PS05.02.03 STRUCTURE AND CONFORMATION OF SEQUENTIALLY RELATED PEPTIDES: CRYSTAL STRUCTURE OF L-PHENYLALANYLGLYCYLGLYCINE (FGG). T. Srikrishnan and Seth Hoffman, Center for Crystallographic Research and Department of Biophysics, Roswell Park Cancer Institute, Buffalo N.Y. 14263

A systematic structural investigation of sequentially related peptides is of great importance for the elucidation of the structure-function relationship of peptides and in deducing the possible conformations of polypeptides. Although GGG has an extended anti-parallel ß-structure, crystal structures of other tripeptides of the sequence GGX and XGG show a wider range of conformations ranging from the extended, many kinds of folded conformations to a few helical conformations. In this line of investigation, the crystal structure of FGG was undertaken in our laboratory. Crystals of FGG ($C_{13}H_{17}N_3O_4$), grown by slow evaporation from an aqueous ethanol solution, are orthorhombic, space group $P2_12_12_1$, with the following cell dimensions: a= 5.459 (5), b=15.299 (6), c=16.047 (6) Å, V= 1340.2 Å^3, D_o= 1.38 g/c.c, D_c= 1.384 g/c.c and Z=4. Complete three dimensional data was collected on a CAD 4 diffractometer (2643 reflections, 2305>3σ). The structure was solved by the application of direct methods and refined to a final R factor of 0.031. The molecule exists as a zwitterion in the crystal. The peptide units are trans planar (ω_1= -178.6 and ω_2 = 175.6 °). The peptide backbone is folded with the torsion angles of Ψ_1 = -116.7, ω_1= -178.6, Φ_2= 88.8, Ψ_2=29.4, ω_2= 175.6, Φ_3= -135.6 and Ψ_3= -8.2°. For the phenyalanine side chain, χ_1= 123.4 and χ_2= -56.3°. The molecules are linked together intermolecularly in an infinite sequence by head to tail hydrogen bonds, as is typical of charged peptides.

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PS05.02.04 STRUCTURAL FEATURES OF STEREOISOMERIC ANALOGS OF CYCLOTETRADEPSIPEPTIDE [-(MeVal-Hyi)2-]. G. Tishchenko, Institute of Crystallography, Moscow Russia

DLLD(1),LDLD(2),DDDL(3),LDDD(4), DDDD(5), LLDD(6) stereoisomers of c[-(MeVal-Hyi)2-] were investi- gated by X-ray structure analysis. Cycles 1-5 have slightly elongated forms, asymmetric in 3,4, 5, centrosymmetric in 1, with C2 pseudoaxis in 2. The cycle 6 is square. Ester groups are trans in all cases, amide - cis in 1-5 and trans in 6. C=O groups are disposed in pairs under and above mean cycle plain in 1,6; on one side of it in 2,3. One C=O group (of Hyi2 in 4, of Val3 in 5)is directed inside the cycle, opposite to three others.In all molecules, exept 3, experimental conformations are close to calculated ones with minimal total energy. There is the conformation with energy slightly differing from minimal one in 3. The calculation was not carried out for the unique all-trans conformation 6.In crystal 5 there are two independent molecules with very close conformations. The most pronounced difference between these molecules is the side chains orientation of the residue 4 (trans and gauche). Experimental phi,psi-points are situated mainly near k and p-q minima on conformational maps for the model compounds Ac-L-MeVal-OMe and Ac-D-Hyi-NMe2. Exept the residues MeVal in 6, Hyi in 3, MeVal3 and Hyi2 in 5. This result agrees well with phi, psi-points arrangement near the other minima on conformational maps: l and r for 6 and 3, l and r simultaneously for 5 (minimum r is weak), as well as with yealds of cyclization reactions of the linear molecules. If for 1,2,4 yeald is 70-75%, for 3 and 6 40-45%, then for 5 it is only 8%. All structures were solved by direct method with full-matrix least squares refinement. R-factors are 0.066, 0.086, 0.11, 0.055, 0.051 and 0.049 for structures 1-6 respectively.

PS05.02.05 CRYSTAL STRUCTURES OF PEPTIDES DESIGNED TO MIMIC PROTEIN SECONDARY STRUCTURAL ELEMENTS K. R. Rajashankar, S. Ramakumar, V. S. Chauhan, Department of Physics, Indian Institute of Science, Bangalore, India and ICGEB, Aruna Asaf Ali Marg, New Delhi, India

Peptides containing a,ß-dehydroamino acid residues are found to exhibit specific conformational preference and altered biological activity. They are found in many naturally occurring peptides and proteins of microbial and fungal origin. In particular, a,ß-dehydro phenylalanine (ΔPhe), has become one of the most promising conformation restricting residue useful in peptide design. Theoretical and experimental studies on oligopeptides containing ΔPhe residues have demonstrated the potential of ΔPhe residues to induce folded conformation. In order to understand the effect of the number and relative positioning of ΔPhe residues on the overall conformation of peptide sequences, we have carried out a systematic study of a number of peptides containing ΔPhe residue/s. In this paper crystal structure of nine peptides containing ΔPhe residue/s will be discussed, highlighting the utility of ΔPhe as a 'designer residue'. The sequence and conformation of the peptides studied are listed in the table below.

