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Formation and transformation of struvite and newberyite in aqueous solutions under conditions similar to physiological

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Abstract The precipitation of magnesium phosphates in the system $MgCl_2$-$NH_4H_2PO_4$-NaOH-H_2O was studied at a wide range of reactant concentrations at 37°C and an initial pH_i of 7.4. Precipitates were aged for 24 h and characterized by means of optical and scanning electron microscopy, x-ray diffractometry, FT-IR spectroscopy and thermogravimetry. Struvite was found to precipitate in nearly the whole concentration region investigated. Pure newberyite and a mixture of struvite and newberyite were obtained in a narrow range only with a $pH_{24\,h} < 6.4$. The transformation of struvite into newberyite was studied by following changes in the liquid and solid phases. Thus, the changes of pH and the content of struvite in the precipitate as a function of time were recorded. The influence of the initial pH_i and temperature on the transformation process is discussed. Analysis of the experimental data suggests a solution mediated transformation process as a possible mechanism of struvite transformation.

Keywords Struvite · Newberyite · Precipitation · Transformation

Introduction

The formation of urinary stones is a serious health problem as about 4–15% of the human population suffer from this disease [1]. After the Second World War, the manifestation of this disease has increased in industrialized countries. This has been presumed to be the consequence of an increase in standard of living and of changes in nutritional practice of the population.

Most of the human renal calculi (about 75%) are composed of calcium salts, primarily of calcium oxalates and phosphates, and only about 10–12% are predominantly composed of uric acid [2]. Calcium and/or magnesium phosphates are reported to be components of about 25% of the urinary calculi [3].

Urine is supersaturated for most of the stone forming constituents, but it also contains numerous substances (citrate, pyrophosphate, peptide, glycoproteins, glycosaminoglycans), which act as natural crystallization inhibitors. Nucleation of a solid phase(s), for which urine is supersaturated, can be provoked by small changes in the urine composition (intensified secretion of stone-forming substances, reduced secretion of crystallization inhibitors), as well as by a range of other causes (metabolic disorders, genetic factors, life habits, kidney changes, urodynamic obstructions). Growth of the forming nucleus and its aggregation into a calculus are possible only if this nucleus attaches itself inside the kidney or at some other place in the urinary tract. If this does not happen, it will be washed out by urine [4].

A separate group of phosphate-containing calculi are the so-called "infection stones". Among them, 10–20% are predominantly composed of struvite ($MgNH_4PO_4{\cdot}6H_2O$) often mixed to various amounts with hydroxyapatite ($Ca_5(PO_4)_3OH$) and carbonate apatite ($Ca_5(PO_4,CO_3,OH)_3OH$) [3, 5]. These stones form in humans as a result of urinary tract infection with ureolithic microorganisms [2, 6]. Such stones are also found in animals [7]. The metabolic product of these microorganisms is the enzyme urease, which hydrolyses urea to ammonia and carbon dioxide. The consequence is an increase in the urine pH and the content of NH_4^+. Normally, owing to the complex composition of urine, its ionic strength is about 0.33 mol dm^{-3} and, depending on the urine composition, the pH varies from 4.5 to 7.5 [8]. Urine from a healthy person contains 2.5–7.1 mmol dm^{-3} magnesium, 7.7–60.0 mmol dm^{-3} phosphate and 13.0–112.0 mmol dm^{-3} ammonium [9], and is undersaturated with $MgNH_4PO_4{\cdot}6H_2O$. Because of the urine composition, the conditions provoked by urease-pro-

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ducing microorganisms lead to the precipitation of struvite and hydroxyapatite. In this particular case, the sediment can easily attach to particles of organic matter, formed as a consequence of the infection, rather than to localized places inside the kidney. Such a mechanism favours the acceleration of crystal deposition and crystal aggregation in the urine, so that the struvite calculi grow extremely quickly.

Such findings led several groups to study the process of struvite formation under different conditions. Thus, investigations have been made in aqueous solutions containing only magnesium, phosphate and ammonium ions [10, 11, 12, 13, 14] and in aqueous solutions simulating urine composition [15,16]. Much useful information has been obtained on the kinetics of spontaneous precipitation and the dissolution of struvite, the concentration range within which it precipitates, its morphology and transformation into newberyite ($MgHPO_4 \cdot 3H_2O$) [17].

