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Dan Caşcaval[a]; Alexandra-Cristina Blaga[a]; Maria Cămăruţ[a]; Anca-Irina Galaction[b]
[a] Faculty of Chemical Engineering, Department of Biochemical Engineering, Technical University "Gh. Asachi" of Iasi, Iasi, Romania [b] Faculty of Medical Bioengineering, Department of Biotechnology, University of Medicine and Pharmacy, Iasi, Romania

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Comparative Study on Reactive Extraction of Nicotinic Acid with Amberlite LA-2 and D2EHPA

Dan Caşcaval, Alexandra-Cristina Blaga, and Maria Cămăruţ
Technical University "Gh. Asachi" of Iasi, , Faculty of Chemical Engineering, Department of Biochemical Engineering, Iasi Romania

Anca-Irina Galaction
University of Medicine and Pharmacy, Faculty of Medical Bioengineering, Department of Biotechnology, Iasi, Romania

Abstract: The comparative study of reactive extraction of nicotinic acid with Amberlite LA-2 and D2EHPA in three solvents with different polarity indicated that the extractant type and solvent polarity control the extraction mechanism. Thus, the reactive extraction with Amberlite LA-2 in low-polar solvents occurs by means of the interfacial formation of an aminic adduct with 3 or 2 extractant molecules. If solvents with higher polarity are used, each reactant participates with one molecule to the interfacial reaction. The mechanism of reactive extraction with D2EHPA involves in all cases the formation of a salt as the product of the interfacial reaction between one molecule of each reactant.

Keywords: Nicotinic acid, reactive extraction, Amberlite LA-2, D2EHPA, extraction mechanism, extraction constant, solvent polarity

INTRODUCTION

Niacin, also called vitamin PP or vitamin B_3, is a water-soluble vitamin which includes nicotinic acid and nicotinamide. Both compounds participate in

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Address correspondence to Dan Caşcaval, Technical University "Gh. Asachi" of Iasi, Faculty of Chemical Engineering, Department of Biochemical Engineering, D. Mangeron Avenue 71, 700050 Iasi, Romania. E-mail: dancasca@ch.tuiasi.ro

the formation of NAD (nicotinamide-adenine-dinucleotide) and NADP (nicotinamide-adenine-dinucleotide-phosphate) coenzymes, playing a key-role in the redox reactions in cells. NAD is involved in the catabolism of carbohydrates, fats, and proteins with energy production. The NADP functions consist especially of anabolic processes of fatty acids and cholesterol synthesis (1–3).

As indicated in the literature, niacin is directly referred to as nicotinic acid (4). Niacin deficiency leads to pellagra, which is associated with poor alimentation based on cereals, like corn and/or sorghum. The symptoms of this disease consist of dermatitis, red tongue, vomiting, diarrhea, headache, apathy, depression, disorientation, and memory loss (3–5). If left untreated, pellagra could become fatal ultimately.

Pellagra prevention and treatment are made by including niacin in the dietary intake, in relation with age, sex, and the health of the subjects. Moreover, it was observed that niacin induces the amelioration of other diseases, namely cancer (5–9), diabetes (10, 11) and cardiovascular diseases associated with high level of cholesterol (12–14), and AIDS (15, 16).

Because the human body does not have the ability to produce niacin, its intake by food and/or nutritional supplements represents the main way for avoiding niacin deficiency. The world-wide production of niacin strongly increased in the last several years to about 22,000 tonnes/year (over 65% is nicotinic acid), the major producers of nicotinic acid being Lonza (Switzerland), Degussa, BASF (Germany), Nepera, Reilly Industries (ex-Vitachem) (US), and Yuki Gosei (Japan) (14, 17, 18).

Nicotinic acid is mainly obtained by chemical synthesis, using 3-picoline or 2-methyl-5-ethyl-pyridine as starting-materials, at high temperature and pressure (4). Besides the technological conditions, the ensuring of the desired quality, the physical, and the chemical properties of the final product and the ecological problems complicate the chemical synthesis methods. For these reasons, the actual technologies for nicotinic acid production will become unattractive in the future.

