X-Ray Crystallographic Evidence for the Conformation of Gramicidin S

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Summary Evidence is presented for the invariance of the conformation of the peptide antibiotic gramicidin S in the copper complex.

IN the last few years much interest has been centred on conformational aspects of natural cyclopeptides as peptide antibiotics.

Conformational studies based on theoretical calculations[1] as well as experimental results (mainly from n.m.r. experiments)[2] have shown that these peptides have definable conformations. We have studied the conformation of gramicidin S, a natural cyclodecapeptide corresponding to the formula:

$$\text{—(Pro–Val–Orn–Leu–D-Phe-)}_2$$

as a part of a research programme on the stability of the conformations of polypeptide chains.[3]

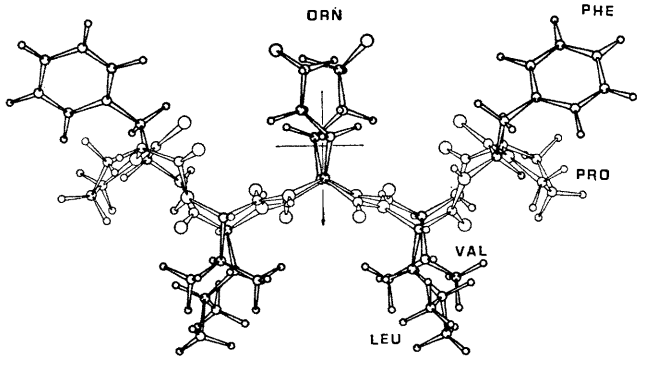

FIGURE 1. *Projection of molecular conformation of Gramicidin S on a plane containing the dyad axis.*

Crystallographic studies were initiated some fifteen years ago by Hodgkin and Oughton[4] but no conclusive results have been obtained so far.

Recently we derived a molecular conformation of gramicidin S,[5] on the basis of conformational calculations taking into account the available experimental data. This conformation is characterized by a dyad axis which relates the two chemically equivalent parts of the molecule, containing four hydrogen bonds; other structural features are consistent with the experimental evidence.

The projection of the molecular structure on a plane containing the dyad axis is shown in Figure 1. As may be seen, one feature of this conformation is the proximity of the δ-amino-groups of the two ornithine residues. To confirm this point we tried to synthesize a gramicidin S derivative where the two δ-amino-groups were linked, while at the same time preserving the molecular conformation.

Thus we prepared the salicylaldehyde Schiff base(reaction with both amino-groups) in ethanol solution and then the

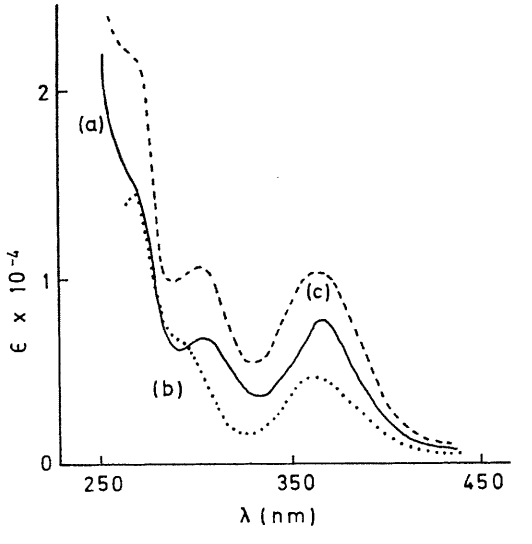

FIGURE 2. *U.v. absorption spectra of* Cu-*bis-salicylaldiminato-gramicidin-S*; (a) *and copper chelates of salicylaldimine* (b) *and* N *-methylsalicylaldimine* (c).

Cu^{II} complex of the gramicidin S bis-salicylaldiminato-derivative by addition of a stoicheiometric quantity of copper acetate in the presence of sodium acetate.

The u.v. absorption spectrum ($CHCl_3$) of the complex is shown in Figure 2, together with those of related copper chelates of salicylaldimine.[6] The common features suggest that both the Schiff-base functions at the δ-amino-groups of the ornithine residues are involved in the complexation and that a 1 : 1 complex is formed.

The complex crystallizes from pyridine–ethanol on slow evaporation at room temperature in well formed olive-green hexagonal crystals.

The space group is hexagonal $P6_122$ or the enantiomorphous one $P6_522$, $Z = 18$, $a = b = 27{\cdot}0$, $c = 55{\cdot}2$ Å (using a precession camera with Cu-K_α radiation).

The reflection pattern suggests the presence of three quasi-equivalent stacks of molecules containing six-fold screw axes; this rules out the formation of dimers or oligomers.

The cell parameters as well as the distribution of the intensities are very similar to those found by Hodgkin for acetyl-, chloroacetyl-, and iodoacetyl-gramicidin S.[4]

This strict isomorphism proves the invariance of the molecular conformation of gramicidin S in the copper complex and consequently gives support to an important aspect of the molecular structure in agreement with our model.

The analysis of the crystal structure is in progress.

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