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Covalent modification of calcium hydroxyapatite surface by grafting phenyl phosphonate moieties

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Abstract

The reaction between phenyl phosphonic dichloride ($C_6H_5P(O)Cl_2$) and synthetic calcium hydroxy- and fluorapatite has been investigated. The presence of mono- or polymeric (C_6H_5PO) fragment bound to hydroxyapatite was evidenced by IR, and solid-state ^{31}P NMR spectroscopy. X-ray powder analysis has shown that the apatitic structure remains unchanged during the reaction. In contrast, no reaction was found using fluorapatite. According to the results found for these two different apatites a mechanism was proposed for the formation of covalent P–O–P bonds as the result of a reaction between the $C_6H_5P(O)Cl_2$ organic reagent and $(HPO_4)^-$ and/or OH^- ions of the hydroxyapatite.

Keywords: Hydroxyapatite; Phosphonate; ^{31}P NMR; Hybrid materials

1. Introduction

Modification of surfaces is an efficient way to obtain materials having specific properties. Mostly, surface modifications concern metals and metal oxides [1]. The modifications of calcium hydroxyapatite (CaHAp) surfaces appear to be of great interest owing to the role played by this mineral in biomaterials [2] or as support for catalysts [3–5]. CaHAps are able to adsorb different organic substrates, e.g. carboxylic acids, phenolates and carboxylates, [6,7] isocyanates [8,9] sulfonic acids and sulfonates [10,11]. In the development of organic/inorganic hybrid materials, the bonding nature between inorganic and organic fragments remains of first importance especially when the organic moieties further interact with molecules present in a liquid phase as it is the case for example between a grafted chromatographic support and a liquid mobile phase.

Recently, Fadeev and colleagues [12] have reported interesting results about the covalent surface modification of CaHAp using *n*-alkyl and *n*-fluoroalkylphosphonic acids. From their results, the authors have proposed a reaction between the surface "P–O–H" groups (named Ps–O–H) and the phosphonic acid, this reaction leading, through water elimination, to the formation of Ps–O–P bonds. Therefore, the organic fragment appears to be covalently bound to the apatite surface, while there are only electrostatic interactions in the case of organic acids. Nevertheless, according to the relatively low Ca/P ratio (1.55) and the IR spectra of the compounds obtained by Fadeev it is more a Ca-deficient apatitic phosphate than a true hydroxyapatite. In order to increase the specific surface area of hydroxyapatites, phenylphosphonic and

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phenylphosphinic acids were used during their synthesis [13]. Further, the organic groups are removed by thermal treatment. In this case also the bond nature between the apatite surface and the organic moieties is not clearly evidenced. Lee et al. have reported the surface modification of hydroxyapatite nanocrystals by grafting polymers containing phosphonic acid groups through the formation of a "(CaHAp)-O" radical generated from "(CaHAp)-OH" [14]. Recently, the action of bisphosphonates on bone was studied [15–17].

Taking in consideration these results and the better reactivity of dichlorophosphonate $RP(O)Cl_2$ compared to the corresponding acids $RP(O)(OH)_2$, we have studied the reaction of a CaHAp and calcium fluorapatite (CaFAp) with $C_6H_5P(O)Cl_2$.

2. Experimental

2.1. Synthesis

CaHAp was obtained using a double decomposition method in a boiling basic aqueous medium according to Ref. [18] and CaFAp according to Ref. [19]. Their chemical compositions are given in Table 1.

The reaction with phenyl phosphonic dichloride was carried out as following: to a vigorously stirred suspension of 0.5 g of CaHAp or CaFAp in 50 mL of dichloromethane, were added 0.9 or 1.8 g of $C_6H_5P(O)Cl_2$ (Acros-Organic). The suspension was allowed to stir for 48 h at 25 °C. The mixture was filtered, washed with dichloromethane and dried at 100 °C for 12 h. The obtained solid material 0.6 and 0.8 g, respectively, are named $CaHAp_{10}$ and $CaHAp_{20}$ according to the $C_6H_5P(O)Cl_2$ amount used. Saturation in organic bonded fragment is reached for $CaHAp_{20}$.

