

# Recovery of Nicotinic Acid from Aqueous Solution using Reactive Extraction with Tri-*n*-Octyl Phosphine Oxide (TOPO) in Kerosene

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## Abstract

*Nicotinic acid (also known as pyridine-3-carboxylic acid) is widely used in food, pharmaceutical and biochemical industries. The extraction of nicotinic acid by tri-*n*-octylphosphine oxide (TOPO) with kerosene (diluent) 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.L<sup>-1</sup>) and found to decrease with increasing initial acid concentration (0.02 to 0.12 mol.L<sup>-1</sup>). The number of TOPO molecules in the acid:TOPO complex is estimated through 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 of TOPO and acid with loading ratio of less than 0.5. The extraction equilibrium constants are also determined. Equilibrium extraction constant ( $K_{E1}$ ) is found to be 3.27 L.mol<sup>-1</sup> in the complete range of acid concentrations and extractant (TOPO) concentrations.*

## **Introduction**

Niacin, also known as nicotinic acid or vitamin B3, is a water-soluble vitamin whose derivatives such as NADH (reduced form of NAD) play essential roles in energy metabolism in the living cell. Nicotinic acid (3-pyridine carboxylic acid) widely used in food, pharmaceutical and biochemical industries is an important chemical, mainly obtained by chemical synthesis, using 3-picoline or 2-methyl-5-ethyl-pyridine 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 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, 2009). Very recently amidase-catalyzed production of nicotinic acid in batch and continuous stirred membrane reactors has been studied by Cantarella et al (2008). 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.

Many separation processes such as liquid extraction, ultra filtration, electro-dialysis, direct distillation, liquid surfactant membrane extraction, anion exchange, precipitation and adsorption in chemical industries have been employed to recover the organic acids from aqueous solution. 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).

Organophosphorus compounds and long-chain aliphatic amines are effective extractants for the separation of carboxylic acids from dilute aqueous solution (Kertes and King, 1986). Phosphorus-bonded, oxygen-containing extractants have a phosphoryl group and a stronger Lewis basicity than those of carbon-bonded oxygen-containing solvents. Phosphorus-bonded, oxygen-containing extractants can only co-extract small amounts of water, and show low solubilities in water. When organophosphorus extractants are used, the solvation has a higher specificity. The distribution of nicotinic acid between water and Alamine 300 (tri-n-octylamine) dissolved in polar and non-polar 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. Compared to D2EHPA, the use of Amberlite LA-2 allows the possibility to reach higher extraction efficiency, the extraction degree being supplementarily increased by increasing the solvent polarity. 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. The aim of the present study is to provide the extraction equilibrium data on the reactive extraction of nicotinic acid (3-pyridine carboxylic acid) with tri-n-octyl phosphine oxide (TOPO) as an extractant dissolved in kerosene for intensification of nicotinic acid production via enzymatic route. 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 graphical method as well as an optimization procedure. Population based search algorithm, differential evolution is used as optimization algorithm.

## **Theory**

The extraction of nicotinic acid occurs by means of a successful competition of the solvating phosphoryl group in TOPO against water molecules between the aqueous and organic phase. The physical extraction of acid is neglected due to strong interactions between acid and extractant (TOPO) molecules. The extraction mechanism of nicotinic acid (HNc) using TOPO as an extractant with various 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 ( $\text{p}K_a$ ) in Eq. (3) results Eq. (4)

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

or

$$\log K_D + \log \left(1 + \frac{K_a}{[\text{H}^+]}\right) = \log K_E + n \log [\text{S}_{\text{org}}] \quad (5)$$

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

$$[S_{org}] = [S_{org}]_{in} - n[\overline{HNcS}_{n(org)}] \quad (6)$$

Putting the value of  $[S_{org}]$  from Eq. (6) in the Eq. (5) results Eq. (7)

$$\log K_D + \log \left( 1 + \frac{K_H}{[H^+]} \right) = \log K_E + n \log \left( [S_{org}]_{in} - n[\overline{HNcS}_{n(org)}] \right) \quad (7)$$

Due to apparition of  $n$  under logarithm, an optimization route for estimation of  $n$  and  $K_E$  may also be applied.

