

# Reactive Extraction of Nicotinic Acid with Tri-*n*-Octylamine (TOA) Dissolved in Different Diluents

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## Abstract

*The production of nicotinic acid and nicotinamide can be intensified by enzymatic conversion of 3-cyanopyridine. This fermentation process requires an economic and efficient separation method to compete with the synthetic process. In the present study, equilibrium data for the extraction of nicotinic acid using TOA dissolved in different diluents such as toluene and butyl acetate and *n*-dodecane are presented. Different parameters like distribution coefficient, degree of extraction, loading ratio, and equilibrium complexation constants were determined. The highest strength of the complex solvation is found for toluene with a maximum loading ratio ( $Z = 0.154$ ) followed by butyl acetate ( $Z = 0.121$ ) and dodecane promoting probably (1,1) acid-TOA complex formation. An optimization procedure (differential evolution algorithm) is used for the determination of the equilibrium extraction constant ( $K_E$ ) and the number of reacting acid molecules ( $m$ ) per TOA molecule through mass action law modeling approach (Chemodel).*

## Introduction

Nicotinic acid (3-pyridine carboxylic acid) widely used in food, pharmaceutical and biochemical industries is an important chemical. Due to ecological problems and complicate the synthesis methods, the chemical route for nicotinic 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. Nitrilases enzymes are gaining popularity as biocatalysts for the mild and selective hydrolysis of nitriles. The production of nicotinic acid and nicotinamide can be

intensified by enzymatic conversion of 3-cyanopyridine or biosynthesis (Kumar and Babu, 2009a). 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. Among various available alternate processes for simultaneous removal of the product, extraction is often the most suitable one. So a reactive extraction method has been proposed to be an effective primary separation step for the recovery of bio-products from a dilute fermentation process (Kumar et al, 2008).

Long-chain aliphatic amines are found to be effective extractants for the separation of carboxylic acids from dilute aqueous solution (Kertes and King, 1986). Generally, these extractants are dissolved in a diluent such as ketone, alcohol, hydrocarbon, etc. to provide appropriate physical properties for use in the extraction process. Since the presence of hydroxyl and carboxylic groups increases the solubility of acids in the aqueous 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. The distribution of nicotinic acid (constant concentration only) between water and Alamine 300 dissolved in diluents is studied at 298 K using a phase ratio of 1:1 (v/v) by Senol (2002). The comparative study of the reactive extraction of nicotinic acid with Amberlite LA-2 (lauryl-trialkyl-methylamine) and di-(2-ethylhexyl)-phosphoric acid (D2EHPA) has been presented by Cascaval et al, 2007. Kumar et al (2008) studied reactive extraction of nicotinic acid with TBP and TOPO at a fixed initial acid concentration to intensify the recovery from fermentation broth. Very recently Kumar and group (Kumar and Baba, 2009b and 2009c) also performed the extraction of nicotinic acid by TOPO in different diluents. The aim of the present work is to study the reactive extraction of nicotinic acid from aqueous solutions using TOA in 3 different diluents covering wide range of categories (toluene, butyl acetate and n-dodecane) to provide the extraction equilibrium data for intensification of nicotinic acid production via enzymatic route. The effects of initial acid concentration and composition of extractant (TOA) are also studied. Population based search algorithm, differential evolution (Babu, 2004) as optimization algorithm is used to determine the

equilibrium extraction constants ( $K_E$ ) and the stoichiometry of reactive extraction through a proposed equilibrium model (Mass Action Law based Chemodel).

