Crystal Structure of Valinomycin Potassium Picrate: Anion Effects on Valinomycin Cation Complexes

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Abstract: The crystal structure of a complex of valinomycin with potassium picrate has been determined by single-crystal X-ray diffraction. The crystals are monoclinic of space group $P2_1$, two molecules of valinomycin potassium picrate per unit cell, with dimensions a = 13.240 (10) Å, b = 22.343 (16) Å, c = 13.685 (10) Å, and β = 108.82 (3)°. The structure was determined by rotation–translation search methods and refined by difference Fourier and least-squares methods. The final R was 0.12 for all observed data. The structure revealed a weak but definite interaction between the potassium ion inside the valinomycin cavity and an oxygen atom of the para-nitro group of the picrate anion. This finding is significant since anions (especially picrate and the chemically similar trinitro cresolate anion) change the membrane transport observed for valinomycin and other ion-transporting antibiotics. The mechanism by which this occurs is not yet fully understood.

Valinomycin (VAL) is a cyclic dodecadepsipeptide containing D-valine, D-α-hydroxyvaleric acid, L-valine, and L-lactic acid in the sequence cyclo(L-Val-D-Hyv-D-Val-L-Lac)$_3$ (Figure 1). Valinomycin is one of the most intensively studied of the ion-transporting antibiotics. Crystal structure studies have been published by Pinkerton et al.,[1] Smith et al.,[2] Karle,[3] and Neupert-Laves and Dobler.[4] Nuclear magnetic resonance has been used to probe the structure in solution,[5-7] and membrane studies have been carried out to examine the factors influencing its ion-transport function.[8-12]

In early investigations on membrane transport the function of the anion was thought to be merely one of providing electroneutrality. Tosteson and co-workers[13] showed that the cation specificity of the valinomycin-induced conductances and ion permeabilities in lipid bilayer and red blood cell membranes was nearly abolished when trinitro-*m*-cresolate (TNC^-) was used as the anion. In addition valinomycin showed reduced cation selectivities when TNC^- was present in the aqueous phase (measurement of partition coefficients). Rose and Henkins[14] showed that the choice of anion or solvent could change the cation selectivity of valinomycin in solution. They used the method of solution complexation, the results being determined by using circular dichroism. Davis and Tosteson[6] extended the range of anions and solvents and studied their interaction with valinomycin cation complexes. Ginsburg et al.[15] studied the effects of TNC^- on valinomycin-induced transport in lipid bilayers and also looked at the effects with picrate as anion.[16]

Table I. Potassium(1+) Valinomycin Picrate(1−) Crystal Data

a = 13.240 (10) Å	space group $P2_1$
b = 22.343 (16) Å	Z = 2
c = 13.685 (10) Å	V = 3831.9 Å^3
β = 108.82 (3)°	

Table II. The Largest Peaks in the Cross-Rotation Function between the (Known) Valinomycin Molecule in a Large Triclinic Unit Cell and the (Unknown) Valinomycin Potassium Picrate Complex[a]

θ_1	θ_2	θ_3	R	ψ	ϕ
30	60	15	50	30	−32
15	105	270	42	62	82
30	165	315	46	30	−24
90	105	315	46	30	−30
60	45	165	42	40	−22
60	60	90	44	82	39
60	150	270	43	40	−20
90	90	180	51	30	−30

[a] θ_1, θ_2, and θ_3 are the Eulerian angles (deg) and ψ and ϕ are the Spherical polar angles (deg) corresponding to the direction of the noncrystallographic threefold axis of the molecule.

The method by which the anion influences the membrane transport is not well understood. It has been suggested that some experimental observations can be explained by adsorption of the anion, e.g., picrate, on the membrane surface which changes the surface potential and increases the conductance of the potassium valinomycin or nonactin complex.[16] The synergistic conductance effect of potassium picrate itself plus potassium picrate in the presence of valinomycin has been explained by distortion of the hydrocarbon chains in the lipid bilayer in the proximity of the antibiotic molecules. This "free volume" would facilitate the passage of soluble anions through the membrane.[15,16] This latter theory does not involve any direct chemical interaction between the antibiotic and the anion. However, Davis and Tosteson[6] concluded from nuclear magnetic resonance studies that different conformations could exist for the sodium valinomycin complex depending on the anion present. They also concluded that in low polarity solvent an additional coordination site of the sodium could be occupied by the anion (bromide, thiocyanate (SCN^-), or TNC^-), giving an asymmetric character to the association of sodium with the depsipeptide ligands. With bulkier anions (tetraphenyl boron (TPB^-)) the sodium ion occupies an octahedral coordination site at the pseudoinversion center of the valinomycin. In contrast the potassium complex of valinomycin is always in

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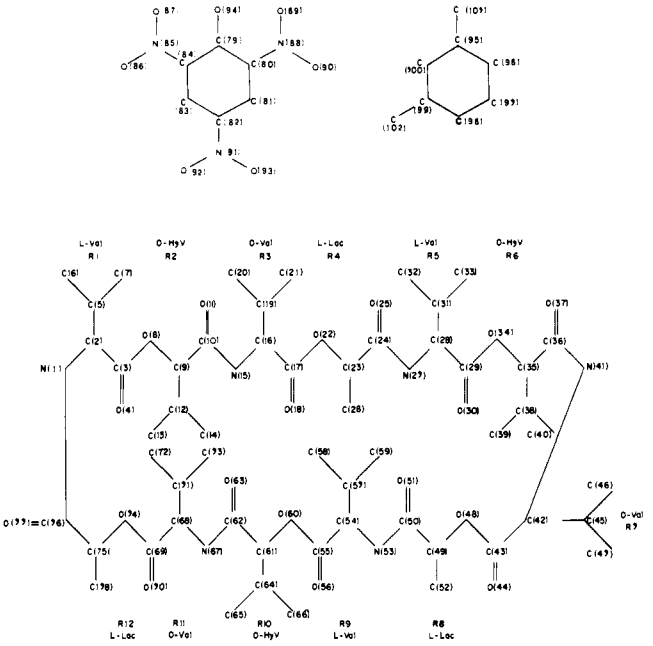

Figure 1. The numbering scheme of the valinomycin, picrate and xylene molecules.

this latter, more symmetric conformation. Thus an absence of anion binding is inferred.