Elemental analyses were performed at the Service Central d'Analyses-CNRS, Vernaison (France). The IR spectra were recorded on a Bio-Rad FTS FT-IR spectrophotometer as KBr pellets in the 4000–250 cm^{-1} region. Solid-state ^{31}P MAS NMR spectra were recorded at 162 MHz on a Bruker spectrometer Avance 400 (rotor 4 mm, spinning rate 2–12 kHz). X-ray powder diffractions were performed at room temperature on a vertical Philips PW1050/25 goniometer mounted in the Bragg–Brentano configuration (θ, 2θ) using Ni-filtered Cu–Kα radiation ($\lambda = 1.5418$ Å) and were analyzed using EVA software [20,21] and FULLPROF [22] softwares.

The thermal analysis experiments were performed in an airflow of 100 mL/min at a heating rate of 10°/min in a Pt crucible up to 1000 °C with Setaram LabSys 2000 equipment. The sample mass was about 33 mg.

Specific surface areas (SSAs) m^2/g measurements were performed by BET-method (adsorptive gas N_2, carrier gas He, heating temperature 150 °C) using sorptometer EMS-53 and KELVIN 1040/1042 (Costech International).

Table 1
Chemical composition (±0.05%) of apatites before and after reaction with phenyl phosphonic dichloride

Sample	Ca (%)	P (%)	Ca/P	C (%)	H (%)	F (%)	SSA (m^2/g)
CaHAp	38.89	18.50	1.63	–	–	0	34.6±0.5
$CaHAp_{10}$	30.30	16.20	1.45	2.23	0.83	0	–
$CaHAp_{20}$	27.50	15.20	1.40	3.82	1.11	0	–
CaFAp	37.85	18.43	1.60	–	–	4.20	27.4±0.5
$CaFAp_{10}$	35.80	17.40	1.59	⩽0.3	–	4.34	–
$CaFAp_{20}$	35.50	17.40	1.58	⩽0.3	–	4.37	–

3. Results and discussion

3.1. Elemental analysis

The exact compositions of the starting CaHAp and CaFAp and of the $CaHAp_{10,20}$ and $CaFAp_{10,20}$ reaction products were determined from elemental analysis and are given in Table 1.

Based on the chemical analysis of $CaHAp_{10}$ and $CaHAp_{20}$ (2.23% C and 3.82% C, respectively) and the surface area of CaHAp (34.6 m^2/g), surface concentration (grafting density) of the $PhP(O)O_2$ moieties is 5.63 molecule/nm^2 ($CaHAp_{10}$) and 9.92 molecules/nm^2 ($CaHAp_{20}$). It is noted that both numbers are substantially greater than the monolayer capacity (for $RP(O)O_2$ estimated ~4.3 molecules/nm^2), suggesting the presence of polyphosphonates (with "vertical" P–O–P bonding) on the surface. The presence of polyphosphonates can be explained by a partial hydrolysis of the chlorine of the starting material $C_6H_5P(O)Cl_2$ along the reaction process due to the presence of residual water on the surface of the apatite according to:

$$C_6H_5P(O)Cl_2 + OH\text{-}Ap \rightarrow [C_6H_5P(O)Cl]{-}O\text{-}Ap + HCl,$$

$$[C_6H_5P(O)Cl]{-}O\text{-}Ap + H_2O \rightarrow [C_6H_5P(O)OH]{-}O\text{-}Ap + HCl,$$

$$[C_6H_5P(O)OH]{-}O\text{-}Ap + C_6H_5P(O)Cl_2 \rightarrow [C_6H_5P(O)OPCl(O)C_6H_5]{-}O\text{-}Ap + HCl.$$

3.2. Thermal analysis

The results of thermal analysis are presented in Fig. 1. In DTA curves of the modified CaHAp an exothermal effect is observed in the temperature range 250–500 °C with a peak top at 410°. This peak corresponds to the combustion of the organic material ("C_6H_5PO" group). The peak intensity, as well as the corresponding mass loss, is in accordance with the amount of "C_6H_5PO" bound to apatite as determined by chemical analysis (Table 1).

