SYNTHESIS OF CALCIUM PHOSPHATES FROM ALKYL PHOSPHATES BY THE SOL-GEL METHOD

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Syntheses of calcium phosphates from methyl-, ethyl-, i-propyl and n-butyl phosphates and calcium acetate in acidic and basic water-alcoholic solutions were studied. The composition of calcium phosphates depended mainly on the type of the used catalyst. Mixture of hydroxyapatite and β-tricalcium phosphate (β-TCP) was received by reaction of all alkylphosphates with calcium acetate in acidic solution. Calcium pyrophosphate was received when reaction proceeded in the presence of amonium hydroxide. Hydroxyapatite with admixture of calcium pyrophosphate or β-TCP were prepared by means of monoethanolamine or diethanolamine catalysts. It was found that the hydrolysis of P-OR bound played important role in calcium phosphate syntheses. The mechanism of the syntheses was proposed.

INTRODUCTION

Calcium phosphates play a significant role in medicine in particular as substitutes of the bone ossein. They may be employed in the form of bulk hydroxyapatite ceramics [1], in that of bioglasses [2] or as coatings on metal substrates [3]. Most calcium phosphates are biologically active. The biological activity may be so high that it can result in biological degradation of the phosphate in the organism. The stability of calcium phosphates in the organism increases in the sequence: hydroxyapatite > β-$Ca_3(PO_4)_2$ > α-$Ca_3(PO_4)_2$ > $Ca_2P_2O_7$ > amorphous phosphates $Ca_x(PO_4)_y$ [4]. Hydroxyapatite is therefore the most suitable form for biological applications. Its preparation has been described in numerous communications and summarized e.g. in [5, 6].

Most "wet" methods of preparation of stoichiometric hydroxyapatite powders $Ca_5(PO_4)_3OH$ are based on similar reactions, namely that of phosphoric acid (or its soluble salts) with Ca^{2+} salts at a molar ratio Ca/P = 1.667 in aqueous medium at *pH* 8 to 12. When the *pH* of the reaction solution is kept within the range of 4.5 to 7, non-stoichiometric hydroxyapatites of variable composition with a Ca/P molar ratio higher than 1.67 are formed [7]. Inversely, hydroxyapatite precipitates enriched with Ca^{2+} ions [8] separate from strongly alkaline phosphate solutions containing excess Ca^{2+} (Ca/P > 1.667). Whereas the synthesis of hydroxyapatites in aqueous medium has been studied for almost 50 years, syntheses of hydroxyapatites in anhydrous media were rarely described in the literature [9], [10].

The present work has the aim to describe the chemical behavior of aqueous-alcoholic solutions of alkyl phosphates and their calcium salts and to find the conditions of preparation which would yield hydroxyapatite as the main product.

EXPERIMENTAL PART

Preparation of alkyl phosphates

Methylesters, ethylesters, isopropylesters and butylesters of phosphoric acid were prepared by reacting phosphoric oxide (p.a. Fluka) with anhydrous alcohols – methanol (p.a., Lachema), ethanol (p.a., Lachema), i-propanol (p.a., Lachema) and n-butanol (p.a., Lachema). The respective alcohol, dried with calcium and redistilled, was cooled down to 18 °C in a sealed reactor. Phosphoric oxide was added to the alcohol while agitating the mixture extensively. The reaction heat raised the mixture temperature to 40 °C and following additional heating to 60 °C the reaction was continued for another 1 hour. The reaction proceeded according to the summary equation:

$$P_2O_5 + 3\ ROH \rightleftharpoons R_2HPO_4 + RH_2PO_4$$

(R = Me, Et, i-Pr, n-Bu)

The alcohols employed, the amounts of the reagents, the time of the reaction and the concentrations of P in the esters are listed in table 1.