These results suggest that a comparison of the crystal structure of valinomycin potassium picrate with that of valinomycin sodium picrate (picrate being similar to TNC^-) would be useful in understanding the mechanism of influence of the anion. Results of the crystal structure determination of valinomycin potassium picrate are presented here. Work on the structure of the sodium picrate complex is in progress.

Experimental Section

Crystallization and Crystal Data for Valinomycin Potassium Picrate. Valinomycin was a gift from Eli Lilly and Co. Crystals of the potassium picrate complex were prepared by dissolving equimolar amounts of valinomycin and potassium picrate in chloroform and crystallizing by slow evaporation from a xylene–chloroform mixture. The unit cell data at −165 °C are shown in Table The observed volume was significantly higher than that calculated for a unit cell containing two valinomycin potassium picrate complexes, suggesting the presence of solvent molecules.

Three-dimensional diffraction data consisting of 2248 unique reflections (only those reflections for which $F_o > \sigma(F_o)$ with $(\sin\theta)/\lambda < 0.424$ Å^{-1}) were recorded on a Picker four-circle automated diffractometer in the Structure Center of Indiana University at Bloomington, IN. The crystal used for data collection was chosen to minimize absorption, and Mo Kα radiation was used. No absorption corrections were made. The crystal was mounted in a cold stream from liquid nitrogen (−165 °C) during data collection.

Structure Determination and Refinement. In this structure potassium is not large enough to be used for the heavy-atom method of phase determination. The crystal structure was determined by rotation-translation methods. The self-rotation function[7] search for the expected threefold molecular symmetry of valinomycin[1,4] gave a result in which the second strongest solution, Figure 2, was correct. The strongest peak on Figure 2 we now know corresponded to the direction of the threefold axis of the picrate ion, which, ignoring the phenolate atom, does indeed have threefold molecular symmetry. The correct orientation was obtained from a cross-rotation function calculated between the structure and a model valinomycin alone. Coordinates for the valinomycin model were obtained from the crystal structure of valinomycin potassium aurichloride[1] and were placed in a large triclinic cell ($a = b = c = 25$ Å, $\alpha = \beta = \gamma = 90°$). The large cell is to avoid intermolecular interference.[18] This rotation function produced eight high peaks, six of which

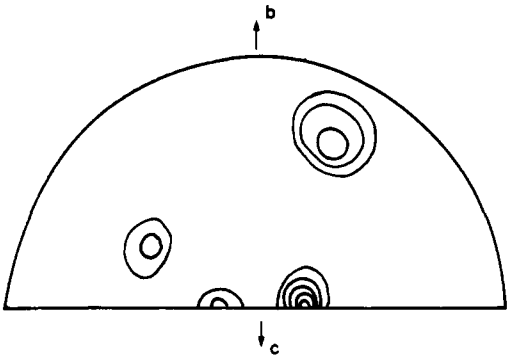

Figure 2. Self-rotation function to determine the direction of the noncrystallographic threefold axis ($\chi = 120°$) of the valinomycin molecule. The rotation function was calculated with 528 reflections between 2- and 10-Å resolution.

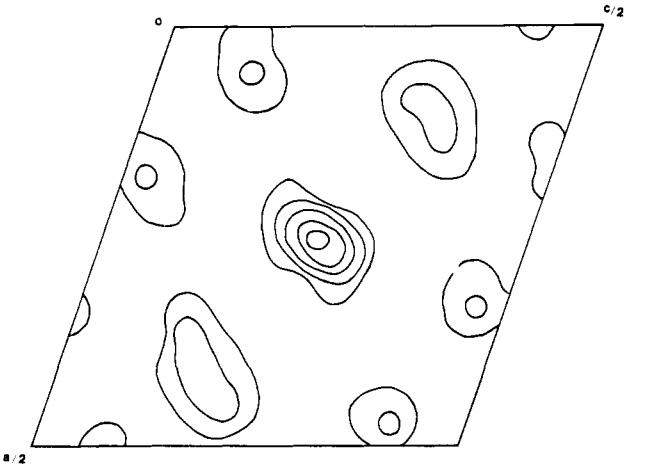

Figure 3. Q function: only the data between 2- and 10-Å resolution were used in the calculation.

are related due to the $\bar{3}$ symmetry of the valinomycin model and agreed with the second highest peak of the previous self-rotation function. The model in the correct orientation was now systematically translated in the x,z plane (the origin along the y axis is arbitrary in space group $P2_1$). The results of this (the Q-function[20] calculation) using the valinomycin backbone atoms and the potassium atom are given in Figure 3. With use of the rotational and translational parameters thus obtained, the trial coordinates of valinomycin and potassium were refined by conventional least squares by using all observed reflections at unity weighting factor. Several cycles decreased the R value to 0.35 only. Refinement was shifted to 12 cycles of difference Fourier synthesis in which each residue in turn was omitted and then relocated in the next cycle. During this the picrate was also located and subsequently one xylene molecule. Least-squares refinement on the 103 nonhydrogen atoms gave a final R index of 0.12 by using individual isotropic temperature parameters for all atoms except the potassium which was anisotropic. The weighting scheme of $1/\sigma(F)$ for the least-squares refinement was also tried but did not produce a significant improvement. Some of the bond lengths in the structure show high standard deviations due to the low resolution of the data. Crystals of the potassium picrate complex of valinomycin were poorly diffracting.

Scattering factors were taken from ref 21. In the picrate molecules the O^- form factors were used for the ionized oxygen. All computer programs were from the X-RAY 76 system except for that used for the rotation-translation calculations (written by us).

