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The Mechanism of Precipitation of Biological Minerals. The Phosphates, Oxalates and Carbonates of Calcium*

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The precipitation of the phosphates, oxalates, and carbonates of calcium is complicated by the possible formation of different precursor phases involving polymorphs, hydrates, and acid salts. In order to elucidate the mechanisms of the reactions, it is necessary to study the kinetics under conditions of controlled supersaturation calculated from the activities of free ionic species. In general, the rates of formation of the salts are proportional to the (supersaturation)^n, where n = 1.25—2.0 suggesting a surface controlled process. However, in the case of the calcium phosphate phases, the precipitation of the thermodynamically most stable hydroxyapatite is often complicated by the formation of precursor phases which form and subsequently dissolve during the overall reactions. The sensitivity of the various solid phases to the presence of crystal growth inhibitors is markedly different. Thus in the case of calcium carbonate, it is possible to selectively inhibit calcite and aragonite by adding traces of phosphonate inhibitor, thereby encouraging the formation of vaterite, the most thermodynamically unstable phase. Such selective inhibition may explain the existence of thermodynamically unstable phases in biological systems.

INTRODUCTION

Minerals containing calcium ion are almost ubiquitous in biological systems and an understanding of the formation and dissolution of these phases offers a considerable challenge for the physical chemist. The precipitation of calcium salts is involved in vital problems dealing with normal mineralization such as the formation of bone and tooth and pathological processes such as bone disease, carious lesions, and stone formation in the kidney and pancreas. Pathological mineral deposits such as those which occur in dental calculus, bursitis, and arthritis and various other forms of ectopic calcification involve apatitic-like materials. Calcium carbonate may either be involved as a major mineral phase in pathological stone deposits or, together with calcium phosphate, in carbonate apatites. In urolothiasis, or renal stone formation, it is now generally accepted that urine is ordinarily supersaturated with respect to calcium oxalate

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hydrates.[1] Renal stones may result from the failure of natural inhibitors which, in normal subjects, prevent the formation of crystalluria.

Elucidation of the mechanism of the precipitation processes is complicated by the difficulty of defining the degree of supersaturation in biological systems due to uncertainties in the nature and stabilities of the possible metal complexes which can be formed. Although the number of mineral phases which is involved is relatively small, many of these salts can precipitate as different phases and polymorphs. In addition, mixed crystal formation may take place through the poisoning of one phase by organic constituents and the renucleation of the second phase on the surface.[2] Although it is not possible at the present time to confirm unequivocally true epitaxial growth of these mixed phases, the presence of the substrate allows nucleation and growth of the new phase at supersaturations considerably lower than those required for homogeneous precipitation. The production of solid phases in the biological fluids such as serum, saliva, and urine, must be mediated by factors, familiar to the physical chemist, which control the formation of the nuclei and their subsequent crystallization.

Many of the kinetic studies which have been concerned with the formation of solid mineral phases in solution have involved conditions which are considerably more supersaturated than those typical of in vivo solutions. Thus in the case of calcium phosphates at least five different phases may form, in order of increasing solubility: hydroxyapatite ($Ca_5(PO_4)_3OH$; HAP), tricalcium phosphate ($Ca_3(PO_4)_2$; TCP), octacalcium phosphate ($Ca_4H(PO_4)_3 \cdot 2.5H_2O$; OCP) and dicalcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$; DCPD). Although HAP is the most stable phase under physiological conditions, it becomes less stable than DCPD if the solution is sufficiently acid. Surfaces may then be covered by a more acidic calcium phosphate phase and the apparent solubility will be quite different from that of HAP. These phase changes have probably been the source of the widely discrepant data in the literature for the solubilities of calcium phosphate phases. In order to calculate to the degree of supersaturation ,it is necessary to take into account ion-pair and complex formation. These corrections may be substantial in the case of solid phases such as HAP. During the precipitation, precursor phases are involved which may form and subsequently dissolve during the reactions and it is now well established that kinetic factors may be considerably more important in determining the nature of the solid phases present than are considerations based solely on equilibrium data.