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. (8)

$$Z = \frac{\overline{C}_{HNc}}{[S_{org}]_{in}} \quad (8)$$

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 (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. (9):

$$\frac{Z}{1-Z} = K_{E1} [HNc] \quad (9)$$

## Experimental

### Materials

Tri-n-octyl phosphine oxide (TOPO), a phosphorus-bonded oxygen donor supplied by Sigma-Aldrich Co. USA, with purity of 99% is a white powder with the molar mass of 386.65 g.mol<sup>-1</sup>. Nicotinic acid, a white powdered material as analytical grade reagents (99.5%) is procured from HIMEDIA, India. Kerosene (diluent) of commercial grade is used. Organic solutions are prepared using TOPO as extractant dissolved in the diluent. The initial TOPO concentrations are varied in the range of 0.10 to 0.60 mol.L<sup>-1</sup>. De-ionized water is used to prepare the aqueous solutions of various concentrations of nicotinic acid. Since acid concentration in the fermentation broth is found very low, the aqueous solutions of acid are prepared in the range of (0.02 to 0.12) mol.L<sup>-1</sup>. All chemicals are used without any pretreatment.

### Procedure

The extraction equilibrium experiments are carried out at constant temperature (298 K) with equal volumes (16 cm<sup>3</sup>) 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. 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 using the separating funnel of 125 mL for separation. 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 initial and equilibrium pH values of aqueous solutions are measured using a digital pH-meter of Arm-Field Instruments (PCT 40, Basic Process Module) which varied in the range of (2.45 to 2.92) and (3.41 to 3.94) respectively. The reproducibility is checked by carrying out the experiments twice in some selected cases. The results are found to be reproducible within  $\pm 5\%$ .

The extraction process is analyzed by means of the degree of extraction and distribution coefficient. The distribution coefficient,  $K_D$ , is calculated using Eq. (3). 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. (10).

$$E = \frac{K_D}{1 + K_D} \times 100 \quad (10)$$

## Results and Discussion

The physical extraction of nicotinic acid in pure kerosene is remarkably small with a value of distribution coefficient of about 0.017 as given by Kumar et al, (2008). It is extracted by phosphorous-bonded oxygen-bearing extractants with a significantly higher distribution ratio than carbon-bonded oxygen-bearing extractants under comparable conditions. Tri-n-octyl phosphine oxide (TOPO) is used as extractant to study the extraction equilibria of nicotinic acid because of its excellent chemical stability, higher basicity and low solubility in water. 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 isotherms for nicotinic acid are determined from five aqueous solution concentrations, four concentrations of TOPO dissolved in kerosene as shown in Figure 1. The concentration of components is expressed in molar units ( $\text{mol.L}^{-1}$ ). For a higher range of TOPO concentration, there is a linear relationship between acid concentration in the two phases, and slightly nonlinear relationship for lower concentrations of TOPO. It may be noted that for low concentrations of acid with respect to higher range of TOPO concentrations, Henry's law is valid.

