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SYNERGIC EXTRACTION OF PANTOTHENIC ACID WITH TWO DIFFERENT EXTRACTANTS

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Abstract - The influences of extractants concentrations and solvent polarity on the efficiency of pantothenic acid separation by synergic extraction with tri-n-octylamine (TOA) and di(2-ethylhexyl) phosphoric acid (D2EHPA) mixture have been analyzed. The results indicated the formation of an interfacial compound which includes one molecule of pantothenic acid and one of D2EHPA, its hydrophobicity being increased by solvation with additional TOA molecules. For solvents with lower dielectric constants, n-heptane and n-butyl acetate, the number of amine molecules participating in the interfacial complex formation was controlled by solvent polarity and D2EHPA concentration, decreasing with the increase of these two parameters. For dichloromethane, the chemical structure of the extracted compound remained the same regardless of D2EHPA concentration. The most important synergic effect corresponded to the extractant mixture dissolved in n-heptane, at low D2EHPA concentration in the organic phase (5 g/l).

Keywords: Pantothenic acid; Tri-n-octylamine; Di(2-ethylhexyl) phosphoric acid; Synergic extraction; Synergistic coefficient; Distribution coefficient.

INTRODUCTION

The phenomenon of synergism was first noted in biological systems as the combined actions of two or more bioactive compounds. Translated to the extraction process, it appears when the efficiency of reactive extraction using a mixture of extractants is superior to the sum of the efficiencies of each individual extractant (Schugerl, 1994; Matsumoto *et al*., 2001). In the extraction systems, the synergic effect can be quantitatively described by means of the synergistic coefficient, C_S, usually calculated as a function of the distribution coefficients or extraction yields (Matsumoto *et al*., 2001; Keshav *et al*., 2009; Caşcaval *et al*., 2012). Therefore, in the case of reactive extraction with the extractants A and B, the synergistic coefficient represents the ratio between the distribution coefficients corresponding to the extractants mixture and the sum of the distribution coefficients obtained separately for each extractant (Matsumoto *et al*., 2001; Keshav *et al*., 2009; Caşcaval *et al*., 2012):

$$C_S = \frac{D_{AB}}{D_A + D_B} \tag{1}$$

The synergism is obtained if the synergistic coefficient is greater than 1; if less than 1, the effect is called “negative synergism” (Matsumoto *et al*., 2001).

Although there are some reports in the literature concerning the appearance of this phenomenon in extraction, the mechanism of synergic extraction has not been completely elucidated. However, it was accepted that the main effect consists of the improvement of the hydrophobicity of the extracted complex produced by reaction between the solute dissolved in aqueous solution and the extractants from the or-

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*To whom correspondence should be addressed ganic phase. In this case, the synergism is the result of two simultaneous phenomena (Matsumoto *et al.*, 2001; Caşcaval *et al.*, 2012):

- the modification of the individual extraction capacity of each extractant
- the modification of the chemical structure of the extracted compound compared to the extraction with the individual extractant.

Consequently, it could be assumed that one extractant reacts with the solute, forming a solute - extractant complex soluble in the organic phase, while the other one increases the complex hydrophobicity by solvation. The synergic effect is amplified by increasing the difference between the polarities of the extractants (Keshav *et al.*, 2009).

The previous studies on the synergic extraction of carboxylic acids used mainly two neutral extractants, namely a mixture of tri-n-butylphosphate and tri-n-octylamine (Matsumoto *et al.*, 2001; Keshav *et al.*, 2009), or mixtures of amine extractants (Hong and Hong, 1999; Hong and Hong, 2000; Keshav *et al.*, 2009). However, the use of a mixture of an amine extractant and an acidic one of the organophosphoric acid type induced an important synergic effect in the extraction of carboxylic acids (Caşcaval *et al.*, 2012).

Pantothenic acid, also known as vitamin B5, is the amide of pantoic acid with β-alanine (Figure 1). This compound is a water-soluble vitamin involved in the conversion of carbohydrates into glucose needed to produce energy, synthesis of coenzyme A, synthesis and metabolism of proteins, carbohydrates and fats (Coates *et al.*, 2005).

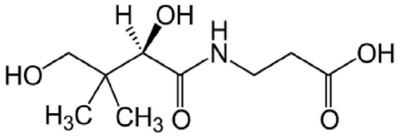

Figure 1: The chemical structure of pantothenic acid.

In the human body, pantothenic acid plays a major role in the health of the digestive, nervous, circulatory, and skeletal systems, skin and hair, and synthesis of hormones (insulin, adrenaline). It is also a booster for the imune system.

Generally, pantothenic acid is obtained by extraction from natural sources (bread yeast, mushrooms, cereals, eggs, peanuts, soybeans, lentil, liver of various animals or birds, etc.) or chemical synthesis (Gonthier *et al.*, 1998; Kroschwitz and Kirk-Othmer, 2001, Kivrk, 2015). Its biosynthesis by microorganisms (*Brucella abortus*, *Azotobacter vinelandii*, *Escherichia coli*, *Fusarium oxysporum*) represents an attractive alternative, mainly due to the reduction of the required process steps and consumption of materials and energy (Weetall, 1980; Martinez-Toledo *et al.*, 1996; Drauz *et al.*, 2012).