Preparation of calcium phosphates

The reactor was charged with alkyl phosphate diluted with the respective alcohol to concentrations of about 0.6 mol P l^{-1}. While stirring with a propeller agitator and irradiating simultaneously with ultrasound a 50 % solution of the base was introduced until the *pH* of the reaction mixture attained the value of about 9. Saturated aqueous solution of calcium acetate was then added. The resulting precipitate was agitated for about 1 hour at 20 °C and then allowed to rest for about 16 hours. After

Table 1. Conditions of the syntheses of alkyl phosphates.

alkyl phosphate	alcohol	Volume of alcohol (ml)	P_2O_5 (g)	time of reaction (hours)	concentration of alkylphosphate (mol P l^{-1})
Methyl	methanol	2000	283,35	1,5	1,903
Ethyl	ethanol	2000	286,84	2	1,737
i-propyl-1	i-propanol	2000	150,08	2	1,185
i-propyl-2	i-propanol	3000	438,48	2	1,976
n-butyl	n-butanol	2000	291,87	2	1,930

Table 2. Conditions of the syntheses of calcium phosphates.

sample No.	alkyl-phosphate	concentration of alkylphosphate (mol Pl^{-1})	volume of alkylphosphate (ml)	concentration of Ca-acetate (mol Ca l^{-1})	volume of Ca-acetate (ml)	mol. ratio Ca/P	base	*pH*
1	methyl	1.903	101.0	1.70	200.0	1.77	-	5.2
2	ethyl	1.737	100.0	1.70	200.0	1.96	-	5.2
3	propyl-2	1.976	65.0	1.70	200.0	2.65	-	5.2
4	butyl	1.930	98.0	1.70	200.0	1.78	-	5.2
5	methyl	1.903	100.1	1.69	201.5	1.79	NH_4OH	9
6	ethyl	1.737	99.0	1.55	220.0	1.98	NH_4OH	9
7	propyl-2	1.976	64.7	1.55	220.0	2.66	NH_4OH	9
8	butyl	1.930	97.3	1.55	220.0	1.81	NH_4OH	9
9	methyl	1.903	100.1	1.69	207.4	1.84	MEA	9
10	ethyl	1.737	99.0	1.62	216.6	2.03	MEA	9
11	propyl-1	1.185	300.3	1.78	150.9	0.75	MEA	9
12	propyl-2	1.976	64.7	1.69	183.7	2.36	MEA	8
13	propyl-2	1.976	64.7	1.69	207.4	2.76	MEA	9
14	butyl	1.930	97.3	1.62	216.0	1.86	MEA	10
15	methyl	1.903	100.1	1.62	206.7	1.75	DEA	8
16	ethyl	1.737	99.0	1.79	186.6	1.94	DEA	8
17	ethyl	1.737	99.0	1.62	206.7	1.94	DEA	8
18	propyl-2	1.976	64.7	1.62	206.7	2.62	DEA	8
19	propyl-2	1.976	64.7	1.62	206.7	2.61	DEA	8
20	butyl	1.930	97.3	1.62	206.7	1.78	DEA	8

filtering and drying at 120 °C the reaction product was annealed for 2 hours at 1100 °C, or at first washed with water (till disappearance of Ca^{2+} ions from the filtrate, checked with oxalic acid) and only then annealed for 2 hours at 1100 °C. The alkyl phosphate employed, the base type and the Ca/P molar ratio are listed in table 2.

Analysis of the reaction products

– Phase composition

The phase composition of annealed or dried reaction products was established by the D-500 diffractometer (Siemens) in the median semifocusing (Bragg-Brentan's) arrangement by CoK_α radiation using a directionally sensitive detector. The quantitative phase composition of the samples was determined by means of the PPF1-1-ICDD-JCPDS database [11]. The semiquantitative determination of the content of phases was based on modelling the diffraction spectra by the XQPA92 program [12].

– Microstructure

The size and shape of the reaction product particles were studied by means of scanning electron microscopy on the JXA apparatus (Jeol).

– Determination of Ca and P content

The content of phosphorus and calcium was established by ICP spectroscopy.

– Particle size distribution

The particle size was determined in aqueous suspensions by the LA500 laser diffraction analyzer (Horiba).

