Metal Complexes of α-Hydroxyiminophosphonic Acid Derivatives. Preparation and Crystal Structures of Calcium and Cadmium Complexes of Methyl (*E*)-α-Hydroxyiminobenzylphosphonate†

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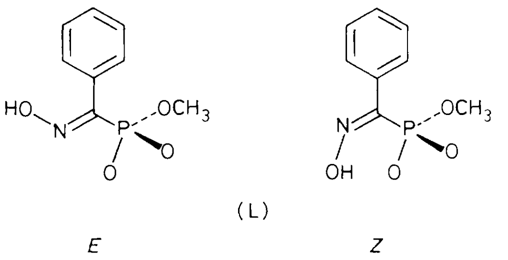
Both Ca^{2+} and Cd^{2+} react with methyl (*E*)-α-hydroxyiminobenzylphosphonate in aqueous solution to yield insoluble polymeric species which have been characterized by single-crystal *X*-ray diffraction studies. The two isomorphic compounds crystallize in the monoclinic system in the space group $P2_1/c$. Unit-cell parameters: Ca^{2+}, $a = 13.169(1)$, $b = 8.623(1)$, $c = 19.161(2)$ Å, $\beta = 90.93(1)°$, $Z = 4$; Cd^{2+}, $a = 13.010(1)$, $b = 8.666(1)$, $c = 18.906(2)$ Å, $\beta = 91.84(1)°$, $Z = 4$. The metal ions are seven-co-ordinate with a distorted pentagonal bipyramidal geometry generated by two bidentate, two unidentate phosphonate ligands, and one water molecule. The ligands act simultaneously in a chelating bidentate mode (through the oxyimino nitrogen and the phosphonate oxygen) and in a bridging mode. The bond distances and angles are similar to those observed for the calcium complexes of bisphosphonate drugs.

The recognition that inorganic pyrophosphate inhibits crystallization and aggregation of calcium phosphate on the one hand,[1] and inhibits the dissolution of crystals on the other,[2] led to the development of a relatively new set of drugs, bisphosphonates. The strong affinity of these compounds to calcium phosphate crystals has been utilized in the treatment of various metabolic diseases of bone, the targets being excessive bone resorption and impaired calcification and ossification.[3,4] While pyrophosphates are readily hydrolyzed in the presence of pyrophosphatase, the bisphosphonates are stable and retain their activity.[5]

It has been shown that bisphosphonates and especially those of the 'P–C–P' type are capable of effecting calcium hydroxyapatite $[Ca_5(OH)(PO_4)_3]$ crystal growth both *in vitro* and *in vivo*.[6-8] 1-Hydroxyethylene-1,1-diphosphonate $C(CH_3)(OH)(PO_3H_2)_2$ (hedp) has attracted considerable attention and the interaction of hedp and other 1,1-diphosphonates with Ca^{2+} has been studied.[9,10] Structural studies have indicated that these compounds act simultaneously as bidentate and bridging ligands to the calcium ions.[9,10]

It appears that there is a need for compounds which have a greater margin between the bone resorption inhibiting effect and that inhibiting mineralization, without increased toxicity. The on-going chemical research in this field is largely limited to side chain modification of conventional 'P–C–P' bisphosphonates. Consequently, it is important to extend synthetic efforts to other ligands which can be expected to interact with calcium in the above mentioned fashion. We have recently prepared and characterized a novel class of compounds, α-hydroxyiminophosphonates,[11,12] for example, methyl α-hydroxyiminobenzylphosphonate (L), and studied their metal binding properties.[13,14] Thus, we have undertaken a study of the interaction of calcium with α-hydroxyiminophosphonates and we report the preparation and *X*-ray diffraction study of the calcium complex (**1**) of methyl (*E*)-α-hydroxyiminobenzylphosphonate. In the course of our studies we discovered that the corresponding complex (**2**) of cadmium is isomorphous and so we included it in the present report.



