STRUCTURAL INVESTIGATION OF CALCIUM COMPLEXES OF LOW MOLECULAR WEIGHT SPECIES OF BIOLOGICAL IMPORTANCE

By

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CHAPTER I

INTRODUCTION

Recent studies of the mast cell and of basophilic leukocytes have shown these cells to be centrally involved in acute allergic and inflammatory disease(1). In 1879, Ehrlich noted the unique cytoplasmic granular matrix contained within mast cells, following exposure of the cells to basic staining dyes. Investigations by Uvnas and coworkers revealed that histamine found within mast cells is loosely bound to carboxyl groups of the protein part of the heparin--protein complex in these granules(2). R. W. Schayer observed that histamine is derived from l-histidine taken up and decarboxylated by the cells. When rat mast cells were incubated in a solution of ^{14}C-histidine, labelled ^{14}C-histamine became incorporated into the granules(3). It has been known for sometime that the release of histamine and other mediators from these cells leads to the signs and symptoms of immediate hypersensitivity (anaphylactic) reactions, yet the exact biochemical mechanism which results in histamine release has remained unclear. The numerous mechanisms postulated to date seem to agree on three basic steps which must preceed this non-cytotoxic mediator release. Activation begins when the cell is challenged by

an appropriate antigen, which in turn triggers several different biochemical processes. Next, an influx of calcium ions across the cell membrane must occur. This influx is followed rapidly by the exocytosis of granules from within the cell and the subsequent release of histamine and other mediators.

The large number of chemical substances possessing the ability to initiate histamine release from these target cells has greatly increased the complexity involved in the elucidation of an accurate mechanism. Vast differences in the physical and chemical properties of these compounds, which range from small proteins to low molecular weight drugs, clearly prevents the assumption that one mechanism of activation exists for all such reaginic agents. A review of several allergenic compounds and their proposed involvement in activation of these target cells provides verification of this fact. Most of the information gathered to date has originated from experimentation on rat mast cells, since they are readily available and easily isolated in an almost pure cell population.

The most common activation among small proteins and peptides begins with the formation of a reaginic antibody (anti-IgE) by complexation with immunoglobin E molecules. The anti-IgE then bridges adjacent IgE receptors, which are located only on the surfaces of mast cells and basophils. Ishizaka, Foreman and coworkers observed that rabbit anti-IgE antibodies caused the uptake

of radioactive $^{45}Ca^{+2}$ cations by isolated rat mast cells. The increased permeability of the membrane toward calcium ions resulted in the release of histamine(4). Dimerization of receptor sites may also be induced by lectins, such as Concanavalin A (Con A). Ennis, Truneh, and Pearce(5) reported a dose dependent release of histamine from rat peritoneal mast cells in the presence of calcium ions. Concanavalin A has been shown to bind to the carbohydrate moieties of cell bound IgE molecules in order to stimulate histamine secretion. Maximum histamine release occurred at an extracellular Ca^{+2} concentration of 10^{-3} M. Suboptimal release also occurred in the absence of extracellular Ca^{+2}, demonstrating the ability of Con A to use intracellular pools of Ca^{+2}.

The most studied group of histamine liberators are basic oligo and polymeric compounds. This group is typified by compound 48/80, a condensation product of formaldehyde with p-methoxy-phenethylmethylamine, originally synthesized by Baltzly(6). Gel-electrophoresis studies(7) indicated the most active constituents of 48/80 were tetramers to octamers. Paton(8) originally demonstrated the ability of compound 48/80 to release histamine from mast cells over 35 years ago, yet relatively little is known about its role in mast cell activation. He recorded the lowering of the blood pressure in both dogs and cats as well as the lengthening of blood coagulation times resulting from the histamine released by the compound. Release is due to non-cytotoxic,

selective degranulation as reported by Johnson and Moran (9). During degranulation, no additional protein, lactate dehydrogenase (LDH, a cytoplasmic enzyme), or labelled $^{42}K^{+}$ which had been incorporated into the cells was detected. Compound 48/80 can induce substantial histamine release even in a calcium-free medium. Cochrane and Douglas(10) followed the extrusion of the secretory granules by phase contrast microscopy after rat peritoneal mast cells were exposed to the ionophore both in the presence and the absence of extracellular calcium. Removal of intracellular calcium was then accomplished by incubating the cells in EDTA (a calcium chelating agent). Mast cells treated in this manner exhibited no degranulation when challenged with compound 48/80. This evidence suggests the ability of the liberator to utilize intracellular and extracellular calcium ions with comparable efficiency.

Histamine release can be activated by a number of low molecular weight chemical compounds, but less is generally known about their actual role in activating the target cells. Diamant and Kruger(11) noted major differences in the mechanism of histamine release induced by compound 48/80 and adenosine 5'-triphosphate (ATP). In contrast to the ionophore, the presence of extracellular calcium is indespensible for ATP-initiated histamine release to occur. Bennett, Cockcroft, and Gomperts(12) observed an increase in membrane permeability toward a $^{45}Ca^{+2}$-EDTA complex following exposure to ATP.

Ionophores which display the ability to transport divalent cations across lipid membranes, such as compounds A23187 and X537A, have become the focus of a number of studies of the secretory process of histamine release. A23187 is a monocarboxylic antibiotic isolated by Reed and Lardy(13). Their experiments revealed that this compound was able to transport Ca^{+2} and Mg^{+2} cations from an aqueous phase at pH=7.4 into an organic phase (30% 1-butanol, 70% toluene), but could not transport K^{+} cations. Transport of the divalent cations across mitochondrial membranes was also noted. X537A, also a monocarboxylic antibiotic, is a derivative of salicylic acid. It differs from A23187 in the fact that it can transport monovalent cations as well. Contradictory results exist concerning the dependence of X537A on extracellular calcium during cell activation. Yet Cochrane and Douglas(10) were able to follow the degranulation of rat mast cells by phase contrast microscopy upon exposure of the cells to A23187 and X537A in the presence of Ca^{+2} ions, in the same manner as that induced by compound 48/80.

Dose dependent histamine release has also been observed for other drugs and antibiotics. Ellis, Johnson, and Moran(14) investigated selective release initiated by several analgesics and antibiotics. Polymyxin B, stilbamidine, tubocurarine, and morphine were all found to induce histamine release (order is in decreasing potency) by non-cytotoxic actions.

Following the immunological or pharmacological activation of mast cells and basophils, two major biochemical changes are initiated. Their respective roles in the mobilization of extracellular calcium are currently undefined, but the main events characterized thus far are summarized below.

Phosphatidylinositol (PI) metabolism (Fig. 1) has been observed to increase with antigen-induced calcium influx in rat mast cells. Cockcroft and Gomperts(15) noticed a four-fold increase in the rate of incorporation of $(^{32}P)\ PO_4^{-4}$ into mast cell PI upon challenge of the cells with Con A. Likewise, cells exposed to ovalbumin revealed a four-fold increase in labelled PI by using (^{3}H) inositol. The amount of histamine released was affected by the presence of Ca^{+2}, yet no effect was shown on the rate of isotopic labelling due to the presence or absence of extracellular calcium. Kennerly and coworkers(16) recorded similar results when anti-IgE, Con A, and compound 48/80 were used to initiate activation of rat mast cells. Most importantly, they observed alterations in the PI metabolism within three to eight seconds, well in advance of mediator release. It is interesting that antigens which activate target cells by different mechanisms yielded similar changes in the phospholipid metabolism.

The methylation of phospholipids has also been studied in relation to cell activation and calcium influx. This sequence (Fig. 2) of events has been demonstrated in

PI RESPONSE

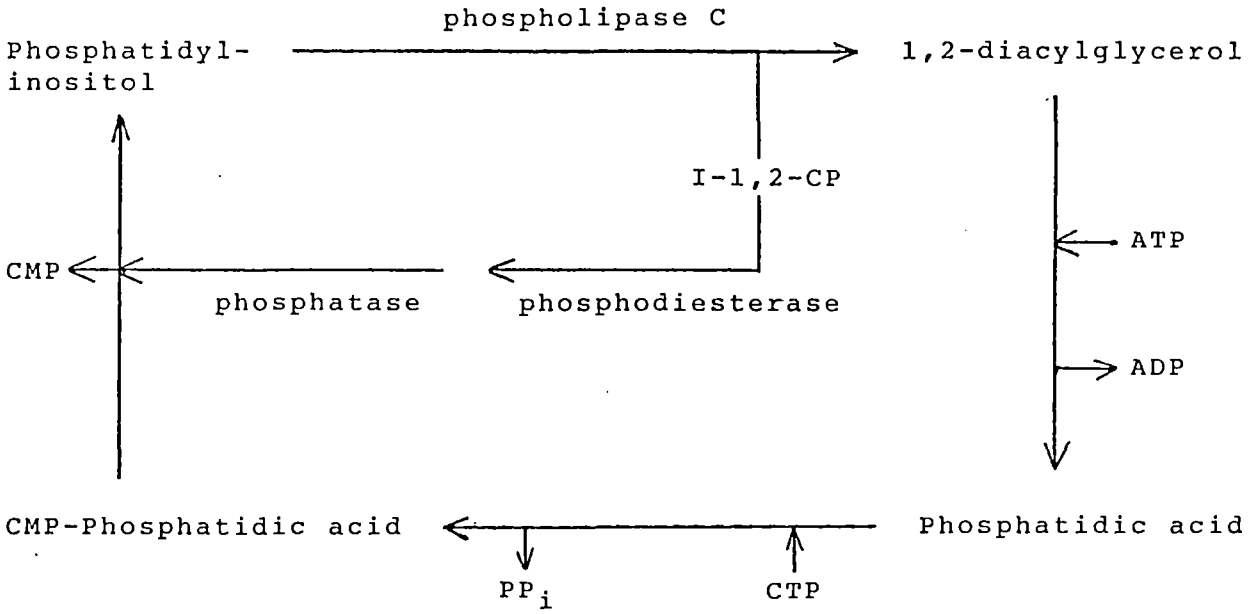

Figure 1. Phosphatidylinositol Response

both rat mast cells and in rat basophils. Two membrane bound enzymes are responsible for the successive methylations of phosphatidylethanolamine (PE) to phosphatidylcholine (PC). Methyltransferase I is bound to the cytoplasmic side of the membrane and transfers one methyl group to PE, while methyltransferase II is located on the external face and catalyzes the transfer of the final two methyl groups to complete the conversion. As the methylations occur, the intermediate phospholipids must transverse the membrane leading to an increase in membrane fluidity. Crews, Morita, et al. monitored the incorporation of ^{3}H-methyl groups into phospholipids and the subsequent calcium influx when rat basophilic leukocytes were treated with ovalbumin and the ionophore A23187(17). Ovalbumin caused an increase in labelled phospholipids, followed by the influx of $^{45}Ca^{+2}$, while A23187 caused a small decrease in the amount of ^{3}H-phospholipids. Similar studies and results have been reported by Axelrod and Hirata(18) and by Ishizaka and coworkers(19). The relevance of phospholipid methylation in relation to calcium influx is postulated to be linked to the increase in the membrane fluidity.

Activation of mast cells and basophils results in the increase in the concentration of ionized calcium in the cell cytosol, which then triggers the release of histamine and other chemical mediatiors. The earliest recognition of the involvement of calcium in the anaphylatic process was reported by Mongar and Schild(20). Sensitized guinea-pig

PHOSPHOLIPID METHYLATION

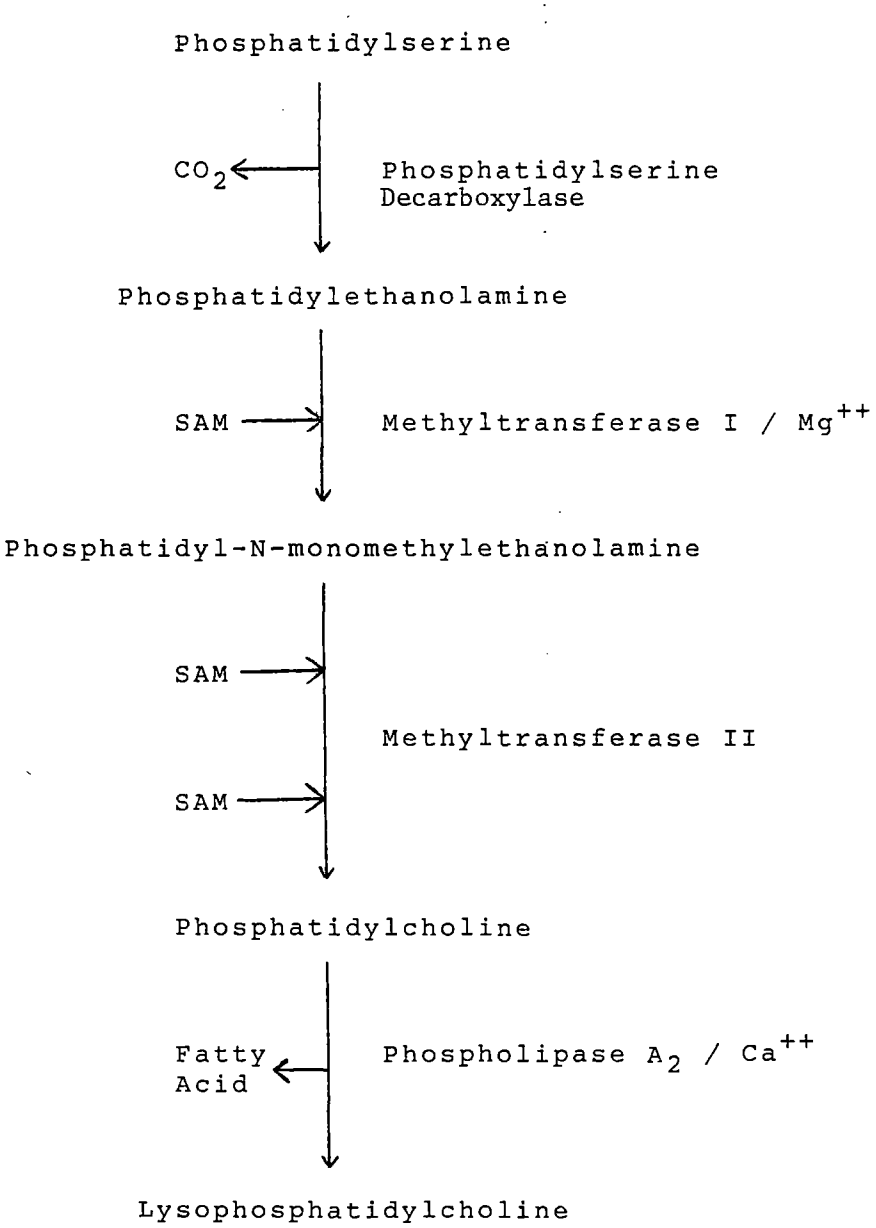

Figure 2. Phospholipid Methylation

lung tissue, when placed in a calcium containing solution (Tyrode's solution), was observed to release histamine upon exposure to an antigen. If $CaCl_2$ was omitted from the Tyrode solution, the same experiment yielded only 10% of the original amount of histamine released previously. This amount was reduced to the level of the control (less than 2%) when the tissue was treated with EDTA. Similar tissue was placed in a 0.9% NaCl solution and challenged with antigen, yet minimal histamine was released. The addition of $CaCl_2$ to the solution was then shown to reestablish the anaphylactic mechanism. Further experiments using an isotonic sucrose solution as the medium produced similar results. These workers continued their study of histamine release with respect to pH. In the range between pH=6 to pH=8.5, spontaneous histamine release was neglible. Lung tissue was combined with antigen and Tyrode's solution in a phosphate buffer and the pH of the solution was varied. The maximum percentage of histamine released was recorded at pH=7.75. A twenty five-fold increase occurred during the pH increase from 6.3 to 7.75. Soon after the discovery of the ionophore A23187, Foreman, Mongar and Gomperts(21) published results indicating its ability to transport extracellular $^{45}Ca^{+2}$ into mast cells, and the subsequent triggering of the release of histamine. Strontium cations were also able to cause the release of histamine in the presence of A23187, but it is important to note that the release was only 10% of that induced by calcium and that intracellular calcium was

not removed. Additional evidence in support of calcium's importance has come from experiments in which degranulation was induced after direct microinjection of calcium ions into the cytoplasm of rat mast cells. Kanno, Cochrane, and Douglas(22) reported that of twenty six cells injected with Ca^{+2} ions, all but one showed granule extrusion. The response, monitored by microscopy, revealed the formation of an irregular cell surface accompanied by the expulsion of a few granules within a few seconds after injection. This degranulation could not be distinguished from that induced by 48/80, antigen, or ionophores. No degranulation was seen when the tip of the micropipette was placed just outside the cell wall.

Investigation of the sequence involved in calcium and antigen addition with respect to histamine release were carried out by Foreman and Garland(23) on mixed peritoneal cells. No release (less than 2%) was measured when these cells were challenged with ovalbumin in the absence of calcium. Once calcium had been added, the reaction was initiated but decayed rapidly with time, exhibiting a half-life of one minute and near completion after four minutes. It was also found that after the initial reaction had finished, subsequent additions of antigen, A23187, or calcium had no effect. The combination of mast cells with A23187 produced no histamine release until calcium was added, yet no reduction in the amount of mediator released was seen due to the time delayed addition. It was noted

that when antigen was added four minutes prior to calcium, the percentage of histamine released dropped sharply.

In 1979, Bennett, Cockcroft, and Gomperts(24) published a study which explored the use of the antibiotic ionomycin, in an attempt to gain greater insight into the mechanisms by which ionophores induce histamine release. It was observed that ionomycin formed a lipid-soluble complex, and thus had the ability to transport $^{45}Ca^{+2}$ across biological membranes. Ionomycin-induced histamine release was found to be non-cytotoxic, similar to A23187, since no lactate dehydrogenase was detected during the release. The authors concluded from their experiments that ionomycin stimulated mast cell secretion solely as a result of its ionophoric characteristics. Further investigation of the role of increased membrane permeability toward Ca^{+2} in allergic reactions was carried out by the authors using ATP as the antigen(12). Rat mast cells exposed to micromolar concentrations of ATP were shown to allow the direct passage of a $^{45}Ca^{+2}$-EDTA complex into the cytosol. When the solution was buffered so that the total ATP concentration existed primarily as ATP^{-4}, histamine release became dose dependent upon the ATP concentration in the presence of extracellular calcium.

A comparison of the release of histamine induced by antigen and A23187 from human basophils was conducted by L. M. Lichtenstein at the Johns Hopskins University School of Medicine(25). Blood from patients allergic to ragweed

provided the basophils for antigen experimentation, while that of normal patients was used in combination with A23187. A23187 caused histamine release from all thirty patients tested in the presence of extracellular calcium. The release was shown to be dose dependent when the calcium concentration was 0.6 mM, the optimal concentration found in the antigen-induced reaction. Similar to the antigen, no LDH was detected, indicating a non-cytotoxic mechanism of degranulation. Removal of calcium during a reaction induced by either compound resulted in immediate termination. Detection of histamine released by A23187 was very rapid, but with the antigen a slight time lag was noted. Once release began, the rates of extrusion were observed to be very similar. In previous work(26), the author divided the antigen-induced release mechanism into two stages, a calcium-independent first stage and a calcium-dependent second stage. These results have led to the conclusion that the final stages of antigen and ionophoric induced release are very similar. A cooperative effect was observed when suboptimal concentrations of both antigen and A23187 were combined with mast cells to produce an increase in the percentage of histamine released. The concentrations of antigen and A23187 which yielded 9% and 12% release respectively when separate, combined to produce 87% release. Additional support of this hypothesis was provided when 2-deoxyglucose, an inhibitor of the latter stage of antigen induced release, displayed similar inhibition of ionophore

induced release. In summation, it appears that A23187 seems to be able to short cut many of the initial steps involved in antigen activation, but once calcium has been transported into the mast cell, the final steps resulting in degranulation are very similar.

The dependence of the anaphylactic reaction on the influx of calcium is also supported by the fact that no other cation has been found which can replace calcium in this sequence of events. Mongar and Schild noted in their early investigations that the omission of either K^+ or Mg^{+2} ions from Tyrode's solution had no effect on the amount of histamine released(20). In the microinjection experiments of Kanno, et al.(22) introduction of Mg^{+2} or K^+ into the cytoplasm failed to evoke granule extrusion. Likewise, Cochrane and Douglas(10) reported that in the abscence of calcium, the addition of Mg^{+2}, Na^+, or K^+ did not duplicate the degranulation induced by any of the three ionophores.

Pearce and White(27) have reported that cations of the lanthanide series inhibit antigen, Con A, and 48/80 induced histamine release from rat mast cells. In micromolar concentrations, all lanthanides were shown to inhibit anti-IgE induced histamine release even in the presence of 1 mM calcium. When tested with Con A, lanthanum was relatively ineffective, but the higher cations of the series yielded up to 90% inhibition. Similar results were obtained with 48/80. A possible explanation is that the similar size of the lanthanides allows for competition for

the binding sites on the cell surface with calcium, but the higher valency gives the lanthanides a greater affinity for those same sites. $LaCl_3$ interference with the transmembrane movement of calcium ions reported by Lichtenstein(25) in human basophils appears to give support to this idea.

Thus the involvement of calcium is well established, but the specificity for calcium as opposed to magnesium in the sequence of events which leads to mediator release is still unclear. The intracellular concentration of magnesium is greater than that of calcium by a factor of 10^3, yet magnesium appears to lack any direct involvement as a divalent cation in an anaphylactic reaction. In order to gain a better understanding of the participation of calcium in this process, it is important to investigate the differences in the physical and chemical properties between these two alkaline earth cations. A comparison of the effective ionic radii of the two cations reveals a marked difference in their respective sizes(28). First, it is important to notice a strong dependence of the effective ionic radii on the coordination number for all metal ions. The ionic radii of calcium in coordination numbers from six to nine are 1.00, 1.06, 1.12, and 1.18 Å respectively. Magnesium radii for coordination numbers of six and eight are 0.72 and 0.89 Å. Thus when comparing these cations in the same coordination, calcium is at least 0.23 Å greater in size. This difference becomes even larger when they are compared in their most common coordination; calcium prefers eight

ligands while magnesium desires only six, leading to a size differential of 0.40 Å. Calcium's size allows it a greater diversity not only in the number of ligands it can accommodate, but also in its geometries of complexation. In contrast, magnesium strongly adheres to six-fold octahedral coordination. The charge to size ratio for calcium (+2/1.12 Å) is much lower than that of magnesium (+2/0.72 Å) when the cations are compared in their most common coordination geometries. Therefore, calcium has less control over its ligands and deviations in its geometry are common. The addition of more ligands to calcium causes less perturbation in the bonding to those ligands already present. The geometrical restraints on magnesium are reflected in the narrow range exhibited in metal-oxygen bond distances, typically ranging between 2.0 and 2.1 Å. Calcium-oxygen bond distances vary from 2.3 to 2.8 Å.

Although the hard-soft acid base theory(29) identifies both calcium and magnesium as hard acids which should prefer to complex to hard bases such as oxygen and nitrogen, calcium exhibits a strong preference for ligands with oxygen donors. This was suggested to be supported by the longer Ca-N than Ca-O bond lengths found in crystal structures of nitrilotriacetate and EDTA complexes(30). Additional support results from calcium's preferential bonding to oxygen instead of nitrogen in numerous cases where both atoms are available at the binding site of a ligand. Similar results can be seen in the calcium complex with the

antibiotic A23187(31). Conversely, magnesium forms more stable complexes when bound to nitrogen and sulfur atoms. Calcium is also observed to be more comfortable than magnesium in complexation with large multidentate, anionic ligands. Higher stability constants are found when Ca^{+2} coordinates with nitriloacetate, EGTA, and EDTA than those noted when Mg^{+2} is complexed with the same ligands(32). Additional evidence comes from the relative rates of substitution for inner-sphere water molecules. The rate for displacement of water molecules of calcium is about 10^3 times that of magnesium, presumably due to the restricted ability of the latter to reduce or enlarge its coordination sphere from six donors and to the tighter cation-oxygen binding.

These differences in physical and chemical properties must contribute to the binding selectivity of a large number of biologically active ligands which complex to calcium preferentially. Exact geometrical criteria for ligand binding to calcium remain unclear. Inspection of calcium binding sites in these biological systems reveals that the most common ligating atoms are oxygen atoms from water molecules, carboxylates, and carbonyl groups. Consideration of the crystallographic studies involving small calcium complexes reported in the literature provides some information about the geometrical constraints found when calcium is coordinated in more elaborate systems.

A review of approximately 150 examples of calcium-

water interactions in crystalline hydrates has been completed by Einspahr and Bugg(34). The authors divided the vast number of different environments of calcium-water interactions into two classes, dependent on the number of additional interactions in which the water molecule was involved. "Class 1" examples are those in which the water was observed to maintain two other interactions (hydrogen bonding donor type) in addition to that with the calcium cation. This class includes nearly two-thirds of the examples studied. In "Class 2" examples, the water must serve as a hydrogen-bond acceptor in addition to possible hydrogen bonding (donor) interactions. Three fundamental observations about the geometries found in calcium-water bonds were reported. First, the calcium ion tends to lie on the plane which bisects the H-O-H angle of the water molecule. Next, the angle between the Ca-O bond and the dipole moment vector is acute, typically ranging from 0^{o} to 60^{o}. And finally, this same angle appears to have slightly higher values in the Class 2 examples than in those of Class 1. The average Ca-O bond length in these examples is 2.42 Å, with the majority of the distances falling between 2.3 and 2.5 Å. Seven and eight coordinate complexes were by far the most common. Shorter Ca-O distances correlate with Ca-O-dipole moment angle as the angle approachs zero.

A similar study examining the geometries of 170 examples of calcium-carboxylate interactions has also been reported by Einspahr and Bugg(34). Carboxylate groups

occur nearly twice as often as any other ligand group in the coordination sphere of Ca-binding proteins and can be found in the inner-coordination sphere of all such proteins. Ca-carboxylate coordinations have been divided into three main categories; (1) a unidentate mode in which only one of the carboxylate oxygen atoms binds to calcium, (2) a bidentate mode, in which both oxygen atoms chelate to the cation, and (3) an alpha mode. The alpha mode is observed when a suitable ligand atom (O or N) is attached to a carbon atom alpha to the carboxylate group. Alpha chelation then incorporates one carboxylate O atom and the "alpha" atom in binding the calcium ion. Unidentate coordination (1) is the most commonly encountered mode.

Their study of the distribution of the calcium-carboxylate geometries led the authors to several important conclusions about these interactions. It was first observed that calcium ions are generally located near the plane of the carboxylate C, O, O atoms. The tendency for the calcium to be colinear with a C-O bond was neglible. When exhibiting unidentate chelation, the calcium ions were more often displaced towards the second noncoordinated oxygen atom at C-O-Ca angles ranging from 120° to 150°, but at angles ranging from 140° to 160° when located on the other side of the C-O bond. Bidentate coordination places the calcium roughly equidistant from the two oxygen atoms and at C-O-Ca angles near 90°. Typical C-O-Ca angles range from 110° to 130° in alpha mode chelation.

A description of the distribution of Ca-O bond distances found in calcium-carboxylate interactions is similar to that of the calcium-water interactions. Most of the Ca-O lengths fall between 2.3 and 2.5 Å, with extremes of 2.2 Å and 2.8 Å reported. The three modes display slightly different Ca-O averages, 2.38 (unidentate), 2.42 (alpha), and 2.53 Å (bidentate). As expected, most of the calcium-carboxylate complexes were found to display seven or eight-fold overall coordination.

By the same approach(35, 36), the geometries of calcium-carbonyl complexes have been examined. In proteins, calcium binding carbonyl ligands may belong to the side chains of asparagine and glutamine residues, but more often belong to the backbone of the peptide chains. In the study of calcium coordination to amino acids and small peptides, the division of calcium-carbonyl chelation into three groups is much the same as that for the carboxylates. Unidentate coodination involves only the oxygen atom of the carbonyl groups. Several multidentate ligands were found in which the polar atoms of an adjacent group are directed toward the calcium ion. Some examples of this group are urea (bidentate), B-diketo- functions (bidentate), and 3-oxa-5-keto- groups (tridentate). An additional pattern of carbonyl chelation was indentified for cyclic-peptides which could envelop calcium. The features which characterize calcium-carbonyl complexes are; (1) the calcium is often found to lie near the plane of the carbonyl and alpha atoms,

but a number of examples violate this generality, (2) C-O-Ca angles range from 110° to 150°, (3) but in contrast to the carboxylate groups, calcium is most commonly found to be colinear with the carbonyl bond.

The same general trend was found in the Ca-O bond lengths, with most of the observations in the range between 2.3 and 2.45 Å. A significant increase in the number of bond distances in the 2.2 to 2.3 Å range was noted. This may result from the fact that unlike the calcium-water and calcium-carboxylate interactions, nearly one-third of the Ca-carbonyl examples studied displayed six coordinate geometries.

These reviews have provided some information about the general binding patterns exhibited by calcium to small model compounds of specific types; carboxylates, water molecules and carbonyl groups. Yet a lack of structural documentation of calcium complexation to low molecular weight molecules of biological significance still exists. More information is needed about competitive binding of these and other ligating groups to calcium and about binding patterns exhibited when more than one calcium atom is involved in order to elucidate possible mechanisms involving calcium in secretory processes such as the release of histamine. It is unclear whether calcium interacts directly with allergens of low molecular weight, and if so, how this interaction results in the transport of calcium across the cell membrane of mast cells and basophils. Some of the

allergens might exhibit ionophoric properties and serve to enfold the cation inside a nonpolar shell, but this is untested by experiment. Although a large number of compounds able to induce the release of histamine have nitrogen containing functional groups, does calcium's reluctance toward nitrogen coordination diminish if the nitrogen is incorporated into multidentate ligands? The reasons behind the differentiation between calcium and magnesium in biological systems are not completely understood and this understanding is hindered by the lack of structural data for magnesium complexation to organic molecules and by the lack of structural knowledge of relative calcium and magnesium binding patterns to the same ligand. Therefore, a project was undertaken to synthesize and structurally characterize calcium and magnesium complexes of low molecular weight species which have shown involvement in allergic reactions. The focus of this research has been to extend the current knowledge of calcium-allergen interactions at the molecular level, and thus lead to better ideas of how to interrupt pharmacologically the sequence of events which results in the release of histamine and the anaphylactic reaction.

CHAPTER II

X-RAY CRYSTALLOGRAPHY

For the determination of a single crystal X-ray structure, a crystal of appropriate dimensions (maximum dimension 0.5 mm) was mounted on a glass fiber which was afixed to a brass nib. Crystal which were unstable in air, were mounted in sealed glass capillaries presaturated with the vapour of the mother liquor. The brass nib was inserted into a goniometer which was then positioned on a four-circle Syntex P3 automated diffractometer. With the instrument circles oriented perpendicular to the view of the microscope, the crystal was visually centered. A rotation photograph was taken to elucidate crystal quality and to provide starting information for the automated centering program of the diffractometer. A reflection of χ close to 90^{o} and 2θ less than 20^{o} was selected and used to precisely adjust the height of the crystal. Fourteen additional independent reflections were chosed from the polaroid photograph and centered, to determine the optimum $2\theta, \omega, \phi$, and χ angles for each reflection. An indexing routine(37) provided possible cell edges and angles from which a set was chosen with maximum symmetry and minimum volume. On occasion, the presence of a mirror plane within the unit cell

chosen was confirmed or disproved by taking an axial photograph about the appropriate cell edge. A least square fit of the diffractometer centered angles of the fifteen reflections to the unit cell edges yielded the final cell parameters, their associated errors, and the orientation matrix required for data collection(37). If the errors in the cell parameters were unusually high, a fast scan of a low angle subset of the data was completed to find fifteen independent reflections of high intensity and 2Θ angles greater than 15°. The unit cell determination was repeated, yielding a cell which displayed more acceptable errors.

The extent of data collection was dependent upon the crystal class. A data set was collected such that the diffraction symmetry of the cell generated a complete sphere of data(38). Specific details of data collection for each compound are recorded in the respective crystal data tables. The diffractometer records the intensity data, I_{hkl}, associated with each reflection in the following format(37):

Sequence number (negative for standard reflections), h, k, l, $2\Theta, \omega, \phi, \chi$, 2Θ scan rate, scan speed, peak profile, left background, peak count, right background, scaled net count on a 1°/minute basis, standard deviation, and crystal exposure hours.

Diffraction data is reduced by a locally modified computer program, DATRDN(39), which applies the corrections, (i) background correction, (ii) Lorentz effect, (iii) polarization correction and (ix) decomposition corrections

to the data.

Correction for the left and right background (i) is as follows:

$$I_{int} = (I_{meas}\text{-Lbg-Rbg}) \text{ X Scan rate} \quad (1)$$

$$\sigma I_{int} = (I_{meas}\text{+Lbg-Rbg})^{1/2} \text{ X Scan rate} \quad (2)$$

where I_{int} = Integrated intensity

σI_{int} = Standard deviation of I_{int}

I_{meas} = Measured intensity

Lbg = Left background

Rbg = Right background

The reflection is then considered to be observed if:

$$I_{int} > 3\sigma(I_{int}) \quad (3)$$

The Lorentz effect (ii) is a factor which stems from the fact that the measured intensity of a reflection is dependent upon the magnitude of 2θ. During data colletion, the crystal is rotated at a constant angular velocity. Thus reflections measured at low 2θ values spend more time in the beam and thus are statistically more strongly diffracting than those measured at high 2θ values. The Lorentz factor (L) is given by:

$$L = 1 / \sin 2\theta \quad (4)$$

The polarization correction (iii) is necessary because the efficiency of diffraction of components of the X-ray beam varies with the angle of diffraction, resulting in polarization of the diffracted beam. The incident (nonpolarized) X-ray beam exhibits a parallel component equal to the perpendicular component with respect to the

orientation of the diffracting planes. However, the parallel component is represented to a greater extent in the diffracted beam as a result of higher diffraction efficiency. The diffraction of the perpendicular component varies with the angle θ, being less efficiently diffracted at higher values of θ. Since the loss due to polarization of diffracted beam intensity is a simple function of 2θ, the polarization correction (p) is accomplished by the following equation:

$$p = (1 + \cos^2 2\theta) / 2 \qquad (5)$$

Commonly, the corrections (ii) and (iii) are combined into one equation and referred to as the Lorentz-polarization factor (Lp):

$$Lp = (1 + \cos^2 2\theta) / 2 (\sin 2\theta) \qquad (6)$$

The final correction (iv) must be made only in those cases in which the crystal decomposed during data collection. This correction assumes that decomposition was linear with respect to time. Thus the decomposition correction is calculated by the equation:

$$I_{orig} / I_{ave} \qquad (7)$$

where I_{orig} = Original intensity of the standard reflection and

I_{ave} = Average current intensity of the standard reflections determined every 100 reflections.

Thus the corrected intensity, I_{cor}, is arrived at by the combination of these four corrections and represented by:

$$I_{cor} = I_{int} \times (1 / Lp) \times (I_{orig} / I_{ave}). \qquad (8)$$

Once the data has been collected and reduced, the resulting set of structure factors for all reflections (hkl) is the basis for the calculation of the three-dimensional electron density distribution, which is recognized as the image of the molecule in the crystal. The structure factor F_{hkl} is an expression of the amplitude as well as the phase of a given reflection and is independent of the method and conditions of data collection. The structure amplitude $|F_{hkl}|$ can be abstracted directly from the diffractometer data as follows:

$$|F_{hkl}| = (I_{cor})^{1/2} \qquad (9)$$

but to the present date, there is no experimental method available to measure the phase (α) of each reflection. The phase is defined as the difference in period, expressed as an angle, between the wave resulting from a given set of planes and the wave resulting from scattering at the origin. The inability to measure the phase of each reflection constitutes the "phase problem" of modern crystallography. However, the solution of crystal structures is being accomplished by employing techniques which determine the approximate phases of some of the reflections, while solution refinements extend the knowledge of phases to all reflections.

