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Calcium Complexation by α-Hydroxy Ketones. Characterization of a Calcium Complex of Phenacyl Alcohol

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Solution and solid-state structural data are presented for a discrete complex of phenacyl alcohol with calcium chloride, $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$, in which phenacyl alcohol serves as a bidentate ligand, with coordination of calcium to both the carbonyl oxygen and the hydroxyl group. This constitutes the first structural characterization of a calcium complex with the important pharmacophoric α-hydroxy ketone functionality.

The ubiquitous role of calcium in biochemical systems is well-established.[1] Recognition of the critical dependence of many important biochemical processes on calcium ion concentration has led to a wide range of studies of calcium complexation.[2] Numerous naturally-occurring[3] and synthetic[4] ionophores for calcium have been identified, and an appreciable understanding of the structural features important for efficient calcium complexation has been developed.

We were struck by an early report of the use of calcium complexation in the purification of a simple phenacyl alcohol derivative, in which Robinson described isolation of a crystalline, air-stable complex with a discrete melting point.[5] Although calcium complexation by α-hydroxy carboxylates is well-known,[6] calcium complexation by α-hydroxy ketones has only rarely been inferred,[5,7] and to our knowledge no crystallographic structural characterizations of such complexes have been reported. Given the occurrence of the α-hydroxy ketone functionality in a number of important pharmaceutical compounds (including, for example, the corticosteroids and the tetracycline antibiotics), and a scattering of reports suggesting the potential interaction of such pharmaceuticals with calcium ion *in vivo*,[7,8] we chose to examine the interactions of this class of compounds with calcium ion. We report herein evidence for the formation of a complex of calcium chloride with phenacyl alcohol in solution and the results of an X-ray crystallographic analysis of the isolated complex.

Experimental Section

Preparation of $C_6H_5COCH_2OH$. Chloroacetophenone (6.00 g, 38.8 mmol) was dissolved in a mixture of 50 mL of absolute ethanol and 2 mL of acetic acid. To this solution was added potassium acetate (7.00 g, 71.3 mmol). The stirred mixture was heated at reflux for ca. 3.5 h, at which time TLC (10% pentane in ether, silica) showed the reaction to be complete. The pale-yellow mixture was poured over 200 mL of ice, causing a yellow oil, which soon crystallized, to separate. The mixture was allowed to stand overnight and then filtered, affording crude acetoxyacetophenone (76%), mp 42.5–43.5 °C. This crude material (1.00 g, 5.61 mmol) was dissolved in 100 mL of water to which was added 1 mL of concentrated aqueous HCl. The stirred mixture was heated at reflux for 1.5–3 h, at which time TLC (10% pentane in ether, silica) showed the reaction to be complete. The mixture was cooled and then extracted thrice with ether (total volume 100 mL). Removal of solvent on a rotary evaporator afforded a viscous yellow oil which crystallized after being scratched and allowed to stand overnight. The pale-yellow crude product was recrystallized from water (treatment of an ethereal solution with activated charcoal also served to purify the crude material), affording the pure alcohol (46%), mp 85–86 °C (lit.[9] mp 85–86 °C). ^1H and ^{13}C NMR data are presented in Table I. IR (KBr): $\nu_{C=O} = 1693\ cm^{-1}$, $\nu_{C-O} = 1112\ cm^{-1}$. IR ($CHCl_3$): $\nu_{C=O} = 1688\ cm^{-1}$. IR ($CH_3OH$): $\nu_{C=O} = 1697\ cm^{-1}$.

