Calcium Complexation to Derivatives of Isonicotinic Acid: [Tetraaquabis(isonicotinamide)calcium] Dichloride and Tetraaquabis(isonicotinato)calcium, $C_{12}H_{20}CaCl_2N_4O_6$ and $C_{12}H_{16}CaN_2O_8$

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Abstract

[Calcium(isonicotinamide)$_2$(H$_2$O)$_4$]Cl$_2$ (I), C_{12}-$H_{20}CaCl_2N_4O_6$: molecular weight = 427.3, triclinic, $P\bar{1}$, $a = 9.778(5)$, $b = 8.623(4)$, $c = 7.363(3)$ Å, $\alpha = 115.09(3)$, $\beta = 73.40(4)$, $\gamma = 75.98(3)°$, $V = 489.3(3)$ Å^3, $Z = 2$, $D_x = 1.450$ g cm^{-3}, $F(000) = 222$, λ(Mo Kα) = 0.71069 Å, μ(Mo Kα) = 6.195 cm^{-1}, 295 K, final $R = 4.7\%$, $R_w = 6.6\%$ for 1985 observed reflections [$I > 3\sigma(I)$].

[Calcium(isonicotinate)$_2$(H$_2$O)$_4$] (II), $C_{12}H_{16}CaN_2$-O_8: molecular weight = 356.3, monoclinic, $P2_1/a$, $a = 7.208(3)$, $b = 36.368(28)$, $c = 6.159(2)$ Å, $\beta = 104.74(3)°$, $V = 1561(1)$ Å^3, $Z = 4$, $D_x = 1.516$ g cm^{-3}, $F(000) = 744$, λ(Mo Kα) = 0.71069 Å, μ(Mo Kα) = 4.312 cm^{-1}, final $R = 6.4\%$, $R_w = 8.3\%$ for 1819 observed reflections [$I > 3\sigma(I)$].

In [calcium(isonicotinamide)$_2$(H$_2$O)$_4$]Cl$_2$, [C_{12}-$H_{20}CaCl_2N_4O_6$] (I), calcium is octahedrally coordinated to six oxygen atoms; four from water molecules and the carbonyl oxygen atoms of amide groups of two different isonicotinamide molecules. Amide and hetero-ring nitrogen atoms are unbound to calcium. Chloride atoms in the cell are hydrogen bonded to hydrogen atoms of amide groups. The seven coordinate calcium atom in calcium(isonicotinate)$_2$(H$_2$O)$_4$, [$C_{12}H_{16}CaN_2O_8$] (II), is coordinated to four water molecule oxygen atoms, two oxygen atoms of a bidentate carboxylate group of one isonicotinate molecule and to the nitrogen atom of a second isonicotinate molecule.

Introduction

In vitro studies have shown calcium to be a necessary participant in chemically mediated histamine release from mast cells [1–3]. Mast cells challenged with allergen in calcium free media do not release histamine [2], however, the addition of calcium to the medium leads to release. Other literature suggests that calcium may enter the mast cell in its mechanistic role. Direct injection of calcium into a mast cell triggers histamine release in the absence of allergen [4]. Mast cells in the presence of calcium and known calcium ionophores release histamine [2]. Thus there is reason to be interested in the role calcium may play in this immunological system and to seek specific knowledge of calcium binding patterns with small molecules that may serve as allergens or be present in the mast cell environment.

The crystalline complexes formed by calcium with allergens of low molecular weight: nicotinic acid [5], paraaminosalicylate [6], penicillin V [7], and salicylate [8] have shown calcium atoms lying in layers, bridged by carboxylate groups or other polar organic functional groups which lie above and below the calcium layers. In this series of structures, calcium displays flexibility in geometry and coordination number and appears capable of movement within these layers by finding alternate binding groups on slight movement. These structures suggest a view of calcium able to travel between sheets of oxygen atoms because of its flexibility in adapting to various binding geometries.

Calcium in these structures tends to maximize use of ligation sites, with ligands arranged so that all unshared pairs of electrons are pulled inward towards the alkaline earth metal, the ligand turning a hydrophobic facade to the surrounding environment. Water molecules are common in the calcium coordination sphere. Complex networks of hydrogen bonding link together bound functional groups.

The solid-state structure of calcium bound to an inhibitor; calcium bis(2,4-dinitrophenoxide) heptahydrate shows a dimer of calcium atoms bridged by two water molecules [9]. The dimeric species is isolated from other dimers in the unit cell.

