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First Principles Calculations of NMR Parameters in Biocompatible Materials Science: The Case Study of Calcium Phosphates, β- and γ-$Ca(PO_3)_2$. Combination with MAS-J Experiments

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Calcium phosphates are of paramount importance in the field of biocompatible materials, because of their tissue repair and regenerative applications.[1] The biocompatibility of such materials is intimately related to chemical composition and structure, as exemplified by hydroxyapatite (HAp), $Ca_{10}(PO_4)_6(OH)_2$. However, synthetic stoichiometric HAp, though comparable to the inorganic component of natural bone, is not well suited for bone substitution because of modulus mismatch and limited bioresorption. Recently, calcium polyphosphates (such as $Ca(PO_3)_2$) have shown potential applications in various fields, including: (i) bone substitution due to very high bioresorption and osteoconductivity,[2] (ii) drug delivery systems,[3] and (iii) ceramic–polymer composite biomaterials.[4] As the chemical and/or physical properties of the materials are strongly related to subtle variations in composition, their full understanding requires the precise characterization of the corresponding structures. Besides vibrational spectroscopic techniques, SEM (scanning electronic microscopy) and XRD (X-ray diffraction), solid state NMR (nuclear magnetic resonance) offers unique perspectives for the fine description of biocompatible calcium phosphates. It is well established that ^{31}P MAS (magic angle spinning) and CP (cross polarization) MAS NMR are adequate tools of investigation,[5] because the ^{31}P isotropic chemical shift ($\delta_{iso.}$) and chemical shift anisotropy (CSA) can be considered as local spies of the chemical environment around the nuclei. Moreover, "dialogues" between spins can be established, allowing for the description of *spatial* or *chemical connectivities* within the materials. The spatial connectivities are established through the dipolar interaction D (with $D \propto r_{I\text{-}S}{}^{-3}$, where $r_{I\text{-}S}$ stands for the internuclear distance), whereas the chemical connectivities are established through the scalar J coupling.[6] Recently, several ^{31}P solid state NMR structural studies involving synthetic and natural calcium phosphates (including HAp) were published in the literature.[7]

As a matter of fact, high resolution ^{31}P MAS NMR experiments can lead to complex spectral data for which assignments are not directly obvious (through the combination of empirical rules,[8] and multidimensional NMR experiments can be helpful for that purpose). This is particularly true (i) when ^{31}P resonances corresponding to the repeat unit of a given structure are located in a restricted range of isotropic chemical shift (see below) and (ii) when distributions of chemical shift are involved (amorphous calcium phosphate phases). From our point of view, a "bridge" must be established between the experimental 1D or 2D ^{31}P MAS data and the corresponding calcium phosphate structures. This bridge corresponds actually to the *first principles calculations* of NMR parameters, starting from XRD data.

The goal of this Communication is to demonstrate that the combination of such calculations and 2D MAS NMR experiments allows for full assignment of ^{31}P spectra related to calcium phosphates. Thereafter, we will refer to the FPC-NMR approach (First Principles Calculations-NMR). The GIPAW (gauge including projector augmented wave) method, first developped by Pickard and Mauri,[9] is suited for the calculation of NMR parameters in the case of periodic systems. It is based on density functional theory (DFT), pseudopotentials, and periodic boundary conditions. The cluster approximation is therefore avoided. The partially covalent nature of the Ca–O bond has been taken into account in an important contribution by Profeta et al.[9b] Such calculations provide the principal components of the CSA tensors (δ_{ii}, $i = 1$–3) and the absolute tensor orientations toward the crystallographic axes for each ^{31}P site of a given structure. To the best of our knowledge, few GIPAW ^{31}P calculations were published so far in the literature[10–12] (results related to silicates, oxides, and small organic

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molecules have been published during the past few years).[13] The validation of this approach involves two polymorphs of $Ca(PO_3)_2$, namely, β-$Ca(PO_3)_2$, and the newly reported γ-$Ca(PO_3)_2$ phase[14a] (a new phase corresponding to α-$Ca(PO_3)_2$ has been reported very recently;[14b] for calculations, almost 900 electrons per unit cell have to be considered: this reaches the limits of the calculator possibilities).