Preparation of $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$. Phenacyl alcohol (0.500 g, 3.67 mmol) was dissolved in 30 mL of absolute methanol, with warming to effect complete dissolution. Anhydrous $CaCl_2$ (0.204 g, 1.84 mmol) was added, and the mixture was heated at reflux for 4 h. After the solution was cooled to room temperature, the solvent was evaporated under a stream of nitrogen. The resulting solid was further dried in a vacuum oven for 2 h at 30 °C, then stored in a desiccator overnight, affording the complex in quantitative yield, mp 105–107 °C. Dissolution in methanol, layering with pentane, and slow evaporation afforded white, crystalline material and a small amount of green, oily residue. Physical removal of the oily material by wiping with absorbent tissue afforded the complex, mp 106–108 °C, in analytically pure form. Anal. Calcd for $C_{16}H_{24}CaCl_2O_8$: C, 42.20; H 5.31. Found: C, 42.18, 42.26; H, 5.55, 5.51. ^1H and ^{13}C NMR data are presented in Table I. IR (KBr): $\nu_{C=O} = 1660\ cm^{-1}$, $\nu_{C-O} = 1093\ cm^{-1}$. IR ($CH_3OH$): $\nu_{C=O} = 1684\ cm^{-1}$. The same complex has also been prepared in $CHCl_3$ solution, effecting complex formation through slow addition of excess anhydrous $CaCl_2$ to a refluxing solution of phenacyl alcohol.

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Table I. ^{1}H and ^{13}C NMR Chemical Shifts [δ, in ppm relative to internal $Si(CH_3)_4$] for Uncomplexed ("free") Phenacyl Alcohol and Its $CaCl_2$ Complex in CD_3OD

		C=O	CH_2	OH	*ipso*-C	*o*-CH	*m*-CH	*p*-CH
^{1}H	free		4.79	4.77		7.81 (d, 7.3)	7.37 ("t", 7.3)	7.49 (t, 7.3)
	complex		5.27	(exchanged)		8.01 (d, 7.4)	7.51 ("t", 7.4)	7.67 (t, 7.4)
^{13}C	free	200.1	66.4		135.6	128.6	129.8	134.7
	complex	203.7	67.2		133.4	128.8	129.8	135.9

Table II. Details of Crystallographic Data Collection for $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$

empirical formula	$C_{16}H_{24}CaCl_2O_8$
formula weight	455.4
temperature (K)	120
crystal size (mm)	0.3 × 0.4 × 0.6
crystal system	orthorhombic
appearance	colorless block
radiation	Mo Kα
wavelength (Å)	0.71069
monochromator	highly oriented graphite crystal
space group	*Pbcn*
a (Å)	7.374(3)
b (Å)	23.314(5)
c (Å)	12.458(3)
V (Å^3)	2141.9(11)
Z	4
ρ_{calcd} (g cm^{-3})	1.412
μ (mm^{-1})	0.572
F(000)	952
scan rate (deg min^{-1})	60.00
scan range (ω)	1.00°
reflections collected	5442
number of independent reflections	2467 (R_{int} = 3.81%)
number of observed reflections [$F > 6\sigma(F)$]	1571
2θ range (deg)	0.0–55.0
data collected	$+h, \pm k, +l$
number of parameters refined	124
final *R* indices (obs data)	R = 4.19%, R_w = 7.41%
final *R* indices (all data)	R = 7.17%, R_w = 14.24%
goodness-of-fit	0.46
largest and mean Δ/σ	0.070, 0.016
data-to-parameter ratio	12.7:1
max., min. in final difference map	+0.42, −0.32 e Å^{-3}

Vapor diffusion of hexanes into a so-prepared solution of the complex in $CHCl_3$ afforded crystals suitable for X-ray diffraction analysis

X-ray Crystallographic Analysis of $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$. The complex crystallized in the orthorhombic space group *Pbcn* with a = 7.374 (3) Å, b = 23.314 (5) Å, and c = 12.458 (3) Å, V = 2141.9 (11) Å^3, and Z = 8. Data were collected on a Siemens R3m/V diffractometer, using Mo Kα radiation, to a maximum of 2θ = 55.0°, giving 2467 unique reflections. The final discrepancy index was R = 0.0419, R_w = 0.0741 for 1571 independent reflections with $F > 6\sigma(F)$.

