51. The Crystal Structure of a K^+ Complex of Valinomycin

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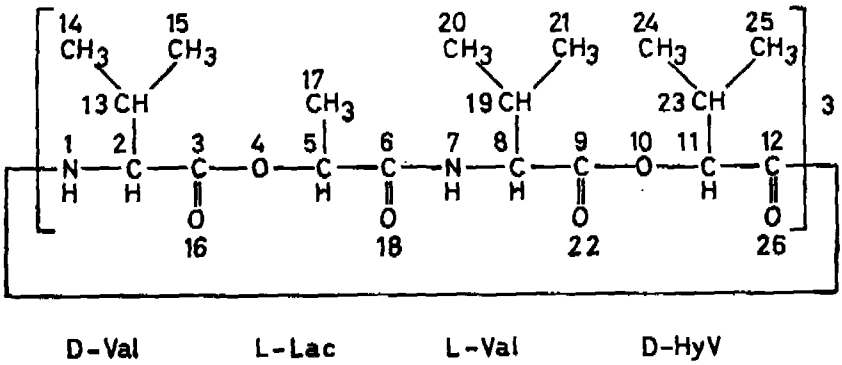
Summary. A KI_3/KI_5 complex of the cyclododecadepsipeptide antibiotic valinomycin crystallizes in the space group $C222_1$, $a = 13.34$, $b = 24.65$, $c = 46.96$ Å. The crystal structure investigation shows that K^+ is coordinated octahedrally by six carbonyl oxygen atoms. The macrocyclic ring skeleton adopts non-crystallographic S_6 symmetry. Six hydrogen bonds involving amide nitrogen atoms and carbonyl oxygen atoms form a belt around the molecule.

The cyclododecadepsipeptide antibiotic valinomycin (1) has been shown to act as an ionophore with both biological and artificial membranes [1–3] and to exhibit a marked specificity for potassium ions.



(1)

The conformations of valinomycin and its K^+ complex in solution have been studied by IR., ORD., CD. and NMR. techniques [4–7]. For uncomplexed valinomycin a solvent-dependent equilibrium mixture of at least three conformations with a varying number of amide hydrogen bonds was found. Whereas in unpolar solvents all six amide hydrogen atoms are involved in intramolecular hydrogen bonds, in polar solvents there are only three such bonds, with the other three amide hydrogen atoms probably forming hydrogen bonds to solvent molecules. The secondary structure of the K^+ complex was characterized as a series of β-turns [6] involving all amide hydrogen atoms in intramolecular hydrogen bonds. On this basis conformational energy calculations were used to determine a minimum energy model constrained to S_6 symmetry of the 36-membered ring skeleton with β-carbon atoms included [8]. The calculated model seems to be in good agreement with results of an earlier crystal structure analysis of the $KAuCl_4$ complex [9]. Although atomic coordinates for this structure were not published, and positions of side chains were not completely defined, it was established that the K^+ ion is octahedrally coordinated

to carbonyl oxygen atoms and that the six amide hydrogen atoms form a belt of hydrogen bonds around the molecule.

The crystal structure of the KI_3/KI_5 complex reported here confirms these results and also establishes the positions of the side chains. We find that the non-crystallographic threefold rotation symmetry also holds (with the exception of C(25*)) for the side chains. If the difference between the side chains in L-Lac (methyl) and D-HyV (isopropyl) is ignored, the approximate symmetry is raised to S_6. The $K^+ \ldots O$ distances are 2.69–2.83 Å (mean 2.756 Å) and the N–H ... O hydrogen bond distances are 2.88–2.98 Å (mean 2.932 Å). Two types of anion, I_3^- and I_5^-, both on crystallographic twofold rotation axes, are present in the crystal.

A crystal structure determination of uncomplexed valinomycin [10] [11] gave a conformation which is completely different from the one in the K^+ complex. All six amide hydrogen atoms form intramolecular hydrogen bonds but two of these involve other carbonyl oxygen atoms than in the K^+ complex. Of the other six carbonyl oxygen atoms two point inwards, two outwards and two upwards.

Crystallographic Data. – Crystalline complexes of valinomycin appear to show a strong tendency to polymorphism. The following crystal modifications were obtained.

a) with KI: (1) from chloroform/hexane; trigonal $P321$, $a = b = 13.7$, $c = 25.7$ Å, $U = 4177$ Å^3, $Z = 2$. (2) from ethyl acetate; trigonal $R32$, $a = b = 23.5$, $c = 74.2$ Å, $U = 35487$ Å^3, $Z = 18$. (3) from acetone/hexane; monoclinic $P2$, $a = 14.4$, $b = 10.4$, $c = 22.9$ Å, $\beta = 99.5°$, $U = 3382$ Å^3, $Z = 2$.

b) with KI and I_2: (4) from ethyl acetate; triclinic $P1$, $a = 13.6$, $b = 13.8$, $c = 23.3$ Å, $\alpha = 92°$, $\beta = 97.2°$, $\gamma = 118.4°$, $U = 3824$ Å^3, $Z = 2$. (5) from ethyl acetate; triclinic $P1$, $a = 16.3$, $b = 15.0$, $c = 20.3$ Å, $\alpha = 97.1°$, $\beta = 104.7°$, $\gamma = 126°$, $U = 3641$ Å^3, $Z = 2$. (6) from ethyl acetate/water; orthorhombic $C222_1$, $a = 13.34$, $b = 24.65$, $c = 46.96$ Å, $U = 15443$ Å^3, $Z = 8$.

Several other modifications of poor quality showed either disorder or twinning. The variation in the apparent molecular volume (1700–2100 Å^3) in the KI complexes suggests that variable amounts or kinds of solvent molecules are included in the crystals. The variation in the KI/I_2 complexes is less pronounced (1820–1930 Å^3) but still considerable.