The appearance of newberyite, however, is still a matter of debate. Some authors do not support the idea of newberyite deposition in the calculi [11], although a few examples of the occurrence of newberyite in human urinary calculi have been reported [18, 19]. The explanation for these cases was found in the probable decomposition of struvite under specific conditions in the urine. In order to explain the formation of struvite calculi and the possible appearance of newberyite in these calculi, a systematic physicochemical study is necessary. Although a considerable number of investigations of struvite have already been undertaken and the results published, every new insight into this matter is valuable. The more so as struvite stones are large and cause substantial pain, bleeding, infection or obstruction and a reduction in urine production. These stones cannot be washed out and require surgical removal.

Because of the complexity of precipitation (nucleation, crystal growth, transformation, aggregation and other aging processes), and the extreme complexity of a natural system such as urine, this work used simplified, model systems. The spontaneous precipitation of struvite and its transformation into newberyite was investigated in aqueous solutions under conditions which, in some respects, imitated the physiological ones (37°C, $pH = 5.0–9.0$). These investigations are a continuation of those in which the influence of temperature, initial pH and aging time of the precipitate were studied (unpublished data) and are also part of a study that will be continued under more complex conditions using artificial and real urine.

Materials and methods

All solutions were prepared from analytically pure chemicals and the water was of high purity (conductivity $< 0.1\ \mu S\ cm^{-1}$). Concentrated stock solutions of $MgCl_2$, $NH_4H_2PO_4$, NaOH and HCl were standardized by classical analytical methods [20], i.e. magnesium was determined by complexometric titration, phosphate spectrophotometrically as the phosphomolybdenvanadato complex and sodium hydroxide by titration with the standard hydrochloric solution.

Precipitation systems, investigated for the construction of precipitation diagrams, were prepared by mixing equal volumes ($5.0\ cm^3$) of known concentrations of magnesium chloride solutions with ammonium dihydrogenphosphate solutions, both previously thermostated at the temperature of experiment. The latter solutions were preadjusted to $pH = 7.4$ by adding the required amounts of NaOH. After initial mixing of the reactant solutions, the systems were tightly closed and no other agitation was employed. All experiments were performed at 37°C and the precipitation systems were aged for 24 h. After this period, the morphology of the precipitate was determined by optical and scanning electron microscopy (SEM). The pH of the systems was measured by means of a combined glass-calomel electrode (GK 2401 C) connected to a pH meter and standardized by a series of buffers $4.005 < pH < 10.012$ (all Radiometer). The composition of the precipitates was identified by x-ray diffraction, XRD (Philips counter diffractometer with graphite monochromatized Cu-Kα radiation), Fourier transform infrared, FT-IR, spectroscopy (Mattson FT-IR spectrophotometer, Genesis Series) and thermogravimetry, TGA (Mettler TG 50 thermo balance with TC 11 TA processor).

For the transformation experiments, a vessel tightly closed by a Teflon stopper was used. The system was thermostated and stirred magnetically at a constant rate. The experiments were started by mixing equal volumes ($60.0\ cm^3$) of magnesium chloride and ammonium dihydrogenphosphate solutions of known concentrations, both previously adjusted to the initial pH of the experiment by the addition of NaOH and thermostated at the temperature of the experiment. These experiments were performed in a wide range of initial pHs: $5.00 \leq pH_i \leq 9.00$. During the experiments, the changes both in the liquid and in the solid phase were recorded. Thus, the propagation of the process was followed by a continuous measurement of the pH of the system by means of the combined glass-calomel electrode, placed in the stopper and dipping into the solution. Before each experiment, the pH meter was standardized by means of two buffers, $pH = 7.000$ and $pH = 10.012$ at 25°C. During the process, aliquots of the suspension were taken from the system at intervals of between 20 min and 1 h depending on the speed of the changes in the system, filtered through 0.45 μm membrane filters, washed with small portions of water and dried at 50°C. The struvite content in the solid phase was determined quantitatively on the basis of FT-IR spectrophotometry and the KBr pellet technique was employed. The band area obtained at $1{,}442.42\ cm^{-1}$, which is the band characteristic of struvite, was used as a measure for the content of this compound in the mixture. Well-defined mixtures of struvite and newberyite were prepared as standards and the calibration curves were obtained by plotting absorbances of the struvite and newberyite bands as a function of masses of struvite and newberyite, respectively.