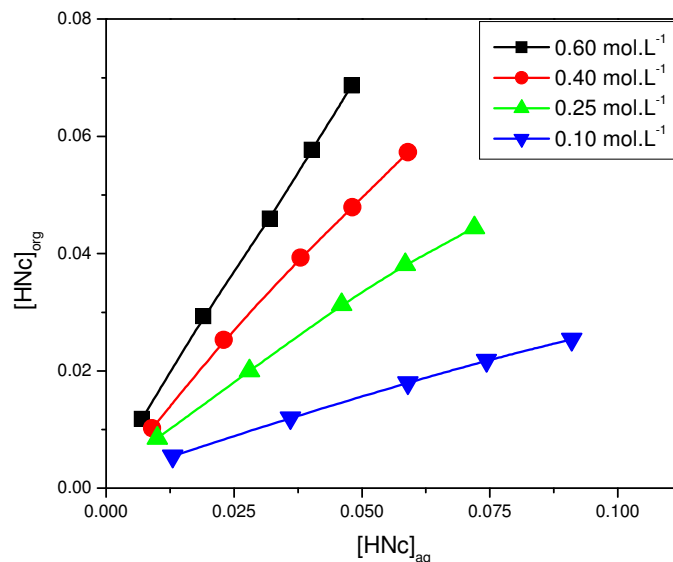


Figure 1. Equilibrium isotherms of nicotinic acid for different concentrations of TOPO dissolved in kerosene

The degree of extraction ( $E$ ) is found to increase with an increase in TOPO concentration (0.10 to 0.60 mol.L<sup>-1</sup>) as shown in Fig (2) with different concentrations of acid (0.02, 0.05, 0.08 and 0.12 mol.L<sup>-1</sup>). Initial concentration of nicotinic acid also affects the extraction efficiency as shown in Fig (3). The degree of extraction ( $E$ ) decrease when the concentration of acid is increased from (0.02 to 0.12) mol·m<sup>-3</sup>. Different concentrations of extractant (TOPO) have been used to derive the effect of initial acid concentration on extraction efficiency. From Fig. (3), the effect of acid concentration on the degree of extraction is more significant at the low concentration of TOPO. The trends in experimental results of this study on equilibrium concentrations of acid in aqueous phase are in good agreement with the results reported by Kertes and King (1986).

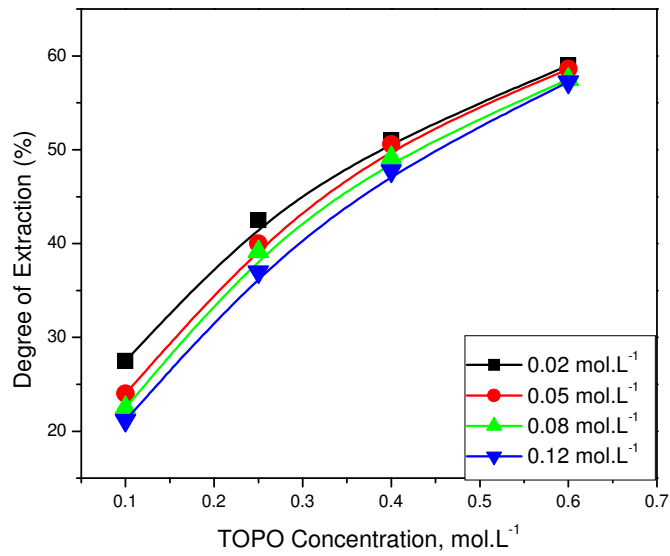


Figure 2. Effect of TOPO concentration on degree of extraction with different acid concentration

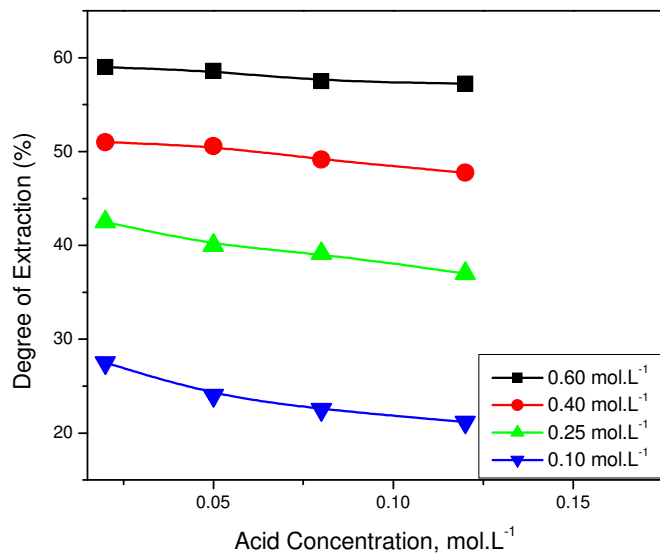


Figure 3. Effect of initial acid concentration on degree of extraction with different TOPO concentration