Modification (6) was chosen for crystal structure analysis. KI_3/KI_5 complex of valinomycin, $C_{54}O_{18}N_6H_{90} \cdot KI_4$, M. W. = 1628. Orthorhombic, $a = 13.342(20)$, $b = 24.648(37)$, $c = 46.961(70)$ Å, $U = 15443$ Å^3, $Z = 8$. Space group $C222_1$ (D_2^5), $D_x = 1.40$ g cm^{-3}. Cell constants were obtained from 30° precession photographs (CuKα radiation) and diffractometer measurements (MoKα radiation).

Data Collection. – The intensities of the 5900 reflections in the range $\theta < 23°$ were measured with a computer-controlled four-circle diffractometer (*Hilger & Watts* Y290) using graphite-monochromatized MoKα radiation, from a crystal with dimensions $0.25 \times 0.3 \times 0.15$ mm. The reflections were processed in the usual way, giving 4656 unique reflections with $F_o > 3\sigma(F_o)$. Corrections for absorption effects were not applied ($\mu = 12.5$ cm^{-1} for MoKα radiation), giving rise to some errors in the measured intensities.

Structure Analysis. – Our initial attempts to solve the structure were based on the assumption that the crystal was a KI_3 complex. From a sharpened *Patterson* map the position of a linear I_3^- ion with its central atom on a twofold rotation axis at (0, y, 1/4) was found. Further prominent vectors indicated the presence of a second I_3^- unit on the twofold axis at (x, 0, 0). Here, however, the angle at the central atom was about 90°, which was quite incompatible with the expected linearity of the I_3^- anion. A *Fourier* map calculated with phases from the linear ion alone clearly showed the three other peaks again, with indications of two weaker peaks on the extension of the angular triatomic unit. These peaks were first thought to be spurious, but after several attempts to find alternative interpretations of the *Patterson* and *Fourier* map had failed, we had to conclude that they were genuine, and that the angular unit was actually an I_5^- anion, bent at the central atom, linear at the two adjacent ones.

Once this model was adopted as a basis for phasing calculations, the potassium ion and all the non-hydrogen atoms in the valinomycin molecule could be placed in stages from three successive *Fourier* maps. Refinement was carried out by block-diagonal least-squares calculations. After five cycles with isotropic temperature factors, a (F_o-F_c)-*Fourier* map showed peaks corresponding to many of the hydrogen atoms. However, the H atoms were included in the structure model at positions calculated from stereochemical assumptions (C–H, equal angles with the three attached bonds; CH_3 groups, staggered conformation, H–C–H bond angle 109°, H–C distance 1.09 Å). The (F_o-F_c)-maps also show residual electron density (1.3 e A^{-3}) between valinomycin molecules, which may suggest that disordered solvent molecules are occluded in the crystal structure. The refinement was completed with four cycles of block-diagonal least-squares calculations using anisotropic temperature factors for the K^+ and iodine atoms. In the final cycle three atoms with scattering factors $f_c/2$ were introduced to simulate the residual electron density attributed to the disordered solvent molecules. The final R factor, based on the 4656 reflections with $F_o > 3\sigma(F_o)$ was 5.9%[1]).

Results. – The results are summarized in Tables. Fractional atomic coordinates, vibrational parameters and calculated hydrogen atom positions are given in Tables 1, 2 and 3. Standard deviations (in parentheses) were estimated by inversion of the least-squares normal equations. Bond lengths and angles and some torsion angles relevant to the ligand conformation are given in Tables 4 and 5. The corresponding estimated standard deviations are 0.015–0.020 Å for C–C, C–O and C–N bonds of the ring system, 0.017–0.026 Å for C–C bonds of the methyl and isopropyl substituents and 1.0–1.5° for bond angles.

Discussion. – The structure of the K^+ complex of valinomycin is depicted in Fig. 1. The conformation of the ligand is characterized by a non-crystallographic approximate threefold rotation axis (corresponding to the threefold repetition of units in the chemical formula) and approximate S_6 symmetry of the 36-membered macrocyclic ring skeleton. To test how well these approximate symmetry elements hold, the atom coordinates were first transformed to the best plane through the

[1]) A table of observed structure amplitudes is available on request.

Table 1. *Fractional coordinates and isotropic temperature factors* (estimated standard deviations × 10^4)

