Calcium Complexation to Penicillin V

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Calcium has been identified as a necessary participant in the sequence of events leading to chemically mediated histamine release from mast cells [1–3], a phenomenon experienced as an allergic reaction. The specific role of the alkaline earth cation is unknown, however, calcium transport into the mast cell has been demonstrated to initiate histamine release [4, 5].

Penicillins are among the most common chemical mediators [6] of histamine release. Therefore it is of importance to evaluate the ionophoric character of complexes formed by calcium and penicillin derivatives. Direct involvement of the alkaline earth cation with penicillin in stoichiometries of 1:1 and 1:2 in solution has been indicated by conductometric measurements [7]. We have isolated a crystalline 1:2 complex of calcium with phenoxypenicillin (penicillin V) and determined its solid state structure using single crystal X-ray diffraction: Ca(phenoxymethylpenicillinate)$_2$(H_2O)$_2$, a = 10.057(7), b = 29.178(18), c = 6.508(2) Å, β = 108.84(4)°, monoclinic space group $P2_1$, Z = 2, D_{calc} = 1.424 g cm^{-3}, R = 9.4% for 2081 observed reflections** in which calcium is six coordinate, bound to two unidentate carboxylate groups and to two amide carbonyl oxygen atoms of four different phenoxymethylpenicillinate molecules as well as to the oxygen atoms of two water molecules (Fig. 1). The 1:2 calcium:penicillin V complex leaves unbound the beta lactam carbonyl oxygen atom. Calcium–penicillin binding appears strong, Ca–O distances (2.33(2) Å av.) (Table I) being at the short end of the range of Ca–O distances (2.30–3.20 Å) observed in the literature. An overall view of the binding (Fig. 2) shows calcium atoms widely spaced and bridged by penicillin V molecules with the beta lactam carbonyl group an average of 3.1 Å from the amide nitrogen atom and thus involved in only weak hydrogen bonding. Similarly, the water oxygen atoms are an average of 3.2 Å from amide carbonyl oxygen

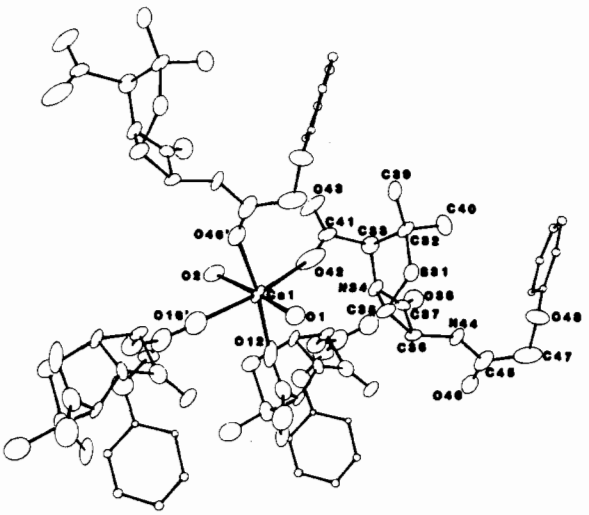

Fig. 1. Coordination sphere of calcium with identification of atoms of S31–O43 penicillin molecule and showing S31–O43 in x, y, z and $1+x, y, 1+z$ modifications; S1–O13 in x, y, z and $1+x, y, z$ modifications.

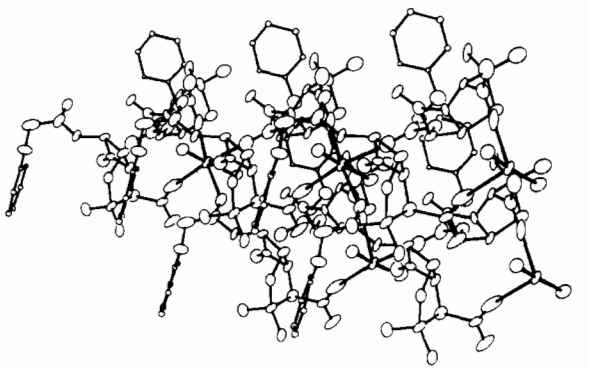

Fig. 2. Packing view of Ca(phenoxymethylpenicillinate)$_2$-(H_2O)$_2$.

TABLE I. Selected Bond Angles (°) and Distances (Å) for Ca($C_{16}H_{17}N_2O_5S$)$_2$(H_2O)$_2$

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)
		O2–Ca1–O42	93(1)
		O2–Ca1–O16	83(1)
		O2–Ca1–O46	88(1)
		O12–Ca1–O42	98(1)
		O12–Ca1–O16	90(1)
		O12–Ca1–O46	171(1)
		O42–Ca1–O16	171(1)
		O42–Ca1–O46	91(1)
		O16–Ca1–O46	81(1)

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**Formula, $C_{32}H_{38}CaN_4O_{12}S_2$; MWT 774.9 g mol^{-1}; V = 1807(2) Å^3; F(000), 812; μMo Kα, 3.423 cm^{-1}; data collected on a Syntex P3 automated diffractometer using Mo Kα radiation, λ = 0.71069 Å; 4647 refl. measured in octants $\pm h$, $+k$, $+l$; observed data criterion, $I > 3.0\,\sigma(I)$.

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atoms, distances not indicative of strong hydrogen bonding. The complex appears to present nonpolar methyl and phenyl groups to the external environment. However the complex does not resemble traditional carrier ionophores in which the ion is embedded in an organic mass which presents a uniformly nonpolar exterior. This complex might better be viewed as polymeric, perhaps simultaneously forming in external regions, passing intact through a channel in the cell wall and dissociating in the cell interior, capable of calcium transport in a continuous mode rather than the traditional 'one complex transporting one ion' mode usually envisioned.

Two previous structural observations of penicillins complexed to alkali cations have been recorded. Penicillin G complexed to potassium [8–10] utilizes all three possible ligation sites to provide seven ligation sites to K^+ from four different ligands. Sodium complexation to 5-methyl-3-phenyl-4-isoxazolylpenicillin [11] involved bidentate carboxylate and lactam carbonyl binding of two different pencillin molecules (amide carbonyl groups uncoordinated). There are no previous structural observation of penicillins bound to alkaline earth cations. In agreement with the observations of penicillins bound to alkali metals, penicillin V bound to calcium displays β methyl axial, α methyl equatorial, α carboxyl axial conformation of substituents on the thiazolide ring.

Calcium complexation to Penicillin V does not show the layer structure of close but noninterative calcium atoms (Ca–Ca, 4.055 Å) bridged by ligating groups seen in $Ca(nicotinate)_2(H_2O)_2(H_2O)_3$ [12]. As in calcium complexation to histamine itself [13] and to the calcium inhibitor, 2,4-dinitrophenoxide [14], water molecules serve as ligating groups along with the larger organic molecules.

Supplementary Material

Tables of thermal and positional parameters and structure factors may be obtained from the Editor-in-Chief.

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