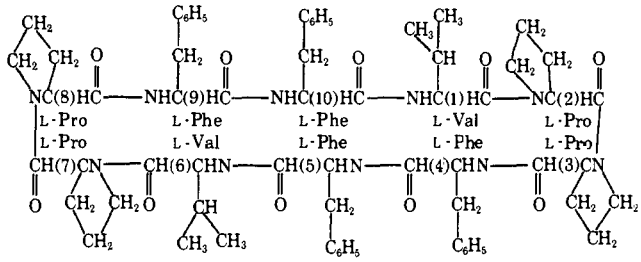
[Phe⁴,Val⁶]Antamanide Crystallized from Methyl Acetate/*n*-Hexane. Conformation and Packing

Isabella L. Karle

Contribution from the Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C. 20375. *Received February 22, 1977*

Abstract: [Phe⁴,Val⁶]Antamanide, a biologically active synthetic analogue of naturally occurring antamanide, crystallizes from *n*-hexane/methyl acetate in space group $P2_12_12$ with $a = 14.853$ (4), $b = 21.773$ (7), and $c = 12.061$ (6) Å, and $Z = 2$. The cyclic decapeptide backbone is elongated, rather than folded as in the alkali metal complexes of antamanide, with cis peptide linkages between the two pairs of Pro-Pro residues. Three molecules of H_2O are contained in the interior of the peptide ring and hydrogen bonding between the water molecules and NH or C=O groups of the peptide makes the 30-membered ring quite rigid. The peptide ring is also stabilized by two 5→1 hydrogen bonds (NH···O=C) of a type not previously encountered. The conformation is quite different than any conformations proposed for antamanide in solution based on nuclear magnetic resonance data or minimum energy calculations. Channels of a large diameter are formed in the lattice by the [Phe⁴,Val⁶]antamanide molecules in which the solvent molecules, *n*-hexane and/or methyl acetate, are grossly disordered.

The synthetic, biologically active, symmetric analogue of antamanide with the following formula (and numbering sequence):



has been crystallized from a solution of *n*-hexane and methyl acetate. This analogue is labeled [Phe⁴,Val⁶]antamanide since the Ala and Phe in positions 4 and 6, respectively, of natural antamanide have been replaced by Phe and Val residues.[1] Natural antamanide isolated from *Amanita phalloides,* as well as the [Phe⁴,Val⁶] analogue, antidotes to the liver toxin phalloidin, form Na^+ and Ca^{2+} complexes[1] selectively over K^+. Clues to the mechanism of complexation may be available from the study of the conformations of antamanides in the complexed and uncomplexed state, as well as the effect of polarity of the solvent on the conformation. The complexes Li^+-antamanide·CH_3CN[2,3] and Na^+-[Phe⁴,Val⁶]antamanide·C_2H_5OH[4] are isostructural with the alkali metal ion located in the interior in a polar cup while the exterior surface is covered by the lipophilic side chains, and the cup containing the alkali metal ion is covered with a molecule of the solvent such as ethanol, acetone, or acetonitrile. The only crystallographic study thus far of the uncomplexed state is the present one in which [Phe⁴,Val⁶]antamanide was crystallized from a mixture of nonpolar solvents, *n*-hexane and methyl acetate. The peptide backbone in the uncomplexed molecule is elongated as compared to the folded backbone in the alkali metal ion complex. Furthermore, several carbonyl groups have flipped to the exterior while all the NH groups are directed toward the interior in the uncomplexed state. These conformational changes between the complexed and uncomplexed states are reflected particularly in the changes in the torsional angles ψ_3 and ψ_8 from near +145 to +6° and in ϕ_5 and ϕ_{10} from near −96 to +60°.

A comparison between the conformations of the alkali metal ion complexes and the uncomplexed [Phe⁴,Val⁶]antamanide has already appeared in the literature.[5] The present paper is concerned with the structural details of [Phe⁴,Val⁶]antamanide, particularly the complexation of three H_2O molecules in the interior of the molecule, and the unusually large channels in the lattice containing the solvent molecules.