One such technique, Patterson mapping, involves Fourier transformation of the squared $|F_{hkl}|$s. Squaring of the structure amplitude eliminates the phase term(40). "Maps", calculated by the Fourier transformation of $|F_{hkl}|^2$

for all reflections, are interpreted by considering each peak to be the end of a vector between atoms of the cell, translated to the origin. Each atom thus gives rise to a vector to every other atom in the cell. Since the weight of these vectors is proportional to the product of the number of electrons in each atom, vectors between heavy atoms (atoms of greater number of electrons) are the most visible. The space group general equivalent positions sometimes result in each atom having a vector to a symmetry related atom that ends on a specific line or plane. These are called Harker vectors. The positional parameters of the heavy atoms can then be determined by the combined interpretation of the Harker vectors and other nonspecific vectors seen in the Patterson map. This method is known as the "heavy atom method"(39) and allows the positioning only of the heavy atoms of the unit cell.

"Direct methods" seek to solve the phase problem by the interpretation of phase relationships based on the observed intensities. Sigma 1 relationships allow the determination of phase of a small number of reflections using the Harper-Kasper inequalities(38). Sigma 2 relationships and symbolic addition procedures then expand the number of reflections for which intensities and phases have been correlated. The normalized structure factors(41), E_{hkl}, can now be calculated by:

$$E^2_{hkl} = (F_{hkl})^2 / \varepsilon \Sigma f_i^2 \qquad (10)$$

where f_i = scattering factors for atom i

ε = an integer (usually 1), but space group dependent.

The set of normalized structure factors represents the relative scattering efficiency of the sets of planes corrected for less efficient scattering observed at higher values of 2θ. A Fourier transfomation of the small set of phased E_{hkl} values yields an electron density map, from which the positional parameters of the atoms in the molecule can be extracted.

Once the heavy atoms have been positioned by either of the previously discussed methods, phased structure factors (F_{calc}) can be calculated and compared with those measured (F_{obs}) for the entire data set. The accuracy of the "model" structure , ie. the agreement between F_{calc} and F_{obs}, is described by the Residual factor (R), defined by:

$$R = (\Sigma \; ||F_{obs}|-|F_{calc}||) \; / \; (\Sigma \; |F_{obs}|) \qquad (11)$$

As the correctness of the model increases, the difference between F_{obs} and F_{calc} decreases and the R factor is lowered. Any remaining missing atoms can now be located from a Fourier map of the residual electron density, (difference Fourier) generated by the fourier transformation on the quantities $||F_{obs}|-|F_{calc}||$ for each reflection. Least squares refinement of the position parameters (x, y, z) and the thermal parameter, U(isotropic), is then carried out to maximize the agreement between F_{obs} and F_{calc}. The size of the thermal parameter is an indication of the

correctness of the indentity of an atom, based on its electronic configuration. Successive cycles of least squares refinement and difference Fourier syntheses are continued until no other atoms appear in the difference Fourier. A least squares refinement allowing temperature factors of each atom to refine anisotropically, generating the anisotropic thermal parameters (U11, U22, U33, U12, U13, U23) follows and should result in an R value of less than 10%. Hydrogen atoms can often be located from a difference Fourier at this point, but this is highly dependent on the quality of the data. Derived bond distances, bond angles, and the connectivity of the model itself must all be chemically reasonable. The positional parameters and anisotropic thermal parameters are used to generate a visual, three-dimensional projection of the molecule, whose atoms are drawn as ellipsoids of 90% probability of electron enclosure(42).

CHAPTER III

EXPERIMENTAL

The chemicals used in syntheses were of reagent quality and purchased from Aldrich, Sigma, or Fisher chemical companies. Melting points techniques were used to monitor the purity of solid ligand starting materials, which were used without further purification. Materials whose melting points deviated from values reported in the literature were recrystallized. Crystallization of calcium and magnesium complexes was accomplished by allowing slow evaporation of a solution at room temperature to near dryness. Synthetic methods such as gel-growth and diffusion were also investigated, but were generally less successful in producing X-ray quality crystalline products. The synthetic procedures for the individual compounds are detailed in the following sections.

$(Ca(nicotinate)_2(H_2O)_2)(H_2O)_3$ (I):

50 mL (12.5 mmole) of a 0.25 M aqueous solution of $CaCl_2$ was mixed with 50 mL (25 mmole) of a 0.5 M aqueous solution of Na(nicotinate) and allowed to crystallize slowly at room temperature. After thirty-six hours, clear colorless prisms were observed and isolated. Because of the instability of the crystals in air, a single crystal of appropriate

size (maximum dimension 0.5 mm) was sealed in a capillary tube in an atmosphere of the vapour of the mother liquor for X-ray diffraction data collection.

$(Mg(H_2O)_6)(nicotinate)_2(H_2O)_4$ (II):

Long clear needles of Mg(nicotinate)$_2$ hydrate were isolated by recrystallizing a commercial sample (Pfaltz and Bauer) from water. Similar to the calcium salt, these needles showed a tendency to degrade to powder on standing in air and were thus mounted in a sealed glass capillary along with a drop of the mother liquor to provide a stabilizing atmosphere. Diffraction data was collected on a single crystal of suitable dimensions.

$(Ca(isonicotinamide)_2(H_2O)_4)Cl_2$ (III):

A clear solution was made by the addition of 0.2442 g (2 mmole) of isonicotinamide to 10 mL of H_2O. After the addition of 4 mL (2 mmole) of 0.5 M $CaCl_2$ solution, the mixture was allowed to evaporate slowly at room temperature. Forty-eight hours later the solution had evaporated to near dryness yielding long clear needles. A single crystal suitable for X-ray data collection was cleaved from a long needle and mounted on a glass fiber.

$Ca(isonicotinate)_2(H_2O)_4$ (IV):

1.2311 g (10 mmole) of isonicotinic acid was added to 40 mL of H_2O. A clear, colorless solution was formed on addition of 10 mL (10 mmole) of a 1 N standard solution of NaOH with boiling. Subsequent addition of 10 mL (5 mmole) of a 0.5 M $CaCl_2$ solution resulted in the formation of a

small amount of white precipitate. The precipitate was removed by gravity filtration into a 100 mL beaker and the clear solution was allowed to crystallize at room temperature. Large clear needles appeared after seventy-two hours. One large needle was cleaved to yield a chunk of suitable size, which was mounted on a glass fiber for X-ray data collection.

$(Ca_{1.5}(salicylate)_2(acetate)(H_2O)_2)(acetic\ acid)$ (V):

0.7909 g (5 mmole) of $Ca(OAc)_2$ and 1.8015 g (10 mmole) of acetylsalicylic acid were dissolved in 40 mL of 75% aqueous MeOH solution with stirring. The solution was allowed to evaporate nearly to dryness at room temperature for several weeks and yielded long clear plates. One plate of appropriate size was mounted on a glass fiber for the collection of X-ray diffraction data. The compound was relatively stable in air.

$Mg(salicylate)_2(H_2O)_4$ (VI):

0.4289 g (2 mmole) of $Mg(OAc)_2$ and 0.5524 g (4 mmole) of salicylic acid were combined in 50 mL of H_2O. A clear solution resulted after boiling the mixture for five minutes. The odor of HOAc formed by the reaction was notable. Evaporation over a one week period yielded a solid, white microcrystalline precipitate. This suspension was then dissolved in 10 mL of hot H_2O, filtered to remove minor amounts of non-dissolved solid matter and allowed to concentrate at room temperature. Forty-eight hours later, clear prismatic needles were evident. X-ray diffraction data was

collected on a crystal mounted on a glass fiber.

(Ca(p-aminosalicylate)(acetate)(H_2O))(H_2O) (VII):

0.7655 g (5 mmole) of p-aminosalicylic acid and 0.3954 g (2.5 mmole) of calcium acetate hydrate were dissolved in 75 mL of MeOH by stirring the mixture for thirty minutes. Gravity filtration removed the small amount of white precipitate which remained in suspension. Slow evaporation of the clear tan solution at room temperature yielded small platelets after a period of one week. Because of its instability in air, a single crystal with suitable dimensions was mounted in a sealed capillary in the vapour of the mother liquor to provide an inert atmosphere. The X-ray diffraction analysis was then undertaken.

Mg(p-aminosalicylate)$_2$(H_2O)$_4$ (VIII):

0.7655 (5 mmole) of p-aminosalicylic acid was mixed with 6 mL (6 mmole) of a 1 N NaOH solution and 5 mL water added. 5 mL (2.5 mmole) of a 0.5 M aqueous $MgCl_2$ solution were added to the clear solution followed by 30 minutes of stirring. During this time, the colorless solution began to darken to a light brown color. Evaporation was allowed to proceed in air at room temperature. Several days later, clear tan needles were removed from the dark brown solution and mounted on a glass fiber to be used for X-ray diffraction studies.

Na(p-aminosalicylate)(H_2O)$_2$ (IX):

0.3062 g (2 mmole) of p-aminosalicylic acid was added to 20 mL of H_2O and dissolved to form a clear solution

upon addition of 2.5 (2.5 mmole) of a 1 N solution of NaOH with warming. Following the addition of 2 mL (1 mmole) of a 0.5 M aqueous $CaCl_2$ solution with continued heating, the clear solution was observed to darken to a light tan color. After gravity filtration into a 50 mL beaker, the solution was allowed to crystallize at room temperature, but the color continued to darken. After forty-eight hours, small, tan rhombohedra were removed from the brown mother liquor. A single crystal of suitable size was mounted on a glass fiber for X-ray diffraction data collection. No crystals of calcium containing material were isolated.

(Mg(2,6-pyridinedicarboxylate)$(H_2O)_3$)$(H_2O)_2$ (X):

To 20 mL of H_2O, 0.3342 g (2 mmole) of 2,6-pyridinedicarboxylic acid and 8 mL (8 mmole) of a 1 N aqueous solution of NaOH were added. Gentle boiling of the mixture yielded a clear solution. The addition of 8 mL (4 mmole) of a 0.5 M aqueous $MgCl_2$ solution produced a heavy white precipitate which could not be redissolved on heating. The mixture was then filtered by gravity into a 100 mL beaker and allowed to evaporate at room temperature. Clear, small prisms were observed twenty-four hours later. For X-ray diffraction studies a single crystal of suitable size was sealed inside a 0.3 mm capillary tube in an environment of the vapor of the mother liquor.

Ca(phenoxymethylpenicillinate)$_2(H_2O)_2$ (XI):

0.3504 g (1 mmole) of phenoxymethylpenicillinic acid was stirred with 25 mL of water and dissolved upon

addition of 1 mL (1 mmole) of a 1 N solution of NaOH. 10 mL (5 mmole) of a 0.5 M solution of $CaCl_2$ were added and the resulting solution filtered into a 50 mL beaker. After evaporation at room temperature for twenty-four hours, small, clear, colorless plates were observed. Crystals of suitable size for X-ray diffraction work (1 mm x 1 mm x 0.5 mm) were isolated after seventy-two hours. A single crystal was mounted on a glass fiber for further work.

$(CaCl_4(H_2O)_2)(CaCl_2(H_2O)_2(histamine.H^+)_2)$ (XII):

0.1110 g (1 mmole) of histamine was dissolved in 20 mL of water to which 4 mL (2 mmole) of a 0.5 M aqueous solution of $CaCl_2$ was added. The solution was allowed to stand for a two week period under nitrogen at room temperature. The fine white precipitate which was observed at the end of that time was removed by filtration and the solution was returned to a nitrogen atmosphere and allowed to evaporate to near dryness to give clear, colorless plates. A single plate was mounted in a sealed glass capillary for X-ray diffraction data collection.

Histamine hydrobromide (XIII):

1.1115 g (1 mmole) of histamine and 1.1800 g (5 mmole) of $CaBr_2$ dihydrate were mixed in 50 mL of water and the clear solution refrigerated. After forty-eight hours, the fine white precipatate which appeared was removed by filtration and the solution allowed to evaporate to near dryness. One week later, clear plated were observed one of which was mounted in a glass capillary for the collection of

X-ray diffraction data.

Histamine hydrochloride (XIV):

1.1115 g (10 mmole) of histamine was dissolved in 50 mL of H_2O to which 1.1110 g (10 mmole) of anhydrous $CaCl_2$ were added. The clear solution was refrigerated. A small amount of white precipitate was observed after forty-eight hours. The solution was filtered and then allowed to evaporate to near dryness. After eight days, clear platelets of suitable size were observed. One single plate was mounted on a glass fiber for X-ray diffraction data collection.

$(ZnCl_4)(histamine.H_2^{++})$ (XV):

0.3682 g (2 mmole) of histamine were dissolved in 60 mL absolute EtOH to which was added 0.1110 g (1 mmole) of $CaCl_2$ and 0.1363 g (1 mmole) of $ZnCl_2$. Within five minutes, the formation of small crystals was observed. These were redissolved upon addition of 50 mL of anhydrous MeOH. Long clear plates grew over a seventy-two hour period at room temperature. A single clear plat of appropriate size was mounted on a glass fiber and used for X-ray diffraction experiments.

$(ZnCl_4)(procaine.H^+)_2$ (XVI):

0.5456 g (2 mmole) of procaine was dissolved in 30 mL of dry EtOH, followed by the addition of 0.1110 g (1 mmole) of anhydrous $CaCl_2$ and 0.1363 g (1 mmole) $ZnCl_2$. Stirring the mixture resulted in the rapid precipitation of a white solution, which redissolved upon addition of 20 mL

of water. Clear colorless prisms formed during a one week period. X-ray diffraction data was collected on a single crystal which had been mounted on a glass fiber.

(Ca(2,4-dinitrophenoxide)$(H_2O)_6$)(2,4-dinitrophenoxide)(H_2O) (XVII):

0.5523 g (3 mmole) of 2,4-dinitrophenol and 8 mL (8 mmole) of a 1 N NaOH solution were added to 50 mL of water. After stirring for 5 minutes, a clear yellow solution formed. A heavy yellow precipitate resulted upon addition of 30 mL (15 mmole) of a 0.5 M aqueous $CaCl_2$ solution. Recrystallization of a small portion of the solid from water yielded long yellow needles. Since the needles displayed air sensitivity, becoming powder on standing, a single crystal was sealed in a glass capillary in an atmosphere of the vapour of the mother liquor. Single crystal X-ray studies were carried out on this crystal.

$(Mg(H_2O)_6)$(2,4-dinitrophenoxide)$_2(H_2O)_2$ (XVIII):

0.1841 g (1 mmole) of 2,4-dinitrophenol and 0.1067 g (2.7 mmole) of NaOH were added to 20 mL of water, forming a clear yellow solution upon stirring for five minutes. The addition of 10 mL (5 mmole) of a 0.5 M aqueous $MgCl_2$ solution resulted in the formation of a cloudy yellow suspension. Gravity filtration effected no change, but the addition of 20 mL of 95% EtOH resulted in a clear yellow solution. Partial evaporation of the aqueous alcohol solution produced long yellow needles which decomposed on standing in air. A suitable single crystal was mounted in a

sealed glass capillary in an atmosphere saturated with the vapor of the mother liquor and used for X-ray diffraction analysis.

Crystal growth by diffusion of suitable reactants through gel media is a relatively old technique, prominent in the literature of the early 1900's. The early work was reviewed by Holmes(43) and more recently by Armington and O'Connor(44). Three basic synthetic methods of gel growth were investigated in attemps to grow calcium and magnesium complexes with several acidic ligands. The simplest arrangement involved mixing the ligand, which was dissolved in water or acetic acid, with an aqueous solution of the gel (sodium metasilicate) and allowing it to set in a partially filled test tube or beaker. The gel solution will then become firm upon the abstraction of a proton from the ligand. An aqueous solution of the alkaline earth metal was then layered on top of the gel, permitting reation only after the alkaline earth cations diffused through the gel media to reach the ligand. This slow reaction results in the formation of an insoluble complex in crystalline form. If precipitation occurred too rapidly resulting in powder rather than crystalline products, a derivation of the first method was employed. A second gel layer was created between the ligand layer and the aqueous solution above. The upper gel layer consisted only of a gel formed by reaction with a mineral acid but no ligand. This intermediate layer slowed the rate of alkaline earth cation's complexation with the

ligand, thus avoiding rapid precipitation. Calcium malonate crystals were grown by Oskarsson, et al. by this method(45). The third method involved partially filling a U-tube with a neutral gel. Once the gel was firm, each reactant was layered on top of the gel in a separate arm of the U-tube and the reaction again proceeded after diffusion of the reactants. Very large PbI_2 crystals have been grown by Patel and Rao(46) using this type of diffusion experiment.

Experimentally, aqueous silica gel is the most commonly used medium for crystal growth. Two basic requirements must be met; (1) the reactants must be soluble in the solvent (water) yet the product must be relatively insoluble, and (2) the gel must remain inert to the reactants and products. The method used during this investigation was similar to that preferred by Armington and O'Connor(44) in their review.

A stock solution of sodium metasilicate was prepared by mixing 244 g of $Na_2SiO_3.9H_2O$ with 500 mL of water. Several 25 mL aliquots of 1 N acetic acid (HOAc) were then titrated to a variety of pH values. At pH=3.5, the resulting gel required about three days to set. The gel became firm after only one day when titrated to a pH=4.5, but set in about one hour when at a pH=5.5. Above pH=6, the solution "freezes", becoming a solid white precipitate. Next, 50 mL of a 0.5 M tartaric acid solution was titrated to a pH=4.0 with the stock sodium metasilicate solution and allowed to set for two days. When the gel was then layered

with 25 mL of 0.5 M $CaCl_2$ solution, small crystals of calcium tartarate formed at the water-gel interface within two hours. Large, well defined crystals also began to form deeper in the gel layer over a two week period. Ligands other than tartaric acid were then tested, but none yielded crystals suitable for X-ray analysis. The use of acetylsalicylic acid (aspirin) or salicylic acid as ligands gave rise to two major problems. Initially, the solubility of the two ligands in water was low and thus only a few drops of the stock metasilicate solution were required to titrate a large volume of the aqueous ligand solution to a pH=4.5. This gel solution did not harden. Aspirin, in the presence of an aqueous base such as sodium metasilicate, hydrolized easily to form the salicylate anion and acetic acid. Thus attempts to prepare complexes of calcium and these two ligands using gel growth techniques were unsuccessful.

The preparation of calcium and magnesium complexes of nicotinic acid was also attempted by gel growth techniques. Nicotinic acid was dissolved in 1 N HOAc , titrated with the stock metasilicate solution, and allowed to gel. Layering with the appropriate alkaline earth halide solution produced no crystals. Crystals of a calcium and magnesium nicotinate complexes were obtained using solution techniques, but only at very high concentrations, suggesting that these complexes were too water soluble to crystallize from the gel.

Alkaline earth complexes of ethacrynic acid and

three tetracyclines were sought by gel growth methods. Gels of good quality were formed when ethacrynic acid, tetracycline, oxytetracycline, and chlortetracycline were dissolved in 1 N HOAc and titrated with stock metasilicate solution, but addition of the aqueous calcium and magnesium halide solutions onto the gel resulted in precipitation at the interface. The tetracycline gels tended to darken within several days. Thus no crystalline complexes of these ligands have been isolated by solution growth methods due to their high insolubilities in the gel media.

Attempts were made to complex a wide variety of other small molecules of biological interest with calcium and magnesium, but suitable crystalline products were not obtained. These ligands in three basic categories; (1) the tetracyclines, (2) penicillins and cephalosporins, and (3) local anesthetics. A brief review of these experiments is given in the sections below.

Tetracyclines:

Tetracycline and two derivatives, oxytetracycline and chlortetracycline, were dissolved in water upon addition of an equimolar amount of NaOH, giving clear tan solutions. The addition of calcium and magnesium cations produced a heavy orange to tan precipitate which was insoluble in water, alcohols, ether, and acetone. The colored filtrate blackened overnight, in air or under N_2 gas in a dry box. When dioxane was used as the solvent, less precipitation occurred, yet the low vapor pressure of dioxane prevented

rapid evaporation and darkening occurred over a two day period. Several tetracyclines have been shown to exist in a zwitterionic form at a pH=6.0(47) and since a mercuric chloride complex with zwitterionic oxytetracycline has been crystallized(48) from aqueous methanol, similar experiments were undertaken with calcium and magnesium and tetracyclines. Aqueous methanol (50%), ethanol, and acetone solutions were used as solvents of the ligands with $CaBr_2$, $CaCl_2$, and $MgCl_2$. These solutions were placed under a N_2 atmosphere in a dry box. One week later, all solutions had darkened without crystal formation.

Penicillins and cephalosporins:

Phenoxypenicillin is the only penicillin to have been successfully crystallized as a calcium salt in the course of this work, although benzylpenicillin, methicillin, ampicillin, amoxicillin, cephalexin, and cephalosporin C were tried. All are readily soluble as sodium salts in aqueous solutions. Addition of $CaCl_2$, $CaBr_2$, and $MgCl_2$ to these basic solutions and slow evaporation resulted in yellow oily materials. Ampicillin and amoxicillin exist as zwitterions in aqueous solutions(49, 50, 51). Cephalexin has the same side chain as ampicillin while cephalosporin C has a side chain which resembles the amino acids, therefore these antibiotics should also be expected to exist as zwitterions in water. As the zwitterion, the carboxylate group of these latter four ligands should rapidly coordinate to calcium and magnesium, yet all experiments to obtain

these crystalline complexes were unsuccessful.

Local anesthetics:

Aspirin was the major local anesthetic attempted to be isolated as a complex with calcium and magnesium, yet it presented difficulties in crystallization. Numerous solution experiments lead to clear glasses and oils which had the strong odor of HOAc due to hydrolysis in the presence of aqueous base, yielding the salicylate anion and acetic acid. Calcium salicylate crystals were isolated in several instances. Preparation of the calcium aspirin salt, as outlined in a patent to Lee Laboratories(52), yielded a white amorphous powder of which the purity was not verified. All recrystallizations of this powder in dry solvents still gave rise to the odor of acetic acid within a short period of time. Crystals obtained were found to be a calcium salicylate complex. Thus no crystals of the desired aspirin salts have been obtained. Two additional anesthetics, lidocaine and procaine, have also been investigated as possible ligating agents to calcium and magnesium. Reaction of the free bases in solvents such as water, alcohol, acetone, and ether with alkaline earth halides and acetates failed to produce any suitable crystalline products.

CHAPTER IV

RESULTS AND DISCUSSIONS

The evidence for calcium involvement in allergenic reactions is well grounded, yet the reasons behind the differentiation between calcium and magnesium effectiveness in the sequence of events which results in histamine release are unclear. To investigate the ability of calcium, as opposed to magnesium to participate in this sequence, comparative structural studies of calcium and magnesium binding to the same low molecular weight allergens have been made. From the single crystal X-ray diffraction studies of these complexes, it has been shown that calcium does is fact coordinate directly to a variety of multidentate ligands while magnesium is much more rigid in its binding selectivity.

Complexes of calcium and magnesium to nicotinic acid were synthesized. The compound, $(Ca(nicotinate)_2(H_2O)_2)(H_2O)_3$ (I), (53) crystallizes with distorted square antiprism geometry at calcium in the monoclinic space group C2/c (Table I). The projection view of (I) shows the calcium lying on a two-fold symmetry axis and coordinated to eight oxygen atoms (Figure 3). Six of the oxygen atoms are from the carboxylate groups of two nicotinate anions and the

other two oxygen atoms being from water molecules. Each carboxylate group serves as an asymmetric bidentate ligand to one calcium cation (Ca1-O90, 2.797(2) Å, Ca1-O91, 2.412(2) Å) while one of the carboxylate oxygens ligates as well to a second calcium cation in a symmetry related position (Ca1-O90''', 2.345(2) Å, symmetry operation ''' = -x, -y, -z). While carboxylate groups commonly show monodentate, bidentate, or quadridentate ligation when complexed to calcium(34), the compound (I) shows a fourth type of carboxylate binding (tridentate) to calcium. All Ca-O bond distances displayed in (I) are consistent with observations for eight coordinate calcium bound to oxygen found in the current literature(34). An extended projection view of (I) shows the polymeric nature of calcium packing in the unit cell: (Ca-Ca distance 4.055 Å) with strings of calcium atoms surrounded by oxygen atoms of tridentate carboxylate groups and water molecules (Figure 4). The complete listing of bond distances and angles, positional parameters, and anisotropic thermal parameters are presented in Tables II, III, and IV respectively.

In comparison, the complex of $(Mg(H_2O)_6)(nicotinate)_2(H_2O)_4$ (II) (53) displays an entirely different mode of coordination. In the solid state (space group $P2_1/a$, crystallographic details in Table V), magnesium is octahedrally coordinated to six oxygen atoms from water molecules at an average Mg-O distance of 2.064(7) Å. In a projection view (Figure 5), the nicotinate anions are

TABLE I

CRYSTAL DATA FOR $(Ca(nicotinate)_2(H_2O)_2)(H_2O)_3$ (I)

Formula	$C_{12}H_{18}CaN_2O_9$ *
M. W.	374.4 g $mole^{-1}$
a	17.005(5) Å
b	12.432(3)
c	7.764(1)
α	90.0°
β	92.60(2)
γ	90.0
V	1639.6(6) $Å^3$
F(000)	784
μMoK_α	4.18 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.516 g cm^{-3}
Z	4
Meas refl	2561
Obs refl	2132
R	4.3 %
R_w	6.6 %
G. O. F.	8.3
Space group	C2/c
Octants meas	±h, +k, +l

* Asymmetric unit = 1/2 of stoichiometric unit

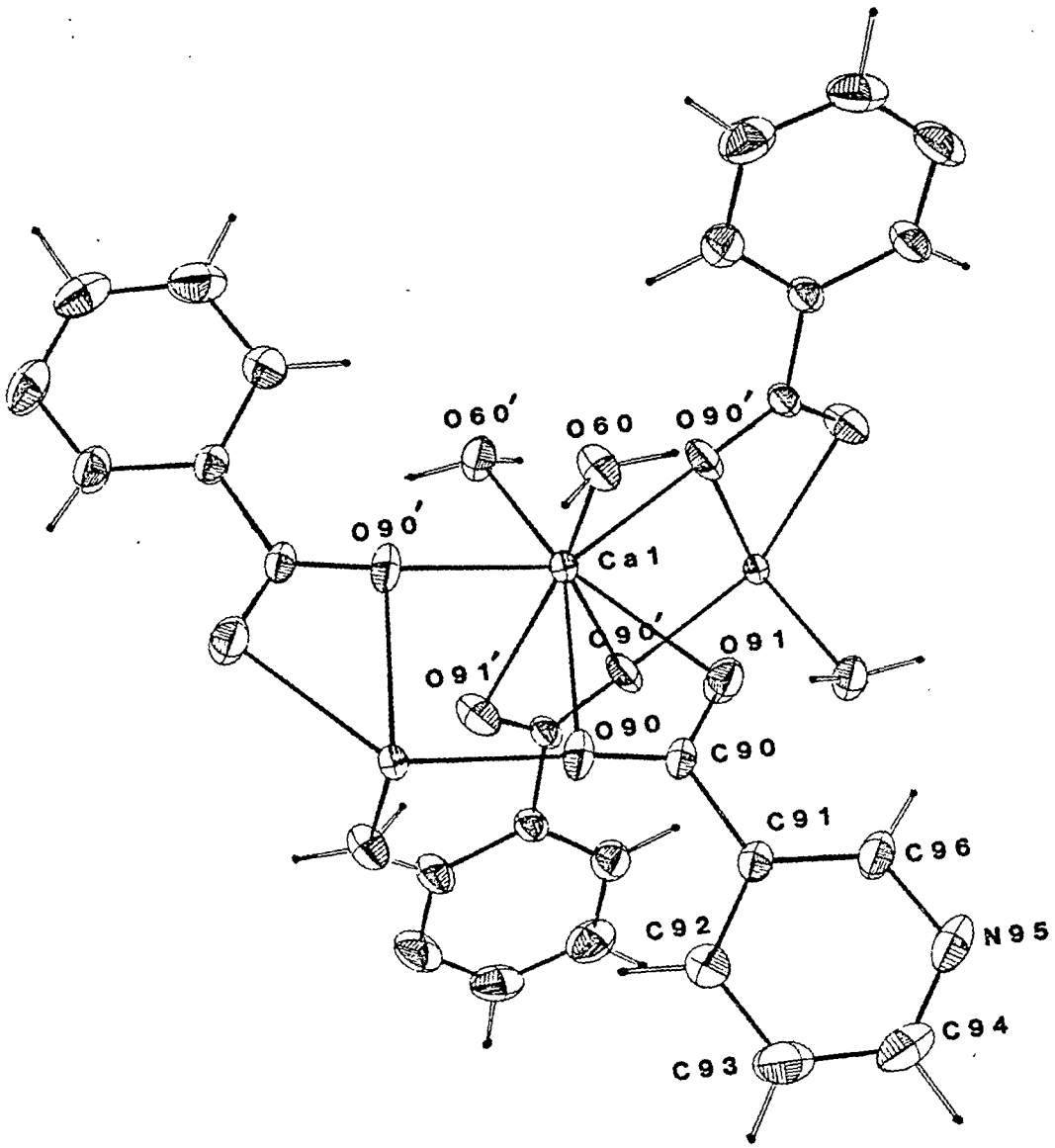

Figure 3. Projection View of I

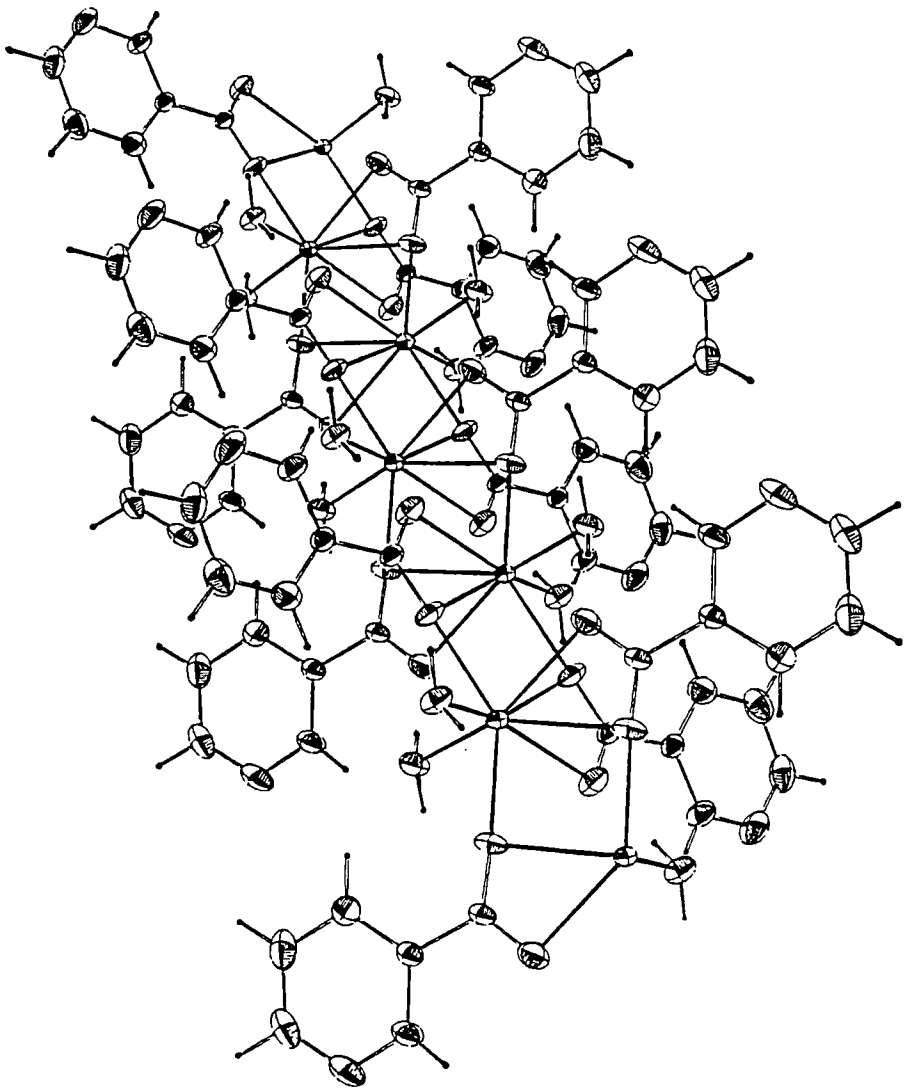

Figure 4. Packing Diagram of I

TABLE II

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

$(Ca(nicotinate)_2(H_2O)_2)(H_2O)_3$ (I)

Ca1-O60	2.402(2)	O60-Ca1-O60'	113.6(1)
Ca1-O90	2.797(2)	O60-Ca1-O90	79.9(1)
Ca1-O90'''	2.345(2)	O60-Ca1-O90'''	75.0(1)
Ca1-O91	2.412(2)	O60-Ca1-O91	85.1(1)
C90-O90	1.255(2)	O90-Ca1-O90'''	76.2(1)
C90-O91	1.260(2)	O90-Ca1-O90''	129.0(1)
C90-C91	1.498(3)	O90-Ca1-O91	49.3(1)
C91-C92	1.386(3)	O91-Ca1-O91'	91.6(1)
C92-C93	1.386(3)	O90-C90-O91	122.1(2)
C93-C94	1.367(4)	O90-C90-C91	119.5(1)
C94-N95	1.344(3)	O91-C90-C91	118.4(2)
N95-C96	1.337(3)	C90-C91-C92	121.4(2)
C96-C91	1.382(3)	C91-C92-C93	118.5(2)
		C92-C93-C94	119.3(2)
		C93-C94-N95	123.0(2)
		C94-N95-C96	117.3(2)
		N95-C96-C91	123.5(2)

' = symmetry operation -x, y, 1/2-z

'' = symmetry operation x, -y, 1/2+z

''' = symmetry operation -x, -y, -z

TABLE III

POSITIONAL PARAMETERS FOR $(Ca(nicotinate)_2(H_2O)_2)(H_2O)_3$ (I)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Ca1	0.0000(0)	-0.04718(4)	0.2500(0)
O10	0.5000(0)	0.0265(3)	0.7500(0)
O30	0.4245(2)	-0.1228(2)	-0.0402(4)
O60	0.1000(1)	-0.1529(1)	0.1214(2)
O90	0.0563(1)	0.1025(1)	0.0167(2)
O91	0.1011(1)	0.0881(1)	0.2860(2)
C90	0.0972(1)	0.1368(1)	0.1437(2)
C91	0.1429(1)	0.2390(1)	0.1271(2)
C92	0.1263(1)	0.3108(2)	-0.0062(3)
C93	0.1708(2)	0.4039(2)	-0.0141(4)
C94	0.2307(2)	0.4208(2)	0.1062(4)
N95	0.2486(1)	0.3513(2)	0.2347(3)
C96	0.2041(1)	0.2630(2)	0.2442(3)
H10	0.4801	-0.0305	-0.1795
H60	0.1463	-0.1500	0.1785
H61	0.1002	-0.1340	0.0201
H92	0.0840	0.2948	-0.0890
H93	0.1593	0.4551	-0.1031
H94	0.2588	0.4907	0.1027
H96	0.2182	0.2224	0.3335

TABLE IV

ANISOTROPIC THERMAL PARAMETERS FOR

$(Ca(nicotinate)_2(H_2O)_2)(H_2O)_3$ (I)

ATOM	U11	U22	U33	U12	U13	U23
Ca1	164(3)	172(3)	175(2)	0	-46(1)	0
O10	1011(20)	519(20)	467(17)	0	114(17)	0
O30	902(20)	393(13)	865(18)	-64(11)	40(15)	-48(11)
O60	263(8)	337(8)	247(6)	87(5)	-25(5)	5(5)
O90	269(8)	338(8)	258(6)	-63(5)	-87(5)	-75(5)
O91	367(9)	314(8)	220(6)	-132(6)	-30(5)	5(5)
C90	153(9)	223(9)	222(7)	-22(5)	-18(5)	-49(5)
C91	175(9)	222(9)	241(7)	-18(6)	0(5)	-31(5)
C92	300(12)	290(11)	344(9)	-9(7)	-25(7)	39(7)
C93	419(15)	266(13)	528(13)	-7(9)	64(10)	97(9)
C94	380(15)	240(12)	553(13)	-87(8)	103(9)	-46(9)
N95	272(12)	380(12)	496(11)	-142(7)	-9(8)	-94(8)
C96	239(11)	318(11)	333(9)	-89(7)	-41(7)	-25(7)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U331^2c^{*2}+2U12hka^*b^* +2U13h1a^*c^*+2U23k1b^*c^*) \times 10^4$$