For the estimation of equilibrium extraction constant ( $K_E$ ) and the number of extractant (TOPO) molecules per acid molecule ( $n$ ), the mass action law modeling approach is used as performed in the section of Theory. A plot of equation (6) by taking,  $\log K_D + \log\left(1 + \frac{K_a}{[H^+]}\right)$  on  $y$ -axis and  $\log[S_{org}]$  on  $x$ -axis yields the straight line with a slope of  $n$  and intercept of  $\log K_E$  as shown in Fig. 4. For the extraction equilibrium of nicotinic acid with TOPO, the slopes of the straight lines suggest the formation of complex between one molecule each of both the reactants in all cases of acid concentration. The results indicate a stoichiometric association between the individual phosphoryl group and individual acid group, and display the effect of acid concentration on the experimentally determined distribution ratio. From Figure 4 and Table 1, it can be seen that there is not a significant difference between the slopes and intercepts for different initial acid concentrations except very low concentration of acid ( $0.02 \text{ mol.L}^{-1}$ ). At very low concentration of acid, kerosene molecules significantly compete with water molecules for the physical extraction.

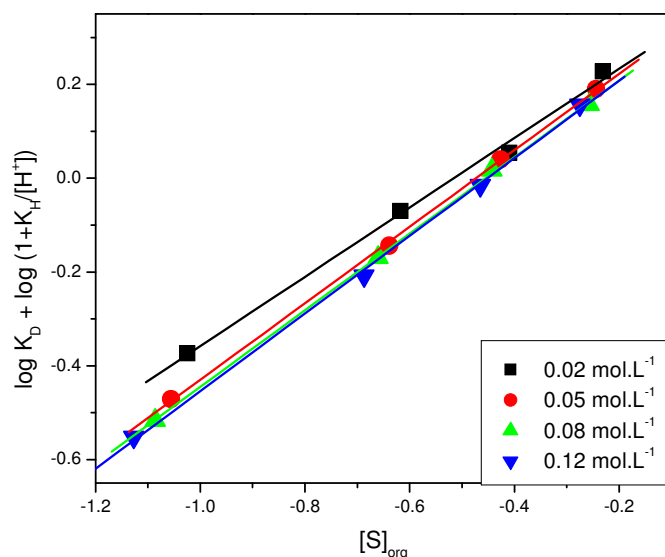


Figure 4. Determination of extraction constants ( $K_E$ ) and apparent number of reacting molecules ( $n$ ) using TOPO dissolved in kerosene with different initial acid concentration

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 proven successful record (Babu, 2004; Babu and Munawar, 2007), is also employed to solve the model equation (7) for estimation of extraction equilibrium constants ( $K_E$ ) and the number of reacting extractant molecules ( $n$ ). An objective function based on least square error between experimental data and predicted value of  $\log K_D + \log\left(1 + \frac{K_a}{[H^+]}\right)$  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 also given in Table 1.

**Table 1. Values of Equilibrium Extraction Constant ( $K_E$ ) and Number of Reacting Extractant (TOPO) Molecules ( $n$ ) with Different Concentrations of Nicotinic Acid.**

[HNc] <sub>in</sub> /mol.L <sup>-1</sup>	Using graphical method (Figure 4)			Using DE (optimization procedure)	
	$K_E$	$n$	$R^2$	$K_E$	$n$
0.02	2.40	0.74	0.99	2.47	0.89
0.05	2.43	0.82	0.99	2.36	0.82
0.08	2.35	0.82	0.99	2.53	0.83
0.12	2.37	0.83	0.99	2.10	0.65

The obtained results of  $K_E$  and  $n$ , for TOPO extractant using computational procedure shows the same trend as obtained by graphical method using 1:1 complex, but more accurate. The diluents, having dielectric constant values and solvent polarity also contribute to the extraction of organic acid and results in a less than one value of stoichiometry coefficients. 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 are showing minimal deviation in the results.