Experimental Section

Colorless, tabular crystals with a hexagonal outline, stable only in their mother liquor, were obtained by dissolving 10 mg of the dry peptide in 0.3 mL of methyl acetate and adding *n*-hexane dropwise until a slight amorphous precipitate appeared. Crystals of suitable size grew within several days. Both the peptide and solvent were carefully dried before crystallization; nevertheless, the crystalline cyclic peptide molecules were found to contain a number of water molecules within their interiors. The crystal used for data collection, a hexagonal tablet of maximum dimensions 0.6 × 0.9 × 0.3 mm, was sealed in a thin-walled glass capillary with a drop of mother liquor and intensity data were recorded on an automatic four-circle diffractometer with Ni-filtered Cu radiation to $2\theta_{max} = 110°$. Reflections beyond $2\theta_{max} = 100°$ were very weak and not included in the least-squares refinement; however, there were a small number of reflections in the 2θ range between 100 and 110° that had sufficiently large $|E_h|$ values to be useful in the phase determination. Parameters pertinent to the crystal are: space group $P2_12_12$ with $a = 14.853$ (4), $b = 21.773$ (7), and $c = 12.061$ (6) Å; $V = 3900.6$ Å³; $Z = 2$; molecular formula $C_{66}H_{82}N_{10}O_{10}\cdot xH_2O$ (where $x_{max} = 3$) + solvent; mol wt 1175.5 + xH_2O + solvent; number of independent reflections ($2\theta_{max} = 100°$) 2683. The cyclic peptide molecule must contain a twofold rotation axis coincident with the *c* axis of the cell.

Phase determination by the symbolic addition procedure[6] was hampered by erroneous indications of relationships among the six symbols used to represent unknown phases. The structure was solved by recognizing a structurally sensible fragment of eight atoms which was translated to the correct location by a translation function[7] and developed to the complete structure by using phases based on the fragment as starting phases for the tangent formula.[8] In retrospect, had all possible combinations of phase values been tried (e.g., 0 and Π for symbols assigned to reflections 202, 10,14,0, 13,1,0, and 041, and 0, Π, ±Π/2 for symbols assigned to 213 and 1,11,2), the correct assignment would have been among them (i.e., 0, 0, Π, Π, Π, and +Π/2, respectively)[9] and would have led to the structure more directly.

The approximate coordinates of the C, N, and O atoms in the peptide molecule obtained from the *E* map were refined by full-matrix least squares with isotropic thermal parameters. Difference maps revealed an atom labeled W_1, on the *c* axis, and another atom labeled W_2, with partial occupancy. The locations of these atoms in the interior of the peptide molecule and at appropriate distances for hydrogen bonding led to the assumption that W_1 and W_2 represent the O atoms of H_2O molecules. The presence of water molecules intimately associated with antamanide is confirmed by elemental analysis of thoroughly dried antamanide.[10,11]

Anisotropic refinement resulted in an agreement factor $R_F = 12.1\%$ for all the measured reflections. Further difference maps contained only random peaks with electron densities less than 0.5 e/Å³, even

Table I. Fractional Coordinates and Thermal Parameters[a]

