03.2-5 RENIN INHIBITORS: STRUCTURAL STUDY REGARDING STATINE IN LINEAR OLIGOPEPTIDES. By G. Précigoux, S. Geoffre, M. Hospital, Lab Cristallography, University of Bordeaux I, Talence, France.

The proteolitic enzyme cleaves the substrate angiotensinogen to yield angiotensin I, the decapeptide substrate transformed by converting enzyme into the octapeptide pressor substance angiotensine II. Interruption of this proteolitic cascade by inhibition of renin could be a way to treat hypertension.

The general aspartyl protease inhibitor pepstatin is a naturally occurring pentapeptide containing two units of statine, an unusual amino acid.

To try to understand the conformational role of the statine residue, we have solved the crystal structures of two pepstatin analogues, I and II.

pepstatin

Isovaleryl - Val - Val - Sta - Ala - Sta

analogues

I Boc - Leu = Leu - Sta - Ala - Sta - OMe

II Boc -DLeu = Leu - Sta - Ala - Sta - OMe

For anologues I and II the notation "=" is an abbreviation for ψ(C=C, *trans*).

In spite of very different environments and interactions in the crystals, the observed conformations for molecules I and II are almost identical at the level of the central statine. The peptide main chain is folded back at the Sta and Ala residues to form a twelve membered ring with an intramolecular hydrogen bond between the carbonyl oxygen of leu and the nitrogen atom of the last statine residue.

03.2-6 CONFORMATIONAL ANALYSIS OF ANGIOTENSINOGEN FRAGMENTS. By S.Geoffre, M.Benkoulouche, M.Cotrait, G.Précigoux, Lab Cristallography, University of Bordeaux I, France.

The (6-13) equine angiotensinogen octapeptide (his-pro-phe-his-leu-leu-val-tyr), is described as the minimum endogenic substrate sequence needed for efficient renin activity. We have studied the conformations of several fragments or analogs, in order to determine the most probable conformation in the neighbourhood of the "leu-leu" scissile bond.

6 *13*

HIS-PRO-PHE-HIS-LEU-LEU-VAL-TYR

I Ac-PRO-PHE-LEU

II LEU-LEU-VAL-TYR (OMe)

III Ac-PRO-PHE-HIS

IV ØOCH2CO-LEU-VAL-PHE (OMe)

V HIS-PRO-PHE-HIS

VI (OH)-LEU-VAL-PHE (OMe)

The I, II, III, IV, VI, oligopeptides have been crystallized in a form suitable for X-Ray analysis. We have observed:

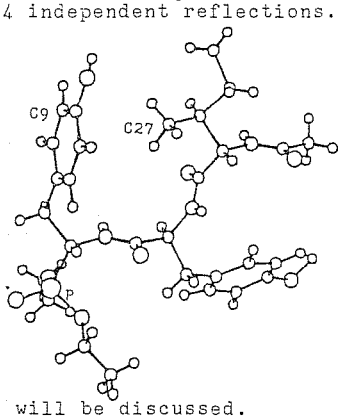
- the(6-9) N-terminal part presents a type I β-bend at pro-phe with intramolecular hydrogen bond between O(Ac) and NH(His).A theoretical conformational analysis of V, confirms this type of β turn.

- the C-terminal part observed in the crystals of II, IV, VI, is in β-pleated sheet conformation with the side chains alternatively situated on the left and right of the main chain.

03.2-7 Structural Study of Novel ACE Inhibitor K26. N.Hirayama,M.Kasai&K.Shirahata,Tokyo Research Laboratories,Kyowa Hakko Kogyo Co.Ltd. 3-6-6 Asahimachi,Machida,Tokyo 194,JAPAN.

K26(N-acetyl-L-Ile-L-Tyr-(-)-1-amino-2-(4-hydroxyphenyl)ethylphosphonic acid)was isolated from the culture broth of Actinomysetes,and shows potent inhibitory activity to angiotensin I converting enzyme(ACE). The X-ray analysis of a diethyl ester of K26 was undertaken to establish the absolute configuration of 1-amino-2-(4-hydroxyphenyl)ethylphosphonic acid moiety(Tyr-P) and the conformation.