Results and discussion

The precipitate was investigated over a wide range of initial reactant concentrations of magnesium ($c_{\mathrm{i}}(\mathrm{Mg})_{\mathrm{tot}=5.0\ 10^{-1}}$–$6.0\ 10^{-5}$ mol dm^{-3}) and phosphate ($c_{\mathrm{i}}(\mathrm{P})_{\mathrm{tot}=c_{\mathrm{i}}}(\mathrm{NH_4})_{\mathrm{tot}} = 5.0\ 10^{-1}$–$1.0\ 10^{-3}$ mol dm^{-3}) at 37°C. In order to reach the initial $\mathrm{pH_i} = 7.4$ of the systems, the required concentrations of NaOH were added. Such a range of reactant concentration was chosen with the aim of approaching physiological conditions and the conditions found in clinical analyses.

Figure 1 shows a precipitation diagram of struvite and newberyite in the system $\mathrm{MgCl_2}$-$\mathrm{NH_4H_2PO_4}$-NaOH-$\mathrm{H_2O}$ at 37°C and a constant initial $\mathrm{pH_i} = 7.4$. The axes of the diagram represent the negative logarithms of total initial concentrations of the variable reactant components, $c_{\mathrm{i}}(\mathrm{Mg})_{\mathrm{tot}}$ and $c_{\mathrm{i}}(\mathrm{P})_{\mathrm{tot}} = c_{\mathrm{i}}(\mathrm{NH_4})_{\mathrm{tot}}$. Open circles linked by a thick solid line denote the precipitation boundary between the clear solution and the first detectable precipitate. Inside the precipitation body, the concentration region of magnesium and phosphate in normal urine is indicated as a hatched area [9]. The systems used for the construction of this diagram were aged for 24 h, a time that was found to be long enough to establish an apparent equilibrium between the solid phase and its supernatant. In support of this is the fact that the precipitation diagrams (not presented here), one characterizing the systems aged for 30 days at 37°C and the other prepared in the same way with an addition of 0.15 mol dm^{-3} NaCl, did not show noticeable changes in the position of the precipitation boundary.

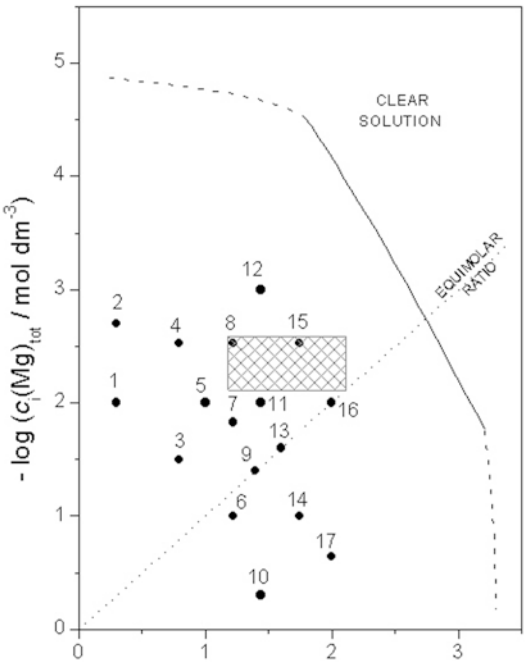


Fig. 1 Precipitation diagram with the assigned precipitation boundary (*thick solid line*) of the system $\mathrm{MgCl_2}$-$\mathrm{NH_4H_2PO_4}$-NaOH-$\mathrm{H_2O}$, $\mathrm{pH_i} = 7.4$, equilibrated for 24 h at 37°C. *Thick dashed lines* mark the uncertain parts of precipitation boundary. *Solid circles* (1–17) denote samples selected for detailed analyses. The *hatched area* indicates the concentration region of magnesium and phosphate in the urine of healthy individuals

