Acta Cryst. (1972). B**28**, 3662

The Crystal Structure of (−)-Ephedrine Dihydrogen Phosphate

By Richard A. Hearn and Charles E. Bugg

Institute of Dental Research and
Department of Biochemistry, University of Alabama Medical Center, University of Alabama in Birmingham,
1919 *Seventh Avenue South, Birmingham, Alabama* 35233, *U.S.A.*

(*Received* 20 *April* 1972)

Crystals of the phosphoric acid salt of (−)-ephedrine are monoclinic, space group $C2$, with $a = 14.738$ (4), $b = 5.710$ (6), $c = 15.302$ (4) Å, and $\beta = 97.17$ (2)°. There are four $C_{10}H_{16}NO.H_2PO_4$ ion pairs in the unit cell. The calculated and observed densities are 1·368 and 1·37 g.cm^{-3}, respectively. By use of 1180 reflections measured on an X-ray diffractometer, the crystal structure was solved by the heavy-atom method and was refined by least-squares to $R = 0.026$. The conformation of the ephedrine cation is in agreement with that found in the crystal structure of ephedrine hydrochloride. The dihydrogen phosphate anions are joined by short hydrogen bonds to form continuous phosphate sheets that lie parallel to the *ab* plane. The sheets of phosphate ions are hydrogen-bonded to the ethanolamine moieties of the ephedrine cations. Similar phosphate interactions may be of importance in biological mineralization processes.

Introduction

We are currently investigating the structures of phosphate salts of peptides to gather information about the possible factors governing the binding of phosphate minerals to protein matrices (Freeman, Hearn & Bugg, 1972). During bone formation, phosphate salts are deposited in collagenous matrices (Glimcher, Francois, Richards & Krane, 1964; Glimcher, Krane, 1964), and several studies have indicated that the lysine and hydroxylysine residues of collagen may play an important role in the collagen–mineral interactions (Schiffman, Martin & Miller, 1970; Glimcher & Krane, 1968). Since lysine and hydroxylysine residues possess protonated amino groups at physiological *p*H levels, these amino acids might provide sites for binding phosphate ions. Examination of space-filling models suggests that hydroxylysine, by utilizing its terminal β-ethanolamine moiety, might provide an especially effective site for hydrogen bonding to phosphate ions. We determined the crystal structure of the phosphoric acid salt of (−)-ephedrine (a β-ethanolamine) in order to examine phosphate interactions with the ethanolamine moiety.

Experimental

Ephedrine phosphate, isolated by lyophilizing an aqueous solution containing equimolar quantities of ephedrine and phosphoric acid, was crystallized by slowly cooling a hot, saturated, aqueous ethanol solution. Two types of crystals were obtained: monoclinic needles and orthorhombic plates. Density measurements and elemental analyses showed that the ephedrine: phosphoric-acid molar ratio is 1:1 for the needles and 2:1 for the plates. The needles were used for the structure analysis reported here.

Weissenberg and oscillation photographs showed the crystals to be monoclinic. Space groups $C2$, Cm and $C2/m$ are indicated by the systematic absence of reflections hkl with $h+k=2n+1$; since ephedrine is optically active, we presumed that the space group is $C2$. A section with approximate dimensions 0·3, 0·2 and 0·1 mm was cut from one of the larger needles and then mounted on a Picker FACS-1 diffractometer with its b axis (the needle axis) slightly inclined to the φ axis of the diffractometer. Approximate cell parameters for use in collection of intensity data were calculated by a least-squares analysis of the angular setting for 8 low angle Cu $K\alpha$ ($\lambda = 1.5418$ Å) reflections.

Intensity data were collected with the diffractometer, using a scintillation counter, nickel-filtered copper radiation ($\lambda = 1.5418$ Å), and a θ–2θ scanning technique. A scan rate of 0·5°/min was used and the background was counted for 20 sec at each terminus of the scans. Measurements were made for the 1180 reflections with $2\theta < 128°$. All reflections were considered observable. Intensity values were assigned variances, $\sigma^2(I)$, according to the statistics of the scan and background counts plus an additional term $(0.03S)^2$, S being the scan counts. The intensities and their variances were corrected for Lorentz and polarization factors, and absorption corrections were applied by use of the program *ORABS* (Wehe, Busing & Levy, 1962). Structure factors and variances were placed on an approximately absolute scale by means of a Wilson plot (Wilson, 1942).

Immediately after data collection, accurate values for the cell parameters were obtained by a least-squares analysis of 2θ values for 15 high angle α_1 reflections ($\lambda = 1.54051$ Å) measured with the diffractometer. Crystal data are listed in Table 1.

The x and z coordinates for the phosphorus atom were obtained from a sharpened, three-dimensional Patterson map; since $C2$ is a polar space group, the y

Table 1. *Crystal data*

The unit-cell parameters were measured at 25±3°C. The reported standard deviations are five times those obtained from the least-squares analysis. The density was measured by flotation in a mixture of benzene and ethylene dibromide.

Stoichiometry	$C_{10}H_{16}NO.H_2PO_4$
Z	4
Space group	$C2$
a	14·738 (4) Å
b	5·710 (6)
c	15·302 (4)
β	97·17 (2)°
ϱ (calculated)	1·368 g.cm^{-3}
ϱ (observed)	1·37
μ	20·4 cm^{-1}

coordinate for one atom can be arbitrarily assigned, and we let $y=0{\cdot}20$ for the phosphorus atom. A Fourier map was calculated by use of phase angles derived from the phosphorus atom. Although this map contained a false mirror plane through the phosphorus atom, we had little difficulty selecting a suitable set of phosphate oxygen atoms. The remaining nonhydrogen atoms were located in a Fourier map calculated with phase angles derived from the phosphate anion. The trial structure was improved initially by several cycles of block-diagonal least-squares, during which the y coordinate of the phosphorus atom refined to a value of 0·2093.