A colorless block (0.3 × 0.4 × 0.6) of the complex was mounted on a glass fiber and cooled to 120 K in a stream of cold nitrogen. Data were collected by use of ω scans between 0.0 and 55.0° in 2θ, over the index ranges $0 \le h \le 9$, $-30 \le k \le 30$, $0 \le l \le 16$ (speed 60.00° min^{-1} in ω); 5442 reflections were collected, of which 2467 were independent reflections. Crystal data are summarized in Table II.

Table III. Atomic Coordinates (×10^4) and Equivalent Isotropic Thermal Parameters (Å^2 × 10^3) for $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$[a]

atom	*x*	*y*	*z*	U_{eq}
Ca	5000	4351(1)	7500	21(1)
Cl	2171(1)	5884(1)	5834(1)	27(1)
C(1)	3618(5)	3670(1)	5357(3)	22(1)
C(2)	2934(5)	4265(1)	5071(2)	22(1)
C(3)	3390(5)	3203(1)	4575(3)	21(1)
C(4)	2611(5)	3301(2)	3562(3)	28(1)
C(5)	2437(5)	2851(2)	2835(3)	31(1)
C(6)	2978(5)	2303(2)	3121(3)	34(1)
C(7)	3746(5)	2198(2)	4134(3)	32(1)
C(8)	3959(5)	2653(1)	4848(3)	25(1)
O(1)	4316(3)	3594(1)	6240(2)	24(1)
O(2)	3379(4)	4639(1)	5929(2)	30(1)
O(3)	5000	5393(1)	7500	30(1)
O(4)	7820(4)	4333(1)	6652(2)	35(1)
O(5)	0	5174(2)	7500	33(1)
H(2A)	3384	4432	4345	21
H(2B)	1568	4237	4969	43
H(4)	2238	3710	3385	31
H(5)	1856	2956	2215	34
H(6)	2880	1958	2624	22
H(7)	4165	1808	4280	32
H(8)	4477	2584	5557	41
H(2)	2874	4961	5744	35
H(3A)	4442	5604	7131	84
H(4A)	7934	4278	5984	12
H(4B)	8662	4584	6792	59
H(5A)	503	5405	7059	44

[a] U_{eq} defined as one-third of the trace of the orthogonalized U_{ij} tensor. Units of each esd in parentheses, are those of the least significant digit of the corresponding parameter.

Table IV. Bond Lengths (Å) for $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$[a]

Ca–O(1)	2.415(3)	Ca–O(2)	2.389(3)
Ca–O(3)	2.429(4)	Ca–O(4)	2.333(3)
Ca–O(1A)	2.415(3)	Ca–O(2A)	2.389(3)
Ca–O(4A)	2.333(3)	C(1)–C(2)	1.519(5)
C(1)–C(3)	1.471(5)	C(1)–O(1)	1.227(4)
C(2)–O(2)	1.417(4)	C(3)–C(4)	1.404(5)
C(3)–C(8)	1.391(4)	C(4)–C(5)	1.392(5)
C(5)–C(6)	1.384(5)	C(6)–C(7)	1.406(5)
C(7)–C(8)	1.393(5)		

[a] Units of each esd, in parentheses, are those of the least significant digit of the corresponding parameter.

The systematic absences unambiguously showed the space group to be *Pbcn*. The structure was solved by direct methods, using the Siemens SHELXTL PLUS (VMS) system. Full-matrix least-squares refinement (on *F*) converged at R = 0.0419, R_w = 0.0741: weighting scheme $w^{-1} = \sigma^2(F) + 0.0239F^2$; 1571 independent reflections with $F > 6\sigma(F)$; 124 parameters refined; all heavy atoms anisotropic; H atoms (excluding water molecules) riding with fixed isotropic *U*. The maximum and minimum peaks on a final difference electron density map were +0.42 and −0.32 e Å^{-3}, respectively. Final atomic positions and thermal parameters are provided in Table III, while representative bond lengths and angles are provided in Tables IV and V. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Results and Discussion