RESULTS

Particle size distribution

The reaction product prepared from methyl phosphate had particles from 0.2 to 50 μm in size, the mean particle size being 12.13 μm. The particle size of product prepared from ethyl phosphate varied from 0.1 to 15 μm, with a mean value of 3.86 μm. The size distribution of particles prepared from isopropyl phosphate was very wide(from 0.1 to 150 μm), the mean being 9.8 μm. The smallest particles were yielded by butyl phosphate, from 0.1 to 11.5 μm, with the mean size amounting to 2.97 μm.

Particle shape

The irregular shape of the reaction products in shown in figures 1 to 4.

Phase composition

The phase composition of unwashed reaction products after firing at 1100 °C is listed in table 3. The reaction products prepared from alkyl esters in the absence of the base contained a mixture of β-TCP and calcium pyrophosphate (methyl ester and butyl ester – see figure 5), or a mixture of hydroxyapatite and β-TCP (ethyl ester and isopropyl ester – see figure 6).
The reaction products prepared from alkyl esters in the presence of ammonia contained calcium pyrophosphate regardless of the alkyl type and the Ca/P molar ratio (see table 3). When monoethanolamine was used as the base, the reaction products comprised first of all hydroxyapatite (see figures 7, 8) with an admixture of calcium oxide or of β-tricalcium phosphate(see table 3). However, pure calcium pyrophosphate was formed at a low C/P molar ratio of 1.0 (see figure 9). The same product was yielded by synthesis from n-butyl ester in the presence of MEA.

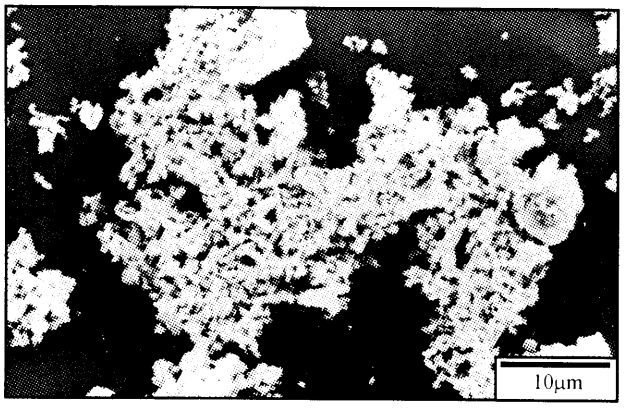


Figure 1. The size and the shape of particles of sample No.1 (prepared from methylester of phosphoric acid, Ca/P = 1.77, *pH* = 5.2, without base).

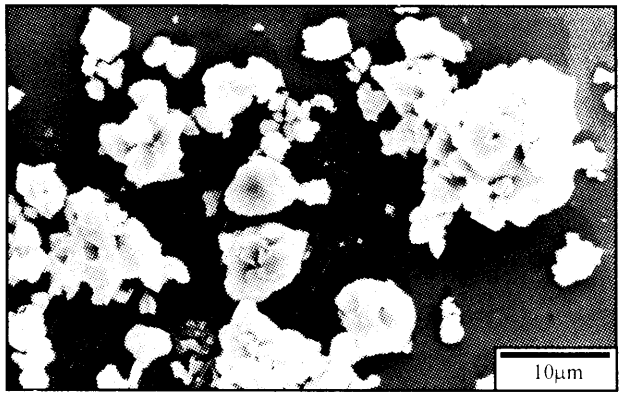


Figure 3. The size and the shape of particles of sample No.3 (prepared from isopropylester of phosphoric acid Ca/P = 2.65, *pH* = 5.2, without base).

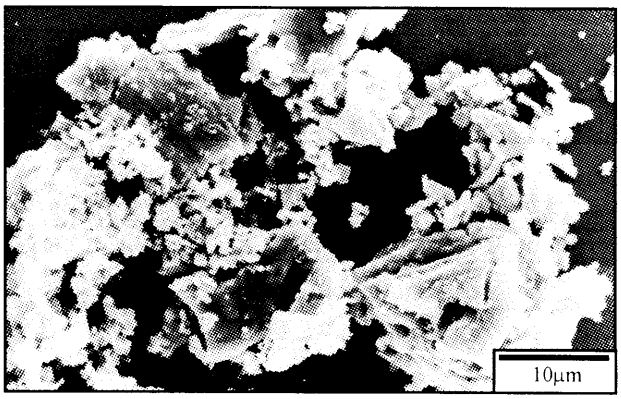


Figure 2. The size and the shape of particles of sample No.2 (prepared from ethylester of phosphoric acid, Ca/P = 1.96, *pH* = 5.2, without base).

