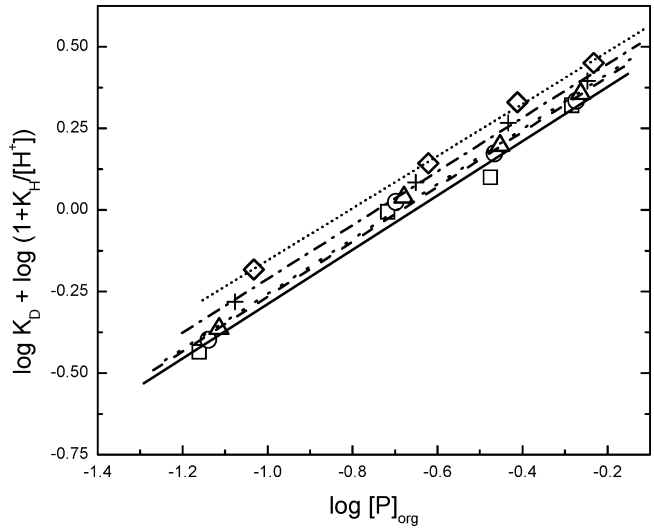

Figure 8. Determination of extraction constants (K_E) and apparent number of reacting molecules (n) using TOPO dissolved in methylbenzene with different initial acid concentration. Symbol: □, data, —, linear fit for 0.12 mol·m^{-3}; ○, data, - - -, linear fit for 0.10 mol·m^{-3}; Δ, data, •••, linear fit for 0.08 mol·m^{-3}; +, data, -•-•-, linear fit for 0.05 mol·m^{-3}; ◇, data, ••••, for 0.02 mol·m^{-3}.

The values of equilibrium extraction constant (K_E) and the number of reacting extractant molecules (n) are also estimated using an optimization routine. A population-based search algorithm, differential evolution (DE), which is simple and robust and has a proven successful record,[38−41] is also employed to solve the model eq 11 for estimation of extraction equilibrium constants (K_E) and the number of reacting extractant molecules (n). An objective function based on least-squares error between

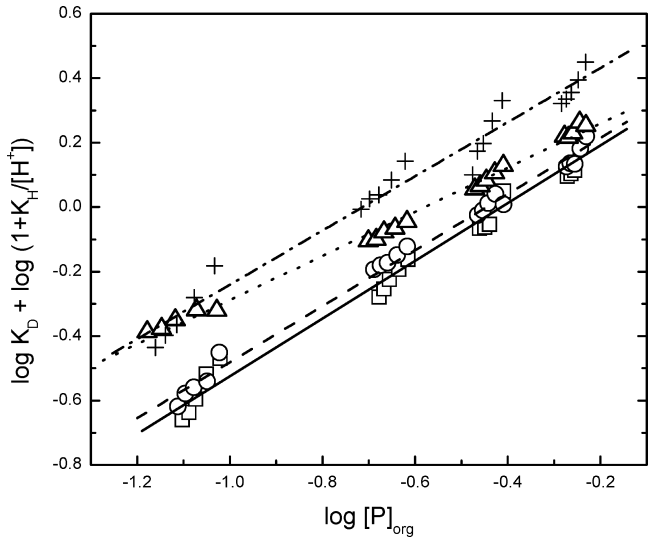

Figure 9. Determination of extraction constants (K_E) and apparent number of reacting molecules (n) using TOPO with various diluents in the entire range of initial acid concentrations. Symbol: □, data, —, linear fit for *n*-octane; ○, data, ----, linear fit for dichloromethane; Δ, data, •••, linear fit for MIBK; +, data, -•-•-, linear fit for toluene.