At this stage, the y coordinate of the phosphorus atom was fixed, and the refinement was continued by use of a modified version of the full-matrix least-squares program *ORFLS* (Busing, Martin & Levy, 1962). The quantity minimized was $\sum w[F_o^2-(1/k^2)F_c^2]^2$, where k is a scale factor and the weight w is equal to $[1/\sigma(F_o^2)]^2$. Atomic scattering factors for the nonhydrogen atoms, as well as the real and imaginary anomalous dispersion corrections for phosphorus and oxygen, were from *International Tables for X-ray Crystallography* (1962). Hydrogen scattering factors were from Stewart, Davidson & Simpson (1965). Hydrogen atoms were located in a difference Fourier map calculated during the final stages of refinement. We refined all positional parameters, anisotropic temperature parameters for the nonhydrogen atoms, isotropic temperature factors for the hydrogen atoms, and Zachariasen's (1963) extinction parameter g (as formulated by Coppens & Hamilton, 1970). Heavy and hydrogen atoms were refined in alternate cycles. The final R index, $(\sum||F_o|-|F_c||/\sum|F_o|)$, for all reflections is 0·026; the goodness-of-fit, $\{\sum[1/\sigma^2(F_o^2)](F_o^2-F_c^2/k^2)^2/(m-s)\}^{1/2}$, is 1·81. During the final cycle of refinement no parameter shifted more than one-fifth of its standard deviation. A final difference Fourier map showed no peaks or troughs exceeding 0·2 e.Å^{-3} in magnitude.

At the conclusion of refinement, the coordinates were inverted and the structure of the enantiomer [(+)-ephedrine] was refined. The enantiomer refined to $R=0{\cdot}027$, and a goodness-of-fit of 1·86.

Results

The nonhydrogen atom parameters and their standard deviations are listed in Table 2; the average estimated standard deviations in these positional parameters range from 0·0015 to 0·004 Å. The hydrogen atom parameters and their standard deviations are given in Table 3; the estimated errors in the hydrogen-atom positional parameters range from 0·03 to 0·06 Å. Table 4 lists observed and calculated structure factors.

Fig. 1 shows the conformation of the ephedrine cation, including the ellipsoids of thermal vibration (Johnson, 1965). Bond lengths are given in Table 5 and bond angles in Table 6. The conformation and the bond lengths and angles of ephedrine are in agreement with those found in the crystal structure of ephedrine hydrochloride (Bergin, 1971); the major discrepancy between this structure and the hydrochloride is a difference of 47° in the torsion angle about the C(7)–O(11)

Table 2. *The final heavy-atom parameters and their standard deviations*

All values have been multiplied by 10^4. The temperature factors are in the form $T=\exp(-\beta_{11}h^2-\beta_{22}k^2-\beta_{33}l^2-2\beta_{12}hk-2\beta_{13}hl-2\beta_{23}kl)$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
P	1391 (1)	2093	405 (1)	24 (1)	253 (2)	28 (1)	−3 (1)	3 (1)	6 (1)
O(P1)	942 (1)	1359 (4)	−485 (1)	28 (1)	409 (8)	30 (1)	−1 (2)	3 (1)	−27 (2)
O(P2)	1590 (1)	4809 (4)	409 (1)	44 (1)	251 (7)	41 (1)	3 (2)	5 (1)	0 (2)
O(P3)	734 (1)	1848 (5)	1120 (1)	32 (1)	443 (8)	31 (1)	−21 (3)	5 (1)	−5 (2)
O(P4)	2267 (1)	837 (4)	726 (1)	30 (1)	277 (6)	41 (1)	9 (2)	0 (1)	5 (2)
C(6)	2177 (2)	7795 (5)	3797 (2)	52 (1)	272(10)	42 (1)	−14 (3)	5 (1)	−4 (3)
C(5)	1742 (2)	7913 (6)	4549 (2)	57 (2)	356 (12)	44 (1)	0 (3)	8 (1)	−33 (3)
C(4)	1162 (2)	6155 (7)	4738 (2)	41 (1)	482 (13)	41 (1)	73 (4)	8 (1)	−10 (4)
C(3)	1017 (2)	4259 (7)	4181 (2)	39 (1)	438 (13)	55 (2)	−26 (4)	12 (1)	2 (4)
C(2)	1450 (2)	4138 (6)	3430 (2)	42 (1)	331 (10)	46 (1)	25 (3)	5 (1)	−16 (3)
C(1)	2041 (2)	5884 (5)	3234 (2)	35 (1)	271 (8)	33 (1)	−2 (3)	−2 (1)	1 (3)
C(7)	2534 (2)	5668 (5)	2429 (2)	40 (1)	289 (10)	30 (1)	−15 (3)	0 (1)	1 (3)
O(11)	2852 (1)	7872 (4)	2150 (1)	57 (1)	309 (8)	39 (1)	−8 (2)	3 (1)	33 (2)
C(8)	3367 (2)	4032 (5)	2604 (2)	40 (1)	269 (9)	30 (1)	−9 (3)	2 (1)	16 (2)
N(12)	3643 (1)	3316 (5)	1727 (1)	31 (1)	264 (7)	33 (1)	−11 (2)	3 (1)	4 (2)
C(9)	4464 (2)	1813 (7)	1744(2)	41 (1)	334 (11)	54 (1)	15 (4)	5 (1)	18 (4)
C(10)	4165 (2)	5147 (7)	3177 (2)	46 (1)	451 (13)	37 (1)	−11 (4)	−8 (1)	−8 (3)

Table 3. *The final hydrogen atom parameters and their estimated standard deviations*

The positional parameters have been multiplied by 10^3.

	x	y	z	B(Å^2)
H(OP2)	213 (2)	509 (8)	003 (2)	7·3 (1·0)
H(OP3)	032 (2)	181 (9)	097 (2)	7·5 (0·9)
H(11)	249 (3)	803 (10)	169 (3)	9·3 (1·2)
H(21)	138 (2)	269 (6)	307 (2)	4·9 (0·7)
H(31)	062 (2)	292 (6)	432 (2)	4·4 (0·6)
H(41)	086 (2)	632 (8)	529 (2)	5·9 (0·7)
H(51)	184 (2)	909 (7)	488 (2)	6·1 (0·8)
H(61)	255 (2)	890 (6)	367 (2)	5·1 (0·7)
H(71)	210 (2)	486 (5)	196 (2)	3·3 (0·5)
H(81)	320 (2)	250 (5)	290 (2)	3·8 (0·6)
H(91)	445 (2)	056 (7)	211 (2)	6·7 (0·9)
H(92)	502 (2)	266 (8)	192 (2)	7·7 (1·0)
H(93)	460 (2)	139 (7)	110 (2)	6·2 (0·8)
H(101)	394 (2)	589 (7)	371 (2)	5·5 (0·7)
H(102)	465 (2)	407 (6)	336 (2)	5·4 (0·7)
H(103)	446 (2)	658 (9)	289 (2)	7·4 (0·9)
H(121)	316 (2)	250 (6)	142 (2)	4·6 (0·6)
H(122)	381 (2)	459 (6)	141 (1)	5·2 (0·7)

bond. The N(12)···O(11) distance of 2·96 Å is only 0·08 Å longer than that found for the hydrochloride. As expected, the phenyl ring is planar within experimental error and has no heavy atom deviations exceeding 0·007 Å. Atom C(7) is displaced 0·05 Å from the phenyl plane.