Magnesium is unable to replace calcium in the role it plays in histamine release. Comparison of calcium and magnesium binding to allergens has shown some significant differences in binding patterns of the two alkaline earth cations [6]. Magnesium displays greater

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rigidity and isolation in its binding to the same ligands. With nicotinic acid and paraaminosalicylate, magnesium forms six coordinate complexes which display little deviation from octahedral geometry. Magnesium often complexes to six water molecules, which may in turn hydrogen bond to the ligand. Complexed magnesium tends to be isolated from other magnesium atoms.

Calcium has been observed to form a 1:2 complex with histamine itself. In $CaCl_4(H_2O)_2CaCl_2(H_2O)_2$-(histamine)$_2$, a calcium atom is observed bound to the nitrogen atoms alpha to the side chains of two histamine imidazole rings and also to two chloride atoms and to the oxygen atoms of two water molecules [10]. The protonated aminoethyl side chain is not involved with calcium in this structure. To further our knowledge of calcium binding patterns with small molecules, we have determined the single crystal X-ray structures of [calcium(isonicotinamide)$_2$(H$_2$O)$_4$]Cl$_2$ (I) and calcium(isonicotinate)$_2$-(H$_2$O)$_4$ (II).

Experimental

[Calcium(isonicotinamide)$_2$(H$_2$O)$_4$]Cl$_2$ (I)

The addition of 0.2442 g (2 mmol) of isonicotinamide to 10 ml of H_2O produced a solution to which 4 ml (2 mmol) of 0.5 M CaCl$_2$ was added. The resulting mixture was allowed to evaporate slowly at room temperature. After 48 h, long, colorless needles were observed to form. A cube, 0.2 × 0.2 × 0.2 mm, was cleaved from a needle and used for diffraction studies.

Calcium(isonicotinate)$_2$(H$_2$O)$_4$ (II)

Isonicotinic acid (1.2311 g, 10 mmol) was added to 40 ml of H_2O. A clear, colorless solution was formed on addition of 10 ml (10 mmol) of a 1 N solution of NaOH with boiling. Subsequent addition of 10 ml (5 mmol) of a 0.5 M CaCl$_2$ solution resulted in the formation of a small amount of white precipitate which was removed by filtration. Large, clear needles were observed in the remaining solution after 22 h. A cube of dimensions 0.2 × 0.1 × 0.2 mm was cut from a single crystal and used for diffraction studies.

Crystals of I and II were sealed in capillaries and mounted on a Syntex P3 automated diffractometer. Unit cell dimensions (Table 1) were determined by least-squares refinement of the best angular positions for fifteen independent reflections ($2\theta > 15°$) during normal alignment procedures using molybdenum radiation ($\lambda = 0.71069$ Å). Data, 2506 points, $\pm h$, $+k$, $\pm l$ for I, 4292 points, $\pm h$, $+k$, $+l$ for II, were collected at room temperature using a variable scan rate, a $\theta - 2\theta$ scan mode and a scan width of 1.2° below $K_{\alpha}1$

TABLE 1. Crystal data for [Ca(isonicotinamide)$_2$(H$_2$O)$_4$]Cl$_2$ (I) and [Ca(isonicotinate)$_2$(H$_2$O)$_4$] (II)

	I	II
Formula	$C_{12}H_{20}CaCl_2N_4O_6$	$C_{12}H_{16}CaN_2O_8$
Molecular weight	427.3	356.3
a (Å)	9.778(5)	7.208(3)
b (Å)	8.623(4)	36.368(28)
c (Å)	7.363(3)	6.159(2)
α (°)	115.09(3)	90.0
β (°)	73.40(4)	104.74(3)
γ (°)	75.98(3)	90.0
V (Å^3)	489.3(3)	1561(1)
$F(000)$	222	744
μ(Mo Kα) (cm^{-1})	6.195	4.312
λ(Mo Kα) (Å)	0.71069	0.71069
D_{calc} (g cm^{-3})	1.450	1.615
Z	2	4
Space group	$P\bar{1}$	$P2_1/a$
Observed reflections	1985	1819
Octants measured	$\pm h, +k, \pm l$	$\pm h, k, l$
R (%)	6.6	6.4