Figure 4. The size and the shape of particles of sample No.4 (prepared from butylester of phosphoric acid, Ca/P = 1.78, *pH* = 5.2, without base).

Table 3. Phase composition of products (unwashed by water) after heat treatment.

sample No.	alkyl Phosphate	phase composition of reaction products [wt%] HA	β-TCP	$Ca_2P_2O_7$	CaO
1	Methyl	-	80	20	-
2	Ethyl	10	88	-	2
3	Propyl-2	38	60	-	2
4	Butyl	-	20	80	-
5	Methyl	-	-	100	-
6	Ethyl	-	-	100	-
7	Propyl-2	-	-	100	-
8	Butyl	-	-	100	-
9	Methyl	90	-	-	10
10	Ethyl	82	13	-	5
11	Propyl-1	-	-	100	-
12	Propyl-2	89	-	-	11
13	Propyl-2	95	-	-	5
14	Butyl	-	-	100	-
15	Methyl	93	7	-	-
16	Ethyl	93	7	-	-
17	Ethyl	90	-	-	10
18	Propyl-2	95	-	-	5
19	Propyl-2	89	9	-	2
20	Butyl	-	33	67	-

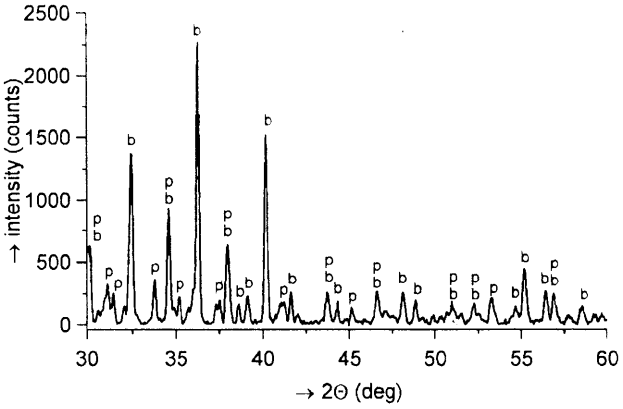


Figure 5. The X-ray diffraction spectrum of sample No.1 (prepared from methylester of phosphoric acid, Ca/P = 1.77, *pH* = 5.2, without base).
p - calcium pyrophosphate, b - β-TCP

The reaction products prepared in the presence of diethanolamine contained mostly hydroxyapatite with an admixture of calcium oxide or β-tricalcium phosphate. The synthesis from butyl ester resulted in a mixture of calcium pyrophosphate and β-tricalcium phosphate (see table 3). Table 4 lists the results of X-ray analyses of reaction products washed with water after filtering and heat treated at 1100 °C. Hydroxyapatite was found in none of the samples analyzed. The samples contained either pure $Ca_2P_2O_7$ (samples Nos. 2, 4 and 14) or a mixture of $Ca_2P_2O_7$ and β-$Ca_3(PO_4)_2$.

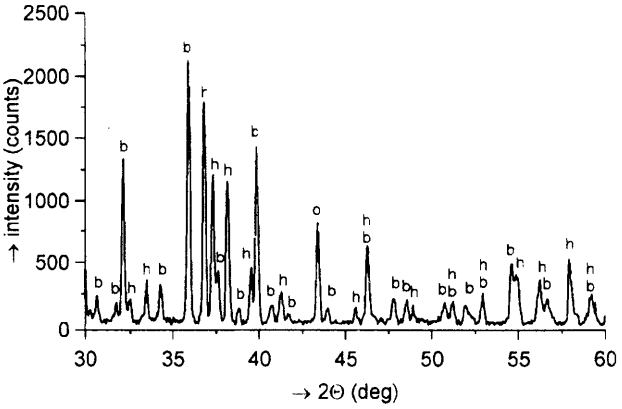


Figure 6. The X-ray diffraction spectrum of sample No.3 (prepared from isopropylester of phosphoric acid, Ca/P = 2.65, *pH* = 5.2, without base).
h - hydroxyapatite, o - calcium oxide, b - β-TCP

