3C-Fe_7Se_8 is isostructural with 3C-Fe_7S_8 (Fleet, 1971; Nakano, Tokonami & Morimoto, 1979). The directions of the cation shifts from the ideal positions are almost the same in both cases. However, Se is more polarizable than S and the magnitudes of the shifts of Fe in the Se sublattice are a little larger than those in the S sublattice. The similarity of the two structures suggests that the enantiomorphic pair exists not only in the specimen of 3C-Fe_7Se_8 but also in that of 3C-Fe_7S_8.

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Structure of Disodium Dihydrogen 1-Hydroxyethylidenediphosphonate Tetrahydrate: A Bone Growth Regulator

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Abstract. $2Na^+.C_2H_6O_7P_2^{2-}.4H_2O$, $Na_2H_2[C_2H_4O_7P_2].4H_2O$, $M_r = 322{\cdot}055$, monoclinic, $P2_1/c$, $a = 10{\cdot}598$ (4), $b = 5{\cdot}993$ (2), $c = 18{\cdot}262$ (6) Å, $\beta = 91{\cdot}77$ (1)° [λ(Cu $K\alpha_1$) = 1·54051 Å], $V = 1159{\cdot}34$ Å^3, $Z = 4$, $D_x = 1{\cdot}845$ Mg m^{-3}. The structure was solved with *MULTAN* and refined to $R(F_o) = 0{\cdot}040$ for 1397 reflections measured with Cu $K\alpha$ radiation. The ligand can act as a tridentate and bidentate chelator. When functioning as a tridentate ligand, the hydroxyl group of 1-hydroxyethylidenediphosphonate (hedp) participates in the coordination. A conformation of the ligand that may influence its polydentate nature is the *W* conformation. The *W* conformation has the phosphonate groups eclipsed so that an O—P—C—P—O linkage forms a planar *W*. For the first time, the multifunctional hedp ligand has been observed to exhibit a tridentate capability where three coordination sites on an atom are occupied by a single ligand. The triangular face, which this ligand provides, furnishes an optimal binding geometry for half of the Ca atoms in the ⟨001⟩ surface of calcium hydroxyapatite, the major constituent in bone. Complex formation in this manner establishes a foundation for the chemisorption of hedp onto calcium hydroxyapatite, which is an essential element in the crystal growth inhibition mechanism of hedp.

Introduction. Disodium dihydrogen 1-hydroxyethylidenediphosphonate, Na_2H_2hedp, has demonstrated the ability to inhibit either dissolution or crystal growth of calcium hydroxyapatite, depending upon the concentration of Na_2H_2hedp (King, Francis & Michael, 1971). We have investigated the crystal structure of Na_2H_2hedp.$4H_2O$ (etidronate disodium, USP) in order to understand the interaction between the hedp ligand and calcium hydroxyapatite, the major constituent of bone.

Crystals of Na_2H_2hedp.$4H_2O$ suitable for X-ray analysis were obtained by slow evaporation from aqueous solution. Four solid phases (three crystalline and one amorphous) of Na_2H_2hedp can be prepared and all form the tetrahydrate from water at room temperature. An elongated parallelepiped of dimensions 0·10 × 0·15 × 0·45 mm was chosen for all X-ray investigations. Preliminary data, which were taken from an intensity-weighted plot of reciprocal space, indicated the Laue group to be $P2/m$ and the systematic absences to be consistent with the uniquely defined space group $P2_1/c$ (No. 14).

Cell dimensions were obtained from least-squares refinement of three instrument angles of 15 general reflections with $85° < 2\theta < 110°$. All X-ray data were measured with Cu $K\alpha$ (1·54178 Å) radiation employ-

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ing a $P2_1$ Syntex four-circle diffractometer that was equipped with a graphite monochromator (2θ = 26·57°) at $T \sim 295$ K.

Three-dimensional intensity data were collected by the θ–2θ techniques; these procedures have been described previously (Barnett, Hartman & Kretschmar, 1977). In order to monitor the stability of the crystal during data collection, the intensities of three reflections (300, 020 and 008) were measured periodically: only a random fluctuation of less than 4% was observed. Lorentz and polarization corrections were made in reducing the intensities to structure factor amplitudes, but no absorption correction was applied (μ = 4·65 mm^{-1}). Of the 1456 independent reflections measured, 1397 (97%) were greater than $2\sigma(I)$ and were included in the structure solution and refinement.