Some of the above–mentioned disadvantages could be avoided using heterogeneous chemical catalysis (Reilly, Lonza) or enzymatic catalysis (BASF, Lonza, Nitto Chemical Industry Japan, Asahi Chemical Corp Japan) (4, 18). The enzymatic production of nicotinic acid becomes the most efficient alternative and implies the total hydrolysis of 3-cyanopyridine by bacterial *nitrilase* from *Acinetobacter, Agrobacterium, Cellulomonas, Microbacterium, Obesumbacterium, Rhodococcus*, at low temperature (5–50°C), $\text{pH} = 4\text{–}10$, the substrate concentration varying from 1.10^{-3} to 1 M.

Indifferent to the used method, nicotinic acid separation is achieved by spray-drying (especially for veterinary use), crystallization, and thermal decomposition of ammonium nicotinate (4, 18). These techniques require high energy and material consumptions (elevated temperature and pressure, inert media, organic liquid vapors at high temperature etc.) and are dependent on nicotinic acid concentration, all of these representing severe limitations of the separation processes.

For many technologies, the liquid-liquid extraction constitutes a viable solution, due to its technical accessibility and high efficiency. But its application is limited for the ionizable compounds, namely the carboxylic acids, due to their low solubility in usual organic solvents. In these cases, the performances of the extraction process can be enhanced by reactive extraction with an extractant added into the organic phase. Thus, the reactive extraction using extractants of organophosphoric or height molecular amines types have been successfully applied to the separation of some carboxylic acids, namely acetic acid, lactic acid, citric acid, succinic acid, malic acid, ascorbic acid, or beta-lactamic antibiotics (19–26).

Due to the insolubility of nicotinic acid in organic solvents, its separation by physical extraction is impossible. But, its extraction could become possible by adding into the solvent of an extractant which could react with nicotinic acid, leading to the formation of a hydrophobic compound, as in the case of the above mentioned acids extraction. Because the chemical structure of nicotinic acid contains an acidic group, -COOH, and a basic one, N from the pyridine core, the reactive extraction could become possible by using extractants of aminic or organophosphoric acid types. For this purpose, in this paper, the comparative study of the reactive extraction of nicotinic acid with Amberlite LA-2 (lauryl-trialkyl-methylamine) and di-(2-ethylhexyl)-phosphoric acid (D2EHPA) is presented. The extraction mechanisms and the influencing factors are discussed in both cases. Because the solvent polarity is an important factor that controls the extraction efficiency, the extraction mechanisms and optimum conditions have been analyzed in direct correlation with the polarity of the three used solvents (n-heptane, n-butyl acetate, dichloromethane).

MATERIALS AND METHOD

The experiments have been carried out using an extraction column with vibratory mixing, which offers a high interfacial area and the possibility to reach rapidly the equilibrium state. The laboratory equipment has been described in detail in previous papers (27). The phase mixing was made by mean of a perforated disk with 45 mm diameter and 20% free section. The vibrations had a frequency of 50 s^{-1} and 5 mm amplitude. The perforated disk position was maintained at the initial contact interface between the aqueous and organic phases. The extraction time was of 1 minute at a constant temperature of 25°C. The resultant emulsion was broken in a centrifugal separator at 5000 rpm.

The initial concentration of nicotinic acid in aqueous solution was of 12 g/l (9.76×10^{-2} M). The reactive extraction was made with Amberlite LA-2 and D2EHPA respectively, both solved in three solvents with different dielectric constants (Table 1). The extractant concentration in the organic phase was varied between 20 and 120 g/l (5.3×10^{-2}–0.32 M for

Table 1. Dielectric constants of the used solvents at 20°C (28)

Solvent	n-Heptane	n-Butyl acetate	Dichloromethane
Dielectric constant	1.90	5.01	9.08

Amberlite LA-2, 6.1×10^{-2}–0.36 M for D2EHPA). The volumetric ratio of the aqueous and organic phase was of 1 (30 ml of each phase).

The pH-value of the initial aqueous solution was varied between 1 and 10. The pH adjustment was made with a solution of 3% sulfuric acid or 3% sodium hydroxide, function on the prescribed pH-value. The pH-values were determined using a digital pH-meter of Consort C836 type and have been recorded throughout each experiment. Any pH change was noted during the extraction experiments.