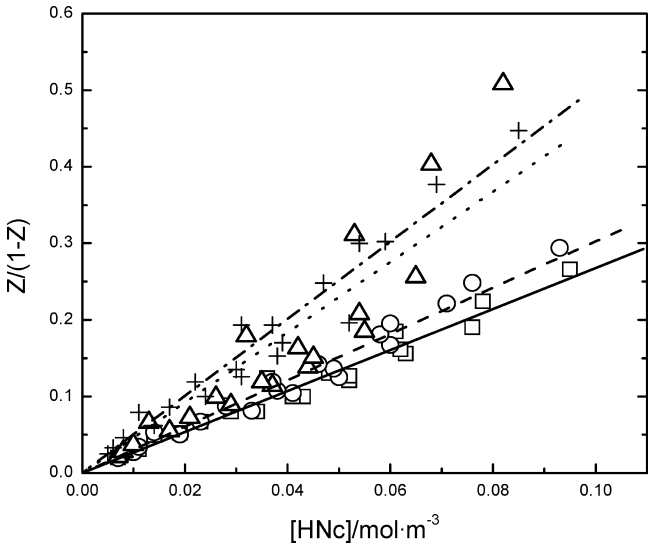

Figure 10. Plot of $Z/(1 - Z)$ versus [HNc] for the estimation of (1:1) nicotinic acid−TOPO equilibrium complexation constant (K_{E1}) with various diluents in the entire range of TOPO concentrations. Symbol: □, data, —, linear fit for *n*-octane; ○, data, - - -, linear fit for dichloromethane; Δ, data, •••, linear fit for MIBK; +, data, -•-•-, linear fit for toluene.

experimental data and the predicted value of $\log K_D + \log(1 + (K_H/[H^+]))$ has been minimized. The values of equilibrium extraction constant (K_E) and the number of reacting extractant molecules (n) determined by this computational procedure are given in Table 9.

Tables 8 and 9 present the calculated values of K_E and n, the results of equilibrium experiments carried out with different initial concentrations of pyridine-3-carboxylic acid. With higher initial acid concentration, the loading of acid on TOPO molecule is increased. The obtained results of K_E and n, for TOPO extractant using a computational procedure, shows the same trend as obtained by the graphical method using a 1:1 complex, but more accurate. The values of K_E and n, using TOPO (0.10 to 0.06) mol·m^{-3} in various diluents with a complete range of initial concentrations of nicotinic acid (0.02 to 0.12) mol·m^{-3}, are presented in Tables 10 and 11. The diluents, having higher dielectric constant values, also contribute to the extraction of

Table 8. Values of Equilibrium Extraction Constant (K_E) and Number of Reacting Extractant Molecules (n) with TOPO in Various Diluents at Different Concentrations of Pyridine-3-carboxylic Acid Using the Graphical Method

diluents	C_{in} / mol·m^{-3}	log K_E	n	R^2	SD
n-octane	0.02	0.42 ± 0.03	0.88 ± 0.05	0.997	0.03
	0.05	0.40 ± 0.03	0.88 ± 0.04	0.998	0.02
	0.08	0.33 ± 0.01	0.86 ± 0.01	0.999	0.01
	0.10	0.34 ± 0.01	0.89 ± 0.01	0.999	0.01
	0.12	0.35 ± 0.01	0.91 ± 0.01	0.999	0.01
methylbenzene	0.02	0.64 ± 0.01	0.80 ± 0.02	0.999	0.013
	0.05	0.61 ± 0.02	0.82 ± 0.02	0.999	0.014
	0.08	0.59 ± 0.02	0.84 ± 0.03	0.998	0.020
	0.10	0.58 ± 0.03	0.84 ± 0.05	0.997	0.030
	0.12	0.54 ± 0.05	0.83 ± 0.07	0.992	0.049
4-methyl-2-pentanone	0.02	0.42 ± 0.03	0.73 ± 0.02	0.999	0.012
	0.05	0.41 ± 0.03	0.70 ± 0.05	0.996	0.029
	0.08	0.39 ± 0.02	0.67 ± 0.03	0.998	0.019
	0.10	0.38 ± 0.02	0.67 ± 0.03	0.998	0.021
	0.12	0.38 ± 0.03	0.66 ± 0.04	0.997	0.025
dichloromethane	0.02	0.38 ± 0.04	0.82 ± 0.06	0.995	0.033
	0.05	0.42 ± 0.02	0.90 ± 0.03	0.999	0.016
	0.08	0.37 ± 0.03	0.85 ± 0.04	0.998	0.024
	0.10	0.38 ± 0.02	0.86 ± 0.03	0.998	0.020
	0.12	0.39 ± 0.03	0.89 ± 0.05	0.997	0.029
decan-1-ol	0.02	−0.38 ± 0.02	0.13 ± 0.04	0.934	0.022
	0.05	−0.43 ± 0.03	0.15 ± 0.04	0.938	0.024
	0.08	−0.43 ± 0.04	0.25 ± 0.06	0.953	0.034
	0.10	−0.41 ± 0.04	0.34 ± 0.06	0.971	0.037
	0.12	−0.43 ± 0.06	0.38 ± 0.09	0.948	0.056