Table 5. *Bond distances*

The standard deviations in bond lengths involving only non-hydrogen atoms are about 0·005 Å. The standard deviations in bond lengths involving hydrogen atoms are about 0·06 Å.

Bond	Distance	Bond	Distance
P——O(P1)	1·498Å	C(7)—H(71)	1·01Å
P——O(P2)	1·578	C(8)—H(81)	1·03
P——O(P3)	1·555	N(12)-H(121)	0·93
P——O(P4)	1·505	N(12)-H(122)	0·93
C(5)-C(6)	1·387	C(6)—H(61)	0·87
C(6)-C(1)	1·389	C(5)—H(51)	0·85
C(5)-C(4)	1·373	C(4)—H(41)	1·01
C(3)-C(4)	1·379	C(3)—H(31)	1·00
C(2)-C(3)	1·384	C(2)—H(21)	0·99
C(1)-C(2)	1·382	O(11)-H(11)	0·85
C(1)-C(7)	1·512	C(10)-H(101)	1·01
C(7)-O(11)	1·427	C(10)-H(102)	0·95
C(7)-C(8)	1·539	C(10)-H(103)	1·05
C(8)-C(10)	1·506	C(9)--H(91)	0·91
C(9)-N(12)	1·481	C(9)—H(92)	0·96
C(8)-N(12)	1·506	C(9)—H(93)	1·07
		O(P2)-H(OP2)	1·06
		O(P3)-H(OP3)	0·63

Fig. 2 depicts the crystal packing. The hydrophobic phenyl and methyl groups are clustered in the central region of the unit cell, and the polar amino, hydroxyl, and phosphate moieties are arranged in layers parallel to the *ab* plane. Thus the structure consists of alternating hydrophobic and polar layers, with the hydrophobic

Table 4. *Observed and calculated structure factors*

From left to right, the columns contain values of h, $10F_o$ and $10F_c$.

