vapor pressure of ordinary water to the prevailing humidity. At low temperatures the solution may separate into two phases, as other macromolecular solutions do (*16*). This process is in accord with observations (*1–6*).

After ordinary water condenses, there would be occurring simultaneously the processes of physical absorption of ordinary water by the solution, diffusion of water and of oligomers of low molecular weight into vapor, and diffusion of water, oligomers, and polymer in the solution. Condensation of ordinary water around the polymer molecules probably terminates or inhibits the growth of the polymer chain. This is suggested by the fact that vapor must be allowed to diffuse to a capillary wall in order to produce polywater. For example, an activated complex consisting of the growing polymer chain, a water molecule, and ions may be important kinetically in a polywater (nonpolar) environment but may be energetically less favored in ordinary water because of the relatively high dielectric constant. Alternatively, site poisoning or termination of chain propagation by water-soluble impurities might occur. The role of ordinary water in inhibiting its own conversion from liquid polymer thus becomes explicable if the polywater has markedly different solvent properties from those of ordinary water; this inhibition would account for the fact that all water does not convert to polywater, although, because of the spontaneous formation, one may conclude that the free energy of the polymer is lower than that of ordinary water.

Since submission of this report, several physical measurements of polywater that are qualitatively consistent with the above proposals have been reported. These include a proton resonance spectrum consisting of a single broad line (*17*), a very low microwave dielectric constant (*18*), and sharp x-ray diffraction rings characteristic of liquid crystals (*19*).

Note added in proof: This report was submitted before the article by Allen and Kollman (*20*) became available. Although CNDO/2 molecular orbital computations on a bridged structure were included in that study, the structure calculated was the diprotonated tetramer, $H_{10}O_4^{2+}$, so the results are not applicable to the present discussion.

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Solution Conformation of Valinomycin–Potassium Ion Complex

Abstract. *The complete conformation of the valinomycin–potassium ion complex in methanol is presented. Extension from the reported secondary structure requires arguments and data relating to ester orientation, direction of coiling, side-chain orientation, and conformational stability. Conformation of the valinomycin–potassium ion complex provides a clear-cut example in which elucidation of conformation is sufficient to gain an understanding of molecular function which, in this case, is selective ion transport by a carrier mechanism.*

Knowledge of primary structure of polypeptides and proteins has afforded limited information concerning the mechanism whereby a biomolecule functions. Certain biomolecules facilitate ion permeation of membranes with a high degree of selectivity of, say, potassium ion over sodium ion. One example is valinomycin, which selectively binds potassium. The solution conformation of the valinomycin–potassium ion complex shows that the potassium ion is held in a polar core of proper dimensions for binding the nonhydrated ion, while at the same time the complex presents a nonpolar exterior to the surrounding

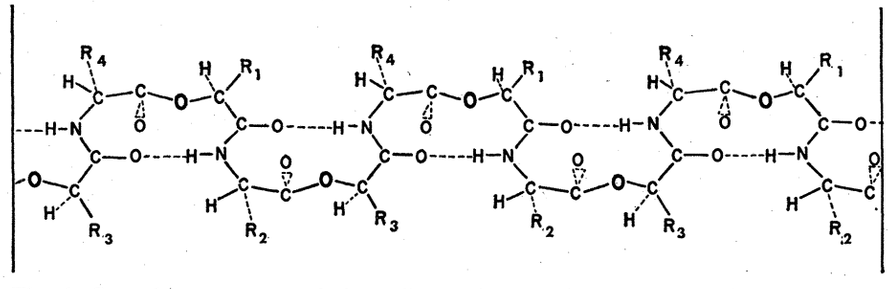

Fig. 1. Secondary structure of the valinomycin–potassium ion complex in methanol solution. The vertical bars at left and right should be brought together by curving the plane of the paper away from the observer. $R_1 = CH_3$; and $R_2 = R_3 = R_4 = CH(CH_3)_2$. The acyl oxygens of the ester moiety are pointing into the paper in accordance with the beta-turn considerations.

medium. Thus the valinomycin–potassium ion complex is presented as a carrier-type model system for approaching the problem of selective ion permeation of membranes.

Valinomycin is a cyclic dodecadepsipeptide antibiotic from *Streptomyces* with threefold symmetry in its sequence of residues [L-Lac-L-Val-D-HyV-D-Val]$_3$ (*1*). Infrared (*2*) and nuclear magnetic resonance (*3*) studies on the valinomycin–potassium ion complex in solution have shown that all six amide protons are intramolecularly hydrogen bonded. These results allow one to conclude that the secondary structure indicated in Fig. 1 is the correct one. A representation of secondary structure falls short of a complete determination of conformation for three reasons. The first reason depends on the orientation of the end ester moiety, that is, whether the acyl oxygen of the ester points up or down. The second reason depends on whether closure occurs to form a ring structure, that is, whether the center of curvature for the closed ring is above or below the plane. The third reason is that the orientation of the side chains needs to be determined. We now report our efforts to clarify these points and thereby present the complete conformation of the valinomycin-K+ complex in methanol.