The separation of pantothenic acid from extracts, synthesis or biosynthesis media has been carried out by crystallization, ion exchange, and chromatography (Zhdanovich *et al.*, 1970; Hudson and Allen, 1984; Moiseenok *et al.*, 1987; Drauz *et al.*, 2012). These methods offer rather low efficiency and require expensive materials and energy costs.

Because pantothenic acid contains both basic and acidic groups, its reactive extraction with extractants of the organophosphoric acid and amine types has been studied and found to be possible (Poştaru *et al.*, 2015). Therefore, based on our previous results on pantothenic acid reactive extraction with tri-n-octylamine (TOA) and, separately, di(2-ethylhexyl) phosphoric acid (D2EHPA), the separation of this acid using the mixture of the two extractants has now been investigated. Beside the use of an Amberlite LA-2 and D2EHPA mixture for extraction of folic acid (Caşcaval *et al.*, 2012), the proposed combination of extractants is original, any information concerning its application for synergic extraction of other carboxylic acids not being reported in literature. In this paper, the influences of the extractants ratio in the mixture, pH-value, and solvent polarity on the magnitude of the synergic effect are discussed.

MATERIALS AND METHOD

The experiments were carried out using an extraction column with vibratory mixing, which offers high interfacial area and the possibility to reach rapidly the equilibrium state. The laboratory equipment, described in detail in previous papers (Caşcaval *et al.*, 2011; Kloetzer *et al.*, 2013), consists of a glass column with internal diameter of 36 mm and height of 250 mm, provided with a thermostatic jacket where the thermal agent (water and ethylene glycol mixture) is circulated at 25 °C. The phases were mixed by means of a perforated disk with 45 mm diameter and 20% free section. The vibrations had the 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 1 min. The resultant emulsion was broken in a centrifugal separator at 8000 rpm.

The initial concentration of pantothenic acid in the aqueous solution was 1 g/l ($4.56x10^{-3}$ M). The reactive extraction was carried out with three solvents possessing different dielectric constants, namely n-heptane (dielectric constant 1.90 at 25 °C (Haynes, 2012)), n-butyl acetate (dielectric constant of 5.01 at 25 °C (Haynes, 2012)), and dichloromethane (dielectric constant 9.08 at 25 °C (Haynes, 2012)). The considered extractants were TOA and D2EHPA. They were used individually and in mixtures, being dissolved in the mentioned solvents. Their concentrations in the organic phase varied between 5 and 60 g/l (0.014 - 0.0.17 M TOA, 0.015-0.18 M D2EHPA). The volumetric ratio of the aqueous and organic phases was 1 (20 ml of each phase).

The pH value of the initial aqueous solution was varied between 1 and 7. The pH adjustment was made with a solution of 3% sulfuric acid or 3% sodium hydroxide, depending on the prescribed pH-value. The pH-values were determined using a Consort C836 digital pH-meter and were recorded throughout each experiment. Any pH change was recorded during the extraction experiments.

The synergic extraction process was analyzed by means of the distribution coefficients and synergistic coefficient. For calculating these parameters, the pantothenic acid concentration in the initial aqueous solution and in the raffinate were measured. For determining the acid concentration in the solvent phase the mass balance was used. For dosing pantothenic acid, HPLC with a concentration gradient was used (Dionex Ultimate 3000, Acclaim PolarAdvantage column type II (PA2), with a diameter of 4.6 mm, length of 150 mm, particle diameter of 5 μm). The equipment was provided with a UV-VIS diode array detector DAD-3000. The injection volume was 20 μl. The mobile phase consisted of acetonitrile (A) and phosphate buffer (pH 3.2, phosphoric acid) (B). The gradient was 0-35% A in the first 14 minutes, at a flow rate of 1 ml min^{-1}. Analyses were carried out at the temperature of 25 °C.

Each experiment has been repeated for two or three times for identical conditions, the average value of the considered parameters being used. The maximum experimental error was of ±4.44%.

RESULTS AND DISCUSSION

As previously stated, pantothenic acid can be reactively extracted with both TOA and D2EHPA (Poştaru *et al.*, 2015). The extraction with TOA (E) is possible due to the carboxylic group in the acid structure, the process occurring by interfacial interactions between solute and extractant of the hydrogen bonding type if pantothenic acid is undissociated in the aqueous phase, or of the ionic type if the acid is partially dissociated (Poştaru *et al.*, 2015):

$$HA_{(aq)} + mE_{(o)} \rightleftarrows HA.E_{m(o)}$$

(*HA* symbolizes pantothenic acid).

