Calcium Binding to Hydroxycarboxylic Acids: Crystal Structure of Calcium Di-DL-glycerate Dihydrate

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Abstract

Crystals of calcium di-DL-glycerate dihydrate, $Ca(C_3H_5O_4)_2.2H_2O$, $2C_3H_5O_4^-.Ca^{2+}.2H_2O$, are monoclinic, space group $P2_1/c$, with $a = 14.402$ (3), $b = 7.646$ (3), $c = 10.410$ (2) Å, $\beta = 97.95$ (2)°, $Z = 4$, ρ(obs.) $= 1.66$ and ρ(calc.) $= 1.67$ Mg m^{-3}. X-ray diffraction intensity data for 1886 independent reflections were measured with an automated diffractometer. A trial structure, obtained by the heavy-atom method, was refined by least squares ($R = 0.04$). The calcium ion binds to two water molecules and to three glycerate anions. Two of the glycerate anions chelate the calcium ion, each using a carboxyl O atom together with an α-hydroxyl O atom. The third glycerate residue is coordinated to the calcium ion through the O atom of its terminal hydroxyl group. The seven O atoms in the calcium coordination shell assume a pentagonal-bipyramidal arrangement.

Introduction

We are currently investigating a series of crystal structures of calcium salts and complexes to obtain general information about calcium-coordination geometries, and about the arrangements of ligands that produce effective calcium-binding sites. Hydroxycarboxylic acids are of interest because of their unusual affinities for calcium ions in aqueous solution. These compounds bind calcium with affinity constants that are some 20–50 times greater than those of the corresponding simple carboxylic acids (Davies, 1938; Greenwald, 1938; Cannan & Kibrick, 1938). The presence of an α-hydroxyl group particularly enhances the calcium binding constants of carboxylic acids, and the calcium affinity is further enhanced, but only slightly, by the presence of an additional hydroxyl group at the β position. The available crystallographic data indicate that α-hydroxycarboxylic acids generally chelate calcium ions in a bidentate fashion, by employing a single O atom of the carboxyl group together with the O atom of the α-hydroxyl group (Cook & Bugg, 1973; Gould,

Gould, Rees & Scott, 1975; Einspahr & Bugg, 1977). The crystal structure of calcium glycerate was determined as the simplest example in which to examine the possible contributions that a hydroxyl group at the β position might make to the calcium-binding patterns of α-hydroxycarboxylic acids.

Experimental

Clear plate-like crystals of the complex were grown by cooling a hot aqueous solution of the calcium salt of DL-glyceric acid. Weissenberg and oscillation photographs showed the crystals to be monoclinic. Space group $P2_1/c$ was indicated by the systematic absence of reflections $0k0$ with k odd and $h0l$ with l odd. A crystal fragment with approximate dimensions $0.33 \times 0.27 \times 0.06$ mm was mounted on a Picker FACS-1 diffractometer with the c axis of the crystal slightly inclined to the φ axis of the diffractometer. Approximate cell parameters for use in collecting intensity data were calculated by a least-squares analysis of the angular settings of twelve high-angle reflections (Cu $K\alpha_1$ radiation, $\lambda = 1.54051$ Å).

Intensity data were collected with the diffractometer by the use of Ni-filtered Cu radiation, a scintillation counter, and a θ–2θ scanning technique. Measurements were made for the 1886 independent reflections with $2\theta < 128°$. Three reference reflections, which were monitored periodically, showed no significant intensity fluctuations during the collection of intensity data. Immediately after data collection, more precise values for the cell parameters were determined by a least-squares analysis of 2θ values for 19 high-angle reflections (Cu $K\alpha_1$); these cell parameters, which were

Table 1. *Crystal data*

Stoichiometry	$Ca(C_3H_5O_4)_2.2H_2O$	μ(Cu $K\alpha$)	5.25 mm^{-1}
Z	4	a	14.402 (3) Å
Space group	$P2_1/c$	b	7.646 (3)
ρ(calc.)	1.67 Mg m^{-3}	c	10.410 (2)
ρ(obs.)	1.66	β	97.95 (2)°

not significantly different from those obtained prior to the measurement of intensity data, are listed in Table 1, along with other crystal data.