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N_1	0.3532	−0.0461	0.0780	4.51	4.74	6.76	0.80	0.72	−0.83
C_1^{α}	0.2621	−0.0237	0.0932	3.85	4.37	9.96	0.90	1.09	−0.34
C_1'	0.2672	0.0454	0.1143	3.70	4.84	6.56	−0.61	1.16	0.61
O_1	0.3320	0.0717	0.1491	4.38	4.99	6.57	−0.39	0.59	0.21
C_1^{β}	0.2204	−0.0546	0.1989	8.15	4.07	14.05	1.38	4.14	1.57
C_{11}^{γ}	0.2042	−0.1249	0.1573	8.18	4.82	17.57	−1.25	−1.11	1.81
C_{12}^{γ}	0.2702	−0.0471	0.3034	10.28	8.20	8.55	0.75	1.21	0.67
N_2	0.1885	0.0766	0.0939	4.38	4.09	8.28	0.32	0.23	−0.14
C_2^{α}	0.1861	0.1430	0.1170	5.78	4.08	7.63	0.53	−0.70	−0.41
C_2'	0.1945	0.1524	0.2436	4.32	6.62	8.13	0.93	1.92	−0.40
O_2	0.1729	0.1138	0.3144	7.97	6.99	7.75	−1.42	2.65	0.28
C_2^{β}	0.0863	0.1611	0.0851	5.28	6.27	12.34	2.08	−1.60	−0.58
C_2^{γ}	0.0431	0.1060	0.0321	6.38	6.62	19.95	1.57	−4.41	−0.78
C_2^{δ}	0.0989	0.0530	0.0515	4.37	5.38	13.52	−0.35	−1.60	−0.85
N_3	0.2323	0.2082	0.2765	4.40	6.09	6.86	−0.03	0.61	−0.92
C_3^{α}	0.2567	0.2591	0.1983	4.53	3.47	9.86	0.32	0.44	−0.50
C_3'	0.3527	0.2586	0.1699	5.79	4.03	6.06	−0.82	−0.81	−0.49
O_3	0.3848	0.3001	0.1128	7.29	6.19	10.13	0.19	−0.49	2.60
C_3^{β}	0.2355	0.3166	0.2764	7.77	5.83	12.31	2.68	0.94	−2.51
C_3^{γ}	0.2528	0.2938	0.3942	12.02	7.82	8.81	0.03	−1.53	−2.70
C_3^{δ}	0.2316	0.2238	0.3977	8.24	9.19	8.23	−0.65	0.35	−3.28
N_4	0.4066	0.2129	0.2081	4.08	3.66	6.73	0.73	0.09	−0.09
C_4^{α}	0.5038	0.2159	0.1969	4.61	4.84	5.58	0.18	0.43	−0.00
C_4'	0.5415	0.1794	0.0940	3.16	4.36	6.22	0.15	−0.53	0.90
O_4	0.6083	0.1970	0.0499	4.68	4.17	8.05	−0.85	1.08	−0.41
C_4^{β}	0.5493	0.1931	0.2970	7.38	10.14	4.31	3.00	0.15	−0.41
C_4^{γ}	0.5162	0.2259	0.4020	5.59	16.27	6.79	3.72	−0.37	2.40
C_{41}^{δ}	0.5286	0.2909	0.4136	10.77	13.60	11.39	0.80	−0.02	−3.05
C_{42}^{δ}	0.4766	0.1941	0.4870	16.91	16.63	8.07	5.44	2.34	3.60
C_{41}^{ϵ}	0.5011	0.3264	0.5053	10.52	18.68	14.75	1.23	−0.23	−4.40
C_{42}^{ϵ}	0.4390	0.2272	0.5873	17.08	24.62	7.98	8.13	1.42	3.43
C_4^{ζ}	0.4671	0.2855	0.5841	12.69	19.60	12.11	2.08	−1.20	−3.57
N_5	0.4966	0.1279	0.0698	3.77	3.91	5.97	0.20	0.07	0.42
C_5^{α}	0.5221	0.0903	−0.0287	3.90	4.44	5.07	0.42	−0.10	−0.29
C_5'	0.6217	0.0668	−0.0237	5.06	3.60	7.24	−0.59	0.65	−0.65
O_5	0.6652	0.0657	−0.1072	5.13	6.73	8.10	1.54	1.47	1.17
C_5^{β}	0.5050	0.1241	−0.1388	4.99	6.37	5.80	0.47	0.24	−0.09
C_5^{γ}	0.4068	0.1397	−0.1516	6.18	5.64	5.01	1.39	−0.43	0.28
C_{51}^{δ}	0.3746	0.1972	−0.1238	7.40	6.05	6.29	2.09	0.76	0.81
C_{52}^{δ}	0.3460	0.0937	−0.1872	6.25	7.90	10.55	1.51	−2.28	−0.99
C_{51}^{ϵ}	0.2820	0.2111	−0.1380	8.54	8.34	9.39	2.53	0.82	2.78
C_{52}^{ϵ}	0.2548	0.1062	−0.1981	7.43	14.91	11.79	−2.35	−2.75	−2.59
C_5^{ζ}	0.2226	0.1690	−0.1749	7.23	12.26	12.38	3.20	−1.08	1.16
W_1	0.5000	0.0000	0.2394	9.51	17.46	5.95	0.00	0.00	0.00
W_2	0.3748	0.0827	0.3829	20.0[b]					

[a] Thermal parameters are of the form $T = \exp[-\frac{1}{4}(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$. [b] Isotropic value.

though there are large voids in the cell between the [Phe⁴,Val⁶]antamanide molecules in which solvent molecules must reside. Large differences between observed and calculated structure factors occur for the 001, 020, and 021 reflections, consistent with solvent molecules occupying the voids. The indications are that the solvent molecules, *n*-hexane and/or methyl acetate, are highly disordered.

Fractional coordinates and thermal parameters are listed in Table I, bond lengths and bond angles are shown in Table II, and Table III contains the conformational angles.

Results

The Peptide Molecule. Several stereodrawings of [Phe⁴,Val⁶]antamanide are shown in Figure 1. The 30-membered ring is elongated rather than folded as occurs in the Li^+ and Na^+ complexes of antamanide,[2-4] Figure 2. There are eight trans peptide linkages and two cis occurring between C_2^{α}–C_3^{α} and C_7^{α}–C_8^{α} of Pro²-Pro³ and Pro⁷-Pro⁸. The Pro-Pro groupings are the only segments that have similar conformations in the alkali metal complexes and the water complex of antamanide. As can be seen schematically in Figure 2, in the Na^+ or Li^+ complex, four carbonyl oxygens are directed toward the interior of the molecule to ligand with the alkali metal ion, while the protons on four NH groups are directed outward. Conversely, in the metal-free antamanide, protons on all six NH groups are directed toward the interior, while six carbonyl oxygens (O_3, O_4, O_5 and O_8, O_9, O_{10}) penetrate the lipophilic exterior.

