Mixed Ca\(^{2+}\)/Na\(^{+}\)(Mg\(^{2+}\)) polyphosphates for polymer matrix filling and their solubility

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Abstract. Mixed cationic Ca\(^{2+}\)/Na\(^{+}\)(Mg\(^{2+}\)) polyphosphates, regarded as potential biocomposite fillers, were fabricated by solid-state reactions. Most of them demonstrated low solubility (assessed also by the Glasser and Jenkins approach) from 1 ± 0.2 g/L for Ca(PO\(_3\))\(_2\) to 5 ± 0.4 g/L for NaCa(PO\(_3\))\(_3\) and 50 ± 2 g/L for soluble phase of NaPO\(_3\). Liquid-state NMR of the soluble part of polyphosphates gave the degree of polymerization of their chains ranging from 10 to 30 for NaCa(PO\(_3\))\(_3\) and ca. 1000 monomeric units for NaPO\(_3\).

1. Introduction

Mixed polyphosphates of Ca/Na are beneficial for bone grafting since polyphosphates (PP\(_i\)) are rather soluble (resorbable) and reveal a cumulative effect due to the long-time splitting of their backbone with the required long-chain chelate features for biomineralization by alkaline phosphatase (ALP) enzyme as compared to orthophosphates (P\(_i\))[1]. They comply with most basic requirements: lack of an immune response and inflammation processes, undesirable chemical reactions shifting pH level from physiological value, the closeness of mechanical characteristics to that of native bone tissue necessary for prevention of bone restoration by stress shielding [2]. Likewise, the macroporous structure of grafts usually described as their osteoconductivity is important for providing favorable conditions for bone ingrowth and neovascularization. The issue of implants with a special porous architecture can be addressed to 3D-printing, e.g. fused deposition modelling technique (FDM), which demands a thermoplastic polymer and an inorganic filler [3].

Coming from the bone mineral, hydroxyapatite (HA), we proposed to replace it as a possible filler with calcium phosphates containing different-length condensed anions such as P\(_2\)O\(_7\)\(_4^-\), P\(_3\)O\(_9\)\(_3^-\), P\(_3\)O\(_{10}\)\(_5^-\), bearing in mind a higher dissolution rate of the corresponding PP\(_i\)[4]. Being subjected to hydrolysis by ALP \textit{in vivo}, these anions produce P\(_i\) anions that are the building material for biogenic HA. Regulation of the rate of hydrolysis is a crucial factor to maintain the optimal rate of dissolution at ca.10 mm per year [1]. As for the organic polymer component, it can be represented, for example by poly(\(\varepsilon\)-caprolactone), poly(D,L-lactide) or bacterial poly(hydroxybutirate). The polymers have suitable melting points, elastic modulus, and time of biodegradation ranging from 1 to 2 years [5]. Thus, this
work is aiming at the synthesis and theoretical assessment of the solubility of the PP, under study through adoption of the thermodynamic model proposed for salts with monomeric anions [6], and its verification. The lengths of PP chains in solid-state and in solution were also evaluated.

2. Materials and methods

Mixed cationic Ca(PO$_3$)$_2$, CaNa(PO$_3$)$_3$, NaPO$_3$ polyphosphates, occurring at the CaO-P$_2$O$_5$-Na$_2$O system, were synthesized via solid-state reactions (1-3). The prepared material is subjected to measurement of the solubility and the determination of the length of PP chains in solution and in the solid state. Note that the prepared compounds have a polymeric structure and the presented formulas (1-3) are stoichiometric.