Intensity values were assigned variances, $\sigma^2(I)$, according to counting statistics plus an additional term, $(0.03S)^2$, S being the scan count. Over 90% of the reflections had $I/\sigma(I) > 1$. All reflections were retained in subsequent calculations, regardless of the $I/\sigma(I)$ ratio. The intensities and variances were corrected for Lorentz and polarization effects; the program *ORABS* (Wehe, Busing & Levy, 1962) was used to make absorption corrections. Transmission factors ranged from 0.37 to 0.73. Structure factors and variances were scaled by means of a Wilson (1942) plot.

The calcium ion was located in a three-dimensional Patterson map. A three-dimensional Fourier synthesis calculated with the phases from the calcium ion revealed the positions of several atoms from the glycerate anions. Subsequent difference Fourier maps produced a complete heavy-atom trial structure. Refinement of the trial structure was initiated with several cycles of block-diagonal least-squares optimization. Subsequent refinement used a modified version of the full-matrix least-squares program *ORFLS* (Busing, Martin & Levy, 1962; Busing, 1971) and minimized the quantity $\sum w(F_o^2 - F_c^2/k^2)^2$, where k is the scale factor, and the weight w is equal to $1/\sigma^2(F_o^2)$. Scattering factors for Ca^{2+}, O, N, and C were from *International Tables for X-ray Crystallography* (1962), and real and imaginary parts of the anomalous-dispersion corrections for these atoms were from Cromer & Liberman (1970). Coordinates for 12 of the 14 H atoms were obtained from a difference Fourier map that was calculated in the final stages of refinement. Two H atoms, that on O(4) of glycerate anion A, and one on water molecule W(2), could not be located. Scattering factors for the H atoms were from Stewart, Davidson & Simpson (1965). Final refinement optimized the scale factor k, the positional and aniso-tropic thermal parameters of the nonhydrogen atoms, and the positional and isotropic thermal parameters for all H atoms except three: the two which could not be located in difference Fourier maps, and H(C3)A which moved to unreasonable positions when included in the refinement. This atom was assigned the approximate isotropic temperature parameter of atom C(3)A and was included in structure factor calculations. Since limited core storage prevented simultaneous variation of all parameters, subsets of parameters were refined in alternate cycles with about half the parameters varied in each cycle. The data set was examined and 19 reflections with $(F_o^2 - F_c^2)/\sigma^2(F_o^2)$ terms between 13–36 were given zero weight in the final refinement. Some, but not all, of these reflections had suspiciously high background intensities. Attempts to refine a secondary-extinction parameter, with or without these reflections, were unsuccessful. In the last cycle of refinement, no

parameter shifted by more than one-fifth of an estimated standard deviation. At the conclusion of refinement, a three-dimensional electron density map showed two peaks of 0.3 e $Å^{-3}$ near W(2) and a peak of 0.7 e $Å^{-3}$ near C(2)A; other regions of the map were featureless. The final R index $(\sum||F_o| - |F_c||/\sum|F_o|)$ is 0.044 and the goodness of fit $\{[\sum w(F_o^2 - F_c^2)^2/(m - s)]^{1/2}$, where m is the number of reflections used and s is the number of parameters refined$\}$ is 2.36.*

Results

The heavy-atom coordinates and their estimated standard deviations are listed in Table 2. H-atom coordinates are given in Table 3. The estimated errors

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* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34095 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Nonhydrogen-atom positional parameters and their standard deviations*

Values for the calcium ion are multiplied by 10^5 and all others by 10^4.