These compounds are representative of biocompatible metaphosphates. The choice of these polymorphs is challenging, as both phases exhibit long polymeric chains of PO_4 groups (Q^2 units). Moreover, *four* inequivalent crystallographic sites are present in both cases.

However, some structural differences can be noted: (i) β-$Ca(PO_3)_2$ exhibits zigzag PO_4 chains arranged in a unidirectional manner throughout the entire structure, whereas γ-$Ca(PO_3)_2$ shows criss-cross arrangement of helical chains.[14] (ii) P···P distances are slightly shorter in the case of γ-$Ca(PO_3)_2$ (∼0.1 Å), and P−O−P angles are slightly smaller (∼10°). β- and γ-$Ca(PO_3)_2$ phases were synthesized by heat treatments of MCPM, $Ca(H_2PO_4)_2 \cdot H_2O$.[22] ^{31}P fast MAS NMR spectra[22] ($\nu_{rot.} = 14$ kHz) are presented in Figure 1. Four isotropic lines are indeed observed for each phase, with a much larger chemical shift range for γ-$Ca(PO_3)_2$. Despite quite similar structures, ^{31}P MAS spectra are strongly different. The GIPAW calculations[22] of ^{31}P parameters for γ-$Ca(PO_3)_2$ are presented in Table 1, and the corresponding calculated spectra are presented in Figure 1. Excellent agreement is obtained between the experimental and the calculated data for both $\delta_{iso.}$ and CSA values (experimental CSA parameters were extracted from ^{31}P slow MAS experiments). It follows that full assignment is obtained for the four P atoms of the γ-$Ca(PO_3)_2$ repeat unit. To confirm experimentally these attributions, a 2D ^{31}P MAS-*J*-INADEQUATE experiment[15] was performed to extract chemically bonded ^{31}P pairs through $^2J_{P\text{-}O\text{-}P}$ couplings (see Figure 2). Strong off-diagonal correlations corresponding to *J*-coupled nuclei are observed.[23] According to the proposed assignments, all expected chemical connectivities are indeed demonstrated.

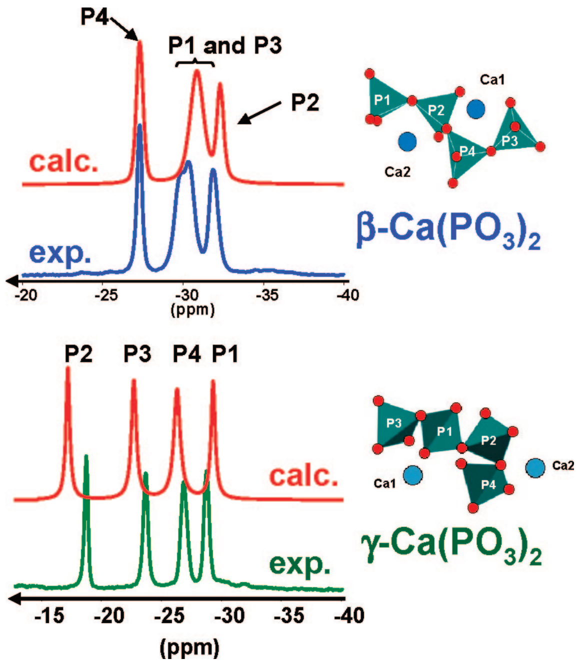

Figure 1. ^{31}P fast MAS NMR spectra of β-$Ca(PO_3)_2$ and γ-$Ca(PO_3)_2$. In blue and green: experimental spectra. In red: calculated spectra using the GIPAW parameters shown in Table 1.