(L)

E *Z*

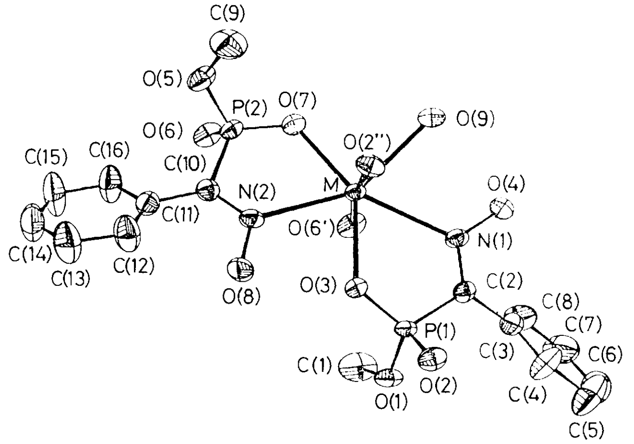


Figure 1. Structure of molecules (**1**) and (**2**) showing 50% probability thermal ellipsoids and atom-labelling scheme. Two symmetry-related oxygen atoms were included to complete the co-ordination sphere

Results and Discussion

Both complexes crystallized on slow evaporation of aqueous solutions and all attempts to dissolve them in various solvents were unsuccessful, polymeric species being formed.

X-Ray Crystallography.—Final non-hydrogen positional parameters, together with their estimated standard deviations (e.s.d.s), for complexes (**1**) and (**2**) appear in Table 1, important

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† *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1989, Issue 1, pp. xvii—xx.

Table 1. Positional parameters with e.s.d.s in parentheses for complexes (**1**) and (**2**)

	(**1**)			(**2**)		
Atom	*x*	*y*	*z*	*x*	*y*	*z*
M*	0.520 71(8)	0.421 4(1)	0.641 72(6)	0.518 94(4)	0.415 85(6)	0.641 05(3)
P(1)	0.580 8(1)	0.039 6(2)	0.690 46(7)	0.578 4(2)	0.035 6(2)	0.693 2(1)
P(2)	0.361 8(1)	0.612 1(2)	0.528 41(8)	0.368 5(2)	0.614 7(2)	0.527 0(1)
O(1)	0.609 9(3)	−0.083 2(5)	0.633 0(2)	0.606 0(4)	−0.085 7(6)	0.634 2(2)
O(2)	0.563 9(3)	−0.053 0(5)	0.754 9(2)	0.567 1(4)	−0.056 3(6)	0.758 8(3)
O(3)	0.498 0(3)	0.146 7(4)	0.666 1(2)	0.490 7(4)	0.138 5(5)	0.670 0(3)
O(4)	0.765 3(3)	0.391 7(5)	0.716 0(2)	0.758 4(4)	0.393 8(6)	0.714 4(3)
O(5)	0.276 6(3)	0.736 6(5)	0.545 3(2)	0.283 6(5)	0.737 5(7)	0.546 9(3)
O(6)	0.381 7(3)	0.629 9(5)	0.452 7(2)	0.383 0(4)	0.638 8(6)	0.449 6(3)
O(7)	0.447 6(3)	0.622 6(5)	0.579 8(2)	0.458 9(4)	0.623 4(6)	0.577 2(3)
O(8)	0.319 1(3)	0.188 9(5)	0.596 3(2)	0.320 9(5)	0.194 5(6)	0.596 4(3)
O(9)	0.625 7(3)	0.628 5(5)	0.698 0(2)	0.623 8(4)	0.625 7(6)	0.696 8(3)
N(1)	0.679 6(4)	0.298 9(5)	0.702 4(2)	0.673 3(5)	0.299 5(7)	0.701 7(3)
N(2)	0.354 5(4)	0.339 0(5)	0.583 7(2)	0.359 9(5)	0.342 3(7)	0.583 0(3)
C(1)	0.623 0(7)	−0.042(1)	0.559 8(3)	0.621(1)	−0.043(1)	0.561 2(5)
C(2)	0.696 8(4)	0.152 7(7)	0.702 8(3)	0.693 0(6)	0.153 4(8)	0.702 7(3)
C(3)	0.795 7(4)	0.074 2(7)	0.711 2(3)	0.794 9(6)	0.078 6(9)	0.711 2(4)
C(4)	0.808 8(6)	−0.042(1)	0.762 0(4)	0.813 4(8)	−0.036(1)	0.760 8(5)
C(5)	0.902 9(7)	−0.120(1)	0.768 0(5)	0.907 3(9)	−0.107(2)	0.764 3(6)
C(6)	0.981 4(6)	−0.086(1)	0.723 2(5)	0.983 2(8)	−0.072(1)	0.719 7(6)
C(7)	0.967 6(6)	0.027(1)	0.671 6(5)	0.964 9(8)	0.038(1)	0.669 1(6)
C(8)	0.874 4(5)	0.109 1(8)	0.665 6(4)	0.870 9(7)	0.114(1)	0.665 6(5)
C(9)	0.266 1(6)	0.798(1)	0.615 2(4)	0.277 4(9)	0.798(1)	0.615 1(5)
C(10)	0.298 0(4)	0.423 7(7)	0.541 5(3)	0.304 8(5)	0.426 6(9)	0.540 5(3)
C(11)	0.201 5(5)	0.381 9(8)	0.507 0(3)	0.205 5(6)	0.389(1)	0.505 2(4)
C(12)	0.133 3(5)	0.279(1)	0.536 3(4)	0.132 8(8)	0.295(2)	0.534 5(6)
C(13)	0.038 5(6)	0.249(1)	0.501 8(5)	0.038 9(9)	0.267(2)	0.500 6(7)
C(14)	0.015 0(6)	0.319(1)	0.438 7(5)	0.018 0(8)	0.327(1)	0.435 2(6)
C(15)	0.083 7(7)	0.421(1)	0.409 6(5)	0.090 0(9)	0.414(2)	0.404 7(6)
C(16)	0.176 2(6)	0.454(1)	0.443 0(4)	0.180 8(8)	0.447(2)	0.438 8(5)