H	-6	0
0	51	53
2	114	116
4	107	105
6	38	37
H	-5	0
1	149	150
3	172	167
5	119	120
7	146	150
9	25	28
11	105	113
H	-4	0
0	90	90
2	302	307
4	389	390
6	174	173
8	38	25
10	163	169
12	25	32
H	-3	0
1	342	345
3	440	446
5	134	127
7	329	329
9	101	102
11	117	114
13	122	120
15	168	168
H	-2	0
0	564	583
2	196	202
4	155	154
6	567	539
8	37	34
10	115	114
12	193	198
14	177	182
16	75	74
H	-1	0
1	347	346
3	173	165
5	466	463
7	165	163
9	178	168
11	140	140
13	245	250
15	84	79
H	0	0
2	1016	1005
4	952	931
6	262	252
8	174	176
10	214	219
12	33	28
14	274	271
16	76	77
H	-6	1
-6	31	30
-4	101	105
-2	44	38
0	147	140
2	67	65
4	90	96
6	63	67
H	-5	1
-11	109	110
-9	41	39
-7	184	193
-5	110	114
-3	44	48
-1	180	182
1	175	169
3	110	117
5	167	174
7	107	108
9	48	46
11	112	112
H	-4	1
-12	95	103
-10	117	114
-8	168	177
-6	88	95
-4	218	237
-2	142	149
0	268	268
2	111	115
4	263	261
6	350	352
8	34	33
10	151	158
12	39	46
H	-3	1
-15	100	99
-13	69	70
-11	148	161
-9	99	102
-7	244	251
-5	66	66
-3	287	303
-1	599	602
1	288	282
3	361	370
5	495	492
7	311	308
9	86	83
11	91	84
13	122	123
15	153	149
H	-2	1
-16	78	76
-14	185	188
-12	115	117
-10	165	171
-8	185	183
-6	273	270
-4	408	421
-2	336	355
0	769	744
2	397	399
4	624	624
6	229	226
8	141	133
10	127	128
12	147	147
14	127	128
16	104	109
H	-1	1
-15	85	84
-13	85	83
-11	305	307
-9	431	423
-7	91	96
-5	356	365
-3	384	396
-1	706	691
1	1311	1204
3	1592	1482
5	680	678
7	241	229
9	368	354
11	131	137
13	216	217
15	81	83
H	0	1
-16	42	39
-14	240	240
-12	37	42
-10	281	284
-8	119	125
-6	78	75
-4	522	522
-2	90	92
0	719	828
2	103	109
4	46	36
6	45	48
8	220	213
10	391	388
12	43	41
14	261	257
16	83	86
H	-6	2
-6	50	46
-4	63	60
-2	73	70
0	44	42
2	138	130
4	24	16
6	58	62
H	-5	2
-11	115	116
-9	23	27
-7	97	102
-5	35	31
-3	95	94
-1	34	32
1	163	160
3	235	228
5	56	49
7	122	119
9	31	34
H	-4	2
-12	100	100
-10	180	182
-8	214	223
-6	88	93
-4	239	255
-2	108	111
0	287	272
2	343	340
4	145	143
6	358	356
8	105	101
10	155	145
12	23	14
H	-3	2
-15	125	125
-13	45	39
-11	215	221
-9	53	52
-7	243	252
-5	367	382
-3	415	416
-1	369	364
1	223	217
3	364	375
5	80	80
7	254	255
9	149	150
11	72	74
13	153	155
H	-2	2
-16	136	133
-14	141	143
-12	205	214
-10	155	149
-8	299	290
-6	269	258
-4	523	526
-2	302	316
0	558	541
2	438	438
4	505	510
6	301	307
8	200	198
10	164	167
12	108	109
14	138	137
H	-1	2
-17	31	37
-15	181	181
-13	125	128
-11	262	264
-9	94	96
-7	497	479
-5	512	506
-3	342	350
-1	1300	1203
1	620	607
3	353	380
5	344	347
7	240	231
9	246	252
11	140	143
13	283	288
15	57	55
H	0	2
-16	25	23
-14	135	139
-12	179	184
-10	133	136
-8	329	345
-6	107	108
-4	618	620
-2	173	175
0	326	321
2	562	552
4	1096	1073
6	125	130
8	133	130
10	88	86
12	149	157
14	31	22
16	92	94
H	-6	3
-6	41	41
-4	55	53
-2	39	34
0	94	90
2	91	86
4	98	98
6	111	111
H	-5	3
-11	76	74
-9	43	43
-7	38	32
-5	64	64
-3	97	98
-1	117	113
1	138	130
3	243	234
5	120	122
7	109	111
9	62	59
H	-4	3
-12	70	69
-10	181	192
-8	342	353
-6	42	36
-4	231	236
-2	171	173
0	203	199
2	274	266
4	330	328
6	369	368
8	89	83
10	112	110
12	25	19
H	-3	3
-15	116	116
-13	134	131
-11	222	223
-9	120	125
-7	265	271
-5	247	248
-3	269	257
-1	318	317
1	72	68
3	364	360
5	360	356
7	43	40
9	132	134
11	38	33
13	80	81
H	-2	3
-16	137	137
-14	79	75
-12	294	295
-10	207	207
-8	255	262
-6	120	123
-4	109	111
-2	414	419
0	493	487
2	179	183
4	172	173
6	18	17
8	206	201
10	132	128
12	101	101
14	163	164
H	-1	3
-15	148	149
-13	192	192
-11	262	263
-9	265	266
-7	472	464
-5	272	275
-3	423	413
-1	1133	1099
1	331	344
3	923	894
5	777	750
7	649	633
9	237	243
11	177	179
13	190	195
15	46	53
H	0	3
-16	70	70
-14	219	213
-12	291	284
-10	94	88
-8	180	186
-6	323	317
-4	862	883
-2	990	1013
0	408	399
2	1663	1641
4	197	197
6	63	67
8	83	85
10	183	187
12	331	340
14	83	80
16	147	148
H	-6	4
-6	67	68
-4	30	33
-2	62	66
0	43	41
2	136	127
4	34	33
H	-5	4
-11	55	58
-9	125	126
-7	64	68
-5	207	207
-3	121	121
-1	126	132
1	121	122
3	64	65
5	113	115
7	91	88
9	88	83
H	-4	4
-12	136	140
-10	82	81
-8	278	278
-6	71	55
-4	91	84
-2	113	116
0	59	61
2	235	232
4	143	146
6	341	341
8	157	159
10	69	76
12	39	31
H	-3	4
-15	74	75
-13	104	106
-11	113	108
-9	128	129
-7	170	171
-5	327	329
-3	142	142
-1	341	341
1	117	115
3	479	464
5	324	318
7	240	241
9	307	310
11	172	179
13	135	131
H	-2	4
-16	108	109
-14	57	57
-12	256	260
-10	141	146
-8	316	316
-6	216	204
-4	308	303
-2	263	276
0	140	134
2	265	273
4	365	368
6	392	391
8	275	276
10	119	113
12	40	41
14	123	120
H	-1	4
-15	157	157
-13	156	154
-11	302	296
-9	432	428
-7	194	185
-5	145	140
-3	610	592
-1	478	494
1	545	539
3	218	193
5	432	450
7	310	325
9	244	253
11	138	134
13	139	142
15	29	26
H	0	4
-16	182	183
-14	178	178
-12	462	458
-10	253	251
-8	556	552
-6	443	420
-4	944	928
-2	77	80
0	255	250
2	876	901
4	467	454
6	220	224
8	100	106
10	466	466
12	463	465
14	66	60
16	146	149
H	-6	5
-6	22	27
-4	60	61
-2	91	94
0	40	36
2	126	113
4	59	56
H	-5	5
-9	122	122
-7	34	31
-5	163	160
-3	77	72
-1	152	158
1	146	139
3	182	177
5	139	139
7	136	133
9	58	60
H	-4	5
-12	112	108
-10	106	108
-8	144	143
-6	99	92
-4	60	67
-2	137	135
0	146	142
2	352	344
4	97	102
6	134	129
8	84	80
10	104	100
12	43	40
H	-3	5
-15	65	64
-13	106	102
-11	132	132
-9	361	364
-7	278	276
-5	405	403
-3	304	294
-1	276	271
1	210	208
3	205	204
5	335	336
7	194	197
9	250	249
11	50	51
13	144	142
H	-2	5
-16	80	81
-14	68	68
-12	273	273
-10	99	99
-8	384	381
-6	270	279
-4	220	220
-2	181	184
0	540	523
2	383	372
4	247	237
6	300	295
8	235	245
10	258	263
12	194	200
14	182	182
H	-1	5
-15	164	165
-13	380	377
-11	32	37
-9	345	349
-7	295	298
-5	115	117
-3	538	515
-1	300	289
1	227	224
3	134	125
5	337	336
7	199	204
9	127	130
11	137	136
13	128	129
15	88	87
H	0	5
-16	31	34
-14	76	76
-12	328	333
-10	126	130
-8	593	591
-6	244	252
-4	123	117
-2	316	339
0	59	64
2	739	763
4	145	152
6	505	492
8	146	149
10	266	264
12	74	75
14	91	90
H	-6	6
-4	35	34
-2	120	124
0	61	55
2	97	92
H	-5	6
-9	126	123
-7	60	59
-5	88	89
-3	89	95
-1	129	136
1	52	46
3	171	170
5	93	90
7	81	80
H	-4	6
-12	87	83
-10	32	29
-8	188	190
-6	255	254
-4	52	43
-2	240	237
0	40	34
2	358	349
4	340	330
6	137	132
8	117	118
10	152	149
H	-3	6
-13	156	153
-11	108	107
-9	420	423
-7	230	228
-5	202	209
-3	257	259
-1	101	99
1	324	312
3	229	225
5	357	353
7	130	129
9	158	161
11	79	83
13	103	108
H	-2	6
-14	171	168
-12	169	166
-10	285	284
-8	195	195
-6	237	235
-4	297	299
-2	186	181
0	93	93
2	216	207
4	142	148
6	227	235
8	283	284
10	255	260
12	85	83
14	37	38
H	-1	6
-15	44	45
-13	214	214
-11	212	205
-9	312	308
-7	281	276
-5	552	532