In this paper, recent work on the kinetics of crystallization of calcium phosphates, oxalate, and carbonate, will be discussed. The techniques used have involved seeded systems which, in general, avoid problems introduced by chance nucleation in studies of spontaneous precipitation. The use of such seeded systems, may be much more appropriate for modelling biological mineralization since in these systems, crystallization usually takes place in the presence of existing solid phases.

The first detailed models for crystal growth recognize the non-equivalence of sites on the crystal surface and propose the formation of monomolecular layers in a layer-by-layer growth mechanism. Initiation of a layer by two dimensional nucleation has a particularly unfavourable energy requirement

with a stepwise energy barrier as each layer is completed. This requires the formation of new two dimensional nuclei for the continuation of crystallization. Such a model is not supported by experiments since crystals grow at supersaturations much lower than that required for two dimensional surface nucleation. Since the increase in rate of nucleation with increase in concentration is much greater than that for crystal growth, if the formation of a surface nucleus is rapid, a new layer may start before the development of the underlying layer is complete. Thus several nuclei may intergrow in each layer and this multiplicity leads to polynuclear or birth and spread growth models.[3,4]

In the classical work of Frank and his co-workers,[5,6] the formation of growth spirals on the crystal surface was postulated. These workers pointed out that real crystals are imperfect and that the growth of singular faces intersected by screw dislocations was quite different from that of perfect faces. The screw dislocations give rise to steps on the crystal surface and as crystallization takes place at the energetically preferential sites offered by the ledges, growth spirals develop on the crystal surface. These spirals provide perpetual steps for crystallization and avoids the necessity for twodimensional nucleation. This model therefore is capable of explaining why crystals grow at very low supersaturation. Dehydration or partial dehydration must also take place during the crystallization reaction.

If bulk diffusion of material up to the crystal surface were rate determining, the crystallization rate would be linearly proportional to the supersaturation. There is now considerable evidence for numerous sparingly soluble electrolytes but this model does not explain the experimental results. Activation energies for crystal growth are normally considerably higher than those to be expected for simple bulk diffusion and, in addition, the rates of crystallization are normally little affected by changes in fluid dynamics at the crystal surface. For many sparingly soluble inorganic minerals, a surface controlled deposition rate is much more likely and in general, for salts of the type $M_a X_b$, the rate of crystallization is given by equation 1:

$$\text{Rate} = d(M_a X_b)/dt = -k_g s K_{so}^{n/\nu} \sigma^n \qquad (1)$$

In equation 1, k_g is the rate constant for surface controlled crystallization, K_{so} is the solubility product, $(a + b) = \nu$, and $\sigma = ([M^{m+}]^a [X^{x-}]^b]^{1/\nu} - K_{so}^{1/\nu})/K_{so}^{1/\nu}$. In these equations, the parenthesis enclose either concentrations or activities of the lattice ions and s is a function of the surface area of the crystals. For calcium oxalate monohydrate, calcite and DCPD, the rate of crystallization follows a parabolic dependence upon supersaturation with a value of the effective order of the reaction in equation 1, $n = 2$. This is consistent with a screw dislocation crystallization model and can also be interpreted in terms of a rate determining step involving the dehydration of calcium ions at the crystal surface.[7] For cases where the growth varies more strongly with supersaturation (eg. OCP with $n > 2$ in equation 1), a polynucleur mechanism may be postulated. It is clearly important to establish not only the dependence of the rate of crystal growth upon supersaturation but also the influence of solid/solution ratio, stirring dynamics, and temperature. For surface controlled processes, the activation energy would be typically ~ 40 kJ mol^{-1} as compared with an expected ~ 12 kJ mol^{-1} for bulk transport control.