Solution Studies. Coordination of a cationic species to a carbonyl is in general expected to result in a lowering of the C=O stretching energy (ν_{CO}). Indeed, a definite reduction in ν_{CO} upon calcium complexation is observed for both phenacyl alcohol and for methoxyacetophenone in methanol. The latter compound was examined to determine whether the presence of an intramolecular hydrogen bond in phenacyl alcohol,[10] which presumably is disrupted upon formation of the complex, might mask changes in ν_{CO}. In fact, methoxyacetophenone does display

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Table V. Bond Angles (deg) for $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$[a]

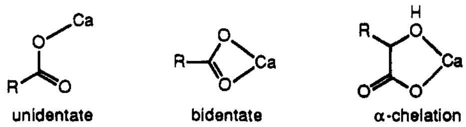
O(1)–Ca–O(2)	64.4(1)	O(1)–Ca–O(3)	137.0(1)
O(2)–Ca–O(3)	73.7(1)	O(1)–Ca–O(4)	83.0(1)
O(2)–Ca–O(4)	94.6(1)	O(3)–Ca–O(4)	91.1(1)
O(1)–Ca–O(1A)	86.1(1)	O(2)–Ca–O(1A)	147.3(1)
O(3)–Ca–O(1A)	137.0(1)	O(4)–Ca–O(1A)	95.4(1)
O(1)–Ca–O(2A)	147.3(1)	O(2)–Ca–O(2A)	147.4(1)
O(3)–Ca–O(2A)	73.7(1)	O(4)–Ca–O(2A)	86.0(1)
O(1A)–Ca–O(2A)	64.4(1)	O(1)–Ca–O(4A)	95.4(1)
O(2)–Ca–O(4A)	86.0(1)	O(3)–Ca–O(4A)	91.1(1)
O(4)–Ca–O(4A)	177.9(1)	O(1A)–Ca–O(4A)	83.0(1)
O(2A)–Ca–O(4A)	94.6(1)	C(2)–C(1)–C(3)	118.9(3)
C(2)–C(1)–O(1)	118.8(3)	C(3)–C(1)–O(1)	122.3(3)
C(1)–C(2)–O(2)	107.9(3)	C(1)–C(3)–C(4)	121.4(3)
C(1)–C(3)–C(8)	119.1(3)	C(4)–C(3)–C(8)	119.5(3)
C(3)–C(4)–C(5)	120.0(3)	C(4)–C(5)–C(6)	120.0(3)
C(5)–C(6)–C(7)	120.6(3)	C(6)–C(7)–C(8)	119.0(3)
C(3)–C(8)–C(7)	120.8(3)	Ca–O(1)–C(1)	124.4(2)
Ca–O(2)–C(2)	124.1(2)		

[a] Units of each esd, in parentheses, are those of the least significant digit of the corresponding parameter.

a higher ν_{CO} than phenacyl aclohol in $CHCl_3$ (1702 vs 1687 cm^{-1}), supporting a weakening of the C═O bond by the hydrogen bonding interaction. In methanol, however, both the alcohol and the ether display a ν_{CO} of ca. 1697 cm^{-1}. The isolated calcium chloride complex of phenacyl alcohol, when redissolved in methanol, displays a ν_{CO} of 1684 cm^{-1}. Some uncomplexed phenacyl alcohol is also apparent in this spectrum, suggesting establishment of equilibrium between complex and free phenacyl alcohol under these concentration conditions. Addition of 40 equiv of calcium chloride results in a further shift in ν_{CO}, to 1679 cm^{-1}, consistent with driving equilibria further toward formation of the complex. The very broad absorption observed in this case may reflect establishment of other equilibria under these conditions. Similarly, ν_{CO} for methoxyacetophenone is shifted from 1698 to 1682 cm^{-1} in the presence of 40 equiv of calcium chloride. In this case, uncomplexed methoxyacetophenone is also resolved in the infrared spectrum.