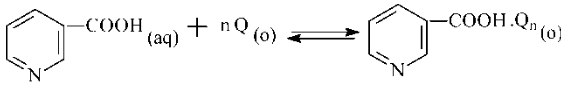
The extraction process was analyzed by means of the extraction degree and distribution coefficient. The extraction degree has been calculated as the ratio between the nicotinic acid concentration in the extract phase and in the initial aqueous solution respectively. For calculating these parameters, the nicotinic acid concentrations in the initial solution was measured by high performance liquid chromatography technique (HPLC) with a Shodex OHpak SB-802.5 HQ column (8 mm diameter, 300 mm length, 6 μm porous particle), provided with UV detector at 260 nm. The mobile phase was a phosphate buffer ($pH = 7$) with a flow rate of 2 ml/min. For calculating the nicotinic acid concentration in organic phase the mass balance has been used.

Each experiment has been carried out three or four times, for identical conditions, the average value of the considered parameters being used. The maximum experimental error was of ±4.33%.

RESULTS AND DISCUSSION

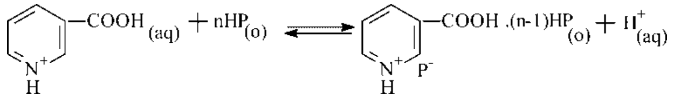
Indifferent to the extractant type, the reactive extraction of nicotinic acid occurs by means of the formation of a strong hydrophobic compound at the interface between the aqueous and organic phases. The chemical structure of this compound and the extraction parameters depend on the extractant type.

The carboxylic group of the nicotinic acid is involved in the reactive extraction process with Amberlite LA-2 (Q). The interfacial interactions between the acid and the extractant could be of hydrogen bonding type with the undissociated carboxylic groups, or of ionic type, if the acid dissociates in the aqueous solution:



Furthermore, in the function of the structures of system components and solvent polarity, the acidic or aminic adducts could be formed at the interface (19, 29). But, as it was observed for reactive extraction with Amberlite LA-2 of other compounds having voluminous molecules and due to the initial concentration of nicotinic acid, which is lower than that of Amberlite LA-2, it could be assumed that the formation of acidic adducts is steric hindered (19, 24, 25, 29). Therefore, the interfacial compounds could be of ammonium salt type, formed by neutralization of the carboxylic group with one extractant molecule, or by aminic adducts type, where $n \leq 2$. In the second case, the formation of these molecular associations is more pronounced in low-polar solvents and increases the hydrophobicity of the interfacial compound (19).

Because the nicotinic acid contains the N pyridinic, it could react with acidic extractants, like D2EHPA (HP). In this case, the reactive extraction could occur by means of an interfacial reaction of the ion-exchanging type, which requires the acid to be on protonated form into the aqueous solution:



The pH-value of the aqueous phase exhibits a significant influence on the reactive extraction degree. As can be observed from Fig. 1, for both used extractants a certain value of pH-value corresponding to the maximum of reactive extraction degree in n-butyl acetate was recorded.

For the extraction with Amberlite LA-2, the maximum is the result of the N pyridinic ionization at a strong acidic pH-domain, this phenomena limiting

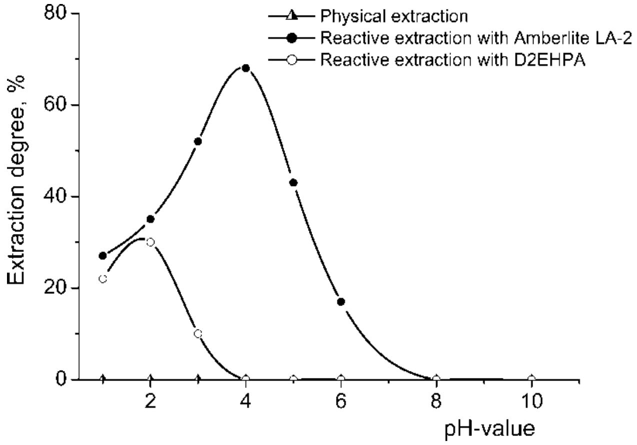


Figure 1. Influence of pH-value of aqueous phase on efficiency of reactive extraction of nicotinic acid with Amberlite LA-2 and D2EHPA (solvent: n-butyl acetate, extractant concentration 40 g/l).

the extraction efficiency. The optimum value of aqueous phase pH is 4, higher values of pH inducing the -COOH group dissociation and, consequently, the decreasing of extraction yield ($pK_a = 4.85$ (28)).