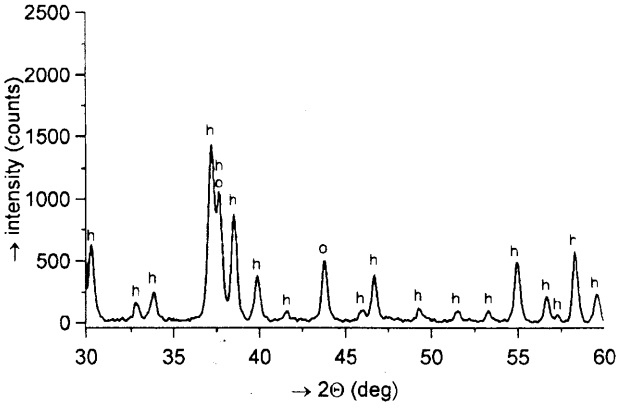


Figure 7. The X-ray diffraction spectrum of sample No.9 (prepared from methylester of phosphoric acid, Ca/P = 1.84, *pH* = 9, MEA).
h - hydroxyapatite, o - calcium oxide

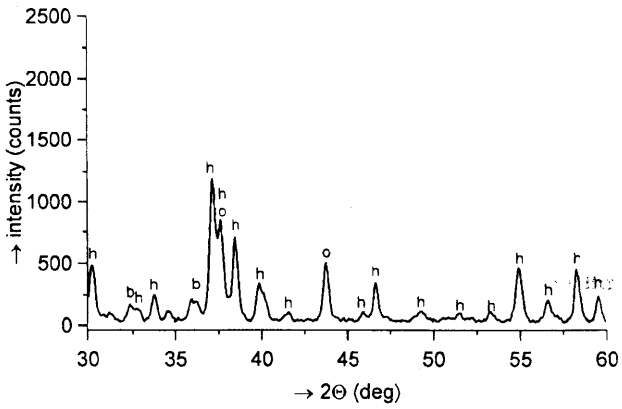


Figure 8. The X-ray diffraction spectrum of sample No.10 (prepared from ethylester of phosphoric acid, Ca/P = 2.03, *pH* = 9, MEA).
h - hydroxyapatite, o - calcium oxide, b - β-TCP

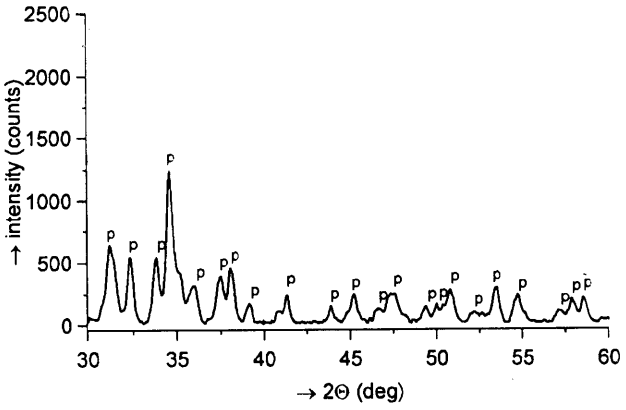


Figure 9. The X-ray diffraction spectrum of sample No.11 (prepared from isopropylester of phosphoric acid, Ca/P = 0.75, *pH* = 9, MEA).
p - calcium pyrophosphate

Table 4. Phase composition of the samples (washed by water).