	x	y	z
Ca	22900 (4)	45003 (7)	36420 (5)
W(1)	1007 (2)	2705 (4)	2899 (3)
W(2)	3671 (2)	6085 (3)	4322 (3)
O(1)A	3014 (2)	2182 (3)	4887 (2)
O(2)A	3453 (2)	−580 (3)	4985 (2)
C(1)A	3311 (2)	836 (4)	4394 (3)
C(2)A	3474 (2)	934 (4)	2972 (3)
O(3)A	3217 (2)	2630 (2)	2490 (2)
C(3)A	4492 (3)	540 (6)	2876 (4)
O(4)B	4660 (2)	583 (4)	1581 (2)
O(1)B	1615 (2)	10351 (3)	592 (2)
O(2)B	701 (1)	9174 (3)	1901 (2)
C(1)B	1102 (2)	9160 (4)	892 (3)
C(2)B	934 (2)	7577 (4)	2 (3)
O(3)B	1460 (2)	7828 (3)	−1047 (2)
C(3)B	1190 (2)	5890 (4)	735 (3)
O(4)B	2081 (2)	5972 (3)	1539 (2)

Table 3. *Hydrogen-atom positional parameters and their standard deviations* $(\times 10^3)$

Parameters for H(C3)A were not refined.

	x	x	z
H(W1)	51 (3)	297 (5)	299 (4)
H'(W1)	93 (2)	185 (6)	250 (4)
H(W2)	365 (3)	701 (6)	440 (4)
H(C2)A	305 (2)	−5 (4)	245 (3)
H(C3)A	496 (−)	127 (−)	308 (−)
H'(C3)A	474 (3)	−64 (6)	333 (4)
H(O3)A	311 (3)	262 (5)	187 (3)
H(C2)B	28 (3)	748 (4)	−28 (3)
H(C3)B	113 (2)	495 (5)	10 (3)
H'(C3)B	69 (2)	563 (4)	131 (3)
H(O3)B	131 (3)	709 (6)	−156 (4)
H(O4)B	251 (3)	583 (5)	95 (4)

in positional coordinates are about 0·0006 Å for the Ca ion, 0·004 Å for C, N, and O atoms, and 0·05 Å for H atoms.

The crystal-packing and hydrogen-bonding schemes are depicted in Fig. 1. Since we were unable to locate two of the H atoms that are likely to participate in hydrogen bonding, certain features of the proposed hydrogen-bonding scheme are somewhat tentative. However, it appears that all the H atoms of the water molecules and the hydroxyl groups participate in hydrogen bonding. Distances and angles for the proposed hydrogen bonds are listed in Table 4. One possible explanation for our inability to locate the H atom from hydroxyl group $O(4)A$ and one of those from water molecule $W(2)$ is that these H atoms are involved in a disordered hydrogen-bonding scheme. It can be seen that atoms $O(4)A$ and $W(2)$, and symmetry equivalents of these two atoms, form a nearly square array whose mid-point coincides with an
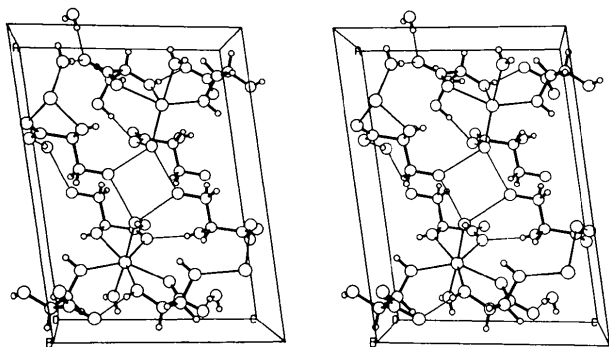

Fig. 1. Stereoview of the unit cell viewed approximately down the b axis. Heavy lines represent covalent bonds; thin lines represent Ca--O interactions and hydrogen bonds. |Figs. 1–5 were prepared by using the computer program ORTEP (Johnson, 1965).|

Table 4. *Hydrogen-bond distances* (Å) *and angles* (°)

Atoms of glycerate ions A and B are designated by the respective letter. Estimated standard deviations are 0·006 Å for $D\cdots A$ distances, 0·06 Å for $H\cdots A$ distances, and 3° for $D-H\cdots A$ angles.