Detailed analyses were performed on 17 systems inside the region within which the precipitate was formed. Table 1 gives the initial reactant concentrations of these systems, the final pH measured and the qualitative analyses of the precipitates obtained 24 h after mixing the reactants. According to the three methods used to characterize the precipitates [21, 22], struvite was found to precipitate in nearly the whole concentration range investigated. The investigations performed under similar conditions (low supersaturations, $6.2 \leq \mathrm{pH} \leq 8.0$, 25°C and 37°C) also showed the appearance of struvite [10, 13, 14]. In addition, struvite always precipitated when the magnesium and phosphate concentrations were within the range of concentrations found in the urine of healthy persons (Table 1, see also Fig. 1). Pure newberyite was obtained only in systems 6, 10, 14 and 17 in which the apparent equilibrium was at $\mathrm{pH}_{24\ \mathrm{h}} \leq 6.4$ and in system 9 in which newberyite precipitated mixed with struvite. Figure 2 shows typical morphologies of struvite and newberyite crystals obtained in our experiments. The observations from this work are in accordance with some previous findings according to which newberyite is the stable form at low pH and high concentrations of $\mathrm{Mg^{2+}}$ ions [11, 12, 14], and the simultaneous formation of the two solid phases occurs in a limited concentration range [23].

System 9, in which a mixture of struvite and newberyite was obtained 24 h after mixing the reactants, was chosen for the investigation of the transformation of struvite into newberyite. The changes in this system at a wide range of the initial $\mathrm{pH_i}$ were continuously followed during the first 5 h. The results are summarized in Table 2. In the range $\mathrm{pH_i} = 5.00$–7.00, no struvite was precipitated and the only initial solid phase formed was newberyite. The induction times for the appearance of the solid phase in the systems initiated at $\mathrm{pH_i} = 5.00$ and $\mathrm{pH_i} = 6.00$ were 10 and 5 min, respectively. In these systems, the values of $\mathrm{pH} = 4.6$ and 5.0 were measured after 5 h of the process. In the system initiated at $\mathrm{pH_i} = 7.00$, the precipitation started immediately after mixing the reactants and an abrupt decrease of pH to 6.0 was obtained in the first minute of the process. Newberyite formed in all of these systems and did not undergo any changes, since it is stable at $\mathrm{pH} < 6.0$. In the system in which the initial $\mathrm{pH_i} = 7.40$, the first precipitate appeared to be a mixture of newberyite and struvite. The mixtures of these two salts were also obtained in the systems initiated at $\mathrm{pH_i} = 8.00$ and $\mathrm{pH_i} = 9.00$. During the precipitation process initiated at $\mathrm{pH_i} = 7.40$, the content of struvite decreased from 22.1 wt. %, measured in the first minute of the process, to 0.0 wt. %, obtained

Table 1 Initial reactant concentrations, pH values of the systems and composition of the precipitate 24 h after mixing the reactants. Descriptions: S struvite, N newberyite

System	$c_i(P)_{tot} = c_i(NH_4)_{tot}$ /mol dm^{-3}	$c_i(Mg)_{tot}$ /mol dm^{-3}	pH (24 h)	Precipitate (24 h)
1	0.500	0.010	7.34	S
2	0.500	0.002	7.38	S
3	0.160	0.032	6.82	S
4	0.160	0.003	7.36	S
5	0.100	0.010	7.14	S
6	0.060	0.100	5.76	N
7	0.060	0.015	6.82	S
8	0.060	0.003	7.38	S
9	0.040	0.040	6.05	S + N
10	0.036	0.500	5.92	N
11	0.036	0.010	6.85	S
12	0.036	0.001	7.35	S
13	0.025	0.025	6.42	S
14	0.018	0.100	6.40	N
15	0.018	0.003	7.23	S
16	0.010	0.010	7.02	S
17	0.100	0.230	4.87	N

5 h later. By increasing the initial pH_i further, the content of struvite in the initial precipitate increased to 28.8 wt. % at $pH_i = 8.00$ and to 52.6 wt. % at $pH_i = 9.00$. After 5 h, the struvite content in these systems equaled 3.4 wt. % and 72.9 wt. %, respectively. It is obvious that at an initial $pH_i > 7.0$, the conditions for nucleation of struvite were established. Thus, in the system initiated at $pH_i = 7.4$, struvite was formed immediately after mixing the reactants, although the value of $pH = 6.02$, measured in the first minute of the reaction, might be more in favour of newberyite formation. The reason can be found in the rate of nucleation of struvite being greater than that of newberyite [11]. Struvite formed under such conditions started to transform into newberyite soon afterwards. The FT-IR analyses showed that struvite disappeared from the system within approximately 80 min, so that only newberyite continued to grow afterwards. The disappearance (dissolution) of struvite from the system was also evident by a gradual increase in pH. This increase was caused by the new protolytic equilibria that were brought about simultaneously by the dissolution of struvite and growth of newberyite. The most influential among these equilibria are: $NH_4^+ \rightleftarrows NH_3 + H^+$, $PO_4^{3-} + H^+ \rightleftarrows HPO_4^{2-}$, and $HPO_4^{2-} + H^+ \rightleftarrows H_2PO_4^-$. The subsequent decrease in pH in the system was caused by the crystal growth of