The mass loss in the temperature interval 100–150 °C is caused by evaporation of solvent, at temperatures

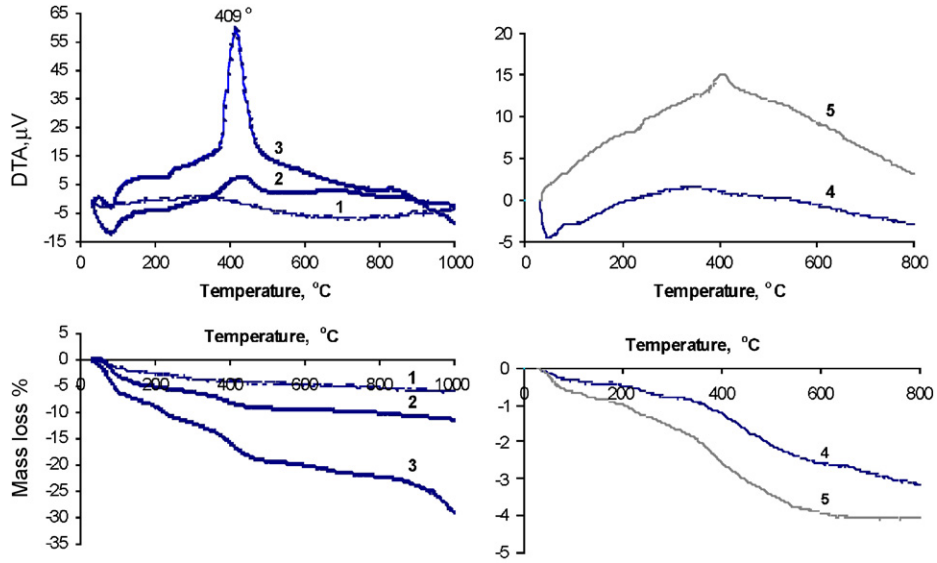

Fig. 1. TGA and DTA curves in an airflow: (1) CaHAp, (2) $CaHAp_{10}$; (3) $CaHAp_{20}$; (4) CaFAp and (5) $CaFAp_{20}$.

above 700 °C by decomposition of apatite with H_2O evolvement due to a reaction with condensed phosphates. XRD analysis reveals that the product of calcination up to 1000 °C consists of $Ca_3(PO_4)_2$ and $Ca_2P_2O_7$ (see XRD section). This fact is in accordance with the Ca/P mole ratio equal to 1.4 and 1.45 in $CaHAp_{20}$ and $CAHAp_{10}$, respectively. For CaFAp these changes are hardly visible.

3.3. IR spectroscopy

CaHAp and CaFAp show the classical IR spectra of apatites [3]. For CaHAp the peak at 875 cm^{-1} indicates the presence of $(HPO_4)^-$ ions in the apatite structure in accordance with the chemical composition (molar ratio Ca/P = 1.60). In all the studied apatites, bands at 3400 and 1631 cm^{-1} show the presence of water in the starting material.

No significant change is observed after the reaction of CaFAp with $C_6H_5P(O)Cl_2$ even when 20 equivalents were used. For CaHAp new strong peaks are observed at: 1640, 1450, 1224, 1195, 976, 946, 748, 720, 694 and 534 cm^{-1}. The difference spectra $\Delta(IR)_{10} = [CaHAp_{10}–CaHAp]$ (bottom) and $\Delta(IR)_{20} = [CaHAp_{20}–CaHAp]$ are shown in Fig. 2. They do not correspond neither to the starting organic reagent $C_6H_5P(O)Cl_2$ nor to the $C_6H_5P(O)(OH)_2$ corresponding acid. Therefore these new peaks could be tentatively attributed to νP–O, P–O–P and C=C vibrations belonging to the "C_6H_5PO" organic moieties grafted on the apatite surface. The disappearance of the peak at 875 cm^{-1} (corresponding to the $(HPO_4)^-$ anion) and the absence of modifications in the IR spectra for the CaFAp apatite free of $(HPO_4)^-$ and OH^- anion support that these latter could be involved in the reaction between the apatite and $C_6H_5P(O)Cl_2$ organic reagent.