Donor D	Hydrogen H	Acceptor A	$D\cdots A$	$H\cdots A$	$\angle D-H\cdots A$
$W(1)$	$H(W1)$	$O(2)B^i$	2·738	1·99	167
$W(1)$	$H'(W1)$	$O(2)B^{ii}$	2·904	2·16	164
$W(2)$	$H'(W2)$	$O(2)A^{iii}$	2·672	1·97	166
$W(2)^*$	–	$O(4)A^{iv}$	2·762	–	–
$W(2)^*$	–	$O(4)A^v$	2·874	–	–
$O(3)A$	$H(O3)A$	$O(1)A^{vi}$	2·689	2·05	169
$O(3)B$	$H(O3)B$	$O(2)B^{vii}$	2·731	1·97	162
$O(4)B$	$H(O4)B$	$O(2)A^{vi}$	2·738	1·81	173

Symmetry code

(i)	$-x, y - \frac{1}{2}, \frac{1}{2} - z$	(v)	$x, \frac{1}{2} - y, z + \frac{1}{2}$
(ii)	$x, y - 1, z$	(vi)	$x, \frac{1}{2} - y, z - \frac{1}{2}$
(iii)	$x, y + 1, z$	(vii)	$x, \frac{1}{2} - y, z - \frac{1}{2}$
(iv)	$1 - x, y + \frac{1}{2}, \frac{1}{2} - z$		

* Since $H(W2)$ and $H(O4)A$ were not located it is not possible to assign donor and acceptor in these bonds.

inversion center (see, for example, the center of the unit cell in Fig. 1). The short $O\cdots O$ distances within this square-like array suggest that O atoms at adjacent vertices are hydrogen-bonded. Although the H atoms in these bonds are expected to lie near the plane of the four O atoms, two chemically distinct arrangements are possible: the H atom on $O(4)A$ is approximately *trans* to the $C(2)A-C(3)A$ bond, and the four O—H bonds point toward acceptors in a counterclockwise direction in Fig. 1; or the H atom on $O(4)A$ is *cis* to the $C(2)A-C(3)A$ bond, and the O—H bonds point in a clockwise direction in Fig. 1. Our inability to locate the H atoms involved in the array may be due to an approximately equal representation of the two alternative arrangements in the crystal structure.

Fig. 2 shows the environment of the calcium ion, which is coordinated to three glycerate ions and to two water molecules. Two of the glycerate ions, anions A and B, chelate the calcium ion through their carboxyl O atoms $O(1)$ and through their α-hydroxyl O atoms $O(3)$. The third glycerate moiety, a symmetry-equivalent anion B, is coordinated to the calcium through the single hydroxyl O atom $O(4)$. Therefore, the calcium ion is surrounded by a shell composed of seven O atoms: two from water molecules and five from glycerate ions.

The geometry of the calcium-ion coordination polyhedron is shown in more detail in Fig. 3. The seven atoms that are bound to the calcium ion assume a pentagonal-bipyramidal arrangement, with Ca--O distances ranging from 2·346 to 2·443 Å. No hydrogen bonds exist between atoms within the coordination polyhedron and only those contacts within the polyhedron that are between atoms of the same glycerate moiety are shorter than double the van der Waals radius of O.

The conformations of the glycerate anions, together with bond lengths and angles involving only non-hydrogen atoms, are shown in Fig. 4; torsion angles are listed in Table 5. For both glycerate anions, the α-hydroxyl group is nearly coplanar with the carboxyl group, as found in other α-hydroxycarboxylic acids (Newton & Jeffrey, 1977).
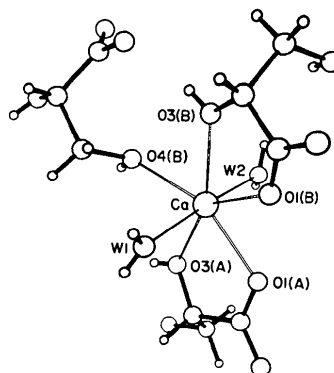

Fig. 2. A representation of the environment of the calcium ion.