Depending on the solvent polarity, the acidic or amine adducts could be formed at the interface. However, for pantothenic acid it was observed that the formation of acidic adducts is hindered, due both to the steric hindrance induced by the voluminous molecule of pantothenic acid and to its initial concentration, which is lower compared to that of TOA (Poştaru *et al.*, 2015). In this case, the interfacial compound could be of the ammonium salt type, resulting from neutralization of the solute carboxylic group with one extractant molecule, or of amine type adducts for m ≥ 2. The formation of these molecular associations was more pronounced in solvents with low dielectric constant, the values of m varying as follows: m=4 for n-heptane, m=2 for n-butyl acetate, and m=1 for dichloromethane (Poştaru *et al.*, 2015).

Therefore, at equilibrium, the distribution coefficient of pantothenic acid between the aqueous and organic phases corresponding to the reactive extraction with TOA is:

$$D_{TOA} = \frac{\left[HA.E_{m(o)}\right]}{\left[HA_{(aq)}\right]} \tag{2}$$

where D_{TOA} is the distribution coefficient for reactive extraction with TOA.

The variation of this distribution coefficient with the pH of aqueous phase is plotted in Figure 2.

In all cases, from Figure 2 it can be observed that the distribution coefficient initially increases slowly with the increase of pH from 1 to 2, decreasing strongly for higher pH-values. This variation is the result of carboxylic group dissociation, which becomes unable to react with the amine extractant for pH-values over 3 (pKa = 4.41 at 25 °C (Haynes, 2012)). At the same time, the chemical stability of pantothenic acid is significantly affected in the pH-domains below 3 and over 7 (Poştaru *et al.*, 2015), leading to an apparent lower extraction yield of pantothenic acid for pH=1 compared to that reached for pH=2. The reduction of solvent polarity exhibits a negative effect on the distribution coefficients, decreasing from 14 for dichloromethane to 1.9 for n-heptane at pH=2 (Figure 2).

The variation of the distribution coefficient with the increase of TOA concentration in the organic phase is graphically indicated in Figure 3 and suggests different correlations depending on the solvent used.

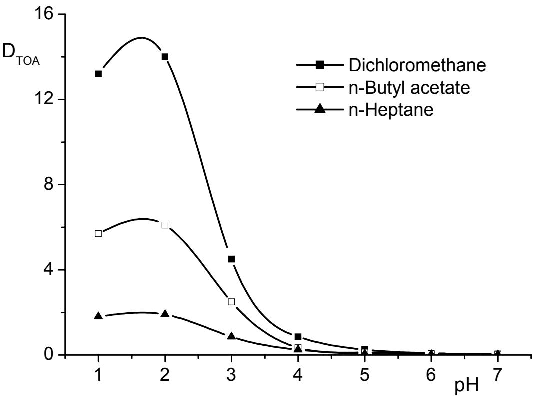

Figure 2: Influence of pH-value of the aqueous phase and solvent polarity on the pantothenic acid distribution coefficient for reactive extraction with TOA (TOA concentration = 40 g/l).

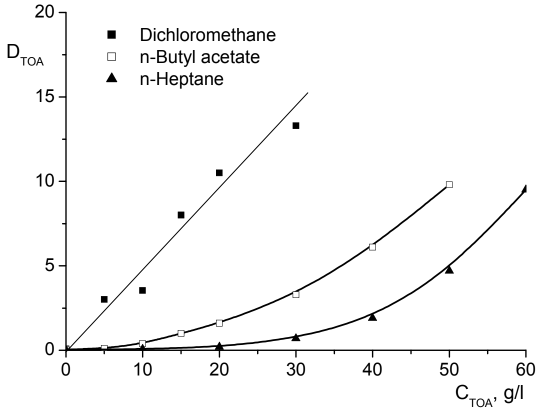

Figure 3: Influence of extractant concentration on the pantothenic acid distribution coefficient for reactive extraction with *TOA* (pH = 2).

For dichloromethane, the linear dependence between D_{TOA} and extractant concentration can be seen. For Figure 3 the solvents with lower dielectric constant, this dependence becomes of the polynomial type, being second-order for n-butyl acetate and fourth-order for n-heptane. These results confirm the extraction mechanisms related to each studied solvent, respectively the number of extractant molecule which react with pantothenic acid.

Because pantothenic acid contains one amide group which could exhibits a basic character of the carbonyl group, it can react with acidic extractants, including D2EHPA (HP). Consequently, the reactive extraction occurs by means of an interfacial reaction of the ion-exchange type, which requires the solute to be in the protonated form in the aqueous phase (at carbonyl oxygen) (Poştaru *et al.*, 2015):

$$H_2A^+_{(aq)} + n\ HP_{(o)} \rightleftarrows HA.HP_{n\ (o)} + H^+_{(aq)}$$

For the same reason as discussed above, the formation of the adducts containing many molecules of pantothenic acid is also hindered in the extraction with D2EHPA, the number of extractant molecules participating in the interfacial reaction being n=2 for n-heptane and n-butyl acetate, and n=1 for dichloromethane (Poştaru *et al.*, 2015).