3.4. X-ray diffraction

XRD patterns of the reacted CaHAp, and CaFAp compared to the starting apatites reveal that the apatite structure is not modified (see Fig. 3). In the case of CaHAp, some extra-lines indicated by arrows correspond to an impurity, likely a residual salt from the reaction medium.

XRD diffraction patterns after calcinations of the reacted CaHAp with $C_6H_5P(O)Cl_2$ show a significant change while the starting CaHAp remains unchanged after heating to 1000 °C. This result indicates that a reaction takes place at high temperature between the apatite and the organic moieties (Fig. 4).

3.5. Solid-state NMR spectroscopy

For CaHAp and CaFAp, an isotropic ^{31}P NMR signal is observed at +2.8 ppm corresponding to the $(PO_4)^{3-}$ anion [23,24]. After reaction we do not observed change in the spectra for CaFAp. In contrast, the ^{31}P spectrum for reacted CaHAp consists on two signals, one at +2.8 ppm $(PO_4)^{3-}$ and −6.3 ppm (phosphonate), respectively. The last signal becomes also sharper under ^1H decoupling (Fig. 5). In contrast, a ^{31}P NMR signal was found at 12 ppm for calcium phosphonate salt [13] suggesting that in the case of $C_6H_5P(O)Cl_2$ we have another mode of grafting of the phosphonate fragment.

For $CaHAp_{10}$, under quantitative conditions, i.e. short flip angle c.a. 15° and long relaxation delay (10 s), without proton decoupling, and 12 kHz spinning rate, integration of the two ^{31}P isotropic signals leads to a 8% (±1%) ratio of organic phosphorous versus total phosphorous. This ratio reaches 15% (±2%) for $CaHAp_{20}$.

