FA4-MS37-P17

Vitamin D analogous – structure and charge density analysis. Maura Malinska[a], Andrzej Kutner[b], Krzysztof Wozniak[a], [a]*Faculty of Chemistry, University of Warsaw, Poland,* [b]*Pharmaceutical Research Institute, Warsaw, Poland*
E-mail: mmalinska@chem.uw.edu.pl

The biological actions of the hormonally active form of vitamin D3, 1,25-dihydroxyvitamin or calcitriol and its synthetic analogs are mediated by the nuclear vitamin receptor VDR [1], which is also involved in cell proliferation, differentiation, and immunomodulation. For example, activated T and B lymphocytes, prostate, breast, and colon cancer cells exhibit increased level of VDR protein when compared with their normal counterparts. This activation or disease-specific up-regulation of VDR protein provides an opportunity to treat these conditions with VDR ligands. Calcipotriol, Calcitriol and Alfacalcidol are examples of vitamin D analogs that have undergone clinical trials with positive outcome [2,3].Conformational analysis and multipole model based on Hansen-Coppens formalism [4] obtained from theoretical structure factors. This approach revealed differences between the above analogous. The conformation of the cyclohexane A-ring is especially important as it does participate in protein binding. This ring exist in the two chair conformations, called α-form and ß-form, in which hydroxyl at C3 is in equatorial and axial positions, respectively. Studies of the vitamin D receptor (VDR) ligand binding domain, indicated strong hydrogen bonds between C1-OH and C3-OH hydroxyls and aminoacid residues Thr415 and Tyr401, respectively [5]. The charge density analysis shows that the change in side chain exert an influence on the whole molecule. Study of hydrated and anhydrous crystal structures and obtained multipole model demonstrate conformational and charge density distribution differences in molecules with α and ß-forms of A-ring.

[1] Nagpal S., Na S., Rathnachalam R., *Endocrine Review*, 2004, 26, 662. [2] Fogh K., Kragballe K., *Curr Pharm Des,* 2000, 6, 961. [3] Slatopolsky E., Brown A.J., *Blood Purif,* 2002, 20, 109. [4] Hansen N.K., Coppens P., *Acta Cryst.*, 1978, A34, 909. [5] Wurtz J.M., Guillot G., Moras D., in: Norman A.W., Bouillon R., Thomasset M., Vitamin D. *Chemistry, Biology and Clinical Applications of the Steroid Hormone*, 1997.

Keywords: vitamin D, structure and charge-density analysis

FA4-MS37-P18

Charge Density of Lysozyme by the Maximum Entropy Method. Jeanette Netzel, Sander van Smaalen
Laboratory of Crystallography, University of Bayreuth, Germany
E-mail: jeanette.netzel@uni-bayreuth.de

The Maximum Entropy Method (MEM) is applied to high-resolution X-ray diffraction data of hen egg-white lysozyme [1] (PDB reference: 2vb1, d_{min} = 0.65 Å) to reconstruct model-independently its charge density. Disorder in main- and side-chain residues and atomic sites can be revealed and described by the MEM without introducing constraints on the parameters to be refined. The electron density at bond critical points, their principal curvatures and their Laplacians are determined according to Bader's Atoms in Molecules Theory [2]. Energy densities at bond critical points are calculated according to Abramov [3]. Geometrical, topological and energetic properties of chemical bonds and non-bonded interactions are characterized to allow a structural and thus a functional study of this enzyme.

[1] Wang, J.; Dauter, M.; Alkire, R.; Joachimiak, A.; Dauter, Z., *Acta Cryst. D* 2007, 63, 1254. [2] Bader, R.F.W., *AIM – A Quantum Theory*, Oxford University Press 1994. [3] Abramov, Y.A., *Acta Cryst. A*. 1997, 53, 264.