	Peptide Sequence	Conformation
1	Boc^0-Val^1- ΔPhe^2-Phe^3-Ala^4-Phe^5- ΔPhe^6-Val^7- ΔPhe^8-Gly^9-OMe	TR
2	Boc^0-Leu^1-Phe^2-Ala^3- ΔPhe^4-Leu^5-OMe	TR
3	Boc^0-Leu^1- ΔPhe^2- ΔPhe^3-Ala^4-Phe^5-NHMe	TR
4	Boc^0-Val^1- ΔPhe^2- ΔPhe^3- ΔPhe^4-Val^5-OMe	TL
5	Boc^0-Val^1- ΔPhe^2-Ala^3-Leu^4-Gly^5-OMe	AR
6	Boc^0-Pro^1- ΔPhe^2-Ala^3- ΔPhe^4-Ala^5-OMe	B
7	Boc^0-Val^1- ΔPhe^2-Leu^3-Phe^4-Ala^5- ΔPhe^6-Leu^7-OMe	TRS
8	Boc^0-Val^1- ΔPhe^2-Phe^3-Ala^4-Leu^5-Ala^6- ΔPhe^7-Leu^8-OMe	TRS
9	Ac^0- ΔPhe^1-Val^2- ΔPhe^3-Phe^4-Ala^5-Val^6- ΔPhe^7-Gly^8-OMe	A/TRS

PS05.02.06 CONFORMATION OF CYCLOSPORIN IN DIFFERENT CRYSTAL FORMS. Michal Husák, Jan Ondrácek and Alexandr Jegorov, Department of Solid State Chemistry, Prague Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic, Galena Co., R & D., Branisovská 31, 370 05 Èeské Budìjovice, Czech Republic

Cyclosporin is a general name for the cyclic undecapeptides related to the structure of cyclosporin A: *cyclo*-[MeBmt-α-Abu-Sar-MeLeu-Val-MeLeu-Ala-D-Ala-MeLeu-MeLeu-MeVal], where MeBmt is (*2S,3R,4R,6E*)-3-hydroxy-4-methyl-2-methylamino-6-octenoic acid. Cyclosporin A has been successfully used as an immunosuppressant in the field of organ transplantation (Consupren®, Galena, Sandimmun®, Sandoz) and moreover some of its derivatives exhibit some potential for the treatment of multidrug resistance and even of AIDS. Despite the intensive investigations, the details of their mechanism of action still remains obscure. Since the solid state conformation of cyclosporin could be used as a starting point for molecular dynamic simulation, a study of two new cyclosporin crystal forms was undertaken.

Two new solid state modification of cyclosporin are reported. The first one is the structure of cyklosporin A arlasolve solvate (a = 15.521(2), b=20.833(3), c=12.949(3) Å , β= 100.21(1)°, $P2_1$, Z=2). The second one is the structure of cyclosporin H monohydrate (a = 12.338(1), b=18.964(1), c=11.111 Å , β= 96.21(1)°, I2, Z=4) the degradation product of cyclosporin A having as [D-MeVal] instead of the original L-amino acid.

Conformation of the title compounds has been compared with 3 known solid state conformations of cyclosporin A, and 2 types of conformation of cyklosporin complexed either to cyclophilin or with

cyclosporin complexed to the FAB fragment of an antibody.

The results lead to following conclusion: Cyclosporin has in solid state 4 different stable conformations, the first one occurs in cyclosporin A monohydrate, cyclosporin A dihydrate, and cyclosporin H, the second is common for thiocyclosporin and cyclosporin A arlasolv solvate, the third is typical for all complexes of cyclosporin with cyclophilin and the fourth one was found for the cyclosporin complex with the FAB fragment of an antibody.

PS05.02,07 CENTROSYMMETRIC CRYSTALS OF A DESIGNED, ALPHA-HELICAL PEPTIDE. William R. Patterson and David Eisenberg, UCLA-DOE Laboratory of Structural Biology and Molecular Medicine and Department of Chemistry and Biochemistry, University of California, Los Angeles, California.