## Theory

The physical extraction of acid is neglected due to strong interactions between acid and extractant (TOA) molecules. The extraction mechanism of nicotinic acid (HNc) using TOA with different diluents is described by Eq. (1), showing equilibrium in the formation of complexes between acid and extractant:



The extraction equilibrium constant,  $K_E$ , can be calculated using Eq. (2):

$$K_E = \frac{[\overline{\text{HNcS}}_{n(\text{org})}]}{[\text{HNc}_{\text{aq}}][\text{S}_{\text{org}}]^n} \quad (2)$$

The experimentally accessible distribution coefficient,  $K_D$ , is calculated with Eq. (3).

$$K_D = \frac{\overline{C}_{\text{HNc}}}{C_{\text{HNc}}} = \frac{[\overline{\text{HNcS}}_{n(\text{org})}]}{[\text{HNc}_{\text{aq}}] + [\text{Nc}_{\text{aq}}]^-} \quad (3)$$

where  $[\overline{\text{HNcS}}_{n(\text{org})}]$  refers to the concentration of acid in organic phase;  $[\text{HNc}_{\text{aq}}]$  and  $[\text{Nc}_{\text{aq}}]^-$  symbolize non-dissociated and dissociated concentrations of acid in aqueous phase respectively at equilibrium.

Using the values of  $[\overline{\text{HNcS}}_{n(\text{org})}]$  from Eq. (2) and  $[\text{Nc}_{\text{aq}}]^-$  from dissociation constant ( $pK_a$ ) in Eq. (3) results Eq. (4)

$$K_D = \frac{K_E [\text{S}_{\text{org}}]^n}{\left(1 + \frac{K_a}{[\text{H}^+]}\right)} \quad (4)$$

where,  $[\text{S}_{\text{org}}]$  is the free TOA concentration in the organic phase, represented as:

$$[\text{S}_{\text{org}}] = [\text{S}_{\text{org}}]_{\text{in}} - n[\overline{\text{HNcS}}_{n(\text{org})}] \quad (5)$$

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 TOA concentration) as given by Eq. (6)

$$Z = \frac{\bar{C}_{\text{HNc}}}{[\text{S}_{\text{org}}]_{\text{in}}} \quad (6)$$

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 ( $Z < 0.5$ ), 1:1 complex of acid and extractant (TOA) is formed. A plot of  $Z/(1-Z)$  versus  $[\text{HNc}]$  yields a straight line with a slope of complexation constant ( $K_{E1}$ ) as given by Eq. (7):

$$\frac{Z}{1-Z} = K_{E1}[\text{HNc}] \quad (7)$$

## Experimental

### Materials

The materials used in this study are nicotinic acid, extractant [tri-*n*-octylamine (TOA)] and diluents [toluene and butyl acetate and *n*-dodecane], which are listed in Table 1.

**Table 1. Reagents used in the study**

S. No.	Reagents	IUPAC name	CAS #	Suppliers	Purity %	Mol. Wt., g/mol	Specific gravity, g/cm <sup>3</sup>
1.	Nicotinic acid	pyridine-3-carboxylic acid	59-67-6	HIMEDIA, India.	99.5	123.10	1473
2.	Tri- <i>n</i> -octylamine (TOA)	N,N-dioctyloctan-1-amine	1116-76-3	Fluka, USA.	98	353.68	809
3.	Toluene	Methyl benzene	108-88-3	Spectrochem. Pvt. Ltd., India	99.7	92.14	867
4.	Butyl acetate	Butyl ethanoate	123-86-4	S. D. Fine-Chem Ltd., India	98	116.16	0.88
5.	Dodecane	Dodecane	112-40-3	Spectrochem. Pvt. Ltd., India	98	170.34	750

### Procedure

The extraction equilibrium experiments are carried out at constant temperature (298 K) with equal volumes (16 mL of each phase) of the aqueous and organic solutions shaken at 100 rpm for 8 hours in conical flasks of 100 mL on a temperature controlled reciprocal shaker bath. The

initial concentration of nicotinic acid in aqueous solutions is varied between 0.02 - 0.12 mol/L. TOA concentration in organic phase is kept in the range of 0.23 – 1.38 mol/L. The concentration of acid in the aqueous phase is determined using an UV spectrophotometer (Systronics, 119 model, 262 nm). The acid concentration in the organic phase is calculated by mass balance. The equilibrium pH values of aqueous solutions are measured using a digital pH-meter of Arm-Field Instruments (PCT 40, Basic Process Module).