and 1.2° above $K_{\alpha}2$ to a maximum 2θ value of 60°. Backgrounds were measured at each side of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were remeasured after every 97 reflections and as the intensities of these reflections showed less than 4% variation, corrections for decomposition were deemed unnecessary. Data were corrected for Lorentz, polarization and background effects. After removal of redundant and space group forbidden data, 1985 for I, 1819 for II, reflections were considered observed, $I > 3.0\sigma(I)$. The structures were solved by direct methods using MULTAN [11]. Refinement of scale factor, positional and anisotropic thermal parameters for nonhydrogen atoms was continued to convergence [12]. Hydrogen atom positions were located from a difference Fourier synthesis and hydrogen positional parameters with isotropic thermal parameters were included in the final cycles of refinement but were held invariant. The final cycles of refinement [function minimized, $\Sigma(|F_o| - |F_c|)^2$] led to a final agreement factor $R = 4.7\%$ for I, 6.4% for II $[R = (\Sigma||F_o| - |F_c||/\Sigma|F_o| \times 100]$. In the final cycles of refinement, weights equal to $1/\sigma(F)^2$ were used. Scattering factors were taken from Cromer and Mann [13]. Anomalous dispersion corrections were applied for calcium [14].

Discussion

A projection view of I is shown in Fig. 1 based on the positional parameters of Table 2.

Calcium is located on an inversion center and bound to the oxygen atoms of four water molecules
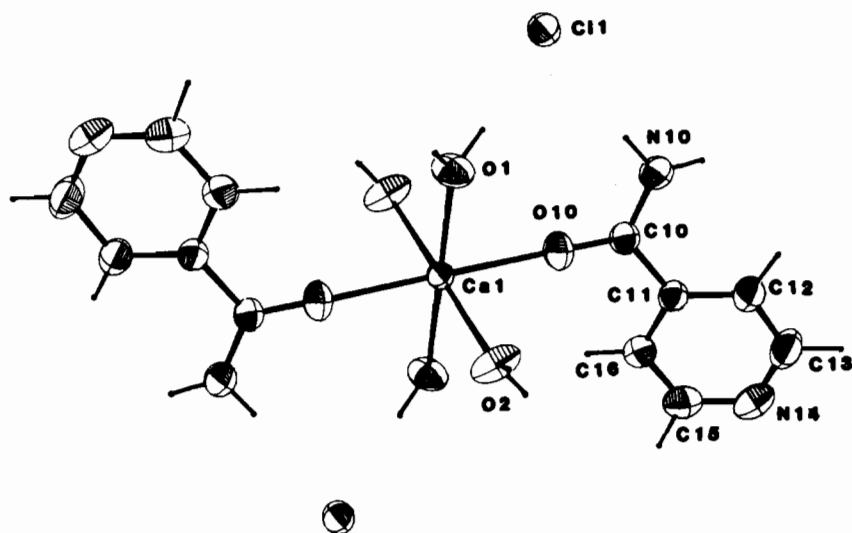
Fig. 1. Calcium complexation of [calcium(isonicotinamide)$_2$(H$_2$O)$_4$]Cl$_2$ (I).

TABLE 2. Positional parameters for (Ca(isonicotinamide)$_2$-(H$_2$O)$_4$)Cl$_2$ (I)

Atom	x $(\sigma(x))$	y $(\sigma(y))$	z $(\sigma(z))$
Ca1	1.0000	0.0000	1.0000
Cl1	0.7938(1)	0.4773(1)	0.8733(1)
O1	1.0002(3)	0.2878(3)	1.0528(4)
O2	0.9132(3)	0.1046(3)	1.3784(4)
O10	1.2613(2)	−0.1315(4)	0.9093(4)
N10	1.4583(3)	−0.3871(4)	0.8234(5)
C10	1.4027(3)	−0.2300(4)	0.8253(5)
C11	1.5202(3)	−0.1721(4)	0.7216(4)
C12	1.6755(3)	−0.2947(4)	0.5756(5)
C13	1.7745(4)	−0.2251(5)	0.4924(6)
N14	1.7278(3)	−0.0479(4)	0.5434(5)
C15	1.5776(4)	0.0676(5)	0.6830(5)
C16	1.4695(4)	0.0128(4)	0.7757(5)

TABLE 3. Bond distances (A) and angles (°) for (Ca(iso-nicotinamide)$_2$(H$_2$O)$_4$)Cl$_2$ (I)