METHODS

In conventional crystallization experiments, metastable supersaturated solutions are inoculated with seed crystals and the rate of reaction is determined by measuring the decrease in concentration of lattice ions as a function of time. In terms of the Ostwald-Lussac Law of Stages,[8] the phase with the highest solubility forms preferentially during sequential precipitation as the lattice ion concentrations are allowed to decrease. In these experiments, therefore, different phases may form and redissolve during the overall reaction. Moreover, as the process approaches equilibrium, the changes in lattice ion concentrations are too small to allow reliable estimates of either the stoichiometries or rates of the solid phases formed. These problems have been overcome by using a technique in which the precipitation is studied under conditions of constant activities of ionic species. Following the addition of seed crystals to metastable supersaturated solutions of the mineral phase, the activities of the crystal lattice ions are maintained constant by the simultaneous addition of titrant solutions from mechanically coupled burettes. The titrant addition is controlled by specific ion electrodes which for calcium phosphate and carbonate systems can be either hydrogen ion-glass or specific calcium electrodes and for calcium oxalate, the calcium specific ion eletrode.

The constant composition method allows studies of crystallization to be made at very low supersaturation, thus excluding the possibility of forming precursor phases. This is particularly important in the case of calcium phosphate at physiological pH. At supersaturations similar to those in vivo, macroscopic quantities of stoichiometric highly crystalline HAP can be formed without participation by other calcium phosphate precursor phases. During the crystallization reactions, the developing solid phases are investigated by X-ray, infrared, specific surface area, optical microscopy, scanning electron microscopy, particle size distribution analysis and other methods to relate the observed rates to changes in the solid phases. The excellent reproducibility of the seeded growth constant composition method enables investigations to be made not only of the mechanism of mineralization but also the influence of synthetic and natural inhibitors upon the rate of reaction.

CALCIUM PHOSPHATE MINERALIZATION

It is now well established that in the precipitation of calcium phosphates from solutions supersaturated with respect to all phases, the stoichiometric calcium/phosphate molar ratio of the initially precipitated phase does not correspond to the required value of 1.67 for the thermodynamically favoured HAP. A frequently observed ratio of 1.45 ± 0.05 was attributed to the formation of an amorphous phase with stoichiometry corresponding to that of TCP with autocatalytic transformation to HAP.[9] Both DCPD[10] and OCP[11] have also been proposed as precursors to HAP formation. Typical solubility isotherms for the calcium phosphate phases at 37° C in the system $Ca(OH)_2$—H_3PO_4—KNO_3—H_2O are shown in Figure 1 in which $log\,(T_{Ca}\,T_p)$ is plotted as a function of pH. T_{Ca} and T_p are the molar calcium and phosphate concentrations respectively. It is important to note that the positions of the curves and singular points in Figure 1 will change if the ionic strength of the background electrolyte is varied. It can be seen that although HAP is the most stable phase under many conditions it becomes less stable than DCPD if the solution is sufficiently acid. A calcium phosphate phase exposed to a solution more acid than the corresponding singular point may therefore be expected to be covered by a surface coating of a more acid phase. The apparent solubility behaviour will then be quite different from that of the original phase. At physiological pH, the precipitation process would be expected to be initiated with the formation of DCPD with subsequent transformations through OCP to HAP. The formation of TCP in precipitation reactions at ambient temperatures has never been convincingly demonstrated. The overall precipitation of calcium phosphates,