We are exploring the packing interactions of *de novo* designed, alpha-helical peptides in racemic mixtures for use as novel biomaterials. Crystals of the 12-residue peptide, α-1 (1) were produced by vapor diffusion methods in the presence of both peptide enantiomers. X-ray diffraction data were collected at 92 K and were 87% complete to 2.1 Å with a scaling R-factor of 13.7%. The crystals indexed initially in space group P1 with a=20.79 Å, b=20.35 Å, c=27.95 Å, α=101.48°, β=97.77°, and γ=120.88°. These unit cell parameters are nearly identical to the P1 unit cell of the L-α-1 enantiomer of known structure (2). To test for the presence of inversion symmetry, a cumulative intensity distribution was calculated for the D,L-α-1 and L-α-1 intensity data. The intensity distributions show that the putative, racemic data follow the theoretical centric distribution while the L-α-1 data follow the theoretical acentric distribution. We conclude that the crystals are centrosymmetric and belong to space group P1bar, with 2 peptides in the asymmetric unit. Currently, we are optimizing the racemic crystallization condition to produce larger crystals in an effort to obtain higher resolution data for use with direct methods techniques.

References:

1) Eisenberg, D. et al (1986) The Design, Synthesis, and Crystallization of an Alpha-Helical Peptide. Proteins 1, 16-22.
2) Prive, G. et al. (1996) Packed Protein Bilayers in the 0.92 Å-Resolution Structure of a Designed Alpha-Helical Bundle. Manuscript in preparation.

PS05.02.08 THE 1.2 Å STRUCTURE OF G1, AN α-CONOTOXIN PEPTIDE. L. W. Guddat*, L. Shan#, J. L. Martin*, A. B. Edmundson#, W. R. Gray§* Centre for Drug Design & Development, U. Queensland, Brisbane 4072, QLD, Australia. #Oklahoma Medical Research Foundation, 825 NE 13th Street, Oklahoma City, OK, USA. §201 So. Biology, University of Utah, Salt Lake City, UT 84112,

The crystal structure of a synthetic thirteen residue peptide that represents α-conotoxin G1 from marine snail *Conus Geographus* has been determined to 1.2 Å resolution. Structural studies of G1 are of particular interest because it is known to block synaptic transmission by binding to the acetylcholine receptor. This structure, which contains 117 atoms, was solved by direct methods implementing the program SHAKE-AND-BAKE[1]. The framework of the toxin includes two disulphide bonds that link residues 2-7 and 3-13. The side chain of the amino terminal residue and the amide from the carboxy terminus form a hydrogen bond, making the peptide in the shape of a closed loop. The two termini are further drawn together by additional main chain hydrogen bonds. The two positively charged regions, the amino terminus and the guanidinium group of arg-9 are separated by 15 Å, a value consistent with other acetylcholine agonists such as curare[2,3]. The X-ray structure of G1 will be compared with structures derived by NMR and a predictive model based on a CD spectrum[4-6].

1. Miller, R., Gallo, S. M., Khalak, H. G. & Weeks C. M. (1994) *J. Appl. Cryst.*, **27**, 613-621.
2. Pauling, P. & Petcher, T. J. (1973) *Chem. Biol. Interact.*, 6, 351-365.
3. Hider, R. C. & Dufton, M. J. (1979) in *Natural Toxins* (Eakere, D. & Wadstrom, T., Eds.) pp 515-522, Pergamon, London
4. Pardi, A., Galdes, A., Florance, J. & Maniconte, D. (1989) *Biochemistry*, **28**, 5494-5501
5. Kobayashi, Y., *et al.*, & Go, N. (1989) *Biochemistry*, **28**, 4853-4860.
6. Hider, R. C. (1985) *FEBS*, **184**, 181-184.

PS05.02.09 FOLDING AND AGGREGATION OF HETERODIMERS OF GRAMICIDIN. W. L. Duax, B. Burkhart, D. Langs and W. Pangborn, Hauptman-Woodward Medical Research Inst., 73 High St., Buffalo, NY 14203-1196 USA

Full-matrix refinement of the three-dimensional structures of two crystal forms of wild type gramicidin, a D,L-pentadecapeptide, reveal the presence of heterodimers. Partially occupied tyrosine residues are found at position eleven on only one strand of the antiparallel double helix. The approximate ratio of 11-tyrosine to 11-tryptophan in the heterodimer agrees with typical estimates for the ratio of gramicidin C to gramicidin A in wild type gramicidin. The environments of the 11-substituent in the two crystal forms are distinctly different and include specific interactions with solvent. In the orthorhombic form, which crystallized from ethanol, a network of hydrogen bonds link the tyrosine in one double helix with the backbone of an adjacent helix through an ethanol molecule and a water molecule. In the monoclinic form there is no comparable system linking helices.

The presence of a heterodimer in crystal forms having significantly different crystal packing suggests that heterodimer formation is a property of the gramicidin and not induced by crystal formation. In our hands, efforts to crystallize pure gramicidin A have invariably failed to produce sizable crystals and crystals prepared from wild type gramicidin do not readily redissolve upon addition of more solvent. The heterodimer appears to be the most stable form of gramicidin and is critical to crystal nucleation. Dimers of gramicidin observed in the solid state are composed of two antiparallel β-strands wrapped into a cylindrical tube. Although