The reactive extraction of nicotinic acid with D2EHPA is possible if the N pyridinic is in cationic form, and respectively at a lower pH-value. But, at a strong acidic pH, the extractant is protonated too and thus unable to react with the acid (30). Due to these two opposite phenomena, the optimum pH-value for the extraction with D2EHPA is 2.

The physical extraction of nicotinic acid is not possible. By comparing the reactive extraction degree for a given extractant concentration of 40 g/l, at the optimum pH-values, it can be concluded that Amberlite LA-2 is the most efficient extractant (the difference between the corresponding extraction yields recorded for the two extractants is of 38%).

For analyzing the extraction mechanism of nicotinic acid (HNc) with the two extractants, it was assumed that n extractant (E) molecules and one acid molecule participate in the formation of the interfacial compound, through ionic and hydrogen bonds. Thus, the reactive extraction with Amberlite LA-2 can be described by the following interfacial equilibrium:

$$\mathrm{HNc_{(aq)}} + \mathrm{nE(o)} \rightleftharpoons \mathrm{HNcE_{n(o)}}$$

Therefore, the distribution coefficient, D, is calculated with the relationship:

$$D = \frac{[\mathrm{HNcE_{n(o)}}]}{[\mathrm{HNc_{(aq)}}]} \tag{1}$$

where $[\mathrm{HNc_{(aq)}}]$ and $[\mathrm{HNcE_{n(o)}}]$ symbolize the overall concentrations of nicotinic acid and extracted compound at the equilibrium state.

According to the interfacial equilibrium, the extraction constant, K_E, can be calculated with the following expression:

$$K_E = \frac{[\mathrm{HNcE_{n(o)}}]}{[\overline{\mathrm{HNc_{(aq)}}}] \cdot [\mathrm{E_{(o)}}]^n} \tag{2}$$

$$\Rightarrow [\mathrm{HNcE_{n(o)}}] = K_E \cdot [\overline{\mathrm{HNc_{(aq)}}}] \cdot [\mathrm{E_{(o)}}]^n \tag{3}$$

The study on the mechanism of reactive extraction with D2EHPA was carried out at pH = 4, therefore the concentration of undissociated nicotinic acid from the aqueous phase, $[\mathrm{HNc_{(aq)}}]$, is calculated by means of its overall concentration in the aqueous phase, $[\overline{\mathrm{HNc_{(aq)}}}]$, and the dissociated acid concentration, $[\mathrm{Nc^-(aq)}]$. The dissociation constant, K_a, corresponds to the following dissociation equilibrium:

$$\mathrm{HNc} \rightleftharpoons \mathrm{Nc^-} + \mathrm{H^+}$$

and is determined with the relationship:

$$K_a = \frac{[Nc^-_{(aq)}] \cdot [H^+]}{[HNc_{(aq)}]} \tag{4}$$

Thus, the concentration of undissociated nicotinic acid is:

$$[HNc_{(aq)}] = [\overline{HNc_{(aq)}}] - [Nc^-_{(aq)}] \tag{5}$$

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

$$\Rightarrow [HNc_{(aq)}] = \frac{[\overline{HNc_{(aq)}}]}{1 + K_a/[H^+]} \tag{7}$$

Therefore, by combining eqs. (1), (3) and (7), the following expression for the distribution coefficient, D, is obtained:

$$D = K_E \cdot [E_{(o)}]^n \cdot \left(1 + \frac{K_a}{[H^+]}\right) \tag{8}$$

The correlation (8) represents in logarithmic form the equation of a straight line:

$$\ln D - \ln\left(1 + \frac{K_a}{[H^+]}\right) = \ln K_E + n \cdot \ln[E_{(o)}] \tag{9}$$

Because the initial concentration of the extractant is higher than the initial concentration of nicotinic acid, $[E_{(o)}]$ could be assumed to be the initial concentration of Amberlite LA-2 in the organic phase. Consequently, from the slope of the straight line given by eq. (9) it is possible to determine the number of extractant molecules, n, which participate in the formation of the interfacial compound, and from its intercept the value of extraction constant, K_E.

