THE STRUCTURE OF THE CALCIUM COMPLEX OF A23187, A DIVALENT CATION IONOPHORE ANTIBIOTIC

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The crystal and molecular structures of the calcium complex of A23187 has been determined by X-ray diffraction studies.

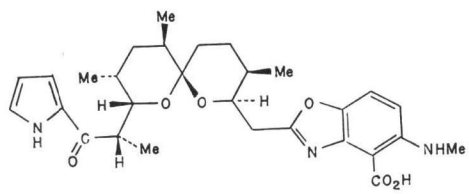


Table 1. Crystal parameters.

Empirical formula	$Ca(C_{29}H_{36}N_3O_6)_2 \cdot 2(C_2H_5OH)$
Molecular weight	1177.5
a	24.120(8) Å
b	17.608(9) Å
c	14.930(9) Å
Space group	$P2_12_12_1$
Molecules/cell	4
Observed density	1.231 g cm^{-1}
Calculated density	1.233 g cm^{-1}

The structure of the free acid form of the divalent cation ionophore antibiotic, A23187, has been previously reported.[1] This antibiotic, which uncouples oxidative phosphorylation and inhibits ATPase,[2] has been widely used to study calcium ion transport across membranes *in vivo* and *in vitro* and as a probe for calcium-potentiated biological processes.[3] The crystal and molecular structures of the calcium complex of A23187 have now been determined by X-ray diffraction studies.

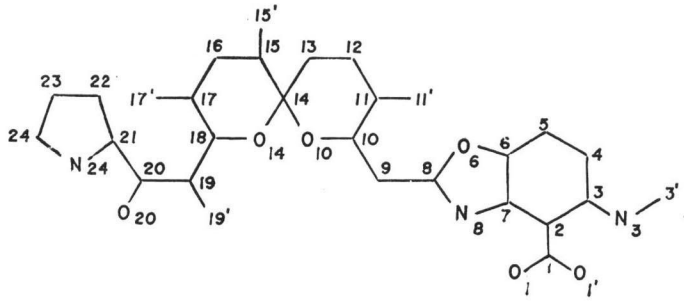
Experimental

The complex, crystallized as colorless prisms from 50 % ethanol, contains two antibiotic molecules and two ethanol molecules per calcium atom. The crystal parameters for the complex are given in Table 1. The intensities of 3,683 independent reflections were measured on a Syntex $P2_1$ computer-automated diffractometer using monochromated copper radiation. Of these data, 2,396 were greater than two standard deviations above background and were taken as observed reflections. The structure was solved by using approximate atomic positions previously determined by the heavy-atom method for the nearly isomorphous manganese-A23187 complex.[4] The calcium complex positions were refined by the least-squares method to a residual of $R=0.13$ with anisotropic temperature factors for all the atoms. Because of disordering in the solvent molecules and the limited intensity data, attempts to refine the structure further have been unsuccessful. The absolute configuration of the complex was not determined, but it was assumed to be the same as that proposed for the free acid.[1] The final atomic coordinates are given in Table 2. The positions of the disordered solvent molecules are not included.

Discussion

In the calcium complex, shown in Fig. 1, the two antibiotic molecules are related by a *pseudo*-twofold axis passing through the calcium atom. The calcium coordination is octahedral

Table 2. Atomic coordinates with standard deviations ($\times 10^3$) for all heavy atoms except solvent.



