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

most of the amino acids in gramicidin A show a statistical preference for β conformation, that preference in tyrosine is highest and significantly greater than that of tryptophan. Apparently as a result of the tight coiling, the ψ,ϕ values of the L residues in the structures are in a sparsely populated region of the Ramachandran plot, while the D-residues are in the most densely populated region corresponding to β-sheet geometry. The properties of the gramicidin heterodimer may relate to analogous properties of prion. The enigmatic behavior of prions, the protein responsible for diseases such as *scrapie* in animals and kuru and Creutzfeldt-Jakob disease in humans, has been attributed to the presence of trace amounts of mutants that induce heterodimer formation or another type of aggregation.

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CNS Agents

PS05.03.01 CONFORMATIONAL ANALYSIS OF (*S*)-6-METHOXY-2-(DIPROPYLAMINO)-TETRALIN. Magnus Brisander,[a] Ingeborg Csöregh,[a] Johanna M. Jansen,[b] Anette M. Johansson[b] and Uli Hacksell.[b], [a]Department of Structural Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden, [b]Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, Uppsala University, Box 574, S-751 23 Uppsala, Sweden.

The conformational behavior of (*S*)-6-methoxy-2-(dipropylamino)-tetralin·HCl (**1**) has been studied by X-ray crystallography, ^{1}H NMR spectroscopy and molecular mechanics calculations (MM2). The X-ray structure was determined using Cu Kα radiation at 20 °C, and the ^{1}H NMR spectral data was obtained at 400 MHz in CD_3OD at 30 °C.

The preferred conformations of **1** in the various states (solid, liquid and gas) were compared. In addition, the conformational preference of **1** was compared with recently published preferred conformations of 5-, 7-, and 8-OH-DPAT.[1]

(1) A. Karlén, A. Helander, A. M. Johansson, L. Kenne, S. Sundell, and U. Hacksell, *J. Chem. Research (M)*, 1993, 3028-3036.

PS05.03.02 STRUCTURE-ACTIVITY RELATIONSHIP INVESTIGATIONS OF 4-ANILINOPIPERIDINES H.A. Karapetyan, V.K. Jingozian, Mol. Struct. Research Center of Nat. Academy of Sciences of Armenia

The most potent narcotic analgesics, that are widely used in medicine are representatives of the 4-anilinopiperidines, the main prototype of which is Fentanyl [1-(2-ethylphenyl)-4-(N-propionylanilino)piperidine]. On the basis of comparison of X-ray single crystal[1] and conformational energy calculations data for isomers of 2,5- and 3,5-dimethyl and 5-Me (correctly this must be named 3-Me) derivatives of Fentanyl with their individual analgesic activities, we have concluded, that the productive conformation of the molecule is that, when N(amide)-C (carbon atom of Ph-ring of aniline) bond elapsed the C(3)-C(4) bond of piperidine cycle. Subsequent exposition of productive conformation of 4-anilinopiperidines let us suppose, that 2-Me group have a negative influence on analgesic properties of the molecule and this influence is minimum when 2-Me group has an axial orientation relative to piperidine ring.

[1]Karapetyan H.A., Struchkov Yu,T., Timofeeva T.V., Martirossian V.H., Vartanian R.S., Vartanian S.H. Structure and activity of phenaridine stereoisomers. Khimiko-Pharmatsevticheskii Zhurnal, 1989, V.23, No 5, P.565-572.

Antibiotics

PS05.04.01 CRYSTAL STRUCTURES OF VANCOMYCIN RELATED GLYCOPEPTIDE ANTIBIOTICS. Martina Schaefer, Thomas R. Schneider, George M. Sheldrick, Universität Göttingen, Germany

Glycopeptide antibiotics related to vancomycin have been of special clinical interest since 1956 when vancomycin itself was first discovered. Vancomycin is often the last hope in the treatment of infections caused by bacteria that have been developed resistance to other antibiotics, but unfortunately cases of vancomycin resistance are not unknown.

We direct our attention to these glycopeptide antibiotics for two reasons:

- With around 400 peptide atoms and 40-50% solvent content per asymetric unit crystals of glycopetide antibiotics have comparable diffraction properties to rubrodoxin, crambin and other small proteins. They should be good test structures for new ab initio approaches for the solution of the phase problem.
- With atomic resolution data (collected at EMBL-Hamburg with Synchrotron radiation) it is possible to obtain detailed structural information, for example in the region of the postulated binding pocket.

We will present new crystal structures of vancomycin related glycopeptide antibiotics that provide interesting details of the solvent structure, in particular in the region of the binding pocket.

PS05.04.02 THE CRYSTAL AND MOLECULAR STRUCTURE OF CHALCOMYCIN. J. Ronald Rubin, Peter W. K. Woo, Parke-Davis Pharmaceutical Research Division of Warner Lambert Comany 2800 Plymouth Road, Ann Arbor, MI. 48105

Chalcomycin ($C_{35}H_{56}O_{14}$, F.W.=700.8) is a macrolide antibiotic produced by *Streptomyces bikiniensis*. It is a member of the 16-membered macrolide ring antibiotic family and is unique in containing the sugars ß-chalcose and ß-mycinose. Colorless needles of the antibiotic were obtained from ethanol solutions. The unit cell parameters and x-ray diffraction data were measured on a CAD-4 diffractometer using CuKα radiation. The crystals are monoclinic, space group $P2_1$, with unit cell parameters, a=8.965(3),b=22.989(9), c=9.280(2) Å and ß=90.78(3) °. The unit cell of V=1913 Å^3 contains two molecules of the antibiotic. A total of 1557 unique reflections were measured using the omega scan technique. The structure was solved using direct methods using the SIR-92 programs and refined to an unweighted R-factor of 0.068. The conformation of the macrolide ring and the two glycosidic sugar residues is roughly planar. The molecule has opposing hydrophilic and hydrophobic surfaces. By extension from the known chirality of the sugar residues the configuation of all of the chiral centers was determined.