Table 9. Values of Equilibrium Extraction Constant (K_E) and Number of Reacting Extractant Molecules (n) with TOPO in Various Diluents at Different Concentrations of Pyridine-3-carboxylic Acid Using DE (Optimization Procedure)

diluents	C_{in} / mol·m^{-3}	K_E	n
n-octane	0.02	2.74	0.95
	0.05	2.71	0.94
	0.08	2.12	0.87
	0.10	2.17	0.90
	0.12	2.16	0.89
methylbenzene	0.02	4.43	0.81
	0.05	4.19	0.84
	0.08	3.81	0.82
	0.10	3.96	0.84
	0.12	2.66	0.64
4-methyl-2-pentanone	0.02	2.69	0.77
	0.05	2.64	0.76
	0.08	2.47	0.72
	0.10	2.44	0.73
	0.12	2.40	0.72
dichloromethane	0.02	2.05	0.75
	0.05	2.55	0.87
	0.08	2.30	0.81
	0.10	2.74	0.99
	0.12	2.19	0.81
decan-1-ol	0.02	0.42	0.14
	0.05	0.38	0.16
	0.08	0.38	0.27
	0.10	0.40	0.37
	0.12	0.40	0.44

organic acid and result in a low value of stoichiometry coefficients ($n = 0.70$) for MIBK having a dielectric constant of 13.1. However, physical extraction of acid in inert diluents (*n*-octane) is not significant; the value of n is found to be close to unity. The solvent polarity represents an important parameter that controls the extraction of ionizable solutes. The dielectric constant may be considered as an indicator of solvent−solute local interactions, inducing the limitation of solute solvation by solvent or extractant, due to the presence of ionizable groups in the solute chemical structure. The values of coefficient of determination (R^2) near about 0.99 and values of standard

Table 10. Values of Equilibrium Extraction Constant (K_E) and Number of Reacting Extractant Molecules (n) Using TOPO as an Extractant with Various Diluents in the Entire Range of Pyridine-3-carboxylic Acid Concentrations from Figure 9

diluents	log K_E	n	R^2	SD
n-octane	0.37 ± 0.02	0.90 ± 0.03	0.990	0.04
dichloromethane	0.39 ± 0.01	0.87 ± 0.02	0.996	0.03
4-methyl-2-pentanone	0.40 ± 0.01	0.69 ± 0.01	0.997	0.02
methylbenzene	0.60 ± 0.02	0.84 ± 0.04	0.985	0.05
decan-1-ol	−0.41 ± 0.04	0.26 ± 0.06	0.750	0.08

Table 11. Equilibrium Extraction Constant (K_{E1}) for 1:1 Complexes of Pyridine-3-carboxylic Acid and TOPO with Various Diluents from Figure 10

diluents	K_{E1} ($mol^{-1}\cdot m^3$)	R^2	SD
n-octane	2.68 ± 0.0.06	0.982	0.01
dichloromethane	3.02 ± 0.06	0.988	0.01
4-methyl-2-pentanone	4.59 ± 0.28	0.921	0.05
methylbenzene	5.03 ± 0.14	0.976	0.03

deviation (SD) near about 0.05 are showing minimal deviation in the results.

Since pyridine-3-carboxylic acid is used in the low concentration range of (0.02 to 0.12) $mol\cdot m^{-3}$ and TOPO is diluted in the range of (0.10 to 0.60) $mol\cdot m^{-3}$, the loading ratio is found to be very low ($Z < 0.5$). 1:1 complexes of acid and TOPO are formed and $Z/(1 - Z)$ versus [HNc] are plotted for the complete range of TOPO concentrations to obtain the value of equilibrium complexation constant (K_{E1}) as shown in Figure 10. The equilibrium extraction constants (K_{E1}) for the 1:1 complex of acid and TOPO at 298 K for the extraction of acid with different diluents are given in Table 11.