The 30-membered ring in metal-free [Phe⁴,Val⁶]antamanide is relatively rigid as indicated by the values of the thermal parameters, mostly in the range 4–7 Å² for B_{ii}, for the "backbone" atoms, Table I (where $B = 8\pi^2\bar{\mu}^2$, $\bar{\mu}^2$ being the mean square amplitude of vibration). The rings in uncomplexed cyclic peptides are usually stabilized by internal transannular NH···O=C bonds of the 3→1, 4→1, and/or 5→1 types.[12] Similar internal hydrogen bonds (one for each of the six NH groups) have also been proposed for uncomplexed antamanide in nonpolar media as a result of spectroscopic analysis and potential energy minimization.[13] However, the present crystal-structure analysis shows that there are only two NH···O=C bonds in the molecule of a 5→1 type not previously reported. The detailed conformation of this 5→1

Table II. Bond Lengths (Å) and Angles (deg)[a]

	Val 1	Pro 2	Pro 3	Phe 4	Phe 5	Av
Bonds						
N_i-C_i^α	1.450	1.472	1.500	1.451	1.491	1.473
C_i^α-C_i'	1.529	1.546	1.467	1.577	1.566	1.537
C_i'-O_i	1.195	1.241	1.232	1.189	1.198	1.211
C_i'-N_{i+1}	1.374	1.394	1.356	1.337	1.358	1.364
C_i^α-C_i^β	1.569	1.581	1.597	1.470	1.540	1.551
C_i^β-C_i^γ	1.63 1.47	1.50	1.53	1.53	1.51	
C_i^γ-C_i^δ		1.44	1.55	1.43[b] 1.37[b]	1.38 1.42	
C_i^δ-C_i^ϵ				1.41[b] 1.51[b]	1.42 1.39	
C_i^ϵ-C_i^ζ				1.39[b] 1.34[b]	1.35 1.48	
C_i^δ-N_i		1.52	1.50			
Angles						
$C_{i-1}'N_iC_i^\alpha$	118.8	118.1	124.2	121.5	120.4	120.6
$N_iC_i^\alpha C_i'$	107.8	108.4	112.0	113.8	112.9	111.0
$C_i^\alpha C_i'N_{i+1}$	114.5	115.4	120.0	114.6	113.7	115.6
$C_i^\alpha C_i'O_i$	124.7	124.6	120.0	119.1	118.9	121.5
$N_{i+1}C_i'O_i$	120.8	119.9	119.9	126.1	127.2	122.8
$C_i'C_i^\alpha C_i^\beta$	107.8	106.4	109.6	108.2	110.2	
$N_iC_i^\alpha C_i^\beta$	109.0	102.8	99.3	111.5	112.6	
$C_i^\alpha C_i^\beta C_i^\gamma$	102 117	108	105	112	111	
$C_i^\beta C_i^\gamma C_i^\delta$		109	108	120 121	121 119	
$C_i^\gamma C_i^\delta N_i$		107	101			
$C_i^\delta N_i C_i^\alpha$		112	116			
$C_i^\delta N_i C_{i-1}'$		130	118			

[a] The standard deviations are of the order of 0.017 Å for bond lengths and 1.0° for bond angles for the backbone atoms and increase considerably for the side chains due to the high thermal parameters associated with atoms in the side chains. [b] The phenyl group in Phe[4] is disordered and the deviation in values for the bond lengths from 1.40 Å is a measure of the uncertainty in the positional coordinates for these atoms.

Table III. Conformational Angles[a] in [Phe[4],Val[6]]Antamanide·xH$_2$O

i	Val 1,6	Pro 2,7	Pro 3,8	Phe 4,9	Phe 5,10
ϕ_i(N-C$^\alpha$)	−112	−67	−98	−97	60
ψ_i(C$^\alpha$-C′)	159	153	4	−35	42
ω_i(C′-N_{i+1})	177	5	−170	177	−179
χ_{i1}	−72 56	−8	30	−54	−60
χ_{i2}		13	−30	−62 120	97 −80
χ_{i3}		−13	17		
χ_{i4}		8	3		
$C_i^\delta N_i C_i^\alpha C_i^\beta$		0	−21		

[a] The convention followed is that proposed by the IUPAC-IUB Commission on Biochemical Nomenclature (1970). The values are expressed in degrees.