The crystal data are as follows: $C_{29}H_{42}O_8N_3P$, C2, a=25.666(9), b=9.590(8), c=13.557(2)Å, β=91.65(2)°, Z=4. The structure was solved by MULTAN75 and refined by full-matrix least-squares to a final R=0.092 for 1444 independent reflections.



The absolute configuration was determined to be (R). Although the tripeptide backbone takes rather extended conformation,the side chain of Ile is located near the phenyl ring of Tyr-P(C9···C27=3.46Å).The χ_1 and χ_2 of Tyr-P are 295 and 139°,respectively. There is an intramolecular environment similar to that of captopril. Interactions between ACE-like proteins and K26 will be discussed.

03.2-8 THE MOLECULAR STRUCTURE OF DIDEMNIN B, AN ANTIVIRAL AND CYTOTOXIC DEPSIPEPTIDE. By M.B, Hossain and D. van der Helm, Department of Chemistry, Oklahoma University, Norman, OK, USA. J. Antel and G.M. Sheldrick, Inst. F. Anorg. Chemie, Universität, Göttingen, FRG. S.K. Sanduja and A.J. Weinheimer, Department of Medicinal Chemistry, University of Houston, Houston, Texas, USA.

Didemnin B, a highly active depsipeptide was originally isolated from a Caribbean tunicate of the family Didemnidae and a chemical structure for the compound was proposed from spectroscopic and chemical studies (K.L. Rinehart, J.B. Gloer, J.C. Cook, S.A. Mizsak and T.A. Scahill, J. Am. Chem. Soc., 1981, 103, 1857-59):

R→ MeLeu→ Threo→ Sta→ Hip→ Leu→ Pro→ Me_2Tyr→ O (cyclic)

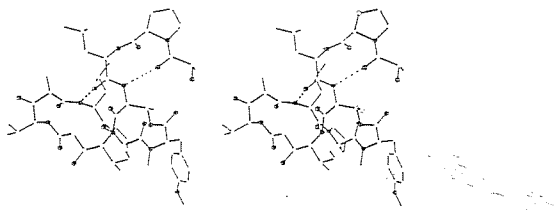
where R = $CH_3CHOHCO$→ N→ CH→ CO→ (CH → CH_2 → CH_2 → CH_2 → N)

and Hip is hydroxyisovalerylpropionyl.

The X-ray structure determination of depsipeptide revealed a slightly modified structure, showing the presence of iso-statine instead of statine. The depsipeptide ring is substantially folded and the overall molecular conformation is stabilized by three intramolecular N-H...O hydrogen bonds (shown by dashed lines in the Figure). Details of structural results will be presented.

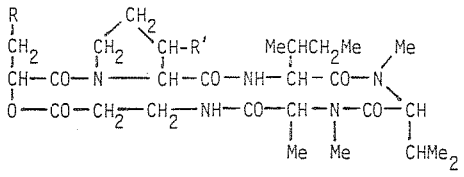
Crystal Data: $C_{57}H_{89}O_{15}N_7 \cdot 1.5C_6H_6 \cdot H_2O$, orthorhombic, $C222_1$, a = 14.990(3), b = 22,574(4), c_3 = 41.112(9) Å, V = 13912 Å^3, Z = 8, D_x = 1.190 gm cm^{-3}, CuKα radiation,

7699 reflections, $2\theta_{max}$ = 150° at 138K. Structure was determined by direct methods (G.M. Sheldrick, "SHELXS-86") and refined by block-diagonal least-squares to a final R = 0.046 for 7074 observed reflections.



03.2-9 THE CRYSTAL STRUCTURE OF DESTRUXIN B. By J. L. Rios Steiner and C. L. Barnes, Department of Chemistry, University of Puerto Rico, Rio Piedras, P.R., U.S.A. 00931.