The distribution coefficient related to this extraction mechanism is defined by the following relationship:

$$D_{D2EHPA} = \frac{\left[HA.HP_{n(o)} \right]}{\left[HA_{(aq)} \right]} \tag{3}$$

D_{D2EHPA} representing the distribution coefficient for reactive extraction with D_{2EHPA}.

The influence of the pH-value of the aqueous solution on the distribution coefficient D_{D2EHPA} is indicated in Figure 4. Therefore, the distribution coefficient is enhanced by increasing the pH-value up to 3, reaches its maximum at pH=3, then decreases. This dependence is the consequence of the phenomena occurring in the acidic domain of pH. Thus, the reactive extraction of pantothenic acid with D_{2EHPA} is possible if its active amide group is in the cationic form at a very low pH-value. However, at strongly acidic pH, D2EHPA is also protonated and becomes unable to react with the acid. Due to these two opposite phenomena, the optimum pH-value for the extraction with D2EHPA was found to be pH=3 (Figure 4). The further increase of the pH-value leads to the dissociation of the carboxylic group, this process reducing further the solubility of pantothenic acid in the organic phase and, implicitly, the distribution coefficient.

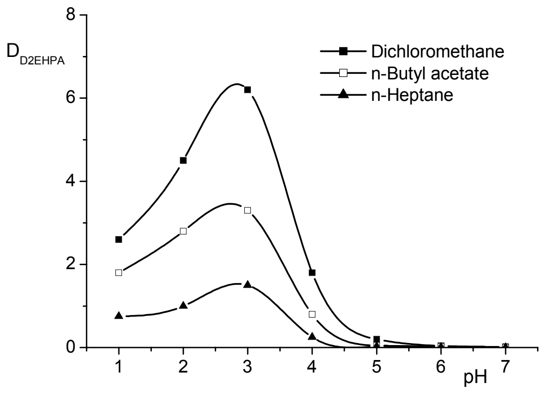

Figure 4: Influence of pH-value of the aqueous phase and solvent polarity on the pantothenic acid distribution coefficient for reactive extraction with D2EHPA (D2EHPA concentration = 40 g/L).

Compared to the reactive extraction with TOA, from Figure 4 it can be observed that the efficiency of pantothenic acid extraction with D2EHPA is inferior, regardless of the solvent polarity.

The mechanisms considered for reactive extraction with D2EHPA in the three solvents are confirmed by Figure 5, because it indicates a linear proportionality between the distribution coefficient and extractant concentration for dichloromethane, and a polynomial dependence of second- order for the other two solvents.

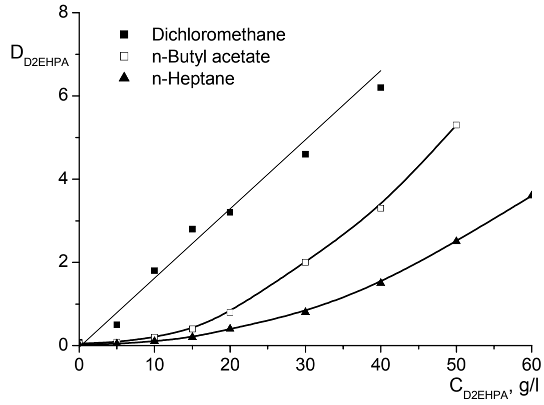

Figure 5: Influence of extractant concentration on the pantothenic acid distribution coefficient for reactive extraction with D2EHPA (pH = 3).

For verifying the potential synergic effect of the extractant mixture, the variation of the synergistic coefficient with the concentrations of TOA and D2EHPA was analyzed. According to expression (1), the synergistic coefficient for the studied extraction system is defined as:

$$C_S = \frac{D_{TOA+D2EHPA}}{D_{TOA} + D_{D2EHPA}} \tag{4}$$

the synergism appearing for $C_S > 1$ ($D_{TOA+D2EHPA}$ - distribution coefficient for reactive extraction with TOA and D2EHPA mixture).

Figures 6 and 7 indicate that the values of the synergistic coefficient are higher for the solvent with lower polarity, namely n-heptane. For a constant concentration of D2EHPA in the organic phase, C_S increases with the increase of TOA concentration (Figure 6).

Depending on the solvent polarity and D2EHPA amount in the solvent phase, the synergic effect is observed for TOA concentrations over 20 - 40 g/l. Thus, by increasing the concentration of D2EHPA from 5 to 40 g/l, the minimum concentration value of TOA corresponding to synergism increases from 20 to 30 g/l for the solvents with lower polarity, namely n-butyl acetate and n-heptane, and from 20 to 40 g/l for dichloromethane.

The results plotted in Figure 6 suggest that TOA contributes to the formation of amine adducts by solvating the complex produced by interfacial reaction between pantothenic acid and D2EHPA. This statement is in concordance both with the mechanism of reactive extraction of pantothenic acid with TOA, and with the superior values of C_S obtained for n-heptane, because the low polarity of the organic phase allows structuring of the aminic associations (Schugerl, 1994).