Table IV. Contacts between Neighboring Molecules

Atoms at xyz[a]	Atoms at $\frac{1}{2}+x, \frac{1}{2}-y, -z$[a]	Separation, Å
O_3	C_2^γ	3.57
O_4	C_2^β	3.51
O_4	C_{51}^ϵ	3.43
O_4	C_5^ζ	3.70
O_5	C_3^β	3.44
C_{41}^ϵ	O_2	3.60
C_{61}^γ	C_{51}^ϵ	3.58

[a] Pairs of atoms with subscripts $i \pm 5$ will give rise to identical separations.

bond is shown in Figure 3. The remainder of the peptide ring is stabilized by the three H_2O molecules nestled in the interior of the peptide, Figure 1. The O atom of one H_2O molecule, W_1, is present at full occupancy and is located in the two-fold rotation axis of the molecule. It is an acceptor for two NH···O bonds (3.09 Å) from N_1 and N_6 and a donor to W_2 and its symmetry equivalent W_2' making weak OH···O bonds of 3.11 Å. W_2 and W_2' are donors to OH···O bonds (2.90 Å) with carbonyl oxygens O_1 and O_6. The protons on N_4 and N_9 are also directed toward W_2 and W_2'; however, the distances are too large to be considered as hydrogen bonds.

Atom sites W_2 and W_2' are only partially occupied. Prolonged drying of antamanide may have extracted some of the bound water. Under the circumstance when one or both W_2 water molecules may be absent from the interior of some of the [Phe[4],Val[6]]antamanide molecules, the phenylmethylene moiety of Phe[4] and Phe[9] can rotate about the C_4^α-C_4^β and C_9^α-C_9^β bonds and fill the void created by the absence of H_2O. The direction and magnitude of the thermal ellipsoids, i.e. the ellipsoids defined by the six B_{ij} values listed for each atom in Table I, associated with the phenyl group of Phe[4] (and Phe[9] by symmetry) indicate motions of 0.4 to 0.5 Å and rotations of the order of 6° about the C$^\alpha$-C$^\beta$ bonds. An examination of Figure 1c shows that the phenyl group in Phe[4] lies parallel to the pyrrolidine ring in Pro[3] and although the van der Waals radii for the two groupings make contact, there is no real barrier to the type of motion described above.

The interior of the water-complexed [Phe[4],Val[6]]antamanide molecule is polar with all six NH groups directed inward. All ten nonpolar side groups are directed to the exterior and the side groups on the four Phe residues are folded against the body of the molecule to make a compact lipophilic surface. The lipophilic surface, however, is not continuous but broken by three separate rows of polar atoms which protrude to the exterior: (1) carbonyl oxygens O_3, O_4, O_5; (2) carbonyl oxygens O_8, O_9, O_{10}; and (3) O_2, W_2, W_1, W_2', O_7. None of these atoms are involved in hydrogen bonding with neighboring molecules; however, the eight carbonyl oxygens that are directed to the exterior surface of the molecule make the closest contacts with atoms of neighboring molecules, Table IV.

The Solvent Channel. The structure reported in this paper represents a system that is only partially crystalline. The [Phe[4],Val[6]]antamanide·3H$_2$O complex obeys the symmetry elements of the space group and is repeated in all three axial directions to make a regular lattice. The packing of these molecules is shown in several views in Figure 4. Views (b) and (c) in Figure 4 show the continuous channels parallel to the a axis with a diameter of at least 4.7 Å, after taking into account the van der Waals radii of the atoms lining the channels. The solvent molecules, n-hexane and/or methyl acetate, that are contained in these channels do not obey crystallographic criteria for lattice formation although the crystalline lattice is not stable in the absence of the mother liquor. As discussed in the Experimental Section, the positions of the solvent molecules are grossly disordered in the channels. The size of the channels can allow free flow of the solvents, particularly of n-hexane where the largest van der Waals cross section is ~4.5 Å as compared to ~4.7 Å for the minimum diameter of the channel, although there is no physical evidence for free flow.

Concluding Remarks. Although the conformations of the Li^+ and Na^+ complexes of natural antamanide[2,3] and