Discussion

The two glycerate anions chelate calcium ions through bidentate sites composed of a carboxyl O atom and the α-hydroxyl group. The detailed geometries of these two similar calcium-chelation sites are shown in Fig. 5. This general mode of chelation, involving a carboxyl O atom acting in concert with a second suitable ligand (O or N) at the α position seems to be a particularly favorable type of interaction. In a recent review, Einspahr & Bugg (1977) examined the calcium–carboxyl inter-
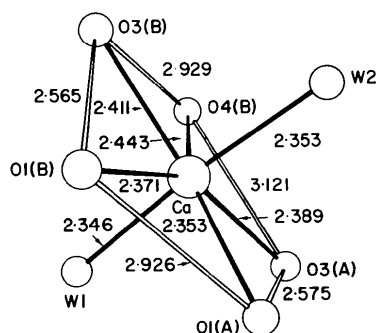

Fig. 3. The calcium-ion coordination shell. Estimated standard deviations are 0·004 Å for Ca--O distances, and 0·006 Å for O···O distances.

actions in a large number of crystal structure determinations. They report 36 examples of the chelation mode described above, which they call α chelation, and an additional 13 examples of more complex chelation patterns, most of which are multidentate elaborations of α chelation. Closer examination of these examples from crystal structures of calcium carboxylate complexes reveals a marked preference for α chelation over other possible modes of calcium binding. Of 45 examples of calcium binding to the carboxylate groups of compounds that have a suitable ligand attached to the α position, only one does not display α chelation. In addition, only three examples are found in which a carboxyl group with a suitable ligand attached to the α position does not bind calcium at all. This general mode of chelation is probably responsible for the interaction of α-hydroxycarboxylic acids with calcium ions in aqueous solutions, and accounts for the observation that the calcium affinities of α-hydroxycarboxylic acids are much higher than those of the unsubstituted acids.

The contribution made by the β-OH groups to the binding of Ca^{2+} by the glycerate ions in this structure is minor; only one of the two groups serves to bind calcium, and it only as a unidentate ligand. The extent to which this latter interaction might contribute to the slight elevation in the calcium affinity of the glycerate ion over that of simple α-hydroxycarboxylates in aqueous solution is not known.

One might have expected the β-OH's to cooperate with other glycerate O atoms to form chelation sites for

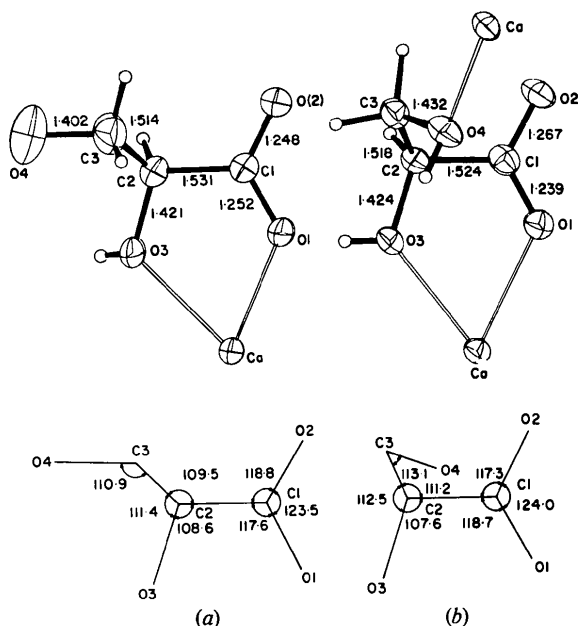Fig. 4. Geometry of the glycerate anions including bond distances (Å) and angles (°) between nonhydrogen atoms. (a) Molecule A, (b) molecule B. Nonhydrogen atoms are represented by thermal ellipsoids scaled to include 50% probability. H atoms are represented by spheres of arbitrary radius. Estimated standard deviations are 0·006 Å for bond lengths, and 0·3° for bond angles. The H atom attached to O(4) of molecule A was not found.