TABLE V

CRYSTAL DATA FOR $(Mg(H_2O)_6)(nicotinate)_2(H_2O)_4$ (II)

Formula	$C_{12}H_{28}MgN_2O_9$
M. W.	448.7 g $mole^{-1}$
a	13.797(5) Å
b	23.228(10)
c	6.904(3)
α	90.0°
β	93.35(3)
γ	90.0
V	2209.1(14) $Å^3$
F(000)	952
μMoK_α	1.39 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.349 g cm^{-1}
Z	4
Meas refl	2761
Obs refl	1998
R	6.8 %
R_w	8.3 %
G. O. F.	4.1
Space group	$P2_1/a$
Octants meas	$\pm h$, +k, +l

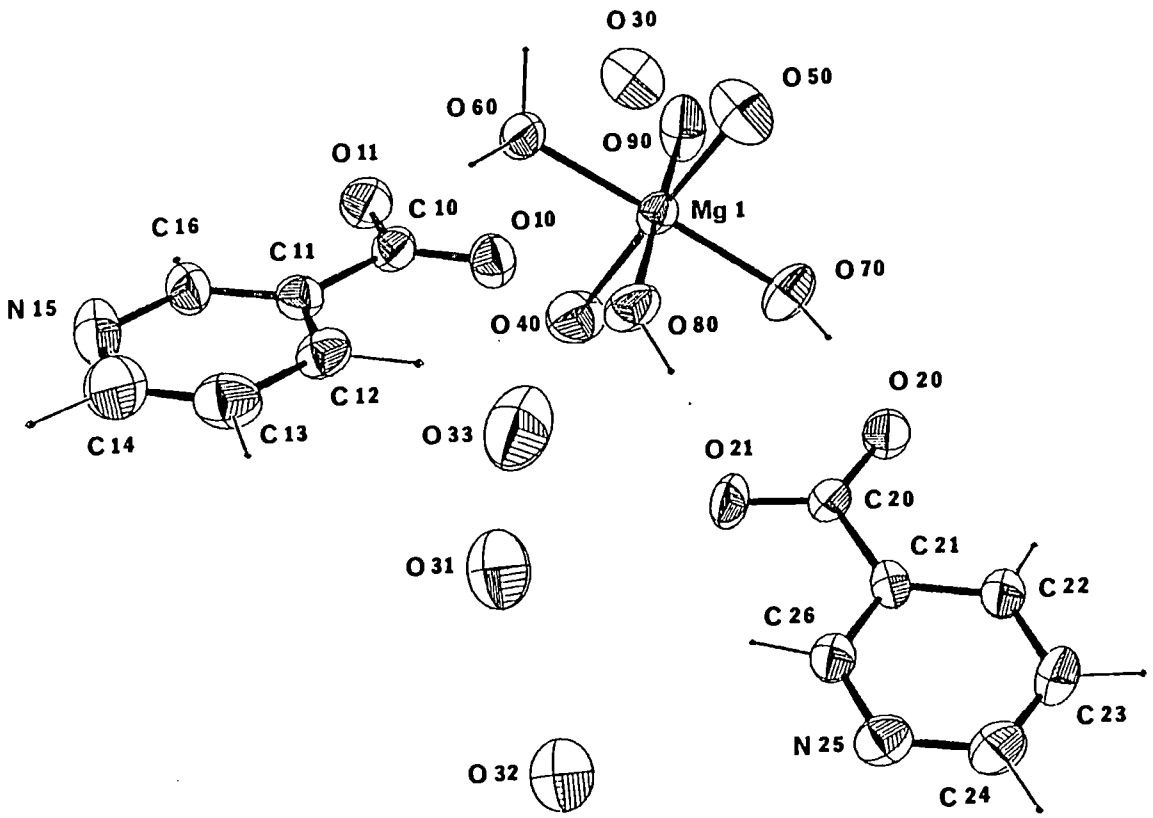

Figure 5. Projection View of II

TABLE VI

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

$(Mg(H_2O)_6)(nicotinate)_2(H_2O)_4$ (II)

Mg1-O40	2.096(7)	O40-Mg1-O50	175.9(4)
Mg1-O50	2.076(7)	O40-Mg1-O60	90.6(3)
Mg1-O60	2.081(6)	O40-Mg1-O70	89.7(3)
Mg1-O70	2.062(6)	O40-Mg1-O80	88.3(3)
Mg1-O80	2.058(6)	O40-Mg1-O90	92.3(3)
Mg1-O90	2.009(6)	O50-Mg1-O60	89.7(3)
C10-O10	1.25(1)	O50-Mg1-O70	89.7(3)
C10-O11	1.27(1)	O50-Mg1-O80	87.7(3)
C10-C11	1.51(1)	O50-Mg1-O90	91.9(3)
C11-C12	1.41(1)	O60-Mg1-O70	176.8(3)
C12-C13	1.39(1)	O60-Mg1-O80	87.9(2)
C13-C14	1.36(1)	O60-Mg1-O90	92.9(2)
C14-N15	1.34(1)	O70-Mg1-O80	88.9(2)
N15-C16	1.34(1)	O70-Mg1-O90	90.2(2)
C16-C11	1.38(1)	O80-Mg1-O90	179.1(6)
C20-O20	1.26(1)	O10-C10-O11	124.5(7)
C20-O21	1.24(1)	C10-C11-C12	120.3(6)
C20-C21	1.51(1)	C16-C11-C12	118.0(7)
C21-C22	1.38(1)	C11-C12-C13	117.9(7)
C22-C23	1.37(1)	C12-C13-C14	119.7(7)
C23-C24	1.35(1)	C13-C14-N15	123.0(9)
C24-N25	1.34(1)	C14-N15-C16	117.7(7)
N25-C26	1.34(1)	N15-C16-C11	123.6(7)

TABLE VI (Continued)

C26-C21	1.37(1)	O20-C20-O21	125.1(6)
		C20-C21-C22	122.6(7)
		C26-C21-C22	117.5(7)
		C21-C22-C23	119.1(8)
		C22-C23-C24	120.3(8)
		C23-C24-N25	122.0(8)
		C24-N25-C26	117.9(6)
		N25-C26-C21	123.3(7)

TABLE VII

POSITIONAL PARAMETERS FOR $(Mg(H_2O)_6)(nicotinate)_2(H_2O)_4$ (II)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Mg1	0.2250(2)	0.4887(1)	0.1839(4)
O10	0.0521(4)	0.3543(2)	0.3982(8)
O11	-0.0532(4)	0.4266(2)	0.3509(8)
O20	0.4160(4)	0.3586(2)	-0.0042(8)
O21	0.2660(4)	0.3265(2)	-0.0707(8)
O30	0.1808(4)	0.4043(2)	0.6707(8)
O31	0.0332(4)	0.1342(3)	0.3392(9)
O32	0.0666(4)	0.0160(3)	0.2830(9)
O33	0.0418(5)	0.0954(3)	0.7245(10)
O40	0.1509(5)	0.4990(3)	-0.0876(9)
O50	0.2965(5)	0.4721(3)	0.4510(9)
O60	0.0979(4)	0.5050(2)	0.3226(9)
O70	0.3494(4)	0.4678(2)	0.0479(9)
O80	0.1859(4)	0.4032(2)	0.1746(9)
O90	0.2654(4)	0.5717(2)	0.1933(11)
C10	-0.0324(5)	0.3737(3)	0.3766(10)
C11	-0.1155(5)	0.3310(3)	0.3786(11)
C12	-0.0969(5)	0.2722(3)	0.4090(11)
C13	-0.1759(7)	0.2350(3)	0.4090(13)
C14	-0.2676(6)	0.2564(4)	0.3819(15)
N15	-0.2863(5)	0.3123(4)	0.3527(12)

TABLE VII (Continued)

C16	-0.2108(5)	0.3485(3)	0.3544(12)
C20	0.3554(5)	0.3197(3)	-0.0504(11)
C21	0.3956(5)	0.2601(3)	-0.0773(10)
C22	0.4941(6)	0.2488(4)	-0.0718(12)
C23	0.5249(6)	0.1935(4)	-0.0952(13)
C24	0.4596(6)	0.1503(3)	-0.1227(13)
N25	0.3639(5)	0.1600(3)	-0.1298(10)
C26	0.3335(5)	0.2145(3)	-0.1085(11)
H12	-0.0212	0.2577	0.4229
H13	-0.1597	0.1909	0.4119
H14	-0.3336	0.2263	0.3867
H16	-0.2219	0.3906	0.3132
H22	0.5312	0.2786	-0.0456
H23	0.5981	0.1874	-0.0768
H24	0.4830	0.1110	-0.1369
H26	0.2664	0.2256	-0.1035
H61	0.1041	0.5322	0.4570
H62	0.0476	0.4812	0.3110
H71	0.3792	0.4326	0.0300
H72	0.3644	0.4871	-0.0448
H81	0.1162	0.3735	0.2371
H82	0.2186	0.3759	0.0969

TABLE VIII

ANISOTROPIC THERMAL PARAMETERS FOR

$(Mg(H_2O)_6)(nicotinate)_2(H_2O)_4$ (II)

ATOM	U11	U22	U33	U12	U13	U23
Mg1	32(1)	28(1)	42(1)	0(1)	6(1)	-1(1)
O10	32(3)	36(3)	53(3)	-1(2)	0(2)	0(2)
O11	44(3)	37(3)	55(3)	-3(3)	7(3)	-6(2)
O20	38(3)	30(3)	62(4)	-1(2)	2(3)	-6(2)
O21	28(3)	41(3)	64(4)	12(2)	0(2)	-4(3)
O30	60(4)	45(3)	48(3)	-6(3)	-3(3)	11(3)
O31	50(4)	68(4)	66(4)	2(3)	-1(3)	12(3)
O32	46(3)	62(4)	62(4)	5(3)	-3(3)	-5(3)
O33	53(4)	78(5)	72(4)	16(3)	9(3)	5(4)
O40	71(4)	65(4)	48(4)	15(3)	-6(3)	-2(3)
O50	65(4)	71(4)	53(4)	-21(3)	-6(3)	17(3)
O60	35(3)	47(3)	65(4)	-8(2)	12(3)	-21(3)
O70	52(3)	34(3)	63(4)	9(2)	24(3)	9(3)
O80	52(3)	32(3)	62(4)	0(2)	15(3)	-11(2)
O90	40(3)	31(3)	112(6)	-3(2)	3(3)	4(3)
C10	31(4)	41(5)	31(4)	3(3)	5(3)	-1(3)
C11	34(4)	38(4)	29(4)	-2(3)	1(3)	-2(3)
C12	42(4)	36(4)	37(4)	-3(4)	12(3)	0(3)
C13	62(6)	32(4)	56(6)	-6(4)	5(4)	-8(4)
C14	56(6)	59(6)	65(6)	-13(5)	12(5)	-8(5)
N15	30(4)	70(6)	75(6)	-3(4)	1(4)	-7(4)

TABLE VIII (Continued)

C16	30(4)	38(4)	58(6)	-4(4)	1(4)	-11(4)
C20	33(4)	37(4)	36(4)	6(4)	2(3)	-6(3)
C21	25(4)	38(4)	36(4)	-2(3)	-2(3)	0(3)
C22	33(4)	38(5)	51(5)	3(4)	-2(4)	-6(4)
C23	37(5)	54(5)	60(6)	18(4)	0(4)	-6(4)
C24	55(5)	34(4)	60(6)	12(4)	0(4)	-6(4)
N25	49(4)	27(3)	49(4)	-1(3)	7(3)	0(3)
C26	33(4)	36(4)	41(4)	4(3)	1(3)	-1(3)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U331^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*) \times 10^3$$

observed to be hydrogen bonded to the inner-sphere water molecules and not coordinated directly to magnesium. Four additional water molecules, not bonded to magnesium, crystallize within the unit cell, and participate in hydrogen bonding. Although magnesium is thought to prefer nitrogen versus oxygen donor ligands in complexation, the nitrogen in the pyridine ring of the nicotinate anion of (II) remained uncoordinated. For example, the literature reports that magnesium complexes to two picolinate (ortho-carboxypyridine) anions via monodentate carboxylate coordination and also to the nitrogen atom of each anion(54). In a related structure, $Mg(isonicotinate)_2(H_2O)_4$ (isonicotinate = paracarboxypyridine), magnesium binds to an oxygen atom of one carboxylate group and to the nitrogen of another isonicotinate anion as well as to four water molecules(55). Thus the isonicotinate anions bridge widely separated pairs of magnesium cations. But in (II), the nitrogen remained uncoordinated to magnesium, perhaps because the coordination either to the nitrogen atom or to the carboxylate group would place the other meta polar moiety in a position of interference with other ligands bound to magnesium. Bidentate coordination of one magnesium atom to both of these ligating sites would force distortion of magnesium's preferred octahedral geometry. Magnesium avoids bidentate coordination to carboxylate groups for similar reasons. The "bite" of the carboxylate group (O--O distance, 2.22 Å av.) is considerably smaller than the

average distance between two oxygen atoms bound to magnesium (2.9 Å av.) in undistorted octahedral geometry. (Complete list of bond distances and angles; Table VI, based on positional parameters and anisotropic thermal parameters; Tables VII and VIII respectively.)

A projection view of (Ca(isonicotinamide)$_2$(H_2O)$_4$) Cl_2 (III) is presented in Figure 6. Crystallizing in the triclinic space group P1 (Table (IX), the calcium atom is positioned on a center of inversion and octahedrally coordinated to six oxygen atoms, four from water molecules (Ca-O, 2.339(3) Å av.) and two carbonyl oxygen atoms of the amide group of the ligands (Ca-O, 2.289(3) Å). As expected, the Ca-O distances are shorter than those in compound (I), consistent with the lower coordination number of calcium in (III). The complete listing of derived bond distances and angles is given in Table X. Both nitrogen atoms of the isonicotinamide ligand remain unbound to calcium, but the protons of the amide nitrogen atom are involved in hydrogen bonding to the chloride anions. The presence of the chloride atoms serves to balance the charge of the cation leaving the unit cell electrically neutral. Atomic positional and thermal parameters are listed in Tables XI and XII.

The compound formed by the complexation of calcium with the anion of isonicotinic acid reveals a different binding geometry calcium can exhibit. Whereas calcium was eight coordinate in (I) and six coordinate in (III), in Ca(isonicotinate)$_2$(H_2O)$_4$ (IV), calcium displays seven-fold

TABLE IX

CRYSTAL DATA FOR (Ca(isonicotinamide)$_2$(H_2O)$_4$)Cl_2 (III)

Formula	$C_{12}H_{20}CaCl_2N_4O_6$ *
M. W.	427.3 g $mole^{-1}$
a	9.778(5) Å
b	8.623(4)
c	7.363(3)
α	115.09(3)°
β	73.40(4)
γ	75.98(3)
V	489.3(3) $Å^3$
F(000)	222
μMoK_α	6.195 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.450 g cm^{-3}
Z	2
Meas refl	2506
Obs refl	1985
R	4.7 %
R_w	6.6 %
G. O. F.	0.38
Space group	$P\bar{1}$
Octants meas	$\pm h$, +k, $\pm l$

* Asymmetric unit = 1/2 of stoichiometric unit

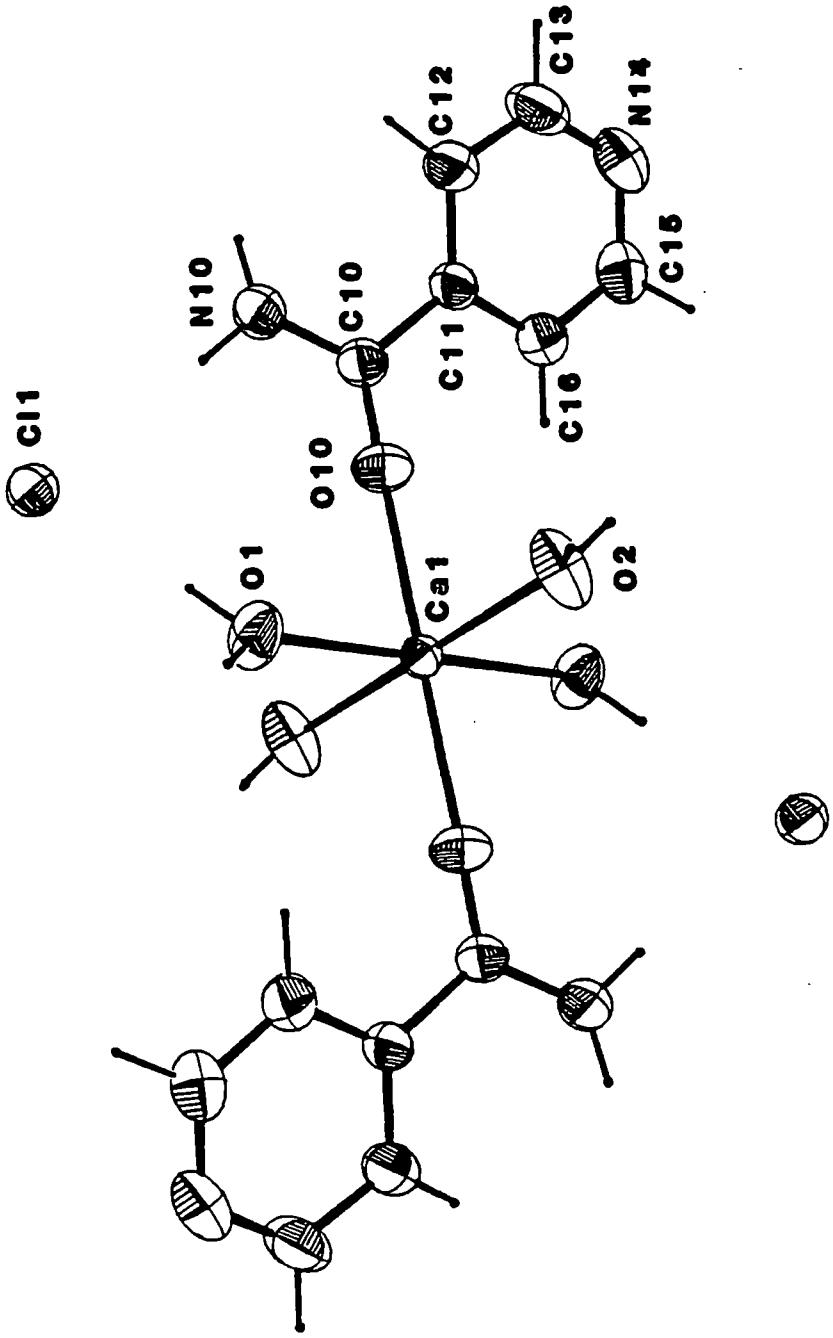

Figure 6. Projection View of III

TABLE X

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

$(Ca(isonicotinamide)_2(H_2O)_4)Cl_2$ (III)

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)

TABLE XI

POSITIONAL PARAMETERS FOR

$(Ca(isonicotinamide)_2(H_2O)_4)Cl_2$ (III)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Ca1	1.0000	0.0000	1.0000
C11	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)
H10	1.5609	-0.4449	0.7931
H11	1.3859	-0.4165	0.8915
H12	1.7177	-0.4368	0.5195
H13	1.8835	-0.3165	0.3814
H15	1.5404	0.2050	0.7119
H16	1.3592	0.1038	0.8811
H101	1.0492	0.3488	1.0823
H102	0.9349	0.3470	1.0056

TABLE XI (Continued)

H201	0.9049	0.1991	1.5046
H202	0.8468	0.0739	1.4306

TABLE XII

ANISOTROPIC THERMAL PARAMETERS FOR

$(Ca(isonicotinamide)_2(H_2O)_4)Cl_2$ (III)

ATOM	U11	U22	U33	U12	U13	U23
Ca1	240(3)	318(4)	410(4)	-131(3)	-131(3)	246(3)
Cl1	343(4)	401(4)	542(4)	-179(3)	-190(3)	294(3)
O1	55(1)	43(1)	79(1)	-32(1)	-39(1)	42(1)
O2	77(1)	68(1)	43(1)	-50(1)	-27(1)	34(1)
O10	26(1)	73(1)	77(1)	-17(1)	-19(1)	51(1)
N10	33(1)	56(1)	71(1)	-22(1)	-20(1)	45(1)
C10	28(1)	48(1)	44(1)	-17(1)	-18(1)	29(1)
C11	30(1)	41(1)	35(1)	-15(1)	-14(1)	22(1)
C12	35(1)	42(1)	51(1)	-14(1)	-10(1)	26(1)
C13	38(1)	58(1)	52(1)	-19(1)	-5(1)	27(1)
N14	59(1)	63(1)	48(1)	-39(1)	-21(1)	35(1)
C15	62(2)	45(1)	45(1)	-26(1)	-23(1)	28(1)
C16	43(1)	42(1)	40(1)	-14(1)	-14(1)	24(1)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^4 \text{ for Ca and Cl,}$$

$$\times 10^3 \text{ for C, N, and O}$$

TABLE XIII

CRYSTAL DATA FOR Ca(isonicotinate)$_2(H_2O)_4$ (IV)

Formula	$C_{12}H_{16}CaN_2O_8$
M. W.	356.3 g $mole^{-1}$
a	7.208(3) Å
b	36.368(28)
c	6.159(2)
α	90.0
β	104.74(3)
γ	90.0
V	1561(1) $Å^3$
F(000)	744
μMoK_α	4.312 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.516 g cm^{-3}
Z	4
Meas refl	4292
Obs refl	1819
R	6.4 %
R_w	8.3 %
G. O. F.	0.30
Space group	$P2_1/a$
Octants meas	$\pm h$, +k, +l

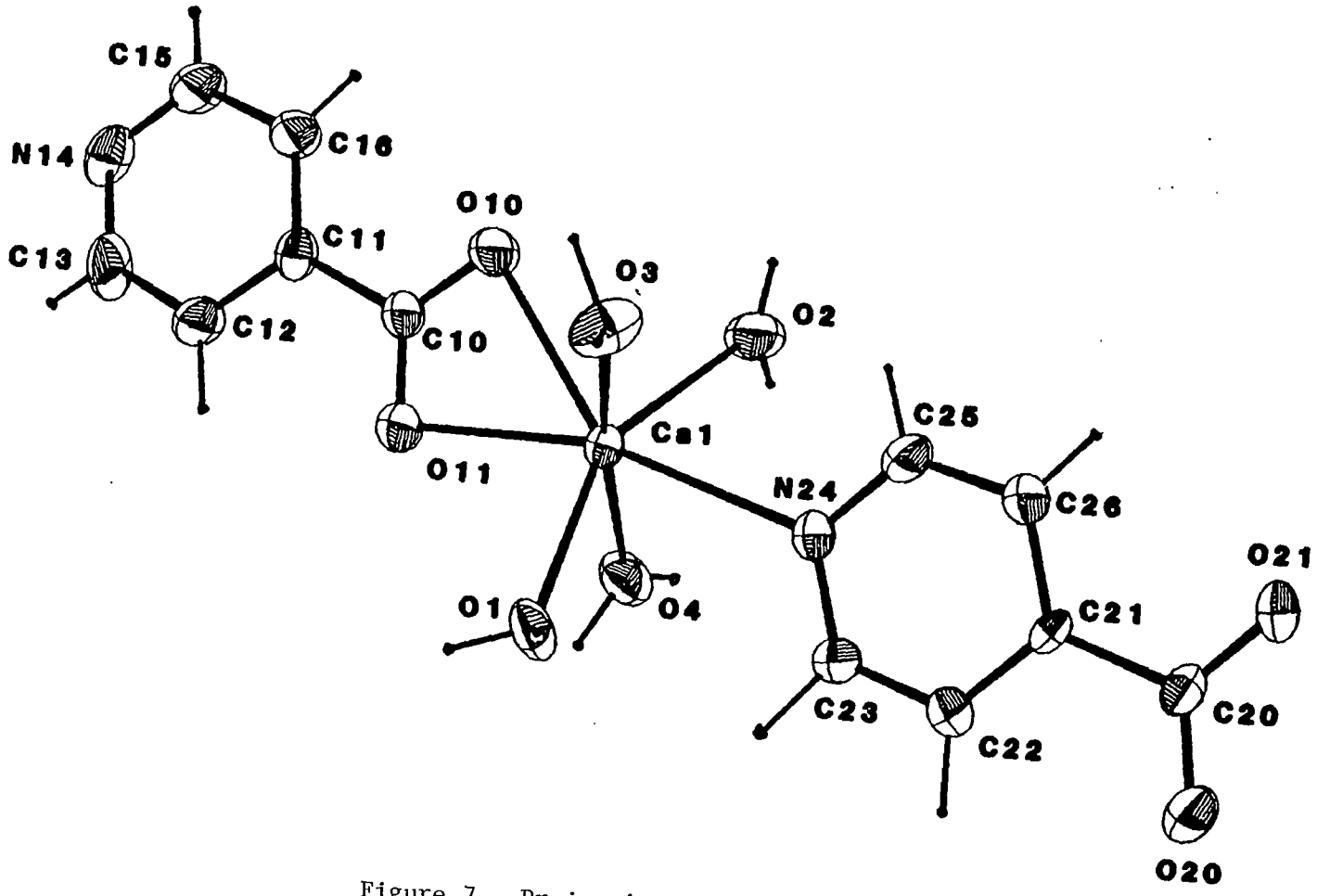

Figure 7. Projection View of IV

TABLE XIV

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

$Ca(isonicotinate)_2(H_2O)_4$ (IV)

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)

TABLE XIV (Continued)

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)
		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)

TABLE XV

POSITIONAL PARAMETERS FOR

Ca(isonicotinate)$_2$(H_2O)$_4$ (IV)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(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)

TABLE XV (Continued)

C25	0.3040(11)	0.0317(2)	0.2814(11)
C26	0.2808(10)	-0.0049(2)	0.2246(10)
H101	-0.0545	0.1186	-0.0696
H102	-0.0136	0.1500	-0.1153
H201	0.6527	0.0966	0.6311
H202	0.6794	0.1000	0.4068
H301	0.1202	0.1200	0.6127
H302	-0.0391	0.1000	0.4294
H401	0.4890	0.1505	-0.1181
H402	0.6445	0.1300	0.0169
H12	0.2889	0.2600	0.2756
H13	0.3572	0.3200	0.4582
H15	0.5105	0.2800	1.0382
H16	0.4716	0.2205	0.9201
H22	0.1387	0.0103	-0.3254
H23	0.2117	0.0700	-0.2270
H25	0.3398	0.0400	0.4365
H26	0.2933	-0.0239	0.3429

TABLE XVI

ANISOTROPIC THERMAL PARAMETERS FOR

$Ca(isonicotinate)_2(H_2O)_4$ (IV)

ATOM	U11	U22	U33	U12	U13	U23
Ca1	363(6)	178(6)	246(6)	3(6)	51(4)	-15(5)
O1	41(2)	20(2)	44(2)	1(2)	-2(2)	8(2)
O2	47(3)	63(3)	29(2)	19(2)	4(2)	-2(2)
O3	50(3)	46(3)	41(2)	-19(2)	21(2)	-12(2)
O4	56(3)	45(3)	37(2)	14(2)	20(2)	15(2)
O10	71(3)	22(2)	28(2)	-2(2)	5(2)	1(1)
O11	76(4)	24(2)	31(2)	8(2)	0(2)	-1(2)
C10	38(3)	20(3)	28(3)	0(2)	6(2)	1(2)
C11	34(3)	19(3)	38(3)	-2(2)	8(2)	-3(2)
C12	54(4)	26(3)	32(3)	-5(3)	7(3)	-4(2)
C13	58(5)	18(3)	63(5)	0(3)	10(4)	0(3)
N14	40(3)	27(3)	52(3)	-7(2)	8(2)	-15(2)
C15	59(5)	33(4)	33(3)	-5(3)	3(3)	-11(3)
C16	49(4)	30(3)	28(3)	-1(3)	-1(3)	-4(2)
O20	52(2)	27(2)	36(2)	-4(2)	10(2)	-7(2)
O21	59(3)	18(2)	38(2)	2(2)	10(2)	2(2)
C20	32(3)	21(3)	30(3)	0(2)	11(2)	-5(2)
C21	36(3)	20(3)	22(2)	4(2)	9(2)	-6(2)
C22	53(4)	26(3)	27(3)	6(3)	10(3)	4(2)
C23	71(5)	26(3)	24(3)	3(3)	6(3)	0(2)
N24	47(3)	18(2)	29(2)	0(2)	7(2)	1(2)

TABLE XVI (Continued)

C25	60(4)	24(3)	28(3)	-4(3)	9(3)	-6(2)
C26	54(4)	23(3)	28(3)	1(3)	3(3)	1(2)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^4 \text{ for Ca,}$$

$$\times 10^3 \text{ for C, N, and O}$$

coordination. The compound crystallizes in the centric monoclinic space group $P2_1/a$ (Table XIII). A view of the asymmetric unit (Figure 7) shows calcium bound to six oxygen atoms (from four water molecules and two from a bidentate carboxylate group of one isonicotinate anion) and to one nitrogen atom (from the pyridine ring of a second isonicotinate anion). All Ca-O distances fall in the range expected for calcium-oxygen interactions (2.344(6) Å to 2.506(4) Å), yet in this example, the carboxylate oxygen atoms are not equidistant from the calcium atom (Ca-O10, 2.506(5) Å, Ca-O11, 2.377(5) Å). The Ca-N bond distance is 2.615(6) Å, slightly longer than the Ca-O distances yet consistent with Ca-N binding (the complete list of derived bond distances and angles; Table XIV). The reasons behind the different binding of the two isonicotinate anions in the asymmetric unit of (IV) to calcium are unclear, but the flexibility of calcium in its binding geometry is clearly shown. In Mg(isonicotinate)$_2$(H_2O)$_4$, the magnesium atom is bound only to one oxygen atom of the carboxylate group of the isonicotinate anion in unidentate fashion and is octahedral in coordination geometry(55). Table XV and Table XVI list the respective positional parameters and the anisotropic thermal parameters of the atoms.

Since aspirin and other salicylate derivatives rank second only to the penicillins as culprits in drug induced allergic reactions(56), it is of interest to investigate the complexation of calcium and magnesium to these

TABLE XVII

CRYSTAL DATA FOR

$(Ca_{1.5}(salicylate)_2(acetate)(H_2O)_2)(acetic\ acid)$ (V)

Formula	$Ca_{1.5}C_{18}H_{21}O_{12}$
M. W.	489.5 g $mole^{-1}$
a	14.778(7) Å
b	8.183(3)
c	19.556(7)
α	90.0°
β	115.15(3)
γ	90.0
V	2142.2(15) $Å^3$
F(000)	1020
μMoK_α	4.61 cm^{-1}
λMoK_α	0.71069 Å
D_{cala}	1.517 g cm^{-3}
Z	4
Meas refl	5391
Obs refl	2576
R	8.0 %
G. O. F.	3.16
Space group	$P2_1/n$
Octants meas	$\pm$h, +k, +l

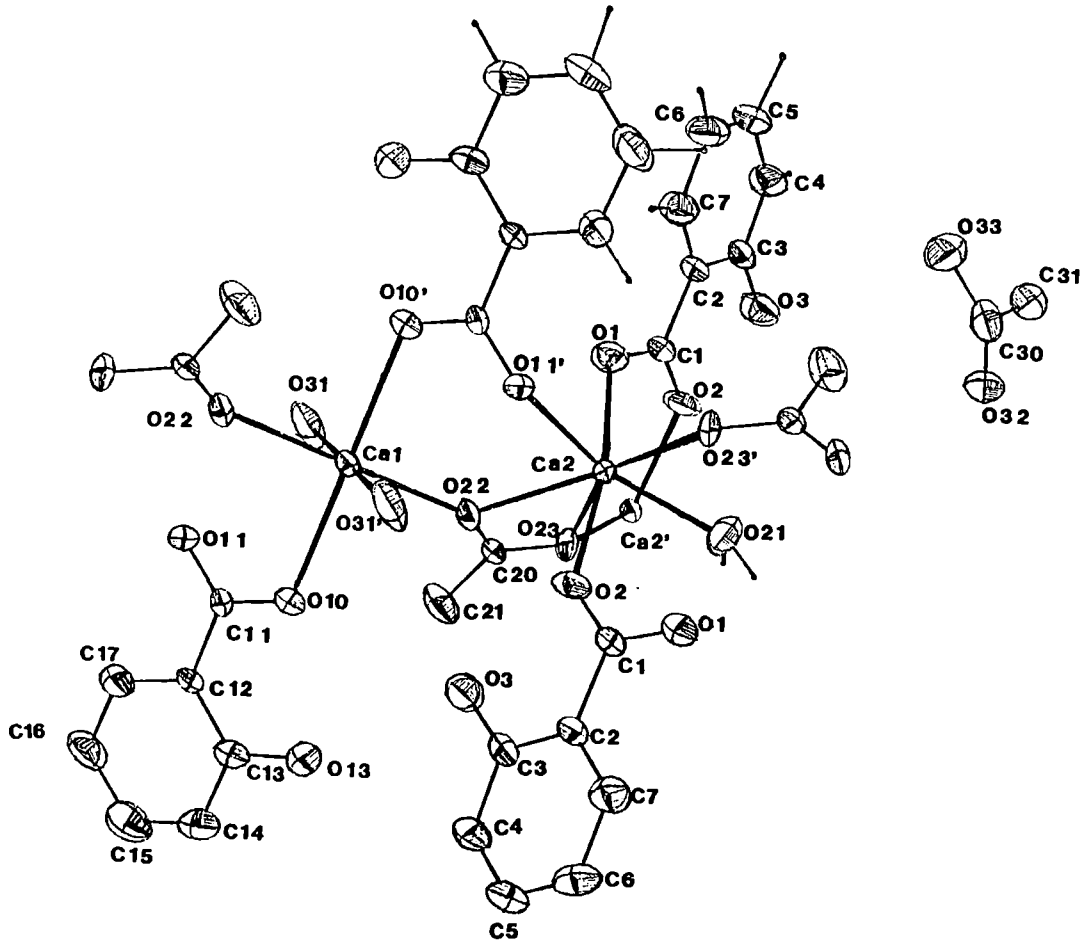

Figure 8. Projection View of V

TABLE XVIII

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

$(Ca_{1.5}(salicylate)_2(acetate)(H_2O)_2)(acetic\ acid)$(V)

Ca1-O10	2.431(7)	O10-Ca1-O22	93.3(2)
Ca1-O22	2.395(5)	O10-Ca1-O31	88.1(3)
Ca1-O31	2.359(8)	O22-Ca1-O31	86.9(2)
Ca2-O1	2.354(8)	O1-Ca2-O2'	169.2(2)
Ca2-O2'	2.361(8)	O1-Ca2-O11'	84.0(2)
Ca2-O11'	2.310(6)	O1-Ca2-O22	94.9(2)
Ca2-O22	2.390(6)	O1-Ca2-O23	85.1(2)
Ca2-O23	2.526(7)	O1-Ca2-O23'	99.2(2)
Ca2-O23'	2.426(6)	O1-Ca2-O21	99.1(2)
Ca2-O21	2.373(5)	O2'-Ca2-O11'	88.0(2)
C1-O1	1.25(1)	O2'-Ca2-O22	76.2(2)
C1-O2	1.27(1)	O2'-Ca2-O23	93.9(3)
C1-C2	1.50(1)	O2'-Ca2-O23'	86.9(2)
C2-C3	1.40(1)	O2'-Ca2-O21	91.1(2)
C3-O3	1.34(1)	O11'-Ca2-O22	78.1(2)
C3-C4	1.41(2)	O11'-Ca2-O23	127.2(2)
C4-C5	1.35(2)	O11'-Ca2-O23'	82.0(2)
C5-C6	1.39(2)	O11'-Ca2-O21	157.4(2)
C6-C7	1.40(2)	O22-Ca2-O23	51.6(2)
C7-C2	1.37(2)	O22-Ca2-O23'	154.3(2)
C11-O10	1.25(1)	O22-Ca2-O21	123.5(2)
C11-O11	1.27(1)	O23-Ca2-O23'	150.8(2)
C11-C12	1.48(1)	O23-Ca2-O21	75.4(2)