Keywords: charge density, maximum entropy method, protein structure interactions

FA4-MS37-P19

Topological properties of gridded charge densities. Prathapa Siriyara Jagannatha[a], Sander van Smaalen[a], Lukas Palatinus[b, a] [a]*Laboratory of Crystallography, University of Bayreuth, Germany,* [b]*Institute of Physics, Na Slovance 2, Prague, Czech Republic*
E-mail: prathap@uni-bayreuth.de

The electron density of α–Glycine has been studied in order to determine the effect of the grid size on the distribution of charge densities and their topological properties. The electron densities of α–Glycine with different grid sizes have been determined according to: (1) The independent atom model, (2) The maximum entropy method and (3) The multipole model. These densities have been analyzed according to Bader's quantum theory of atoms in molecules (QTAIM) [1], using the computer program EDMA [2]. The diffraction data of α–Glycine have been taken from Destro et al [3]. Three different grid sizes (0.08Å, 0.04Å and 0.02Å) have been used for analysis. It has been found that the grid size has no influence on the values of the interpolated electron density at bond critical points, but it does influence the values of the Laplacian of covalent bonds and hydrogen bonds as well as integrated properties, like atomic charges. The Laplacian values for different grid sizes of covalent bonds differ by up to 0.32% for C-H bonds and by 76% for C-O bonds.

[1] Bader R. F. W. Atoms in Molecules. *Oxford University Press*, 1994. [2] L. Platinus and S. van Smaalen, to be published. [3] Destro, R., Roversi, P., Barzaghi, M. and Marsh, R.E. A.; Pastor, A.; Galindo, A.; Ienco, A.; Mealli, C. *J.Phys.Chem.* A 104, 2000, 1047-1054.

Keywords: Maximum entropy method, Charge density study, Atoms in molecule theory

FA4-MS37-P20

The transferability of atomic multipoles for amino acids and peptides Magdalena Woińska[a], Paulina M. Dominiak[a], [a]*Chemistry Department, University of Warsaw, Poland*
E-mail: magdalena.woinska@student.uw.edu.pl

Popular force fields usually employ point charges. Supplementing atomic charges with higher electrostatic moments leads to more accurate charge distribution models. New generation force fields based on multipole models require high level of transferability of atomic multipole moments. The aim of this work was to analyze the level of

transferability achievable with the use of different methods of molecular density partitioning.
Molecular densities (MDs) were calculated for natural amino acids and selected di- and tripeptides in geometries as observed in crystal structures. The MDs were obtained through Fourier space fitting of pseudoatom model to the electron densities computed *ab initio* at B3LYP/6-31G** level. Such procedure was selected in order to be compatible with the idea of building a pseudoatom database [1-3] pursued in the charge density crystallography. Atomic multipole moments expressed in local coordination system were calculated (a) directly from pseudoatoms, (b) from atomic densities computed via stockholder partitioning and (c) from atomic basins derived via topological analysis. As a measure of transferability, standard deviations from averaging over multipole moment components of atoms that are considered equal in their chemical environments were calculated.

[1] Zarychta B., Pichon-Pesme V., Guillot B., Lecomte C. & Jelsch Ch., *Acta Cryst*. 2007, A63, 108. [2] Dominiak P. M., Volkov A., Li X., Messerschmidt M. & Coppens P., *J. Chem. Theory Comput*., 2007, 3, 232. [3] Dittrich B., Hübschle C. B., Luger P. & Spackman M. A., *Acta Cryst*. 2006, D62, 1325.

Keywords: multipole moments, amino acids, transferability

FA4-MS37-P21

Polyhalogenated bipyridines: halogen interactions and building blocks.

Emmanuel Aubert[a], Victor Mamane[b], Mohamed Abboud[a,b], Yves Fort[b], Claude Lecomte[a], [a]*CRM2, Nancy-Universit,* [b]*SOR, SRSMC, Nancy-University*
E-mail: emmanuel.aubert@crm2.uhp-nancy.fr

4,4'-Bipyridine skeleton represents an excellent building block in supramolecular chemistry [1] and biology [2] and is an important intermediate in the synthesis of viologens [3]. Recently, we developed a method to produce new polyhalogenated 4,4'-bipyridines [4], which can then be functionalized, potentially leading to new materials. Beside this use in synthesis, these halogenated molecules are also attractive to study the so-called halogen interactions. In the investigated compounds, which contain Cl, Br and I atoms at various positions on the pyridine rings, type-II halogen···halogen interactions [5] appear predominantly, along with halogen···Lewis base interactions. Interestingly, depending on the presence of one, two or three different halogen atoms on the same molecule, homo or hetero halogen···halogen interactions are observed in the crystal structures. Also, for substitutions at fixed positions on the pyridine ring, the nature of the halogen atom influences the crystal packing, leading to either isostructures or completely different packing schemes. These characteristics are also analyzed on the basis of intermolecular interaction energies by using the Pixel program [6]. Finally, new functionalized bipyridines will be presented together with recently obtained metal complexes, where very short M···halogen (M = Ag, halogen = Cl, Br) interatomic distances are obtained. Used for the building of metal organic frameworks, these M···halogen interactions show their influence on the crystal packing, tuning the porosity of the material.