	X	Y	Z	B		X	Y	Z	B
N(1)	.6983 (8)	.4667 (4)	.1534 (2)	4.0	C(17')	.0972 (12)	.1704 (6)	.1541 (3)	5.1
C(2)	.6464 (10)	.4882 (5)	.1785 (3)	4.1	O(18')	.3150 (7)	.1690 (4)	.1293 (2)	4.3
C(3)	.5352 (10)	.4782 (5)	.1737 (3)	3.9	C(19')	.2475 (11)	.2348 (6)	.0492 (3)	4.5
O(4)	.4814 (7)	.5230 (4)	.1793 (2)	4.5	C(20')	.1392 (13)	.2174 (7)	.0425 (3)	5.6
C(5)	.3719 (12)	.5163 (6)	.1784 (3)	5.1	C(21')	.3126 (13)	.2193 (7)	.0236 (3)	6.0
C(6)	.3377 (11)	.5138 (6)	.1470 (3)	4.7	O(22')	.4184 (7)	.2685 (4)	.0918 (2)	4.3
N(7)	.3946 (10)	.5265 (5)	.1260 (2)	4.6	C(23')	.6217 (13)	.1612 (7)	.0587 (3)	5.6
C(8)	.3601 (10)	.5217 (5)	.0965 (3)	3.8	C(24')	.6053 (13)	.1020 (7)	.0624 (4)	5.9
C(9)	.3304 (10)	.4633 (5)	.0917 (3)	3.7	C(25')	.6042 (15)	.1793 (8)	.0283 (4)	7.5
O(10)	.2396 (6)	.4586 (3)	.0796 (2)	3.6	O(26')	.6892 (7)	.1968 (4)	.1150 (2)	5.1
C(11)	.2041 (11)	.4055 (5)	.0715 (3)	4.1	N(1*)	.5378 (8)	.1734 (4)	.1304 (2)	3.8
C(12)	.1641 (10)	.3738 (5)	.0959 (3)	3.5	C(2*)	.5733 (11)	.1729 (6)	.1600 (3)	4.1
C(13)	.6823 (11)	.4606 (6)	.2054 (3)	4.4	C(3*)	.6110 (10)	.2304 (5)	.1669 (3)	3.8
C(14)	.7949 (14)	.4734 (7)	.2116 (4)	6.2	O(4*)	.7017 (7)	.2288 (4)	.1790 (2)	4.4
C(15)	.8187 (12)	.4775 (7)	.2312 (4)	5.6	C(5*)	.7427 (11)	.2806 (6)	.1882 (3)	4.5
O(16)	.4982 (8)	.4352 (4)	.1670 (2)	5.0	C(6*)	.7769 (11)	.3158 (5)	.1630 (3)	3.9
C(17)	.3290 (16)	.5675 (8)	.1921 (4)	8.2	N(7*)	.7884 (9)	.2913 (4)	.1376 (2)	3.9
O(18)	.2490 (7)	.4960 (4)	.1437 (2)	5.3	C(8*)	.8194 (9)	.3258 (5)	.1134 (3)	3.5
C(19)	.4382 (12)	.5388 (7)	.0741 (3)	5.4	C(9*)	.7422 (9)	.3707 (5)	.1103 (3)	3.4
C(20)	.4571 (16)	.6003 (8)	.0787 (4)	7.7	O(10*)	.7886 (6)	.4186 (3)	.1074 (2)	3.3
C(21)	.4060 (13)	.5258 (7)	.0448 (3)	5.9	C(11*)	.7265 (10)	.4656 (5)	.1007 (3)	4.0
O(22)	.3802 (7)	.4245 (4)	.0984 (2)	4.3	C(12*)	.6735 (10)	.4874 (5)	.1277 (3)	4.0
C(23)	.1265 (12)	.4127 (6)	.0480 (3)	5.0	C(13*)	.4942 (11)	.1539 (6)	.1809 (3)	4.7
C(24)	.0372 (15)	.4450 (8)	.0591 (4)	7.3	C(14*)	.4655 (14)	.0943 (7)	.1750 (4)	6.7
C(25)	.1711 (17)	.4391 (9)	.0220 (4)	8.8	C(15*)	.5299 (13)	.1610 (7)	.2116 (4)	6.4
O(26)	.1312 (7)	.3277 (4)	.0905 (2)	4.3	O(16*)	.5647 (7)	.2711 (4)	.1624 (2)	4.6
N(1')	.1583 (9)	.3948 (4)	.1216 (2)	3.9	C(17*)	.8293 (13)	.2673 (7)	.2087 (3)	6.0
C(2')	.1196 (10)	.3623 (5)	.1450 (3)	4.0	O(18*)	.8004 (7)	.3634 (4)	.1676 (2)	4.8
C(3')	.1829 (10)	.3116 (5)	.1473 (3)	3.8	C(19*)	.8273 (10)	.2914 (5)	.0863 (3)	3.7
O(4')	.1272 (7)	.2660 (4)	.1478 (2)	4.0	C(20*)	.9054 (13)	.2472 (7)	.0900 (4)	5.9
C(5')	.1779 (10)	.2139 (6)	.1515 (3)	4.2	C(21*)	.8570 (13)	.3274 (7)	.0615 (3)	5.8
C(6')	.2442 (10)	.2011 (5)	.1262 (3)	3.4	O(22*)	.6551 (7)	.3647 (3)	.1098 (2)	4.2
N(7')	.2244 (8)	.2226 (4)	.1007 (2)	3.4	C(23*)	.7938 (11)	.5077 (6)	.0869 (3)	4.3
C(8')	.2861 (10)	.2082 (5)	.0761 (3)	3.5	C(24*)	.8695 (12)	.5288 (6)	.1072 (3)	5.6
C(9')	.3928 (11)	.2246 (6)	.0824 (3)	4.2	C(25*)	.7330 (13)	.5523 (6)	.0727 (3)	5.7
O(10')	.4581 (7)	.1848 (3)	.0761 (2)	3.8	O(26*)	.6119 (7)	.5238 (4)	.1251 (2)	4.5
C(11')	.5636 (11)	.1974 (5)	.0798 (3)	4.1	I(1)	.2089 (1)	.1494 (1)	.2311 (0)	
C(12')	.5997 (10)	.1879 (6)	.1091 (3)	4.3	I(2)	.0000 (0)	.1509 (1)	.2500 (0)	
C(13')	.1176 (12)	.3935 (6)	.1735 (3)	5.0	I(3)	.5017 (2)	.3540 (1)	.0318 (0)	
C(14')	.0463 (14)	.4411 (7)	.1711 (4)	6.8	I(4)	.6558 (1)	.4225 (1)	.0162 (0)	
C(15')	.0867 (15)	.3581 (8)	.1980 (4)	7.4	I(5)	.8277 (2)	.5000 (0)	.0000 (0)	
O(16')	.2751 (7)	.3106 (4)	.1491 (2)	4.4	K+	.4651 (2)	.3467 (1)	.1305 (1)	
					SOL1	.4404 (38)	.3266 (18)	.2400 (10)	9.3
					SOL2	.5300 (38)	.3207 (17)	.2422 (10)	8.7
					SOL3	.3955 (38)	.3321 (19)	.2199 (10)	9.5

36 ring atoms. Rotation of $\pm 120°$ around an axis perpendicular to the best plane and passing through the K^+ ion gave deviations of 0.03–0.34 Å (mean 0.13 Å) between 'symmetry equivalent' positions for ring atoms and of 0.05–0.64 Å (mean 0.23 Å) for side chain atoms. The deviations from S_6 symmetry (not including the isopropyl groups of D-Val) are of similar magnitude. The non-crystallographic symmetry therefore holds reasonably well for the side chains, with the exception of