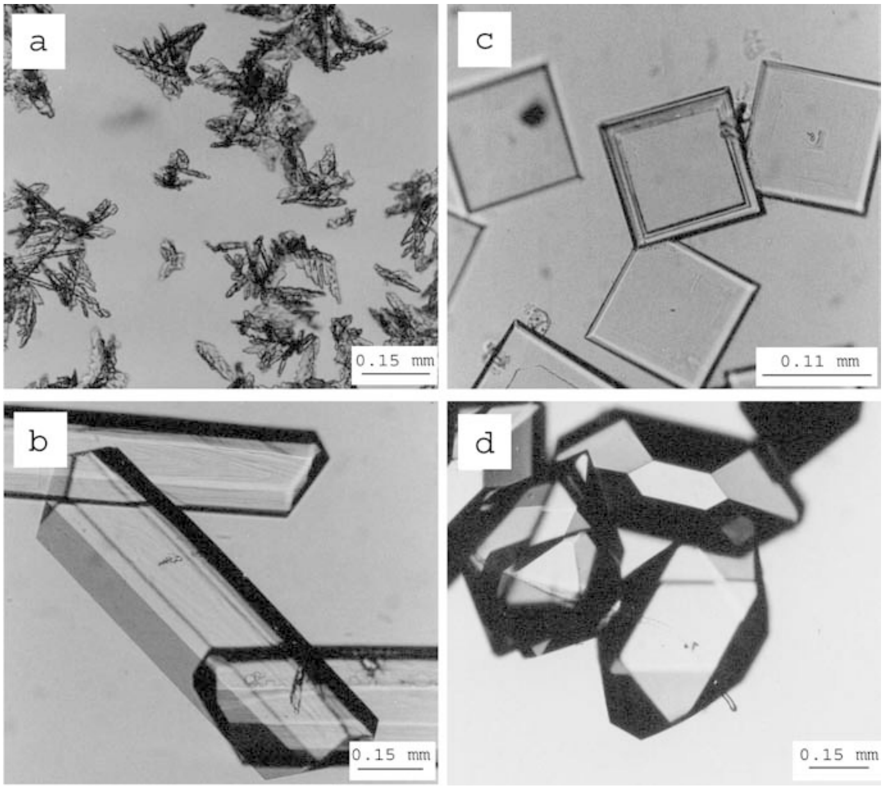


Fig. 2 Micrographs showing the morphology of precipitates obtained in this work: **a**, **b**, **c** struvite, **d** newberyite

Table 2 pH values (1 min) and precipitate composition (1 min and 5 h) in the system $c_i(\mathrm{Mg})_{\mathrm{tot}} = c_i(\mathrm{P})_{\mathrm{tot}} = c_i(\mathrm{NH_4})_{\mathrm{tot}} = 4.0\ 10^{-2}$ mol dm^{-3} at 37°C and a range of the initial pH$_i$. Designations as in Table 1

pH$_i$	pH 1 min	weight % S 1 min	weight % S 5 h
5.00	4.67	0	0
6.00	5.61	0	0
7.00	6.00	0	0
7.40	6.02	22.1	0
8.00	6.12	28.8	3.4
9.00	6.60	52.6	72.9

newberyite, being now the only process. The systems initiated at pH$_i$ = 8.00 and pH$_i$ = 9.00 behaved somewhat differently. The conditions established in these systems immediately after mixing the reactants, primarily pH and concentration of the phosphate species in the solution, became more favourable to struvite nucleation. The amount of struvite formed initially in the system initiated at pH$_i$ = 8.00 underwent a partial transformation into newberyite, i.e. it transformed until an equilibrium between the two solid phases was established. Thus, the mixture of newberyite and struvite in this system remained stable much longer than 5 h. The pH of the system measured 5 h after mixing the reactants was found to be 6.18, the value at which both compounds can exist. In the system initiated at pH$_i$ = 9.00, the amount of struvite initially formed was much larger than in the previous cases (52.6 wt.%). The value of pH = 6.64, established soon after the initial drop caused by the precipitate formation, remained constant up to the end of the 5 h. Nevertheless, during this time the content of struvite in the precipitate gradually increased to 72.9 wt.%. It is obvious that newberyite, although formed initially, gradually disappears from the system, being unstable at this pH value.