[1] (a) Roesky, H. W.; Andruh, M. *Coord. Chem. Rev.*, 2003, 236, 91. (b) Rang, A.; Engeser, M.; Maier, N. M.; Nieger, M.; Lindner, W.; Schalley, C. A. *Chem. Eur. J.*, 2008, 14, 3855. [2] (a) Swahn, B.-M.; Xue, Y.; Arzel, E.; Kallin, E.; Magnus, A.; Plobeck, N.; Viklund, J. *Bioorg. Med. Chem. Lett.*, 2006, 16, 1397. (b) Stanetty, P.; Röhrling, J.; Schnürch, M.; Mihovilovic, M. D. *Tetrahedron*, 2006, 62, 2380. [3] Monk, P. M. S. The Viologens: *Physicochemical Properties, Synthesis and Applications of the Salts of 4,4'-Bipyridines, Wiley, Chichester*, 2001. [4] Abboud, M., Mamane, V., Aubert, E., Lecomte, C., and Fort, Y. *J. Org. Chem.*, accepted. [5] Reddy, C. M.; Kirchner, M. T.; Gundakaram, R. C.; Padmanabhan, K. A.; Desiraju, G. R. *Chem. Eur. J.* 2006, 12, 2222. [6] (a) Gavezzotti, A. *OPiX, A computer program package for the calculation of intermolecular interactions and crystal energies*, University of Milano, 2003. (b) Gavezzotti, A., Eckhardt, C.J., *J.Phys.Chem. B* 2007, 111, 3430.

Keywords: Halogens, pyridine complexes, bonding intermolecular

FA4-MS37-P22

Invariom refinement of two different modifications of Thiostrepton.

Kevin Pröpper, Birger Dittrich,
Georg-August-University Göttingen, Germany
E-mail: kproepper@shelx.uni-ac.gwdg.de

B. Anderson and D. Hodgkin [1] reported the first (but incomplete) monoclinic structure of thiostrepton exactly 40 years ago in 1970. The thiazole-containing antibiotic first isolated from *streptomyces azureus* exhibits activity against Gram-positive bacteria and *plasmodium falciparum*, the causal agent of malaria. Mechanistically, Thiostrepton binds to the GTPase centre of the large subunit 23s RNA [2]. Activity against breast-cancer cells through targeting the transcription factor forkhead box M1 has also been reported. Here the antibiotic selectively induces cell-cycle arrest and cell death in breast cancer cells through down-regulating FOXM1 expression [3]. We have reproduced the original monoclinic and the tetragonal crystal structure [4] to illustrate the benefits of high resolution in protein crystallography: it was e.g. possible to complete the originally published structural model of monoclinic thiostrepton with a missing flexible side chain. Complete and redundant Bragg data to 0.80 Å resolution measured with a CuKα rotating anode at 100K of the monoclinic form and 100 K / 5 K synchrotron data of the tetragonal form were evaluated with the independent atom model (IAM) and the non-spherical scattering factors of the invariom database [5], [6] which is based on the Hansen-Coppens multipole model [7]. Single-crystal diffraction data evaluated with invariom provide not only detailed and accurate molecular geometries but also information on the electron-density distribution and on derived properties. With a view to biological and medical functionality of thiostrepton an analysis of the electrostatic potential and the molecular dipole moment is especially relevant, and both will be reported.

[1] Anderson B., Crowfoot Hodgkin D., Viswamitra MA, Nature, 1970, 225, 223-235. [2] Rosendahl G., Douthwaite S., Nucleic Acids Res., 1994, 22, 357-363. [3] Kwok J., Myatt S., Marson C., Coombes C., Constantinidou D., Lam E., Mol. Cancer Ther., 2008, 7, 2022-2032. [4] Bond C., Shaw P., Alphez M., Hunter W., Acta Cryst, 2001, D57, 755-758. [5] Dittrich B., Koritsánszky T., Luger P., Angew. Chem., 2004, 43, 2713-2721. [6] Dittrich B., Hübschle C., Luger P., Speckman M., Acta Cryst, 2006, D62, 1325-1335. [7] Hansen N., Coppens, P., Acta Cryst, 1978, A34, 909-921.

Keywords: macromolecules, biocrystallography, charge density