Crystallographic Studies of Calcium and Strontium Hydroxyapatites

CURT LAGERGREN and DIEGO CARLSTRÖM

Department of Medical Physics, Karolinska Institutet, Stockholm, Sweden

From X-ray crystallographic investigations on apatites in the system $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ — $\text{Sr}_{10}(\text{PO}_4)_6(\text{OH})_2$ it was found that no solid solutions could be formed in the region $\text{Ca}_2\text{Sr}_8(\text{PO}_4)_6(\text{OH})_2$ to $\text{Ca}_7\text{Sr}_3(\text{PO}_4)_6(\text{OH})_2$. The mixed apatite $\text{Ca}_8\text{Sr}_2(\text{PO}_4)_6(\text{OH})_2$, however, was shown to have a very well ordered lattice. In the light of these experimental findings, it is concluded that strontium ions in the inorganic crystalline phase of bone are probably bound rather firmly to the surface of the extremely small apatite crystallites.

The localization and metabolic control of many trace elements by the skeleton has been known for a number of years. Recently, the number of cationic radioactive emitters found to be preferentially incorporated in bone has increased and of these, strontium, because it has many atomic characteristics and chemical properties similar to calcium and is probably metabolized and incorporated in the same fashion, has received particular attention ^{4,5,15}.

This study was undertaken in order to determine the manner in which strontium is incorporated into the inorganic crystal phase of bone. Although the exact molecular structure of the inorganic bone crystals has not been definitely agreed on by workers in the field, there is general agreement that it differs but little from calcium hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$). In the apatite structure several isomorphic substitutions are known to occur and in some cases a continuous series of solid solutions have been demonstrated to exist. For example the mixed apatites in the system $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ — $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$ — $\text{Ca}_{10}(\text{PO}_4)_6\text{Cl}_2$ have been thoroughly investigated by means of X-ray diffraction ^{16,17} and the calcium-lead-hydroxyapatites have also been shown to form solid solutions ¹⁰. However, relatively little is known about the strontium apatites. Pure strontium hydroxyapatite ($\text{Sr}_{10}(\text{PO}_4)_6(\text{OH})_2$) has been synthesized in several ways ^{8,12} and natural mineral fluorapatite containing less amounts of strontium has been described ⁹, but investigations have not been carried out on the mixed calcium-strontium apatites.

There are three possible ways by which the Sr ion could be incorporated into the inorganic crystalline structure of bone. Because of the extremely

small size (approx. $220 \text{ \AA} \times 50 \text{ \AA}$) of the Ca apatite crystallites in bone^{3,6}, there is consequently a large surface area available to which the Sr ion could be bound. This mode of incorporation has been shown to exist for many other ions. Sr could also be incorporated as part of the apatite lattice as an isomorphic substitution for calcium, or a combination of both isomorphic substitution and surface binding could occur.

Because Sr^{++} has a larger ionic radius than Ca^{++} (1.13 versus 0.99 Å) isomorphic substitution of Sr^{++} for Ca^{++} will result in an enlargement of the unit cell dimensions. This difference in the lengths of the axes of the unit cell can be detected by X-ray diffraction and it should therefore be possible to correlate the degree of expansion of the lattice with the amount of isomorphic substitution of Sr^{++} for Ca^{++} that occurs.

EXPERIMENTAL

Material. Pure calcium and strontium hydroxyapatites, (in the following abbreviated to CaHA and SrHA) were synthesized in aqueous solutions at a pH of about 9 by adding a dilute solution of Na_2HPO_4 to solutions of Ca and Sr nitrate. The precipitates formed were thoroughly washed with water and samples were heated at 900°C for 2 h after which crystallographic homogeneity was determined by X-ray diffraction. No diffraction lines other than those of pure apatite could be detected. In addition, as a control, a commercial strontium phosphate was similarly heated and this sample showed almost pure SrHA containing only small amounts of $\text{Sr}_3(\text{PO}_4)_2$. Since it was not found possible to synthesize the desired mixed apatites in aqueous solutions, these mixed apatites were made in the solid state. Several different methods were tried but the most satisfactory results were obtained by heating mixtures of the respective apatites to high temperatures. After the non-constituent water of the pure CaHA and SrHA were accurately determined a series of mixtures with known mole fractions of Ca and Sr were prepared and these mixtures were heated for 4 h at $1300^\circ \pm 15^\circ\text{C}$. It was found that at lower temperatures and/or shorter durations the reactions did not proceed to completion and that the original apatites could occasionally be detected by X-ray diffraction.