The extraction process is analyzed by means of the degree of extraction and distribution coefficient. The distribution coefficient,  $K_D$ , is calculated using Eq. 8.

$$K_D = \frac{\bar{C}_{HA}}{C_{HA}} \quad (8)$$

where,  $\bar{C}_{HA}$  is the total concentration of carboxylic acid in organic phase and  $C_{HA}$  is the total acid concentration (dissociated and un-dissociated) in 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. 9.

$$E = \frac{K_D}{1 + K_D} \times 100 \quad (9)$$

## Results and Discussion

Equilibrium data are presented for the extraction of nicotinic acid using TOA in toluene, butyl acetate and n-dodecane (Tables 2-4). The isotherms for nicotinic acid are determined from four aqueous solution concentrations, four concentrations of TOA dissolved in different diluents (toluene and butyl acetate). Isotherms of nicotinic acid for the TOA/n-dodecane system are not drawn due insignificant extractability. The highest strength of the complex solvation is found for toluene with a maximum loading ratio ( $Z = 0.154$ ) and followed by butyl acetate ( $Z = 0.121$ ) promoting probably (1,1) acid-TOA complex formation. In all the tested diluents, toluene

containing the benzene ring in the structure with TOA is found to be good solvating agents for nicotinic acid-amine complexation. The distribution coefficients ( $K_D$ ) and degree of extraction ( $E$ ) are found to initially increase, and then decrease with an increase in TOA concentration (0.229 – 1.376 mol/L) at different concentrations of nicotinic acid (0.02 – 0.12 mol/L) in case of toluene (as a diluent). Degree of extraction ( $E$ ) is found to decrease with an increase in TOA concentration (0.229 – 1.376 mol/L) at different concentrations of nicotinic acid (0.02 – 0.12 mol/L) for butyl acetate (as a diluent). The concentration of acid may be the limiting factor for this trend in degree of extraction. These trends in degree of extraction with extractant concentration are also observed for reactive extraction of propionic acid using TBP in different diluents by Keshav *et al.*, (2008). Initial concentration of acid also affects the extraction efficiency. Since, low concentrations of nicotinic acid (0.02 to 0.12 mol/L) are used with respect to extractant, TOA (0.229 – 1.376 mol/L), no exact trends are found for the variation in extraction efficiency with initial acid concentration (Tables 2-4).

**Table 2. Equilibrium results for the extraction of nicotinic acid using TOA dissolved in toluene at 298 K with various concentrations of TOA and acid**

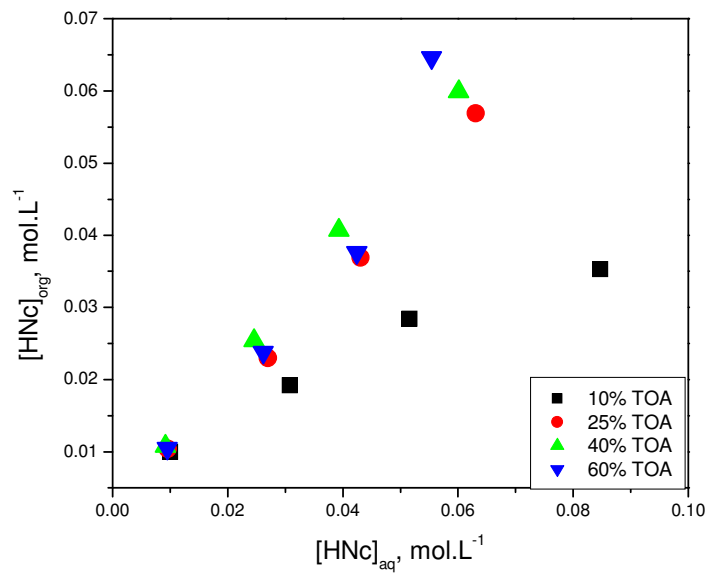
$C_{in}$ mol.L <sup>-1</sup>	$[S_{org}]_{in}$ mol.L <sup>-1</sup>	$C_{HNc}$ mol.L <sup>-1</sup>	$\bar{C}_{HNc}$ mol.L <sup>-1</sup>	$K_D$	$K_{D,pred}$ by Eq. 4	$E$	$Z$	$pH_{eq}$
0.12	0.229	0.0847	0.0353	0.42	0.419	29.42	0.154	3.21
	0.573	0.0631	0.0569	0.9	0.763	47.42	0.099	3.28
	0.917	0.0601	0.0599	1	0.964	49.92	0.065	3.29
	1.376	0.0554	0.0646	1.17	0.825	53.83	0.047	3.3
0.08	0.229	0.0516	0.0284	0.55	0.526	35.5	0.124	3.32
	0.573	0.0431	0.0369	0.86	0.83	46.13	0.064	3.36
	0.917	0.0393	0.0407	1.04	1.017	50.88	0.044	3.38
	1.376	0.0424	0.0376	0.89	0.864	47	0.027	3.36
0.05	0.229	0.0339	0.0161	0.47	0.654	32.2	0.07	3.41
	0.573	0.027	0.023	0.85	0.91	46	0.04	3.46
	0.917	0.0246	0.0254	1.03	1.07	50.8	0.028	3.48
	1.376	0.0262	0.0238	0.91	0.937	47.6	0.017	3.47
0.02	0.10	0.01	0.01	1	1	50	0.044	3.68
	0.25	0.0096	0.0104	1.08	1.08	52	0.018	3.68
	0.40	0.0092	0.0108	1.17	1.162	54	0.012	3.69
	0.60	0.0095	0.0105	1.11	1.089	52.5	0.008	3.69