* M = Ca^{2+} for (**1**) and Cd^{2+} for (**2**).

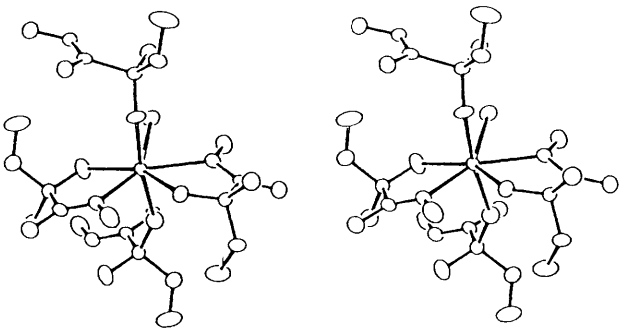

Figure 2. An ORTEP drawing showing a stereoview of the co-ordination sphere of the metal ions. For clarity the phenyl rings are not depicted

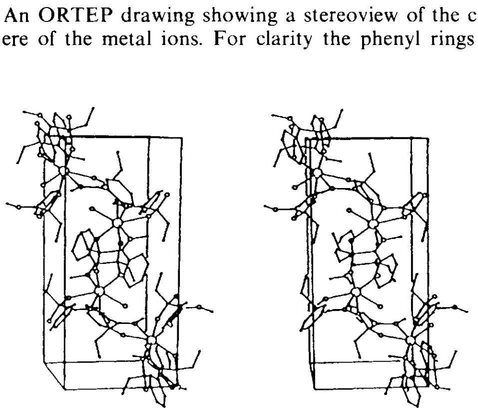

Figure 3. A stereoview of the unit-cell contents displaying the polymeric nature of the crystal lattice

interatomic distances and angles in Table 2. Figure 1 depicts the molecular structure and labelling scheme for both complexes, Figure 2 a stereoview of the co-ordination of the metal ions, and Figure 3 a stereoview of the unit cell.

The metal ions are seven-co-ordinate with a distorted pentagonal bipyramidal geometry, being ligated by five oxygen atoms and two nitrogen atoms. Each metal ion is surrounded by four ligands and one water molecule where two of the ligands are bidentate and two unidentate (see Figure 2). The two bidentate methyl (*E*)-α-hydroxyiminobenzylphosphonate co-ordinate the metal ions through the phosphonate oxygen atom and the oxime nitrogen atom. A fifth co-ordination site is occupied by a water molecule. The remaining two co-ordination sites are occupied by phosphonate oxygens of symmetry-related molecules where O(2″) is generated by the $-x$, $y + \frac{1}{2}$, $\frac{1}{2} - z$ symmetry operation and O(6′) by the $-x$, $-y$, $-z$ operation. Thus, in effect, each ligand acts simultaneously in a chelating and in a bridging mode, generating a polymeric crystal lattice.