Ca1−O1	2.344(3)	O1−Ca1−O2	93.8(1)
Ca1−O2	2.333(3)	O1−Ca1−O10	93.8(1)
Ca1−O10	2.289(3)	O2−Ca1−O10	95.0(1)
C10−O10	1.229(3)	O10−C10−N10	122.8(3)
C10−N10	1.325(5)	O10−C10−C11	119.9(3)
C10−C11	1.500(5)	N10−C10−C11	117.3(2)
C11−C12	1.380(3)	C10−C11−C12	123.0(3)
C12−C13	1.388(6)	C10−C11−C16	118.1(2)
C13−N14	1.327(6)	C16−C11−C12	118.9(3)
N14−C15	1.329(4)	C11−C12−C13	118.1(3)
C15−C16	1.382(6)	C12−C13−N14	123.8(2)
C16−C11	1.383(5)	C13−N14−C15	117.3(3)
		N14−C15−C16	123.6(4)
		C15−C16−C11	118.4(2)

(Ca−O av. 2.338(3) Å, Table 3) as well as to the carbonyl oxygen atoms of the amide groups of two different isonicotinamide molecules (Ca−O, 2.289(3) Å). Amide and hetero-ring nitrogen atoms are not bound to calcium. Calcium displays slight distortion from octahedral geometry with O−Ca−O angles ranging from 93.8(1)−95.0(1) Å.

Calcium atoms show closest interactions (Fig. 2) on the 0 0 1 planes between calcium atoms at the corners of the unit cell and calcium neighbors diagonally placed ($\frac{1}{2} + x, \frac{1}{2} + y, z$) at 5.67 Å distance. N14 shows a close separation from a water molecule hydrogen atom of an adjacent molecule (N14−H2O2, 1.981(4) Å). However three of the four water molecule hydrogen atoms and the two amide protons show a distance of 2.415(2)−2.520(1) Å from a chloride ion. Thus the packing of molecules in the unit cell maximizes hydrogen−chloride interactions.
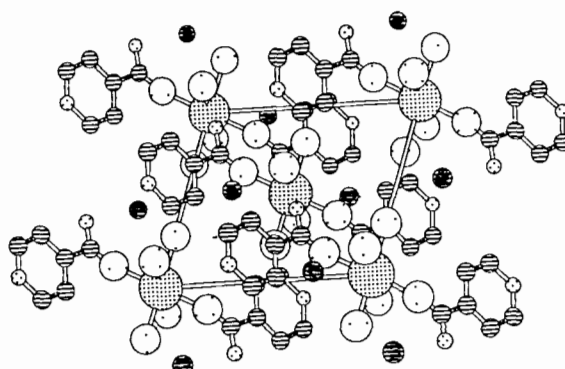

Fig. 2. Packing of I projected on the 0 0 1 plane.

In calcium(isonicotinate)$_2$(H$_2$O)$_4$ (II) calcium is coordinated to the oxygen atoms of four water molecules (Ca−O av. 2.367(5) Å) (Table 4), the

TABLE 4. Bond distances (A) and angles (°) for Ca(iso-nicotinate)$_2$(H$_2$O)$_4$ (II)