The study of the mechanism of reactive extraction with D2EHPA was carried out at pH = 2. In this case, N pyridinic is the active center of the nicotinic acid, the extraction efficiency being controlled by its ionization capacity. The interfacial reaction could be described by the following equilibrium:

$$H_2Nc^+_{(aq)} + nE_{(o)} \rightleftharpoons HNcE_{n(o)} + H^+_{(aq)}$$

According to this interfacial equilibrium, the distribution coefficient, D, is:

$$D = \frac{[HNcE_{n(o)}]}{[H_2Nc^+_{(aq)}]} \tag{10}$$

where $[H_2Nc^+_{(aq)}]$ and $[HNcE_{n(o)}]$ represent the overall concentrations of the considered components at the equilibrium state.

The extraction constant, K_E, can be calculated with the following relationship:

$$K_E = \frac{[HNcE_{n(o)}] \cdot [H^+_{(aq)}]}{[H_2Nc^+_{(aq)}] \cdot [E_{(o)}]^n} = \frac{[HNcE_{n(o)}]^2}{[H_2Nc^+_{(aq)}] \cdot [E_{(o)}]^n} \tag{11}$$

$$\Rightarrow \; [HNcE_{n(o)}]^2 = K_E \cdot [H_2Nc^+_{(aq)}] \cdot [E_{(o)}]^n \tag{12}$$

The ionization constant of N pyridinic is $K_b = 1.26 \times 10^{-11}$ (31), and is calculated related to the following equilibrium:

$$HNc + H_2O \rightleftharpoons H_2Nc^+ + HO^-$$

$$K_b = \frac{[H_2Nc^+_{(aq)}] \cdot [HO^-]}{[HNc_{(aq)}]} = \frac{10^{-14} \cdot [H_2Nc^+_{(aq)}]}{\lfloor HNc_{(aq)} \rfloor \cdot [H^+_{(aq)}]} \tag{13}$$

The concentration of protonated nicotinic acid from the aqueous phase, $[H_2\ Nc^+_{(aq)}]$, is calculated by means of its overall concentration in the aqueous phase, $[\overline{HNc_{(aq)}}]$, and its non-ionized molecules concentration, $\lfloor HNc_{(aq)} \rfloor$.

$$[H_2Nc^+_{(aq)}] = [\overline{HNc_{(aq)}}] - [HNc_{(aq)}] \tag{14}$$

$$[HNc_{(aq)}] = \frac{10^{-14} \cdot [H_2Nc^+_{(aq)}]}{K_b \cdot [H^+_{(aq)}]} \tag{15}$$

$$\Rightarrow \; [H_2Nc^+_{(aq)}] = \frac{[\overline{HNc_{(aq)}}]}{1 + 10^{-14}/K_b \cdot [H^+_{(aq)}]} \tag{16}$$

Thus, the expression for distribution coefficient becomes:

$$D^2 = \frac{[HNcE_{n(o)}]^2}{[H_2Nc^+_{(aq)}]^2} = \frac{K_E \cdot [E_{(o)}]^n}{[H_2Nc^+_{(aq)}]}$$

$$= \frac{K_E \cdot [E_{(o)}]^n \cdot \left(1 + \left(10^{-14}/K_b \cdot [H^+_{(aq)}]\right)\right)}{[\overline{HNc_{(aq)}}]} \tag{17}$$

The logarithmic form of eq. (18) gives a straight line equation:

$$2 \ln D - \ln \frac{1 + \left(10^{-14}/K_b \cdot [H^+_{(aq)}]\right)}{[\overline{HNc_{(aq)}}]} = \ln K_E + n \cdot \ln[E_{(o)}] \tag{18}$$

which is used for the n and K_E graphical determination, similar to the calculations for reactive extraction with Amberlite LA-2 ($[E_{(o)}]$ could also be assumed to be equal with the initial concentration of D2EHPA in the organic solvent).

For determining the number of extractant molecules which react with the nicotinic acid, in correlation with the solvent polarity, the influence of the extractant concentration of the extraction efficiency has been analyzed for the two extractants solved in n-heptane, n-butyl acetate, and dichloromethane respectively.