Atom	Molecule 1			Molecule 2		
	x	y	z	x	y	z
Ca	−190(.3)	210(.5)	231(.5)			
C (1)	−214(1)	262(2)	36(2)	−180(1)	151(1)	414(2)
O (1)	−186(1)	234(1)	100(1)	−194(1)	194(1)	359(1)
O (1′)	−192(1)	286(1)	− 30(1)	−173(1)	160(1)	501(1)
C (2)	−270(1)	261(2)	41(2)	−184(1)	65(2)	399(2)
C (3)	−306(1)	290(2)	− 34(2)	−182(2)	2(2)	467(3)
N (3)	−285(1)	311(2)	−106(1)	−180(1)	20(2)	551(2)
C (3′)	−324(2)	332(2)	−179(2)	−170(1)	− 39(2)	627(2)
C (4)	−366(1)	290(2)	− 17(2)	−176(2)	− 78(2)	434(2)
C (5)	−394(1)	268(2)	63(2)	−179(1)	− 95(2)	346(2)
C (6)	−358(1)	242(1)	131(2)	−180(1)	− 35(2)	288(2)
O (6)	−374(1)	220(1)	221(1)	−181(1)	− 37(1)	186(1)
C (7)	−299(1)	241(1)	128(2)	−183(1)	41(1)	310(2)
C (8)	−323(1)	206(1)	255(2)	−181(1)	37(2)	155(2)
N (8)	−281(1)	216(1)	208(1)	−185(1)	85(1)	225(2)
C (9)	−327(1)	190(2)	356(2)	−176(1)	52(2)	58(2)
C (10)	−314(1)	264(1)	402(2)	−116(1)	73(2)	46(2)
O (10)	−359(1)	314(1)	375(1)	− 82(1)	15(1)	79(1)
C (11)	−306(1)	260(2)	511(2)	−105(1)	92(2)	− 52(2)
C (11′)	−359(1)	221(2)	553(2)	−118(1)	28(2)	−118(2)
C (12)	−301(1)	342(2)	546(2)	− 46(2)	117(2)	− 60(2)
C (13)	−348(1)	400(2)	514(2)	− 6(1)	54(2)	− 18(2)
C (14)	−349(2)	392(2)	409(3)	− 26(1)	30(2)	82(2)
O (14)	−301(1)	424(1)	376(1)	− 10(1)	96(1)	134(1)
C (15)	−401(1)	437(2)	364(2)	8(1)	− 43(2)	123(2)
C (15′)	−457(1)	404(2)	396(3)	− 10(2)	−111(2)	69(3)
C (16)	−402(1)	444(2)	271(2)	− 3(1)	− 54(2)	215(2)
C (17)	−344(1)	477(2)	230(2)	8(1)	19(2)	267(3)
C (17′)	−332(1)	570(2)	255(2)	73(1)	44(2)	270(2)
C (18)	−297(1)	426(1)	279(2)	− 26(1)	90(1)	224(2)
C (19)	−236(1)	449(1)	260(2)	− 13(1)	170(2)	261(2)
C (19′)	−225(1)	456(2)	155(2)	− 27(1)	178(2)	362(2)
C (20)	−201(1)	386(1)	300(2)	− 60(1)	219(2)	218(2)
O (20)	−196(1)	327(1)	258(1)	−106(1)	210(1)	237(1)

Table 2. (Continued)

Atom	Molecule 1			Molecule 2		
	x	y	z	x	y	z
C (21)	−173(1)	394(1)	384(2)	−39(1)	269(2)	152(2)
C (22)	−171(1)	463(2)	437(2)	12(1)	301(2)	124(2)
C (23)	−141(1)	439(2)	511(2)	3(2)	354(2)	54(2)
C (24)	−131(1)	362(2)	507(2)	−54(2)	353(2)	33(2)
N (24)	−154(1)	333(1)	424(1)	−76(1)	302(1)	95(2)

Fig. 1. Conformation of calcium-A23187 complex in the crystal. Black atoms are oxygen, and gray-shaded atoms are nitrogen. The arrow indicates the *pseudo*-twofold axis. For simplicity, the hydrogen bonds and solvent molecules are not shown.