-3	194	205
-1	325	317
1	346	350
3	354	338
5	659	646
7	154	158
9	439	436
11	97	98
13	154	151
15	29	26
H	0	6
-16	172	173
-14	97	96
-12	456	454
-10	143	146
-8	442	441
-6	21	21
-4	809	793
-2	305	322
0	14	19
2	135	130
4	83	86
6	480	485
8	402	397
10	182	180
12	86	85
14	78	76
H	-6	7
-2	97	102
0	43	40
2	74	79
H	-5	7
-9	117	118
-7	97	90
-5	75	78
-3	62	64
-1	74	79
1	65	66
3	48	49
5	124	124
7	81	80
H	-4	7
-12	117	115
-10	168	167
-8	174	170
-6	373	365
-4	35	27
-2	146	149
0	73	78
2	250	245
4	265	262
6	138	139
8	174	170
10	43	55
H	-3	7
-13	58	60
-11	99	96
-9	148	149
-7	110	117
-5	166	169
-3	130	125
-1	174	179
1	223	215
3	152	154
5	299	297
7	157	149
9	114	106
11	135	143
H	-2	7
-14	94	95
-12	72	68
-10	229	231
-8	81	76
-6	204	205
-4	108	102
-2	41	47
0	226	217
2	52	56
4	260	251
6	316	322
8	133	133
10	270	269
12	53	51
H	-1	7
-15	58	54
-13	316	312
-11	75	66
-9	415	412
-7	178	179
-5	406	400
-3	388	391
-1	218	216
1	355	356
3	349	342
5	133	136
7	115	115
9	501	501
11	114	120
13	162	159
H	0	7
-16	111	111
-14	151	147
-12	37	33
-10	184	184
-8	337	331
-6	183	192
-4	1089	1051
-2	658	654
0	485	468
2	169	161
4	554	559
6	350	353
8	544	544
10	144	145
12	170	172
14	35	29
H	-5	8
-9	91	91
-7	134	136
-5	39	37
-3	153	155
-1	27	27
1	99	99
3	43	41
5	57	58
7	48	49
H	-4	8
-12	106	104
-10	164	165
-8	26	19
-6	199	199
-4	57	57
-2	226	235
0	30	29
2	277	269
4	168	164
6	141	143
8	140	136
10	19	16
H	-3	8
-13	99	98
-11	50	51
-9	137	138
-7	169	161
-5	217	214
-3	220	221
-1	205	204
1	111	101
3	114	112
5	192	188
7	215	214
9	207	203
11	100	96
H	-2	8
-14	80	79
-12	113	108
-10	334	330
-8	352	356
-6	291	287
-4	208	211
-2	107	107
0	164	155
2	125	119
4	280	272
6	170	171
8	234	242
10	101	89
12	178	178
H	-1	8
-15	65	59
-13	238	238
-11	132	135
-9	81	76
-7	30	35
-5	378	370
-3	219	217
-1	410	411
1	444	437
3	171	170
5	337	334
7	84	84
9	258	261
11	36	28
13	101	104
H	0	8
-16	144	137
-14	83	82
-12	22	14
-10	124	122
-8	70	46
-6	160	162
-4	116	107
-2	54	55
0	500	497
2	53	44
4	417	419
6	70	70
8	157	155
10	138	138
12	173	173
14	72	70
H	-5	9
-7	109	108
-5	85	83
-3	93	90
-1	130	140
1	106	104
3	32	33
5	97	97
H	-4	9
-10	116	111
-8	61	61
-6	124	128
-4	64	67
-2	210	220
0	122	120
2	99	98
4	115	112
6	82	84
8	46	48
H	-3	9
-13	115	112
-11	80	79
-9	192	193
-7	466	455
-5	188	187
-3	211	217
-1	122	124
1	254	248
3	236	232
5	178	175
7	144	141
9	180	184
11	89	93
H	-2	9
-14	98	99
-12	45	35
-10	201	199
-8	179	179
-6	146	145
-4	132	138
-2	168	168
0	129	128
2	222	224
4	243	239
6	151	159
8	194	196
10	77	74
12	145	147
H	-1	9
-15	103	97
-13	115	114
-11	184	182
-9	247	248
-7	128	129
-5	167	166
-3	341	340
-1	245	240
1	98	96
3	83	75
5	276	275
7	250	248
9	121	122
11	31	30
13	124	118
H	0	9
-14	141	140
-12	91	83
-10	234	227
-8	0	1
-6	375	370
-4	209	216
-2	329	341
0	214	202
2	262	270
4	344	339
6	88	79
8	413	411
10	87	84
12	172	173
H	-5	10
-7	130	134
-5	73	67
-3	81	85
-1	56	58
1	110	110
3	85	86
H	-4	10
-10	113	113
-8	98	92
-6	173	171
-4	138	138
-2	171	177
0	109	103
2	131	130
4	147	144
6	115	109
8	77	76
H	-3	10
-13	89	87
-11	28	20
-9	89	93
-7	235	231
-5	107	108
-3	317	321
-1	146	153
1	346	337
3	136	133
5	149	149
7	120	115
9	34	39
H	-2	10
-14	89	90
-12	41	32
-10	98	94
-8	140	137
-6	328	320
-4	343	344
-2	51	51
0	73	70
2	173	171
4	24	9
6	48	46
8	148	146
10	21	21
H	-1	10
-15	27	28
-13	59	50
-11	103	105
-9	20	23
-7	261	261
-5	126	125
-3	324	327
-1	197	197
1	145	142
3	66	71
5	270	277
7	136	130
9	161	161
11	129	129
H	0	10
-14	105	103
-12	154	143
-10	147	150
-8	73	68
-6	493	490
-4	404	413
-2	489	475
0	433	427
2	111	114
4	302	293
6	0	3
8	447	447
10	229	227
12	46	42
H	-5	11
-5	69	68
-3	56	57
-1	15	17
1	94	87
H	-4	11
-10	119	118
-8	122	122
-6	66	70
-4	174	178
-2	69	73
0	139	132
2	51	48
4	190	188
6	137	134
H	-3	11
-11	103	103
-9	51	48
-7	126	127
-5	201	201
-3	253	257
-1	23	26
1	207	205
3	24	23
5	106	106
7	111	110
9	73	75
H	-2	11
-12	12	17
-10	97	94
-8	161	162
-6	181	183
-4	299	307
-2	226	226
0	219	218
2	93	92
4	43	45
6	33	31
8	114	117
10	55	52
H	-1	11
-13	43	34
-11	73	70
-9	34	26
-7	169	170
-5	168	172
-3	442	436
-1	393	404
1	221	225
3	225	225
5	208	214
7	139	139
9	46	44
11	162	167
H	0	11
-14	123	119
-12	48	41
-10	65	67
-8	27	33
-6	94	93
-4	320	327
-2	274	275
0	338	339
2	144	150
4	127	124
6	157	161
8	190	183
10	29	27
12	41	39
H	-4	12
-8	137	139
-6	109	108
-4	99	96
-2	158	170
0	204	197
2	68	64
4	83	80
H	-3	12
-11	128	126
-9	66	65
-7	80	81
-5	145	144
-3	163	167
-1	158	165
1	134	135
3	89	81
5	28	27
7	69	70
H	-2	12
-12	39	36
-10	45	49
-8	123	126
-6	95	98
-4	375	385
-2	198	196
0	345	332
2	167	163
4	226	223
6	10	12
8	111	114
10	96	99
H	-1	12
-13	109	109
-11	125	127
-9	101	109
-7	154	157
-5	222	223
-3	302	302
-1	80	81
1	382	379
3	125	120
5	92	93
7	111	109
9	55	54
H	0	12
-14	76	70
-12	20	13
-10	69	74
-8	72	68
-6	118	121
-4	355	363
-2	77	76
0	222	224
2	36	38
4	80	79
6	70	65
8	17	6
10	106	109
H	-4	13
-6	69	67
-4	106	109
-2	84	87
0	267	256
2	92	81
4	73	74
H	-3	13
-9	57	55
-7	93	92
-5	194	198
-3	149	162
-1	191	205
1	148	148
3	174	173
5	116	113
7	29	28
H	-2	13
-12	78	73
-10	51	48
-8	142	142
-6	112	114
-4	84	83
-2	74	70
0	94	90
2	159	161
4	113	112
6	38	41
8	21	21
H	-1	13
-11	70	66
-9	34	43
-7	88	85
-5	160	162
-3	254	255
-1	204	215
1	328	317
3	142	139
5	86	91
7	127	126
9	46	48
H	0	13
-12	72	71
-10	156	149
-8	216	229
-6	87	88
-4	394	398
-2	144	150
0	230	228
2	91	88
4	318	319
6	172	173
8	62	59
10	109	111
H	-4	14
-4	61	64
-2	50	50
0	89	86
H	-3	14
-7	112	114
-5	69	72
-3	124	140
-1	97	103
1	112	105
3	190	182
5	57	53
H	-2	14
-10	74	64
-8	132	135
-6	46	49
-4	138	139
-2	53	55
0	168	165
2	33	29
4	114	118
6	108	104
H	-1	14
-11	87	76
-9	20	18
-7	156	159
-5	191	201
-3	69	68
-1	140	142
1	146	145
3	29	29
5	165	172
7	89	91
H	0	14
-12	67	64
-10	79	71
-8	107	111
-6	55	45
-4	254	256
-2	128	130
0	367	384
2	94	86
4	251	256
6	142	139
8	19	14
H	-3	15
-5	64	68
-3	48	47
-1	154	163
1	73	74
3	139	133
H	-2	15
-8	73	76
-6	37	33
-4	129	132
-2	135	140
0	121	118
2	124	121
4	61	56
H	-1	15
-9	88	91
-7	107	107
-5	140	152
-3	46	45
-1	125	130
1	97	99
3	183	179
5	37	27
7	54	59
H	0	15
-10	101	98
-8	142	138
-6	81	81
-4	253	258
-2	65	48
0	112	112
2	15	8
4	32	20
6	34	35
H	-2	16
-6	36	30
-4	62	66
-2	52	50
0	78	75
2	61	59
H	-1	16
-9	75	72
-7	109	109
-5	41	46
-3	65	66
-1	176	184
1	80	75
3	161	159
5	111	113
H	0	16
-8	165	169
-6	17	15
-4	126	131
-2	100	102
0	40	39
2	91	89
4	114	122
H	-2	17
-2	11	4
H	-1	17
-5	106	107
-3	48	46
-1	65	67
1	41	36
H	0	17
-6	16	9
-4	36	35
-2	35	37
0	9	13
2	189	182