As an example, the pH and wt(S) % vs time curves for the transformation of struvite into newberyite at the initial pH$_i$ = 8.00 are shown in Fig. 3. The changes in the liquid phase during this process were obtained by measuring pH (Fig. 3a) and the changes of the solid phase composition (Fig. 3b) were obtained from the FT-IR spectra. Figure 4 shows the FT-IR spectra, recorded in the region from 2,000 to 800 cm^{-1}, in which at the transmittances of struvite (1,442.42 cm^{-1}) and newberyite (1,237.82 cm^{-1}, 1,171.34 cm^{-1} and 890.02 cm^{-1}) characteristic bands appear [22]. These spectra correspond to four samples taken during the process. At the very beginning of struvite transformation (1 min), the presence of both struvite and newberyite was noticed. Later (15 and 40 min), a decreasing content of struvite was observed until its content remained approximately the same (5 h). A scanning electron micrograph of such a mixture isolated during the transformation process shows both dendritic crystals of struvite and small crystals of newberyite (Fig. 5).

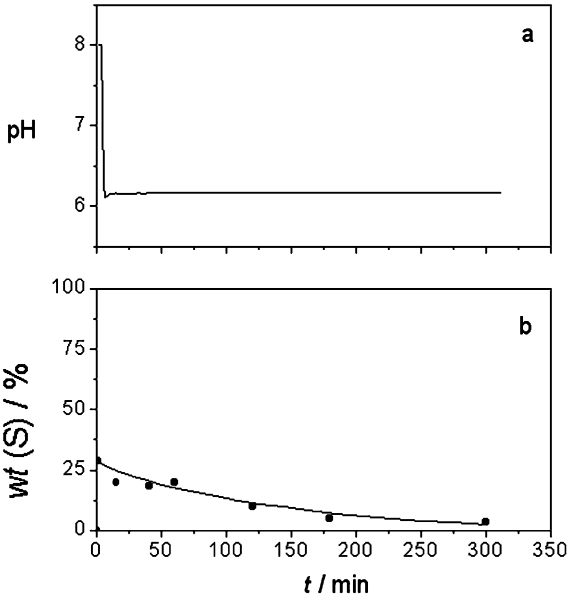


Fig. 3 Changes in: **a** pH and **b** weight (%) of struvite in the solid phase during the transformation of struvite into newberyite in the system $c_i(\mathrm{Mg})_{\mathrm{tot}} = 4.0{\cdot}10^{-2}$ mol dm^{-3} and $c_i(\mathrm{PO_4})_{\mathrm{tot}} = c_i(\mathrm{NH_4})_{\mathrm{tot}} = 4.0{\cdot}10^{-2}$ mol dm^{-3}, at 37°C and initial pH$_i$ = 8.00