Results and Discussion

The numbering scheme for the valinomycin molecular complex is given in Figure 1. A stereoview of the complex is given in Figure 4 and a stereodiagram of the packing in the unit cell in Figure 5. The final fractional coordinates and thermal parameters are listed in Table III. The bond lengths for the structural asymmetric

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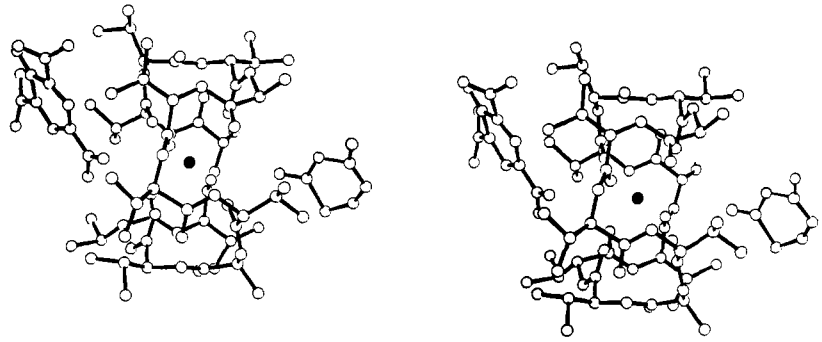

Figure 4. A stereoview of the valinomycin potassium picrate complex with the xylene molecule included. The para-nitro group of the picrate molecule can be seen pointing into the cavity to complex with the potassium ion. The xylene molecule points toward the cleft at the opposite side of the valinomycin molecule.