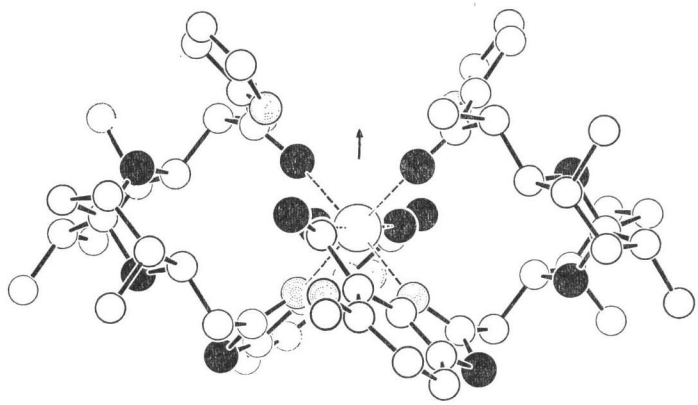


Table 3. Selected bond distances and angles with standard deviations. Asterisk indicates atom in molecule 2.

Atom 2	Atom 1	Atom 3	Distance (Å) Angle (°)
Ca	O(1)		2.01(2)
	O(1)*		1.92(2)
	N(8)		2.21(2)
	N(8)*		2.22(2)
	O(20)		2.10(2)
	O(20)*		2.02(2)
Ca	O(1)	O(1)*	176.3(7)
		N(8)	83.7(8)
		N(8)*	99.3(8)
		O(20)*	89.2(7)
		O(20)	89.5(7)
	O(1)*	N(8)	96.6(8)
		N(8)*	84.3(8)
		O(20)	87.2(7)
		O(20)*	90.1(7)
	N(8)	N(8)*	95.1(8)
		O(20)	85.2(8)
		O(20)*	173.1(8)
	N(8)*	O(20)	171.5(8)
		O(20)*	87.1(8)
	O(20)	O(20)*	93.6(7)
O(1)	N(24)*		2.91(3)
O(1)*	N(24)		2.80(3)
O(1′)	N(3)		2.54(3)
O(1′)*	N(3)*		2.58(3)

(dotted lines) with three ligands, O(1), N(8), and O(20), from each molecule. The bond distances and angles for the atoms involved in coordination are given in Table 3. The molecules of the complex are further held together by head-to-tail hydrogen bonds (Table 3) from N(24) of one molecule to O(1) of the other molecule. As in the free acid,[1] there is an intramolecular hydrogen bond from N(3) to O(1′) of each molecule. One of the disordered ethanol molecules is hydrogen-bonded to O(1′), and the other ethanol molecule is hydrogen-bonded to the first. Both solvent molecules are located on the exterior surface of the complex and appear to play no important role in its stability. There are no other intermolecular hydrogen bonds.

In the free acid structure,[1] the atoms O(1), N(8), and O(20) are arranged in a nearly equilateral triangular pattern in the interior of the molecule. These atoms appear to be ideally situated for coordination, and their relative orientation is preserved in the complex. In passing from the relatively

Table 4. Selected torsion angles for complex and free acid.

Atom 1	Atom 2	Atom 3	Atom 4	Molecule 1	Molecule 2	Free acid	Average Δ
O (6)	C (8)	C (9)	C (10)	−97°	−100°	132°	129°
C (8)	C (9)	C (10)	O (10)	66	57	174	−113
O (14)	C (18)	C (19)	C (20)	62	73	66	2
C (18)	C (19)	C (20)	C (21)	−103	−111	−158	51

planar free acid molecule to the complexed molecule, the principal rotations are in the bonds C(8)-C(9), C(9)-C(10), C(18)-C(19), and C(19)-C(20). Table 4 gives the torsion angles for these bonds in the complex and free acid, as well as the average angular rotation (Δ) going from the free acid to the complex. The sign convention for the torsion angles is as follows: viewed down the central bond (2-3) with atom 2 closest to the observer, a clockwise rotation of atom 1, to bring it into eclipse with atom 4, is defined as a positive angle.

Biological implications of the structure and a possible mechanism for formation of the calcium complex will be discussed in a subsequent publication.

Acknowledgments

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References

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