Sample No.	alkyl phosphate	phase composition of the samples (wt.%) β-TCP	$Ca_2P_2O_7$
1	methyl	10	90
2	ethyl	-	100
4	butyl	-	100
9	methyl	20	80
10	ethyl	20	80
12	propyl-2	5	95
14	butyl	-	100
15	methyl	40	60
16	ethyl	50	50
18	propyl-2	20	80
20	butyl	30	70

DISCUSSION

Effect of the Ca/P molar ratio

At the beginning of the reaction, the Ca/P molar ratio was higher than 1.67 in most of the instances. 1.67 is a value recommended for classical syntheses of stoichiometric hydroxyapatite in aqueous medium. The classical syntheses at Ca/P higher than 1.67 may lead to non-stoichiometric or amorphous hydroxyapatites since the formation of calcium phosphates with a molar ratio Ca/P ≤ 1,5 ($CaHPO_3$, $Ca_2P_2O_7$, ß-$Ca_3(PO_4)_2$) is suppressed. Our results indicate that phosphates of the types $Ca_2P_2O_7$ or β-$Ca_3(PO_4)_2$ were contained not only in sample No. 11 (molar ratio Ca/P = 0.75), but also in samples prepared at Ca/P > 1.67. Samples Nos. 5,6,7,8 and 14 contained crystalline $Ca_2P_2O_7$ which is usually formed by thermal decomposition of products prepared in aqueous medium at Ca/P = 1 [13]. The given result implies that with the samples mentioned the alkyl phosphates were capable of binding in insoluble phosphates only a part of Ca^{2+} and the rest of $(CH_3COO)_2Ca$ was removed from the reaction mixture in the form of soluble component (filtrate) during filtration of the precipitate. The *pH* value of the reaction mixture was in no explicit relation to the composition of the products. Syntheses in acidic aqueous medium (*pH* 3 to 5) as a rule yield $CaHPO_4$ [14], while at *pH* of about 6.7, $Ca_3(PO_4)_2$ [15] is formed and at *pH* of about 7 to 9 it is hydroxyapatite [16]. Syntheses of Ca phosphates from alkyl phosphates did not produce hydroxyapatite in some cases (samples Nos.5, 6, 7, 8 and 14), not even at *pH* 9 to 10. As already mentioned, the idea is that the alkyl esters either did not react with Ca^{2+} or combined with it to form soluble compounds.

Effect of the base

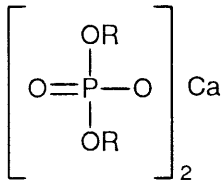
The bases used to catalyse the hydrolysis of the alkyl phosphates had a significant effect on the composition of the products. Reactions of alkyl esters with Ca^{2+} in the presence of NH_4OH yielded $Ca_2P_2O_7$. In the majority of cases, the presence of MEA or DEA was associated with products having a high content of hydroxyapatite. The authors assume that the difference between NH_4OH and ethanolamines is due to the higher basicity of the latter, which increases in the order NH_4OH<MEA ~DEA. Hydrolysis of the alkyl phosphates is also probably subject to acidic catalysis, and hydroxyapatite therefore also forms at *pH* < 7 (samples Nos.2 and 3). It appears that for the formation of hydroxyapatite in aqueous-alcoholic medium, hydrolysis of the P-OR bond in the alkyl ester is more important than the *pH* value higher than 7.

Effect of the ester

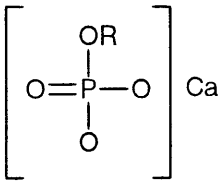
Methyl-, ethyl- as well as isopropyl phosphates yielded products of similar composition. Hydrolysis of the P-OR bonds (R=Me, Et, i-Pr) therefore proceeded at similar rates. The P-OBut bond in butyl ester hydrolyzed more slowly, probably as a result of partial immiscibility of n-butanol with water.

The course of reactions yielding calcium phosphates from alkyl phosphates and Ca carboxylates in aqueous alkaline medium can be described by the following steps:

1. Alkyl phosphates prepared by reacting alcohols with P_2O_5 are composed of a mixture of mono- and dialkyl esters at a 1:1 molar ratio [16].
   Theoretically, dialkyl esters can form type (I) compounds with Ca^{2+} while monoalkyl esters can yield type (II) compounds.