Methods. A Philips diffractometer unit with nickel-filtered copper radiation was used. In order to get the highest possible precision and to avoid errors depending on the varying absorption in the specimens, a standard substance (silicon) with an accurately known lattice constant ($a = 5.4306 \text{ \AA}$) was mixed with all samples. As it was evident that several of the solid solutions gave badly defined diffraction lines only the strongest reflections could be used for measurements. However, as the $(00 \cdot 4)$ — reflection was superimposed on the $(40 \cdot 2 - 04 \cdot 2)$ -reflection when the specimens contained large amounts of strontium the c-axis could not be determined with sufficient accuracy in all cases and it was therefore decided to determine only the a-axis by measuring the $(14 \cdot 0 - 41 \cdot 0)$ -line. For the pure CaHA and SrHA which gave well defined diffraction patterns it was possible to determine both axes with high precision by measuring reflections in the region $60^\circ - 70^\circ \theta$.

RESULTS

The lattice constants for pure CaHA and SrHA were found to have the following values:

$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$	$a = 9.42_3 \text{ \AA}$	$c = 6.88_4 \text{ \AA}$	$c/a = 0.7306$
$\text{Sr}_{10}(\text{PO}_4)_6(\text{OH})_2$	$a = 9.76_1 \text{ \AA}$	$c = 7.27_7 \text{ \AA}$	$c/a = 0.7455$

The axes dimensions of CaHA are in very good agreement with earlier published precision measurements^{1,3,11,13} whereas those for SrHA showed a much larger deviation from the only other measurements in the literature

Fig. 1. Graph showing the relationship between the length of the a -axis and the degree of substitution in mixed Ca-Sr-hydroxyapatites.

($a = 9.74$; $c = 7.20$ kX) ⁸. The change in the c/a ratio causes the general appearance of the diffraction pattern of SrHA to differ considerably from that of CaHA.

The diffraction patterns of the mixed Ca-Sr-HA were of a varying character. The diffraction lines showed a noticeable broadening when one Sr^{++} was introduced in the CaHA-unit cell, and with two Sr^{++} ions in the lattice the reflections were almost impossible to measure. The solid solutions, $\text{Ca}_7\text{Sr}_3\text{HA}$ and $\text{Ca}_6\text{Sr}_4\text{HA}$, gave no recognizable patterns at all. On the other hand the compound $\text{Ca}_5\text{Sr}_5\text{HA}$ appeared to have an almost perfect lattice and the diffraction lines were as well defined as in the pure Ca or SrHA. The next member in the series, $\text{Ca}_4\text{Sr}_6\text{HA}$, again gave an extremely bad diffraction pattern without identifiable reflections. With increasing amounts of Sr in the lattice the diffraction patterns became better and better and that of $\text{Ca}_1\text{Sr}_9\text{HA}$ was almost as good as that of pure SrHA. The lengths of the a -axis for the mixed apatites in the Ca-SrHA-system have been plotted in Fig. 1. In order to compare the pure members (CaHA, SrHA) with the mixed ones in this series under comparable conditions, pure CaHA, and SrHA were also heated to 1 300°C. This resulted in a decrease of the a -axis of 0.02 Å. In order to find at what temperature ranges this effect occurred, 6 different samples of CaHA were heated for 4 h at temperatures between 900° and 1 300°C. The result is shown in Fig. 2.

DISCUSSION AND CONCLUSIONS

From Fig. 1 it is evident that the alteration in the a -axis dimension is directly proportional to the degree of substitution as long as the amount of substitution is low. The well crystallized apatite, $\text{Ca}_5\text{Sr}_5\text{HA}$, also shows an