2.1. Chemical reactions

\[ \text{Ca}(H_2P_4O_{10}) \cdot H_2O \rightarrow \text{Ca}(PO_3)_2 + H_2O \]  
\[ \text{NaH}_2\text{PO}_4 \rightarrow \text{NaPO}_3 + H_2O \]  
\[ \text{NaH}_2\text{PO}_4 + \text{Ca}(H_2P_4O_{10}) \cdot H_2O \rightarrow \text{NaCa}(PO_3)_3 + 4H_2O \]

2.2. Used equipment

Thermogravimetric and differential thermal analysis (TG/DTA) were provided by DTA Thermo (Rigaku, Japan) in air at a heating rate of 5 °C/min from r.t. to 1000 °C. X-ray powder diffraction analysis (XRD) was made by RINT-Ultima III (Rigaku, Japan) at Cu Kx irradiation within the range of 2Θ angles 5° - 80°. Phase identification was made by the ‘Match!’ and ‘WinXPOW’ programs with the ICDD PDF-2 database.

The solubility of the powders was measured by ICP-OES with SPS3520UV-DD (Hitachi, Japan). The optical emission bands were as follows: Na – 589.0 nm, Ca – 396.8 nm, P – 177.5 nm. $^{31}$P NMR spectra were recorded using a JEOL AL300BX NMR spectrometer operating at 300 MHz ($^1$H), the number of scans is in the range from 64 to 7620. Chemical shifts were referenced to 0 ppm using an external phosphoric acid standard. Each spectrum showed a peak corresponding to outerphosphate groups ($\alpha$ peak at $\sim$ -9±1 ppm) and a second peak corresponding to internal phosphate groups (1 at -23±1 ppm); for some samples, a third peak was also observed, corresponding to phosphates neighboring to the external residues ($\beta$ peak at $-21\pm1$ ppm) and a forth peak ($\sim -4\pm1$ ppm) corresponding to P. Quantitative analysis was performed using peak area integration. Each PP has 2 $\alpha$ residues and 1 internal phosphorus atoms (including the $\beta$ peak when present). The total polymer lengths n equals to 2 + i[7].

3. Results and discussion

The phase diagrams for systems CaO-P$_2$O$_5$-Na$_2$O(MgO) were revised. Potentially prospective as well as non-studied or doubtful areas of the PPpolymer existence were outlined. Temperatures and duration for completion of the reactions (1-3) were determined using DTA and XRD (figure 1 a, b).

All samples containing Na or Ca(PO$_3$)$_2$ met the requirements of the 400-800 °C interval to complete all required phase transformations, otherwise depolymerized P$_i$s were formed (figure 1 a). Phase purity and possible polymorphs were checked by XRD (figure 2 b). Na containing phases appeared more crystalline (narrow peaks) due to the lower lattice energy coming from less charged Na$^+$. All samples of NaCa(PO$_3$)$_3$ annealed within the interval specified above demonstrated the same XRD pattern (figure 1 b) identical to that from PDF-file # 00-023-0669.

The solubility of different Ca$^{2+}$/Na$^{+}$(Mg$^{2+}$)PP compounds were assessed according to the volume-based thermodynamic model proposed by Glasser and Jenkins [6]. Within this approach, the absolute standard entropies of individual polyphosphate phases and the enthalpies of their lattices depend explicitly on the molar volumes of the phases derived from XRD- and/or pycnometry data. The lattice enthalpy is related to the molar volume through generalized Kapustinskii equation. The change in the standard Gibbs free energy of solubility in water can be found as $\Delta G_{sol}^{298} = \Delta H_{sol}^{298} - 298 \times \Delta S_{sol}^{298}$. 

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Enthalpy and entropy contributions were defined the sum of two consequent processes: the conversion of the crystal lattice into constituent gaseous ions and the following hydration of them.

The results of calculation are presented in table 1. Most Ca containing P\textsubscript{i} phases have limited solubility, however, PP\textsubscript{i} phases are theoretically soluble making them rather promising as a filler in the composite bone implants (bearing in mind their morphogenetic activity [8]). The main contribution into the Gibbs energy of dissolution for PP\textsubscript{i} came from the enthalpy term. These mix-cationic polyphosphates possess comparable solubility to other promising phosphates, e.g.CaKPO\textsubscript{4} and CaNaPO\textsubscript{4}[9].