^1H and ^{13}C NMR spectra provide clear evidence for complex formation in solution. Treatment of a CD_3OD solution of phenacyl alcohol with excess $CaCl_2$ results in appreciable changes in the chemical shifts of the protons and carbons of the α-hydroxy ketone group (Table I), while other resonances display negligible or only modest changes in chemical shift. Titration of a CD_3OD solution of phenacyl alcohol with increments of $CaCl_2$ gives downfield chemical shift changes until 0.5 equiv of $CaCl_2$ has been added, after which addition of additional $CaCl_2$ results in negligible changes in chemical shift, suggesting the formation of a complex incorporating 2 equiv of phenacyl alcohol. This solution stoichiometry is supported by potentiometric speciation studies.[11]

A number of calcium complexes of α-hydroxy acids and α-amino acids have been structurally characterized.[12] The most common bonding mode is simple η^1 (unidentate) coordination to a single carboxylate oxygen, although bidentate coordination to the carboxylate and "α-chelation mode" coordination to one carboxylate oxygen and an α-substituent are not uncommon.



In contrast, no complexes of α-hydroxy ketones have been structurally characterized. The solution NMR evidence presented above supports an "α-chelation" mode for phenacyl alcohol, with both the hydroxyl group and the ketone oxygen coordinated to calcium. As we discuss below, solid-state structural study fully supports this bonding mode.

Solid-State Studies. Evaporation of a methanolic solution of phenacyl alcohol containing 0.5 equiv of $CaCl_2$ affords $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$ as an air-stable solid. This complex may be prepared from less-polar media by taking advantage of the ability of phenacyl alcohol to solubilize $CaCl_2$ in such solvents. Thus, slow addition of excess solid $CaCl_2$ to a refluxing chloroform solution of phenacyl alcohol followed by filtration and evaporation affords the same complex. This complex may be recrystallized from methanol/pentane solution by slow evaporation, or from chloroform solution by vapor diffusion with hexanes, affording colorless, air-stable crystals. The complex displays a discrete melting point, 106–108 °C, which is significantly higher than that of the uncomplexed alcohol (85–86 °C). The solid-state infrared spectrum (KBr pellet) of the complex supports complexation to the carbonyl oxygen of phenacyl alcohol, with the significant lowering of the C═O stretching frequency (from 1693 cm^{-1} in the free ketol to 1660 cm^{-1} in the complex) consistent with withdrawal of electron density from the C═O double bond by the positively charged calcium ion. The only other significant changes observed in the solid-state infrared spectrum of phenacyl alcohol upon calcium complexation are a significant broadening of the O–H stretching band and a reduction of the C–O single bond stretching frequency (from 1112 cm^{-1} in the uncomplexed alcohol to 1093 cm^{-1} in the calcium complex), also supporting the proposed "α-chelation" mode of binding to calcium.

The stoichiometry of the complex is confirmed by single-crystal X-ray diffraction analysis (Figures 1 and 2). The calcium ion is coordinated by two bidentate phenacyl alcohol molecules and three water molecules, providing an overall seven-coordinate complex. The two chloride counterions, at a distance of 4.63 Å from the calcium ion, and a fourth water molecule (distance 4.16 Å) are clearly not within the primary coordination shell. The coordination geometry around calcium (Figure 3) is very nearly pentagonal bipyramidal, with two waters in the axial positions (O–Ca–O angle 177.9°) and the two phenacyl alcohol units plus an additional water in the equatorial plane. The average $O_{equatorial}$–Ca–$O_{equatorial}$ bond angle of 72.5° and average $O_{equatorial}$–Ca–O_{axial} bond angle of 90.0° are in accord with this geometric formulation. The primary distortion from idealized pentagonal bipyramidal geometry arises from a ca. 23° twist of the two roughly planar phenacyl alcohol chelate units with respect to each other, leaving the calcium ion, the two alcohol oxygens, and the equatorial water coplanar and placing the carbonyl oxygens slightly above and below this plane. Interestingly, this twist, which may help minimize steric repulsions between the two phenacyl alcohol chelates, imparts a chirality to each calcium chelate; packing of such chelates in the centrosymmetric space group *Pbcn* requires alternation of left- and right-handed twists, as is shown in the packing diagram (Figure 4). In addition, the O–Ca–O angles within