The phase determination was accomplished by direct methods (Germain, Main & Woolfson, 1971). In the most probable E map, all non-hydrogen atoms were clearly evident as well as the four water O positions. Subsequent chemical analyses on bulk Na_2H_2hedp were consistent with a tetrahydrate phase. Refinement was by full-matrix least squares to minimize $\sum w||F_o| - |F_c||^2$ with weights equal to $1/\sigma^2(|F_o|)$ where σ is from counting statistics. The H atoms were located from a difference synthesis. The non-hydrogen parameters were refined anisotropically together with an overall scale factor. The final R ($= \sum||F_o| - |F_c||/\sum|F_o|$) and R_w [$= (\sum w||F_o| - |F_c||^2/\sum w|F_o|^2)^{1/2}$] for 1397 reflections were 0·040 and 0·050 respectively.

Atomic scattering factors were obtained from Cromer & Waber (1974). All calculations were performed with standard crystallographic programs that were modified for a Nova 1200 computer by Syntex Analytical Instruments. Final atomic parameters are given in Table 1.* The estimated standard deviations were calculated from the inverse matrix of the final full-matrix least-squares cycle.

Table 1. *Atomic parameters* (×10⁴)

	x	y	z
Na(1)	1315 (2)	8764 (3)	1210 (1)
Na(2)	−589 (2)	3740 (4)	784 (1)
P(1)	1694 (1)	3899 (2)	2219 (1)
P(2)	2411 (1)	3924 (2)	595 (1)
O(1)	683 (3)	5763 (6)	2016 (2)
O(2)	1108 (3)	1637 (5)	2082 (2)
O(3)	2226 (3)	4284 (6)	2978 (2)
O(4)	3602 (3)	4542 (5)	141 (2)
O(5)	1324 (3)	5462 (5)	416 (1)
O(6)	2147 (3)	1472 (5)	472 (2)
O(7)	3222 (3)	6747 (5)	1617 (2)
C(1)	2931 (4)	4399 (7)	1553 (2)
C(2)	4083 (5)	2935 (8)	1759 (3)
O(8)*W*	−764 (3)	9659 (6)	807 (2)
O(9)*W*	−2262 (4)	3934 (6)	1556 (2)
O(10)*W*	3843 (4)	8747 (6)	−158 (2)
O(11)*W*	5659 (3)	7702 (7)	1246 (2)
H(1)	4750	3250	1400
H(2)	4380	3470	2230
H(3)	3890	1350	1730
H(4)	−40	5970	2330
H(5)	−3580	6130	30
H(6)	4150	7070	1480
H(7)	−1290	9800	1160
H(8)	−1140	9070	360
H(9)	−2470	2580	1790
H(10)	−2500	4620	1980
H(11)	3630	8430	−480
H(12)	3190	9710	10
H(13)	5870	6920	940
H(14)	6350	8360	1590

Discussion. The crystal structure of Na_2H_2hedp.$4H_2O$ consists of an intricate network of hydrogen bonds and ligand-bridged coordination complexes, so that no discrete molecules exist. A description of the crystal structure is best appreciated once the coordination about both Na atoms, as well as the hedp ligand geometry, are defined. In Fig. 1, the perspective drawing illustrates not only the different environment of each Na atom, but also the various chelating capabilities and the conformation of the ligand. About Na(1) the coordination is nearly octahedral, while the coordination about Na(2) is approximately square pyramidal. The diphosphonate ligand binds as a bidentate ligand [O(2) and O(6)] and as a tridentate ligand [O(1), O(5) and O(7)]. The orientations of the phosphonate O atoms form a nearly planar *W* configuration [O(4), P(2), C(1), P(1) and O(3)]. The torsion angles for O(3)–P(1)–C(1)–P(2) and P(1)–C(1)–P(2)–O(4) are 178·7 and 177·9° respectively. Chemically equivalent bond distances and angles agree

* Lists of structure factors, thermal parameters and bond angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34175 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