Table III. Fractional Atomic Parameters with Their Estimated Standard Deviations

	x	y	z	U, Å^2
K	−2461 (5)	0	−2214 (4)	
N(1)	−5588 (15)	886 (9)	−3880 (4)	3.3 (6)
C(2)	−5072 (21)	1453 (12)	−4092 (19)	4.3 (8)
C(3)	−3934 (22)	1368 (12)	−4019 (20)	5.0 (8)
O(4)	−3280 (13)	1050 (7)	−3313 (12)	4.6 (5)
C(5)	−5088 (23)	1927 (13)	−3264 (20)	5.4 (8)
C(6)	−6242 (26)	2044 (15)	−3274 (23)	7.7 (10)
C(7)	−4666 (23)	2541 (13)	−3617 (21)	6.2 (9)
O(8)	−3658 (13)	1574 (7)	−4788 (12)	4.3 (5)
C(9)	−2582 (21)	1526 (11)	−4789 (18)	4.1 (8)
C(10)	−2360 (22)	936 (13)	−5016 (19)	5.0 (8)
O(11)	−1418 (13)	738 (7)	−4871 (11)	3.9 (5)
C(12)	−2479 (20)	1987 (11)	−5601 (18)	3.9 (7)
C(13)	−1370 (26)	1991 (15)	−5671 (24)	7.8 (10)
C(14)	−2774 (22)	2609 (12)	−5274 (20)	5.0 (8)
N(15)	−3213 (16)	527 (9)	−5547 (14)	3.7 (6)
C(16)	−2891 (20)	−62 (12)	−5836 (17)	3.8 (7)
C(17)	−2201 (19)	−392 (10)	−4891 (16)	2.8 (7)
O(18)	−2395 (13)	−418 (7)	−4069 (11)	4.0 (5)
C(19)	−3972 (20)	−407 (11)	−6401 (17)	3.5 (7)
C(20)	−3637 (22)	−1050 (12)	−6686 (19)	4.9 (8)
C(21)	−4567 (21)	−88 (12)	−7360 (18)	4.4 (8)
O(22)	−1339 (13)	−651 (7)	−5090 (12)	4.3 (5)
C(23)	−716 (20)	−1041 (12)	−4256 (18)	4.0 (7)
C(24)	85 (23)	−646 (13)	−3468 (20)	5.6 (9)
O(25)	678 (14)	−925 (8)	−2664 (12)	5.2 (5)
C(26)	−113 (30)	−1431 (16)	−4789 (26)	9.2 (12)
N(27)	170 (16)	−55 (10)	−3629 (14)	4.4 (6)
C(28)	932 (20)	281 (11)	−2732 (18)	4.0 (8)
C(29)	555 (21)	201 (12)	−1842 (18)	4.3 (8)
O(30)	−358 (13)	223 (7)	−1822 (12)	4.3 (5)
C(31)	898 (22)	945 (13)	−3023 (20)	5.2 (8)
C(32)	1685 (26)	1291 (15)	−2067 (24)	8.0 (11)
C(33)	1263 (23)	1046 (13)	−3964 (20)	5.6 (9)
O(34)	1360 (13)	69 (8)	−966 (11)	4.2 (5)
C(35)	1093 (23)	40 (14)	−33 (20)	5.9 (9)
C(36)	576 (19)	−610 (11)	77 (17)	3.3 (7)
O(37)	278 (14)	−654 (8)	825 (12)	4.9 (5)
C(38)	2280 (23)	87 (14)	897 (21)	6.1 (9)
C(39)	2802 (36)	620 (21)	632 (34)	13.9 (17)
C(40)	2104 (30)	141 (18)	1892 (27)	10.3 (13)
N(41)	548 (16)	−999 (9)	−623 (14)	4.2 (6)
C(42)	−9 (18)	−1572 (10)	−499 (15)	2.0 (6)
C(43)	−1120 (20)	−1389 (11)	−498 (17)	3.6 (7)
O(44)	−1699 (13)	−1068 (7)	−1155 (11)	3.6 (5)
C(45)	−4 (23)	−2013 (13)	−1335 (21)	5.5 (9)
C(46)	1107 (22)	−2194 (12)	−1320 (20)	5.2 (8)
C(47)	−648 (23)	−2551 (13)	−1249 (20)	5.5 (9)
O(48)	−1386 (14)	−1649 (8)	220 (12)	5.3 (5)
C(49)	−2487 (24)	−1568 (13)	221 (21)	6.1 (9)
C(50)	−2642 (21)	−966 (12)	688 (19)	4.9 (8)
O(51)	−3615 (14)	−798 (8)	559 (12)	5.3 (5)
C(52)	−2776 (30)	−2076 (17)	821 (28)	10.0 (13)
N(53)	−1756 (16)	−632 (9)	1106 (14)	4.0 (6)
C(54)	−1992 (20)	−6 (12)	1422 (18)	4.0 (7)
C(55)	−2672 (20)	287 (11)	483 (18)	3.9 (8)
O(56)	−2569 (13)	292 (8)	−359 (12)	4.6 (5)
C(57)	−886 (24)	326 (4)	1836 (22)	6.3 (9)
C(58)	−1120 (24)	976 (14)	2024 (22)	6.8 (10)
C(59)	−174 (22)	10 (13)	2906 (20)	5.5 (8)
O(60)	−3438 (13)	607 (7)	690 (12)	4.5 (5)
C(61)	−4110 (23)	997 (14)	−109 (21)	6.2 (9)
C(62)	−4941 (20)	593 (11)	−936 (18)	3.5 (7)
O(63)	−5510 (14)	853 (8)	−1761 (13)	5.6 (5)
C(64)	−4744 (27)	1406 (15)	455 (24)	7.9 (11)
C(65)	−3768 (38)	1801 (22)	1245 (35)	14.4 (17)
C(66)	−5266 (48)	1815 (29)	−257 (45)	19.6 (24)
N(67)	−5037 (17)	19 (10)	−748 (15)	4.8 (6)
C(68)	−5824 (21)	−322 (11)	−1621 (18)	4.1 (8)
C(69)	−5477 (23)	−241 (12)	−2498 (20)	5.6 (9)
O(70)	−4588 (14)	−311 (8)	−2571 (12)	5.0 (5)
C(71)	−5762 (20)	−984 (12)	−1269 (18)	3.7 (7)
C(72)	−6503 (24)	−1366 (14)	−2212 (22)	6.5 (9)
C(73)	−6215 (22)	−1069 (13)	−392 (20)	5.3 (9)
O(74)	−6347 (15)	−143 (8)	−3427 (13)	5.9 (6)
C(75)	−6134 (22)	−138 (12)	−4362 (19)	5.2 (8)
C(76)	−5612 (19)	436 (11)	−4545 (17)	3.1 (7)
O(77)	−5286 (13)	473 (7)	−5256 (11)	4.3 (5)
C(78)	−7229 (29)	−183 (15)	−5179 (24)	8.1 (11)
C(79)	−1237 (27)	3357 (16)	−2754 (25)	8.7 (11)
C(80)	−654 (26)	2854 (15)	−2528 (24)	7.5 (10)
C(81)	−601 (20)	2336 (11)	−2030 (18)	3.9 (7)
C(82)	−1355 (23)	2271 (13)	−1594 (21)	5.9 (9)
C(83)	−2321 (20)	2733 (11)	−1742 (17)	3.6 (7)
C(84)	−2075 (21)	3196 (11)	−2264 (18)	3.9 (8)
N(85)	−3046 (23)	3648 (13)	−2445 (21)	9.4 (9)
O(86)	−3377 (19)	3909 (12)	−3374 (18)	10.6 (8)
O(87)	−3480 (16)	3674 (9)	−1774 (14)	7.1 (6)
N(88)	234 (20)	2942 (11)	−2908 (18)	7.3 (8)
O(89)	646 (21)	2534 (12)	−3299 (19)	12.0 (9)
O(90)	745 (20)	3424 (12)	−2787 (18)	11.1 (9)
N(91)	−1512 (24)	1757 (14)	−1058 (22)	10.3 (10)
O(92)	−2297 (18)	1757 (10)	−647 (16)	9.3 (7)
O(93)	−801 (18)	1371 (11)	−908 (17)	9.8 (8)
O(94)	−1229 (17)	3774 (10)	−3328 (16)	8.7 (7)
C(95)	−2099 (57)	−2975 (36)	−3789 (55)	25.7 (32)
C(96)	−2714 (37)	−3323 (21)	−3442 (33)	13.9 (17)
C(97)	−3562 (32)	−3175 (19)	−3080 (30)	11.7 (14)
C(98)	−4154 (46)	−2694 (29)	−2782 (44)	19.9 (24)
C(99)	−3499 (30)	−2166 (17)	−3310 (27)	9.8 (12)
C(100)	−2710 (27)	−2320 (16)	−3769 (24)	8.4 (11)
C(101)	−1387 (60)	−2899 (39)	−4031 (59)	28.3 (37)
C(102)	−4068 (44)	−1610 (27)	−3319 (41)	18.3 (22)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
K	2.54 (41)	5.02 (38)	3.27 (31)	1.04 (33)	0.05 (27)	1.04 (31)

[a] Positional parameters have been multiplied by 10^4 and thermal parameters by 10^2. The isotropic temperature factor is of the form $T = \exp[-8\pi^2 U(\sin^2\theta)/\lambda^2]$ and the anisotropic factor $T = \exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2hka^*b^*U_{12} + 2hla^*c^*U_{13} + 2klb^*c^*U_{23}]$.

unit are listed in Table IV and the corresponding angles in Table V. The potassium coordination distances are given in Table VI. The intramolecular hydrogen bond distances are given in Table VII.