The equatorial positions of the pentagonal bipyramid are occupied by the two chelating ligands [O(3), N(1) and O(7), N(2)] and a water molecule [O(9)], with the symmetry-related atoms [O(2″), O(6′)] occupying the axial positions. The two chelating ligands are transposed *trans* to each other probably to minimize steric interaction between the oxime oxygens [O(4) and O(8)]. A *trans* disposition has been observed previously for the copper and zinc complexes.[13,14] The Ca–O distances range from 2.279(4) to 2.493(4) Å and the Ca–N distances are slightly longer, 2.541(5) and 2.602(5) Å. The metal–oxygen distances in the cadmium complex range from 2.220(5) to 2.495(5) Å and the Cd–N distances are 2.494(6) and 2.398(6) Å. The Ca–O contacts fall in the range previously reported.[10] In an ideal pentagonal

Table 2. Bond lengths (Å) and angles(°) for complexes (**1**) and (**2**)

	(**1**)	(**2**)		(**1**)	(**2**)
M–O(2″)	2.300(4)	2.244(5)	P(2)–O(6)	1.487(4)	1.495(5)
M–O(3)	2.434(4)	2.495(5)	P(2)–O(7)	1.489(4)	1.490(6)
M–O(6′)	2.279(4)	2.220(5)	P(2)–C(10)	1.849(6)	1.851(8)
M–O(7)	2.305(4)	2.289(5)	O(1)–C(1)	1.461(8)	1.45(1)
M–O(9)	2.493(4)	2.487(5)	O(4)–N(1)	1.405(6)	1.391(8)
M–N(1)	2.602(5)	2.494(6)	O(5)–C(9)	1.451(9)	1.40(1)
M–N(2)	2.541(5)	2.398(6)	O(8)–N(2)	1.398(6)	1.403(8)
P(1)–O(1)	1.579(4)	1.583(5)	N(1)–C(2)	1.281(7)	1.291(9)
P(1)–O(2)	1.489(4)	1.484(5)	N(2)–C(10)	1.311(7)	1.286(9)
P(1)–O(3)	1.497(4)	1.502(5)	C(2)–C(3)	1.474(8)	1.48(1)
P(1)–C(2)	1.825(6)	1.811(7)	C(10)–C(11)	1.468(8)	1.47(1)
P(2)–O(5)	1.590(5)	1.588(6)			
O(2″)–M–O(3)	80.6(2)	82.3(1)	O(1)–P(1)–O(3)	112.1(3)	112.3(2)
O(2″)–M–O(6′)	171.6(2)	171.8(2)	O(1)–P(1)–C(2)	103.8(3)	103.7(2)
O(2″)–M–O(7)	100.9(2)	99.6(1)	O(2)–P(1)–O(3)	117.9(3)	118.1(2)
O(2″)–M–O(9)	81.1(2)	80.3(1)	O(2)–P(1)–C(2)	108.9(3)	108.4(2)
O(2″)–M–N(1)	94.1(2)	92.9(1)	O(3)–P(1)–C(2)	108.0(3)	108.3(2)
O(2″)–M–N(2)	88.2(2)	88.7(1)	O(5)–P(2)–O(6)	104.5(3)	105.3(2)
O(3)–M–O(6′)	93.2(2)	92.1(1)	O(5)–P(2)–O(7)	110.8(3)	110.8(2)
O(3)–M–O(7)	145.3(2)	141.3(1)	O(5)–P(2)–C(10)	103.9(3)	104.0(3)
O(3)–M–O(9)	133.9(2)	133.1(1)	O(6)–P(2)–O(7)	119.6(3)	119.7(3)
O(3)–M–N(1)	68.4(2)	67.6(1)	O(6)–P(2)–C(10)	109.2(3)	108.1(2)
O(3)–M–N(2)	73.3(2)	72.8(1)	O(7)–P(2)–C(10)	107.7(3)	107.8(2)
O(6′)–M–O(7)	87.4(2)	88.5(2)	P(1)–O(1)–C(1)	123.0(5)	122.7(4)
O(6′)–M–O(9)	99.3(2)	99.6(1)	P(2)–O(5)–C(9)	122.2(6)	120.9(4)
O(6′)–M–N(1)	78.2(2)	79.4(1)	O(4)–N(1)–C(2)	114.7(6)	114.8(5)
O(6′)–M–N(2)	95.6(2)	95.2(2)	O(8)–N(2)–C(10)	115.7(6)	115.8(5)
O(7)–M–O(9)	79.8(2)	84.7(1)	P(1)–C(2)–N(1)	112.9(5)	112.2(4)
O(7)–M–N(1)	144.7(2)	149.6(2)	P(1)–C(2)–C(3)	119.7(5)	120.4(6)
O(7)–M–N(2)	72.1(2)	68.6(1)	N(1)–C(2)–C(3)	127.4(7)	127.4(5)
O(9)–M–N(1)	71.2(2)	70.2(1)	P(2)–C(10)–N(2)	110.1(5)	108.6(4)
O(9)–M–N(2)	147.4(2)	149.0(1)	P(2)–C(10)–C(11)	121.4(6)	123.2(4)
N(1)–M–N(2)	140.7(2)	139.8(2)	N(2)–C(10)–C(11)	128.5(7)	128.2(6)
O(1)–P(1)–O(2)	105.3(3)	105.0(2)			