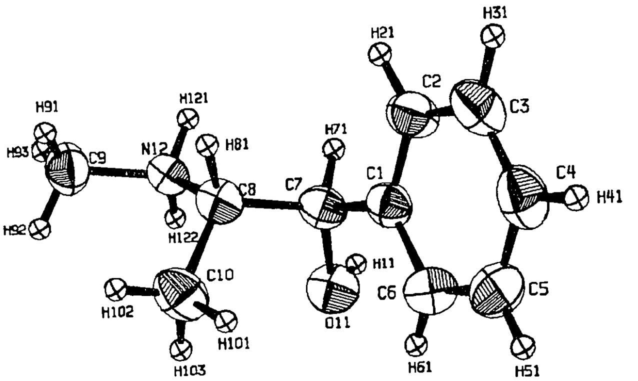

Fig. 1. The conformation of the ephedrine cation. The heavy atoms are represented by ellipsoids defined by the principal axes of thermal vibration and scaled to include 50% probability. The hydrogen atoms are represented by spheres of 0·1 Å radius.

portions sandwiched between polar regions. Fig. 2 also shows the hydrogen bonding scheme. Hydrogen bond lengths and angles are given in Table 7. All hydrogen atoms covalently bonded to oxygen or nitrogen atoms participate in hydrogen bonding. The nitrogen and oxygen atoms of the ethanolamine moiety donate hydrogen bonds to phosphate oxygen atoms. The two phosphate hydrogen atoms are utilized in phosphate–phosphate hydrogen bonding. Phosphate anions are hydrogen bonded around twofold rotation axes to form dimers that involve two short (2·55 Å) hydrogen bonds (Fig. 2). The second phosphate hydrogen atom is involved in hydrogen bonding between phosphate dimers. The phosphate–phosphate hydrogen bonding results in cohesive, continuous sheets of phosphate ions running parallel to the *ab* plane. Fig. 3 depicts hydrogen bonding within these sheets.

Discussion

An outstanding feature of this crystal structure is the aggregation of phosphate anions, leading to the formation of continuous phosphate sheets, wherein an extensive system of hydrogen bonds connects the phosphates. Each phosphate forms a total of four hydrogen bonds to three adjacent phosphates. The exceptional shortness (2·55 and 2·63 Å) of the phosphate–phosphate hydrogen bonds is suggestive of strong interactions between neighboring phosphate anions. The importance of phosphate–phosphate hydrogen bonding has been stressed previously (Phillippot & Lindqvist, 1971; Calleri & Speakman, 1964). The literature contains numerous examples of crystal structures in which hydrogen phosphates are joined by short (<2·65 Å) hydrogen bonds (Smith, Brown & Lehr, 1955; Iitaka & Huse, 1965; Huse & Iitaka, 1969; Philippot & Lindqvist, 1971; Sundaralingam & Putkey, 1970; Putkey & Sundaralingam, 1970; Calleri & Speakman, 1964; Preston & Stewart, 1970; Chieh & Palenik, 1971; Veidis, Palenik, Schaffrin & Trotter, 1969; Aoki, Nagano & Iitaka, 1971; Freeman, Hearn & Bugg, 1972). These hydrogen bonds are sometimes shorter than 2·5 Å, and

Table 6. *Bond angles*

The standard deviations in bond angles involving only nonhydrogen atoms are about 0·4°. The standard deviations in bond angles involving hydrogen atoms are about 4°.