Table 2. *Anisotropic vibrational parameters, expressed in the form* $\exp(-2\pi(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + 2U_{12}a^*b^*hk + 2U_{13}a^*c^*hl + 2U_{23}b^*c^*kl))$

	U11	U22	U33	U12	U13	U23
K+	.043	.037	.067	-.002	-.003	-.003
I(1)	.094	.114	.078	-.005	.000	.000
I(2)	.088	.068	.067	.000	-.014	.000
I(3)	.225	.086	.190	-.007	.105	.006
I(4)	.119	.098	.067	.032	.014	.012
I(5)	.081	.231	.078	.000	.000	.012

Table 3. *Calculated hydrogen atom fractional coordinates*

	X	Y	Z		X	Y	Z
H(1)	.750	.438	.155	H(17')	.053	.178	.171
H(2)	.674	.526	.180	H(19')	.253	.275	.051
H(5)	.335	.482	.184	H(20')	.116	.235	.025
H(7)	.464	.540	.130	H(20')	.094	.228	.058
H(8)	.291	.538	.096	H(20')	.136	.177	.040
H(11)	.275	.392	.069	H(21')	.286	.237	.006
H(13)	.666	.421	.204	H(21')	.312	.179	.021
H(14)	.817	.455	.229	H(21')	.383	.231	.027
H(14)	.804	.513	.214	H(23')	.696	.163	.060
H(14)	.838	.461	.195	H(24')	.645	.081	.048
H(15)	.644	.459	.249	H(24')	.533	.093	.060
H(15)	.547	.467	.228	H(24')	.627	.091	.082
H(15)	.623	.518	.234	H(25')	.642	.156	.015
H(17)	.254	.566	.192	H(25')	.627	.218	.026
H(17)	.351	.600	.181	H(25')	.531	.177	.024
H(17)	.354	.571	.212	H(1*)	.467	.163	.126
H(19)	.509	.526	.075	H(2*)	.640	.155	.161
H(20)	.508	.614	.065	H(5*)	.674	.295	.192
H(20)	.483	.607	.098	H(7*)	.776	.251	.135
H(20)	.393	.621	.076	H(8*)	.892	.335	.115
H(21)	.459	.538	.031	H(11*)	.656	.457	.095
H(21)	.342	.545	.040	H(13*)	.424	.169	.180
H(21)	.395	.486	.043	H(14*)	.477	.148	.225
H(23)	.087	.379	.045	H(14*)	.544	.200	.215
H(24)	-.014	.450	.044	H(14*)	.592	.139	.215
H(24)	.060	.482	.066	H(15*)	.413	.082	.189
H(24)	.005	.425	.075	H(15*)	.526	.071	.177
H(25)	.119	.443	.007	H(15*)	.438	.091	.155
H(25)	.227	.416	.014	H(17*)	.861	.302	.216
H(25)	.198	.476	.027	H(17*)	.881	.245	.199
H(1')	.181	.433	.125	H(17*)	.803	.246	.225
H(2')	.045	.357	.143	H(19*)	.755	.281	.085
H(5')	.247	.216	.159	H(20*)	.910	.225	.072
H(7')	.167	.248	.098	H(20*)	.886	.223	.106
H(8')	.278	.168	.075	H(20*)	.972	.264	.094
H(11')	.578	.237	.078	H(21*)	.862	.305	.044
H(13')	.191	.401	.175	H(21*)	.923	.345	.065
H(14')	.086	.380	.216	H(21*)	.805	.356	.059
H(14')	.135	.327	.200	H(23*)	.858	.492	.080
H(14')	.018	.343	.195	H(24*)	.913	.556	.098
H(15')	.044	.462	.189	H(24*)	.913	.498	.114
H(15')	-.023	.428	.167	H(24*)	.835	.546	.124
H(15')	.069	.466	.156	H(25*)	.779	.580	.064
H(17')	.129	.134	.157	H(25*)	.690	.571	.087
H(17')	.055	.170	.137	H(25*)	.689	.536	.058

Table 4. *Molecular topography*: *Bond lengths and angles*. Values related by the non-crystallographic threefold rotation axis are grouped together