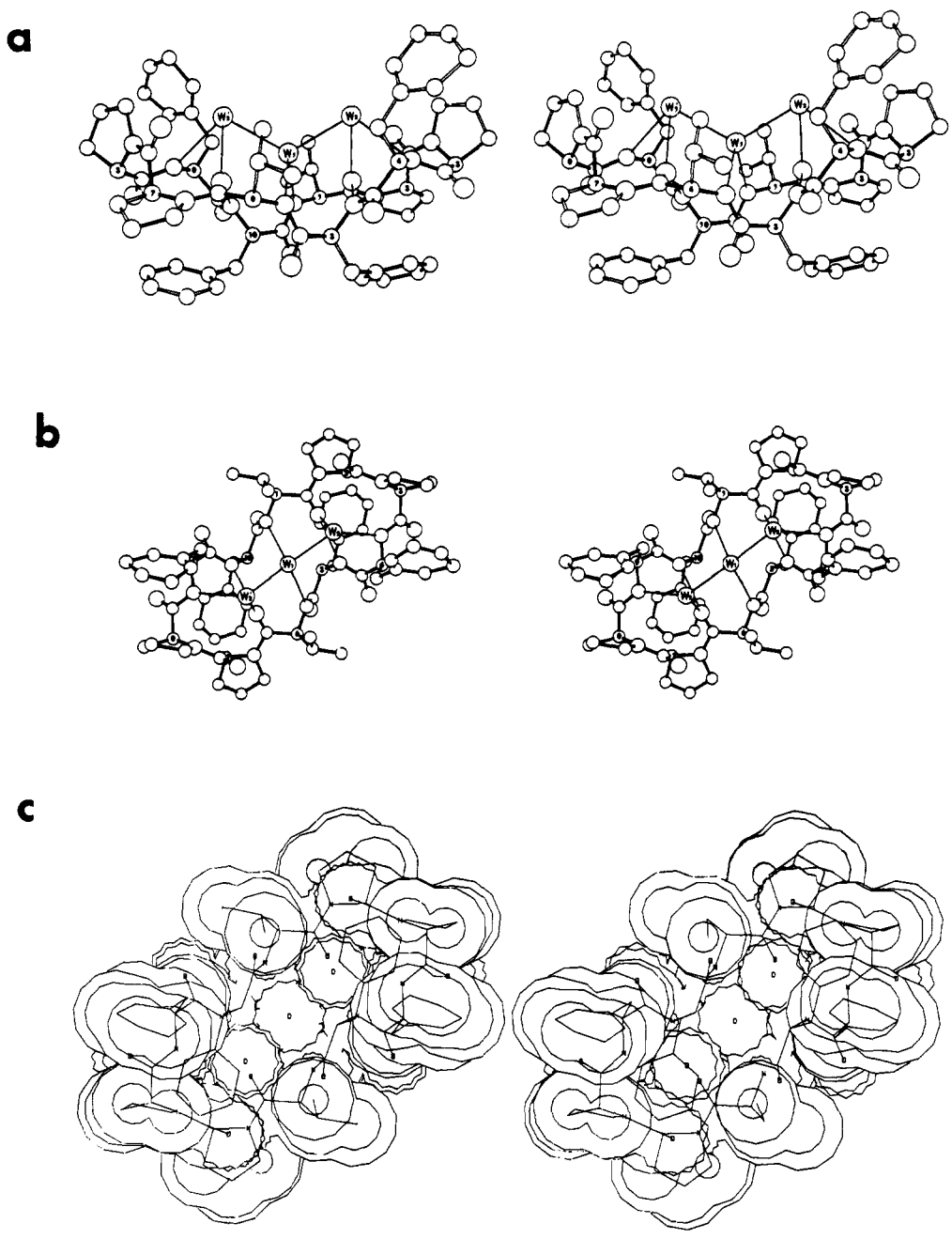


Figure 1. (a and b) Two views of [Phe^4,Val^6]antamanide·3H_2O at right angles to each other. The 30-membered ring is outlined by heavy bonds and the C^α atoms are numbered 1-10. The three atoms labeled W_1, W_2, and W_2' are the O atoms of three H_2O molecules. Hydrogen bonds are indicated by light lines. The stereodrawings were made by a computer program prepared by C. K. Johnson[17] using the experimentally determined coordinates listed in Table I. (c) van der Waals surfaces in [Phe^4,Val^6]antamanide·3H_2O (compare to view b). Radii for the atoms are r_C = 1.8 Å, r_O = 1.55 Å, and r_N = 1.45 Å with jagged edges for the N and O atoms surfaces. The sections were computed 1 Å apart. The stereodrawing was prepared by J. C. Hanson with the van der Waals surface program.[18]

[Phe^4,Val^6]antamanide[4] have been shown to be isostructural, independent of the nature of the polar solvent and substitution of some side groups, and the conformation of uncomplexed [Phe^4,Val^6]antamanide crystallized from nonpolar solvents has been shown to be grossly different from that in the alkali metal complexes, many questions still remain. Spectroscopic data on antamanide dissolved in various solvents[14,15] indicate large changes in conformation in going from polar to nonpolar solvents. Furthermore, substitution of cyclohexyl groups for phenyl groups renders antamanide biologically inactive even though this analogue still forms alkali metal complexes.[1] It is also believed that the Ca^{2+} complex is the biologically significant one.[16] Accordingly, crystals have been prepared and crystallographic data collected for the complexes and analogues shown in Table V. The structures have not been deduced yet; however, some observations can be drawn from the cell parameters and the intensity patterns. For example, perhydro[Phe^4,Val^6]antamanide crystallized from CH_3CN, a very polar solvent, and crystallized from a mixture of *n*-hexane and methyl acetate, nonpolar solvents, forms isomorphous crystals; hence it is expected that the conformation of this antamanide analogue in the crystal is not affected by the polarity of the solvent. In addition, many features of the diffraction pattern of [Phe^4,Val^6]antamanide, crystallized from polar solvents, are similar to those of the perhydro compounds, which is biologically inactive whereas the [Phe^4,Val^6] analogue is active. Finally, there are many similarities in the intensities for the *hk*0 reflections, as well as in the cell parameters, for