TABLE XVIII (Continued)

C12-C13	1.40(1)	O23'-Ca2-O21	75.4(2)
C13-O13	1.34(1)	O1-C1-O2	123.2(10)
C13-C14	1.42(2)	O1-C1-C2	118.4(8)
C14-C15	1.38(1)	O2-C1-C2	118.4(8)
C15-C16	1.38(2)	C1-C2-C3	120.7(8)
C16-C17	1.39(2)	C1-C2-C7	119.1(8)
C17-C12	1.39(1)	C3-C2-C7	120.2(10)
C20-O22	1.26(1)	C2-C3-C4	118.8(9)
C20-O23	1.27(1)	C2-C3-O3	123.0(10)
C20-C21	1.50(2)	C4-C3-O3	118.1(9)
C30-O32	1.21(2)	C3-C4-C5	120.7(10)
C30-O33	1.33(1)	C4-C5-C6	120.8(12)
C30-C31	1.52(2)	C5-C6-C7	119.6(11)
		C6-C7-C2	119.7(10)
		O10-C11-O11	121.6(9)
		O10-C11-C12	119.4(7)
		O11-C11-C12	119.1(7)
		C11-C12-C13	121.4(7)
		C11-C12-C17	119.5(8)
		C13-C12-C17	119.0(9)
		C12-C13-O13	122.9(10)
		C14-C13-O13	117.8(9)
		C12-C13-C14	119.2(8)
		C13-C14-C15	119.6(10)
		C14-C15-C16	121.9(13)

TABLE XVIII (Continued)

	C15-C16-C17	118.2(10)
	C16-C17-C12	122.0(9)
	O22-C20-C21	120.5(7)
	O23-C20-C21	120.5(8)
	O22-C20-O23	119.0(8)
	O32-C30-C31	125(1)
	O33-C30-C31	114(1)
	O32-C30-O33	121(1)

TABLE XIX

POSITIONAL PARAMETERS FOR

$(Ca_{1.5}(salicylate)_2(acetate)(H_2O)_2)(acetic\ acid)$ (V)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Ca1	1.0000	0.0000	1.0000
Ca2	0.7923(1)	-0.0215(2)	0.7748(1)
C1	0.8533(6)	0.2288(12)	0.6737(4)
C2	0.9031(6)	0.2300(11)	0.6208(4)
C3	0.8752(6)	0.3442(12)	0.5618(4)
C4	0.4273(8)	0.1534(15)	0.0161(5)
C5	0.5015(8)	0.2605(17)	0.0278(6)
C6	0.0277(8)	0.1232(16)	0.5846(6)
C7	0.9778(7)	0.1193(13)	0.6317(5)
O1	0.8888(4)	0.1390(8)	0.7309(3)
O2	0.7783(5)	0.3211(9)	0.6590(3)
O3	0.3003(5)	0.0482(9)	0.0466(4)
C11	0.9681(6)	0.1299(11)	0.1409(4)
C12	0.9196(6)	0.1918(11)	0.1884(4)
C13	0.8188(7)	0.1625(13)	0.1695(5)
C14	0.7759(8)	0.2246(15)	0.2169(6)
C15	0.8340(9)	0.3130(15)	0.2803(6)
C16	0.9338(9)	0.3432(15)	0.2999(6)
C17	0.9760(7)	0.2790(13)	0.2542(5)
O10	0.9173(4)	0.0513(9)	0.0820(3)
O11	0.0597(4)	0.1608(8)	0.1603(3)

TABLE XIX (Continued)

O13	0.7591(5)	0.0793(10)	0.1074(4)
O22	0.8564(4)	0.1104(8)	0.9014(3)
O23	0.7406(4)	0.2478(8)	0.8105(3)
C20	0.2954(6)	0.2722(11)	0.3806(4)
C21	0.2835(8)	0.1633(13)	0.4382(5)
O32	0.5487(5)	0.1257(12)	0.3827(4)
O33	0.5856(5)	0.2598(11)	0.2993(4)
C30	0.6096(8)	0.1630(15)	0.3594(6)
C31	0.7170(8)	0.1007(18)	0.3915(6)
O21	0.6316(4)	0.0313(8)	0.6768(3)
O31	0.0669(6)	0.2665(10)	0.0188(3)
H4	0.410	0.065	0.982
H5	0.534	0.279	0.985
H6	0.571	0.492	0.090
H7	0.501	0.464	0.165
H14	0.701	0.185	0.204
H15	0.796	0.371	0.307
H16	0.987	0.402	0.355
H17	1.048	0.308	0.270
H211	0.599	0.146	0.674
H212	0.575	-0.026	0.664

TABLE XX

ANISOTROPIC THERMAL PARAMETERS FOR

$(Ca_{1.5}(salicylate)_2(acetate)(H_2O)_2)(acetic\ acid)$ (V)

ATOM	U11	U22	U33	U12	U13	U23
Ca1	24(1)	51(2)	16(1)	7(1)	11(1)	5(1)
Ca2	20(1)	33(1)	17(1)	-2(1)	8(0)	-1(1)
C1	30(4)	46(6)	22(4)	0(4)	16(3)	1(4)
C2	26(4)	42(5)	28(4)	-3(4)	16(3)	-2(4)
C3	36(5)	55(6)	23(4)	4(4)	15(4)	1(4)
C4	47(6)	68(7)	36(6)	2(5)	27(5)	-13(5)
C5	47(6)	96(9)	47(6)	-4(6)	37(5)	-2(6)
C6	46(6)	90(9)	61(7)	24(6)	36(6)	2(7)
C7	42(5)	53(6)	38(5)	13(5)	21(4)	7(5)
O1	34(3)	58(4)	36(3)	4(3)	21(3)	13(3)
O2	43(4)	67(5)	35(3)	18(3)	29(3)	8(3)
O3	60(4)	77(6)	42(4)	-33(4)	32(3)	-24(4)
C11	27(4)	41(5)	16(4)	5(4)	8(3)	4(3)
C12	30(4)	43(5)	21(4)	2(4)	14(3)	-1(4)
C13	37(5)	61(7)	35(5)	1(5)	23(4)	-8(5)
C14	50(6)	74(8)	57(7)	-3(6)	39(6)	-4(6)
C15	84(9)	71(8)	44(6)	2(7)	49(6)	-8(6)
C16	75(8)	74(8)	38(6)	-16(7)	36(6)	-18(6)
C17	40(5)	62(7)	30(5)	-16(5)	17(4)	-10(4)
O10	32(3)	70(5)	25(3)	0(3)	17(2)	-5(3)
O11	24(3)	54(4)	30(3)	4(3)	15(2)	4(3)

TABLE XX (Continued)

O13	32(4)	96(6)	40(4)	-14(4)	16(3)	-18(4)
O22	31(3)	49(4)	18(3)	8(3)	8(2)	4(3)
O23	28(3)	45(4)	20(3)	1(3)	4(2)	6(3)
C20	24(4)	38(5)	23(4)	3(3)	12(3)	5(4)
C21	79(8)	55(7)	31(5)	-16(6)	30(5)	8(5)
O32	47(4)	118(7)	44(4)	-29(5)	31(4)	-17(4)
O33	53(4)	97(6)	41(4)	-3(4)	23(4)	2(4)
C30	58(7)	66(8)	37(6)	-13(6)	20(5)	-13(5)
C31	40(6)	107(10)	48(6)	7(6)	16(5)	9(7)
O21	25(3)	52(4)	46(4)	-2(3)	7(3)	-9(3)
O31	79(5)	70(5)	27(3)	-16(4)	25(4)	-5(4)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^3$$

low molecular weight species. The compound ($Ca_{1.5}$(salicylate)$_2$(acetate)(H_2O)$_2$)(acetic acid) (V) crystallizes in a form suitable for single crystal X-ray study (monoclinic space group $P2_1/n$, Table XVII). Two independent calcium atoms exist in the asymmetric unit. One calcium atom is positioned on a center of inversion. A projection view of (V) reveals the different structural modes of binding and bridging displayed by salicylate and acetate ligands to the two cations (Figure 8). Ca1, positioned on a center of inversion, is octahedrally coordinated to six oxygen atoms while Ca2 is bonded to seven oxygen atoms. The coordination sphere of Ca1 consists of one water molecule, one oxygen atom of an acetate anion, and one oxygen atom of a salicylate anion (plus three similar interactions with the ligands related by symmetry). Ca2 is bonded to two different salicylate anions, one acetate anion, and one water molecule. Each of the salicylate anions are bidentate, one of which bridges Ca1 and Ca2 (C10 ligand). The second salicylate anion (C1 ligand) bridges two symmetry related Ca2 atoms. The acetate anion is quadridentate, being bidentate with respect to the Ca2 atom but unidentate with respect to Ca1 and a symmetry related version of Ca2 (Ca2', ' = 1/2-x, -1/2+y, 1/2-z). Ca-O bond distances range from 2.310 Å to 2.526 Å and are consistent with those observed in the literature(34). A molecule of nonbonded acetic acid completes the asymmetric unit. (Positional parameters and anisotropic thermal parameters are listed in Tables XIX and

XX respectively.)

$Mg(salicylate)_2(H_2O)_4$ (VI) similarly crystallizes in the monoclinic space group $P2_1/n$ (Table XXI). Figure 9 shows the atoms of the asymmetric unit with the magnesium atom on an inversion center. Six oxygen atoms from four water molecules and the unidentate carboxylate group of two salicylate anions complete the octahedral coordination sphere of magnesium, with an average Mg-O distance of 2.07(1) Å. Similar to the complex of magnesium and the nicotinate anion (II), the magnesium of (VI) avoids bidentate coordination to the ligand, the bite of the carboxylate group (O10...O11 distance, 2.215(3) Å) being too small to permit positioning the oxygen atoms at vertices of the octahedral coordination sphere (av. O...O distance required for the magnesium octahedron, 2.9 Å). Bidentate coordination using one carboxylate oxygen atom and the phenolic oxygen atom also places the two oxygens too close to each other (O10...O12 distance, 2.489(3) Å) to meet this distance requirement. Table XXII contains bond distances and angles, derived from positional parameters, and anisotropic thermal parameters of Tables XXIII and XXIV.

The complexation of the anion of p-aminosalicylic acid (an analgesic) to calcium, magnesium, and sodium ions reveals binding patterns similar to those observed in compounds V and VI. In the complex (Ca(p-aminosalicylate)(acetate)(H_2O))(H_2O) (VII) (space group $P2_1/n$, Table XXV), the calcium atom is shown to be eight coordinate (projection

TABLE XXI

CRYSTAL DATA FOR $Mg(salicylate)_2(H_2O)_4$ (VI)

Formula	$C_{14}H_{18}MgO_{10}$ *
M. W.	370.6 g $mole^{-1}$
a	23.088(10) Å
b	5.202(1)
c	6.840(1)
α	90.0°
β	90.27(3)
γ	90.0
V	821.5(4) $Å^3$
F(000)	388
μMoK_α	1.523 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.498 g cm^{-3}
Z	4
Meas refl	2261
Obs refl	1308
R	5.5 %
R_w	7.4 %
G. O. F.	0.33
Space group	$P2_1/n$
Octants meas	±h, +k, +l

* Asymmetric unit = 1/2 of stoichiometric unit

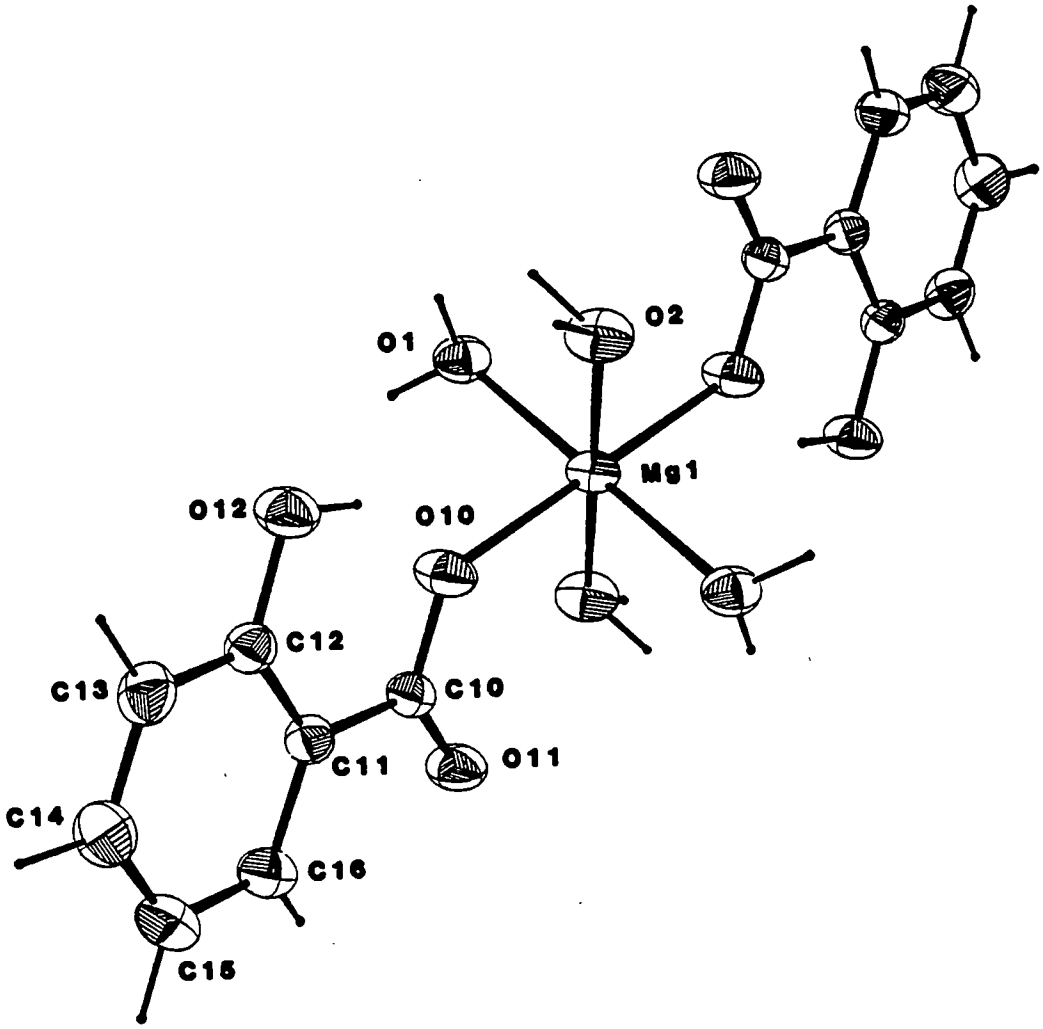

Figure 9. Projection View of VI

TABLE XXII

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

$Mg(salicylate)_2(H_2O)_4$ (VI)

Mg1-O1	2.120(13)	O1-Mg1-O2	90.9(5)
Mg1-O2	2.058(13)	O1-Mg1-O10	90.2(5)
Mg1-O10	2.022(14)	O2-Mg1-O10	92.9(6)
C10-O10	1.293(4)	O10-C10-O11	122.5(3)
C10-O11	1.233(4)	O10-C10-C11	115.3(3)
C10-C11	1.493(4)	O11-C10-C11	122.2(3)
C11-C12	1.410(4)	C10-C11-C12	121.6(2)
C12-O12	1.362(4)	C10-C11-C16	120.1(3)
C12-C13	1.379(5)	C12-C11-C16	118.3(3)
C13-C14	1.377(5)	C11-C12-O12	120.9(3)
C14-C15	1.384(6)	O12-C12-C13	118.6(3)
C15-C16	1.383(6)	C11-C12-C13	120.5(3)
C16-C11	1.401(4)	C12-C13-C14	119.9(3)
		C13-C14-C15	121.1(3)
		C14-C15-C16	119.4(3)
		C15-C16-C11	120.9(3)

TABLE XXIII

POSITIONAL PARAMTERS FOR $Mg(salicylate)_2(H_2O)_4$ (VI)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Mg1	1.0000	0.0000	0.5000
O1	0.9438(1)	0.2042(5)	0.6887(3)
O2	0.9977(1)	0.2960(5)	0.3004(3)
O10	1.0695(1)	0.1479(5)	0.6416(3)
O11	1.0692(1)	-0.0032(5)	0.9442(3)
C10	1.0877(1)	0.1479(6)	0.8206(4)
C11	1.1322(1)	0.3470(6)	0.8681(4)
C12	1.1532(1)	0.5177(6)	0.7249(4)
O12	1.1350(1)	0.5011(5)	0.5357(3)
C13	1.1940(2)	0.7011(7)	0.7731(5)
C14	1.2141(2)	0.7195(8)	0.9625(5)
C15	1.1941(2)	0.5558(8)	1.1068(5)
C16	1.1536(2)	0.3700(8)	1.0595(5)
H12	1.1064	0.3706	0.5307
H13	1.2090	0.8002	0.6665
H14	1.2466	0.8359	0.9888
H15	1.2074	0.5700	1.2402
H16	1.1424	0.2253	1.1482
H101	0.9340	0.0982	0.7828
H102	0.9099	0.2725	0.6403
H201	1.0172	0.4502	0.2857
H202	1.0256	0.3400	0.2072

TABLE XXIV

ANISOTROPIC THERMAL PARAMETERS FOR

$Mg(salicylate)_2(H_2O)_4$ (VI)

ATOM	U11	U22	U33	U12	U13	U23
Mg1	336(8)	182(7)	209(7)	-31(7)	-26(6)	5(6)
O1	41(1)	31(1)	27(1)	3(1)	0(1)	6(1)
O2	51(1)	23(1)	31(1)	-9(1)	-1(1)	7(1)
O10	43(1)	35(1)	24(1)	-11(1)	-6(0)	5(1)
O11	43(1)	43(1)	25(1)	-12(1)	-1(1)	7(1)
C10	27(1)	27(1)	23(1)	1(1)	-2(1)	0(1)
C11	26(1)	27(1)	26(1)	0(1)	0(1)	-1(1)
C12	27(1)	29(1)	25(1)	3(1)	0(1)	-1(1)
O12	44(1)	41(1)	26(1)	-9(1)	-5(1)	8(1)
C13	33(2)	34(1)	37(1)	-8(1)	4(1)	0(1)
C14	39(2)	41(2)	43(2)	-12(1)	0(1)	-7(1)
C15	42(2)	56(2)	32(1)	-9(2)	-7(1)	-8(1)
C16	37(2)	43(2)	26(1)	-2(1)	-2(1)	1(1)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^4 \text{ for Mg,}$$

$$\times 10^3 \text{ for C and O}$$

view, Figure 10). Seven ligation sites are occupied by oxygen atoms, donated by a water molecule, one p-aminosalicylate anion, and one acetate anion. The carboxylate group of the p-aminosalicylate anion displays bidentate coordination toward calcium (Ca-O distance, 2.50(1) Å av.) while the acetate anion displays quadridentate coordination involving three calcium atoms (Ca-O distance, 2.48(1) Å av.). The acetate anion shows bidentate coordination to a single calcium atom, but each oxygen atom of the carboxylate moiety is shown to bind to another (symmetry related) calcium atom as well. The remaining site in calcium's coordination sphere is filled by the nitrogen atom of a symmetry related p-aminosalicylate anion (Ca1-N14''', 2.61(1) Å, ''' = -1/2+x,1/2-y,-1/2+z). Thus both ligands bridge calcium atoms related by symmetry elements. During refinement of the structure, the p-aminosalicylate anion was observed to be disordered. The phenolic oxygen atom was refined in two positions (O12 and O125), each of 50% occupancy. Atom O12 is bound to C12, and O125 (not shown in Figure 10) is bound to C16. Thus the disorder can be viewed as a 180° rotation of the anion about an axis through the atoms N14, C14, C11, and C10. The disorder of the phenolic hydroxyl groups provides no additional binding opportunities as the hydroxyl is not involved binding. The complete list of the derived bond distances and angles is reported in Table XXVI. Atomic positional and thermal parameters are listed in Tables XXVII and XXVIII.

TABLE XXV

CRYSTAL DATA FOR

(Ca(p-aminosalicylate)(acetate)(H_2O))(H_2O) (VII)

Formula	$C_9H_{13}CaNO_7$
M. W.	287.3 g $mole^{-1}$
a	19.530(18) Å
b	9.564(5)
c	6.852(4)
α	90.0°
β	110.75(6)
γ	90.0
V	1197(1) $Å^3$
F(000)	600
μMoK_α	5.348 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.594 g cm^{-3}
Z	4
Meas refl	1580
Obs refl	915
R	9.5 %
R_w	13.1 %
G. O. F.	0.49
Space group	$P2_1/n$
Octants meas	±h, +k, +l

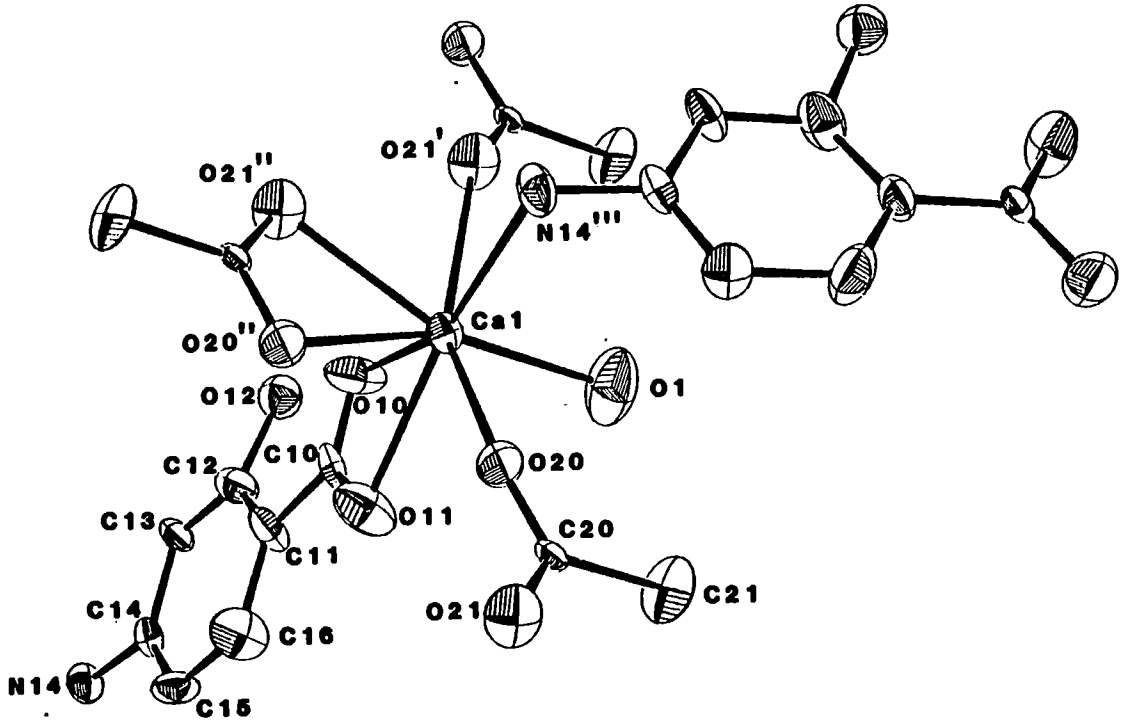

Figure 10. Projection View of VII

TABLE XXVI

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

(Ca(p-aminosalicylate)(acetate)(H_2O))(H_2O) (VII)

Ca1-O1	2.38(1)	O1-Ca1-O10	88.9(5)
Ca1-O10	2.52(1)	O1-Ca1-O11	88.5(4)
Ca1-O11	2.48(1)	O1-Ca1-O20	84.5(5)
Ca1-O20	2.43(1)	O1-Ca1-O21'	84.7(5)
Ca1-O21'	2.46(1)	O1-Ca1-O20''	154.9(5)
Ca1-O20''	2.52(1)	O1-Ca1-O21''	154.5(5)
Ca1-O21''	2.49(1)	O1-Ca1-N14'''	95.7(4)
Ca1-N14'''	2.61(1)	O10-Ca1-O11	51.0(4)
C10-O10	1.21(3)	O10-Ca1-O20	129.5(4)
C10-O11	1.29(2)	O10-Ca1-O21'	79.2(4)
C10-O11	1.47(2)	O10-Ca1-O20'	103.4(4)
C11-C12	1.39(3)	O10-Ca1-O21''	81.4(4)
C12-O12	1.42(3)	O10-Ca1-N14'''	158.9(5)
C12-C13	1.38(2)	O11-Ca1-O20	78.8(4)
C13-C14	1.44(2)	O11-Ca1-O21'	129.8(5)
C14-N14	1.41(2)	O11-Ca1-O20''	82.8(4)
C14-C15	1.37(3)	O11-Ca1-O21''	103.1(4)
C15-C16	1.44(3)	O11-Ca1-N14'''	154.5(5)
C16-C11	1.41(2)	O20-Ca1-O21'	149.0(4)
C16-O125	1.37(3)	O20-Ca1-O20''	70.8(4)
C20-O20	1.23(2)	O20-Ca1-O21''	119.8(4)
C20-O21	1.24(3)	O20-Ca1-N14'''	76.6(4)
C20-C21	1.55(2)	O21'-Ca1-O20''	118.7(4)

TABLE XXVI (Continued)

021''-Ca1-020''	118.7(4)
021''-Ca1-021''	70.3(4)
021''-Ca1-N14'''	75.7(5)
020''-Ca1-021''	50.5(4)
020''-Ca1-N14'''	82.9(4)
021''-Ca1-N14'''	83.6(4)
010-C10-011	119(1)
011-C10-C11	122(2)
011-C10-C11	119(1)
C16-C11-C12	118(2)
C10-C11-C12	120(1)
C11-C12-012	122(2)
012-C12-C13	113(2)
C11-C12-C13	124(1)
C12-C13-C14	117(2)
C13-C14-N14	118(2)
N14-C14-C15	120(1)
C13-C14-C15	122(1)
C14-C15-C16	119(1)
C15-C16-C11	120(2)
C15-C16-0125	115(2)
0125-C16-C11	124(2)
C16-C11-C10	121(2)
020-C20-021	120(1)
020-C20-C21	120(1)

TABLE XXVI (Continued)

	021-C20-C21	120(2)

' = symmetry operation x, y, 1-z

'' = symmetry operation 1-x, -y, 1-z

''' = symmetry operation -1/2 + x, 1/2 - y, -1/2 + z

TABLE XXVII

POSITIONAL PARAMETERS FOR

(Ca(p-aminosalicylate)(acetate)(H_2O))(H_2O) (VII)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Ca1	0.4805(2)	0.1058(4)	0.2309(5)
O1	0.400(1)	0.302(2)	0.149(2)
O3	0.027(2)	0.031(3)	0.146(7)
O35	0.023(2)	0.023(3)	0.416(5)
O10	0.578(1)	0.256(2)	0.169(2)
O11	0.575(1)	0.256(1)	0.481(2)
C10	0.605(1)	0.291(2)	0.350(3)
C11	0.674(1)	0.373(2)	0.423(3)
C12	0.708(1)	0.423(2)	0.284(3)
O12	0.671(1)	0.409(3)	0.064(4)
O125	0.671(1)	0.409(3)	0.774(3)
C13	0.774(1)	0.412(2)	0.343(2)
C14	0.807(1)	0.520(2)	0.559(3)
N14	0.878(1)	0.583(1)	0.626(2)
C15	0.776(1)	0.484(2)	0.703(3)
C16	0.707(1)	0.411(2)	0.634(3)
O20	0.447(1)	0.088(1)	0.540(2)
O21	0.446(1)	0.083(1)	0.851(2)
C20	0.427(1)	0.139(2)	0.677(2)
C21	0.374(1)	0.267(2)	0.625(3)

TABLE XXVIII

ANISOTROPIC THERMAL PARAMETERS FOR

(Ca(p-aminosalicylate)(acetate)(H_2O))(H_2O) (VII)

ATOM	U11	U22	U33	U12	U13	U23
Ca1	21(1)	24(1)	22(1)	1(1)	6(1)	2(1)
O1	66(10)	80(10)	62(9)	38(9)	31(8)	31(9)
O3	5(1)	60(23)	59(23)	201(45)	-38(18)	36(23)
O35	5(1)	79(24)	44(19)	84(26)	-13(17)	-7(17)
O10	50(8)	57(9)	35(8)	-24(7)	16(6)	-20(7)
O11	45(8)	67(10)	30(7)	-19(7)	8(6)	3(6)
C10	11(8)	27(9)	28(10)	1(7)	1(7)	8(8)
C11	17(8)	57(12)	20(8)	-4(9)	1(7)	4(10)
C12	29(9)	58(13)	25(10)	-1(10)	5(8)	-10(10)
O12	5(1)	43(14)	70(19)	30(14)	-14(14)	23(11)
O125	5(1)	54(15)	73(19)	8(11)	-32(14)	11(10)
C13	17(9)	52(12)	18(9)	1(8)	1(7)	-7(8)
C14	14(8)	34(10)	30(9)	3(7)	2(7)	-2(8)
N14	22(7)	22(8)	41(9)	-3(6)	1(6)	-6(7)
C15	35(10)	48(12)	21(9)	-6(9)	15(8)	-10(8)
C16	41(10)	63(14)	40(12)	-18(11)	22(9)	1(10)
O20	31(6)	51(8)	27(6)	5(6)	11(5)	-4(6)
O21	43(7)	47(8)	37(7)	2(6)	23(6)	11(6)
C20	13(8)	16(9)	11(9)	1(6)	-2(6)	1(7)
C21	58(13)	18(10)	65(13)	25(9)	16(10)	10(9)

TABLE XXVIII (Continued)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U331^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^3$$ for Ca, C, N, and O.

TABLE XXIX

CRYSTAL DATA FOR Mg(p-aminosalicylate)$_2$(H_2O)$_4$ (VIII)

Formula	$C_{14}H_{20}MgN_2O_{10}$ *
M. W.	400.6 g $mole^{-1}$
a	9.595(6) Å
b	13.257(4)
c	6.766(2)
α	90.0°
β	97.12(4)
γ	90.0
V	854.1(7) $Å^3$
F(000)	420
μMoK_α	1.554 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.558 g cm^{-3}
Z	4
Meas refl	2164
Obs refl	1233
R	6.7 %
R_w	9.3 %
G. O. F.	0.39
Space group	$P2_1/a$
Octants meas	±h, +k, +l

* Asymmetric unit = 1/2 of stoichiometric unit

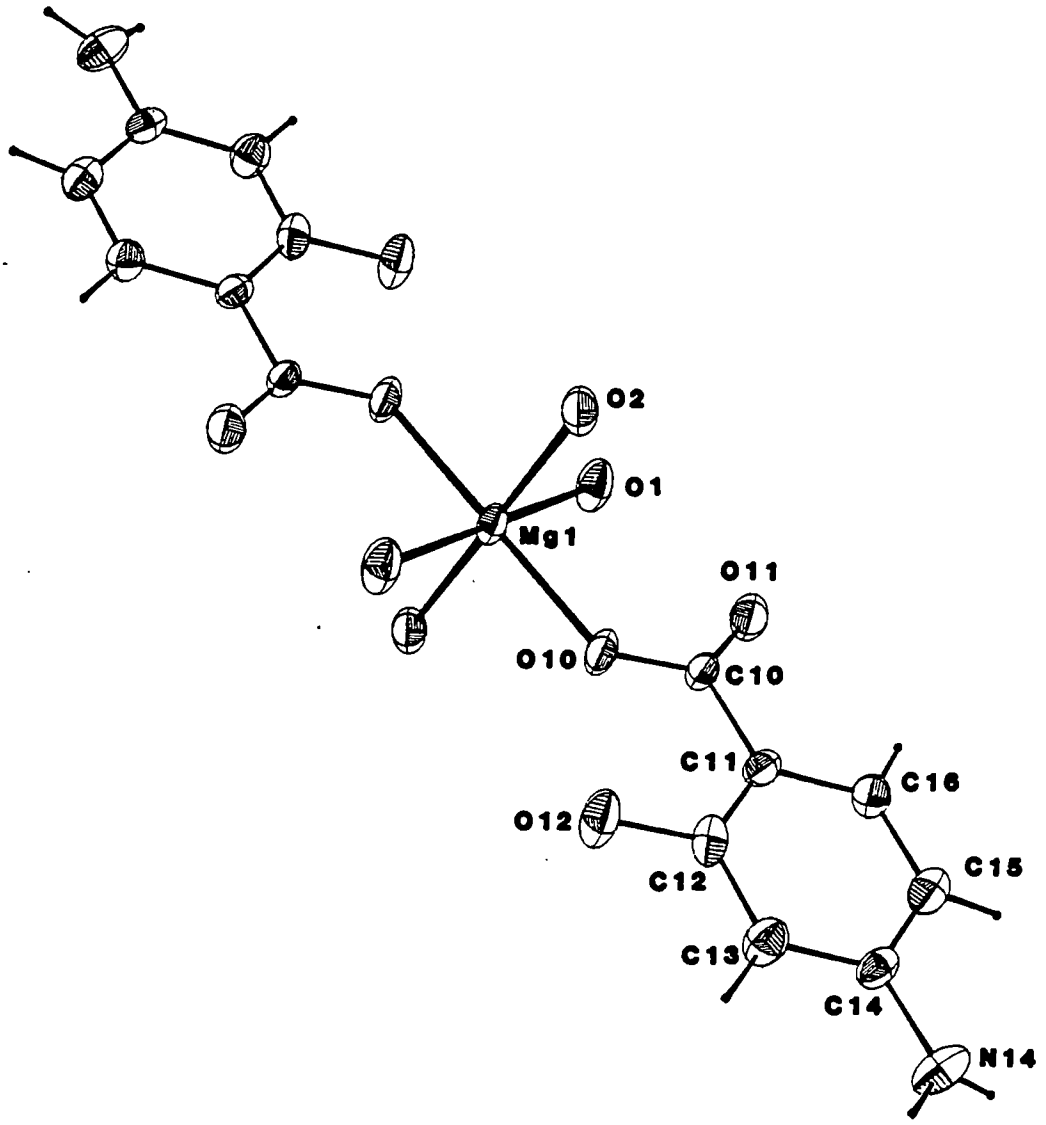

Figure 11. Projection View of VIII

TABLE XXX

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

Mg(p-aminosalicylate)$_2$(H_2O)$_2$ (VIII)

Mg1-O1	1.998(4)	O1-Mg1-O2	90.6(2)
Mg1-O2	2.149(4)	O1-Mg1-O10	90.2(1)
Mg1-O10	2.098(3)	O2-Mg1-O10	88.2(1)
C10-O10	1.284(5)	O10-C10-O11	122.9(4)
C10-O11	1.244(6)	O10-C10-C11	117.0(4)
C10-C11	1.494(7)	O11-C10-C11	120.0(4)
C11-C12	1.396(7)	C10-C11-C12	122.0(4)
C12-O12	1.363(6)	C10-C11-C16	120.5(4)
C12-C13	1.386(7)	C12-C11-C16	117.4(4)
C13-C14	1.394(7)	C11-C12-O12	121.3(4)
C14-N14	1.403(6)	O12-C12-C13	117.5(5)
C14-C15	1.380(8)	C11-C12-C13	121.2(4)
C15-C16	1.370(7)	C12-C13-C14	119.8(5)
C16-C11	1.401(7)	C13-C14-N14	119.9(5)
		N14-C14-C15	120.5(4)
		C13-C14-C15	119.4(4)
		C14-C15-C16	120.5(5)
		C15-C16-C11	121.5(5)

TABLE XXXI

POSITIONAL PARAMETERS FOR

Mg(p-aminosalicylate)$_2$(H_2O)$_4$ (VIII)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Mg1	0.5000	0.0000	1.0000
O1	0.4630(4)	0.1094(3)	1.1899(5)
O2	0.6269(4)	0.1008(3)	0.8492(5)
O10	0.3258(4)	0.0466(3)	0.8030(5)
O11	0.3456(4)	-0.0404(3)	0.5274(5)
C10	0.2866(5)	0.0249(4)	0.6197(7)
C11	0.1621(5)	0.0803(4)	0.5186(7)
C12	0.0896(6)	0.1515(4)	0.6184(7)
O12	0.1344(4)	0.1781(3)	0.8104(5)
C13	-0.0320(6)	0.1966(4)	0.5271(7)
C14	-0.0833(5)	0.1711(4)	0.3317(7)
N14	-0.2024(5)	0.2204(3)	0.2358(7)
C15	-0.0093(6)	0.1039(4)	0.2289(7)
C16	0.1094(5)	0.0582(4)	0.3209(7)
H13	-0.0828	0.2462	0.6008
H141	-0.2505	0.1792	0.1395
H142	-0.2381	0.2700	0.2950
H15	-0.0517	0.0864	0.1040
H16	0.1592	0.0000	0.2598

TABLE XXXII

ANISOTROPIC THERMAL PARAMETERS FOR

$Mg(p\text{-aminosalicylate})_2(H_2O)_4$ (VIII)

ATOM	U11	U22	U33	U12	U13	U23
Mg1	25(1)	24(1)	15(1)	4(1)	-3(1)	-3(1)
O1	44(2)	35(2)	22(1)	13(1)	-4(1)	-8(1)
O2	35(2)	37(2)	19(1)	-2(1)	1(1)	2(1)
O10	31(2)	39(2)	16(1)	5(1)	-6(1)	1(1)
O11	35(2)	42(2)	22(1)	9(1)	0(1)	-1(1)
C10	20(2)	29(2)	18(2)	-1(2)	-2(1)	3(1)
C11	18(2)	26(2)	23(2)	-2(1)	-1(1)	5(1)
C12	36(3)	26(2)	18(2)	-3(2)	1(1)	2(2)
O12	47(2)	37(2)	22(1)	11(1)	-7(1)	-6(1)
C13	32(3)	28(3)	29(2)	5(2)	-2(2)	1(2)
C14	21(2)	25(2)	27(2)	-4(1)	-3(1)	11(2)
N14	30(2)	29(2)	44(2)	3(2)	-12(2)	4(2)
C15	30(2)	31(3)	26(2)	-2(2)	-4(2)	2(2)
C16	28(2)	32(3)	22(2)	1(2)	1(2)	2(2)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U331^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^3$$ for Mg, C, N, and O

Mg(p-aminosalicylate)$(H_2O)_4$ (VIII) crystallizes in monoclinic space group $P2_1/a$ (Table XXIX). A projection view of the complex (Figure 11) shows the structure (VIII) to be almost isostructural with compound (VI). The magnesium atom of (VIII) is positioned on a center of inversion and is octahedral in coordination. Similar to (VI), the magnesium atom is bound to six oxygen atoms, four from water molecules, and two from the unidentate carboxylate groups of the p-aminosalicylate anions. The Mg-O distances display a greater range than is usually observed for magnesium interactions (Mg1-O1, 1.998(4) Å, Mg1-O2, 2.149(4) Å, Mg1-O10, 2.098(3) Å). The differences are real as no difficulty indicative of disorder was encountered during refinement of the structure. The preferential coordination of oxygen versus nitrogen by magnesium observed in this work is somewhat unexpected in view of literature reports to the contrary(32). Magnesium's requirement for octahedral geometry appears to take precedence over the choice of ligand. Possibly, packing of ligands about magnesium also dictates ligand choice since coordination of magnesium to the nitrogen atom would place ortho substituents on the ligand too close to other polar groups within the coordination sphere. (Bond distances and angles; Table XXX. Positional parameters and anisotropic thermal parameters; Tables XXXI and XXXII, respectively.)