The experimental results, plotted in Fig. 2, indicated that the extraction efficiency increases with the solvent polarity for both used extractants (for 40 g/l extractant in an organic solvent, the extraction degree in dichloromethane was about 12 times greater than that in n-heptane if Amberlite LA-2 is used, respectively and about 10 times greater in the case of D2EHPA).

By means of the experimental data from Fig. 2 and by plotting the eqs. (9) and (19), the straight lines from Fig. 3 have been obtained for the two extractants and three solvents considered.

The values of the straight lines slope depend on extractant type and solvent polarity, varying as follows:

- ***reactive extraction with Amberlite LA-2***
  - n-heptane n = 2.97
  - n-butyl acetate n = 1.99
  - dichloromethane n = 1.15
- ***reactive extraction with D2EHPA***
  - n-heptane n = 1.08
  - n-butyl acetate n = 1.15
  - dichloromethane n = 1.11

The obtained values indicate the modification of the chemical structure of the interfacial compound in function of the used extractant–solvent combination. Therefore, reactive extraction with Amberlite LA-2 in low-polar solvents (n-heptane, n-butyl acetate) occurs by means of the interfacial

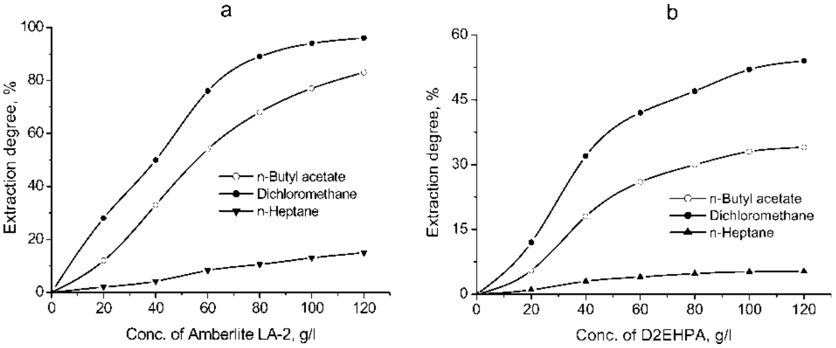


Figure 2. Influence of concentration of Amberlite LA-2 (a) and D2EHPA (b) on efficiency of reactive extraction of nicotinic acid in different solvents (a: pH = 4, b: pH = 2).

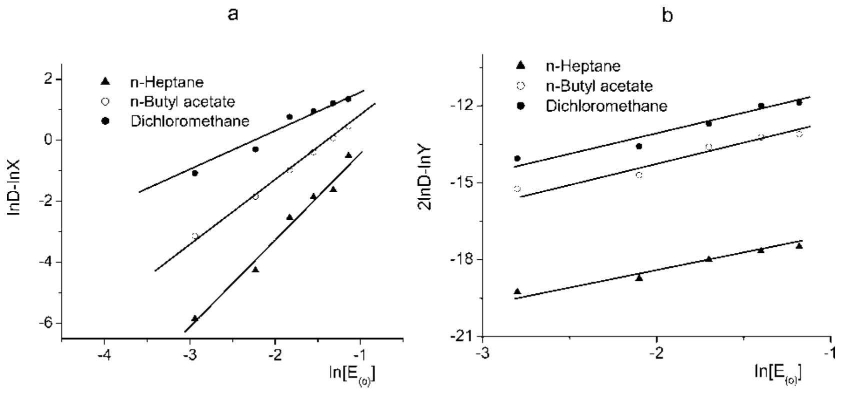


Figure 3. Graphical representation of the straight lines given by equations (9), for reactive extraction with Amberlite LA-2 (a), and (19), for reactive extraction with D2EHPA (b) (a: $X = \left(1 + \frac{K_a}{[H^+]}\right)$, b: $Y = \frac{1 + \left(10^{-14}/K_b \cdot [H^+_{(aq)}]\right)}{[\overline{HNc}_{(aq)}]}$)

formation of an aminic adduct with 3 or 2 extractant molecules respectively. If solvents with higher polarity are used (dichloromethane), each reactant participates with one molecule to the interfacial reaction.