Table IV. Intramolecular Bond Lengths (Å) and Standard Deviations

	Valinomycin Molecule		
N(1)-C(2)	1.51 (3)	C(38)-C(39)	1.48 (6)
N(1)-C(76)	1.35 (3)	C(38)-C(40)	1.46 (5)
C(2)-C(3)	1.49 (4)	N(41)-C(42)	1.51 (3)
C(2)-C(5)	1.56 (4)	C(42)-C(43)	1.53 (4)
C(3)-O(4)	1.28 (3)	C(42)-C(45)	1.51 (4)
C(3)-O(8)	1.30 (4)	C(43)-O(44)	1.21 (3)
C(5)-C(6)	1.55 (5)	C(43)-O(48)	1.28 (3)
C(5)-C(7)	1.61 (4)	C(45)-C(46)	1.52 (4)
O(8)-C(9)	1.43 (3)	C(45)-C(47)	1.50 (4)
C(9)-C(10)	1.41 (4)	O(48)-C(49)	1.47 (4)
C(9)-C(12)	1.55 (4)	C(49)-C(50)	1.53 (4)
C(10)-O(11)	1.28 (3)	C(49)-C(52)	1.52 (5)
C(10)-N(15)	1.45 (4)	C(50)-O(51)	1.30 (3)
C(12)-C(13)	1.50 (5)	C(50)-N(53)	1.35 (4)
C(12)-C(14)	1.55 (4)	N(53)-C(54)	1.53 (3)
N(15)-C(16)	1.48 (3)	C(54)-C(55)	1.46 (3)
C(16)-C(17)	1.51 (4)	C(54)-C(57)	1.57 (4)
C(16)-C(19)	1.59 (4)	C(55)-O(56)	1.20 (3)
C(17)-O(18)	1.23 (3)	C(55)-O(60)	1.34 (3)
C(17)-O(22)	1.38 (3)	C(57)-C(58)	1.52 (5)
C(19)-C(20)	1.59 (4)	C(57)-C(59)	1.63 (4)
C(19)-C(21)	1.48 (4)	O(60)-C(61)	1.46 (4)
O(22)-C(23)	1.46 (3)	C(61)-C(62)	1.58 (4)
C(23)-C(24)	1.53 (4)	C(61)-C(64)	1.60 (5)
C(23)-C(26)	1.52 (5)	C(62)-O(63)	1.28 (3)
C(24)-O(25)	1.29 (4)	C(62)-N(67)	1.32 (3)
C(24)-N(27)	1.35 (4)	C(64)-C(65)	1.65 (6)
N(27)-C(28)	1.51 (4)	C(64)-C(66)	1.35 (7)
C(28)-C(29)	1.47 (4)	N(67)-C(68)	1.51 (4)
C(28)-C(31)	1.53 (4)	C(68)-C(69)	1.43 (4)
C(29)-O(30)	1.22 (3)	C(68)-C(71)	1.55 (4)
C(29)-O(34)	1.36 (4)	C(69)-O(74)	1.43 (4)
C(31)-C(32)	1.59 (5)	C(69)-O(70)	1.22 (4)
C(31)-C(33)	1.53 (5)	C(71)-C(72)	1.59 (4)
O(34)-C(35)	1.43 (4)	C(71)-C(73)	1.52 (5)
C(35)-C(36)	1.63 (4)	O(74)-C(75)	1.40 (4)
C(35)-C(38)	1.68 (5)	C(75)-C(76)	1.52 (4)
C(36)-O(37)	1.21 (3)	C(75)-C(78)	1.52 (5)
C(36)-N(41)	1.29 (3)	C(76)-O(77)	1.19 (3)
	Xylene Molecule		
C(95)-C(96)	1.32 (10)	C(97)-C(98)	1.47 (8)
C(95)-C(100)	1.68 (9)	C(98)-C(99)	1.75 (8)
C(95)-C(101)	1.11 (12)	C(99)-C(100)	1.42 (6)
C(96)-C(97)	1.41 (7)	C(99)-C(102)	1.45 (7)
	Picrate Anion		
C(79)-C(80)	1.34 (5)	C(83)-C(84)	1.36 (4)
C(79)-C(84)	1.51 (5)	C(84)-N(85)	1.59 (4)
C(79)-O(94)	1.22 (4)	N(85)-O(86)	1.34 (4)
C(80)-C(81)	1.33 (4)	N(85)-O(87)	1.23 (4)
C(80)-N(88)	1.44 (5)	N(88)-O(89)	1.27 (4)
C(81)-C(82)	1.33 (4)	N(88)-O(90)	1.25 (4)
C(82)-C(83)	1.60 (4)	N(91)-O(92)	1.33 (5)
C(82)-N(91)	1.41 (5)	N(91)-O(93)	1.24 (4)

Description of the Structure. The overall features of the potassium valinomycin complex with picrate as anion are comparable to those found for potassium valinomycin with iodide[4] as anion and with aurichloride[1] as anion. The six intramolecular hydrogen bonds are still intact, and their bond distances and angles are shown in Table VII. The molecular threefold symmetry is well maintained in all three structures for the backbone atoms and most of the side-chain atoms. The valyl side chains point slightly inward to the center of the complex whereas those of the lactyl and isovaleryl residues point slightly outward. Because of this the valyl side chains are in a crowded environment, whereas the isovaleryl side chains seem to have more freedom. Rotations about the C^{α}–C^{β} bonds of the valyl and isovaleryl residues are highly restricted. The isopropyl groups have a large barrier to rotation in at least one position. All L-valyl residues have the isopropyl groups in the same rotational conformation. All D-valyl residues have the isopropyl groups in the mirror image conformation. This generalization holds for the structures of uncomplexed valinomycin as well. The isopropyl groups of the isovaleryl residues, however,