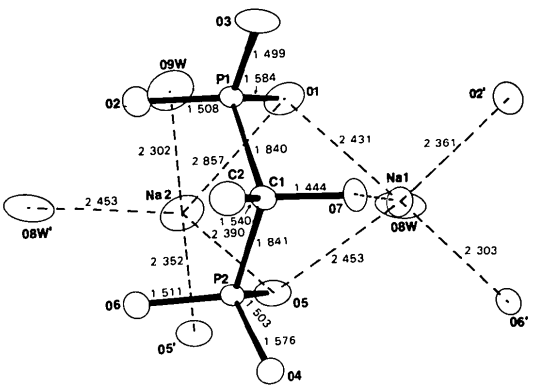

Fig. 1. Coordination and ligand geometry for Na_2H_2hedp. Distances are in Å and the estimated standard deviations lie in the range 0·003 to 0·006 Å. Distances Na(1)–O(8)*W* 2·363 Å, Na(1)–O(7) 2·450 Å and all H atoms are excluded for clarity.

within experimental error and are nearly identical to those in the free acid of hedp (Uchtman & Gloss, 1972). Fig. 2 illustrates the principle features of the structure in a projection of the unit-cell contents down the *b* axis. A column of water molecules is located at the center of the unit cell and is directed parallel to the viewing direction. On either side of the water column and at $\frac{1}{4}$ and $\frac{3}{4}$ of the **c** direction, the methyl groups are separated by van der Waals distances also along the viewing direction. Although a complete bilayer is not evident in the packing diagram, a complete bilayer is formed by the neighboring unit cell along the **a** direction.

Biological activity of hedp rests principally on the interaction between this ligand and Ca, especially during bone formation. Chemisorption of hedp on calcium hydroxyapatite (ha), the major constituent of teeth and bone, has been suggested in the mechanism for crystal growth inhibition during the development of bone (King, Francis & Michael, 1971). The multidentate capabilities of hedp provide a simple rationale for this mechanism. On the ⟨001⟩ surface of ha where the crystal growth is most prominent, alternate layers are composed of crystallographically distinct Ca atoms – each with different coordination environments (Kay, Young & Posner, 1964). One Ca has an irregular seven-coordinate environment that could bind in a number of ways to the polydentate ligand. More importantly the second Ca in ha has a symmetrical trigonal-prismatic coordination with the triangular faces 2·93 and 3·02 Å on edge respectively. The triangular face of hedp is 3·02 by 3·02 by 2·95 Å which would easily satisfy the trigonal coordination sites in calcium hydroxyapatite. Coordination in this manner would poison the crystal surface and would prevent further crystal growth.

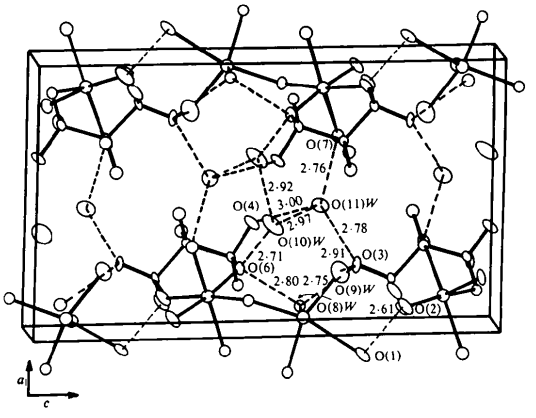

Fig. 2. Unit-cell packing diagram for $Na_2H_2hedp.4H_2O$. Distances between hydrogen-bonded O atoms are in Å; the O(10)*W*···O(4) distance (2·59 Å) is not included. H atoms are excluded for clarity.

Other geminal diphosphonates, such as dichloromethylenediphosphonate, and pyrophosphate, are also chemisorbed onto the surface of calcium hydroxyapatite by formation of mono- or bidentate complexes to calcium ions; significant tridentate complexes are unlikely. Potentially geminal diphosphonates and pyrophosphate ligands could also bind in a tetradentate coordination, but the binding sites in calcium hydroxyapatite would not accommodate such a complex without severely distorting the ligands. The observations that these ligands can be displaced from calcium hydroxyapatite by hedp (Jung, Bisaz & Fleisch, 1973) suggests that the tridentate coordination capability of hedp is important to its preferential chemisorption to the calcium hydroxyapatite surface. Any geminal diphosphonate which also has a coordinating ligand such as the hydroxy group in hedp, *i.e.* hydroxymethylenediphosphonate, should bind preferentially to the surface of calcium hydroxyapatite microcrystallites.

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