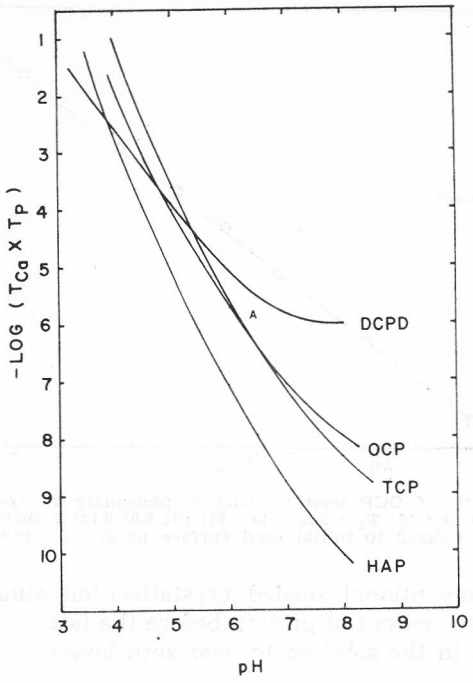

Figure 1. Solubility isotherms for calcium phosphates at 37 °C. Calculated at $I = 0.15$ M.

may therefore be interpreted in terms of the formation of a precursor phase followed by partial or complete transformation to HAP depending upon the rate of reaction.[12,13]

One of the problems is using isotherms such as those shown in Figure 1 is the necessity for establishing that the systems are at equilibrium in order to be able to use the thermodynamic solubility products which refer to the free energy of single solid phases. There is now little doubt that kinetic factors may be considerably more important in determining the nature of the solid phase present than are considerations based solely upon equilibrium solubility data. Thus, recently, the constant composition method has been used to demonstrate the exclusive formation of OCP, in supersaturated solutions ranging in pH from 6.0 to 7.0 and corresponding to the region of supersaturation, *A*, in Figure 1. The method may be used to grow relatively large quantities of pure OCP and the use of this material as seed, when added to supersaturated solutions of calcium phosphate results in the typical plot[14] of titrant volume as a function of time shown in Figure 2. It can be seen that following the addition of seed crystals at time 0, the rate of crystallization of OCP is linear for long periods of time. Experiments as a function of supersaturation indicate an effective order of reaction in Equation 1, $n = 4$, suggesting a polynuclear crystallization mechanism. In contrast, the crystallization of well characterized seed crystals of DCPD and HAP is best represented by a surface controlled dislocation mechanism[13,15] with $n = 1.25$—2.0 in Equation 1. An important advantage of the constant composition method is the possibility of pre-growing crystals to achieve lattice perfection prior to use as seed in crystallization

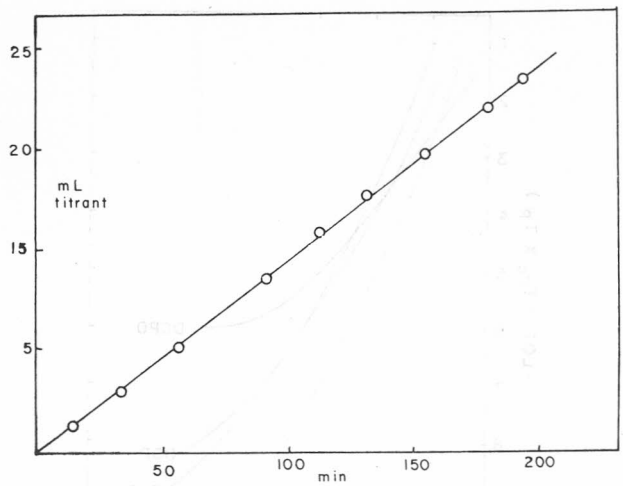

Figure 2. Crystal growth of OCP seed in calcium phosphate supersaturated solution (region A, Figure 2, $T_{Ca} = 4.38 \times 10^{-3}$ M; $T_p = 3.28 \times 10^{-3}$ M; pH 6.0; 0.102 g OCP seed L^{-1}). Plot of titrant volume (normalized to initial seed surface area) as a function of time.

experiments. In conventional seeded crystallization studies, it is impossible to achieve a sufficient extent of growth before the lattice concentrations reduce the supersaturation in the solution to near zero levels.