N(1)	-C(2)	-C(3)	1.523	106.3	N(1')	-C(2')	-C(3')	1.512	108.1	N(1*)	-C(2*)	-C(3*)	1.538	107.2
N(1)	-C(2)	-C(13)	1.511	111.1	N(1')	-C(2')	-C(13')	1.545	112.8	N(1*)	-C(2*)	-C(13*)	1.514	112.9
C(3)	-C(2)	-C(13)		111.2	C(3')	-C(2')	-C(13')		111.0	C(3*)	-C(2*)	-C(13*)		112.2
C(2)	-C(13)	-C(14)	1.563	111.7	C(2')	-C(13')	-C(14')	1.514	109.3	C(2*)	-C(13*)	-C(14*)	1.542	110.7
C(2)	-C(13)	-C(15)	1.535	111.2	C(2')	-C(13')	-C(15')	1.503	112.3	C(2*)	-C(13*)	-C(15*)	1.529	110.9
C(14)	-C(13)	-C(15)		109.2	C(14')	-C(13')	-C(15')		109.6	C(14*)	-C(13*)	-C(15*)		110.7
C(2)	-C(3)	-Ø(4)	1.345	110.9	C(2')	-C(3')	-Ø(4')	1.349	112.5	C(2*)	-C(3*)	-Ø(4*)	1.337	111.0
C(2)	-C(3)	-Ø(16)	1.210	125.4	C(2')	-C(3')	-Ø(16')	1.234	125.4	C(2*)	-C(3*)	-Ø(16*)	1.197	124.6
Ø(4)	-C(3)	-Ø(16)		123.6	Ø(4')	-C(3')	-Ø(16')		122.1	Ø(4*)	-C(3*)	-C(16*)		124.4
C(3)	-Ø(4)	-C(5)	1.472	115.6	C(3')	-Ø(4')	-C(5')	1.462	118.6	C(3*)	-Ø(4*)	-C(5*)	1.457	116.2
Ø(4)	-C(5)	-C(6)	1.546	109.0	Ø(4')	-C(5')	-C(6')	1.516	111.1	Ø(4*)	-C(5*)	-C(6*)	1.538	112.1
Ø(4)	-C(5)	-C(17)	1.527	105.5	Ø(4')	-C(5')	-C(17')	1.525	107.5	Ø(4*)	-C(5*)	-C(17*)	1.539	106.4
C(6)	-C(5)	-C(17)		108.9	C(6')	-C(5')	-C(17')		109.2	C(6*)	-C(5*)	-C(17*)		112.4
C(5)	-C(6)	-N(7)	1.284	123.3	C(5')	-C(6')	-N(7')	1.334	120.4	C(5*)	-C(6*)	-N(7*)	1.345	117.6
C(5)	-C(6)	-Ø(18)	1.273	113.9	C(5')	-C(6')	-Ø(18')	1.241	118.9	C(5*)	-C(6*)	-Ø(18*)	1.233	118.5
N(7)	-C(6)	-Ø(18)		122.7	N(7')	-C(6')	-Ø(18')		120.7	N(7*)	-C(6*)	-Ø(18*)		123.6
C(6)	-N(7)	-C(8)	1.462	121.4	C(6')	-N(7')	-C(8')	1.461	120.0	C(6*)	-N(7*)	-C(8*)	1.478	117.0
N(7)	-C(8)	-C(9)	1.509	107.6	N(7')	-C(8')	-C(9')	1.510	108.3	N(7*)	-C(8*)	-C(9*)	1.520	107.7
N(7)	-C(8)	-C(19)	1.524	114.3	N(7')	-C(8')	-C(19')	1.516	111.3	N(7*)	-C(8*)	-C(19*)	1.533	109.9
C(9)	-C(8)	-C(19)		109.6	C(9')	-C(8')	-C(19')		111.6	C(9*)	-C(8*)	-C(19*)		111.6
C(8)	-C(19)	-C(20)	1.554	106.3	C(8')	-C(19')	-C(20')	1.541	111.7	C(8*)	-C(19*)	-C(20*)	1.518	110.4
C(8)	-C(19)	-C(21)	1.476	112.4	C(8')	-C(19')	-C(21')	1.530	110.8	C(8*)	-C(19*)	-C(21*)	1.515	109.4
C(20)	-C(19)	-C(21)		113.0	C(20')	-C(19')	-C(21')		107.6	C(20*)	-C(19*)	-C(21*)		109.1
C(8)	-C(9)	-Ø(10)	1.344	112.5	C(8')	-C(9')	-Ø(10')	1.345	111.9	C(8*)	-C(9*)	-Ø(10*)	1.339	109.8
C(8)	-C(9)	-Ø(22)	1.206	124.9	C(8')	-C(9')	-Ø(22')	1.215	125.0	C(8*)	-C(9*)	-Ø(22*)	1.173	125.6
Ø(10)	-C(9)	-Ø(22)		122.6	Ø(10')	-C(9')	-Ø(22')		123.1	Ø(10*)	-C(9*)	-Ø(22*)		124.6
C(9)	-Ø(10)	-C(11)	1.442	119.0	C(9')	-Ø(10')	-C(11')	1.452	116.5	C(9*)	-Ø(10*)	-C(11*)	1.460	117.3
Ø(10)	-C(11)	-C(12)	1.485	113.2	Ø(10')	-C(11')	-C(12')	1.476	113.1	Ø(10*)	-C(11*)	-C(12*)	1.548	111.1
Ø(10)	-C(11)	-C(23)	1.525	108.0	Ø(10')	-C(11')	-C(23')	1.543	106.7	Ø(10*)	-C(11*)	-C(23*)	1.517	107.4
C(12)	-C(11)	-C(23)		112.0	C(12')	-C(11')	-C(23')		110.0	C(12*)	-C(11*)	-C(23*)		112.5
C(11)	-C(23)	-C(24)	1.525	110.2	C(11')	-C(23')	-C(24')	1.487	114.7	C(11*)	-C(23*)	-C(24*)	1.482	111.8
C(11)	-C(23)	-C(25)	1.507	111.7	C(11')	-C(23')	-C(25')	1.511	110.9	C(11*)	-C(23*)	-C(25*)	1.521	111.4
C(24)	-C(23)	-C(25)		111.1	C(24')	-C(23')	-C(25')		112.3	C(24*)	-C(23*)	-C(25*)		113.1
C(11)	-C(12)	-N(1')	1.315	121.3	C(11')	-C(12')	-N(1*)	1.345	122.3	C(11*)	-C(12*)	-N(1)	1.351	119.1
C(11)	-C(12)	-Ø(26)	1.244	116.9	C(11')	-C(12')	-Ø(26')	1.247	119.6	C(11*)	-C(12*)	-Ø(26*)	1.222	118.8
N(1')	-C(12)	-Ø(26)		121.7	N(1*)	-C(12')	-Ø(26')		117.9	N(1)	-C(12*)	-O(26*)		122.1
C(12)	-N(1')	-C(2')	1.455	119.8	C(12')	-N(1*)	-C(2*)	1.472	120.6	C(12*)	-N(1)	-C(2)	1.468	117.7
K+	-Ø(16)		2.809		K+	-Ø(16')		2.826		K+	-Ø(16*)		2.738	
K+	-Ø(22)		2.688		K+	-Ø(22')		2.723		K+	-Ø(22*)		2.751	
Ø(18)	..N(1')		2.959		Ø(18')	..N(1*)		2.976		Ø(18*)	..N(1)		2.964	
Ø(26)	..N(7')		2.914		Ø(26')	..N(7*)		2.880		Ø(26*)	..N(7)		2.901	
I(1)	-I(2)	2.925	I(1)	-I(2)	-I(1)	178.6								
I(3)	-I(4)	2.760	I(3)	-I(4)	-I(5)	178.8								
I(4)	-I(5)	3.080	I(4)	-I(5)	-I(4)	83.8								