Table V. Bond Angles (Deg) with Standard Deviations

	Valinomycin Molecules		
C(2)-N(1)-C(76)	114 (2)	C(35)-C(38)-C(40)	109 (3)
N(1)-C(2)-C(3)	113 (2)	C(39)-C(38)-C(40)	113 (3)
N(1)-C(2)-C(5)	109 (2)	C(43)-C(42)-C(45)	114 (2)
C(3)-C(2)-C(5)	107 (2)	C(36)-N(41)-C(42)	113 (2)
C(2)-C(3)-O(4)	123 (3)	N(41)-C(42)-C(43)	106 (2)
C(2)-C(3)-O(8)	116 (2)	N(41)-C(42)-C(45)	110 (2)
O(4)-C(3)-O(8)	121 (3)	C(42)-C(43)-O(48)	112 (2)
C(2)-C(5)-C(6)	111 (2)	O(44)-C(43)-O(48)	125 (3)
C(2)-C(5)-C(7)	106 (2)	C(42)-C(45)-C(46)	114 (2)
C(6)-C(5)-C(7)	107 (2)	C(42)-C(45)-C(47)	109 (3)
C(3)-O(8)-C(9)	121 (2)	C(46)-C(45)-C(47)	111 (2)
O(8)-C(9)-C(10)	110 (2)	C(43)-O(48)-C(49)	118 (2)
O(8)-C(9)-C(12)	106 (2)	O(48)-C(49)-C(50)	112 (2)
C(10)-C(9)-C(12)	113 (2)	O(48)-C(49)-C(52)	109 (2)
C(9)-C(10)-O(11)	124 (2)	O(50)-C(49)-C(52)	110 (3)
C(9)-C(10)-N(15)	121 (2)	C(49)-C(50)-O(51)	117 (2)
O(11)-C(10)-N(15)	115 (2)	C(49)-C(50)-N(53)	117 (2)
C(9)-C(12)-C(13)	111 (2)	O(51)-C(50)-N(53)	126 (2)
C(9)-C(12)-C(14)	107 (2)	C(50)-N(53)-C(54)	113 (2)
C(13)-C(12)-C(14)	111 (2)	N(53)-C(54)-C(55)	107 (2)
C(10)-N(15)-C(16)	117 (2)	N(53)-C(54)-C(57)	106 (2)
N(15)-C(16)-C(17)	111 (2)	C(55)-C(54)-C(57)	110 (2)
N(15)-C(16)-C(19)	106 (2)	C(54)-C(55)-O(56)	128 (3)
C(17)-C(16)-C(19)	112 (2)	C(54)-C(55)-O(60)	110 (2)
C(16)-C(17)-O(18)	124 (2)	O(56)-C(55)-O(60)	122 (2)
C(16)-C(17)-O(22)	110 (2)	C(54)-C(57)-C(58)	107 (2)
O(18)-C(17)-O(22)	126 (2)	C(54)-C(57)-C(59)	109 (2)
C(16)-C(19)-C(20)	106 (2)	C(58)-C(57)-C(59)	111 (2)
C(16)-C(19)-C(21)	110 (2)	C(55)-O(60)-C(61)	119 (2)
C(20)-C(19)-C(21)	109 (2)	O(60)-C(61)-C(62)	108 (2)
C(17)-O(22)-C(23)	113 (2)	O(60)-C(61)-C(64)	106 (2)
O(22)-C(23)-C(24)	107 (2)	C(62)-C(61)-C(64)	109 (2)
O(22)-C(23)-C(26)	103 (2)	C(61)-C(62)-O(63)	117 (2)
C(24)-C(23)-C(26)	109 (2)	C(61)-C(62)-N(67)	120 (2)
C(23)-C(24)-O(25)	115 (2)	O(63)-C(62)-N(67)	123 (2)
C(23)-C(24)-N(27)	122 (2)	C(61)-C(64)-C(65)	102 (3)
O(25)-C(24)-N(27)	124 (2)	C(61)-C(64)-C(66)	105 (4)
C(24)-N(27)-C(28)	115 (2)	C(65)-C(64)-C(66)	103 (4)
N(27)-C(28)-C(29)	107 (2)	C(62)-N(67)-C(68)	115 (2)
N(27)-C(28)-C(31)	108 (2)	N(67)-C(68)-C(69)	106 (2)
C(29)-C(28)-C(31)	110 (2)	N(67)-C(68)-C(71)	106 (2)
C(28)-C(29)-O(30)	128 (2)	C(69)-C(68)-C(71)	112 (2)
C(28)-C(29)-O(34)	112 (2)	C(68)-C(69)-O(70)	129 (2)
O(30)-C(29)-O(34)	119 (2)	C(68)-C(69)-O(74)	112 (2)
C(28)-C(31)-C(32)	108 (2)	O(70)-C(69)-O(74)	118 (3)
C(28)-C(31)-C(33)	112 (2)	C(68)-C(71)-C(72)	108 (2)
C(32)-C(31)-C(33)	109 (2)	C(68)-C(71)-C(73)	112 (2)
C(29)-O(34)-C(35)	117 (2)	C(72)-C(71)-C(73)	106 (2)
O(34)-C(35)-C(36)	111 (2)	C(69)-O(74)-C(75)	118 (2)
O(34)-C(35)-C(38)	103 (2)	O(74)-C(75)-C(76)	113 (2)
C(36)-C(35)-C(38)	108 (2)	O(74)-C(75)-C(78)	104 (3)
C(35)-C(36)-O(37)	114 (2)	C(76)-C(75)-C(78)	108 (2)
C(35)-C(36)-N(41)	116 (2)	C(75)-C(76)-O(77)	120 (2)
O(37)-C(36)-N(41)	129 (2)	C(75)-C(76)-N(1)	116 (2)
C(35)-C(38)-C(39)	105 (2)	N(1)-C(76)-O(77)	124 (2)
	Picrate Anion		
C(80)-C(79)-C(84)	99 (3)	C(83)-C(84)-N(85)	104 (3)
C(80)-C(79)-O(94)	132 (4)	C(79)-C(84)-N(85)	117 (2)
C(84)-C(79)-O(94)	129 (3)	C(84)-N(85)-O(86)	115 (3)
C(79)-C(80)-C(81)	141 (4)	C(84)-N(85)-O(87)	117 (2)
C(79)-C(80)-N(88)	106 (3)	O(86)-N(85)-O(87)	127 (3)
C(81)-C(80)-N(88)	113 (3)	C(80)-N(88)-O(89)	124 (3)
C(80)-C(81)-C(82)	114 (3)	C(80)-N(88)-O(90)	122 (3)
C(81)-C(82)-C(83)	124 (3)	O(89)-N(88)-O(90)	113 (3)
C(81)-C(82)-N(91)	125 (3)	C(82)-N(91)-O(92)	119 (3)
C(83)-C(82)-N(91)	110 (3)	C(82)-N(91)-O(93)	115 (3)
C(82)-C(83)-C(84)	104 (2)	O(92)-N(91)-O(93)	126 (3)
C(83)-C(84)-C(79)	139 (3)		
	Xylene Molecule		
C(96)-C(95)-C(100)	99 (6)	C(97)-C(98)-C(99)	90 (4)
C(96)-C(95)-C(101)	152 (9)	C(98)-C(99)-C(100)	123 (4)
C(100)-C(95)-C(101)	109 (7)	C(98)-C(99)-C(102)	105 (4)
C(95)-C(96)-C(97)	130 (5)	C(100)-C(99)-C(102)	131 (4)
C(96)-C(97)-C(98)	146 (5)	C(99)-C(100)-C(95)	130 (4)