bipyramidal geometry the angles between the axial ligands should be 180°, between the axial and equatorial 90°, and between the equatorial positions 72 and 144°.[15] It is clear that, while there are deviations from the ideal geometry, the co-ordination sphere has the pentagonal bipyramidal geometry.

The *E* isomer of methyl α-hydroxyiminobenzylphosphonate acts as a chelating agent through the oxyimino nitrogen and the phosphonate oxygen. The geometry of the ligands in these complexes does not deviate significantly from that of the free ligand.[13] All the P–O distances are equivalent and fall within the normal ranges. The chelating moieties are nearly planar as indicated by the N–C–P–O torsion angles [13.3(5) and −10.5(6)° for the calcium complex and 12.8(6) and −7.8(6)° for the cadmium complex]. These torsion angles generate bite distances of 2.806(6) and 2.738(6) Å for (**1**) and 2.803(8) and 2.760(8) Å for (**2**). The phenyl rings are tilted relative to the best planes calculated for the chelating moieties and the dihedral angles between them are 54.5(2) and 27.9(2)° for (**1**) and 53.5(3) and 32.4(3)° for (**2**). No stacking interactions between the phenyl rings in the crystal lattice were observed.

Previous crystallographic work on calcium complexes of various bisphosphonates has shown the Ca^{2+} to have co-ordination numbers of 7—9 possessing various geometries.[9,10] In all these compounds, including that of hedp, the bisphosphonates have been found to act as both bidentate and bridging ligands.[10] This led Nardelli *et al.*[10] to suggest that the previous hypothesis, that the activity of hedp was due to its ability to act as a tridentate ligand, was incorrect. They attributed the activity to the conformation of the anions and particularly to the O $\cdots$ O bite distances of 2.9—3.1 Å. Methyl (*E*)-α-hydroxyiminobenzylphosphonate acts both as a chelating and a bridging ligand towards the calcium ion. While the bite distances of this ligand fall in the range of 2.7—2.8 Å, it does form stable complexes with Ca^{2+} and Cd^{2+} with 'normal' bond lengths, angles, and co-ordination numbers generating an insoluble polymer. Since the ligands used in this study are monoanions they form a 2:1 complex with Ca^{2+} while the bisphosphonates are dianions and thus form 1:1 complexes.

Conclusions

The *E* isomer of methyl α-hydroxyiminobenzylphosphonate forms insoluble complexes with calcium and cadmium by acting simultaneously as a bidenate and a bridging ligand. The metrical parameters of the crystal structure compare favourably with those of the active bisphosphonate complexes. This is the first example demonstrating calcium binding by this novel class of ligands, the α-hydroxyiminophosphonates. We are continuing to explore the chemistry of these and closely related ligands towards metal ions in general and towards calcium binding in particular, in an attempt to prepare compounds which can be utilized in the treatment of diseases of the bone.