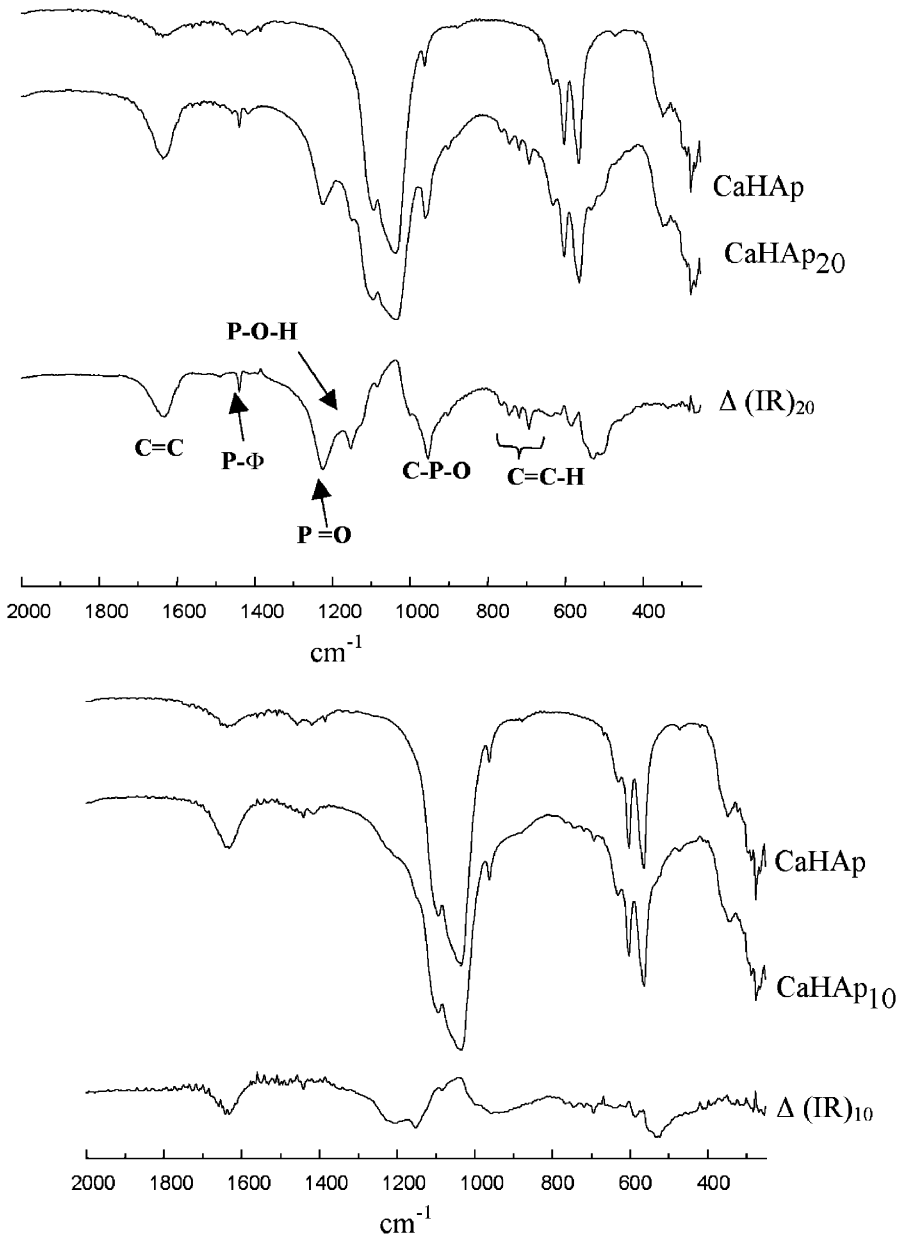

Fig. 2. IR spectra of CaHAp, $CaHAp_{10}$ and the difference $\Delta(IR)_{10}$ (bottom); IR spectra of CaHAp, $CaHAp_{20}$ and the difference $\Delta(IR)_{20}$ (top).

From the results obtained for CaHAp and their comparison with those from CaFAp it appears clearly that a "C_6H_5PO" fragment is bound to the CaHAp apatite surfaces mainly by the mediation of $(HPO_4)^-$ and/or OH^- ions. The low difference in SSA between CaFAp ($27.4\,m^2/g$) and CaHAp ($34.6\,m^2/g$) cannot explain the observed dramatic change in reactivity. Therefore, we propose that the mechanism leading to the grafting of the "C_6H_5PO" fragment results from a reaction between the organic phosphorous bearing the chloride atoms and the phosphorous hydroxyl groups located at the surface of the apatite according to the following Scheme 1.

4. Conclusion

The reaction of dichlorophosphonate with CaHAp is effective and leads to a grafted organic phosphonate moiety at the apatitic surface. To our knowledge reaction of phosphonic acids with HAp leads to grafted organic moieties bonded by electrostatic interactions between Ca^{2+} ions and phosphonate ions. Covalent bonds were suggested when using fluorophosphonic acids. This duality in reaction is not possible for phenylphosphonic chloride, although a partial hydrolysis cannot be excluded. The main reaction that takes place is the elimination of HCl prior to the formation of a P–O–P bond between the

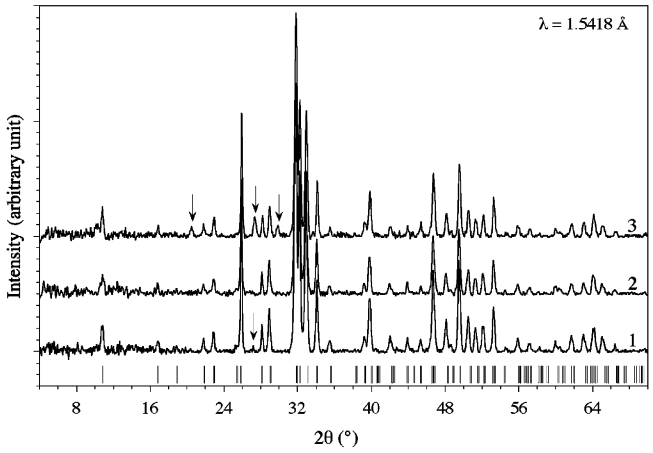

Fig. 3. X-ray powder diffraction patterns of CaHAp (1), $CaHAp_{10}$ (2), $CaHAp_{20}$ (3). The short vertical lines below X-ray powder pattern mark the positions of all Bragg reflections for the CaHAp.