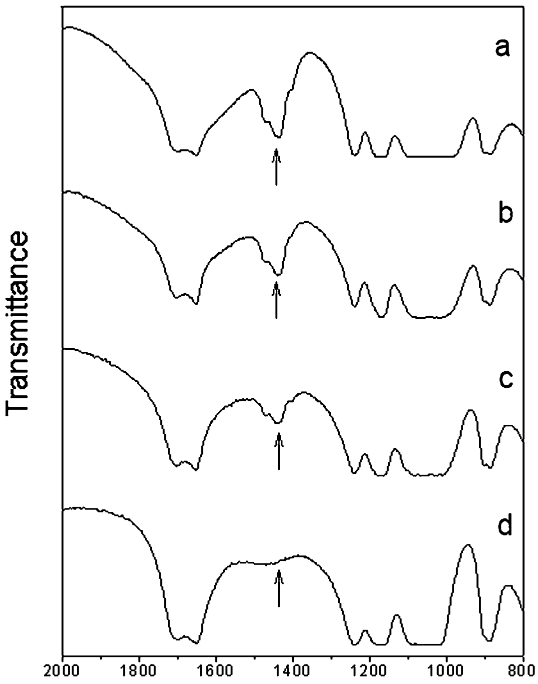


Fig. 4 Compilation of FT-IR bands for struvite and newberyite, corresponding to four samples from a study of the transformation of struvite into newberyite, taken from the system: $c_i(\mathrm{Mg})_{\mathrm{tot}} = 4.0{\cdot}10^{-2}$ mol dm^{-3}, $c_i(\mathrm{PO_4})_{\mathrm{tot}} = c_i(\mathrm{NH_4})_{\mathrm{tot}} = 4.0{\cdot}10^{-2}$ mol dm^{-3}, 37°C and initial pH$_i$ = 8.00, at: **a** 1 min, **b** 15 min, **c** 40 min and **d** 5 h. The band at 1,442.42 cm^{-1}, characteristic for struvite, is marked by *arrows*

Figure 6 shows the influence of temperature on the transformation process of struvite into newberyite. In this case, the reactant concentrations corresponding to precipitation system 17 (see Table 1 and Fig. 1) were

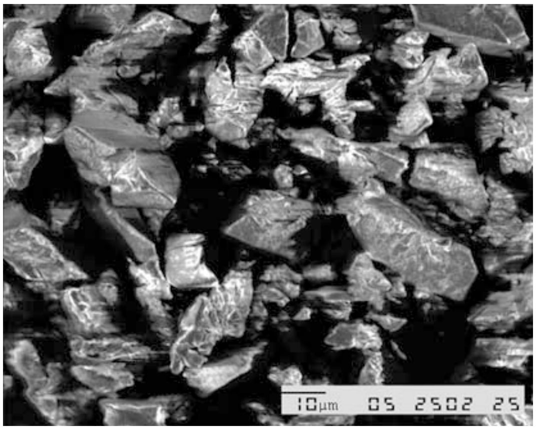


Fig. 5 Scanning electron micrograph of the sample taken during the transformation of struvite into newberyite in the system: $c_i(\mathrm{Mg})_{tot} = 4.0 \cdot 10^{-2}$ mol dm^{-3}, $c_i(\mathrm{PO_4})_{tot} = c_i(\mathrm{NH_4})_{tot} = 4.0 \cdot 10^{-2}$ mol dm^{-3}, 37°C and initial $\mathrm{pH_i} = 8.00$. The mixture of dendritic struvite crystals and small newberyite crystals is seen

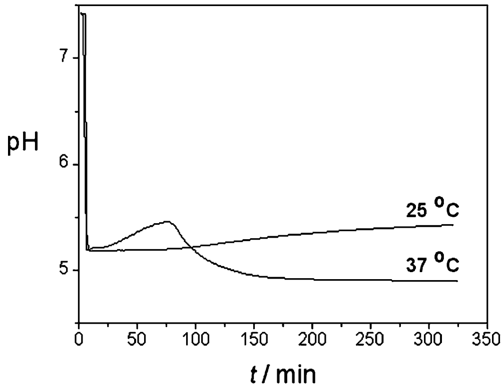
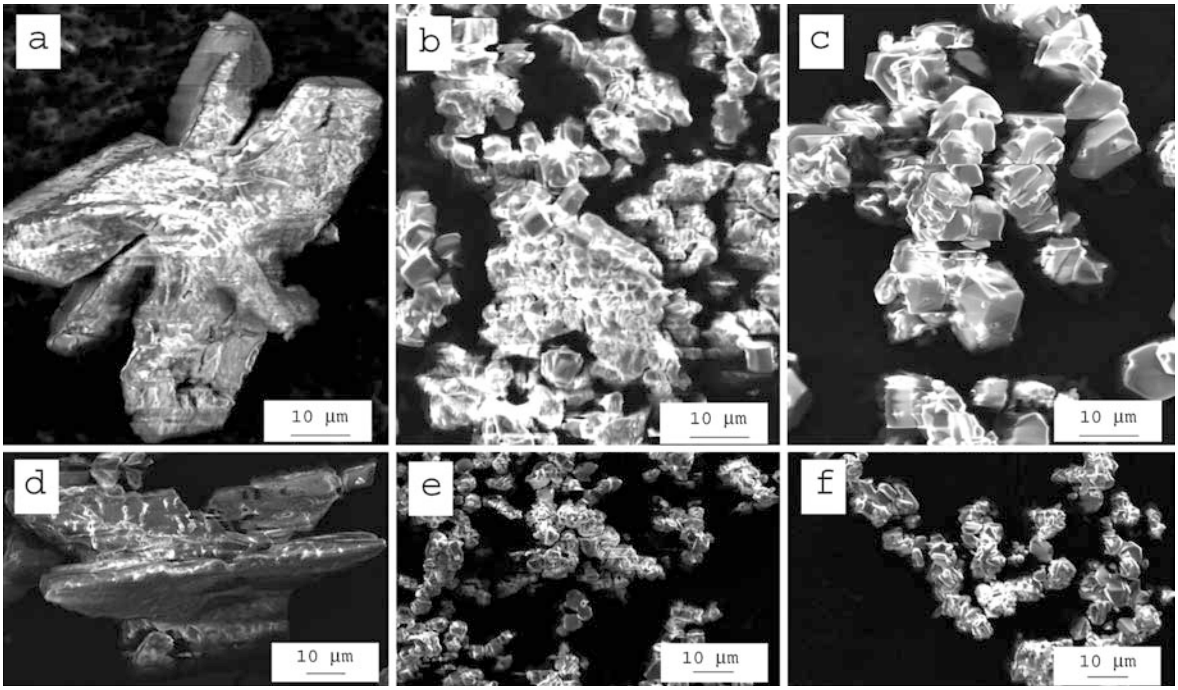