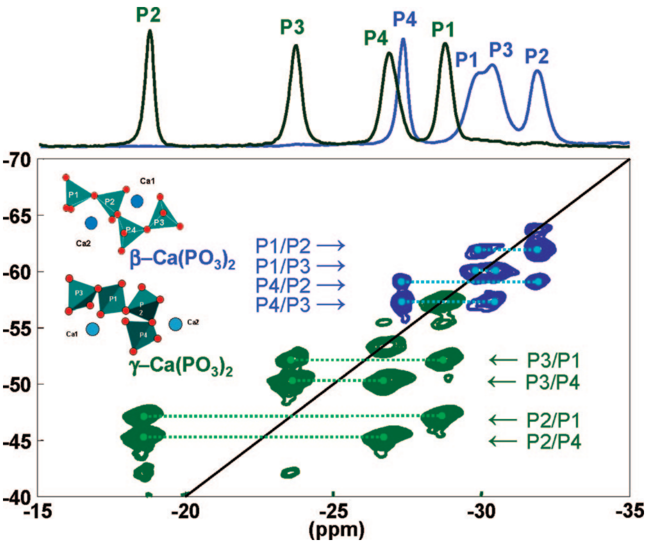

Figure 2. 2D ^{31}P MAS-*J*-INADEQUATE for β-$Ca(PO_3)_2$ and γ-$Ca(PO_3)_2$. Off-diagonal peaks indicate $^2J_{P\text{-}O\text{-}P}$ through-bond correlations. Blue: β-$Ca(PO_3)_2$. Green: γ-$Ca(PO_3)_2$.

The ^{31}P resonances related to β-$Ca(PO_3)_2$ are located in the range [−27.3, −32.3 ppm] (Figure 1). When compared to γ-$Ca(PO_3)_2$, a global shielding of the lines is observed. The GIPAW calculations (Figure 1,Table 1) are again in very good agreement with the experimental data and account for the global shielding of the ^{31}P resonances in β-$Ca(PO_3)_2$. Non-ambiguous assignments can be proposed for P2 and P4, corresponding to the most and less shielded resonances, respectively. However, the question of the attribution of P1 and P3 remains open, as calculated values are almost similar ($\delta_{calc.} = -30.8$ and -30.9 ppm). To answer this question, a 2D ^{31}P MAS-*J*-INADEQUATE experiment was performed (Figure 2). As P4 ($\delta_{exp.} = -27.3$ ppm) is connected to P2 *and* P3 through $^2J_{P\text{-}O\text{-}P}$ couplings, the resonance centered at

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Table 1. GIPAW calculated and experimental ^{31}P parameters for β-$Ca(PO_3)_2$ and γ-$Ca(PO_3)_2$. Definitions of $\delta_{iso.}$ and δ_{ii} are given in ref 22. Estimated errors: 0.1 ppm for δ_{iso}, 3 ppm for $\delta_{aniso} = \delta_{33} - \delta_{iso}$.

	$\delta_{iso.}$ (ppm) calcd (exp)	δ (ppm) calcd (exp)	δ_{22} (ppm) calcd (exp)	δ_{33} (ppm) calcd (exp)
		β-$Ca(PO_3)_2$		
P1	−30.8 (−29.9)	67.8 (61.9)	3.5 (−3.1)	−163.9 (−148.5)
P2	−32.3 (−31.8)	66.6 (59.1)	10.1 (3.0)	−173.7 (−158.1)
P3	−30.9 (−30.3)	65.4 (61.5)	−3.2 (−3.7)	−155.0 (−149.0)
P4	−27.3 (−27.3)	57.2 (52.6)	−2.6 (−7.3)	−136.4 (−127.3)
		γ-$Ca(PO_3)_2$		
P1	−29.3 (−28.9)	74.1 (69.9)	9.9 (4.0)	−172.0 (−160.6)
P2	−17.2 (−18.7)	68.6 (61.5)	11.3 (8.0)	−131.5 (−125.7)
P3	−22.7 (−23. 6)	75.2 (72.1)	11.8 (4.2)	−155.1 (−147.1)
P4	−26.3 (−27.0)	78.1 (71.8)	10.1 (6.0)	−167.2 (−158.7)

$\delta_{exp.} = -30.3$ ppm is assigned definitely to P3. As for γ-$Ca(PO_3)_2$, the FPC-NMR approach allowed for full interpretation of ^{31}P MAS spectra.