Table 1. Theoretical and experimental assessment of solubility properties of mix-cationic polyphosphates.

| Phases          | log\textsubscript{10}K\textsubscript{s}(theoretical data) | Solubility (experimental data) |
|-----------------|--------------------------------------------------------|--------------------------------|
| Ca(PO\textsubscript{3})\textsubscript{2}       | -47.9 ± 3                                               | 1 ± 0.2 g/L                    |
| Ca\textsubscript{3}(PO\textsubscript{4})\textsubscript{2} | 27.7 ± 2                                               | Not measured                   |
| Mg(PO\textsubscript{3})\textsubscript{2}       | -75.8 ± 4                                               | Not measured                   |
| NaPO\textsubscript{4}                    | -34.3 ± 3                                               | 50 ± 2 g/L                     |
| NaCa(PO\textsubscript{3})\textsubscript{3}    | -45.2 ± 3                                               | 5 ± 0.4 g/L                    |
| Na\textsubscript{2}Ca(PO\textsubscript{3})\textsubscript{6} | -41.5 ± 3                                               | Not measured                   |
| CaMg(PO\textsubscript{3})\textsubscript{4}    | -64.0 ± 4                                               | Not measured                   |

Figure 1. (a) DTA for mix-cationic polyphosphates, NaCa(PO\textsubscript{3})\textsubscript{3}, NaPO\textsubscript{3}, Ca(PO\textsubscript{3})\textsubscript{2}. (b) XRD spectra of NaCa(PO\textsubscript{3})\textsubscript{3} obtained at 400-700 °C for 2 h.

Figure 2. (a) Liquid-state NMR spectra for NaCa(PO\textsubscript{3})\textsubscript{3} samples obtained at different temperatures. (b) NaPO\textsubscript{3} obtained at different temperatures and time of treatment (used precursor NaH\textsubscript{2}PO\textsubscript{4}).
Estimation of the chain length of the dissolved part of PP\textsubscript{r}s using liquid-state NMR was performed (figure 2 a). Upon increasing temperature during synthesis, the concentration of monomer P\textsubscript{i} (peak around 0 ppm) was increasing compared to PP\textsubscript{r}\textalpha-peak (around -10 ppm, terminal polyphosphate groups) and PP\textsubscript{r} internal polyphosphate peak (around -23 ppm). An unidentified wide resonance within the range from -20 to -25 ppm might be assigned to polyphosphates with a partially cross-linked structure (and therefore less soluble). NMR spectra for NaPO\textsubscript{3} (figure 2 b) demonstrate a strong difference between NaPO\textsubscript{3} (400°C, 2h), NaPO\textsubscript{3} (400 °C, 12 h), which are forming poorly soluble very long chains of PP\textsubscript{r}, and those synthesized at higher temperatures NaPO\textsubscript{3} (500 °C-600 °C, 2 h), which are completely soluble with relatively shorter chains of PP\textsubscript{r}s.

4. Conclusions
Mixed cationic Ca\textsuperscript{2+}/Na\textsuperscript{+}(Mg\textsuperscript{2+})PP\textsubscript{i} which are promising for regenerative medicine were synthesized. Most PP\textsubscript{r} materials demonstrated low solubility from 1 ± 0.2 g/L for Ca(PO\textsubscript{3})\textsubscript{2} to 5 ± 0.4 g/L for NaCa(PO\textsubscript{3})\textsubscript{3} and 50 ± 2 g/L for the soluble phase of NaPO\textsubscript{3}. The discrepancy between experimental data and calculations might be caused by the limited applicability of the volume-based model to polyanions. The liquid-state NMR of the soluble part of PP\textsubscript{r} gave the degree of polymerization of PP\textsubscript{r} chains ranging from 10 to 30 for NaCa(PO\textsubscript{3})\textsubscript{3} and ca.1000 for NaPO\textsubscript{3}.

Acknowledgments
The work was funded by RFBR grants №18-08-01473, 16-38-60203,18-33-00789 and 18-53-00034.D.M.Z. was supported by MSU - NIMS Cooperative Graduate School Program OH-1619-2014-5. Equipment purchased through the Program for Development of MSU was used.

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