The TOPO/diluent system favors the formation of not overloaded polar acid−TOPO structures (p:q) corresponding to the Z factors restricted mainly between 0.02 and 0.40. The strength of the complex solvation was found to be in the decreasing order (methylbenzene < 4-methyl-2-pentanone < dichloromethane < *n*-octane < decan-1-ol) promoting probably (1:1) acid−extractant complex formation. In all the tested diluents methylbenzene containing the benzene ring in the structure is the best solvating agents for acid−TOPO complexation giving ($K_E = 5.04$), which is indicative of the interaction between aromatic π systems at the complexation stage leading to a high solvation degree. Extremely low values of equilibrium extraction constant ($K_E = 0.40$) and the number of reacting extractant (TOPO) molecules ($n = 0.26$) with protic, decan-1-ol are found. It may be possible to have strong interactions between the hydroxyl group of diluent and a phosphoryl group (>P═O) of TOPO or to have an adverse effect of the pyridine group in the pyridine-3-carboxylic acid structure on the complex formation with TOPO. The synergistic extraction power of the TOPO/methylbenzene system is noticeably larger than that of other systems yielding a maximum value of K_D (2.4 in this case). Therefore, the dielectric constant and the dipole moments of the diluents control the extraction constant through its influence on separation efficiency and mechanism.

Different approaches have been used to quantify the effect of diluents on the 1:1 complexation. Both partition and self-association constants are strongly dependent on the nature of the diluents. The thermodynamic activity of the species taking part in the organic phase equilibrium is changed with diluent type. Attempts have been made to correlate the extraction efficiency in terms of K_E values with solvent properties such as molecular mass, boiling point, density, refractive index, dielectric constant, dipole moment, and E_T parameter.[33,42] In the pyridine-3-carboxylic acid extraction with TOPO, K_E values (Table 10) are also correlated well with solvent dipole moment μ and the parameter E_T which is based on the absorption spectrum of pyridinium-*N*-phenolbetaine. Since values of μ and E_T parameter cannot be predicted for all the diluents, methylbenzene ($\mu = 0.39$ D; $E_T = 33.9$ kcal·mol^{-1}), octane ($\mu = 0.02$ D; $E_T = 31.1$ kcal·mol^{-1}), and dichloromethane ($\mu = 1.80$ D; $E_T = 40.7$ kcal·mol^{-1})[43] are used to predict the K_E value from the μ and E_T parameter values in the following eq 14.

$$K_E = 1.9053\cdot10^9\mu^{0.3439}E_T^{-5.5776} \quad (14)$$

However, for similar type diluents such as inerts (hexane and heptane) or aromatics (benzene and toluene), the dependence on molar mass, boiling point, and specific gravity can also be made. An increase in molar mass, boiling point, and specific gravity hinders the dissolution of the acid−TOPO complex and hence lowers the equilibrium extraction coefficient. Hence, the correlation of K_E (eq 14) in terms of the solvent dipole moment (μ) and the absorption spectrum parameter (E_T) is very useful to quantify the effect of diluents on the extraction of pyridine-3-carboxylic acid.

Conclusions

The studies on reactive extraction of pyridine-3-carboxylic acid with 1-dioctylphosphoryloctane (TOPO) dissolved in different diluents covering a wide range of categories (aliphatic hydrocarbon, chlorinated hydrocarbon, ketone, aromatic, and alcohol), at various TOPO and acid concentrations, indicated that the reactive extraction occurs by means of the interfacial formation of solvates between acid and extractants. The experimental data clearly show that the chemical extraction using the organophosphorus compound (TOPO) is far better than the physical extraction.

The distribution coefficients (K_D) and degree of extraction (E) are found to increase with an increase in TOPO concentration in different diluents and found to decrease when the concentration of acid is increased from (0.02 to 0.12) $mol\cdot m^{-3}$. Different parameters like distribution coefficient, degree of extraction, loading ratio, and equilibrium complexation constants were determined. The chemical modeling approach is used for the determination of the equilibrium extraction constant (K_E) and the number of extractant reacting molecules (n), and the estimated values of K_E and n depend on the applied method. More exact values of K_E and n have been found when the optimization procedure (differential evolution algorithm) is used to solve the model equations. Since the loading ratio was less than 0.5 in all the cases, no overloading was obtained, and only 1:1 complexes of acid and TOPO were formed using the graphical method and the differential evolution algorithm. The diluents, having higher dielectric constant values, also contribute to the extraction of acid and result in a low value of stoichiometry coefficients ($n = 0.70$) for 4-methyl-2-pentanone. The dielectric constant and dipole moments of the diluents control the extraction constant through its influence on separation efficiency and mechanism. In all the tested diluents, methylbenzene containing the benzene ring in the structure is the best solvating agents for acid−TOPO complexation giving a value of K_{E1} as 5.04, which is indicative of the interaction between aromatic π systems at the complexation stage leading to a high solvation degree.

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Received for review February 23, 2009. Accepted April 12, 2009.

JE900205H