O(P1)-P——O(P2)	109·8°	H(41)—C(4)—C(5)	117·4°
O(P1)-P——O(P3)	111·8	H(41)—C(4)—C(3)	122·8
O(P1)-P——O(P4)	115·3	H(51)—C(5)—C(6)	118·5
O(P2)-P——O(P3)	102·6	H(51)—C(5)—C(4)	121·2
O(P2)-P——O(P4)	108·4	H(61)—C(6)—C(5)	121·2
O(P3)-P——O(P4)	108·2	H(61)—C(6)—C(1)	118·4
C(6)—C(1)—C(2)	118·6	H(71)—C(7)—C(1)	113·1
C(6)—C(1)—C(7)	121·5	H(71)—C(7)—O(11)	105·2
C(2)—C(1)—C(7)	119·9	H(71)—C(7)—C(8)	112·4
C(3)—C(2)—C(1)	120·9	H(81)—C(8)—C(7)	111·2
C(4)—C(3)—C(2)	120·0	H(81)—C(8)—N(12)	105·5
C(5)—C(4)—C(3)	119·8	H(81)—C(8)—C(10)	108·4
C(6)—C(5)—C(4)	120·3	H(91)—C(9)—H(92)	108·4
C(5)—C(6)—C(1)	120·5	H(91)—C(9)—H(93)	114·8
C(1)—C(7)—O(11)	112·4	H(91)—C(9)—N(12)	112·3
C(1)—C(7)—C(8)	111·2	H(92)—C(9)—H(93)	96·7
O(11)-C(7)—C(8)	107·6	H(92)—C(9)—N(12)	111·6
C(7)—C(8)—N(12)	108·0	H(101)—C(10)-H(102)	109·6
C(7)—C(8)—C(10)	112·9	H(101)—C(10)-H(103)	101·7
N(12)-C(8)—C(10)	110·6	H(101)—C(10)-C(8)	109·5
C(8)—N(12)-C(9)	117·0	H(102)—C(10)-H(103)	107·4
		H(102)—C(10)-C(8)	113·4
H(OP2)-O(P2)-P	107·6	H(103)—C(10)-C(8)	114·6
H(OP3)-O(P3)-P	113·6	H(11)—O(11)-C(7)	98·6
H(21)—C(2)—C(1)	120·6	H(121)—N(12)-H(122)	111·0
H(21)—C(2)—C(3)	118·2	H(121)—N(12)-C(8)	108·8
H(31)—C(3)—C(4)	120·9	H(121)—N(12)-C(9)	106·5
H(31)—C(3)—C(2)	119·1	H(122)—N(12)-C(8)	112·0
		H(122)—N(12)-C(9)	101·2

evidence of the existence of symmetric phosphate–phosphate hydrogen bonds has been presented (Philippot & Lindqvist, 1971; Putkey & Sundaralingam, 1970; Calleri & Speakman, 1964). In the case of dihydrogen phosphate anions, with their two donor sites and multiple acceptor sites, phosphate–phosphate interactions usually lead to continuous arrays of hydrogen-bonded phosphates. We have examined the phosphate interactions in most published crystal structures that contain dihydrogen phosphate anions, and have found no structures in which phosphate–phosphate hydrogen bonding is not present. In all cases, each dihydrogen phosphate forms at least two hydrogen bonds to adjacent phosphates. Hydrogen bonding between phosphates is also an important interaction in aqueous solution (Selvaratnum & Spiro, 1965). In view of the widespread occurrence of hydrogen bonding between phosphates, it would be surprising if interactions of this type do not occur in biological systems.

Another important feature of this crystal structure is the binding of the phosphate aggregates to the *β*-ethanolamine moiety of ephedrine. As indicated in Fig. 4, the ethanolamine group possesses hydrogen-bond donor sites that are suitably arranged for binding the phosphate aggregates. The ethanolamine is joined to three phosphates by two hydrogen bonds from the nitrogen atom and one hydrogen bond from the hydroxyl group. These three phosphate ions are hydrogen bonded together. Since the phosphate ions are connected by single hydrogen bonds, this same type of phosphate–ethanolamine binding could also occur with monohydrogen phosphates. The three phosphate ions shown in Fig. 4 are joined by double hydrogen bonds to additional phosphates, resulting in the complete sheet of phosphate ions depicted in Fig. 3. Thus the ethanolamine moiety serves as a site for binding three phosphates ions which, in turn, bind other phosphates.

It is possible that these two features – formation of phosphate aggregates and hydrogen bonding of these aggregates to *β*-ethanolamine moieties – are important in biological mineralization. At physiological *p*H levels, orthophosphate would exist primarily as a mixture of monohydrogen and dihydrogen phosphate anions. Hydrogen bonding between these phosphate anions might lead to phosphate aggregates of sufficient size to initiate the formation of mineral phases. Hydroxylysine, a component of collagen, has been implicated in bone mineralization (Solomons & Irving, 1958; Schiffman, Martin & Miller, 1970; Wuthier, Grøn & Irving, 1964; Glimcher & Krane, 1968). The *β*-ethanolamine moiety of hydroxylysine could hydro-

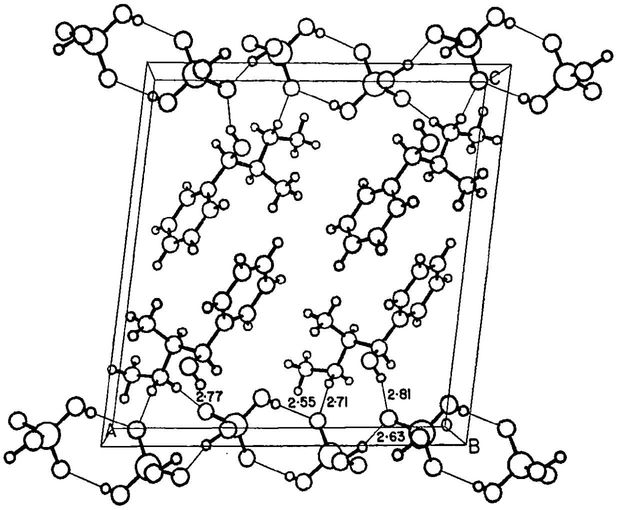

Fig. 2. The crystal structure viewed down the *b* axis. Thin lines represent hydrogen bonds; donor–acceptor distances are shown.