Ca1–O1	2.415(4)	O1–Ca1–O2	151.6(2)
Ca1–O2	2.360(5)	O1–Ca1–O3	87.6(2)
Ca1–O3	2.344(6)	O1–Ca1–O4	86.1(2)
Ca1–O4	2.348(6)	O1–Ca1–O10	128.9(2)
Ca1–O10	2.506(4)	O1–Ca1–O11	86.1(2)
Ca1–O11	2.377(5)	O1–Ca1–N24	77.0(1)
Ca1–N24	2.615(6)	O2–Ca1–O3	98.6(2)
C10–O10	1.248(8)	O2–Ca1–O4	83.1(2)
C10–O11	1.248(8)	O2–Ca1–O10	79.2(2)
C10–C11	1.506(9)	O2–Ca1–O11	119.2(2)
C11–C12	1.384(8)	O2–Ca1–N24	76.5(2)
C12–C13	1.372(10)	O3–Ca1–O4	169.1(2)
C13–N14	1.336(10)	O3–Ca1–O10	74.6(2)
N14–C15	1.327(9)	O3–Ca1–O11	101.9(2)
C15–C16	1.399(10)	O3–Ca1–N24	81.7(2)
C16–C11	1.369(9)	O4–Ca1–O10	116.2(2)
C20–O20	1.249(8)	O4–Ca1–O11	86.4(2)
C20–O21	1.247(8)	O4–Ca1–N24	88.2(2)
C20–C21	1.518(8)	O10–Ca1–O11	53.3(1)
C21–C22	1.383(9)	O10–Ca1–N24	142.9(2)
C22–C23	1.371(9)	O11–Ca1–N24	162.5(2)
C23–N24	1.341(8)	O10–C10–O11	122.8(6)
N24–C25	1.334(8)	O10–C10–C11	119.1(5)
C25–C26	1.374(9)	O11–C10–C11	118.0(5)
C26–C21	1.380(9)	C10–C11–C12	120.0(6)
		C10–C11–C16	121.8(6)
		C16–C11–C12	118.2(6)
		C11–C12–C13	119.1(6)
		C12–C13–N14	123.7(6)
		C13–N14–C15	117.0(6)
		N14–C15–C16	123.1(6)
		C15–C16–C11	118.8(6)
		O20–C20–O21	126.1(6)
		O20–C20–C21	116.0(5)
		O21–C20–C21	117.9(5)
		C20–C21–C22	120.3(5)
		C20–C21–C26	122.8(5)
		C26–C21–C22	117.0(6)

(continued)

TABLE 4. (continued)

C21–C22–C23	120.4(6)
C22–C23–N24	122.8(6)
C23–N24–C25	116.4(5)
N24–C25–C26	124.2(6)
C25–C26–C21	119.2(6)

nitrogen atom of one isonicotinate molecule (Ca–N, 2.615(6) Å) and to a bidentate carboxylate group of another isonicotinate molecule (Ca–O, 2.506(5), 2.377(5) Å), achieving seven coordination (Fig. 3 based on the coordinates of Table 5). The carboxylate group is bidentate to a single calcium atom and does not show any interaction with other calcium atoms in the cell unlike [Ca(nicotinate)$_2$(H$_2$O)$_2$]-(H$_2$O)$_3$ [5] in which carboxylate groups serve as bidentate ligands to one calcium atom while bridging to a second one or calcium malonate dihydrate in which a single carboxylate atom bridged three calcium atoms [15, 16]. The carboxylate group of the nitrogen bound isonicotinate molecule does not bind to calcium.

The clusters are packed (Fig. 4) in the narrow cell such that calcium atoms are 6.159(2) Å apart in the z direction and 7.208(3) Å in the x direction of the neighboring cell. Thus this solid-state structure is unlike the layer structure of [Ca(nicotinate)$_2$-(H$_2$O)$_2$](H$_2$O)$_3$ [5] in which calcium atoms are separated by 4.055 Å, Ca$_2$(acetate)$_4$(HOH)$_2$ [8] in which the minimum Ca–Ca separation is 3.93 Å or Ca$_{1.5}$(salicylate)$_2$(acetate)(H$_2$O)$_2$ [8] in which linear arrays of three calcium atoms (Ca–Ca separation 4.15 Å) are bridged by carboxylate groups.

The non-coordinated carboxylate group (O20, O21) and nitrogen atom (N14) are involved in hydrogen bonding with hydrogen atoms of water molecules of calcium clusters in adjacent unit cells
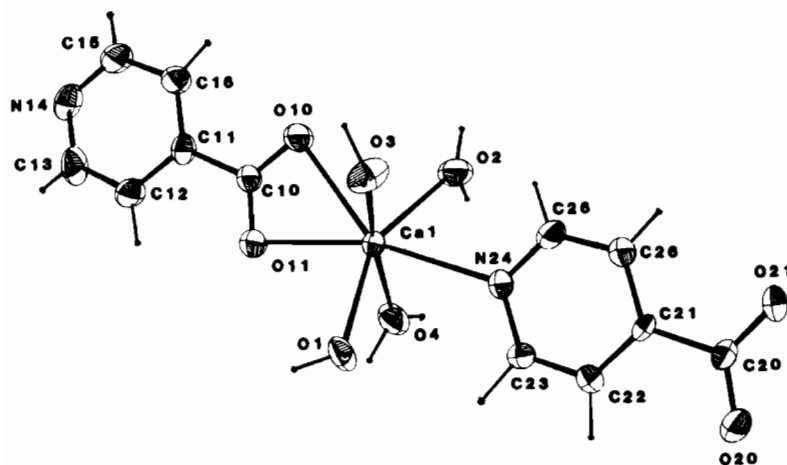

Fig. 3. Asymmetric unit of [calcium(isonicotinate)$_2$(H$_2$O)$_4$] (II).