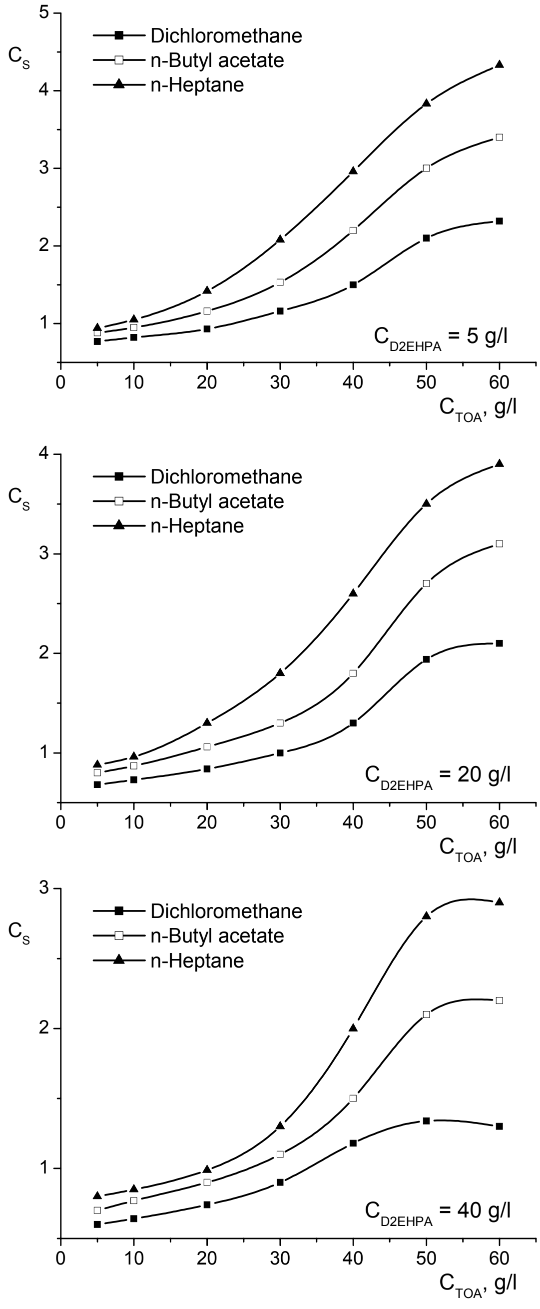

Figure 6: Influence of TOA concentration on the synergistic coefficient (pH = 2).

Regardless of the solvent polarity or D2EHPA concentration, for TOA concentrations over 50 g/L, the enhancement of the synergistic coefficient is attenuated or it decreases slowly. This diminution of the synergic effect magnitude could be attributed to the chemical reaction in the solvent phase between the two extractants. The phenomenon is more obvious for dichloromethane, because this reaction becomes more important both at higher TOA concentration and with the increase of solvent polarity, due to the prevention of amine associations.

At constant TOA amount in the solvent phase, the increase of D2EHPA concentration leads to a contrary variation of the synergistic coefficient (Figure 7). As mentioned above, the increase of D2EHPA concentration prevents the formation of amine adducts and, consequently, affects the hydrophobicity of the interfacial complex with pantothenic acid. For these reasons, the diminution of C_S is more important for dichloromethane. This effect is additionally confirmed by the recorded values of C_S for 5 g/l TOA, which are lower than 1 for the entire considered domain of D2EHPA concentration (negative synergism (Matsumoto *et al.*, 2001)).

The increase of TOA concentration in the organic phase together with the decrease of solvent dielectric constant counteracts the negative influence on synergism due to increased D2EHPA concentration. Therefore, for 20 g/L TOA, the synergic effect was observed for D2EHPA concentrations up to 30 g/L for n-butyl acetate and up to 50 g/L for n-heptane, while for dichloromethane only for D2EHPA concentration below 10 g/L. At higher concentration of aminic extractant (40 g/l), for the two solvents with lower polarities synergism was observed for the entire investigated domain of organophosphoric extractant. At this concentration of TOA, the domain of D2EHPA concentration corresponding to the values of C_S over 1 is also extended in the case of dichloromethane, the superior limit becoming 40 g/l.

For modeling the synergism and establishing the chemical structure of the extracted compound formed by reaction between pantothenic acid, TOA, and D2EHPA, the results of the individual extraction with the two extractants at pH = 2 and the above discussed phenomena were taken into account. In these circumstances, the following interfacial mechanism of the synergic extraction of pantothenic acid was proposed:

$$HA_{(aq)} + n\ E_{(o)} + HP_{(o)} \rightleftarrows HA.HP.E_{n(o)}$$

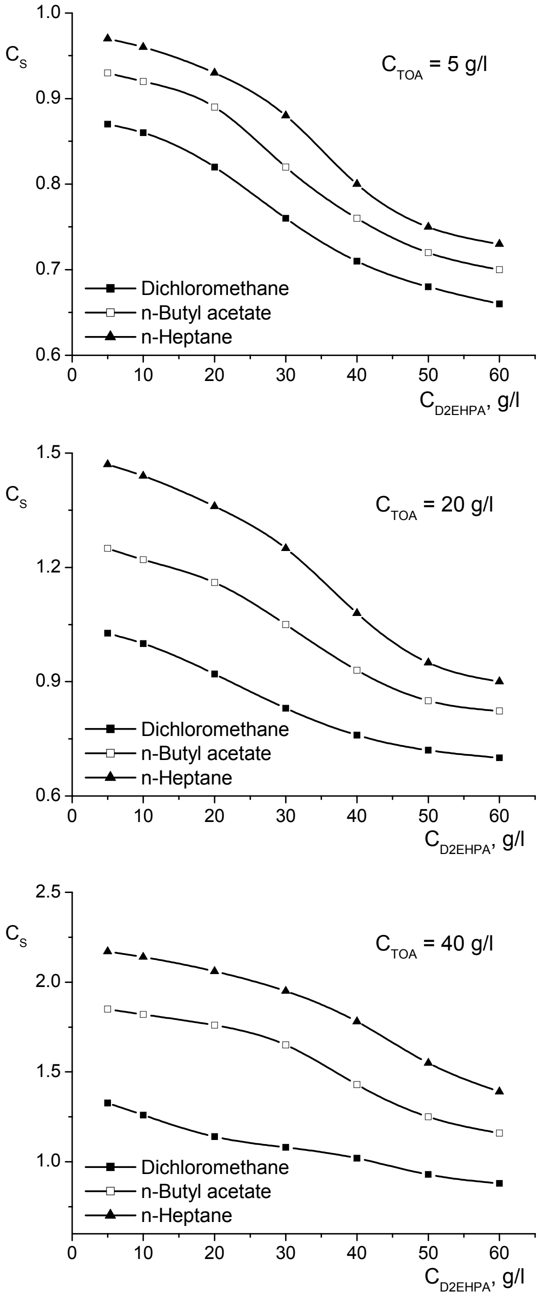

Figure 7: Influence of D2EHPA concentration on the synergistic coefficient (pH = 2).

For calculating the number of TOA molecules participating in the formation of the interfacial amine adduct, the following relationship for the synergic extraction constant is considered (the components concentrations are given in mol/L):

$$K_E = \frac{\left[HA.HP.E_{n(o)}\right]}{\left[HA_{(aq)}\right] \cdot \left[HP_{(o)}\right] \cdot \left[E_{(o)}\right]^n} \tag{5}$$

where K_E is the synergic extraction constant (depending on the extraction mechanism).

The synergistic coefficient could be expressed as a function of the concentrations of the extraction system components in the equilibrium state:

$$C_S = \frac{D_{TOA+D2EHPA}}{D_{TOA} + D_{D2EHPA}} = \frac{\dfrac{\left[HA.HP.E_{n(o)}\right]}{\left[HA_{(aq)}\right]}}{\dfrac{\left[HA.E_{n(o)}\right]}{\left[HA_{(aq)}\right]} + \dfrac{\left[HA.HP_{(o)}\right]}{\left[HA_{(aq)}\right]}} = \frac{\left[HA.HP.E_{n(o)}\right]}{\left[HA.E_{n(o)}\right] + \left[HA.HP_{(o)}\right]} \quad (6)$$

The concentration of interfacial amine complex formed during the extraction process is:

$$\left[HA.HP.E_{n(o)}\right] = C_S \cdot \left(\left[HA.E_{n(o)}\right] + \left[HA.HP_{(o)}\right]\right) \quad (7)$$

By combining Equations (5), (6), and (7), the synergic extraction constant can be expressed as:

$$K_E = \frac{C_S \cdot \left(\left[HA.E_{n(o)}\right] + \left[HA.HP_{(o)}\right]\right)}{\left[HA_{(aq)}\right] \cdot \left[HP_{(o)}\right] \cdot \left[E_{(o)}\right]^n} = \frac{C_S \cdot \left(D_{TOA} + D_{LD2EHPA}\right)}{\left[HP_{(o)}\right] \cdot \left[E_{(o)}\right]^n} \quad (8)$$

Consequently, the synergistic coefficient can be calculated as:

$$C_S = \frac{K_E \cdot \left[HP_{(o)}\right] \cdot \left[E_{(o)}\right]^n}{D_{TOA} + D_{D2EHPA}} \quad (9)$$

The correlation (9) represents, in logarithmic form, the equation of a straight line:

$$\ln \frac{C_S \cdot \left(D_{TOA} + D_{D2EHPA}\right)}{\left[HP_{(o)}\right]} = \ln K_E + n \cdot \ln\left[E_{(o)}\right] \quad (10)$$

From the slope of the straight line given by Equation (10) it is possible to determine the number of amine extractant molecules, n, which participate to the formation of the interfacial adduct, and from its intercept the value of the synergic extraction constant, K_E. Because the initial concentrations of both extractants are considerably higher than that of pantothenic acid, their equilibrium concentrations are assumed to be equal to the initial ones. Moreover, the calculations were considered for an optimum pH-value of 2, pantothenic acid being non-dissociated in the aqueous phase.