The third complex of this series is Na(p-aminosalicylate)$(H_2O)_2$ (IX). (Monoclinic space group $P2_1/c$,

crystallographic details in Table XXXIII). Figure 12 (a projection view of (IX)) shows the sodium atom to be octahedral in its coordination to three related ligands related by symmetry and to three water molecules (two of which are also symmetry related). Each sodium atom is bound to one oxygen atom from the unidentate carboxylate group of one ligand, to the phenolic oxygen atom of a second ligand, and to the nitrogen atom of the para-amino- group of a third ligand. The three additional ligation sites are occupied by oxygen atoms from water molecules. Thus the p-aminosalicylate anion is a tridentate ligand in this complex, although it is only bidentate when complexed to calcium in compound (VII), and unidentate in compound (VIII) with magnesium. Na-O bond distances range from 2.383(4) Å (Na1-O12) to 2.915(6) Å (Na1-O1), and are consistent with Na-O interactions observed in the current structural literature. The complete list of derived bond distances and angles, positional parameters, and anisotropic thermal parameters are presented in Tables XXXIV, XXXV, and XXXVI respectively.

A crystal structure of calcium dipicolinate (the anion of 2,6-pyridinedicarboxylic acid) trihydrate has been reported by Strahs and Dickerson(57). This complex had previously been reported to be present in bacterial spores by Bailey, Karp, and Sacks(58). The calcium atom was shown to be eight coordinate, bound to two dipicolinate anions and to four water molecules. Each dipicolinate anion

TABLE XXXIII

CRYSTAL DATA FOR Na(p-aminosalicylate)$(H_2O)_2$ (IX)

Formula	$C_7H_{10}NNaO_5$
M. W.	211.1 g $mole^{-1}$
a	8.799(4) Å
b	14.620(5)
c	6.965(2)
α	90.0°
β	97.90(3)
γ	90.0
V	887.5(5) $Å^3$
F(000)	440
μMoK_α	1.64 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.580 g cm^{-3}
Z	4
Meas refl	2298
Obs refl	943
R	5.7 %
R_w	7.5 %
G. O. F.	0.31
Space group	$P2_1/c$
Octants meas	$\pm h$, +k, +l

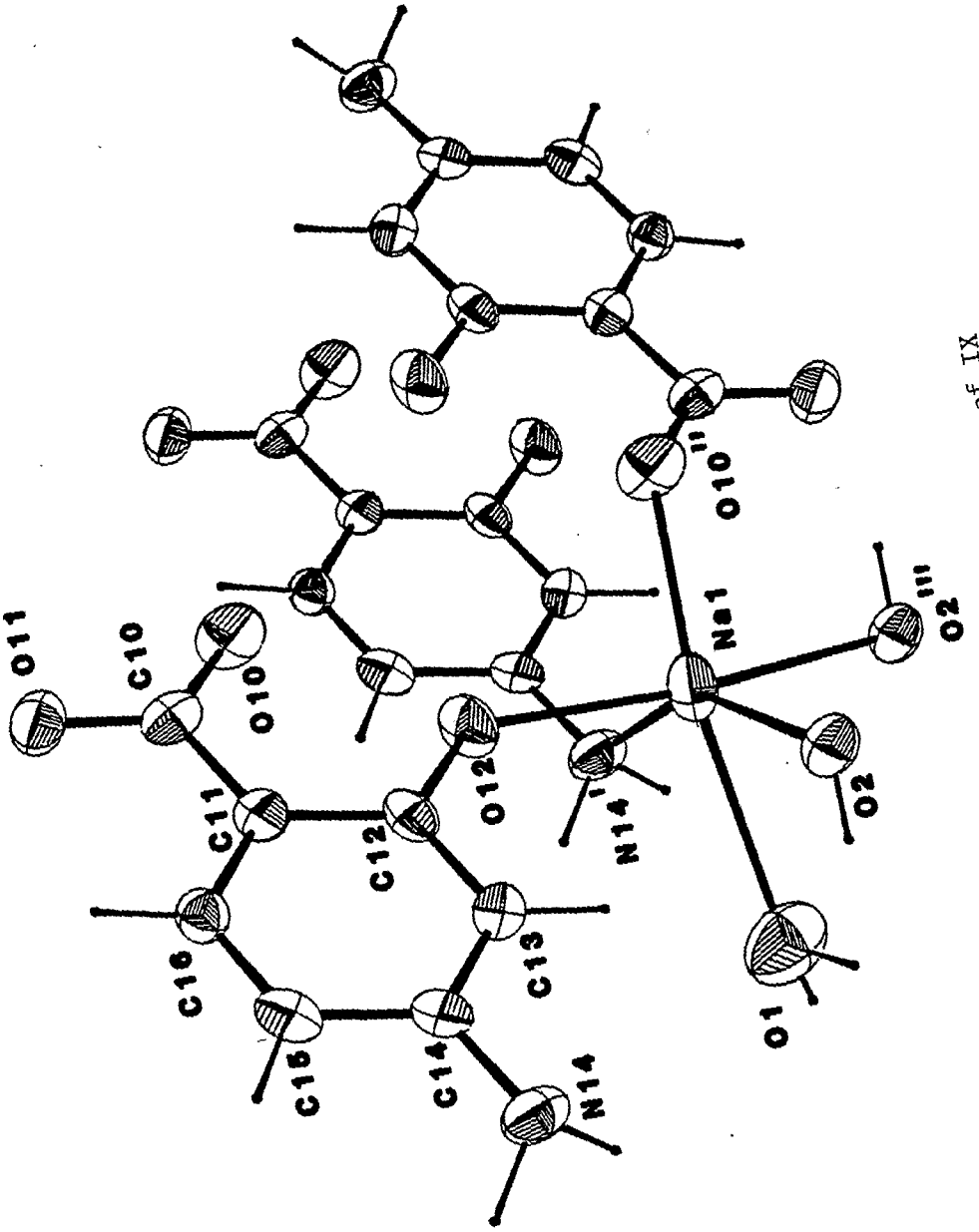

Figure 12. Projection View of IX

Table XXXIV

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

Na(p-aminosalicylate)$(H_2O)_2$ (IX)

Na1-01	2.915(6)	01-Na1-02	77.0(2)
Na1-02	2.343(5)	01-Na1-02'''	81.3(2)
Na1-02'''	2.429(4)	01-Na1-010''	157.3(2)
Na1-010''	2.395(5)	01-Na1-012	103.8(2)
Na1-012	2.383(4)	01-Na1-N14'	71.2(2)
Na1-N14'	2.494(6)	02-Na1-02'''	86.7(1)
C10-010	1.263(6)	02-Na1-010''	116.2(2)
C10-011	1.258(6)	02-Na1-012	99.8(1)
C10-C11	1.469(8)	02-Na1-N14'	148.2(2)
C11-C12	1.421(7)	02'''-Na1-010''	81.1(2)
C12-012	1.360(6)	02'''-Na1-012	172.5(2)
C12-C13	1.390(8)	02'''-Na1-N14'	91.1(2)
C13-C14	1.381(2)	010''-Na1-012	92.5(2)
C14-N14	1.400(8)	010''-Na1-N14'	94.8(2)
C14-C15	1.403(7)	012-Na1-N14'	85.4(2)
C15-C16	1.363(8)	010-C10-011	122.2(5)
C16-C11	1.400(7)	010-C10-C11	198.6(4)
		011-C10-C11	119.2(4)
		C10-C11-C12	121.3(4)
		C10-C11-C16	121.9(4)
		C16-C11-C12	116.9(4)
		C11-C12-012	120.1(5)
		012-C12-C13	119.1(4)

TABLE XXXIV (Continued)

	C11-C12-C13	120.8(5)
	C12-C13-C14	120.6(5)
	C13-C14-N14	120.5(5)
	N14-C14-C15	120.3(5)
	C13-C14-C15	119.1(5)
	C14-C15-C16	120.4(5)
	C15-C16-C11	122.3(4)

' = symmetry operation x, y, -1+z

'' = symmetry operation 2-x, -y, -z

''' = symmetry operation 1-x, -y, -z

TABLE XXXV

POSITIONAL PARAMETERS FOR Na(p-aminosalicylate)$(H_2O)_2$ (IX)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Na1	0.6829(3)	0.0442(2)	-0.0010(3)
O1	0.4919(6)	0.2022(4)	0.0558(8)
O2	0.5382(4)	-0.0066(3)	0.2366(5)
O10	1.2033(5)	0.0723(3)	0.1765(5)
O11	1.3730(4)	0.1173(3)	0.4214(6)
C10	1.2368(6)	0.1018(4)	0.3475(7)
C11	1.1119(6)	0.1195(4)	0.4625(7)
C12	0.9559(6)	0.1058(4)	0.3438(7)
O12	0.9196(4)	0.0764(3)	0.1975(5)
C13	0.8386(6)	0.1239(4)	0.4928(8)
C14	0.8715(6)	0.1557(4)	0.6806(8)
N14	0.7536(5)	0.1722(4)	0.7917(7)
C15	1.0251(6)	0.1693(4)	0.7602(8)
C16	1.1403(6)	0.1507(4)	0.6538(7)
H101	0.4181	0.1800	0.1329
H102	0.4325	0.2573	-0.0018
H201	0.4924	0.0400	0.3047
H202	0.5922	-0.0400	0.3520
H13	0.7295	0.1122	0.4396
H141	0.6582	0.2000	0.7278
H142	0.7663	0.2200	0.9112

TABLE XXXV (Continued)

H15	1.0332	0.1946	0.8925
H16	1.2483	0.1568	0.7068

TABLE XXXVI

ANISOTROPIC THERMAL PARAMETERS FOR

Na(p-aminosalicylate)$(H_2O)_2$ (IX)

ATOM	U11	U22	U33	U12	U13	U23
Na1	35(1)	75(1)	27(1)	-20(1)	7(1)	-8(1)
O1	69(3)	77(4)	87(4)	2(3)	37(3)	16(3)
O2	29(2)	45(2)	29(1)	3(1)	2(1)	3(1)
O10	45(2)	67(3)	23(2)	10(2)	3(1)	-4(2)
O11	27(2)	57(3)	43(2)	0(2)	5(1)	-8(2)
C10	32(3)	29(3)	31(3)	5(2)	8(2)	8(2)
C11	29(2)	26(3)	25(2)	0(2)	1(2)	2(2)
C12	34(2)	21(3)	26(2)	-4(2)	-1(2)	1(2)
O12	40(2)	56(2)	23(1)	-5(2)	-4(1)	-9(1)
C13	25(2)	35(3)	38(3)	0(2)	2(2)	-3(2)
C14	36(3)	22(2)	29(2)	0(2)	4(2)	-3(2)
N14	34(2)	46(3)	41(2)	6(2)	12(2)	-6(2)
C15	43(3)	26(3)	25(2)	-4(2)	5(2)	-2(2)
C16	26(2)	29(3)	27(2)	0(2)	-1(2)	0(2)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U331^2c^{*2}+2U12hka^*b^* +2U23h1a^*c^*+2U23k1b^*c^*)) \times 10^3$$ for Na, C, N, and O

coordinated to calcium via one oxygen atom from each of the carboxylate groups and the nitrogen atom of the pyridine ring. The oxygen atoms involved in the binding of the ligand were observed to be bidentate, binding as well to adjacent calcium atoms, while the noncoordinated oxygen atoms (of the carboxylate groups) were found to be involved in hydrogen bonding to water molecules. Thus it is of interest to examine the comparison structure of magnesium with the same anion. (Mg(2,6-pyridinedicarboxylate)$(H_2O)_3$) $(H_2O)_2$ (X) crystallizes in monoclinic space group $P2_1/n$ (Table XXXVII), the same space group in which the calcium complex crystallized. However the two materials are not isostructural in the solid state. In a projection view (Figure 13) of (X), magnesium is observed to be six coordinate, but the coordination octahedron is distorted. Oxygen atoms of three water molecules are bound to magnesium at an average Mg-O distance of 2.029(4) Å. Magnesium distances to two carboxylate oxygen atoms are slightly longer (av. 2.163(4) Å). The Mg1-N1 bond distance is 2.093(4) Å. Two additional water molecules of crystallization complete the asymmetric unit. A unique feature of (X) is the severe distortion of the octahedron surrounding the magnesium atom. In order to accomodate the bite of the tridentate ligand, two trans ligation sites in the octahedron must forego their regular linear ligand-Mg-ligand positioning and move toward each other. The O71-Mg1-O81 angle is observed to be 148.3(1)° (Table XXXVIII contains

TABLE XXXVII

CRYSTAL DATA FOR

(Mg(2,6-pyridinedicarboxylate)$(H_2O)_3)(H_2O)_2$ (X)

Formula	$C_7H_{13}MgNO_9$
M. W.	279.4 g $mole^{-1}$
a	8.920(3) Å
b	9.980(5)
c	13.249(9)
α	90.0°
β	96.89(4)
γ	90.0
V	1171(1) $Å^3$
F(000)	584
μMoK_α	1.831 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.585 g cm^{-3}
Z	4
Meas refl	2768
Obs refl	1449
R	5.3 %
R_w	6.7 %
G. O. F.	0.28
Space group	$P2_1/n$
Octants meas	±h, +k, +l

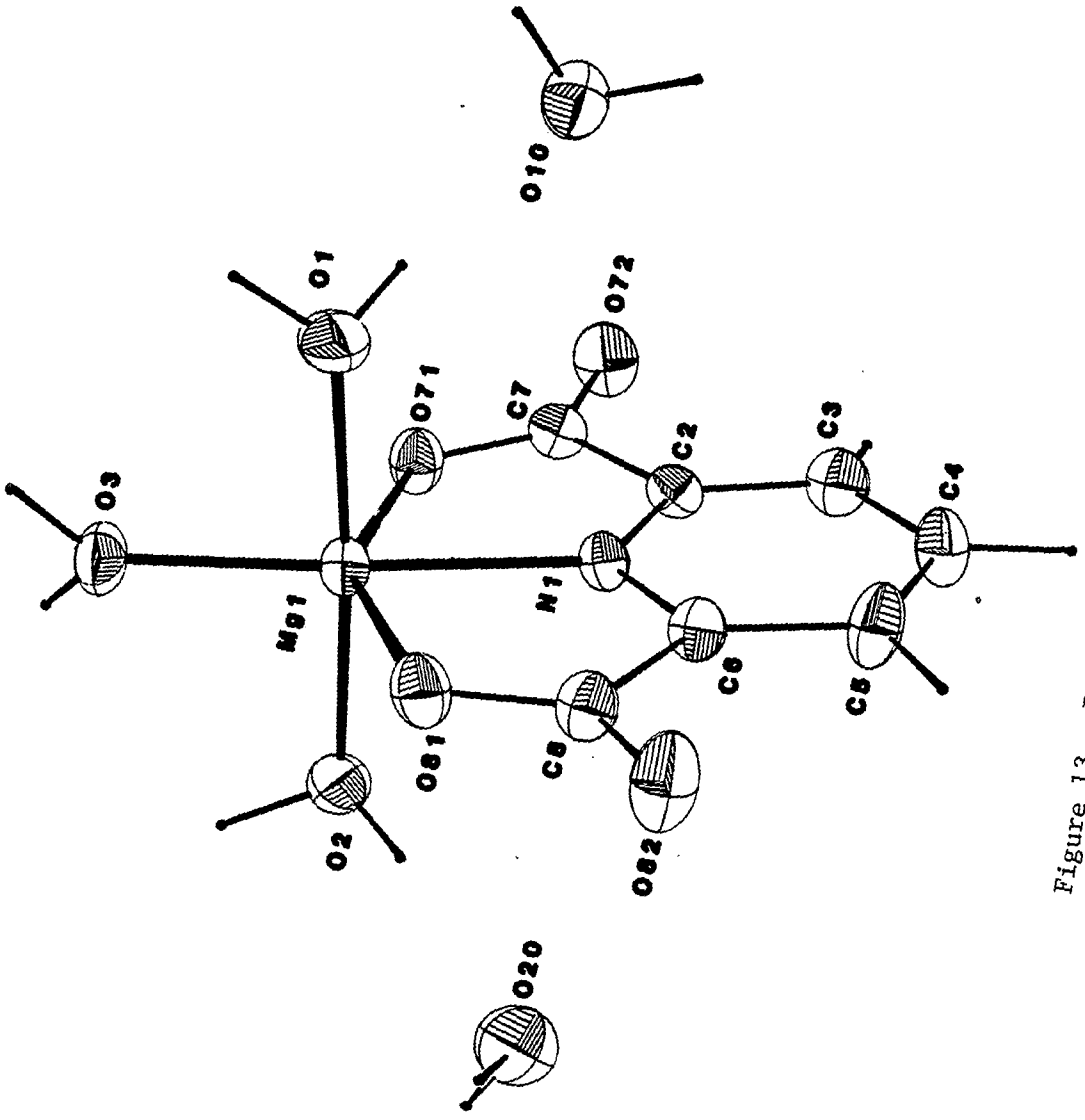

Figure 13. Projection View of X

TABLE XXXVIII

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

(Mg(2,6-pyridinedicarboxlyate)$(H_2O)_3$)$(H_2O)_2$ (X)

Mg1-O1	2.034(4)	O1-Mg1-O2	175.(4)
Mg1-O2	2.053(4)	O1-Mg1-O3	88.7(1)
Mg1-O3	1.999(4)	O1-Mg1-N1	89.7(1)
Mg1-N1	2.093(4)	O1-Mg1-O71	90.1(1)
Mg1-O71	2.149(4)	O1-Mg1-O81	90.7(1)
Mg1-O81	2.178(3)	O2-Mg1-O3	87.6(1)
N1-C2	1.338(5)	O2-Mg1-N1	94.1(1)
C2-C3	1.373(3)	O2-Mg1-O71	92.4(1)
C3-C4	1.379(6)	O2-Mg1-O81	88.9(1)
C4-C5	1.381(7)	O3-Mg1-N1	175.2(3)
C5-C6	1.386(6)	O3-Mg1-O71	101.0(1)
C6-N1	1.325(5)	O3-Mg1-O81	110.6(1)
C7-C2	1.503(6)	N1-Mg1-O71	74.4(1)
C7-O71	1.266(6)	N1-Mg1-O81	73.9(1)
C7-O72	1.248(6)	O71-Mg1-O81	148.3(1)
C8-C6	1.522(6)	C6-N1-C2	120.5(4)
C8-O81	1.260(5)	N1-C2-C7	112.1(4)
C8-O82	1.244(5)	C7-C2-C3	126.6(4)
		N1-C2-C3	121.2(4)
		C2-C3-C4	118.8(4)
		C3-C4-C5	119.8(4)
		C4-C5-C6	118.3(4)
		C5-C6-C8	126.3(4)

TABLE XXXVIII (Continued)

	C8-C6-N1	112.2(4)
	C5-C6-N1	121.4(4)
	O71-C7-O72	125.6(4)
	O71-C7-C2	115.9(4)
	O72-C7-C2	118.4(4)
	O81-C8-O82	125.8(4)
	O81-C8-C6	115.5(4)
	O82-C8-C6	118.6(4)

TABLE XXXIX

POSITIONAL PARAMETERS FOR

(Mg(2,6-pyridinedicarboxylate)$(H_2O)_3$)$(H_2O)_2$ (X)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Mg1	0.5526(2)	0.2760(1)	0.2714(1)
O1	0.3823(4)	0.1419(4)	0.2378(2)
O2	0.7296(4)	0.4083(3)	0.2952(2)
O3	0.5569(4)	0.3036(3)	0.1223(2)
O10	0.1362(4)	0.1201(3)	0.3510(2)
O20	0.9794(4)	0.3315(4)	0.4312(3)
N1	0.5308(4)	0.2557(3)	0.4261(2)
C2	0.4302(4)	0.3316(4)	0.4670(3)
C3	0.4101(5)	0.3201(5)	0.5678(3)
C4	0.4965(5)	0.2286(5)	0.6272(3)
C5	0.6005(6)	0.1508(5)	0.5848(3)
C6	0.6140(5)	0.1671(4)	0.4824(3)
C7	0.3468(5)	0.4244(4)	0.3904(3)
O71	0.3916(3)	0.4257(3)	0.3033(2)
O72	0.2397(4)	0.4914(3)	0.4165(2)
C8	0.7146(5)	0.0858(4)	0.4204(3)
O81	0.7058(3)	0.1155(3)	0.3274(2)
O82	0.7955(4)	-0.0034(3)	0.4638(2)
H11	0.2948	0.1605	0.2681
H12	0.3434	0.1063	0.1722
H21	0.8037	0.3728	0.3416

TABLE XXXIX (Continued)

H22	0.7774	0.4216	0.2266
H31	0.5855	0.3783	0.0900
H32	0.5138	0.2486	0.0621
H101	0.0901	0.0523	0.3062
H102	0.1350	0.0580	0.4177
H201	1.0283	0.4195	0.4128
H202	1.0249	0.2481	0.4080
H3	0.3446	0.3872	0.5909
H4	0.4882	0.2310	0.7072
H5	0.6717	0.0865	0.6191

TABLE XL

ANISOTROPIC THERMAL PARAMETERS FOR

(Mg(2,6-pyridinedicarboxylate)$(H_2O)_3)(H_2O)_2$ (X)

ATOM	U11	U22	U33	U12	U13	U23
Mg1	259(8)	230(8)	178(7)	2(6)	34(5)	8(6)
O1	36(2)	48(2)	35(2)	-17(1)	8(1)	-11(1)
O2	30(1)	34(2)	30(1)	-5(1)	1(1)	5(1)
O3	52(2)	48(2)	18(1)	-23(1)	4(1)	1(1)
O10	44(2)	33(2)	29(1)	0(1)	3(1)	0(1)
O20	44(2)	44(2)	49(2)	5(1)	4(1)	10(1)
N1	24(1)	16(2)	18(1)	2(1)	5(1)	0(1)
C2	20(2)	19(2)	25(2)	3(1)	5(1)	1(1)
C3	34(2)	27(2)	28(2)	4(2)	6(1)	-5(1)
C4	42(2)	36(2)	20(2)	5(2)	9(1)	0(2)
C5	45(2)	30(2)	19(2)	13(2)	0(1)	4(1)
C6	27(2)	19(2)	21(2)	1(1)	3(1)	-2(1)
C7	24(2)	21(2)	27(2)	1(1)	3(1)	0(1)
O71	32(1)	32(1)	23(1)	9(1)	4(1)	2(1)
O72	37(2)	40(2)	37(2)	17(1)	8(1)	4(1)
C8	30(2)	22(2)	22(2)	3(1)	3(1)	-3(1)
O81	33(1)	25(1)	23(1)	6(1)	8(1)	0(1)
O82	50(2)	43(2)	25(1)	26(1)	4(1)	2(1)

TABLE XL (Continued)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U331^2c^{*2}+U12hka^*b^* +2U13h1a^*c^*+2U23k1b^*c^*)) \times 10^4 \text{ for Mg,}$$

$$\times 10^3 \text{ for C, N, and O}$$

the complete list of derived bond distances and angles), The dipicolinate anion is shown to be relatively planar. Table XXXIX and Table XL list the respective positional parameters and the anisotropic thermal parameters of (X).

Penicillin and its derivatives are the most common cause of allergic drug reactions(56). Although numerous attempts were made to complex these antibiotics with calcium and magnesium in crystalline form (reviewed in chapter 3), only the compound Ca(phenoxymethylpenicillinate)$_2$(H_2O)$_2$ (XI) was isolated in a suitable form for X-ray diffraction analysis. (Crystallographic details, Table XLI). A projection view (Figure 14) displays view of the calcium coordination sphere which is incomplete, for clarity. In this complex, calcium is six coordinate, bound to six oxygen atoms in distorted octahedral geometry. Two of the oxygen atoms bound to calcium are from the unidentate carboxylate groups of two independent ligands (Ca1-O12, 2.28(2) Å, Ca1-O42, 2.25(2) Å), two are from amide carbonyl groups in the side chains of two symmetry related ligands (Ca1-O16', 2.37(2) Å, symmetry operation ' = 1+x, y, z and Ca1-O46'', 2.35(2) Å, symmetry operation '' = 1+x, y, 1+z), and the remaining two oxygen atoms are from water molecules (Ca1-O1, 2.38(2) Å, Ca1-O2, 2.36(2) Å). The complete view of calcium's coordination sphere, which reveals distorted octahedral geometry can be viewed in Figure 15. The crystals isolated of complex (XI) were small thin plates and were weakly diffracting, thus the number of reflections

TABLE XLI

CRYSTAL DATA FOR Ca(phenoxymethylpenicillinate)$_2$(H_2O)$_2$ (XI)

Formula	$C_{32}H_{38}CaN_4O_{12}S_2$
M. W.	774.9 g $mole^{-1}$
a	10.057(7) Å
b	29.178(18)
c	6.508(2)
α	90.0°
β	108.84(4)
γ	90.0
V	1807(2) $Å^3$
F(000)	812
μMoK_α	3.423 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.424 g cm^{-3}
Z	2
Meas refl	4647
Obs refl	2081
R	9.4 %
R_w	14.2 %
G. O. F.	3.9
Space group	$P2_1$
Octants meas	$\pm h$, +k, $\pm l$

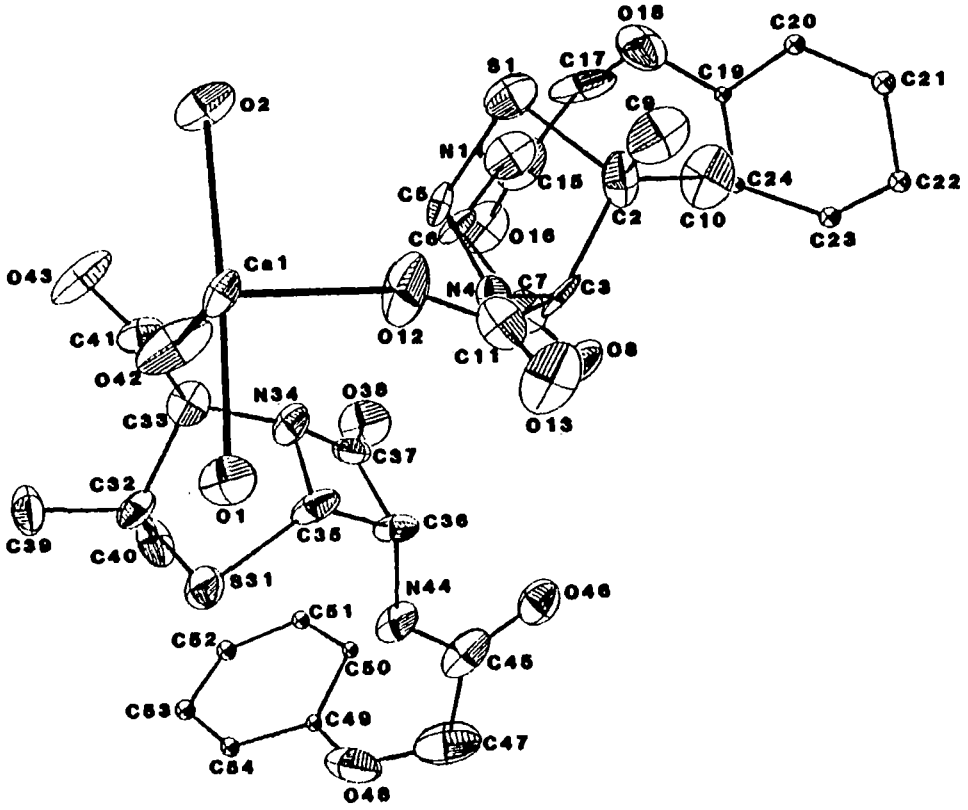

Figure 14. Projection View (partial) of XI

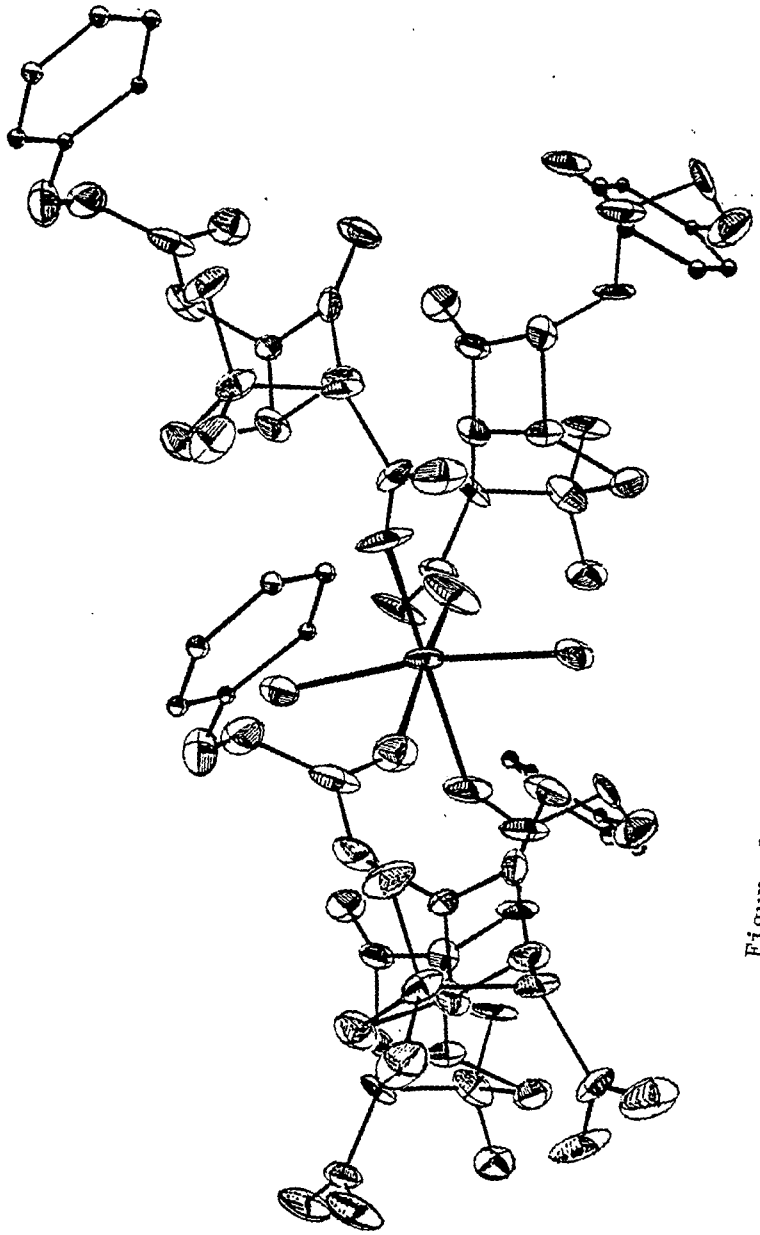

Figure 15. Projection View of XI

TABLE XLII

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

Ca(phenoxymethylpenicillinate)$_2$(H_2O)$_2$ (XI)

Ca1-O1	2.38(2)	O1-Ca1-O2	170(1)
Ca1-O2	2.36(2)	O1-Ca1-O12	93(1)
Ca1-O12	2.28(2)	O1-Ca1-O42	95(1)
Ca1-O42	2.25(2)	O1-Ca1-O16'	88(1)
Ca1-O16'	2.37(2)	O1-Ca1-O46''	85(1)
Ca1-O46''	2.35(2)	O2-Ca1-O12	93(1)
S1-C2	1.87(3)	O2-Ca1-O42	93(1)
S1-C5	1.82(3)	O2-Ca1-O16'	83(1)
C2-C3	1.63(4)	O2-Ca1-O46''	88(1)
C2-C9	1.54(4)	O12-Ca1-O42	98(1)
C2-C10	1.52(4)	O12-Ca1-O16'	90(1)
C3-C11	1.52(4)	O12-Ca1-O46''	171(1)
C3-N4	1.43(4)	O42-Ca1-O16'	171(1)
N4-C5	1.45(3)	O42-Ca1-O46''	91(1)
N4-C7	1.38(3)	O16'-Ca1-O46''	81(1)
C5-C6	1.59(4)	C2-S1-C5	96(1)
C6-C7	1.60(3)	S1-C2-C3	101(1)
C6-N14	1.43(3)	S1-C2-C9	108(2)
C7-O8	1.15(2)	S1-C2-C10	110(2)
C11-O12	1.26(3)	C3-C2-C9	112(2)
C11-O13	1.23(4)	C3-C2-C10	113(2)
N14-C15	1.30(4)	C9-C2-C10	111(2)
C15-O16	1.26(3)	C2-C3-N4	105(2)