a-axis dimension midway between the pure CaHA and pure SrHA. However, the *a*-axis dimension of the strontium apatites deviates more and more from the straight line as their content of calcium increases and the *a*-axis of $\text{Ca}_3\text{Sr}_7\text{HA}$ corresponds in reality to the one expected for $\text{Ca}_2\text{Sr}_8\text{HA}$. Since, as already has been pointed out, the diffraction patterns of these compounds were very poorly defined, it was impossible to measure the position of the reflections with accuracy, or to judge whether these solid solutions were pure, or if they were instead made up of several badly crystallized products. Thus, it seems most possible that the apatite which is indicated in the diagram in the position of $\text{Ca}_3\text{Sr}_7\text{HA}$ was not formed during the heating but rather it was mainly composed of the solid solution $\text{Ca}_2\text{Sr}_8\text{HA}$. With the exception of the intermediate apatite $\text{Ca}_5\text{Sr}_5\text{HA}$, it is evident that only about two Sr ions or two Ca ions can be forced into the respective CaHA and SrHA lattices without a total collapse of the structure. But even at this moderate degree of substitution the lattice is badly distorted and evidently no solid solutions can be formed in the range $\text{Ca}_3\text{Sr}_7\text{HA}$ to $\text{Ca}_7\text{Sr}_3\text{HA}$. This conclusion was very surprising in the light of the statement¹⁰ that a continuous series of solid solutions could be formed in the system $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2\text{—Pb}_{10}(\text{PO}_4)_6(\text{OH})_2$, as it seemed by all means that Sr^{++} should be easier to introduce into the lattice than the larger Pb^{++} . However, on careful examination of the paper by Müller¹⁰ on the calcium-lead apatites, it appears that he did not synthesize or investigate the solid solutions between $\text{Ca}_7\text{Pb}_3\text{HA}$ and $\text{Ca}_2\text{Pb}_8\text{HA}$ with exception of the intermediate apatite $\text{Ca}_5\text{Pb}_5\text{HA}$. From this work it is also evident that in spite of heat treatment $\text{Ca}_7\text{Pb}_3\text{HA}$ was so badly crystallized that only the strongest reflections in the X-ray diffraction pattern could be measured. For these reasons it seems most likely that the conclusions reached above regarding the Ca—Sr apatites also apply to the Ca—Pb apatites, and that both Sr^{++} and Pb^{++} deviate too much in size from Ca^{++} to be able to form continuous series of solid solutions. It is interesting to note that the intermediate $\text{Ca}_5\text{Sr}_5\text{HA}$ and $\text{Ca}_5\text{Pb}_5\text{HA}$ both exist, and apparently these mixed, apatites are not solid solutions but have a more or less ordered structure possibly forming a superlattice.

The contraction of the *a*-axis of CaHA at temperatures above 1 000°C (see Fig. 2) has not been described before. It has long been known that a total loss of the constitutional water of CaHA is inconsistent with the apatite structure and that a pure oxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{O}_2$) does not exist, but it has been shown² that a partial loss of the water can occur without the destruction of the apatite lattice. As no special efforts were made to measure the loss of water or to work in an absolutely water-free atmosphere (CaHA can be synthesized from perfectly dry components in the presence of water vapour even at 1 000°C^{7,14}), no definite explanation can be given to the shrinkage of the *a*-axis, but it seems most reasonable that this phenomenon is due to a partial loss of the constitutional water.

From the work by Müller on Ca-Pb apatites¹⁰ it is clear that the precipitates of mixed apatites which he prepared were very badly crystallized. The same almost noncrystalline state was found in the precipitates of Ca-Sr-apatites. In several cases in which the precipitates were heated in order to increase their crystallinity, additional lines were obtained in the diffraction

Fig. 2. Plot of the change in the a -axis dimension of calcium hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) versus temperature.

patterns, resulting from the presence of triphosphate compounds. For that reason we abandoned the latter method of preparing the mixed apatites. However, as the heating of an apatite precipitate above 500–600°C not only causes a growth of the crystallites but also implies a total reorganization of the lattice, with the introduction into the lattice of ions previously adsorbed to the surface of the crystallites, or even creation of compounds other than those originally present, it is impossible to judge if the badly crystallized original precipitate consisted of one or several phases with or without adsorbed or surface bound ions. Thus, no direct conclusions can be drawn regarding the nature of the precipitates formed in solutions containing both Ca and Sr ions, but it is clear that even small amounts of strontium in a solution containing calcium and phosphate ions considerably inhibits the orderly crystallization of an apatite. This is a further indication that strontium ions do not easily replace Ca^{++} in the CaHA lattice.

It thus appears that because of its size the Sr ion is not well suited for any great amount of isomorphic ion exchange with calcium for positions in the lattice, particularly in the formation of the apatite lattice from dilute solutions comparable to those occurring in the body fluids. We are thus inclined to conclude that Sr^{++} introduced in the body will be bound mainly to the surface of the extremely small apatite crystallites of bone, the surface area of which has been shown to have very great binding properties for ions of various kinds³. The similarity in the metabolism of Ca^{++} and Sr^{++} , demonstrated in experiments with radioactive isotopes, suggests that Sr ions on the surface of the bone crystallites may be as tightly bound as Ca ions in surface positions.

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