(I)

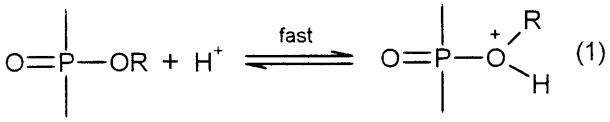


(II)

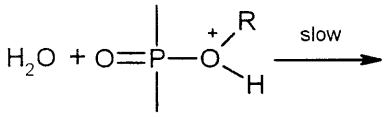
Even mixed calcium compounds containing alkyl phosphate and acetate anions are not ruled out. On the basis of analogy with inorganic calcium phosphates it is probable that mixed organocalcium compounds, as well as those of type I are partially soluble in aqueous-alcoholic medium. Compounds of type II will be probably less soluble.

2. In an aqueous-alcoholic medium the P-OR bond may hydrolyze, more readily that in dialkyl ester than that in monoalkyl ester.
On the basis of analogy with hydrolysis of Si-OR bonds it may be assumed that the hydrolysis of P-OR bonds is catalyzed by both basic and acidic media:

a) acid-catalyzed hydrolysis of P-OR



(1)



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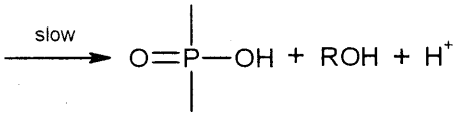
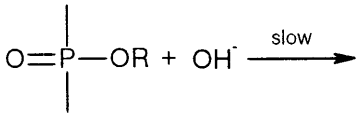


b) base-catalyzed hydrolysis of P-OR



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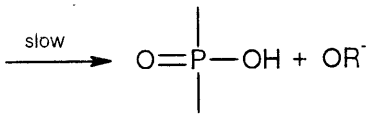
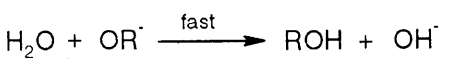
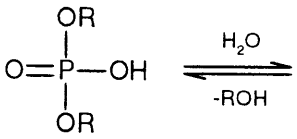




(4)

Phosphoric acid is the final product of hydrolysis of alkyl esters.



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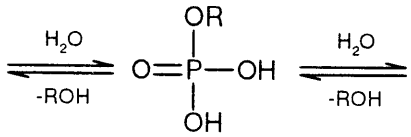
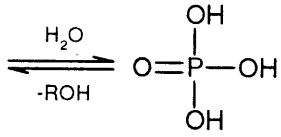
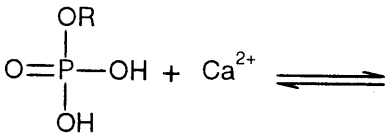




3. Reactions of hydroxyl groups of alkyl phosphates with Ca^{2+} yielded precipitates which, according to X-ray analysis, did not belong among known calcium phosphates. It is therefore assumed that poorly soluble type (II) calcium alkyl phosphates were formed preferentially by reaction (6)



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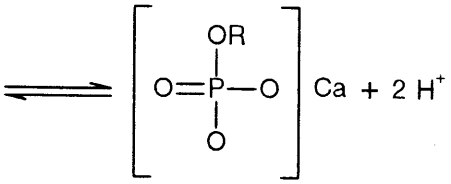
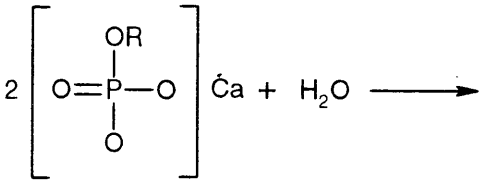


4. Heat treatment of the reaction products (precipitates) produced three types of calcium phosphates in dependence on Ca^{2+} content in the precipitate (such as $Ca(CH_3COO)_2$):