The straight lines obtained for three given values of D2EHPA concentration and different TOA concentrations are plotted in Figure 8 for all screened solvents. According to Figure 8, the number of amine molecules included in the interfacial adducts depends on the solvent polarity and organophosphoric extractant concentration (Table 1).

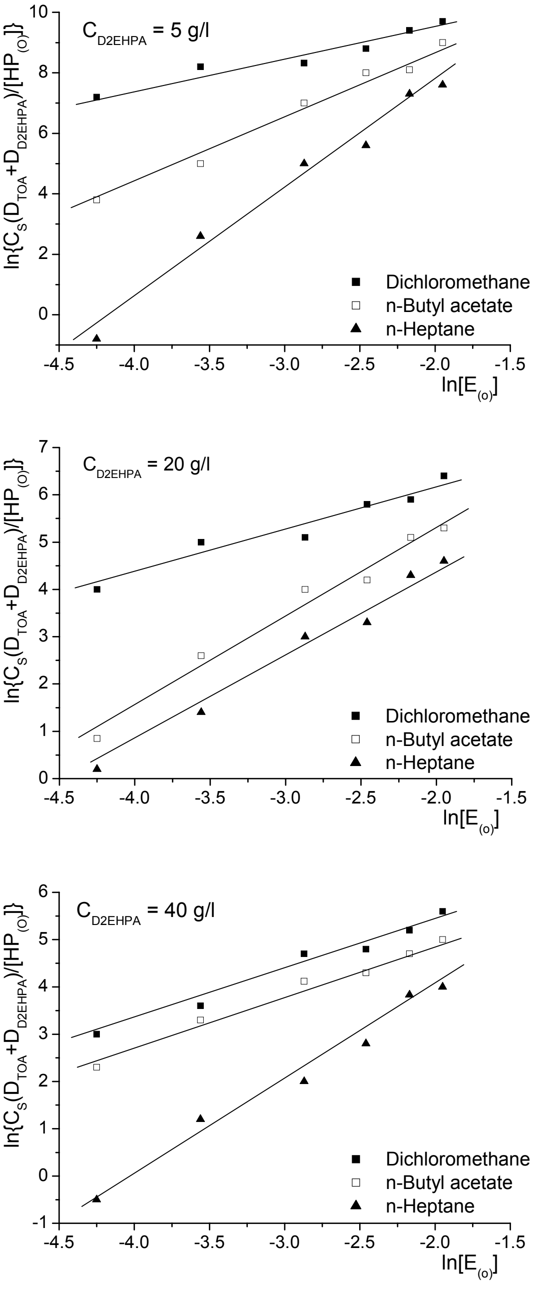

Figure 8: Graphical representation of the straight lines given by Equation (10).

Table 1: Number of aminic extractant molecules included in the extracted compound.

D2EHPA concentration	Solvent	Number of TOA molecules (n)
5 g/L	n-Heptane	4.11 (≈ 4)
	n-Butyl acetate	1.91 (≈ 2)
	Dichloromethane	1.06 (≈ 1)
20 g/L	n-Heptane	1.91 (≈ 2)
	n-Butyl acetate	2.05 (≈ 2)
	Dichloromethane	0.92 (≈ 1)
40 g/L	n-Heptane	2.09 (≈ 2)
	n-Butyl acetate	1.08 (≈ 1)
	Dichloromethane	1.11 (≈ 1)

The n values underline the dependence of the interfacial complex structure on the solvent polarity and D2EHPA concentration. Thus, for dichloromethane, due to its high polarity, the chemical structure of the extracted compound remains HA.HP.E, regardless of the concentration of organophosphoric extractant in the organic phase. For the other two solvents with lower dielectric constants, the increase of D2EHPA concentration leads to the decrease of the number of TOA molecules participating in the reaction with pantothenic acid, the magnitude of this effect depending on the solvent polarity. Therefore, for n-butyl acetate, the chemical structure of the interfacial product is HA.HP.E$_2$ for D2EHPA concentration up to 20 g/l, becoming HA.HP.E for 40 g/l D2EHPA. In the case of n-heptane, at 5 g/l D2EHPA, the extracted compound has the structure HA.HP.E$_4$, being modified into HA.HP.E$_2$ for higher concentrations of organophosphoric extractant.

The above results confirm the negative influences of the increase of D2EHPA concentration and solvent polarity on the number of TOA molecules participating in the solvation of the interfacial complex. Implicitly, these factors control the extraction efficiency and the magnitude of the synergic effect.

The values of the synergic extraction constant are given in Table 2 and are also dependent on the concentration of D2EHPA and organic phase polarity. Similarly to the synergic effect, K$_E$ is affected by increasing the D2EHPA concentration and solvent polarity, this variation emphasizing the direct relation between the complex hydrophobicity, number of TOA molecules included in its chemical structure, and the performance of synergic extraction.