Table 5. *Torsion angles for the 36-membered ring, carbonyl groups, methyl- and isopropyl groups.* Values related by the non-crystallographic threefold rotation axis are grouped together

C(12*)-N(1)	-C(2)	-C(3)	58.6	C(12)	-N(1')	-C(2')	-C(3')	57.2	C(12')-N(1*)	-C(2*)	-C(3*)	57.6
N(1)	-C(2)	-C(3)	-Ø(4)	-132.7	N(1')	-C(2')	-C(3')	-Ø(4')	-128.7	N(1*)	-C(2*)	-C(3*)	-Ø(4*)	-131.2
C(2)	-C(3)	-Ø(4)	-C(5)	-173.5	C(2')	-C(3')	-Ø(4')	-C(5')	-176.8	C(2*)	-C(3*)	-Ø(4*)	-C(5*)	-176.0
C(3)	-Ø(4)	-C(5)	-C(6)	-76.2	C(3')	-Ø(4')	-C(5')	-C(6')	-66.0	C(3*)	-Ø(4*)	-C(5*)	-C(6*)	-73.1
Ø(4)	-C(5)	-C(6)	-N(7)	-12.3	Ø(4')	-C(5')	-C(6')	-N(7')	-25.1	Ø(4*)	-C(5*)	-C(6*)	-N(7*)	-15.9
C(5)	-C(6)	-N(7)	-C(8)	177.8	C(5')	-C(6')	-N(7')	-C(8')	-177.5	C(5*)	-C(6*)	-N(7*)	-C(8*)	178.9
C(6)	-N(7)	-C(8)	-C(9)	-58.3	C(6')	-N(7')	-C(8')	-C(9')	-60.0	C(6*)	-N(7*)	-C(8*)	-C(9*)	-57.4
N(7)	-C(8)	-C(9)	-Ø(10)	130.9	N(7')	-C(8')	-C(9')	-Ø(10')	132.7	N(7*)	-C(8*)	-C(9*)	-Ø(10*)	132.9
C(8)	-C(9)	-Ø(10)	-C(11)	175.1	C(8')	-C(9')	-Ø(10')-C(11')		176.6	C(8*)	-C(9*)	-Ø(10*)-C(11*)		172.8
C(9)	-Ø(10)	-C(11)	-C(12)	79.4	C(9')	-Ø(10')-C(11')-C(12')			86.4	C(9*)	-Ø(10*)-C(11*)-C(12*)			79.4
Ø(10)	-C(11)	-C(12)	-N(1')	3.3	Ø(10')-C(11')-C(12')-N(1*)				-5.1	Ø(10*)-C(11*)-C(12*)-N(1)				8.0
C(11)	-C(12)	-N(1')	-C(2')	-179.4	C(11')-C(12')-N(1*) -C(2*)				-170.1	C(11*)-C(12*)-N(1) -C(2)				-179.9
Ø(16)	-C(3)	-Ø(4)	-C(5)	3.2	Ø(16')-C(3')	-Ø(4')	-C(5')		1.9	Ø(16*)-C(3*)	-Ø(4*)	-C(5*)		2.9
Ø(22)	-C(9)	-Ø(10)	-C(11)	-6.5	Ø(22')-C(9')	-Ø(10')-C(11')			-3.0	Ø(22*)-C(9*)	-Ø(10*)-C(11*)			-5.6
Ø(26*)-C(12*)-N(1)			-C(2)	1.8	Ø(26)	-C(12)	-N(1')	-C(2')	4.7	Ø(26')-C(12')-N(1*)		-C(2*)		5.4
Ø(18)	-C(6)	-N(7)	-C(8)	0.7	Ø(18')-C(6')	-N(7')	-C(8')		0.3	Ø(18*)-C(6*)	-N(7*)	-C(8*)		-7.7
C(3)	-Ø(4)	-C(5)	-C(17)	167.0	C(3')	-Ø(4')	-C(5')	-C(17')	174.6	C(3*)	-Ø(4*)	-C(5*)	-C(17*)	163.7
N(1)	-C(2)	-C(13)	-C(14)	65.2	N(1')	-C(2')	-C(13')-C(14')		63.5	N(1*)	-C(2*)	-C(13*)-C(14*)		64.1
C(3)	-C(2)	-C(13)	-C(15)	-54.3	C(3')	-C(2')	-C(13')-C(15')		-53.1	C(3*)	-C(2*)	-C(13*)-C(15*)		-51.4
N(7)	-C(8)	-C(19)	-C(20)	-64.3	N(7')	-C(8')	-C(19')-C(20')		-59.9	N(7*)	-C(8*)	-C(19*)-C(20*)		-61.0
C(9)	-C(8)	-C(19)	-C(21)	50.8	C(9')	-C(8')	-C(19')-C(21')		59.1	C(9*)	-C(8*)	-C(19*)-C(21*)		59.4
Ø(10)	-C(11)	-C(23)	-C(24)	-62.5	Ø(10')-C(11')-C(23')-C(24')				-58.2	Ø(10*)-C(11*)-C(23*)-C(24*)				-66.3
C(12)	-C(11)	-C(23)	-C(25)	-173.3	C(12')-C(11')-C(23')-C(25')				-166.5	C(12*)-C(11*)-C(23*)-C(25*)				-71.4