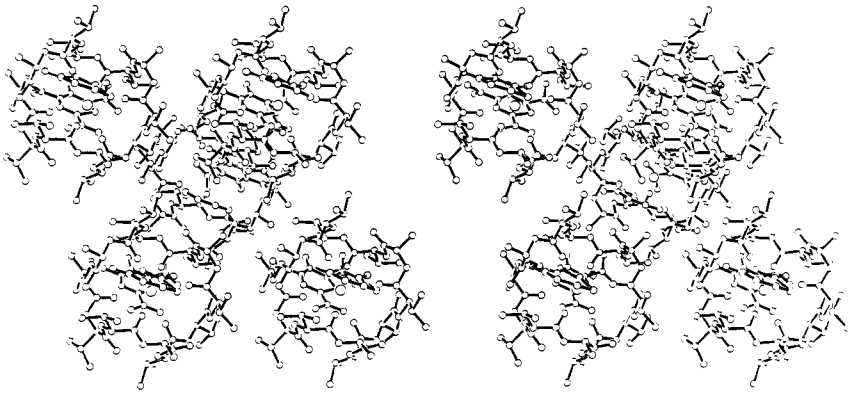

Figure 5. A stereoview of the packing in the unit cell.

Table VI. Coordination Distances (Å) around the Potassium Ion

coordinating atoms	distance	dist[a]
K···O(4)	2.809 (24)	2.751
K···O(18)	2.733 (18)	2.809
K···O(30)	2.707 (25)	2.688
K···O(44)	2.804 (22)	2.826
K···O(56)	2.669 (19)	2.723
K···O(70)	2.786 (24)	2.738
K···O(93)	3.857 (38)[b]	

[a] Neupert-Laves and Dobler[4] valinomycin potassium iodide. Average standard deviation 0.015–0.02 Å. [b] Picrate.

Table VII. Intramolecular Hydrogen Bond Lengths

hydrogen bond	length, Å	N···O–C, angle, deg
N(1)-H···O(63)	2.88	135
N(15)-H···O(77)	2.89	135
N(27)-H···O(11)	2.85	145
N(41)-H···O(25)	2.87	132
N(53)-H···O(37)	2.85	136
N(67)-H···O(51)	2.82	137

seem to have more conformational flexibility. This is reflected in the disorder of the side-chain atoms of the isovaleryl residue in the potassium valinomycin aurichloride structure,[1] different forms of the uncomplexed valinomycin,[2,3] and the potassium valinomycin iodide structure.[4] The isovaleryl side-chain atoms deviate from the molecular threefold symmetry in all previous valinomycin structures but not in this present potassium valinomycin picrate where all side-chain atoms follow the molecular threefold symmetry. The temperature parameters, however, of the isovaleryl side-chain atoms are all significantly higher than those of the valyl residues (Table III).

Davis and Tosteson[6] had proposed from their nuclear magnetic resonance studies that valinomycin complexes with sodium could exist in at least three distinct conformational states depending on the anion and the solvent. These different conformations for the sodium valinomycin complexes may be described in terms of the ligands in the coordination shell of the sodium ion. In low polarity solvents, where the sodium complexes exist predominantly as ion pairs, it was proposed that only three of the six available valine carbonyl groups of the depsipeptide were coordinated strongly to the sodium ion when bromide, SCN^-, or TNC^- was the counterion. An additional coordination site on the sodium ion was assumed to be occupied by the anion, thus giving an asymmetric character to the association between the sodium and the depsipeptide ligands.

Since our contention was that picrate would behave similarly to its chemical relative TNC^- and since our structural studies showed a weak interaction between the picrate anion and the potassium (Table VI), we looked for asymmetry in the coordination distances around the potassium ion. These distances are given in Table VI with those from the potassium valinomycin iodide[4] structure for comparison. The two crystal structures show identical coordination distances (within experimental error) with no asymmetry present. This agrees with Davis and Tosteson for the potassium valinomycin structure in the presence of picrate. We are starting investigation on the sodium valinomycin picrate to see if the picrate–sodium ion interaction is stronger and if asymmetry will show there.

In other ion–antibiotic complexes which have involved picrate as counterion, rubidium prolinomycin[22] (a synthetic analogue of valinomycin) showed no interaction between the rubidium and picrate—in fact the picrate anions were sandwiched between the valinomycin cylinders, far away from either of the open ends. Beauvericin barium picrate[23,24] always appears as a dimer with three picrate anions playing an important part in holding the dimer together and coordinating strongly to the barium ion. In this case involvement of the anion in the transporting cluster can explain the observed membrane transport results.[23]

The top and bottom of the valinomycin cation complex form pockets inviting the entry of a suitably shaped guest; an overall negative charge on the guest would help such as is the case of picrate on which the single negative charge is delocalized and not confined to the phenolate oxygen. As can be seen in the stereo drawing, the picrate and the xylene occupy these two pockets. The xylene fits rather loosely in the lactyl residue end, making one contact less than 3.5 Å and six others less than 4.0 Å. One methyl group of the xylene points directly into the bottom of the pocket and makes the closest contact.