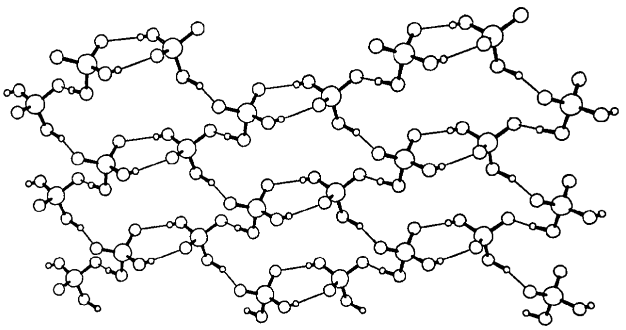

Fig. 3. Sheets of hydrogen bonded phosphate anions, as viewed down the *c* axis. The sheets are parallel to the *ab* plane. The thin lines represent hydrogen bonds.

Table 7. *Hydrogen bond distances and angles*

Donor atom	Hydrogen atom	Acceptor atom	Distances Donor–acceptor	Hydrogen–acceptor	Donor–hydrogen–acceptor angle
O(P3)	H(OP3)	O(P1) (*a*)	2·554 Å	1·93 Å	175°
O(P2)	H(OP2)	O(P4) (*b*)	2·632	1·60	164
N(12)	H(122)	O(P1) (*b*)	2·702	1·81	160
N(12)	H(121)	O(P4) (*c*)	2·772	1·84	176
O(11)	H(11)	O(P4) (*d*)	2·808	2·17	133

(a) $-x, \quad y, \ -z$
(*b*) $\frac{1}{2}-x, \frac{1}{2}+y, \ -z$
(c) $x, \quad y, \quad z$
(*d*) $x, y+1, \quad z$

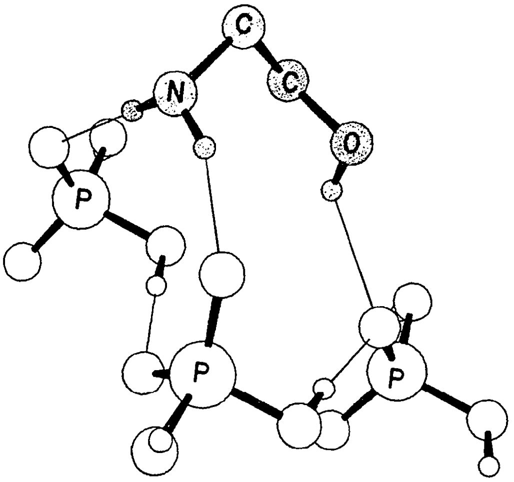

Fig. 4. Binding of phosphate ions to the β-ethanolamine moiety of ephedrine. The thin lines represent hydrogen bonds. Each of these phosphate ions is joined by two hydrogen bonds to an additional phosphate ion, resulting in the phosphate sheets shown in Fig. 3.

gen bond to phosphate anions, through interactions of the type depicted in Fig. 4. As demonstrated in this crystal structure, a single ethanolamine moiety can hydrogen bond directly to three phosphate anions which can, in turn, hydrogen bond to additional phosphates. Such interactions might result in collagen-bound phosphate aggregates that could serve as mineralization nucleation sites.

References

Aoki, K., Nagano, K. & Iitaka, Y. (1971). *Acta Cryst.* B**27**, 11.

Bergin, R. (1971). *Acta Cryst.* B**27**, 381.

Busing, W. R., Martin, K. O. & Levy, H. A. (1962). *ORFLS*. Report ORNL-TM-305, Oak Ridge National Laboratory, Tennessee.

Calleri, M. & Speakman, J. C. (1964). *Acta Cryst.* **17**, 1097.

Chieh, P. C. & Palenik, G. J. (1971). *J. Chem. Soc.* (*A*) p. 576.

Coppens, P. & Hamilton, W. C. (1970). *Acta Cryst.* A**26**, 71.

Freeman, G. R., Hearn, R. A. & Bugg, C. E. (1972). *Acta Cryst.* B**28**, 2906.

Glimcher, M. J., Francois, C. J., Richards, L. & Krane, S. M. (1964). *Biochim. Biophys. Acta*, **93**, 585.

Glimcher, M. J. & Krane, S. M. (1964). *Biochemistry*, **3**, 195.

Glimcher, M. J. & Krane, S. M. (1968). In *Treatise on Collagen*, Vol. 2, Part B, p. 153. Edited by B. S. Gould. New York: Academic Press.

Huse, Y. & Iitaka, Y. (1969). *Acta Cryst.* B**25**, 498.

Iitaka, Y. & Huse, Y. (1965). *Acta Cryst.* **18**, 110.

International Tables for X-ray Crystallography (1962). Vol. III, pp. 202, 214. Birmingham: Kynoch Press.

Johnson, C. K. (1965). *ORTEP*. Report ORNL-3794 revised, Oak Ridge National Laboratory, Tennessee.

Philippot, E. & Lindqvist, O. (1971). *Acta Chem. Scand.* **25**, 512.

Preston, H. S. & Stewart, J. M. (1970). *J. Chem. Soc.* (*D*), p. 1142.

Putkey, E. & Sundaralingam, M. (1970). *Acta Cryst.* B**26**, 782.

Schiffman, E., Martin, G. R. & Miller, E. J. (1970). In *Biological Calcification Cellular and Molecular Aspects*. Edited by H. Schraer, p. 27. New York: Meredith.

Selvaratnum, M. & Spiro, M. (1965). *Trans. Faraday Soc.* **61**, 360.

Smith, J. P., Brown, W. E. & Lehr, J. R. (1955). *J. Amer. Chem. Soc.* **77**, 2728.

Solomons, C. C. & Irving, J. T. (1958). *Biochem. J.* **68**, 499.

Stewart, R. F., Davidson, E. R. & Simpson, W. T. (1965). *J. Chem. Phys.* **42**, 3175.

Sundaralingam, M. & Putkey, E. F. (1970). *Acta Cryst.* B**26**, 790.

Veidis, M. V., Palenik, G. J., Schaffrin, R. & Trotter, J. (1969). *J. Chem. Soc.* (*A*), p. 2659.

Wehe, D. J., Busing, W. R. & Levy, H. A. (1962). *ORABS*. Report ORNL-TM-229, Oak Ridge National Laboratory, Tennessee.

Wilson, A. J. C. (1942). *Nature, Lond.* **150**, 152.

Wuthier, R. E., Grøn, R. & Irving, J. J. (1964). *Biochem. J.* **92**, 205.

Zachariasen, W. H. (1963). *Acta Cryst.* **16**, 1139.