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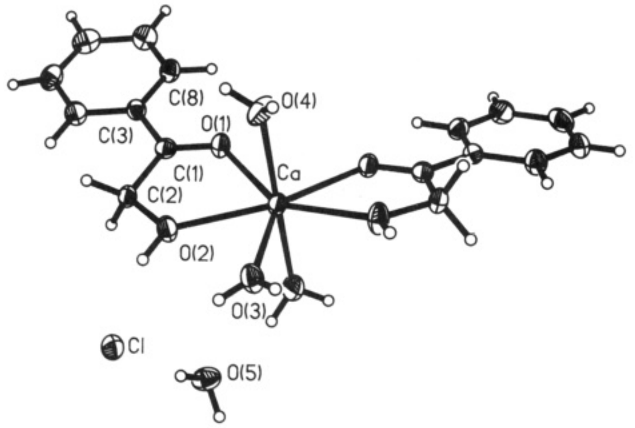

Figure 1. Molecular structure of $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$.

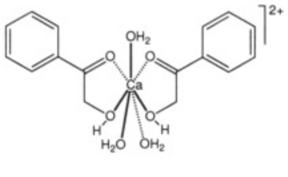

Figure 2. Schematic depiction of structure/connectivity of the cationic species of $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$, omitting counterions and noncoordinated water for clarity.

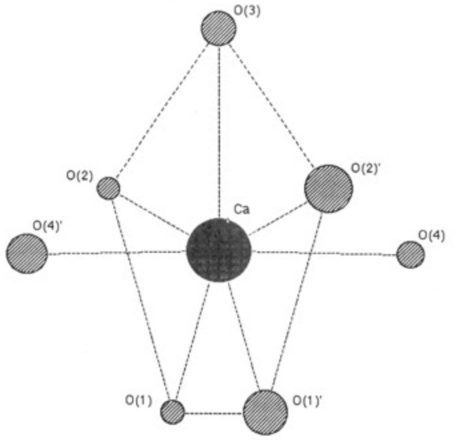

Figure 3. Calcium coordination geometry in $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$, displaying near-pentagonal bipyramidal arrangement of ligand oxygens.

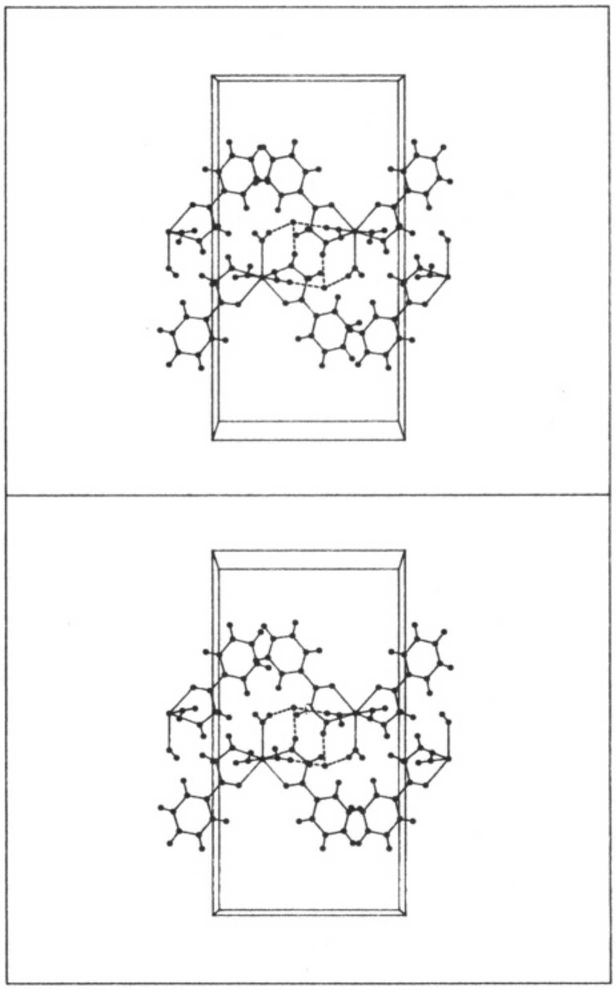

Figure 4. Packing diagram for $[(C_6H_5COCH_2OH)_2Ca(H_2O)_3]^{2+}\cdot 2Cl^-\cdot H_2O$, showing alternation of left- and right-handed twisted forms of the complex.