The picrate is an equally flat disk but of greater diameter than xylene. Only the para-nitro group is capable of reaching into the pocket of the other (isovaleryl) side, the phenolate oxygen being framed and hindered by the ortho-nitro groups. The two oxygen atoms O(93) and O(92) of the para-nitro group impact with carbonyl atoms O(30), 3.03 Å, and O(56), 3.33 Å. Between them the potassium ion makes a weak contact of 3.86 Å with O(93) of the nitro group; a closer approach is prevented by O(30) and O(56). The picrate rests on the side of the pocket. The ortho-nitro groups contact two of the outward pointing isopropyl groups of the isovaleryl residues. Twenty-five contacts less than 4.0 Å are found and seven less than 3.5 Å. The other end of the picrate is pressed against the exterior of a neighboring valinomycin molecule making 34 contacts of less than 4 Å. Of particular interest is that the hydrogen bond between O(37) and N(53) is pressed very close against the picrate, the carbonyl O(37) is within 3.5 Å of O(94) and C(79) of the phenolate, and the peptide N(53) and C(50) are within 3.5 Å of O(90) on the para-nitro group of the picrate. The picrate also makes isolated contacts of less than 4.0 Å to four other neighboring valinomycin molecules.

Conclusions

There is a weak but definite interaction between the picrate anion and the potassium ion in the potassium valinomycin picrate complex. This suggests that the picrate anion could transport through artificial membranes as part of the potassium valinomycin

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complex. However, this complex is neutral and therefore electrically silent, and of itself does not explain the many observations concerning the effects of picrate on valinomycin transport. It may, however, be one of a number of different transport mechanisms operating simultaneously.

The structure seen here with the weak bond and reasonably compact fit between the valinomycin potassium complex and the picrate ion is probably a good model for the ion pair that would be found in a medium of low polarity such as organic solvents or lipid bilayer membranes. The contribution to the electrical conductance would depend on the extent of dissociation

$$(VK^+) + (P^-) \rightleftarrows (VKP)$$

and would be very dependent on the nature of the anion. As an example, it is easy to observe that a solution of valinomycin in chloroform will readily dissolve solid potassium picrate but will not dissolve potassium chloride. Another example would be the experiments of Ashton and Steinrauf,[26] who followed the valinomycin-catalyzed transport of potassium picrate from one water phase through a 1-cm thick barrier of chloroform into another water phase under the influences of different concentrations of potassium picrate and nontransportable ions. They showed that each potassium ion had to be transported with one picrate ion and that no transport took place if the picrate was entirely replaced by chloride. Further evidence for the neutral ion pair was found by Ginsburg et al.,[15] who followed the electrical conductance and cation fluxes of valinomycin facilitated transport through lipid bilayer membranes. Their proposed mechanism involved TNC^- as the principal charge-carrying species and the cation transport was considered due to the movement of neutral ion pairs.

Certainly the observation by Levitt et al.[25] that four water molecules are coupled to the potassium valinomycin complex during transport, a situation that does not hold for the uncomplexed valinomycin on its return through the membrane, can be interpreted as the pockets of the valinomycin–cation complex, providing a means of weakly binding the water molecules. This may be a better mechanism to explain the data of Levitt et al.[25] than having the water molecules in the interstices between the complex and the disordered lipid of the artificial membrane.

The weak association of the picrate does not produce any asymmetry in the coordination distances around the potassium ion. These results agree with previous nuclear magnetic resonance studies in solution for the valinomycin potassium complex in the presence of picrate.

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Supplementary Material Available: A table of observed and calculated structure factors (13 pages). Ordering information is given on any current masthead page.

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Tetraphenylarsonium 1,2,3,4,5-Pentakis(methylmercapto)cyclopentadienide

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Abstract: The title compound was prepared by reaction of stoichiometric amounts of sodium hydride, cyclopentadiene, and methyl disulfide in tetrahydrofuran. The title compound was characterized by NMR, IR, and cyclic voltammetry measurements. A three-dimensional crystal and molecular structure of $[(C_6H_5)_4As][C_5(SCH_3)_5]$ has been determined by an X-ray diffraction study. The compound crystallizes in the centrosymmetric monoclinic space group $P2_1/c$ [C_{2h}^5, No. 14] with a = 12.568 (2) Å, b = 15.948 (3) Å, c = 17.523 (3) Å, β = 106.98 (1)°, V = 3359.21 (10) Å^3, and ρ_{calcd} = 1.342 g cm^{-3} for Z = 4. The structure was solved via the tangent formula and standard Fourier techniques and was refined by using full-matrix least-squares refinement to conventional discrepancy indices of R_F = 8.65% and R_{wF} = 15.76% for the 2652 independent data with $\Delta F/\sigma(F_o) \leq 10.0$ and $F_o \geq \sigma(F_o)$. All atoms with the exception of methyl hydrogens were located. The crystal consists of formula units of $[(C_6H_5)_4As^+][C_5SCH_3)_5^-]$, cations and anions being separated by normal van der Waals distances, as are formula units from each other. All distances and angles within the tetraphenylarsonium cation are normal. The methylmercapto groups of the 1,2,3,4,5-pentakis(methylmercapto)cyclopentadienide anion have their configurations relative to the cyclopentadienyl ring fixed by packing forces within the crystal. Distances and angles within the cyclopentadienyl ring are normal. The S-C distances within the anion are reduced from the sum of the covalent radii for sulfur and sp^2-hybridized carbon which may indicate the possibility of multiple bonding.

In our current attempts to prrepare organic conductors based on neutral radicals,[1] we proposed that solids based on the theoretically relatively stable[2] cyclopentadienyl radical embedded in a chalcogen milieu may give rise to high conductivity. This hypothesis was based on the following facts: (a) pentaphenylcyclopentadienyl (A, Scheme I) is stable at room temperature in the solid state, (b) chalcogens (certainly sulfur[3]) tend to delocalize spin from a carbon framework to the chalcogen, and (c) chalcogens are free radical stabilizing substituents.[1,4]

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