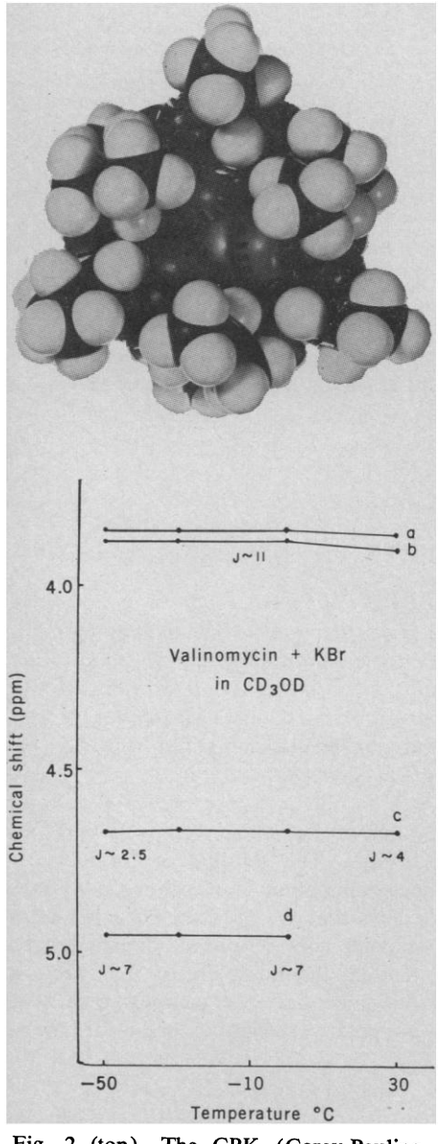

Fig. 2 (top). The CPK (Corey-Pauling-Koltun) molecular model of the "core" structure of the valinomycin–potassium ion complex seen from the R_2 and R_3 end. The αCH-βCH orientation is seen to be *trans* for the L-valyl residue (R_2) and *gauche* for the hydroxyisovaleryl residue (R_3). Fig. 3 (bottom). Temperature effect on the α-proton chemical shift and on the αCH-βCH coupling constant of the valinomycin–potassium ion complex in CD_3OD. These effects indicate a relatively rigid structure. Points at *a* and *b* are assigned to the D- and L-valyl residues, and points *c* and *d* to D-HyV and L-Lac, respectively. *J*, spin-spin coupling constant.

The secondary structure in Fig. 1 is essentially a series of beta turns or beta folds in which the end group is an ester instead of a peptide moiety. As shown by Geddes *et al.* (*4*) in their x-ray analysis of the antiparallel pleated sheet of silk fibroin, the beta turn is preferred when the sequence of residues comprising the turn are a glycyl residue followed by a residue of the L configuration. Venkatachalam (*5*) and Urry and Ohnishi (*6*) have extended conformational energy argument to the sequence D→L and L→D which would result in the acyl oxygen pointing in opposite directions. With the NH_2-terminus on the left and the beta turn seen as an inverted U, the acyl oxygen would point down for D→L and up for L→D. The orientation of the end ester is indicated in Fig. 1 when R_1 = methyl; $R_2 = R_3 = R_4$ = isopropyl; and the absolute configurations are as shown. The sequence numbering corresponds with that of the repeating unit in the opening sentence.

If the structure in Fig. 1 is coiled on a center above the plane, a "pore" structure is formed with a diameter of about 4.5 Å. This is approximately the correct size for hydrated potassium ion. The acyl oxygens would point outward. When the center of curvature is taken below the plane, a "core" structure is obtained with the acyl oxygens pointing in. This leaves a small cavity of proper dimensions for binding nonhydrated potassium ion in an octahedral field formed by acyl oxygens. The demonstration by Haynes *et al.* (*7*) of less than two water molecules per complex argues for the "core" structure shown in Fig. 2. The structure in Fig. 2 is a correction of the conformation in the Ohnishi and Urry paper on the secondary structure (*3*); there the acyl oxygens were pointing up, and the center of curvature was taken above the plane. Even though the difference in end result is subtle, it is significant. The structure in Fig. 2 is consistent with the x-ray studies of Pinkerton *et al.* (*8*). This substantiates the extension of the beta-turn considerations to include end ester groups, in agreement with the x-ray work on enniatin B (*9*).

The conformation of the valinomycin–potassium ion complex is completed by determining the orientation of the isopropyl side chains. The slow exchange of the amide protons in CD_3OD allows assignment of the high-field α proton resonances to valyl residues. These residues exhibit an αCH-βCH coupling constant of 11 hz, indicating the *trans* conformation. At room temperature the αCH-βCH coupling constant for the hydroxyisovaleryl residue is about 4 hz, giving a predominantly *gauche* orientation. Figure 3 contains the coupling constants and chemical shifts for the α protons as a function of temperature. The constancy of the chemical shifts and coupling constants indicates a relatively rigid structure.

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