Since nicotinic acid is used in the low concentration range of 0.02 to 0.12 mol.L<sup>-1</sup> and TOPO is diluted in the range of 0.10 to 0.60 mol.L<sup>-1</sup>, 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 complete range of TOPO concentrations to obtain the value of equilibrium complexation constant ( $K_{E1}$ ) as shown in Figure 5. Equilibrium extraction constant ( $K_{E1}$ ) for 1:1 complex of acid and TOPO at 298 K for the extraction of acid are given in Table 2.

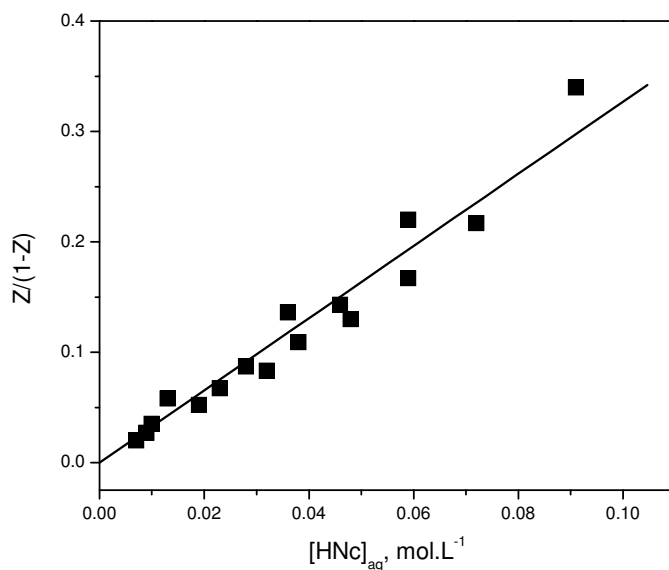


Figure 5. Plot of  $Z/(1 - Z)$  versus  $[HNc]$  for the estimation of (1:1) nicotinic acid-TOPO equilibrium complexation constant ( $K_{E1}$ ) in the entire range of TOPO concentration.

**Table 2. Equilibrium extraction constant ( $K_{EI}$ ) for the extraction of nicotinic acid (0.02 – 0.12 mol.L<sup>-1</sup>) in the entire range (0.10 - 0.60 mol L<sup>-1</sup>) of TOPO from Figure 5**

Extractant system	$K_{EI}$ (mol <sup>-1</sup> ·m <sup>3</sup> )	$R^2$	$SD$
TOPO + kerosene	3.27±0.11	0.97	0.02

## Conclusions

The studies on reactive extraction of nicotinic acid with tri-n-octyl phosphine oxide (TOPO) dissolved in kerosene at various TOPO and acid concentrations indicated that the reactive extraction occurs by means of the interfacial formation of solvates between acid and extractant. The experimental data clearly show that the chemical extraction using 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 (0.10 to 0.60 mol.L<sup>-1</sup>) and found to decrease when the concentration of acid is increased from 0.02 to 0.12 mol.L<sup>-1</sup>. Different parameters like distribution coefficient, degree of extraction, loading ratio, and equilibrium complexation constants are determined. Chemical modeling approach is used for the determination of the equilibrium extraction constant ( $K_E$ ) and the number of extractant reacting molecules ( $n$ ), the estimated values of  $K_E$  and  $n$  depend on the applied method. Optimum values of  $K_E$  and  $n$  have been found when 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 graphical method and differential evolution algorithm. With the assumption of  $n = 1$ , the maximum equilibrium extraction constant is found to be 3.27 L.mol<sup>-1</sup> in the complete range of acid concentrations and extractant (TOPO) concentrations.

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