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

D2EHPA concentration	Solvent	Synergic extraction constant	Value
5 g/L	n-Heptane	$K_E = \frac{\left[HA.HP.E_{4(o)}\right]}{\left[HA_{(aq)}\right]\cdot\left[HP_{(o)}\right]\cdot\left[E_{(o)}\right]^4}$	9.63x10^{6} (L^{5}/mol^{5})
	n-Butyl acetate	$K_E = \frac{\left[HA.HP.E_{2(o)}\right]}{\left[HA_{(aq)}\right]\cdot\left[HP_{(o)}\right]\cdot\left[E_{(o)}\right]^2}$	2.36x10^{5} (L^{3}/mol^{3})
	Dichloromethane	$K_E = \frac{\left[HA.HP.E_{(o)}\right]}{\left[HA_{(aq)}\right]\cdot\left[HP_{(o)}\right]\cdot\left[E_{(o)}\right]}$	9.97x10^{4} (L^{2}/mol^{2})
20 g/L	n-Heptane	$K_E = \frac{\left[HA.HP.E_{2(o)}\right]}{\left[HA_{(aq)}\right]\cdot\left[HP_{(o)}\right]\cdot\left[E_{(o)}\right]^2}$	5.96x10^{3} (L^{3}/mol^{3})
	n-Butyl acetate	$K_E = \frac{\left[HA.HP.E_{2(o)}\right]}{\left[HA_{(aq)}\right]\cdot\left[HP_{(o)}\right]\cdot\left[E_{(o)}\right]^2}$	1.21x10^{4}(L^{3}/mol^{3})
	Dichloromethane	$K_E = \frac{\left[HA.HP.E_{(o)}\right]}{\left[HA_{(aq)}\right]\cdot\left[HP_{(o)}\right]\cdot\left[E_{(o)}\right]}$	3.50x10^{3} (L^{2}/mol^{2})
40 g/L	n-Heptane	$K_E = \frac{\left[HA.HP.E_{2(o)}\right]}{\left[HA_{(aq)}\right]\cdot\left[HP_{(o)}\right]\cdot\left[E_{(o)}\right]^2}$	7.56x10^{3} (L^{3}/mol^{3})
	n-Butyl acetate	$K_E = \frac{\left[HA.HP.E_{(o)}\right]}{\left[HA_{(aq)}\right]\cdot\left[HP_{(o)}\right]\cdot\left[E_{(o)}\right]}$	1.35x10^{3} (L^{2}/mol^{2})
	Dichloromethane	$K_E = \frac{\left[HA.HP.E_{(o)}\right]}{\left[HA_{(aq)}\right]\cdot\left[HP_{(o)}\right]\cdot\left[E_{(o)}\right]}$	2.02x10^{3} (L^{2}/mol^{2})

For the experimental conditions under study, by comparing the information from Table 2 with those previously discussed, it can be affirmed that the most efficient system for synergic reactive extraction of pantothenic acid is that having the extractants mixture dissolved in n-heptane, and a concentration of D2EHPA of 5 g/L. In the case of similar extraction mechanism, namely for n-heptane and n-butyl acetate at 20 g/L D2EHPA, or n-butyl acetate and dichloromethane at 40 g/l D2EHPA, the higher solvent polarity exhibits a positive influence on the value of the synergic extraction constant.

Using the values of the synergic extraction constant and the number of TOA molecules, the synergistic coefficient was calculated for each extraction system by means of Equation (9). It was observed that the calculated values of C_S offer a good concordance with the experimental ones, the average deviation being 6.48%. The most important deviations, maximum 15.77%, are recorded for dichloromethane and D2EHPA concentrations over 40 - 50 g/l, probably due to the chemical reactions between the extractants in organic phase.

CONCLUSIONS

The study of separation of pantothenic acid by reactive extraction with the mixture of TOA and D2EHPA dissolved in three solvents with different polarities indicated the possibility of obtaining a synergic effect. Thus, by maintaining a constant value of D2EHPA concentration and increasing the concentration of TOA, the synergistic coefficient could become higher than 1, its highest values being reached for n-heptane.

The extractants roles in promoting the synergic effect are different: the organophosphoric extractant reacts with pantothenic acid and forms an interfacial compound soluble in the organic phase, while the amine extractant increases the hydrophobicity of this compound by solvation. Except for the solvent with the highest dielectric constant among those studied, namely dichloromethane, the chemical structure of the amine adduct depends on the concentration of D2EHPA and solvent polarity. Thus, for n-heptane and n-butyl acetate, the number of amine molecules included in the interfacial complex is reduced upon increasing D2EHPA concentration from 4 to 2 and, respectively, from 2 to 1. The same influence of organophosphoric extractant concentration was found for the synergic extraction constant.

The most important synergic effect is obtained for the extractant mixture dissolved in n-heptane when the organic phase contains 5 g/L D2EHPA.

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