The destruxins are a family of cyclohexadepsipeptides produced by the entomapathogenic fungus Metarrihzium anisopliae (Pais, M., et al, Phytochemistry, 1981, 20, 715-723). The molecular structure of Destruxin B, a member of this family, is shown below. The backbone conformation of Destruxin B is very similar to that of Roseotoxin B. a related mycotoxin isolated from cultures of Tricothecium roseum (Springer, J. P., et al, J. Am. Chem. Soc., 1984, 106, 2388-2392).



Destruxin B R = $CHMe_2$ R′ = H

Roseotoxin B R = $CH=CH_2$ R′ = Me

Intensity data were collected on an Enraf-Nonius Cad4 diffractometer at room temperature using CuK_α radiation to $2\theta_{max}$=150°. The structure was solved using Direct Methods and refined to a final unweighted R of 5.1% for 3718 observed reflections ($I>3\sigma(I)$).

03.2-10 THE CONFORMATION OF THIOAMIDE CONTAINING PEPTIDES. By Troels la Cour, Department of Chemistry, Aarhus University, Denmark.

Endothiopeptides are oligopeptides in which one or more oxyacyl moities in peptide groups are replaced with thioacyl moities. The paper will describe results from structural studies of small thiopeptide containing peptides. It is shown that the geometry of the peptide backbone is unaffected by this replacement and that the conformations of (ϕ, ψ) around C_α carbon atoms in proteins are also stereochemically favourable for thiopeptides.

The use of thiopeptide analogs of naturally occurring peptides could be of benefice in the study of for example structure/function relationship in enzymic catalysis. Another application of this type of peptide modification is in the field of medicinal chemistry, since the digestion pattern of thiopeptides is different from that of normal dietary proteins.

03.2-11 PREFERRED CONFORMATIONAL STATES OF GLYCINE - CONTAINING PEPTIDES. By E. Subramanian, Department of Crystallography and Biophysics, University of Madras, Madras 600025 and V. Ganesh, Department of Physics, Indian Institute of Technology, Madras 600036, India.

The crystal structures of several tripeptides with defined sequences have been analysed to investigate the influence of immediate neighbours on the conformational states of a given residue. In view of the numerous possible tripeptides (20x20x20 = 8000), the analysis has been restricted to the subsets of tripeptide sequences such as x-gly-gly and gly-gly-x in order to determine the conformational preferences of the middle glycine residue. Presently, crystal structure studies are available for pro-gly-gly (V. Lalitha, E. Subramanian and R. Parthasarathy, Int. J. Peptide Protein Res., 1986, 27, 223), val-gly-gly (V. Lalitha, R. Murali and E. Subramanian, Int. J. Peptide Protein Res., 1986, 27, 472), ala-gly-gly (E. Subramanian, and V. Lalitha, Biopolymers, 1983, 22, 833), leu-gly-gly (K.N. Goswami, V.S. Yadava and V.M. Padmanabhan, Acta Cryst., 1977, B33, 1280), trp-gly-gly (E. Subramanian, unpublished), tyr-gly-gly (W.M. Carson and M.L. Hackert, Acta Cryst., 1978, B34, 1275), leu-gly-gly-gly (T. Srikrishnan and R. Parthasarathy, unpublished), gly-gly-val (V. Lalitha, E. Subramanian and J. Bordner, Int. J. Peptide Protein Res., 1984, 24, 437), gly-gly-ile (V. Lalitha, E. Subramanian and J. Bordner, Int. J. Peptide Protein Res., 1984, 24, 123), gly-gly-phe (R. Murali and E. Subramanian, Int. J. Peptide Protein Res., 1987, in press) and gly-gly-gly (V. Lalitha and E. Subramanian, Cryst. Str. Commun., 1982, 11, 561). We find that the middle glycine adopts a 'D-residue' type of conformation when preceded or followed by a residue with aromatic side-chain or a side-chain with branching at C^γ atom. Empirical energy calculations also confirm this observation.