These results have been also been suggested by the variation of the reactive extraction yield plotted in Fig. 2a. From this figure it can be observed that the extraction degree continuously increases with Amberlite LA-2 concentration for n-heptane and n-butyl acetate. On the other hand, the yield of extraction in dichloromethane increases strongly with the increase of extractant concentration only for Amberlite LA-2 concentration below 60 g/l, value that corresponds to a molar ratio of 1 : 1 between the acid and extractant. Over this level of amine concentration, the extraction degree increases slowly with the extractant concentration.

For the reactive extraction with D2EHPA, the slopes of the straight lines suggest in all cases the formation of the interfacial product of salt type by reaction between one molecule of each reactant. This conclusion has been also indicated by the influence of D2EHPA concentration on the extraction degree plotted in Fig. 2.b. Thus, for the extractant concentration values over 40 g/l, which corresponds to the molar ration of 1 : 1 between the reactants, the influence of this parameter is considerably reduced.

As was presented above, the solvent polarity represents an important parameter that controls the extraction of ionizable solutes. The dielectric constant is considered a characteristic 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 modification of dielectric constant has a smaller effect on the solubility and

Table 2. Expressions and values of extraction constants for the studied systems

Extractant	Solvent	Extraction constant	Value
Amberlite LA-2	n-Heptane	$K_E = [HNcE_{3(o)}] / [HNc_{(aq)}] \cdot [E_{(o)}]^3$	7.24($l^3/mole^3$)
	n-Butyl acetate	$K_E = [HNcE_{2(o)}] / [HNc_{(aq)}] \cdot [E_{(o)}]^2$	10.52 ($l^2/mole^2$)
	Dichloromethane	$K_E = [HNcE_{(o)}] / [HNc_{(aq)}] \cdot [E_{(o)}]$	12.18 (l/mole)
D2EHPA	n-Heptane	$K_E = [HNcE_{(o)}]^2 / [H_2Nc^+_{(aq)}] \cdot [E_{(o)}]$	2.01×10^{-7} (−)
	n-Butyl acetate	$K_E = [HNcE_{(o)}]^2 / [H_2Nc^+_{(aq)}] \cdot [E_{(o)}]$	1.51×10^{-5} (−)
	Dichloromethane	$K_E = [HNcE_{(o)}]^2 / [H_2Nc^+_{(aq)}] \cdot [E_{(o)}]$	3.72×10^{-5} (−)

extraction of nonelectrolytes or weak electrolytes, but it becomes an important factor for the extraction of dissociable solutes.

Therefore, the solvent polarity controls the extraction constant through its influence on separation efficiency and mechanism. For the reactive extraction of nicotinic acid, in Table 2 are given the values of extraction constants graphically determined for the considered extractants and solvents.

By increasing the dielectric constant from 1.90 (n-heptane) to 9.08 (dichloromethane), the extraction constant increases 1.7 times for Amberlite LA-2 and about 185 times for D2EHPA respectively. Due to the formation of the aminic adducts, the product of the interfacial reaction becomes more hydrophobic in the case of reactive extraction with Amberlite LA-2, and, consequently, the influence of solvent polarity is less pronounced.

CONCLUSIONS

The studies on the reactive extraction of nicotinic acid with Amberlite LA-2 and D2EHPA in three solvents with different polarities (n-heptane, n-butyl acetate, dichloromethane), at various extractants concentrations and pH-values of aqueous solutions indicated that the reactive extraction occurs by means of the interfacial reaction of hydrogen bonding or ionic type. The mechanism of the reaction is controlled by the extractant type and solvent polarity.

Compared with 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.

The number of Amberlite LA-2 molecules participating at the interfacial reaction with one molecule of nicotinic acid could be 1, 2, or 3, in direct relation with the solvent polarity (lower number of amine molecules corresponds to the solvent with higher dielectric constant, namely dichloromethane). The mechanism of reactive extraction with D2EHPA involves in all cases the formation of a salt from the interfacial reaction between one molecule of each reactant.

The highest value of the extraction constant has been obtained for reactive extraction with Amberlite LA-2 dissolved in dichloromethane. The influence of solvent polarity on the extraction constant was less important for the extraction processes using this extractant, due to the formation of the aminic adducts which increase the hydrophobicity of the extracted compound.

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