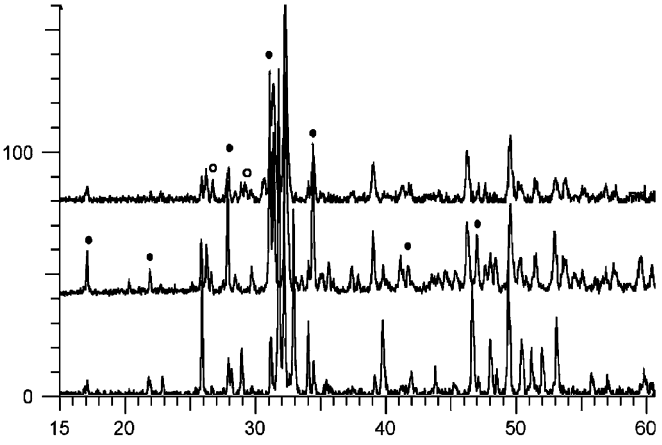

Fig. 4. X-ray powder diffraction patterns of CaHAp after calcination at 1000 °C under N_2 (bottom), $CaHAp_{10}$ after calcination at 1000 °C under N_2 (middle), $CaHAp_{20}$ after calcination at 800 °C under N_2 (top). Extra phases to apatites are β-$Ca_3(PO_4)_2$ (●) and $Ca_2P_2O_7$ (○).

apatite and the organic moieties. The dissolution of apatite due to the presence of HCl is hampered by the high reactivity of the phenylphosphonic chloride, and subsequent grafting. The HCl, thus formed during the reaction is not soluble in the medium and hence it is expelled is the form of a gas.

This result opens the way to the synthesis of new hybrid materials using functionalized phosphonic dichloride.

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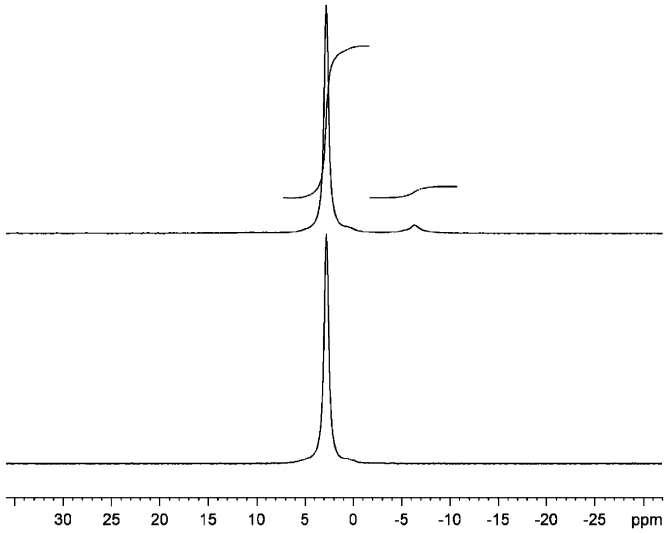
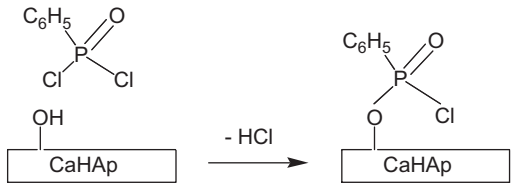


Fig. 5. 162 MHz solid-state ^{31}P MAS-NMR spectra of CaHAp (bottom) and $CaHAp_{10}$ (top). Spining rate 12 kHz; pulse width 1 ms (ca. 15° flip angle); relaxation delay 2 s and 10 s for CaHAp and $CaHAp_{20}$ respectively. The upper spectrum was obtained with high-power proton decoupling using HPDEC program of the Bruker program library.



Scheme 1. Representation of the first step of the reaction between the phenyl phosphonic dichloride and the hydroxyl groups on the surface of the apatite, leading to covalent P–O–P bond with elimination of HCl.

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