Experimental

Preparation of the Complexes of Methyl (E)-*α-Hydroxyiminobenzylphosphonate*.—The ligand was prepared and purified according to the procedures described in refs. 12 and 13. It (0.5 g, 2.1 mmol) was dissolved in deionized water (30 cm^3, pH 7) and to this solution $CaCl_2$ (0.116 g, 1.05 mmol) was

Table 3. Experimental details of the *X*-ray diffraction studies of complexes (**1**) and (**2**) at 23 °C

Crystal parameters[a]	(**1**)	(**2**)
Formula	$C_{16}H_{20}CaN_2O_9P_2$	$C_{16}H_{20}CdN_2O_9P_2$
M	486.37	538.53
a/Å	13.169(1)	13.010(1)
b/Å	8.623(1)	8.666(1)
c/Å	19.161(2)	18.906(2)
β/°	90.93(1)	91.84(1)
U/Å³	2 175(1)	2 130(1)
Space group	$P2_1/c$	$P2_1/c$
Z	4	4
F(000)	992	1 080
D_c/g cm^{-3}	1.423	1.679
Dimensions	0.3 × 0.2 × 0.2	0.4 × 0.3 × 0.2
Treatment of intensity data[b]		
μ/cm^{-1}[c]	4.26	11.04
No. unique data	3 764	3 673
Obs. unique data ($F_o > 6\sigma F_o$)	2 804	2 782
No. of parameters refined	281	281
Max. electron density in final refinement cycle/eÅ^{-3}	0.594	1.019
R[d]	0.0558	0.0434
R'[e]	0.066 4	0.0509

[a] From a least-squares fit to the setting angles of 20 reflections with 2θ > 25°. [b] F_o and $\sigma(F_o)$ were corrected for background radiation, attenuation, and Lorentz polarization effects. [c] No absorption corrections were performed. [d] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [e] $R' = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{\frac{1}{2}}$.

added. Slow evaporation of this solution (3—5 d) afforded clear crystals which were suitable for single-crystal *X*-ray analysis. An analogous procedure was followed for the cadmium complex. One such crystal was mounted on the tip of a glass fibre with epoxy resin and used for structural analysis (Found: C, 39.40; H, 4.00; N, 5.70. Calc. for $C_{16}H_{20}CaN_2O_9P_2$: C, 39.50; H, 4.15; N, 5.75. Found: C, 34.35; H, 3.65; N, 4.85. Calc. for $C_{16}H_{20}CdN_2O_9P_2$: C, 34.40; H, 3.60; N, 5.00%).

X-*Ray Crystallography*.—*Collection and reduction of* X-*ray data*. The crystals were mounted on glass fibres using epoxy resin. Data were collected on a PW 1100 Philips four-circle computer-controlled diffractomer; Mo-K_α (λ = 0.710 69 Å) radiation with a graphite crystal in the incident beam was used. Unit-cell parameters were obtained by a least-squares fit of 25 high-angle reflections (13 < θ < 16°). Both data sets were collected in the ω—2θ scan mode. The scan width, ω, for each reflection was 1° with a scan time of 20 s. Background measurements were made at both limits of each scan. For each data set Lorentz and polarization corrections were applied. None of the data sets displayed any decay in the intensities of the three standard reflections and no correction was applied. No absorption correction was applied. Other information pertinent to data collection and processing is given in Table 3. The space group of the two isomorphous complexes was uniquely determined as $P2_1/c$ by the systematic absences.[16]

Solution and refinement of the structures. The atomic co-ordinates for the metal atoms were obtained by the direct methods program SHELX 86.[17] In both cases, the heavy atoms were placed in their positions and the remaining non-hydrogen atoms were found in a series of subsequent Fourier difference maps. Neutral atom scattering factors and anomalous dispersion corrections were obtained from ref. 18. Anisotropic thermal parameters were used for all the non-hydrogen atoms in both structures. The aromatic hydrogens were placed in their calculated positions C–H 0.95 Å, were constrained to 'ride' on the carbon atoms, and were refined using a common thermal parameter for each aromatic ring.

Using SHELX 76,[19] a full-matrix least-squares refinement was carried out on 281 variables for both structures using unit weights. The refinements converged to reasonable discrepancy indices which are listed in Table 3.

Additional material available from the Cambridge Crystallographic Data Centre comprises thermal parameters and remaining bond distances and angles.

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