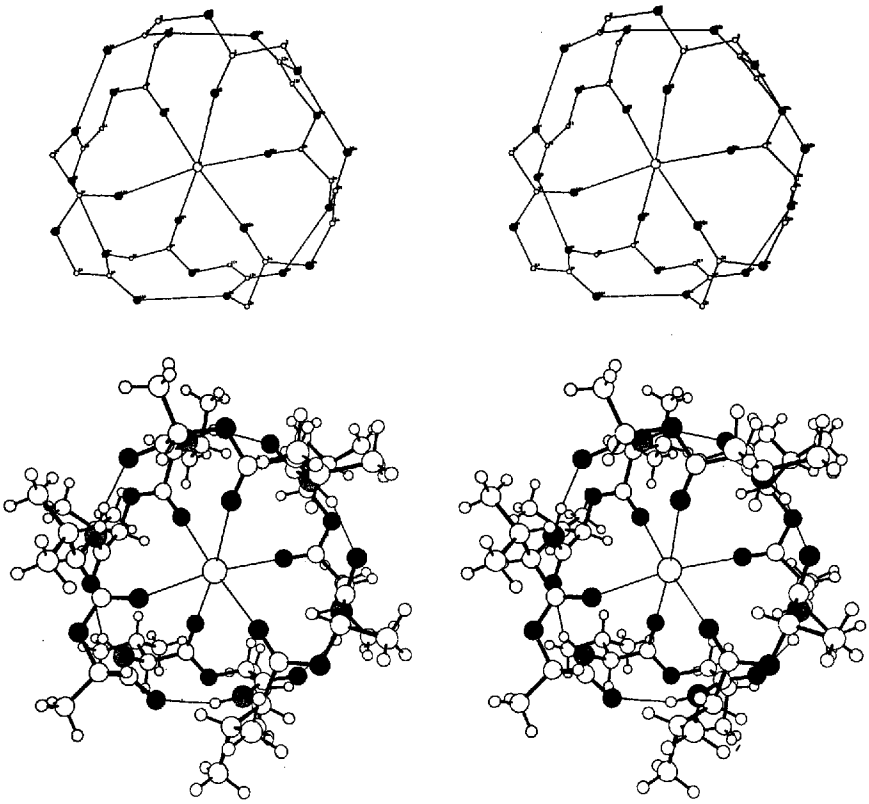


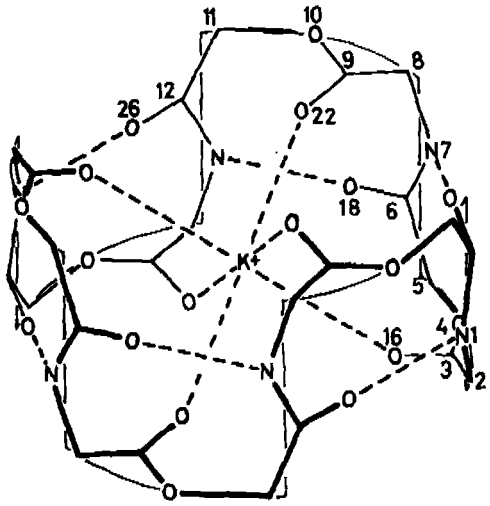
Fig. 1. *Stereoscopic view of the K+ complex of valinomycin*

C(25*). For the isopropyl group of D–HyV the CH(23)–CH_3(24) bond is syn-clinal with respect to the main chain bonds C(11)–C(12) and C(11)–O(10), and CH(23)–CH_3(25) is antiplanar to C(11)–C(12). (Exception: CH(23*)–CH_3(25*) is antiplanar to C(11*)–O(10*)). For the isopropyl groups of D–Val the CH(13)–CH_3(14) and CH(13)–CH_3(15) bonds are antiplanar to C(2)–C(3) and C(2)–N(1) respectively, and for L–Val the CH(19)–CH_3(20) and CH(19)–CH_3(21) bonds are antiplanar to C(8)–C(9) and C(8)–N(7). All these groups are approximately parallel or perpendicular to the pseudo threefold axis of the macrocycle.

Comparison of parameters related by the pseudo S_6 symmetry gives standard deviations of 0.004–0.029 Å (mean 0.015 Å) for corresponding bond lengths, 0.3–2.0° (mean 1.27°) for bond angles and of 0.9–9.5° (mean 3.6°) for torsion angles. These values are of the same order of magnitude as the standard deviations estimated from the least-squares normal equations.

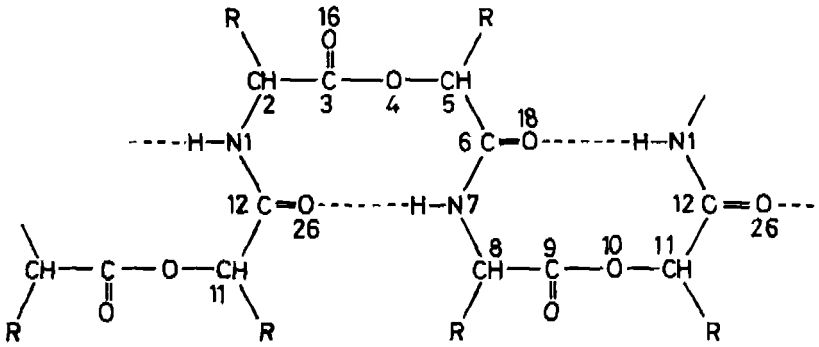
The K^+ ion is coordinated to six carbonyl oxygen atoms of ester groups (O(16), O(22)) in a nearly regular octahedron (*Scheme 2*). The K^+...O distances vary from 2.69–2.83 Å (mean 2.756 Å) and are very similar to the K^+...O(carbonyl) distances in the cubic coordination of nonactin (mean 2.771 Å [12]). The six carbonyl oxygen

Scheme 2. *Schematic illustration of the structure of the K^+ complex of valinomycin, showing S_6 symmetry of the ring skeleton, coordination and hydrogen bonding*



atoms of the amide groups form hydrogen bonds with the N–H-groups. Thus N(7) of L–Val is connected with O(26) of D–HyV three units back in the chain, and N(1) of D–Val with O(18) of L–Lac to form a belt of β-structure elements (*Scheme 3*)

Scheme 3. *The β-structure units in the K^+ complex of valinomycin*



embracing the molecule. The N–H...O distances are 2.88–2.98 Å, with a mean value of 2.932 Å and N...O–C angles are 133 $\pm$ 5°.