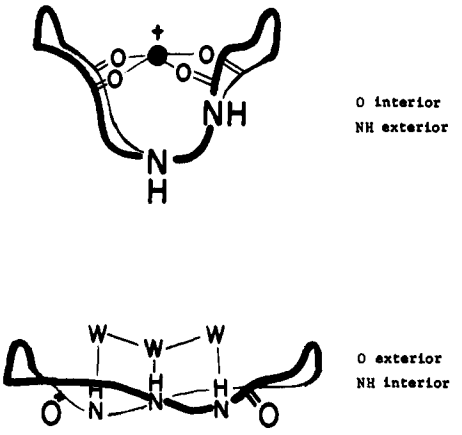


Figure 2. A schematic drawing showing conformational changes between alkali metal complexed antamanide (upper) and the metal-free antamanide (lower).

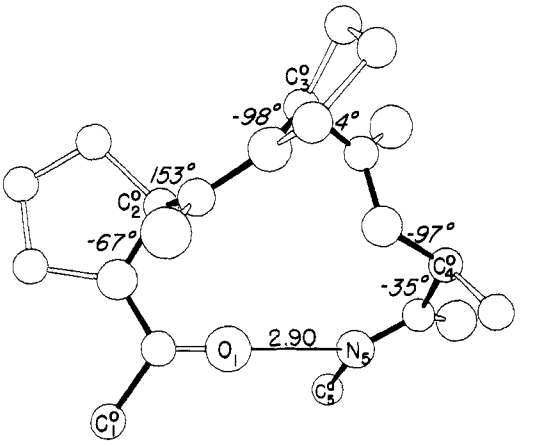


Figure 3. Details of the internal NH···O=C hydrogen bond of a new 5→1 type containing all L peptide groups and one cis peptide linkage. Values for the conformational angles and the $N_5 \rightarrow O_1$ hydrogen bond length are indicated.