each chelate ring, at 64.4°, display a contraction from the 72° expected for perfect pentagonal coordination. This presumably simply reflects the inability of a five-membered ring chelate to span the larger idealized angle. The gross geometry is quite similar to that seen in the α-D-fucose complex of $CaBr_2$, in which two fucose units each chelate the calcium through their vicinal diol functionality.[13]

The equatorial water is a "class 1 water",[12a,14] with both hydrogen atoms involved in hydrogen bonds to the chloride counterions (d_{O-H} = 0.789 Å, d_{H-Cl} = 2.417 Å, O–H–Cl angle = 156.8°). As is commonly seen in hydrated calcium complexes, the calcium ion lies on the plane bisecting this water ligand. The "Ca–O dipole angle" for this ligand (i.e., the angle between the Ca–O bond and the water dipole moment) is approximately 0°. This angle ranges from 0 to as high as 80° in other calcium complexes, with class 1 waters generally displaying lower values than class 2 waters (which, in addition to the two hydrogen bonds characteristic of class 1 waters, also accept a third hydrogen bond).[14] The axial waters each participate in only one hydrogen bond, acting as hydrogen bond donors to the uncoordinated water (d_{O-H} = 0.871 Å, d_{H-O} = 1.909 Å, O–H–Cl angle = 161.0°). Again, the calcium ion lies very close to the plane bisecting these coordinated water molecules. For these ligands, however, the Ca–O dipole angle is approximately 30°, much larger than that for the equatorial water but still well within the range considered typical. Counter to the general correlation between smaller Ca–O dipole angles and shorter bond lengths, the Ca–$O_{equatorial}$ bond length, at 2.429 Å, is appreciably longer than the Ca–O_{axial} bond length of 2.333 Å. It is not clear whether is a reflection of the bonding requirements of the complex or if it is simply a steric or solid-state effect.

In simple carbonyl (generally peptide) and α-hydroxy carboxylate complexes, coordinated calcium is often found close to the plane of the carboxylate or carbonyl group.[12a,15] In the phenacyl alcohol complex, the calcium is ca. 0.3 Å out of the plane of the carbonyl group. The Ca—O=C

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angle, at 124.4°, is typical for the α-chelation mode (range 110–130°) and also falls well within the range seen for simple unidentate coordination of peptide carbonyls (110–140°). The calcium–$O_{carbonyl}$ bond length, at 2.415 Å, correlates well with other calcium carbonyl and carboxylate complexes. Coordination numbers of seven and eight are most commonly observed for α-mode chelate complexes, while seven coordination is relatively uncommon for simple peptide carbonyl complexes, in which six- and eight-coordination is much more common.[12a,15]

The chelate ring appears to accommodate the calcium ion nicely. Only minor distortions of bond angles from their idealized geometries are evident ($CH_2—C=O$ = 118.8°, $HO—CH_2—C$ = 107.9°), and bond distances are completely consistent with those in simple, unstrained calcium complexes.

Conclusions

Phenacyl alcohol, a simple α-hydroxy ketone, forms a discrete complex with calcium chloride in both protic (methanol) and aprotic (chloroform) organic solvents. Solution and solid-state studies indicate complexation is effected through chelation by both the alcohol and the ketone functionality of the α-hydroxy ketone. Although related chelates of α-hydroxy acids have been characterized, this represents the first clear demonstration of calcium chelation by an α-hydroxy ketone.

Given the apparent near-optimum chelation geometry for calcium afforded by phenacyl alcohol, we are continuing to examine the complexation of calcium by other α-hydroxy ketones, focusing on pharmacologically significant compounds, including the corticosteroids and the tetracycline-type antibiotics, and have begun a study of their solution speciation and ion binding affinities and selectivities.

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