Table 5. *Torsion angles* (°) *for the glycerate moieties*

Signs of the angles reflect the conventions of Klyne & Prelog (1960). Estimated standard deviations for these angles are about 0·4°.

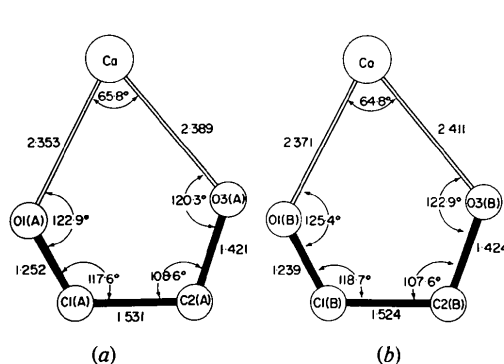|	Glycerate A	Glycerate B
O(1)–C(1)–C(2)–O(3)	−1·2	1·1
O(2)–C(1)–C(2)–O(3)	176·7	−179·1
C(1)–C(2)–C(3)–O(4)	178·8	−46·9
O(3)–C(2)–C(3)–O(4)	−61·1	73·9

Fig. 5. Comparison of the calcium-chelation geometries of the glycerate anions. (a) Molecule A, (b) molecule B.

calcium. A number of examples of such interactions, falling into two main categories, have been observed in crystal structures. The β-OH can join with the α-chelation pattern to form a tridentate site (Furberg & Helland, 1962; Cook & Bugg, 1973; Sicignano, Ghandi & Eriks, 1974; Mazid, Palmer & Balchin, 1976). Alternatively, the β-OH may join with the carboxyl O atom not involved in the α chelation to form a second chelation site (DeLucas, Bugg, Terzis & Rivest, 1975; Taga & Osaki, 1976). Given the predominance of the α-chelation pattern over other possible configurations, the cooperation of the α- and β-OH's to form a simple bidentate site, such as is observed in a number of Ca–carbohydrate complexes (Cook & Bugg, 1977), is not expected. In any case, none of the above possibilities is realized in calcium diglycerate dihydrate. Apart from the single unidentate interaction with Ca^{2+} mentioned above, the β-OH's serve only as participants in hydrogen bonding.

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Structure Moléculaire et Cristalline du Bis(μ-benzènethiolato)-bis[dicarbonyliridium(I)]: Un Exemple d'Empilement en Chaîne d'Entités Dinucléaires

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Abstract

The crystal and molecular structure of bis(μ-benzene-thiolato)-bis[dicarbonyliridium(I)] [Ir(μSC_6H_5)(CO)$_2$]$_2$, $M_r = 714.76$, has been determined from single-crystal X-ray analysis. The space group is $P2_1/c$, with $a = 24.251$ (7), $b = 8.934$ (2), $c = 17.298$ (6) Å, $\beta = 103.95$ (5)°, $Z = 8$, $\rho_x = 2.610$, $\rho_m = 2.61$ (1) Mg m^{-3}, $V = 3637.5$ Å^3. Parameters of 24 non-hydrogen atoms in the asymmetric unit were refined by full-matrix least-squares techniques to a conventional R factor of 0.055. Two types of independent dinuclear [Ir(SC$_6$H$_5$)(CO)$_2$]$_2$ units of comparable geometry are observed. In both cases the iridium atom exhibits a square-planar arrangement of two carbonyl groups and two bridging S atoms of two phenylthiolato groups. The former (A) has an

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