CALCIUM OXALATE MINERALIZATION

The mineralization of calcium oxalate, which is found in more than two--thirds of human urinary stones[16-18] is complicated by the existence of three hydrates. Whewellite (calcium oxalate monohydrate (COM) and weddelite (calcium oxalate dihydrate, COD) are the two major crystalline forms in urinary calculi.[19,20] In aqueous solution, three hydrates can be precipitated: the thermodynamically stable COM, metastable COD, and COT, a tri-hydrate. In the absence of other ions, the only precipitated crystal forms obtained by mixing solutions containing calcium and oxalate ions are COM and COT. In urines, however, it is interesting to note that the results of several studies point to the formation of COD after long periods of time even though COM is the thermodynamically stable form.[20-22] The reason for the co-existence of COD in urinary stones is still not fully understood.

Highly reproducible kinetic studies have been made[23,24] of the dissolution of the calcium oxalate hydrates over a range of temperature, 15—50 °C and ionic medium 0—0.3 M. Dissolution is controlled by the mass transport of calcium and oxalate ions away from the crystal surface and the rate of reaction is proportional to the relative undersaturation. The first order rate constants, k_d fall in the sequence k_d (COT) $>$ k_d (COD) $>$ k_d (COM). Additional evidence for diffusion controlled transport during the dissolution reactions is provided by activation energies of 12—17 kJ mol^{-1}. A constant composition dissolution study of COM was made as a function of concentration, temperature, fluid dynamics, and in the presence of crystallization inhibitors. A striking change in the mechanism dissolution was observed as the undersaturation was reduced. At high undersaturations, the firstorder dependence of rate on the under-

saturation, pointed to a normal diffusion controlled reaction. At very low undersaturations, however, the effective order of reaction appeared to approach the value, $n = 2$, in Equation 1, suggesting a surface controlled process. Moreover, the two regions of undersaturation showed markedly different dependencies on changes in temperature, hydrodynamics, and upon the addition of adsorbing molecules. The dislocation theory of Burton, Cabrera, and Frank[6] predicts a change in reaction order from $n = 1$ to $n = 2$ as the undersaturation decreases. The constant composition studies for COM represent the first indication of such a change in reaction order for the dissolution of a sparingly soluble electrolyte.[25]

Constant composition experiments of the seeded growth of COM are illustrated by the plot of titrant volume as a function of time in Figure 3. The

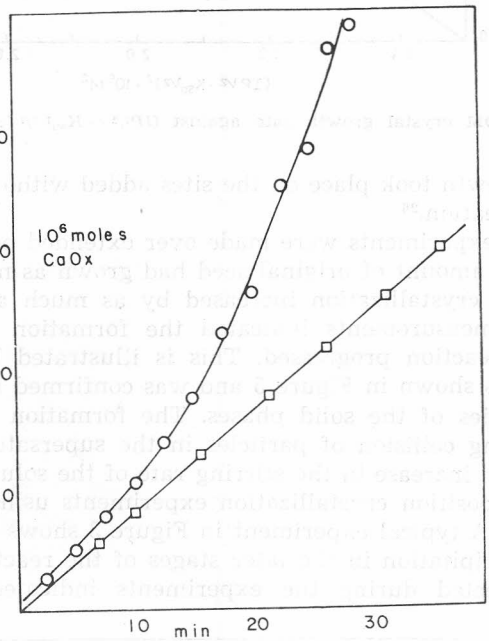

Figure 3. Plots of CaOx crystallized as a function of time .○, COT, $T_{Ca} = T_{Ox} = 5.98 \times 10^{-4}$ M, 0.15 M NaCl, 37 °C, 0.105 g COT seed L^{-1}. □, COM, $T_{Ca} = T_{Ox} = 4.607 \times 10^{-4}$ M, 0.15 M NaCl, 37 °C, 0.024 g COM seed L^{-1}.