TABLE XLII (Continued)

C15-C17	1.57(5)	C2-C3-C11	115(2)
C17-O18	1.26(4)	N4-C3-C11	112(2)
O18-C19	1.36(3)	C3-N4-C5	117(2)
C19-C20	1.33(5)	C3-N4-C7	125(2)
C19-C24	1.38(4)	C5-N4-C7	96(2)
C20-C21	1.34(5)	S1-C5-N4	106(2)
C21-C22	1.45(5)	S1-C5-C6	118(2)
C22-C23	1.24(6)	N4-C5-C6	89(2)
C23-C24	1.41(5)	C5-C6-C7	83(2)
S31-C32	1.86(3)	C5-C6-N14	116(2)
S31-C35	1.84(3)	C7-C6-N14	112(2)
C32-C33	1.62(4)	N4-C7-C6	91(2)
C32-C39	1.52(3)	C6-C7-O8	134(3)
C32-C40	1.52(4)	N4-C7-O8	135(3)
C33-C41	1.54(3)	C3-C11-O12	116(3)
C33-N34	1.46(3)	C3-C11-O13	118(2)
N34-C35	1.47(4)	O12-C11-O13	126(3)
N34-C37	1.35(3)	C6-N14-C15	122(2)
C35-C36	1.52(3)	N14-C15-O16	122(3)
C36-C37	1.52(4)	N14-C15-C17	114(2)
C36-N44	1.46(3)	O16-C15-C17	124(3)
C37-O38	1.21(4)	C15-C17-O18	115(3)
C41-O42	1.28(4)	C17-O18-C19	118(2)
C41-O43	1.18(3)	O18-C19-C20	116(2)
N44-C45	1.34(3)	O18-C19-C24	124(2)

TABLE XLII (Continued)

C45-O46	1.27(4)	C20-C19-C24	120(3)
C45-C47	1.48(4)	C19-C20-C21	121(3)
C47-O48	1.38(4)	C20-C21-C22	121(4)
O48-C49	1.34(4)	C21-C22-C23	114(4)
C49-C50	1.43(5)	C22-C23-C24	127(3)
C49-C54	1.34(5)	C23-C24-C19	115(3)
C50-C51	1.40(6)	C32-S31-C35	96(1)
C51-C52	1.30(6)	S31-C32-C33	103(2)
C52-C53	1.31(6)	S31-C32-C39	108(2)
C53-C54	1.41(6)	S31-C32-C40	110(2)
		C33-C32-C39	114(2)
		C33-C32-C40	108(2)
		C39-C32-C40	114(2)
		C32-C33-N34	105(2)
		C32-C33-C41	114(2)
		N34-C33-C41	111(2)
		C33-N34-C35	118(2)
		C33-N34-C37	125(2)
		C35-N34-C37	95(2)
		S31-C35-N34	104(2)
		S31-C35-C36	118(2)
		N34-C35-C36	87(2)
		C35-C36-C37	86(2)
		C35-C36-N44	118(2)
		C37-C36-N44	114(2)

TABLE XLII (Continued)

N34-C37-C36	91(2)
C36-C37-O38	135(2)
N34-C37-O38	133(2)
C33-C41-O42	115(2)
C33-C41-O43	119(3)
O42-C41-O43	126(2)
C36-N44-C45	126(2)
N44-C45-O46	117(3)
N44-C45-C47	117(3)
O46-C45-C47	126(2)
C45-C47-O48	114(2)
C47-O48-C49	116(3)
O48-C49-C50	126(3)
O48-C49-C54	116(3)
C50-C49-C54	118(3)
C49-C50-C51	117(3)
C50-C51-C52	120(4)
C51-C52-C53	126(4)
C52-C53-C54	116(4)
C53-C54-C49	122(4)

' = symmetry operation 1+x, y, z

'' = symmetry operation 1+x, y, 1+z

TABLE XLIII

POSITIONAL PARAMETERS FOR

Ca(phenoxymethylpenicillinate)$_2$(H_2O)$_2$ (XI)

ATOM	(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Ca1	0.144(1)	0.208(0)	0.071(1)
O1	0.166(2)	0.116(1)	-0.232(3)
O2	0.165(2)	0.251(1)	0.388(3)
S1	-0.193(1)	0.334(1)	0.063(1)
C2	-0.229(3)	0.346(1)	-0.234(4)
C3	-0.228(2)	0.294(1)	-0.328(3)
N4	-0.291(2)	0.266(1)	-0.206(3)
C5	-0.251(2)	0.274(1)	0.026(3)
C6	-0.408(3)	0.263(1)	0.015(3)
C7	-0.434(2)	0.262(1)	-0.242(4)
O8	-0.533(2)	0.262(1)	-0.394(3)
C9	-0.109(3)	0.376(1)	-0.258(4)
C10	-0.370(3)	0.370(1)	-0.326(5)
C11	-0.084(3)	0.277(1)	-0.321(4)
O12	-0.012(2)	0.258(1)	-0.145(3)
O13	-0.048(2)	0.282(1)	-0.483(3)
N14	-0.484(2)	0.299(1)	0.075(3)
C15	-0.610(3)	0.294(1)	0.085(4)
O16	-0.668(2)	0.255(1)	0.055(3)
C17	-0.678(3)	0.338(1)	0.140(5)
O18	-0.633(2)	0.375(1)	0.086(4)

TABLE XLIII (Continued)

C19	-0.684(3)	0.389(1)	-0.125(4)
C20	-0.648(4)	0.430(1)	-0.169(5)
C21	-0.697(4)	0.447(1)	-0.372(6)
C22	-0.789(4)	0.421(1)	-0.550(6)
C23	-0.827(4)	0.384(1)	-0.491(6)
C24	-0.773(3)	0.362(1)	-0.287(4)
S31	-0.194(1)	0.083(0)	-0.257(1)
C32	-0.226(2)	0.071(1)	0.004(4)
C33	-0.229(2)	0.122(1)	0.103(4)
N34	-0.292(2)	0.151(1)	-0.086(3)
C35	-0.252(3)	0.143(1)	-0.281(4)
C36	-0.404(2)	0.153(1)	-0.411(4)
C37	-0.431(2)	0.154(1)	-0.195(4)
O38	-0.534(2)	0.156(1)	-0.138(3)
C39	-0.105(3)	0.041(1)	0.142(5)
C40	-0.370(3)	0.050(1)	-0.038(5)
C41	-0.083(3)	0.140(1)	0.240(4)
O42	-0.012(2)	0.158(1)	0.113(3)
O43	-0.048(2)	0.135(1)	0.430(3)
N44	-0.484(2)	0.117(1)	-0.559(3)
C45	-0.613(3)	0.122(1)	-0.702(4)
O46	-0.668(2)	0.162(1)	-0.723(3)
C47	-0.680(3)	0.081(1)	-0.820(5)
O48	-0.629(2)	0.040(1)	-0.714(3)
C49	-0.687(3)	0.026(1)	-0.566(5)

TABLE XLIII (Continued)

C50	-0.774(3)	0.054(1)	-0.478(5)
C51	-0.824(4)	0.033(1)	-0.323(6)
C52	-0.783(4)	-0.008(1)	-0.253(6)
C53	-0.695(4)	-0.033(1)	-0.313(6)
C54	-0.644(4)	-0.015(1)	-0.473(6)
H3	-0.291	0.295	-0.477
H5	-0.183	0.256	0.124
H6	-0.421	0.236	0.085
H14	-0.439	0.330	0.113
H171	-0.781	0.336	0.073
H172	-0.662	0.339	0.301
H20	-0.584	0.450	-0.054
H21	-0.659	0.479	-0.399
H22	-0.818	0.438	-0.690
H23	-0.900	0.367	-0.611
H24	-0.797	0.330	-0.259
H33	-0.287	0.120	0.199
H35	-0.186	0.162	-0.322
H36	-0.417	0.181	-0.496
H44	-0.438	0.088	-0.552
H471	-0.783	0.084	-0.851
H472	-0.668	0.082	-0.969
H50	-0.802	0.084	-0.530
H51	-0.886	0.054	-0.268
H52	-0.827	-0.023	-0.145

TABLE XLIII (Continued)

H53	-0.665	-0.067	-0.255
H54	-0.570	-0.032	-0.513

TABLE XLIV

ANISOTROPIC THERMAL PARAMETERS FOR

Ca(phenoxymethylpenicillinate)$_2$(H_2O)$_2$ (XI)

ATOM	U11	U22	U33	U12	U13	U23
Ca1	9(1)	43(2)	19(2)	0(2)	1(1)	6(2)
O1	23(9)	53(14)	40(10)	1(8)	11(7)	-8(9)
O2	27(9)	72(15)	23(9)	-3(9)	15(7)	-10(9)
S1	26(3)	51(4)	33(3)	-9(3)	8(2)	-5(3)
C2	42(16)	37(17)	37(15)	17(11)	21(12)	14(12)
C3	20(13)	64(17)	3(10)	23(11)	1(9)	0(10)
N4	18(9)	28(12)	35(11)	12(8)	5(8)	0(9)
C5	15(10)	32(15)	16(10)	0(9)	0(8)	12(10)
C6	29(14)	45(13)	8(9)	0(11)	3(9)	-2(9)
C7	21(13)	34(12)	40(14)	0(9)	17(11)	0(10)
O8	24(9)	58(11)	23(8)	7(8)	-6(7)	-2(8)
C9	37(17)	66(19)	36(15)	-14(14)	23(13)	-1(13)
C10	5(13)	71(18)	60(20)	13(11)	1(13)	7(15)
C11	21(13)	34(16)	50(15)	1(10)	18(11)	1(12)
O12	33(11)	96(14)	45(12)	41(10)	13(9)	20(11)
O13	35(11)	96(17)	40(10)	19(10)	33(9)	13(10)
N14	16(12)	57(12)	38(12)	-14(9)	17(10)	-1(9)
C15	16(16)	76(18)	43(16)	-3(13)	13(13)	3(13)
O16	25(10)	69(11)	42(11)	-8(8)	23(8)	6(8)
C17	24(14)	99(26)	47(18)	17(15)	6(13)	-49(18)
O18	44(13)	34(11)	71(15)	-14(9)	11(11)	-5(9)

TABLE XLIV (Continued)

C19	43(6)					
C20	65(9)					
C21	83(10)					
C22	76(10)					
C23	69(9)					
C24	41(6)					
S31	27(3)	44(4)	29(3)	13(3)	5(2)	0(3)
C32	22(12)	36(15)	19(11)	-9(9)	-1(9)	1(9)
C33	15(12)	38(14)	35(14)	-11(9)	10(10)	3(11)
N34	15(9)	41(12)	25(10)	1(8)	-1(7)	1(9)
C35	26(14)	62(20)	17(11)	4(13)	8(10)	-11(12)
C36	12(11)	39(14)	25(11)	-1(9)	0(9)	-16(10)
C37	27(13)	24(13)	27(12)	2(10)	3(10)	-12(10)
O38	21(10)	65(14)	53(12)	7(10)	18(9)	-10(10)
C39	34(16)	25(15)	55(18)	4(11)	-10(13)	4(13)
C40	25(14)	18(14)	68(21)	-7(10)	0(13)	4(13)
C41	21(13)	37(16)	31(13)	-12(11)	0(10)	-10(11)
O42	26(10)	110(17)	37(11)	-42(10)	13(8)	-12(11)
O43	30(10)	102(19)	17(9)	-18(10)	3(7)	-2(19)
N44	17(12)	66(15)	24(11)	22(10)	-4(9)	-6(10)
C45	15(14)	83(24)	24(12)	10(14)	8(10)	1(14)
O46	30(10)	52(12)	32(10)	3(8)	2(8)	2(8)
C47	35(15)	80(19)	53(18)	-19(14)	15(13)	-33(16)
O48	45(13)	49(13)	55(13)	1(9)	10(10)	-28(10)
C49	48(7)					

TABLE XLIV (Continued)

C50	50(7)
C51	64(9)
C52	77(10)
C53	79(10)
C54	66(10)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U331^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*) \times 10^3$$

which were observed in the data set was low. (The size of the data set limits the number of variables which may be refined during the structure refinement with 45 observed reflections required minimum per atom refined). In order to compensate for the lack of observed reflections, the carbon atoms of the aromatic rings of the ligands were refined isotropically, changing the requirement to 20 observed reflections for these atoms. All other atoms were refined anisotropically. Tables XLII, XLIII, and XLIV contain the respective list of derived bond distances and angles, positional parameters, and thermal parameters for compound (XI). There have been no other structural observations of penicillin derivatives complexed to calcium.

The complex of calcium chloride with histamine is of the stoichiometry: $(CaCl_4(H_2O)_2)(CaCl_2(\text{histamine}.H^+)_2(H_2O)_2)$ (XII) (59). (Unit cell parameters, Table XLV.) A projection view (Figure 16) of (XII) shows two calcium atoms per asymmetric unit, each with a distinct coordination sphere. Ca5 lies on a center of inversion and is bound to four chloride atoms and the oxygen atoms of two water molecules (Ca5-Cl distance, 2.755(13) Å av. and Ca5-O3 distance, 2.325(17) Å) in approximately octahedral geometry. Ca3 is similarly positioned on an inversion center and is octahedrally bound to two chloride atoms (Ca3-Cl1, 2.707(13) Å), two water molecules (Ca3-O1, 2.333(13) Å), and two histamine molecules via the nitrogen atom (Ca3-N2, 2.441(13) Å) of the imidazole ring which is sp^2 hybridized and is to

TABLE XLV

CRYSTAL DATA FOR

$(CaCl_4(H_2O)_2)(CaCl_2(H_2O)_2(histamine.H^+)_2)$ (XII)

Formula	$C_5H_{14}CaCl_3N_3O_2$
M. W.	294.6 g $mole^{-1}$
a	8.437(3) Å
b	11.964(5)
c	6.767(4)
α	92.26(4)°
β	66.04(3)
γ	85.39(3)
V	620.2(4) $Å^3$
F(000)	304
μMoK_α	11.28 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.58 g cm^{-3}
Z	2
Meas refl	3178
Obs refl	2219
R	4.8 %
R_w	7.7 %
G. O. F.	0.40
Space group	$P\bar{1}$
Octants meas	$\pm h$, +k, $\pm l$

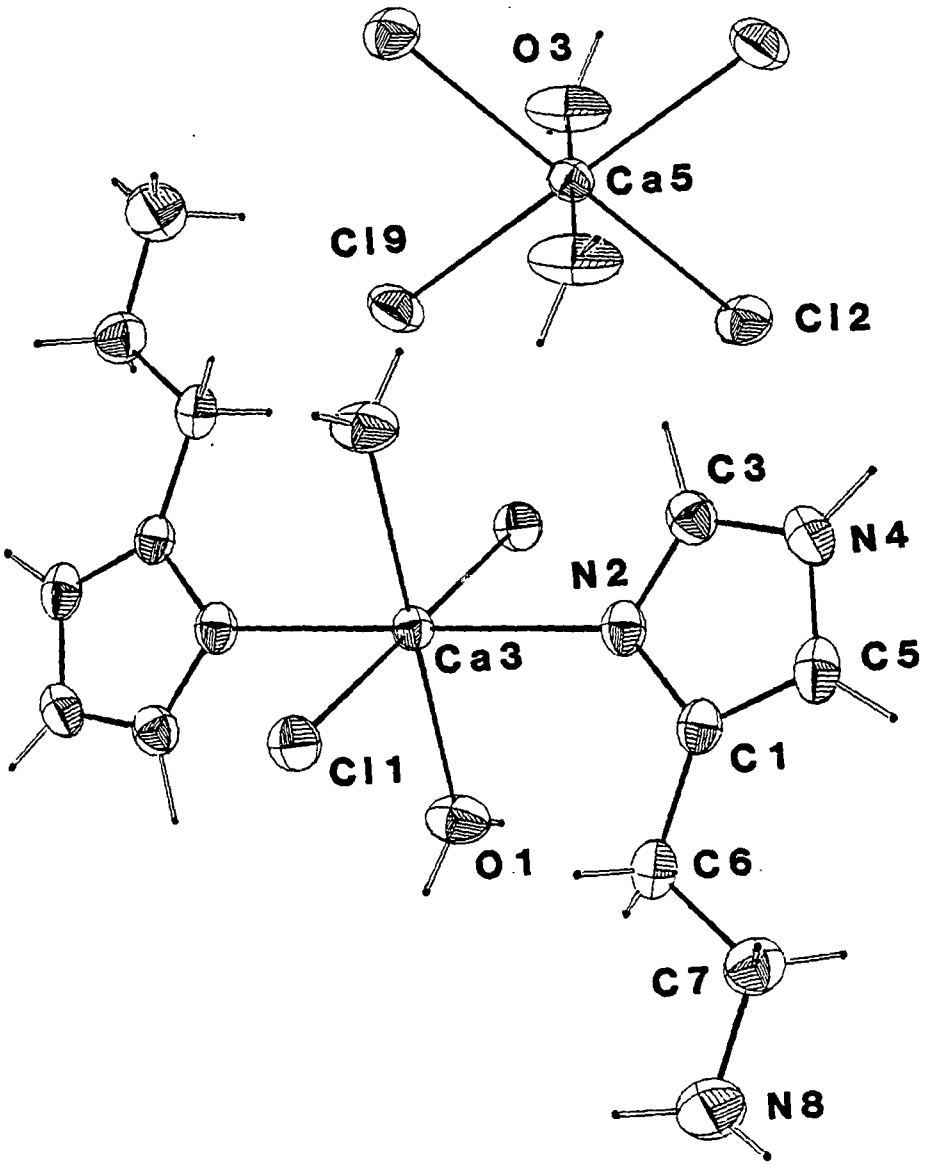

Figure 16. Projection View of XII

TABLE XLVI

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

$(CaCl_4(H_2O)_2)(CaCl_2(H_2O)_2(histamine.H^+)_2)$ (XII)

Ca3-Cl1	2.707(13)	Cl1-Ca3-Cl1'	180.0
Ca3-N2	2.441(13)	N2-Ca3-N2''	180.0
Ca3-O1	2.333(13)	O1-Ca3-O1'''	180.0
Ca5-Cl2	2.748(13)	Cl1-Ca3-N2	89.3(5)
Ca5-Cl9	2.762(13)	Cl1-Ca3-O1	92.9(4)
Ca5-O3	2.325(17)	N2-Ca3-O1	91.3(5)
C1-N2	1.392(6)	$Cl2-Ca5-Cl2^{iv}$	180.0
N2-C3	1.321(6)	$Cl9-Ca5-Cl9^{v}$	180.0
C3-N4	1.339(6)	$O3-Ca5-O3^{v}$	180.0
N4-C5	1.360(7)	Cl2-Ca5-Cl9	97.2(5)
C5-C1	1.360(6)	Cl2-Ca5-O3	88.1(5)
C1-C6	1.501(7)	Cl9-Ca5-O3	81.8(5)
C6-C7	1.511(8)	C5-C1-N2	108.8(4)
C7-N8	1.470(7)	C1-N2-C3	105.4(4)
		N2-C3-N4	111.3(4)
		C3-N4-C5	107.9(4)
		N4-C5-C1	106.6(4)
		C5-C1-C6	130.2(4)
		N2-C1-C6	120.9(4)
		C1-C6-C7	111.7(4)
		C6-C7-N8	110.4(4)

' = symmetry operation -x, -y, 1-z

TABLE XLVI (Continued)

'' = symmetry operation 1-x, -y, -z

''' = symmetry operation -x, -y, -z

iv = symmetry operation -x, 1-y, -z

v = symmetry operation -x, 1-y, 1-z

TABLE XLVII

POSITIONAL PARAMETERS FOR

$(CaCl_4(H_2O)_2)(CaCl_2(H_2O)_2(histamine.H^+)_2)$ (XII)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Ca3	0.0000	0.0000	0.0000
Ca5	0.0000	0.5000	0.5000
Cl1	0.0024(2)	-0.1343(1)	0.6671(2)
Cl2	-0.1655(2)	0.4090(1)	-0.1109(2)
Cl9	0.3223(2)	0.3788(1)	0.3796(2)
O1	0.0222(5)	-0.1520(3)	0.1967(5)
O3	0.1152(7)	0.6197(3)	0.6750(7)
C1	0.5648(5)	-0.0700(4)	0.2163(6)
N2	0.6823(5)	0.0107(3)	0.1671(6)
C3	0.5860(6)	0.1083(4)	0.2141(7)
N4	0.4150(5)	0.0953(3)	0.2900(6)
C5	0.3998(6)	-0.0175(4)	0.2909(7)
C6	0.6265(6)	-0.1929(4)	0.1841(7)
C7	0.4773(7)	-0.2654(4)	0.2431(8)
N8	0.5407(6)	-0.3850(4)	0.2270(8)
H10	0.0103	-0.1445	0.3241
H11	0.0616	-0.2221	0.1571
H30	0.0637	0.7000	0.7064
H31	0.2003	0.6200	0.7460
H3	0.6294	0.1895	0.1991
H4	0.3306	0.1528	0.3341

TABLE XLVII (Continued)

H5	0.2924	-0.0533	0.3357
H60	0.6894	-0.2093	0.0445
H61	0.7123	-0.2270	0.2501
H70	0.3940	-0.2435	0.3876
H71	0.4229	-0.2546	0.1410
H80	0.5930	-0.4028	0.2960
H81	0.4594	-0.4176	0.2595
H82	0.6232	-0.4013	0.0660

TABLE XLVIII

ANISOTROPIC THERMAL PARAMETERS FOR

$(CaCl_4(H_2O)_2)(CaCl_2(H_2O)_2(histamine.H^+)_2)$ (XII)

ATOM	U11	U22	U33	U12	U13	U23
Ca3	204(6)	232(6)	208(5)	-12(4)	-88(4)	17(4)
Ca5	295(7)	279(7)	284(6)	-5(5)	-142(5)	18(4)
Cl1	357(6)	308(5)	230(5)	-32(4)	-128(4)	-12(4)
Cl2	551(8)	398(7)	297(6)	-32(4)	-184(5)	66(5)
Cl9	383(7)	349(7)	604(8)	74(5)	-215(6)	19(6)
O1	62(2)	30(1)	30(1)	0(1)	-25(1)	4(1)
O3	109(3)	32(2)	70(2)	-8(2)	-68(2)	4(1)
C1	23(2)	32(2)	18(1)	-3(1)	-8(1)	2(1)
N2	20(1)	34(2)	25(1)	-1(1)	-9(1)	2(1)
C3	30(2)	31(2)	26(2)	0(1)	-11(1)	0(1)
N4	28(2)	37(2)	24(1)	7(1)	-9(1)	0(1)
C5	20(2)	47(3)	26(2)	-1(1)	-6(1)	6(1)
C6	24(2)	37(2)	25(2)	-4(1)	-5(1)	1(1)
C7	38(2)	33(2)	38(2)	-8(2)	-14(2)	3(1)
N8	44(2)	38(2)	59(3)	-13(2)	-19(2)	0(2)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U331^2c^{*2}+2U12hka^*b^* +2U13h1a^*c^*+2U23k1b^*c^*)) \times 10^4 \text{ for Ca and Cl,}$$

$$\times 10^3 \text{ for C, N, and O}$$

the side chain. The terminal nitrogen atom in the side chain is protonated and involved only in hydrogen bonding to water molecules and to chloride atoms. Although magnesium forms stronger complexes to nitrogen donor ligands than does calcium, no complex of magnesium and histamine has been isolated in crystalline form. (Complete list of bond distances and angles; Table XLVI. Positional parameters and anisotropic thermal parameters; Tables XLVII and XLVIII.)

Histamine hydrobromide (XIII) (59) crystallizes in the monoclinic space group $P2_1/n$ (Table XLIX). A projection view (Figure 17) of (XIII) shows the monovalent histamine molecule to exist in the same tautomeric form as that shown by histamine in (XII), with the nitrogen atom a to the side chain sp^2 hybridized and the terminal amino group of the side chain protonated. The conformation of the side-chain shows NH_3^+ and the imidazole ring to be trans about the C6-C7 bond (dihedral angle, 177.2(7)°), as in (XII). Bromine is within hydrogen bonding distance of three hydrogen atoms; H81, H83, and H4, and is 3.120(1) from a symmetry related H83 atom. Thus H83 is involved in bifurcated hydrogen bonding to two bromide atoms. The nitrogen bearing an unshaired pair of electrons, N2, is 2.160(6) Å from an amine hydrogen, H82, of a second histamine molecule. Thus the packing of molecules of (XIII) into the unit cell serves to maximize hydrogen bonding opportunities. The complete list of derived bond distances and angles is reported in Table L. Positional parameters and anisotropic thermal parameters for

TABLE XLIX

CRYSTAL DATA FOR Histamine Hydrobromide (XIII)

Formula	$C_5H_{10}BrN_3$
M. W.	192.1 g $mole^{-1}$
a	17.647(6) Å
b	9.363(4)
c	4.686(1)
α	90.0°
β	90.40(2)
γ	90.0
V	774.3(4) $Å^3$
F(000)	384
μMoK_α	51.77 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.65 g cm^{-3}
Z	4
Meas refl	1932
Obs refl	1148
R	5.1 %
R_w	6.2 %
G. O. F.	0.33
Space group	$P2_1/n$
Octants meas	$\pm h$, +k, +l

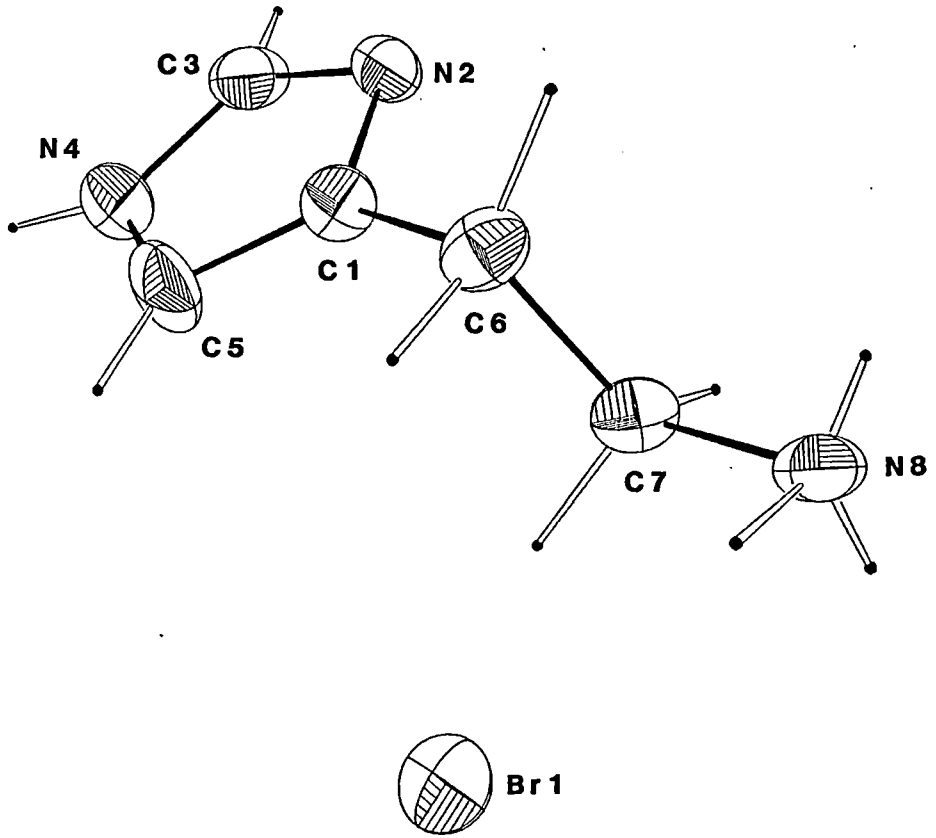

Figure 17. Projection View of XIII

TABLE L

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

Histamine hydrobromide (XIII)

C1-N2	1.390(9)	C5-C1-N2	108.9(6)
N2-C3	1.315(10)	C1-N2-C3	105.2(6)
C3-N4	1.329(10)	N2-C3-N4	111.6(7)
N4-C5	1.363(10)	C3-N4-C5	107.2(6)
C5-C1	1.335(10)	N4-C5-C1	107.1(7)
C1-C6	1.507(10)	C5-C1-C6	129.6(7)
C6-C7	1.504(10)	N2-C1-C6	121.4(6)
C7-N8	1.516(9)	C1-C6-C7	110.9(6)
		C6-C7-N8	109.6(6)

TABLE LI

POSITIONAL PARAMETERS FOR Histamine hydrobromide (XIII)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Br1	0.1147(1)	0.4890(1)	0.1211(2)
C1	0.3630(5)	0.4431(10)	0.8058(20)
N2	0.3841(5)	0.5757(8)	0.6901(18)
C3	0.3294(6)	0.6093(11)	0.5086(22)
N4	0.2753(5)	0.5075(11)	0.4964(18)
C5	0.2974(6)	0.4017(11)	0.6855(25)
C6	0.4120(6)	0.3668(10)	1.0189(21)
C7	0.4696(6)	0.2747(10)	0.8710(21)
N8	0.5207(5)	0.2048(8)	1.0948(17)
H3	0.3421	0.7017	0.3767
H4	0.2649	0.4700	0.3440
H5	0.2730	0.3189	0.7131
H61	0.4328	0.4507	1.1632
H62	0.3782	0.2858	1.0429
H71	0.4366	0.2012	0.7394
H72	0.5070	0.3140	0.7379
H81	0.5406	0.1502	1.0147
H82	0.5390	0.2771	1.1066
H83	0.4811	0.1359	1.2603

TABLE LII

ANISOTROPIC THERMAL PARAMETERS FOR

Histamine hydrobromide (XIII)

ATOM	U11	U22	U33	U12	U13	U23
Br1	248(5)	251(5)	370(5)	19(4)	-42(3)	13(5)
C1	28(5)	24(5)	25(5)	0(3)	1(3)	3(3)
N2	27(4)	23(4)	35(4)	-1(3)	-6(3)	-2(3)
C3	38(6)	24(5)	35(5)	3(4)	-4(4)	-5(4)
N4	30(4)	42(5)	47(4)	-3(4)	-6(3)	-15(4)
C5	26(6)	32(6)	55(7)	-14(4)	0(4)	10(4)
C6	33(5)	27(5)	28(5)	3(4)	5(3)	1(3)
C7	34(5)	25(5)	28(5)	1(4)	1(3)	-2(3)
N8	34(5)	18(4)	32(4)	2(3)	-4(3)	-4(3)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^4 \text{ for Br,}$$

$$\times 10^3 \text{ for C and N}$$

(XIII) are reported in Table LI and Table LII respectively.

The compound, histamine hydrochloride (XIV), is almost isostructural with (XIII), crystallizing in the same monoclinic space group $P2_1/n$ (Table LIII) and displaying similar unit cell dimensions. Figure 18 (a projection view of (XIV)) shows the histamine molecule in the same tautomeric conformation as observed in the two previous compounds, yet a small difference in the hydrogen bonding should be noted. The chlorine atom is within hydrogen bonding distances of three amine hydrogens, H81, H83, and H4, similar to what is observed for the bromine atom in XIII. But the chloride of (XIV) is also weakly hydrogen bonded to H83 and H81 from two symmetrically related histamine molecules, resulting in the formation of two bifurcated hydrogen bonds. The nitrogen atom, N2, which possesses an unshared pair of electrons, is 1.980(6) Å from H82 of another histamine molecule. The packing of the molecules in the unit cell of (XIV) has allowed extensive hydrogen bonding to exist as was observed for (XIII). Table LIV contains complete derived bond distances and angles of (XIII). Figure 18 is based on the positional parameters of Table LV and the anisotropic thermal parameters of Table LVI.

Since the granular matrix (which stores histamine) of the mast cell contains zinc cations(1), attempts were made to form mixed-metal complexes of calcium and zinc with histamine. The compound isolated, however, was $(ZnCl_4)$

TABLE LIII

CRYSTAL DATA FOR Histamine hydrochloride (XIV)

Formula	$C_5H_{10}ClN_3$
M. W.	147.6 g $mole^{-1}$
a	17.417(13) Å
b	9.204(7)
c	4.629(3)
α	90.0°
β	92.30(6)
γ	90.0
V	714.4(9) $Å^3$
F(000)	312
μMoK_α	4.478 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.372 g cm^{-3}
Z	4
Meas refl	1875
Obs refl	759
R	6.5 %
R_w	8.2 %
G. O. F.	0.29
Space group	$P2_1/n$
Octants meas	$\pm h$, +k, +l

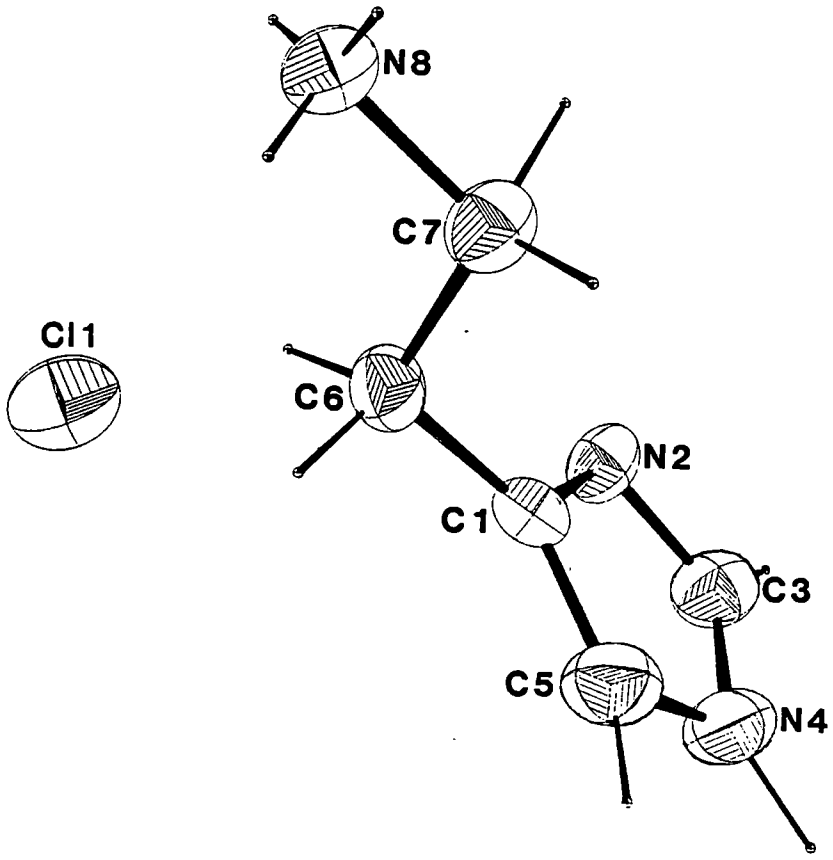

Figure 18. Projection View of XIV

Table LIV

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

Histamine hydrochloride (XIV)

C1-N2	1.381(9)	C5-C1-N2	109.0(6)
N2-C3	1.314(9)	C1-N2-C3	105.5(6)
C3-N4	1.324(10)	N2-C3-N4	112.2(7)
N4-C5	1.381(10)	C3-N4-C5	106.9(6)
C5-C1	1.351(11)	N4-C5-C1	106.4(7)
C1-C6	1.493(10)	C5-C1-C6	128.7(7)
C6-C7	1.500(10)	N2-C1-C6	122.3(6)
C7-N8	1.505(9)	C1-C6-C7	111.2(6)
		C6-C7-N8	110.8(6)

TABLE LV

POSITIONAL PARAMETERS FOR Histamine hydrochloride (XIV)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
C11	0.1085(1)	-0.0148(2)	0.1355(4)
C1	0.3588(4)	-0.0516(7)	0.7936(14)
N2	0.3812(3)	0.0786(6)	0.6749(12)
C3	0.3256(4)	0.1145(8)	0.4880(16)
N4	0.2692(3)	0.0181(7)	0.4794(13)
C5	0.2900(5)	-0.0906(9)	0.6728(18)
C6	0.4081(4)	-0.1319(8)	1.0116(15)
C7	0.4650(4)	-0.2272(8)	0.8676(16)
N8	0.5183(3)	-0.2987(6)	1.0884(13)
H3	0.3336	0.2177	0.3829
H4	0.2203	0.0081	0.3563
H5	0.2474	-0.1628	0.6554
H61	0.4270	-0.0641	1.1723
H62	0.3736	-0.2016	1.1309
H71	0.5158	-0.1759	0.7660
H72	0.4388	-0.3000	0.7325
H81	0.5289	-0.3800	1.0190
H82	0.5459	-0.2296	1.1811
H83	0.4830	-0.3502	1.1603

TABLE LVI

ANISOTROPIC THERMAL PARAMETERS FOR

Histamine hydrochloride (XIV)

ATOM	U11	U22	U33	U12	U13	U23
C11	298(10)	315(9)	405(9)	32(9)	-33(7)	7(9)
C1	25(4)	30(3)	29(3)	0(2)	8(3)	1(2)
N2	37(4)	29(3)	31(3)	0(2)	-6(2)	-6(2)
C3	35(4)	36(4)	43(4)	5(3)	-1(3)	-2(3)
N4	33(3)	49(4)	43(3)	-5(3)	-7(2)	2(3)
C5	34(4)	50(4)	49(5)	-6(3)	0(3)	7(4)
C6	38(4)	39(4)	28(3)	4(3)	2(3)	-3(3)
C7	38(5)	32(4)	36(4)	0(3)	-3(3)	-3(3)
N8	31(3)	26(3)	39(3)	-5(2)	-5(2)	-4(2)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U331^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^4 \text{ for Cl,}$$

$$\times 10^3 \text{ for C and N}$$

(histamine.H_2^{++}) (XV) and contained no calcium. In the solid state (orthorhombic space group $P2_1nb$, crystallographic details in Table LVII), the zinc atom is bound to four chloride atoms in tetrahedral coordination (Zn-Cl distance, 2.276(6) Å av.). Dicationic histamine molecules are hydrogen bonded to chloride atoms through the hydrogen atoms of the terminal ammonium group and the protonated imidazole ring. H81 enters into bifurcated hydrogen bonding with symmetrically related chloride atoms (H81-Cl2, 2.845(6) Å, H81-Cl4, 2.798(6) Å), as does H82 (H82-Cl3, 2.622(5) Å, H82-Cl4, 2.553(5) Å). H83 is hydrogen bonded to a single chloride atom (H83-Cl3, 2.530(6) Å), and H4 of the imidazole ring is hydrogen bonded to Cl1 (2.354(6) Å). A projection view of (XV) (Figure 19) shows the comformation of the side chain of the histamine molecule is similar to that observed in compounds (XII), (XIII), and (XIV) with the imidazole ring approximately trans to the terminal ammonium group about the C6-C7 bond. Complete lists of derived bond distances and angles, positional parameters, and anisotropic thermal parameters are presented in Tables LVIII, LIX, and LX respectively.