**Table 3. Equilibrium results for the extraction of nicotinic acid using TOA dissolved in butyl acetate at 298 K with various concentrations of TOA and acid**

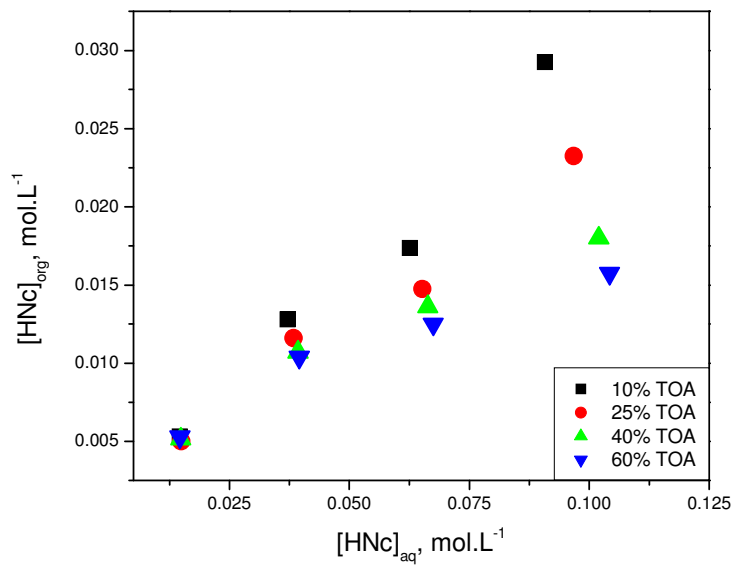
$C_{in}$ $\text{mol.L}^{-1}$	$[S_{org}]_{in}$ $\text{mol.L}^{-1}$	$C_{HNc}$ $\text{mol.L}^{-1}$	$\bar{C}_{HNc}$ $\text{mol.L}^{-1}$	$K_D$	$E$	$Z$	$pH_{eq}$
0.12	0.229	0.0908	0.0292	0.32	24.33	0.128	3.2
	0.573	0.0968	0.0232	0.24	19.33	0.04	3.18
	0.917	0.102	0.018	0.18	15	0.02	3.17
	1.376	0.1043	0.0157	0.15	13.08	0.011	3.17
0.08	0.229	0.0626	0.0174	0.28	21.75	0.076	3.28
	0.573	0.0653	0.0147	0.23	18.38	0.026	3.27
	0.917	0.0664	0.0136	0.2	17	0.015	3.26
	1.376	0.0675	0.0125	0.19	15.63	0.009	3.26
0.05	0.229	0.0372	0.0128	0.34	25.6	0.056	3.39
	0.573	0.0384	0.0116	0.3	23.2	0.02	3.38
	0.917	0.0393	0.0107	0.27	21.4	0.012	3.38
	1.376	0.0396	0.0104	0.26	20.8	0.008	3.39
0.02	0.10	0.0147	0.0053	0.36	26.5	0.023	3.58
	0.25	0.015	0.005	0.33	25	0.009	3.59
	0.40	0.0149	0.0051	0.34	25.5	0.006	3.60
	0.60	0.0147	0.0053	0.36	26.5	0.004	3.60