The present results provide an experimental basis for testing the accuracy of the model obtained from conformational energy calculations [8]. The calculated model has longer K^+...O distances (2.85 Å against 2.75 Å) and shorter hydrogen bonds (2.59 Å against 2.83 Å) resulting in a somewhat reduced radius and increased height of the roughly cylindric molecule. For comparison purposes, coordinates of the atoms related by the non-crystallographic S_6 symmetry were averaged, and the orientation of this averaged structure was fitted to the model structure by a least-squares procedure. Table 6 shows the result. Corresponding atomic positions in the

Table 6. *Coordinates (in Å, referred to orthogonal axes) of the averaged K^+-valinomycin structure, first line, compared to values determined by conformational energy calculations. X is the S_6 symmetry axis*

	X	Y	Z
K+	0.00	0.00	0.00
	0.00	0.00	0.00
N(1)	0.32	4.29	1.21
	0.15	4.10	1.19
C(2)	1.58	4.08	1.94
	1.51	4.00	1.73
C(3)	1.63	2.63	2.35
	1.78	2.56	2.19
O(4)	1.95	2.50	3.65
	1.92	2.41	3.54
C(5)	2.14	1.16	4.16
	2.22	1.05	3.94
C(6)	0.83	0.44	4.38
	0.92	0.28	4.11
C(13)	2.79	4.46	1.10
	2.53	4.38	0.65
O(16)	1.43	1.69	1.63
	1.88	1.64	1.38
C(17)	2.91	1.28	5.45
	2.96	1.07	5.28
O(18)	0.88	-0.77	4.66
	0.94	-0.96	4.21

two structures are displaced by up to 0.5 Å. Although the overall structure is correctly reproduced (partly because the assumed constraints happen to hold rather well), the agreement between detailed structural parameters is not good and is certainly not comparable to what can be obtained from conformational calculations for small molecules.

Two kinds of counter ion, linear I_3^- and bent I_5^-, are present in the crystal. The I_3^- ions lie on the twofold rotation axes at (0, y, 1/4) etc.; the I–I distance is 2.93 Å

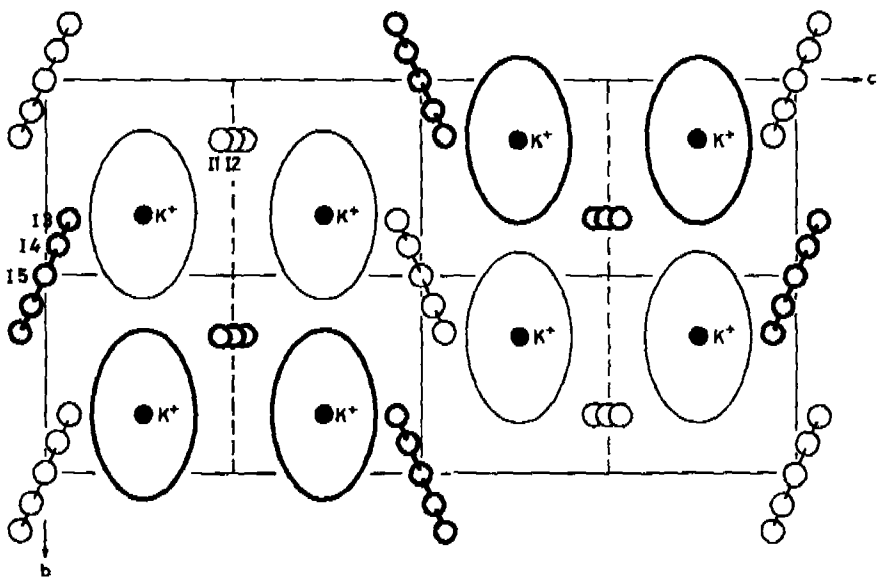


Fig. 2. *Packing of valinomycin units and of I_3^- and I_5^- anions in the unit cell*

and the I–I–I angle is 178.6°. The I_5^- ions lie on the twofold rotation axes (x, 1/2, 0) etc.; atoms I(3), I(4), I(5) are colinear (178.8°) with I(3)–I(4) 3.08 Å and I(4)–I(5) 2.76 Å. The angle I(4)–I(5)–I(4') is 84°.

The packing arrangement is shown diagrammatically in Fig. 5, looking along the *a* axis. The valinomycin units form layers centred at z ~ 1/8, 3/8 etc. Successive layers are separated by layers of I_5^- ions at z = 0, 1/2 etc., and layers of I_8^- ions at z = 1/4, 3/4 etc. Looking along the *c* axis, valinomycin units centred at z = 0.13 and 0.63 and units centred at z = 0.37 and 0.87 form diamond-type hexagonal layers.

The residual electron density in the $(F_0 - F_c)$-maps appears around (0.5, 0.3, 0.25) etc. and may indicate disordered solvent molecules in this otherwise empty region of the structure. There are no abnormally short intermolecular contacts between valinomycin molecules, in particular none that could be responsible for the different conformation of C(25*) of the D–HyV isopropyl group.

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52. Synthese von 2,6-Diencarbonsäuren

Vorläufige Mitteilung[1])

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(20. XII. 74)

Summary. Through sequential *Claisen*- and *Cope* rearrangements the chainlengthening of allylic alcohols by one isoprene unit was achieved. Treatment of (*E*)-**1a** first with lithium N-cyclohexyl-N-isopropylamide at −70°, followed by trimethylsilylchloride and warming up to room temperature yielded after work-up **3a** (R = H), which rearranged at 156° in high yield to (*E*/*Z*)-**4a**. An analogous reaction sequence transformed **6** to **8**. Choosing lithium N-methylanilide as a base (*E*/*Z*)-**9** was selectively rearranged to **12**, which was converted to the *Cecropia* juvenile hormone precursor (*E*/*Z*)-**4b**.

[1]) Eine ausführliche Mitteilung soll in dieser Zeitschrift erscheinen.