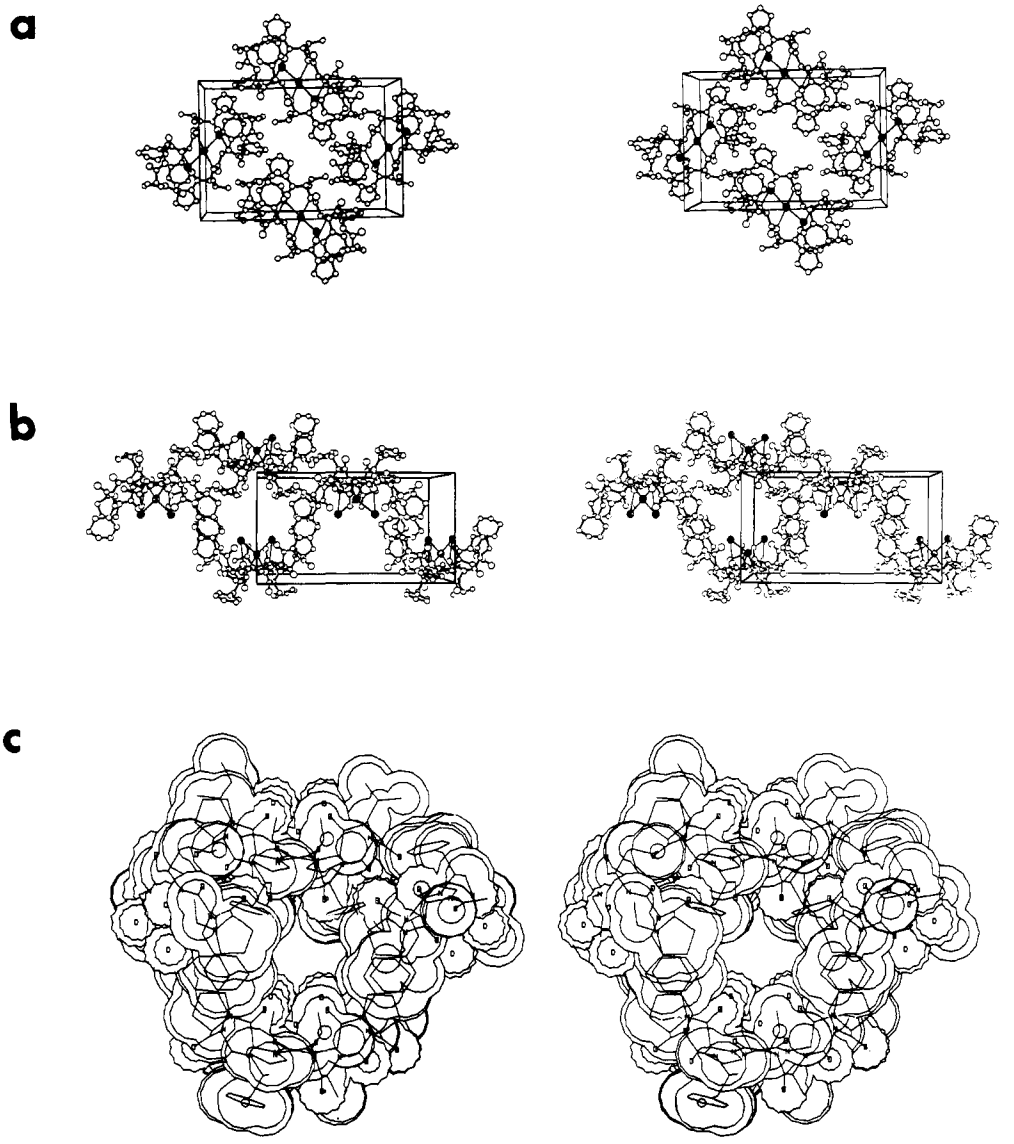


Figure 4. (a and b). Stereodiagrams[17] of the packing of [Phe[4],Val[6]]antamanide·3H_2O with the O atoms of the H_2O molecules indicated by dark circles. In view a the axial directions are: *a*, ↓; *b*, →; and *c* directed up out of the plane of the paper. In view b the axial directions are: *c*, ↑; *b*, →; and *a* directed up. (c) The solvent channel lined with atoms with their van der Waals surfaces (compare to view b). Atoms and their van der Waals surfaces from parts of four molecules within a 12-Å radius of the center of the channel at $y = 0$ are included. Surfaces of N and O atoms are represented by jagged lines. The stereodrawing was made with a computer program prepared by J. C. Hanson et al.[18]

Table V. Comparison of Crystal Parameters for Antamanide Complexes and Analogues

Compound	Solvent	Biol act.	Space group	Cell parameters a	b	c	β (if $\neq 90°$)	Vol/ molecular unit, Å^3	Ref
(Li^+-antamanide·CH_3CN)Br^-	CH_3CN	Yes	$P2_1$	11.91	23.21	13.86	110.7°	1792[a]	2, 3
(Na^+-[Phe^4,Val^6]antamanide·EtOH) Br^-	EtOH	Yes	$P2_12_12_1$	12.88	38.86	13.95		1746	4
Ca^{2+}-[Phe^4,Val^6]antamanide?	CH_3CN / Acetone	Yes	$P2_12_12$	15.08	21.92	11.02		1821	19
[Phe^4,Val^6]antamanide·$3H_2O$	*n*-Hexane / MeAc	Yes	$P2_12_12$	14.85	21.77	12.06		1950[a]	This paper
Natural antamanide	CH_3CN	Yes	$P2_12_12_1$	15.88	34.88	13.61		1885	
[Phe^4,Val^6]Antamanide	H_2O)	Yes	$P2_12_12_1$	20.19	21.12	16.13[e]		1719	
	Acetone[b] / H_2O								
Perhydro[c] [Phe^4,Val^6]antamanide	CH_3CN	No	$P2_12_12_1$	20.51	21.32	17.13[d]		1872	
Perhydro[c] [Phe^4,Val^6]antamanide	*n*-Hexane / MeAc	No	$P2_12_12_1$	20.46	21.14	17.17[d]		1856	

[a] Additional solvent in lattice. [b] Isomorphous with crystals from $EtOH/H_2O$ and Me_2SO/H_2O. [c] All phenyl groups replaced by cyclohexyl groups.[1] [d] Isomorphous. [e] *h*0*l* reflections similar to those in footnote *d*.

[Phe^4,Val^6]antamanide crystallized from a solution containing Ca^{2+} ions and the H_2O complex reported in this paper.[19]

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Supplementary Material Available: Tables of observed and calculated structure factors (12 pages). Ordering information is given on any current masthead page.

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(19) NOTE ADDED IN PROOF. The structure of [Phe^4, Val^6]antamanide crystallized from a solution containing $Ca(NO_3)_2$, acetone and CH_3CN will appear in *Proc. Nat. Acad. Sci. U.S.A.* in July, 1977.