Fig. 6 Changes in pH as a function of time in the system $c_i(\mathrm{Mg})_{tot} = 2.3 \cdot 10^{-1}$ mol dm^{-3}, $c_i(\mathrm{PO_4})_{tot} = c_i(\mathrm{NH_4})_{tot} = 1.0 \cdot 10^{-1}$ mol dm^{-3} at the initial $\mathrm{pH_i} = 7.40$, and at 37°C and 25°C

used, and the transformation was studied at 25°C and 37°C. The initial precipitate at both temperatures was found to be a mixture of struvite and newberyite, the final being newberyite only. Immediately after mixing the reactants at both temperatures, the pH dropped from the initial $\mathrm{pH_i} = 7.4$ to approximately $\mathrm{pH} = 5.2$. At 37°C, the pH vs time curve follows the shape of the curve described above for system 9, initiated at $\mathrm{pH_i} = 7.4$. In contrast to this system, the transformation of struvite was somewhat faster and was completed in about 70 min, reaching $\mathrm{pH} = 5.45$ after the complete dissolution of struvite. A subsequent gradual decrease to $\mathrm{pH} = 4.9$ (5 h) was due to the crystal growth of newberyite, the remaining solid phase in the system. At 25°C the transformation process was much slower. The pH in the system gradually increased from 5.2, measured after the precipitate was formed, to 5.4, obtained 5 h later. During this period, the dissolution of struvite was the predominant process, approaching its maximum at the end of the period. These findings suggest a solution mediated transformation process of struvite into newberyite. Further evidence for such a mechanism is provided by the SEM micrographs shown in Fig. 7. These illustrate typical crystals at the times indicated. In Fig. 7a, corresponding to the process conducted at 37°C, struvite and newberyite crystals are seen. The struvite crystals become smaller and the corners become rounded. New newberyite crystals start to grow on the surface of the dissolving struvite crystals. Similarly, the

Fig. 7 Scanning electron micrographs of the samples corresponding to the transformation processes in Fig. 6 at: 37°C (**a** 1 min, **b** 20 min, **c** 60 min) and 25°C (**d** 1 min, **e** 60 min, **f** 300 min)



transformation of struvite crystals in the process conducted at 25°C is shown in Fig. 7b. Again, the pronounced rounding of the struvite crystals and decrease in size are typical of crystal dissolution, only that the process is much slower.

Our work has demonstrated that at 37°C, within a narrow range of the initial equimolar concentrations of magnesium, phosphate and ammonium similar to those found in urine, both struvite and newberyite could precipitate simultaneously. The stability of such a mixture depends on the pH of the system. At $\mathrm{pH} < 6.0$, newberyite is the stable form, so that struvite readily transforms into newberyite. Thus the possibility exists that under certain conditions struvite and newberyite can coexist in urine as well as calculi. This should to be tested in further investigations.

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