**Table 4. Equilibrium results for the extraction of nicotinic acid using TOA dissolved in n-dodecane at 298 K with various concentrations of TOA and acid**

$C_{in} /$ $\text{mol.L}^{-1}$	$[S_{org}]_{in} /$ $\text{mol.L}^{-1}$	$C_{HNc} /$ $\text{mol.L}^{-1}$	$\bar{C}_{HNc} / \text{mol.L}^{-1}$	$K_D$	$E$	$Z$	$pH_{eq}$
0.12	0.229	0.117	0.003	0.03	2.47	0.013	3.14
	0.573	0.1124	0.0076	0.07	6.32	0.013	3.15
	0.917	0.1101	0.0099	0.09	8.24	0.011	3.15
	1.376	0.1055	0.0145	0.14	12.09	0.011	3.16
0.08	0.229	0.0785	0.0015	0.02	1.83	0.006	3.23
	0.573	0.077	0.003	0.04	3.75	0.005	3.23
	0.917	0.0747	0.0053	0.07	6.64	0.006	3.24
	1.376	0.0693	0.0107	0.15	13.38	0.008	3.26
0.05	0.229	0.0485	0.0015	0.03	2.98	0.007	3.33
	0.573	0.0477	0.0023	0.05	4.52	0.004	3.34
	0.917	0.0454	0.0046	0.1	9.14	0.005	3.35
	1.376	0.0424	0.0077	0.18	15.3	0.006	3.36