Other experiments were directed at the isolation of mixed-metal complexes of calcium and zinc with the local anesthetics, lidocaine and procaine. It has been reported that the ionic complex, $(ZnCl_4)(\text{lidocaine}.H^+)_2$, exerts an inhibitory effect on histamine release from mast cells(60). The only complex isolated in a suitable crystalline form was

TABLE LVII

CRYSTAL DATA FOR $(ZnCl_4)(histamine.H_2^{++})$ (XV)

Formula	$C_5H_{11}Cl_4N_3Zn$
M. W.	320.4 g $mole^{-1}$
a	7.343(6) Å
b	7.619(2)
c	21.455(12)
α	90.0°
β	90.0
γ	90.0
V	1200(1) $Å^3$
F(000)	640
μMoK_α	29.58 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.772 g cm^{-3}
Z	4
Meas refl	1092
Obs refl	738
R	6.4 %
R_w	8.3 %
G. O. F.	0.40
Space group	$P2_1nb$
Octants meas	+h, +k, +l

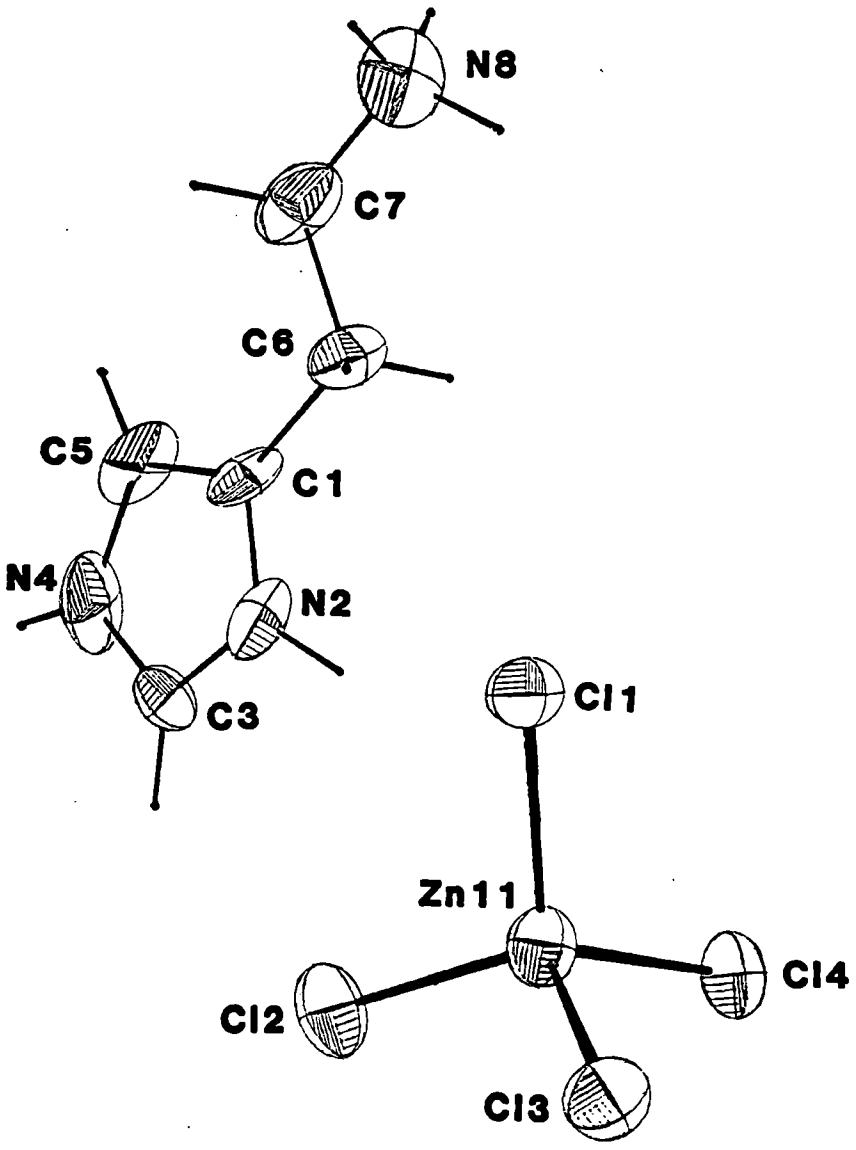

Figure 19. Projection View of XV

TABLE LVIII

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

$(ZnCl_4)(histamine.H_2^{++})$ (XV)

Zn11-Cl1	2.285(6)	Cl1-Zn11-Cl2	110.0(3)
Zn11-Cl2	2.230(7)	Cl1-Zn11-Cl3	106.8(2)
Zn11-Cl3	2.283(7)	Cl1-Zn11-Cl4	110.4(2)
Zn11-Cl4	2.304(5)	Cl2-Zn11-Cl3	114.6(2)
C1-N2	1.30(4)	Cl2-Zn11-Cl4	109.1(2)
N2-C3	1.34(3)	Cl3-Zn11-Cl4	105.9(2)
C3-N4	1.29(3)	C5-C1-N2	105(2)
N4-C5	1.40(4)	C1-N2-C3	115(2)
C5-C1	1.37(4)	N2-C3-N4	104(2)
C1-C6	1.54(4)	C3-N4-C5	111(2)
C6-C7	1.48(4)	N4-C5-C1	105(3)
C7-N8	1.50(4)	C5-C1-C6	131(3)
		N2-C1-C6	124(2)
		C1-C6-C7	111(2)
		C6-C7-N8	111(2)

TABLE LIX

POSITIONAL PARAMETERS FOR $(ZnCl_4)(histamine.H_2^{++})$ (XV)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Zn11	0.6882(0)	0.2275(3)	0.1129(1)
Cl1	0.6941(9)	0.1440(6)	0.2151(3)
Cl2	0.4033(8)	0.2878(7)	0.0840(4)
Cl3	0.8242(8)	0.0080(6)	0.0574(3)
Cl4	0.8665(8)	0.4728(6)	0.0979(3)
C1	0.293(3)	0.306(2)	0.312(1)
N2	0.310(2)	0.304(2)	0.251(1)
C3	0.162(3)	0.358(3)	0.220(1)
N4	0.046(2)	0.398(3)	0.263(1)
C5	0.122(4)	0.373(3)	0.322(2)
C6	0.446(3)	0.252(3)	0.357(1)
C7	0.383(4)	0.259(3)	0.423(1)
N8	0.532(3)	0.206(2)	0.467(1)
H2	0.424	0.272	0.228
H3	0.142	0.363	0.173
H4	-0.077	0.445	0.255
H5	0.063	0.395	0.365
H61	0.485	0.134	0.346
H62	0.548	0.332	0.351
H71	0.338	0.375	0.432
H72	0.281	0.175	0.427

TABLE LIX (Continued)

H81	0.508	0.100	0.480
H82	0.651	0.208	0.444
H83	0.542	0.291	0.501

TABLE LX

ANISOTROPIC THERMAL PARAMETERS FOR

$(ZnCl_4)(histamine.H_2^{++})$ (XV)

ATOM	U11	U22	U33	U12	U13	U23
Zn11	35(1)	40(1)	52(2)	6(1)	0(1)	1(1)
Cl1	34(2)	56(2)	38(5)	18(2)	2(3)	1(2)
Cl2	38(2)	56(2)	76(6)	5(2)	-14(3)	2(3)
Cl3	47(2)	44(2)	47(5)	6(2)	5(3)	-2(2)
Cl4	38(2)	43(2)	68(5)	-5(2)	-3(3)	0(2)
C1	42(11)	30(9)	32(31)	-13(8)	16(14)	20(12)
N2	32(8)	47(9)	60(26)	3(7)	17(12)	18(11)
C3	28(11)	65(13)	40(24)	2(9)	-13(10)	10(12)
N4	18(6)	76(14)	95(28)	9(8)	5(10)	-19(14)
C5	68(16)	62(15)	51(30)	-13(12)	42(18)	-40(16)
C6	49(11)	47(11)	35(23)	6(9)	8(13)	10(11)
C7	76(17)	48(12)	44(29)	-12(12)	28(18)	-18(13)
N8	51(10)	40(9)	76(23)	13(8)	2(12)	5(10)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^3$$

$(ZnCl_4)(procaine.H^+)_2$ (XVI). Crystallographic details are reported in Table LXI. The coordination geometry of the zinc atom is similar to that exhibited in (XV) and can be viewed in Figure 20 (a projection view of (XVI)). The zinc atom is tetrahedrally coordinated to four chloride atoms at an average Zn-Cl distance of 2.260(3) Å. (Complete list of the derived bond distances and angles; Table LXII). The protons of monovalent procaine cations are involved in bifurcated hydrogen bonding to chloride atoms coordinated to two symmetrically related zinc atoms. The hydrogen atoms bound to the quaternary nitrogen atoms of the ligands are involved in bifurcated hydrogen bonds (H9-Cl1, 2.825(3) Å, H9-Cl4, 2.494(2) Å; H29-Cl2, 2.851(3) Å, H29-Cl3, 2.512(2) Å), while one hydrogen atom of each aromatic primary amino group is involved in a single hydrogen bond (H41-Cl3, 2.684(3) Å, H241-Cl4, 2.664(3) Å). The positional parameters and anisotropic thermal parameters for (XVI) are listed in Tables LXIII and LXIV.

A study of the release of histamine from mast cells induced by Ko 1124 indicated that the presence of 2,4-dinitrophenol decreased chemically mediated release(61). Thus experiments were conducted to investigate the possible complexation of this histamine release inhibitor to calcium and to compare the binding pattern of this complex (if coordination to calcium occurs) with the binding patterns of calcium-allergen complexes previously discussed. The compound, (Ca(2,4-dinitrophenoxide)$(H_2O)_6$)(2,4-dinitrophen-

TABLE LXI

CRYSTAL DATA FOR $(ZnCl_4)(procaine.H^+)_2$ (XVI)

Formula	$C_{26}H_{42}Cl_4N_4O_4Zn$
M. W.	621.8 g $mole^{-1}$
a	11.930(3) Å
b	14.878(4)
c	13.984(6)
α	122.13(2)°
β	112.27(2)
γ	51.41(2)
V	1639.0(8) $Å^3$
F(000)	652
μMoK_α	11.18 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.260 g cm^{-3}
Z	2
Meas refl	7238
Obs refl	4059
R	5.4 %
R_w	7.1 %
G. O. F.	0.33
Space group	$P\bar{1}$
Octants meas	$\pm h, +k, \pm l$

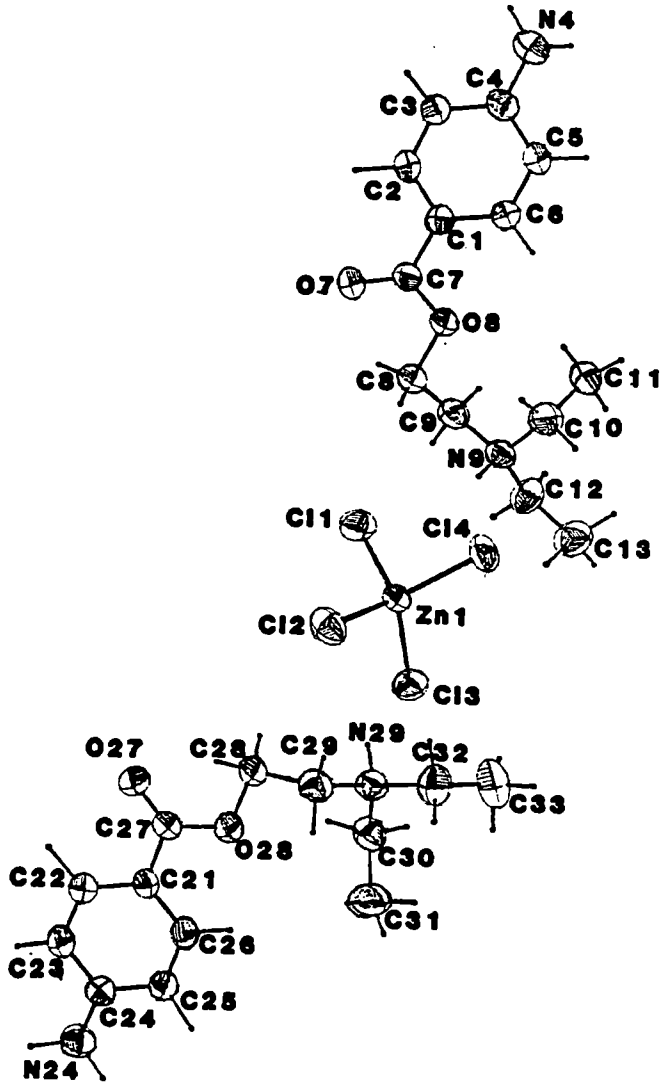

Figure 20. Projection View of XVI

TABLE LXII

BOND DISTANCES (A) AND BOND ANGLES (°) FOR

$(ZnCl_4)(procaine.H^+)_2$ (XVI)

Zn1-Cl1	2.243(3)	Cl1-Zn1-Cl2	113.2(1)
Zn1-Cl2	2.243(3)	Cl1-Zn1-Cl3	107.9(1)
Zn1-Cl3	2.276(2)	Cl1-Zn1-Cl4	105.1(1)
Zn1-Cl4	2.278(3)	Cl2-Zn1-Cl3	105.2(1)
C1-C2	1.389(11)	Cl2-Zn1-Cl4	107.8(1)
C2-C3	1.361(8)	Cl3-Zn1-Cl4	117.9(1)
C3-C4	1.396(12)	C1-C2-C3	121.5(8)
C4-N4	1.362(8)	C2-C3-C4	121.1(8)
C4-C5	1.398(12)	C3-C4-N4	121.0(8)
C5-C6	1.389(8)	N4-C4-C5	120.9(8)
C6-C1	1.386(13)	C3-C4-C5	118.1(6)
C1-C7	1.471(8)	C4-C5-C6	120.2(9)
C7-O7	1.205(11)	C5-C6-C1	120.9(8)
C7-O8	1.347(10)	C6-C1-C2	118.2(5)
O8-C8	1.461(7)	C2-C1-C7	118.8(8)
C8-C9	1.487(11)	C6-C1-C7	123.0(7)
C9-N9	1.512(14)	C1-C7-O7	125.0(8)
N9-C10	1.494(9)	O7-C7-O8	122.0(5)
C10-C11	1.509(9)	C1-C7-O8	113.0(8)
N9-C12	1.505(9)	C7-O8-C8	114.2(7)
C12-C13	1.469(17)	O8-C8-C9	108.3(6)
C21-C22	1.394(13)	C8-C9-N9	115.2(6)

TABLE LXII (Continued)

C22-C23	1.372(8)	C9-N9-C10	113.6(6)
C23-C24	1.398(13)	N9-C10-C11	113.5(6)
C24-N24	1.361(8)	C9-N9-C12	109.1(5)
C24-C25	1.407(13)	N9-C12-C13	114.5(6)
C25-C26	1.381(8)	C10-N9-C12	115.1(7)
C26-C21	1.384(13)	C21-C22-C23	120.9(8)
C21-C27	1.481(7)	C22-C23-C24	121.3(9)
C27-O27	1.195(11)	C23-C24-N24	121.2(8)
C27-O28	1.352(12)	N24-C24-C25	121.0(8)
O28-C28	1.449(7)	C23-C24-C25	117.8(5)
C28-C29	1.498(15)	C24-C25-C26	120.1(9)
C29-N29	1.508(9)	C25-C26-C21	121.8(9)
N29-C30	1.495(7)	C26-C21-C22	118.1(6)
C30-C31	1.493(12)	C22-C21-C27	118.3(8)
N29-C32	1.540(14)	C26-C21-C27	123.6(8)
C32-C33	1.443(12)	C21-C27-O27	125.2(8)
		O27-C27-O28	122.2(6)
		C21-C27-O28	112.5(7)
		C27-O28-C28	114.3(7)
		O28-C28-C29	108.8(8)
		C28-C29-N29	114.4(5)
		C29-N29-C30	111.9(5)
		N29-C30-C31	114.4(5)
		C29-N29-C32	108.4(5)

TABLE LXII (Continued)

	C29-N29-C32	108.4(5)
	N29-C32-C33	114.4(6)
	C30-N29-C32	115.5(7)

TABLE LXIII

POSITIONAL PARAMETERS FOR $(ZnCl_4)(procaine.H^+)_2$ (XVI)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Zn1	0.2500(1)	0.2885(1)	0.7499(1)
Cl1	0.1588(2)	0.3188(2)	0.8856(1)
Cl2	0.3416(2)	0.0918(1)	0.6140(1)
Cl3	0.0663(2)	0.4147(1)	0.6604(1)
Cl4	0.4339(2)	0.3204(2)	0.8398(1)
C1	0.6217(6)	0.2452(5)	0.3599(5)
C2	0.6907(6)	0.1539(5)	0.4008(5)
C3	0.7988(6)	0.1450(5)	0.4842(5)
C4	0.8452(6)	0.2272(5)	0.5313(5)
N4	0.9536(6)	0.2182(6)	0.6147(5)
C5	0.7783(7)	0.3183(6)	0.4896(5)
C6	0.6656(7)	0.3284(6)	0.4065(5)
C7	0.5054(6)	0.2500(6)	0.2698(5)
O7	0.4671(5)	0.1773(4)	0.2247(3)
O8	0.4422(4)	0.3468(4)	0.2419(3)
C8	0.3258(7)	0.3543(6)	0.1529(5)
C9	0.2367(6)	0.4834(6)	0.1567(5)
N9	0.2931(5)	0.5052(4)	0.0957(4)
C10	0.4352(7)	0.4920(6)	0.1455(5)
C11	0.4305(9)	0.5894(8)	0.2645(6)
C12	0.1769(7)	0.6269(6)	0.0824(6)
C13	0.2176(8)	0.6587(7)	0.0230(6)

TABLE LXIII (Continued)

C21	0.1227(6)	-0.0078(5)	0.8591(4)
C22	0.1915(6)	0.0560(5)	0.8998(5)
C23	0.2986(6)	0.0415(6)	0.9854(5)
C24	0.3461(6)	-0.0411(5)	1.0318(5)
N24	0.4540(6)	-0.0570(5)	1.1154(4)
C25	0.2778(7)	-0.1066(6)	0.9901(5)
C26	0.1680(7)	-0.0887(6)	0.9056(5)
C27	0.0050(6)	0.0144(5)	0.7686(5)
O27	-0.0331(5)	0.0805(4)	0.7244(3)
O28	-0.0576(5)	-0.0474(4)	0.7410(3)
C28	-0.1728(7)	-0.0284(6)	0.6524(5)
C29	-0.2637(6)	-0.0638(6)	0.6563(5)
N29	-0.2067(5)	-0.2028(4)	0.5951(4)
C30	-0.0647(7)	-0.2815(5)	0.6454(5)
C31	-0.0672(9)	-0.2555(7)	0.7637(6)
C32	-0.3263(7)	-0.2212(7)	0.5813(6)
C33	-0.2867(8)	-0.3506(7)	0.5227(7)
H2	0.6664	0.0815	0.3599
H3	0.8315	0.0862	0.5159
H41	0.9845	0.1723	0.6561
H42	0.9767	0.2698	0.6415
H5	0.7831	0.4053	0.5354
H6	0.6127	0.4010	0.3800
H81	0.3663	0.2892	0.0753
H82	0.2600	0.3497	0.1774

TABLE LXIII (Continued)

H91	0.2186	0.5559	0.2373
H92	0.1475	0.5000	0.1153
H9	0.3049	0.4452	0.0281
H101	0.5082	0.3980	0.1321
H102	0.4718	0.5000	0.0988
H111	0.4116	0.5773	0.3125
H112	0.3420	0.6818	0.2577
H113	0.5159	0.5917	0.2942
H121	0.1379	0.7011	0.1571
H122	0.0730	0.6356	0.0515
H131	0.1463	0.7428	0.0185
H132	0.2759	0.6990	0.0848
H133	0.2365	0.5823	-0.0557
H22	0.1633	0.1202	0.8596
H23	0.3545	0.0822	1.0149
H241	0.4837	0.0084	1.1547
H242	0.4904	-0.1108	1.1561
H25	0.2862	-0.1457	1.0437
H26	0.1211	-0.1353	0.8778
H281	-0.2236	0.0663	0.6783
H282	-0.1356	-0.0813	0.5729
H291	-0.3649	-0.0151	0.6282
H292	-0.2777	-0.0381	0.7441
H29	-0.1766	-0.2335	0.5171
H301	-0.0342	-0.3719	0.5952

TABLE LXIII (Continued)

H302	0.0000	-0.2617	0.6378
H311	-0.1749	-0.2506	0.7633
H312	-0.1199	-0.1751	0.8013
H313	-0.0148	-0.3025	0.8007
H321	-0.3590	-0.1804	0.6551
H322	-0.4293	-0.1535	0.5363
H331	-0.3633	-0.3610	0.5189
H332	-0.2439	-0.4053	0.4578
H333	-0.1929	-0.4022	0.5786

TABLE LXIV

ANISOTROPIC THERMAL PARAMETERS FOR

$(ZnCl_4)(procaine.H^+)_2$ (XVI)

ATOM	U11	U22	U33	U12	U13	U23
Zn1	405(3)	446(3)	380(3)	-246(3)	-54(2)	188(3)
Cl1	561(9)	915(12)	575(9)	-440(9)	-11(7)	385(9)
Cl2	570(9)	440(8)	563(9)	-240(7)	-22(7)	117(7)
Cl3	647(10)	511(9)	622(10)	-247(9)	-80(8)	351(8)
Cl4	646(10)	848(11)	605(10)	-593(8)	-76(8)	262(9)
C1	45(3)	50(3)	42(3)	-31(2)	-1(2)	21(2)
C2	52(3)	43(3)	44(3)	-31(2)	0(2)	15(2)
C3	49(3)	44(3)	45(3)	-27(2)	-3(2)	21(2)
C4	42(39	53(3)	39(3)	-25(2)	2(2)	18(2)
N4	67(3)	85(4)	64(3)	-54(3)	-25(2)	43(3)
C5	59(3)	58(3)	52(3)	-43(3)	-11(2)	25(3)
C6	64(4)	59(3)	46(3)	-42(3)	-11(2)	30(3)
C7	49(3)	54(3)	40(3)	-32(3)	-1(2)	21(2)
O7	72(3)	66(2)	57(2)	-53(2)	-16(2)	30(2)
O8	61(2)	62(2)	57(2)	-44(2)	-22(2)	38(2)
C8	61(4)	66(4)	59(3)	-44(3)	-19(3)	37(3)
C9	46(3)	62(3)	50(3)	-33(3)	-7(2)	26(3)
N9	50(2)	40(2)	36(2)	-24(2)	0(2)	12(2)
C10	48(3)	75(4)	60(4)	-35(3)	-2(3)	35(3)
C11	103(5)	117(6)	60(4)	-90(5)	-26(4)	47(4)
C12	54(39	48(3)	75(4)	-20(3)	6(3)	32(3)

TABLE LXIV (Continued)

C13	84(5)	59(4)	75(5)	-32(4)	2(4)	36(4)
C21	47(3)	36(2)	37(2)	-25(2)	0(2)	12(2)
C22	53(3)	46(3)	45(3)	-30(2)	-1(2)	20(2)
C23	53(3)	55(3)	52(3)	-38(3)	-5(2)	21(2)
C24	43(3)	43(3)	41(3)	-23(2)	1(2)	14(2)
N24	58(3)	68(3)	61(3)	-37(2)	-20(2)	37(2)
C25	61(3)	55(3)	53(3)	-38(3)	-11(2)	30(3)
C26	62(4)	56(3)	55(3)	-44(3)	-10(3)	25(3)
C27	54(3)	49(3)	39(3)	-33(2)	-6(2)	19(2)
O27	69(2)	66(2)	57(2)	-45(2)	-16(2)	39(2)
O28	66(2)	67(2)	60(2)	-50(2)	-23(2)	38(2)
C28	72(4)	70(4)	57(3)	-54(3)	-27(3)	40(3)
C29	44(3)	51(3)	55(3)	-23(2)	-5(2)	25(2)
N29	48(2)	57(3)	38(2)	-33(2)	2(2)	15(2)
C30	52(3)	39(3)	56(3)	-21(2)	0(2)	15(2)
C31	110(6)	70(4)	59(4)	-48(4)	-18(4)	39(4)
C32	60(4)	67(4)	74(4)	-40(3)	8(3)	25(3)
C33	78(5)	68(4)	88(5)	-51(4)	19(4)	4(4)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^4 \text{ for Zn and Cl,}$$

$$\times 10^3 \text{ for C, N, and O}$$

oxide)(H_2O) (XVII), crystallizes (unit cell parameters; Table LXV) with calcium displaying interactions with eight oxygen atoms(62), six from water molecules (Ca-O av. 2.478(5) Å) and two from a single 2,4-dinitrophenoxide anion which directs the phenoxide oxygen (Ca1-O1, 2.361(5) Å) and one oxygen of an ortho nitro group (Ca1-O21, 2.507(5) Å) toward calcium (Figure 21). The remaining positive charge per calcium ion is balanced by the presence of a second 2,4-dinitrophenoxide group in the asymmetric unit. A center of symmetry relates two calcium cations which are bridged by symmetrically related O11 atoms of water (Ca...Ca, 4.231(2) Å) (Figure 22). Opportunities for hydrogen bonding are many with the nonbonded phenoxide oxygen atom displaying three distances to water oxygen atoms of less than 2.9 Å; one intramolecular O-O distance of 2.805(7) Å between bound water molecules; one intermolecular distance of 2.762(7) Å between the bound phenoxide atom and a bound water oxygen atom of an adjacent calcium atom; three contact distances of less than 2.9 Å between nitro oxygen atoms and water oxygen atoms; and five close contact distances between water molecules including those involving two additional water oxygen atoms, C16 and C17, crystallized in the unit cell. These distances indicate possible hydrogen bonding interactions which cannot be documented structurally because the positions of hydrogen atoms associated with water molecules were not determined. (Complete listing of the derived bond distances and angles; Table LXVI. Positional

TABLE LXV

CRYSTAL DATA FOR

(Ca(2,4-dinitrophenoxide)$(H_2O)_6$)(2,4-dinitrophenoxide)

(H_2O) (XVII)

Formula	$C_{12}H_{20}CaN_4O_{17}$
M. W.	532.4 g $mole^{-1}$
a	10.627 (5) Å
b	25.536 (11)
c	7.922 (2)
α	90.0°
β	92.69 (3)
γ	90.0
V	2147.4 (15) $Å^3$
F(000)	1104
μMoK_α	3.718 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.646 g cm^{-3}
Z	4
Meas refl	5137
Obs refl	2628
R	6.7 %
R_w	9.7 %
G. O. F.	0.45
Space group	$P2_1/a$
Octants meas	$\pm h$, +k, +l

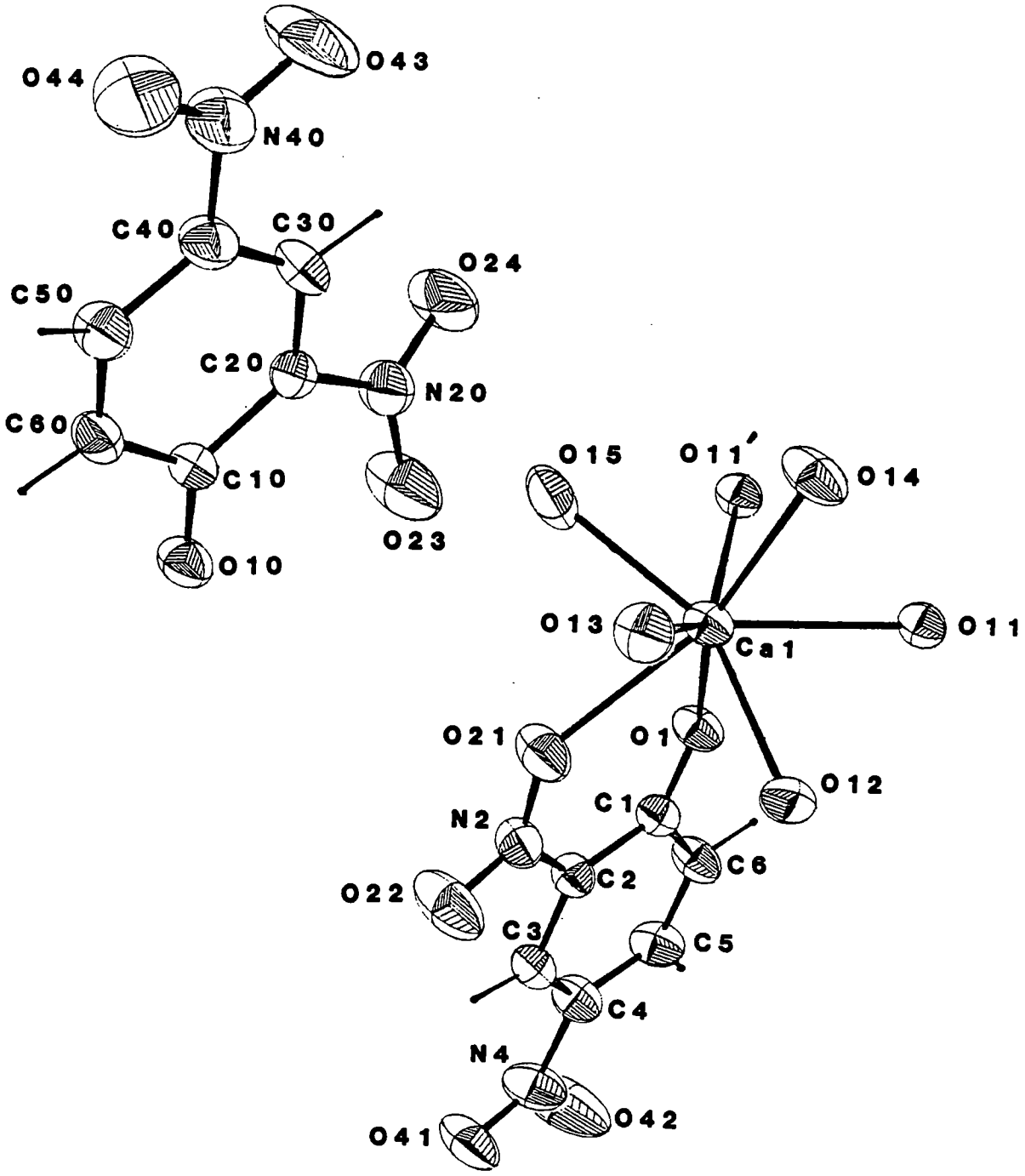

Figure 21. Projection View of XVII

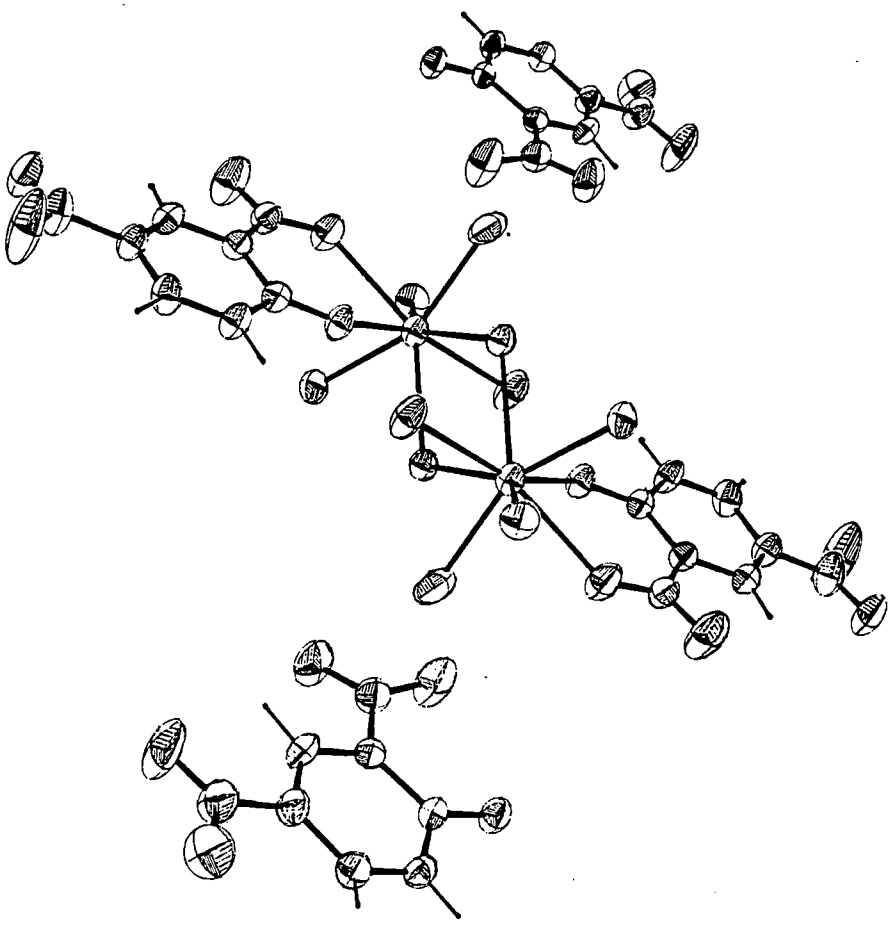

Figure 22. Packing Diagram of XVII

TABLE LXVI

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

(Ca(2,4-dinitrophenoxide)(H_2O)$_6$)(2,4-dinitrophenoxide)