titrant solutions consisted of calcium chloride and sodium oxalate and were added at a rate, controlled by a specific calcium electrode, such as to replace the calcium and oxalate ions removed during the precipitation reaction. The linearity of the plot for COM in Figure 3 is striking.[26] Over large extents of reaction (up to three times the amount of original seed used to inoculate the supersaturated solution) simple correction for increase in the surface area of the growing crystals was made by applying a factor $(w_i/w_t)^{2/3}$ to the measured rate of reaction. w_i and w_t are the masses of crystals present initially and at time t, respectively. In Figure 4, the rate of COM crystallization is plotted against $K_{so}\sigma^2$. It can be seen that the crystallization reaction follows Equation 1 over a wide range of supersaturation with $n = 2$. Moreover, the rate of reaction was proportional to the amount of seed used to inoculate the crystallization

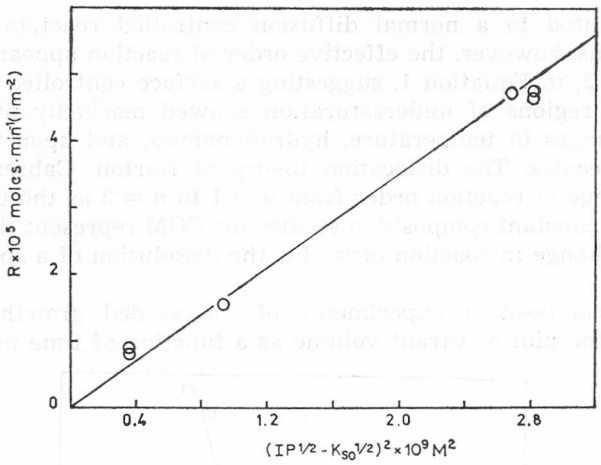

Figure 4. Plots of COM crystal growth rate against $(IP^{1/2} - K_{so}^{1/2})^2$ ($\equiv (K_{so}\,\sigma^2$ in equation 1).

indicating that growth took place on the sites added without complications due to secondary nucleation.[26]

A number of experiments were made over extended periods until as much as eight times the amount of original seed had grown as new phase.[26] In these cases, the rate of crystallization increased by as much as 30% and particle size distribution measurements indicated the formation of additional small particles as the reaction progressed. This is illustrated by the particle size distribution curves shown in Figure 5 and was confirmed by scanning electron micrographic studies of the solid phases. The formation of secondary nuclei was induced during collision of particles in the supersaturated solutions and was increased with increase in the stirring rate of the solution.

Constant composition crystallization experiments using COT seed crystals were also made.[26] A typical experiment in Figure 3 shows the marked increase in the rate of precipitation in the later stages of the reaction. Analysis of the solid phases collected during the experiments indicated the formation of

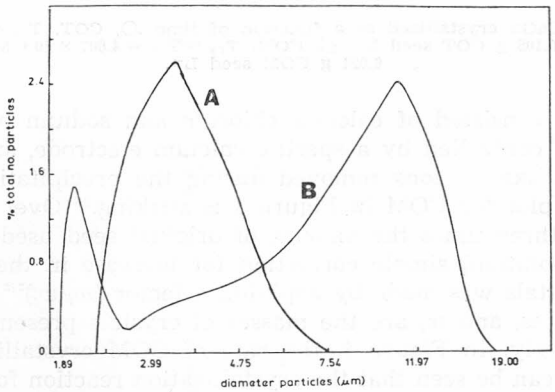

Figure 5. Particle size distribution during the crystallization of COM in 0.15 M NaCl. Curce *A*, COM seed crystals; curve *B*, after 32 min of reaction under concentration conditions given in Figure 3.