**Figure 1. Equilibrium isotherms of nicotinic acid for different concentrations of TOA dissolved in toluene**

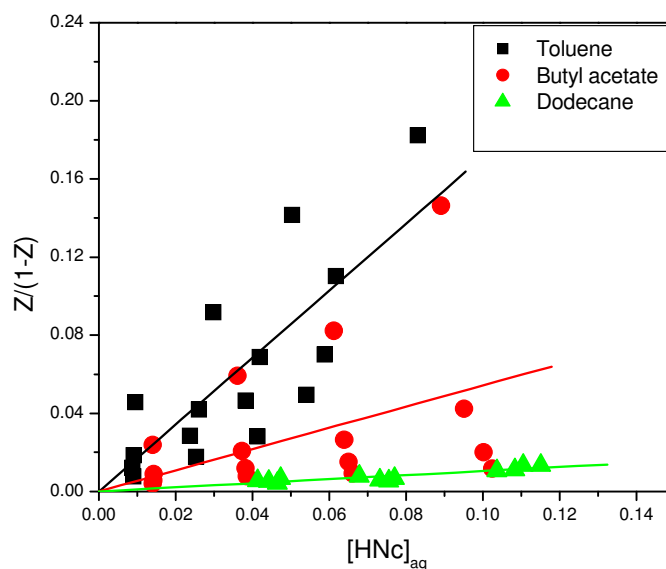


**Figure 2. Equilibrium isotherms of nicotinic acid for different concentrations of TOA dissolved in butyl acetate**

For the estimation of the strength of the complex salivation of acid:TOA, the theoretical study as described by model equations is employed. A Population based search algorithm, differential evolution (DE), which is simple and robust and has proven successful record is also employed to solve the model equation (6) for estimation of extraction equilibrium constants ( $K_E$ ) and the number of nicotinic acid molecules ( $m$ ) per extractant molecule. An objective function based on least square error between experimental data and predicted value of  $K_D$  is minimized. The values of  $K_E$  and  $m$  per TOA molecule determined by this optimization procedure (DE) for TOA/toluene system are given in Table 5. The predicted value of  $K_D$  for TOA/toluene system closely matches with the experimental values of  $K_D$  (Table 2). With the low concentration range of nicotinic acid (0.02 to 0.12 mol/L) and high concentration range of TOA (0.229 to 1.376 mol/L), the loading ratio is found to be very low ( $Z < 0.16$ ) with all type diluents. 1:1 complexes of acid and TOA are formed. The values of  $m < 1$  indicate some physical extraction with toluene as well as few 1:2 complexes formation between acid and amine. In all the tested diluents, toluene containing the benzene ring in the structure is the best solvating agents for nicotinic acid-TOA complexation giving ( $K_E = 1.6$ ), which is indicative of the interaction between aromatic  $\pi$  systems at the complexation stage. The synergistic extraction power of TOA/toulene system is noticeably larger than that of other systems yielding a maximum value of  $K_D$  (1.2). Since extraction efficiency of nicotinic with TOA in butyl acetate and dodecane is found to be very low, the equilibrium extraction parameters using DE approach are estimated only for TOA in toluene (Table 5). The values of equilibrium constants ( $K_{E1}$ ) for the formation of 1:1 complexes are also estimated using Eq. (7) by plotting  $Z/(1 - Z)$  vs  $[HNc]_{aq}$  as shown in Figure 3. The values of  $K_{E1}$  for 1:1 complex of acid and TOA at 298 K for the extraction of acid with different diluents are given in Table 6. The values of  $K_E$  can also be correlated well with solvent dipole moment  $\mu$  and the parameter,  $E_T$  which is based on the absorption spectrum of pyridinium-*N*-phenolbetaine. The model based on dipole moment ( $\mu$ ) and the parameter,  $E_T$  can be used to predict the values of  $K_E$ .

**Table 5. Values of  $K_E$ , the number of reacting acid ( $m$ ) and TOA molecules ( $n$ ) using DE (optimization procedure).**

Diluents	$[S]_{in}, \text{mol.L}^{-1}$	$m$	$n$	$K_E$
toluene	0.229	0.67	1	1.60
	0.573	0.84	1	1.16
	0.915	0.91	1	0.99
	1.376	0.84	1	0.48



**Figure 3. Plot of  $Z/(1 - Z)$  versus  $[HNc]$  for the estimation of (1:1) nicotinic acid-TOA equilibrium constant ( $K_{E1}$ ) with various diluents in the entire range of TOA and acid concentrations.**

**Table 6. Equilibrium Extraction Constant ( $K_{E1}$ ) for 1:1 Complexes of Nicotinic Acid and TOA with Various Diluents from Figure 3.**

Diluents	$K_{E1}$	$R^2$	$SD$
Toluene	$1.71 \pm 0.18$	0.80	0.03
Butyl acetate	$0.54 \pm 0.14$	0.37	0.04
n-Dodecane	$0.105 \pm 0.005$	0.90	0.001

## Conclusions

The studies on reactive extraction of nicotinic acid with TOA dissolved in different diluents (toluene, butyl acetate and dodecane), at various TOA and acid concentrations indicates that the reactive extraction occurs by means of the interfacial formation of complexes between nicotinic acid and TOA. Different parameters like distribution coefficient, degree of extraction, loading ratio, and equilibrium complexation constants are determined. An optimization procedure (differential evolution algorithm) is used for the determination of the equilibrium extraction constant ( $K_E$ ) and the number of reacting acid molecules ( $m$ ) per TOA molecule through Chemodel. Since the loading ratio is less than 0.5 in all the cases, no overloading obtained. In all the tested diluents, toluene containing the benzene ring in the structure is the best solvating agents for acid-TOA complexation giving a value of  $K_E$  as 1.71, which is indicative of the interaction between aromatic  $\pi$  systems at the complexation stage leading to a high solvation degree.

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