(H_2O) (XVII)

Ca1-O11	2.667(5)	O11-Ca1-O11'	70.5(1)
Ca1-O11'	2.512(4)	O11-Ca1-O12	73.3(1)
Ca1-O12	2.405(5)	O11-Ca1-O13	121.5(2)
Ca1-O13	2.521(5)	O11-Ca1-O14	67.4(2)
Ca1-O14	2.365(5)	O11-Ca1-O15	139.5(2)
Ca1-O15	2.403(6)	O11-Ca1-O1	80.8(2)
Ca1-O1	2.361(5)	O11-Ca1-O21	139.5(2)
Ca1-O21	2.507(5)	O12-Ca1-O11'	138.7(2)
O1-C1	1.287(8)	O12-Ca1-O13	75.5(2)
C1-C2	1.437(9)	O12-Ca1-O14	105.9(2)
C2-N2	1.445(9)	O12-Ca1-O15	146.1(2)
N2-O21	1.234(8)	O12-Ca1-O1	80.3(2)
N2-O22	1.222(8)	O12-Ca1-O21	77.0(2)
C2-C3	1.390(10)	O13-Ca1-O11'	141.8(2)
C3-C4	1.374(10)	O13-Ca1-O14	75.5(2)
C4-N4	1.429(9)	O13-Ca1-O15	77.4(2)
N4-O41	1.214(9)	O13-Ca1-O1	139.3(2)
N4-O42	1.214(10)	O13-Ca1-O21	75.3(2)
C4-C5	1.399(10)	O14-Ca1-O11'	77.7(2)
C5-C6	1.345(10)	O14-Ca1-O15	86.3(2)
C6-C1	1.430(9)	O14-Ca1-O1	143.5(2)
O10-C10	1.288(8)	O14-Ca1-O21	148.8(2)

TABLE LXVI (Continued)

C10-C20	1.445(9)	O15-Ca1-O11'	74.2(2)
C20-N20	1.458(9)	O15-Ca1-O1	108.6(2)
N20-O23	1.217(9)	O15-Ca1-O21	76.8(2)
N20-O24	1.216(8)	O1-Ca1-O11'	75.0(2)
C20-C30	1.361(10)	O1-Ca1-O21	67.6(2)
C30-C40	1.373(10)	O21-Ca1-O11'	121.2(2)
C40-N40	1.429(9)	O1-C1-C2	125.1(6)
N40-O43	1.233(10)	O1-C1-C6	120.3(6)
N40-O44	1.232(9)	C2-C1-C6	114.5(6)
C40-C50	1.392(10)	C1-C2-N2	122.7(6)
C50-C60	1.345(10)	N2-C2-C3	115.0(6)
C60-C10	1.427(9)	C2-N2-O21	120.1(5)
		C2-N2-O22	119.5(6)
		O21-N2-O22	120.4(6)
		C1-C2-C3	122.3(6)
		C2-C3-C4	119.2(6)
		C3-C4-N4	118.1(6)
		N4-C4-C5	121.2(7)
		C4-N4-O41	121.3(6)
		C4-N4-O41	117.8(7)
		O41-N4-O42	121.0(7)
		C3-C4-C5	120.7(6)
		C4-C5-C6	120.2(7)
		C5-C6-C1	123.1(6)
		O10-C10-C20	124.3(6)

TABLE LXVI (Continued)

	O10-C10-C60	121.(6)
	C20-C10-C60	113.8(6)
	C10-C20-N20	121.0(6)
	N20-C20-C30	115.9(6)
	C20-N20-O23	119.3(6)
	C20-N20-O24	119.2(6)
	O23-N20-O24	121.5(6)
	C10-C20-C30	123.0(6)
	C20-C30-C40	119.1(6)
	C30-C40-N40	117.9(6)
	N40-C40-C50	120.9(6)
	C40-N40-O43	118.3(6)
	C40-N40-O44	118.4(6)
	O43-N40-O44	123.2(7)
	C30-C40-C50	121.2(6)
	C40-C50-C60	119.6(6)
	C50-C60-C10	123.3(6)

' = symmetry operation 1-x, -y, 1-z

TABLE LXVII

POSITIONAL PARAMETERS FOR

(Ca(2,4-dinitrophenoxide)(H_2O)$_6$)(2,4-dinitrophenoxide)

(H_2O) (XVII)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Ca1	0.3327(1)	-0.0012(1)	0.3444(2)
O11	0.5839(4)	0.0006(2)	0.3535(5)
O12	0.3925(5)	0.0305(2)	0.0737(6)
O13	0.2078(5)	-0.0567(2)	0.1333(6)
O14	0.4220(5)	-0.0857(2)	0.3744(8)
O15	0.1645(5)	0.0337(2)	0.5077(7)
O16	0.3915(5)	0.4934(2)	0.1516(7)
O17	0.1245(5)	0.4166(2)	0.1362(8)
O1	0.3656(4)	0.0881(2)	0.4110(6)
C1	0.3262(6)	0.1332(3)	0.3587(8)
C2	0.2129(6)	0.1422(3)	0.2567(8)
C3	0.1744(6)	0.1921(3)	0.2070(9)
C4	0.2468(7)	0.2345(3)	0.2563(9)
C5	0.3588(7)	0.2277(3)	0.3537(9)
C6	0.3971(6)	0.1794(3)	0.4000(9)
N2	0.1296(5)	0.1003(2)	0.2004(8)
O21	0.1493(5)	0.0551(2)	0.2498(7)
O22	0.0406(6)	0.1100(2)	0.1020(9)
N4	0.2037(7)	0.2855(3)	0.2067(9)
O41	0.1139(5)	0.2912(2)	0.1080(8)

TABLE LXVII (Continued)

O42	0.2601(8)	0.3230(2)	0.2664(10)
O10	0.2693(4)	0.0786(2)	-0.1865(6)
C10	0.2674(6)	0.1289(3)	-0.1990(8)
C20	0.1665(6)	0.1585(3)	-0.2822(8)
C30	0.1670(6)	0.2116(3)	-0.2934(9)
C40	0.2670(7)	0.2390(3)	-0.2212(9)
C50	0.3677(6)	0.2132(3)	-0.1389(9)
C60	0.3682(6)	0.1606(3)	-0.1313(9)
N20	0.0586(6)	0.1321(3)	-0.3646(8)
O23	0.0342(6)	0.0874(2)	-0.3245(9)
O24	-0.0060(5)	0.1556(2)	-0.4704(8)
N40	0.2633(6)	0.2948(3)	-0.2302(9)
O43	0.1765(6)	0.3156(2)	-0.3148(10)
O44	0.3472(6)	0.3199(2)	-0.1542(9)
H3	0.0950	0.1900	0.1357
H5	0.4086	0.2614	0.3944
H6	0.4786	0.1733	0.4687
H30	0.0945	0.2322	-0.3278
H50	0.4293	0.2306	-0.0615
H60	0.4421	0.1468	-0.0731

TABLE LXVIII

ANISOTROPIC THERMAL PARAMETERS FOR

(Ca(2,4-dinitrophenoxide)(H_2O)$_6$)(2,4-dinitrophenoxide)

(H_2O) (XVII)

ATOM	U11	U22	U33	U12	U13	U23
Ca1	358(6)	264(7)	371(6)	-14(6)	-66(5)	-4(6)
O11	34(2)	32(2)	33(2)	0(2)	-5(1)	0(2)
O12	44(3)	50(3)	36(2)	3(2)	-3(2)	12(2)
O13	42(3)	43(3)	49(3)	-8(2)	-8(2)	-2(2)
O14	47(3)	24(3)	86(4)	-1(2)	-26(2)	1(2)
O15	46(3)	80(4)	49(3)	30(3)	0(2)	4(3)
O16	50(3)	47(3)	58(3)	9(2)	-9(2)	-8(2)
O17	67(3)	35(3)	71(4)	9(2)	17(3)	-2(2)
O1	40(2)	24(2)	43(2)	0(2)	-9(2)	-1(2)
C1	34(3)	29(3)	31(3)	2(2)	0(2)	0(2)
C2	31(3)	28(4)	36(3)	1(2)	-2(2)	0(2)
C3	34(3)	34(4)	33(3)	6(3)	-2(2)	0(3)
C4	46(4)	22(4)	45(4)	6(3)	-3(3)	-2(3)
C5	52(4)	26(4)	45(4)	-6(3)	-7(3)	0(3)
C6	37(4)	28(4)	46(4)	0(3)	-16(3)	-1(3)
N2	32(3)	32(3)	47(3)	2(2)	-4(2)	1(2)
O21	38(3)	34(3)	82(4)	-2(2)	-15(2)	7(2)
O22	58(3)	49(3)	104(5)	-4(3)	-45(3)	5(3)
N4	71(5)	28(4)	54(4)	1(3)	-11(3)	2(3)
O41	56(3)	42(3)	83(4)	10(2)	-22(3)	11(3)

TABLE LXVIII (Continued)

O42	140(7)	26(4)	129(6)	-1(4)	-74(5)	4(4)
O10	37(2)	26(2)	51(3)	0(2)	-8(2)	4(2)
C10	30(3)	31(4)	34(3)	2(2)	-1(2)	7(2)
C20	27(3)	32(4)	35(3)	-2(2)	0(2)	4(3)
C30	35(4)	32(4)	40(3)	12(3)	-3(3)	1(3)
C40	38(4)	23(4)	47(4)	1(2)	0(3)	1(3)
C50	35(4)	30(4)	43(4)	-4(3)	-8(3)	-1(3)
C60	29(3)	37(4)	41(4)	0(3)	-7(3)	7(3)
N20	36(3)	40(4)	45(3)	-3(2)	-6(2)	3(2)
O23	59(4)	44(4)	118(5)	-14(3)	-47(3)	15(3)
O24	50(3)	71(4)	76(4)	-8(3)	-36(3)	25(3)
N40	50(4)	29(4)	74(4)	2(3)	1(3)	0(3)
O43	82(4)	29(3)	140(6)	10(3)	-36(4)	17(3)
O44	69(4)	33(3)	102(5)	-11(3)	-4(3)	-7(3)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^4 \text{ for Ca,}$$

$$\times 10^3 \text{ for C, N, and O}$$

parameters and anisotropic thermal parameters; Tables LXVII and LXVIII, respectively.)

In comparison, the complex, $(Mg(H_2O)_6)$(2,4-dinitrophenoxide)$_2(H_2O)_2$ (XVIII), crystallizes (space group $P2_1/c$, unit cell parameters; Table LXIX) with magnesium on a center of symmetry and surrounded by six oxygen atoms of water molecules (Mg-O, 2.066(5) Å av.) arranged in octahedral geometry (O-Mg-O, 88.1-91.9° or 180°, complete listing of derived bond distances and angles; Table LXX) (62). A projection view (Figure 23 based on the positional parameters and anisotropic thermal parameters of Tables LXXI and LXXII) shows that the asymmetric unit contains as well one 2,4-dinitrophenoxide anion which displays hydrogen bonding interactions with two of the water molecules of the octahedral coordination sphere and with O14, the additional water molecule in the asymmetric unit. This 2,4-dinitrophenoxide molecule is disordered by a 9.1° rotation relative to C3, which is common to both of the rings of the disordered solution. Both 50% occupancy rings were clearly discernible and refinement proceeded in satisfactory fashion. The disorder of the 2,4-dinitrophenoxide anion does not provide alternate hydrogen bonding opportunities. Other hydrogen bonded interactions involve the bonded and nonbonded water molecules and oxygen atoms of the ortho and para nitro groups. Magnesium coordination to 2,4-dinitrophenoxide has been previously observed in the crystal structures of Mg(N-methylimidazole)$_2$(2,4-dinitrophenoxide)$_2$

TABLE LXIX

CRYSTAL DATA FOR $(Mg(H_2O)_6)(2,4\text{-dinitrophenoxide})_2(H_2O)_2$ (XVIII)

Formula	$C_{12}H_{22}MgN_4O_{18}$ *
M. W.	534.6 g $mole^{-1}$
a	13.473 (4) Å
b	12.969 (4)
c	6.670 (2)
α	90.0°
β	104.98 (2)
γ	90.0
V	1125.79 (5) $Å^3$
F(000)	556
μMoK_α	1.642 cm^{-1}
λMoK_α	0.71069 Å
D_{calc}	1.577 g cm^{-3}
Z	2
Meas refl	4029
Obs refl	1593
R	8.6 %
R_w	12.3 %
G. O. F.	0.50
Space group	$P2_1/c$
Octants meas	±h, +k, +l

* Asymetric unit = 1/2 of stoichiometric unit

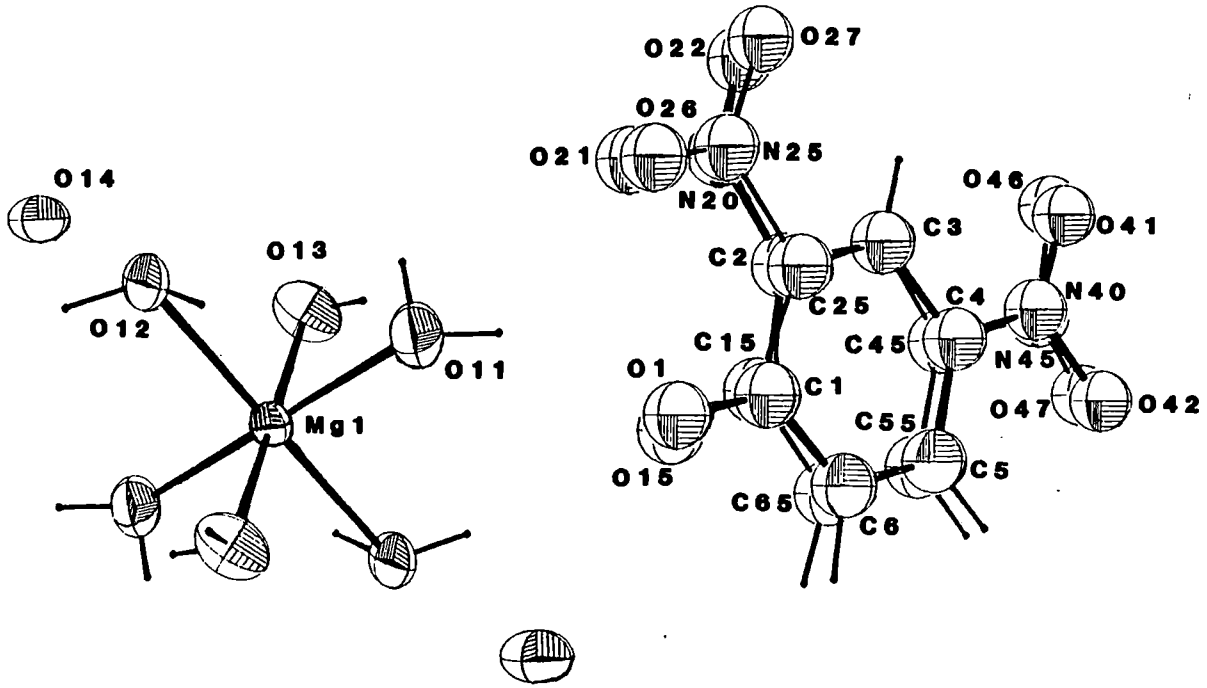

Figure 23. Projection View of XVIII

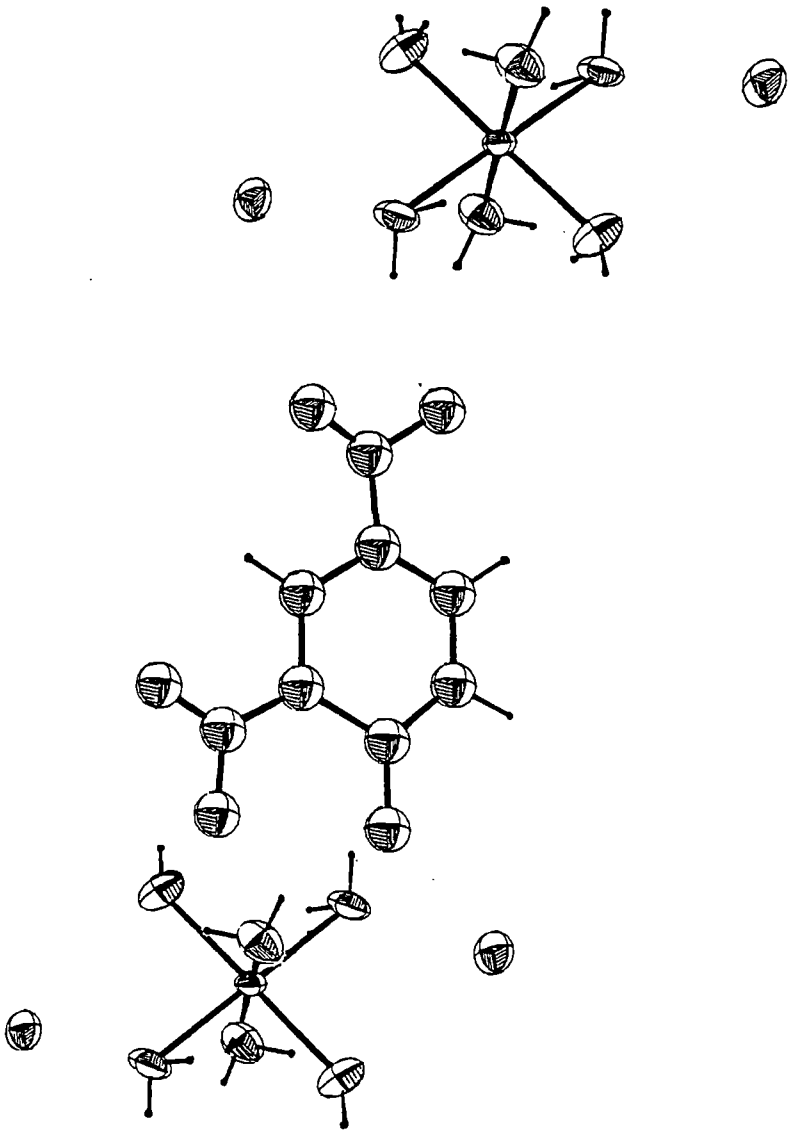

Figure 24. Packing Diagram of XVIII

TABLE LXX

BOND DISTANCES (Å) AND BOND ANGLES (°) FOR

$(Mg(H_2O)_6)(2,4\text{-dinitrophenoxide})_2(H_2O)_2$ (XVIII)

Mg1-O11	2.050(5)	O11-Mg1-O12	88.3(2)
Mg1-O12	2.087(4)	O11-Mg1-O13	90.7(2)
Mg1-O13	2.060(6)	O11-Mg1-O12'	91.7(2)
O1-C1	1.317(16)	O11-Mg1-O13'	89.3(2)
C1-C2	1.520(17)	O12-Mg1-O13'	88.1(2)
C2-N20	1.389(15)	O1-C1-C2	118(1)
N20-O21	1.260(13)	O1-C1-C6	128(1)
N20-O22	1.207(15)	C2-C1-C6	112(1)
C2-C3	1.376(13)	C1-C2-N20	122(1)
C3-C4	1.358(13)	N20-C2-C3	116(1)
C4-N40	1.378(16)	C2-N20-O21	122(1)
N40-O41	1.149(16)	C2-N20-O22	118(1)
N40-O42	1.320(16)	O21-N20-O22	118(1)
C4-C5	1.404(17)	C1-C2-C3	120(1)
C5-C6	1.368(18)	C2-C3-C4	120(1)
C6-C1	1.377(17)	C3-C4-N40	117(1)
O15-C15	1.253(14)	N40-C4-C5	120(1)
C15-C25	1.406(17)	C4-N40-O41	124(1)
C25-N25	1.503(17)	C4-N40-O42	117(1)
N25-O26	1.155(16)	O41-N40-O42	118(1)
N25-O27	1.303(15)	C3-C4-C5	122(1)
C25-C3	1.414(14)	C4-C5-C6	117(1)
C3-C45	1.402(15)	C5-C6-C1	127(1)

TABLE LXX (Continued)

C45-N45	1.513(16)	O15-C15-C25	128(1)
N45-O46	1.308(17)	O15-C15-C65	115(1)
N45-O47	1.181(15)	C25-C15-C65	116(1)
C45-C55	1.456(19)	C15-C25-N25	120(1)
C55-C65	1.352(18)	N25-C25-C3	116(1)
C65-C15	1.481(17)	C25-N25-O26	121(1)
		C25-N25-O27	116(1)
		O26-N25-O27	122(1)
		C15-C25-C3	122(1)
		C25-C3-C45	120(1)
		C3-C45-N45	122(1)
		N45-C45-C55	119(1)
		C45-N45-O46	113(1)
		C45-N45-O47	120(1)
		O46-N45-O47	127(1)
		C3-C45-C55	119(1)
		C45-C55-C65	121(1)
		C55-C65-C15	121(1)

' = symmetry operation 2-x, -y, 2-z

TABLE LXXI

POSITIONAL PARAMETERS FOR

$(Mg(H_2O)_6)(2,4\text{-dinitrophenoxide})_2(H_2O)_2$ (XVIII)

ATOM	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
Mg1	1.0000	0.0000	1.0000
O11	1.0498(4)	0.0703(4)	1.2837(8)
O12	0.8852(3)	0.1119(4)	0.9198(8)
O13	1.0923(4)	0.0948(4)	0.8779(8)
O14	0.9157(4)	0.1754(4)	0.4745(8)
O1	1.2000(7)	0.0097(7)	1.6290(14)
C1	1.3000(10)	0.0241(9)	1.6694(20)
C2	1.3394(9)	0.1308(9)	1.6346(16)
C3	1.4428(5)	0.1522(5)	1.6971(11)
C4	1.5113(8)	0.0746(9)	1.7620(18)
C5	1.4811(9)	-0.0289(9)	1.7653(19)
C6	1.3778(10)	-0.0478(9)	1.7190(18)
N20	1.2748(7)	0.2160(8)	1.5927(15)
O21	1.1784(7)	0.2078(7)	1.5456(15)
O22	1.3106(8)	0.2969(7)	1.5559(19)
N40	1.6139(8)	0.0992(8)	1.7994(21)
O41	1.6449(8)	0.1821(10)	1.8086(26)
O42	1.6807(8)	0.0237(10)	1.8594(22)
O15	0.2087(6)	0.5019(6)	0.1021(15)
C15	0.3003(8)	0.4724(9)	0.1425(16)
C25	0.3380(9)	0.3710(10)	0.1754(19)

TABLE LXXI (Continued)

C45	0.5149(10)	0.4280(11)	0.2239(19)
C55	0.4795(10)	0.5339(10)	0.2283(21)
C65	0.3780(10)	0.5558(10)	0.1832(22)
N25	0.2644(10)	0.2819(9)	0.1246(18)
O26	0.1773(7)	0.2929(7)	0.1053(15)
O27	0.3058(7)	0.1908(7)	0.1312(17)
N45	0.6293(8)	0.4070(10)	0.2836(19)
O46	0.6507(9)	0.3093(9)	0.2713(26)
O47	0.6837(7)	0.4708(7)	0.3123(15)
H11	1.1036	0.0722	1.3816
H12	1.0512	0.1287	1.2391
H21	0.8985	0.0927	1.0513
H22	0.8247	0.0900	0.8454
H31	1.1446	0.0815	0.8084
H32	1.1131	0.1032	0.9925
H3	1.4679	0.2228	1.6949
H5	1.5311	-0.0834	1.8047
H6	1.3575	-0.1216	1.7291
H55	0.5319	0.5889	0.2632
H65	0.3535	0.6262	0.1679

TABLE LXXII

ANISOTROPIC THERMAL PARAMETERS FOR

$(Mg(H_2O)_6)(2,4\text{-dinitrophenoxide})_2(H_2O)_2$ (XVIII)

ATOM	U11	U22	U33	U12	U13	U23
Mg1	15(1)	24(1)	33(1)	-2(1)	2(1)	-1(1)
O11	43(3)	47(3)	39(2)	3(2)	-2(2)	-8(2)
O12	20(2)	37(2)	62(3)	3(1)	-2(2)	-6(2)
O13	48(3)	48(3)	54(3)	-15(2)	28(2)	-6(2)
O14	47(3)	29(2)	60(3)	1(2)	17(2)	0(2)
O1	35(5)	21(4)	40(5)	-2(3)	12(4)	-6(4)
C1	41(7)	11(6)	36(7)	-2(4)	3(5)	1(4)
C2	23(6)	28(6)	11(5)	-6(4)	8(4)	0(4)
C3	26(3)	30(3)	43(4)	-1(2)	5(2)	1(3)
C4	9(5)	31(7)	24(6)	0(4)	7(4)	6(5)
C5	23(6)	26(7)	28(6)	11(5)	6(4)	-2(4)
C6	39(7)	12(5)	17(6)	-11(4)	6(5)	3(4)
N20	5(5)	17(6)	32(5)	-3(3)	11(3)	-5(4)
O21	18(5)	21(5)	45(6)	6(3)	-4(4)	9(4)
O22	49(6)	18(5)	70(9)	6(4)	23(5)	3(5)
N40	23(5)	19(6)	79(9)	17(4)	28(5)	5(5)
O41	7(5)	37(7)	175(14)	-15(4)	11(6)	2(8)
O42	13(5)	79(9)	113(11)	7(5)	5(5)	35(8)
O15	6(4)	26(4)	55(6)	-6(3)	11(3)	0(4)
C15	19(5)	32(7)	12(5)	-8(4)	9(4)	-3(4)
C25	24(6)	24(6)	33(6)	-8(4)	-1(4)	3(5)

TABLE LXXII (Continued)

C45	21(6)	49(8)	27(6)	-16(5)	3(4)	5(5)
C55	26(7)	23(7)	44(8)	-13(5)	4(5)	-2(5)
C65	24(7)	29(7)	51(8)	-14(5)	9(5)	15(6)
N25	53(8)	14(6)	48(6)	-6(5)	8(5)	-11(5)
O26	5(4)	32(5)	59(6)	-3(3)	10(4)	-1(4)
O27	34(5)	10(5)	129(7)	3(3)	7(4)	14(4)
N45	6(5)	71(8)	52(7)	12(5)	8(4)	9(6)
O46	50(7)	26(6)	135(14)	-2(5)	25(8)	-16(8)
O47	19(5)	24(5)	59(6)	-12(3)	5(4)	-1(4)

Anisotropic thermal parameters in the format:

$$\exp(-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12hka^*b^* +2U13hla^*c^*+2U23klb^*c^*)) \times 10^3$$ for Mg, C, N, and O

and Mg(pyridine)$_2$ (2,4-dinitrophenoxide)$_2$ (63), complexes in which magnesium displays binding to 2,4-dinitrophenoxide groups (intraligand O-Mg-O angles, 80.0-81.2^{o}) and two sp^2 hybridized nitrogen atoms of aromatic ring systems. Thus complexation patterns of magnesium may be altered in mixed ligand binding.

CHAPTER V

CONCLUSIONS

This investigation has provided insight into the fundementals of calcium involvement in the secretory process of histamine release from mast cells. Calcium and magnesium have been shown to interact directly with allergens of low molecular weight, but the alkaline earth cations exhibit contrasting binding patterns and geometries when bound to the ligands studied. Structural documentation of these contrasting patterns has led to a clearer understanding of the reasons for the differentiation between calcium and magnesium in this biological system.

Calcium complexation to several low molecular weight organic compounds previously identified as allergens has been studied. The general binding patterns of calcium, which were reviewed in Chapter 1, held true in the complexes of calcium with isonicotinamide (III) and with the anions of nicotinic acid (I), isonicotinic acid (IV), salicylic acid (V), p-aminosalicylic acid (VII), and phenoxymethylpenicillinic acid (XI). But in addition to the observation of calcium coordination to various numbers of ligands (six to eight) and irregular geometries of ligands about calcium, new information about the types of interactions in which

calcium may engage emerges from close examination of this structural work. The flexible geometry of calcium binding readily accommodates ligands which possess multiple sites for complexation, as is common for molecules of biological significance. For example, (Ca(p-aminosalicylate)(acetate)(H_2O))(H_2O) (VII) demonstrates calcium's flexibility in binding a single ligand in its binding to the oxygen of the carboxylate group of one ligand and the nitrogen of the para amino group of a second, symmetrically related p-aminosalicylate anions as well as to the two oxygen atoms of the carboxylate groups of acetate anions which bridge two symmetry related calcium atoms. Calcium has thus bound to all of the available ligands in one fashion or another. Ca(isonicotinate)$(H_2O)_4$ (IV) shows similar flexibility. The calcium atom is seven coordinate, bound to the oxygen atoms of a bidentate carboxylate group of one isonicotinate anion, the nitrogen atom of a second (independent) isonicotinate anion, and to four oxygen atoms of water molecules. In Ca(phenoxymethylpenicillinate) $(H_2O)_2$ (XI), the calcium atom is bound to six oxygen atoms; from the unidentate carboxylate group of two different ligands, the carbonyl oxygen atom of an amide group in the side chain of two ligands related by symmetry, and the oxygen atoms of two water molecules in distorted octahedral geometry. Thus calcium demonstrates the ability to vary its coordination number and geometry to allow coordination to any and all possible ligands. Within this group is observed calcium

binding to water oxygen atoms, mono and bidentate carboxylate groups, carbonyl oxygen atoms, aromatic nitrogen atoms and amine nitrogen atoms. Calcium atoms have bound in shuch a way to maximize use of possible ligands.

In all of the calcium complexes studied during the course of this work, oxygen atoms of water molecules are found in the inner coordination sphere of the calcium atom. The water molecules tend to "fill in" the coordination sites not occupied by the ligand(s), with little restriction in overall geometry. Water molecules are coordinated in complexes of higher and lower coordination numbers. This observation gives rise to the idea that, although the complexes were studied in crystalline form, the large number of water molecules involved in the calcium coordination sphere means that the solid state complexes may be fairly representative of calcium-allergen interactions in aqueous solution. Thus these studies provide a starting point for consideration of the possibility of transport of the allergen bound calcium ion into the mast cell. From the literature, it is clear that compounds which possess the ability to transport calcium (ionophores) across cell membranes may chemically induce histamine release from mast cells. In these ionophore-calcium complexes, the polar functions of the ionophore are directed toward a centrally located calcium atom while the exterior of the complex is nonpolar, permitting the complexed calcium ion to pass through channels in the cell wall without attraction to

charges located in the channel. Ionophoric like complexation is clearly displayed in the (Ca(nicotinate)$_2$(H_2O)$_2$)(H_2O)$_3$ (I), ($Ca_{1.5}$(salicylate)$_2$ (acetate)(H_2O)$_2$)(acetic acid) (V), and Ca(phenoxymethylpenicillinate)$_2$(H_2O)$_2$ (XI) structures. Figure 4, an extended view of compound (I), shows a string of calcium atoms lying in the polar interior of a polymeric array of complexed ligands, yet the exterior surface of this complex consists of relatively nonpolar aromatic rings. This surface would pass through the cell wall without hindrance. Compound (V) reveals a similar arrangement of the ligands in Figure 8. The two calcium atoms exist in the center of the complex bound to the polar functions of the ligands, with the aromatic rings comprising the external surface of the complex. Ca(phenoxymethylpenicillinate)$_2$ (H_2O)$_2$ (XI) , in Figure 15, shows the polar groups of the ligands directed toward the calcium atom at the center of the cluster. This polar coordination sphere is surrounded by the nonpolar regions of the ligand.

With foreknowledge that calcium can bind to and release the ligands of its coordination sphere, it can be envisioned that the "channels" formed in the interior of these structures might provide multiple binding sites for calcium. This in turn would allow calcium to pass through the channel if the complex could diffuse into the lipid membrane of a cell. At the present date, the mode of calcium's entrance into mast cells (to trigger the release of histamine) is unclear. The results reported here suggest

that calcium complexes with low molecular weight allergens have ionophoric character.

Examination of the magnesium complexes studied during the course of this investigation, reveals a marked contrast in magnesium complexation patterns to these low molecular weight compounds as compared to those observed in the corresponding calcium complexes. All magnesium complexes involved in this study were observed to be octahedral in coordination geometry. Only the complex (Mg(2,6-pyridinedicarboxylate)$(H_2O)_3)(H_2O)_2$ (X), showed any significant distortion in octahedral coordination. Compound (X) was the only complex studied in which magnesium was bound to a nitrogen atom, although other nitrogen atoms were present in several ligands. The rigid requirement for octahedral geometry may be held responsible for the observed tendency of magnesium to bind water molecules when the multidentate ligands cannot adapt to octahedral geometry at magnesium. In the complexes, Mg(salicylate)$_2$ $(H_2O)_4$ (VI), Mg(p-aminosalicylate)$_2(H_2O)_4$ (VIII), and (Mg(2,6-pyridine-dicarboxylate)$(H_2O)_3)(H_2O)_2$ (X), magnesium is directly coordinated to the ligands. But magnesium is not observed to arrange ligated molecules to create polarnonpolar regions within the complexes in the same manner as does calcium. More often, magnesium and its coordination sphere of water molecules tends to be somewhat isolated from the ligand and only hydrogen bonded to it in a second sphere interaction. These sharp contrasts in binding requirements must be the

underlying reasons behind the differentiation between calcium and magnesium in many biological systems.

The compounds isolated when calcium and magnesium were complexed to the 2,4-dinitrophenoxide anion support the generalities of cation binding sphere differences described above. Yet 2,4-dinitrophenoxide is an inhibitor of histamine release and a comparison of the structure of calcium complexed to an inhibitor of histamine release with the calcium-allergen complexes previously discussed provides an interesting observation. The extended view of (Ca(2,4-dinitrophenoxide)$(H_2O)_6$)(2,4-dinitrophenoxide)(H_2O) (XVII) reveals calcium coordinated to polar groups of the ligand as expected, but the external surface of this compound contains uncoordinated and highly polar nitro groups (at the para position of the coordinated organic anion). This polar exterior would prevent any possible diffusion of the complex into the nonpolar regions of a lipid membrane. Thus it appears that molecules which behave as inhibitors complex to calcium in such a manner to prevent the calcium from reaching the interior of the mast cell and triggering histamine release.

Experiments aimed at the investigation of zinc as a possible cofactor of calcium in the histamine release mechanism were inconclusive. No zinc-calcium mixed metal complexes were isolated in a suitable crystalline form for X-ray diffraction analysis. In addition, no complexes involving the direct coordination of zinc to the ligands

were identified.

Finally, a complex in which calcium is bound to monovalent histamine has been isolated and characterized by X-ray diffraction techniques. The mechanism by which calcium, once it has entered the mast cell, is involved in histamine release from these cells is unknown. Following the required influx of the specific cation, no permanent increase in the level of intracellular calcium is observed. This suggests that calcium might also be involved in the egress of histamine from the mast cell during the secretion process. Thus one could envision a calcium complex with histamine of suitable ionophoric character providing an opportunity for both calcium and histamine to leave the cell. The complex of calcium and histamine isolated is probably unsuitable due to the positive charge at the nitrogen of the side chain. However other possible structures could be envisioned if the terminal amino group were unprotonated (Figure 16). The displacement of a chloride anion from calcium by the nitrogen of the side chain could form a complex with a structure similar to the calcium-allergen complexes, directing the polar nitrogen atoms toward a centrally located calcium atom and leaving the exterior of the cluster relatively nonpolar.

This investigation has thus increased the structural knowledge of complexation of calcium and magnesium to low molecular weight allergens and has allowed speculation as to the types of roles calcium may play in the

release of histamine from mast cells and basophils. This work points to further experimental approaches. Further complexes of calcium with antagonists warrant study to establish patterns of binding to this category of compounds and to allow a broader basis for comparison with calcium-allergen structural chemistry. Complexes of calcium and mixed ligand systems would allow observation of calcium binding patterns under conditions similar to those found in biological systems.

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VITA 2

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