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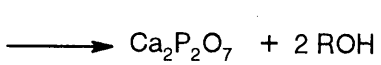
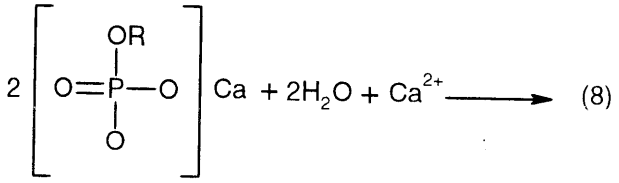
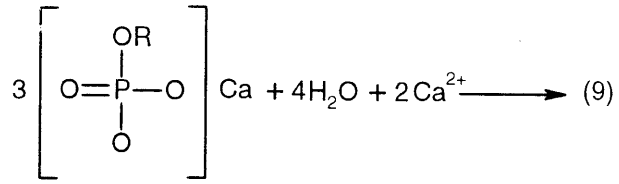




$$2\left[\begin{array}{c}OR\\ |\\ O{=}P{-}O\\ |\\ O\end{array}\right]Ca + 2H_2O + Ca^{2+} \longrightarrow \quad (8)$$

$$\longrightarrow Ca_3(PO_4)_2 + 2\,ROH + 2\,H^+$$



$$3\left[\begin{array}{c}OR\\ |\\ O{=}P{-}O\\ |\\ O\end{array}\right]Ca + 4H_2O + 2Ca^{2+} \longrightarrow \quad (9)$$

$$\longrightarrow Ca_5(PO_4)_3OH + 3ROH + 4H^+$$

The reaction course suggested is in agreement with the results of X-ray analyses of those precipitates which were washed with water prior to heat treatment. In the course of this washing, a part of Ca^{2+} ions was released into aqueous solution and passed into the filtrate. The heat-treated samples did not contain hydroxyapatite, but only $Ca_2P_2O_7$ or a mixture of $Ca_2P_2O_7$ with β-$Ca_3(PO_4)_2$.

CONCLUSION

Hydrolysis of the P-OR bonds plays a distinct part during the reaction of alkyl phosphates with calcium acetate in an aqueous-alcoholic medium.

Supplementing of the suggested mechanism of the synthesis and in particular establishment of suitable conditions for the formation of pure hydroxyapatite compounds will require thorough studies to be made of

- the kinetics of P-OR bond hydrolysis
- reaction kinetics of P-OR with Ca^{2+}
- the composition of the reaction products prior to their heat treatment

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SYNTÉZA FOSFOREČNANŮ VÁPENATÝCH Z ALKYLESTERŮ KYSELINY FOSFOREČNÉ METODOU SOL-GEL

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Byla studována syntéza fosforečnanů vápenatých z alkylesterů (methyl, ethyl, i-propyl a butyl) kyseliny fosforečné a octanu vápenatého (molární poměr reaktantů Ca/P = 0,75-2,76) ve vodněalkoholickém prostředí v přítomnosti hydroxidu amonného, monoethanolaminu, diethanolaminu a bez bazického katalyzátoru.

Reakční produkty byly studovány rentgenovou difrakční fázovou analýzou a rastrovací elektronovou mikroskopií. Distribuce velikosti částic byla studována laserovou difrakcí.

Bylo zjištěno, že se při syntéze výrazným způsobem uplatňovala hydrolýza P-OR (R=Me, Et, i-Pr, Bu) alkylesteru kyseliny fosforečné. Při studiu vlivu typu esteru na syntézu fosforečnanu vápenatého bylo zjištěno, že hydrolýza P-OR (R= Me, Et, i-Pr) probíhala podobnou rychlostí (produkty byly podobného složení) a vazba P-OBu se hydrolyzovala nejpomaleji. Dále byl studován vliv báze na syntézu fosforečnanů vápenatých. V přítomnosti hydroxidu amonného se bez ohledu na použitý alkylester a molární poměr Ca/P tvořil produkt s obsahem difosforečnanu vápenatého. V přítomnosti monoethanolaminu se tvořil především hydroxyapatit s příměsí oxidu vápenatého nebo ß-fosforečnan vápenatý (při molárním poměru Ca/P>1 s použitím methyl, ethyl a i-propylesteru kyseliny fosforečné). V případě použitého diethanolaminu reakční produkty obsahovaly hydroxyapatit s příměsí oxidu vápenatého nebo ß-fosforečnanu vápenatého. V nepřítomnosti báze vznikala směs hydroxyapatitu a ß-fosforečnanu vápenatého nebo ß-fosforečnanu vápenatého a difosforečnanu vápenatého.