COM as the rate of crystallization increased. Scanning electron micrographs confirmed the presence of small crystallites with characteristic COM morphology along with the growing COT crystals. The formation of these smaller particles was also reflected by particle size distribution measurements.[26] Thus during the crystallization of COT, the greater thermodynamic driving force for the formation of the least soluble COM resulted in the nucleation of this phase. The transformation reactions of COD and COT to COM were also studied by conventional crystallization experiments.[24] It was shown that the transformation process was considerably more rapid for COT, being especially sensitive to temperature, ionic strength, and ionic medium composition. The transformation appeared to proceed through dissolution and subsequent surface or secondary nucleation of the new phase and was markedly influenced by the presence of traces of crystal growth inhibitors such as polyphosphate, phytate, pyrophosphate, and whole urine. Thus results of investigations of the extent of adsorption of linear polyphosphate showed that the three hydrates differed markedly in their surface adsorbability, falling in the sequence COM $>$ COD $>$ COT. This may, in part, explain the observed stabilization of metastable hydrates in biological systems since the formation of stable COM is readily inhibited by the greater surface adsorption of protein and other molecules. There is now increasing evidence that the mechanism of dissolution of the hydrates appears to become surface controlled with a rate proportional to the square of the relative supersaturation in the presence of typical inhibitors such as polyphosphate.[24]

CALCIUM CARBONATE MINERALIZATION

It is now quite well established that the mineralization of calcium carbonate also involves the formation of precursor phases which may subsequently dissolve during the reprecipitation of thermodynamically more stable phases. The homogeneously nucleated calcium carbonate particles are thought to consist of amorphous hydrates which are visible for a few minutes and gradually dissolve and grow on heteronucleated crystals. Following the inoculation of metastable supersaturated solutions of calcium carbonate with calcite seed crystals, the rate plots of titrant volume as a function of time are strikingly linear when the data are corrected for changes in surface area of the crystals during growth. A typical kinetic plot of the rate of crystallization as a function of the square of the supersaturation is shown in Figure 6 confirming a proportionality to the square of the supersaturation, σ^2. Constant composition crystallization experiments with calcite seed have been made over a range of molar ionic calcium/carbonate ratios ranging from 14 to 134, and of σ by factors of 40x and 5x, respectively.[27] Despite these wide variations, the value of k_g in Equation 1 was constant to within $\pm 12\%$ when the supersaturation was expressed in terms of the activities of the free calcium and carbonate ionic species. The constancy of the rate of crystallization during the experiments again suggests a deposition of solid phase at a relatively small number of dislocations on the crystal surfaces. The results are in conformity with those expected on the basis of the Burton, Cabrera, Frank growth model.[5,6]

Crystallization experiments of calcite and the less stable aragonite and vaterite phases in the presence of hydroxyethylidene 1—1 diphosphonic acid, HEDP, were particularly interesting. Concentrations as low as 10^{-7} M of this

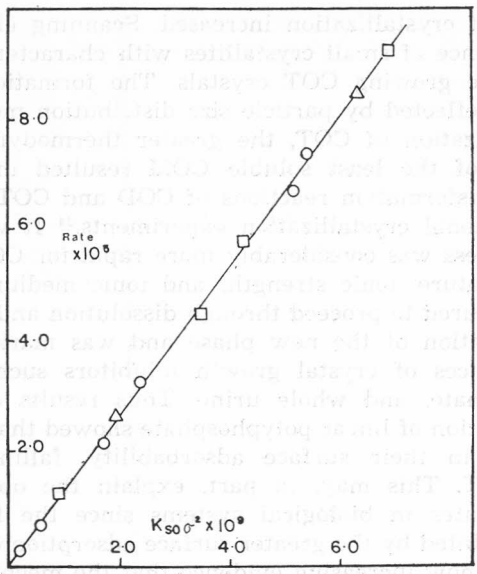

Figure 6. Calcite crystallization rate plotted against $K_{so}\,\sigma^2$ (eqn. 1). $T_{Ca} = 2.49 \times 10^{-3}$ *M*, $T_{carbonate} = 0.975 \times 10^{-3}$ M, pH 9.38, 0.056 g seed L^{-1}, 25 °C.