In this Communication, we have shown that first principles calculations using the GIPAW method are suitable for full understanding of ^{31}P NMR spectra in the frame of calcium polyphosphates. The usefulness of the combination of ab initio calculations and 2D NMR experiments was clearly demonstrated in the case of β-$Ca(PO_3)_2$ and γ-$Ca(PO_3)_2$; those structures present similar characteristics. We strongly believe that the FPC-NMR approach is by no means restricted to metaphosphates derivatives. Moreover, interesting perspectives can be already proposed for future studies: (i) The GIPAW method can be applied to the calculation of NMR parameters for *all nuclei* present in calcium phosphates (^{31}P, ^{17}O, and even ^{1}H for hydrated or hydroxylated phases). ^{17}O solid state NMR appears indeed as a good candidate for spectroscopic purposes.[16] (ii) The FPC-NMR approach can be extended to all calcium phosphate phases involved in the frame of biocompatible materials science, including hydrated phases. (iii) Calculations can also be performed in the case of ill-defined or amorphous materials.[17] This particular point is crucial, as most interfacial properties of biomaterials are related to such components. (iv) Calculations can confirm structural models proposed for nonstoichiometric materials, such as *substituted* HAp structures. Work is in progress in the laboratory toward all these directions.

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(22) Experimental details: MCPM, $Ca(H_2PO_4)_2 \cdot H_2O$, was synthesized by mixing $CaCO_3$ (1.00 g, 1.0×10^{-2} mol) and H_3PO_4 (85%; 2.31 g, 2.0×10^{-2} mol) in 5 mL of distilled water. The solution was strirred until precipitation. Heat treatment of the precipitate at 600 °C for 12 h led to β-$Ca(PO_3)_2$, whereas heat treatment at 250 °C for 24 h led to γ-$Ca(PO_3)_2$. Both metaphosphates were characterized by powder X-ray diffraction. For β-$Ca(PO_3)_2$: JCPDS: 11-0039. For γ-$Ca(PO_3)_2$: JCPDS: 50-0584 and ref 14. Some very minor impurities were detected by ^{31}P MAS NMR. *Solid state NMR*: ^{31}P MAS NMR experiments were performed at 121.44 MHz ($B_0 = 7.0$ T) using a Bruker AVANCE 300 spectrometer and 4 mm Bruker probe ($\nu_{rot.} = 3$, 5, and 14 kHz; number of scans (NS), 32; recycle delay (RD), 10 s with 30° pulse angle). Chemical shifts were referenced to H_3PO_4 (85%). The 2D ^{31}P MAS-*J*-INADEQUATE experiments were performed at 14 kHz. The τ evolution period was synchronized with the rotor period. The magic angle was carefully checked to minimize dipolar effects.[15c] States mode with 64 or 512 increments; RD, 30 s; NS, 32 for each t_1 increment; presaturation of the ^{31}P signal. *Computations*: the first principles calculations based on the GIPAW method[9a] were performed within Kohn–Sham DFT using the PARATEC code.[18] Non-relaxed structures within DFT were used. The PBE generalized gradient approximation[19] was used, and the valence electrons were described by norm conserving pseudopotentials[20] in the Kleinman−Bylander[21] form. The core definition for O is $1s^2$, and it is $1s^22s^22p^6$ for P and Ca. The core radii are 1.5 au for O and 2.0 au for P and Ca. The wave functions are expanded on a plane wave basis set with a kinetic energy cutoff of 80 Ry. The calculations of the EFG and CSA tensors requires from 2 to 10 h on 32 processors, respectively. All computational details can be found in refs 10 and 11. The $\sigma^{ref}(^{31}P)$ (= 300.7 ppm) value was chosen by comparison between experimental and calculated $\delta_{iso.}$ in a series of phosphorus derivatives. The diagonalization of the symmetrical parts of the chemical shift tensors led to the principal components, δ_{ii}, with $|\delta_{33} - \delta_{iso.}| \geq |\delta_{11} - \delta_{iso.}| \geq |\delta_{22} - \delta_{iso.}|$ and $\delta_{iso.} = 1/3(\sum\delta_{ii})$.

(23) On-diagonal correlations observed in the INADEQUATE experiments can be attributed to through-space contributions, without any assistance of *J* coupling (for an in-depth discussion, see ref 15c). The much less intense correlations (off-diagonal) could also correspond to such effects.