TABLE 5. Positional parameters for Ca(isonicotinate)$_2$-(H$_2$O)$_4$ (II)

| Atom	x ($\sigma(x)$)	y ($\sigma(y)$)	z ($\sigma(z)$)
Ca1	0.3249(2)	0.1277(1)	0.2627(2)
O1	0.0602(6)	0.1297(1)	−0.0688(7)
O2	0.6018(8)	0.0993(1)	0.4887(8)
O3	0.1044(7)	0.1091(1)	0.4627(8)
O4	0.5229(7)	0.1368(1)	0.0179(8)
O10	0.3894(8)	0.1681(1)	0.6034(7)
O11	0.2969(8)	0.1928(1)	0.2686(8)
C10	0.3496(9)	0.1954(2)	0.4773(10)
C11	0.3701(9)	0.2333(2)	0.5790(11)
C12	0.3257(11)	0.2639(2)	0.4419(11)
C13	0.3529(12)	0.2982(2)	0.5370(14)
N14	0.4197(9)	0.3041(2)	0.7572(10)
C15	0.4570(12)	0.2746(2)	0.8885(11)
C16	0.4339(10)	0.2387(2)	0.8059(11)
O20	0.1727(7)	−0.0594(1)	−0.2843(8)
O21	0.2395(7)	−0.0790(1)	0.0694(8)
C20	0.2149(9)	−0.0545(2)	−0.0768(10)
C21	0.2407(9)	−0.0148(2)	0.0011(10)
C22	0.2236(10)	0.0134(2)	−0.1536(11)
C23	0.2490(12)	0.0492(2)	−0.0837(11)
N24	0.2885(8)	0.0590(1)	0.1333(8)
C25	0.3040(11)	0.0317(2)	0.2814(11)
C26	0.2808(10)	−0.0049(2)	0.2246(10)
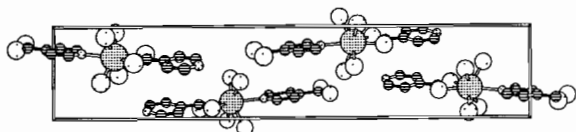
Fig. 4. Packing of calcium clusters of II on the 0 0 1 plane.

in three directions [N14−H102 ($\frac{1}{2} + x$, $\frac{1}{2} - y$, 1.0 + z), 1.855(6); and O21−H101, 1.963(5); O21−H201, 1.920(4); O21−H402, 2.156(5); O20−H202, 2.072(5); O20−H302, 1.862(4) Å]. Thus the non-coordinated hetero nitrogen and carboxylate groups are involved in multiple hydrogen bonds with water molecules coordinated to adjacent calcium atoms. It appears that the strength and multiplicity of this bonding plays a major role in determining the packing of molecules in the unit cell.

The details of the structure of Ca(isonicotinate)$_2$-(H$_2$O)$_4$ (II) may be compared with those of Mg(isonicotinate)$_2$(H$_2$O)$_4$ [17] in which magnesium is coordinated to four water molecule oxygen atoms, the nitrogen of one nicotinate molecule and to a single carboxylate oxygen atom of a second isonicotinate molecule. The change from bidentate carboxylate binding in the calcium structure I to monodentate carboxylate binding in the magnesium structure is achieved by a slight rotation of the isonicotinate molecule with little disruption of the hydrogen bonding networks of non-coordinated groups and with little alteration of unit cell size and

shape. Thus a comparison of the two structures serves to reiterate magnesium preference for octahedral geometry and six coordination.

Thus calcium complexes I and II do not display the close calcium–calcium interactions seen in other complexes previously studied in which bridging groups serve to bring alkaline earth cations into close proximity. In structures I and II, despite the availability of potential bridging groups, cluster packing and ligand usage appears to be determined by the strong networks of hydrogen bonding between water molecules and non-bonded polar groups.

Supplementary Material

Anisotropic thermal parameters, hydrogen positional parameters and structure factor tables are available from the authors on request.

Acknowledgement

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