additive markedly inhibited the seeded crystal growth of calcite and aragonite. This is shown by the results of typical conventional crystallization experiments in Figure 7 in which the concentration of calcium ion remaining in solution following inoculation with seed crystals is plotted as a function of time.[28] In contrast, the influence of HEDP on the crystallization of the least thermodynamically stable phase, vaterite, was considerably less; a concentration level of 2.7×10^{-6} M had little effect on the rate of crystallization. These observations suggest a reason for the stabilization thermodynamically unstable

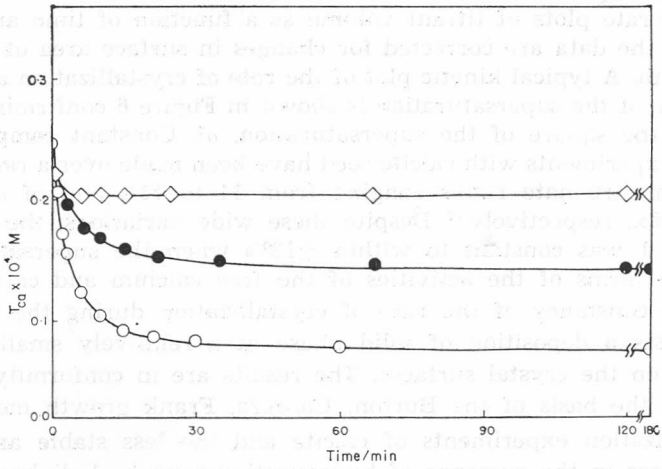

Figure 7. The influence of HEDP (7.0×10^{-8} M) on the seeded growth of: ●, aragonite and ◇, calcite. Curve ○ corresponds to the inhibitor-free crystallization.

phases in a number of natural calcium carbonate precipitation processes since the more thermodynamically stable phases were poisoned by traces of impurities. Thus the addition of vaterite seed crystals to supersaturated solutions of calcium carbonate at 70 °C containing HEDP were shown to proceed with the exclusive formation of vaterite despite the fact that this was the most thermodynamically unstable polymorph. By inhibiting the formation of aragonite and calcite, the crystallization of vaterite was favoured and at 70 °C, the reaction took place with a rate which was appreciably greater than that of either calcite or aragonite. It is clear that the nature of the phase which forms may be dependent upon the seed substrate which is added to the solution and also the possible presence of traces of growth inihibitors which may selectively prevent the precipitation of some calcium carbonate polymorphs and influence the factors governing their interconversion. It is interesting to note that calcium ions in the case of calcium phosphate crystallization, and phosphate ions for calcium carbonate crystallization, effectively retard the rates of the corresponding crystallization reactions.

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SAŽETAK

Mehanizam taloženja bioloških minerala. Fosfati, oksalati i karbonati kalcija

G. H. Nancollas

Tijekom taloženja fosfata, oksalata i karbonata kalcija moguće je stvaranje raznih prekursora kao što su polimorfi, hidrati i kisele soli. Da bi se objasnili mehanizmi tih reakcija, potrebno je proučavati njihovu kinetiku u uvjetima kontroliranog prezasićenja koje se računa s pomoću aktiviteta slobodnih ionskih specija. Općenito, brzine stvaranje tih soli proporcionalne su (prezasićenosti)^n gdje je $1{,}25 \leq n \leq 2{,}0$ što upućuje na proces rasta kontroliran reakcijom na površini kristala. U slučaju taloženja kalcij-fosfata taloženju termodinamički najstabilnije faze, hidroksiapatita, često prethodi taloženje prekursora, koji se stvaraju i otapaju tijekom cjelokupne reakcije. Osjetljivost različitih čvrstih faza na prisutnost inhibitora kristalnog rasta bitno je različita. Tako npr. u slučaju kalcij-karbonata moguće je selektivno inhibirati kalcit i aragonit dodatkom tragova fosfonata. Na taj se način potiče taloženje termodinamički najnestabilnije faze, vaterita. Ovakva selektivna inhibicija može objasniti postojanje termodinamički nestabilnih faza u biološkim sistemima.