Lett., 2005, **94**, 054802.
Keywords: X-ray nanobeam, nanodiffraction, refractive X-ray lenses

MS49 Charge Spin and Momentum Densities in Material Science

Chairpersons: John Charles Spence, Brummerstedt Iversen

MS49.27.1

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High-Energy Synchrotron Radiation for Charge Density and Materials Science Experiments

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Recently it has been shown that high-energy synchrotron radiation is an excellent tool for the measurement of charge densities, because there is no significant affection of the data by absorption and extinction in most practical cases [1,2]. Thus, the enhancement of the data quality compared to 'low-energy' data sets now allows detailed comparisons between experimental and theoretical charge densities, even in the case of 'new materials' like high-Tc superconductors [3].

On the other hand high-energy synchrotron radiation is also very useful for 'classical' materials science experiments, e.g. texture or stress and strain analyses, because of the large intrusion depth, i.e. the possibility of studying not only academic but also 'realistic' samples (size). GKSS is currently building up two high-energy materials science beamlines at DESY, Hamburg, Germany. The concepts of the beamlines will be presented here. Both will be equipped with materials science diffractometers, which can also be used for charge density studies.

[1] Lippmann T., Schneider J.R., *J. Appl. Cryst.*, 2000, **33**, 156. [2] Lippmann T., Schneider J.R., *Acta. Cryst.* , 2000., A**56**, 575. [3] Lippmann T., Blaha P., Andersen N.H., Poulsen H.F., Wolf T., Schneider J.R., *Acta. Cryst.* , 2003., A**59**, 437.

Keywords: synchrotron radiation experimental, charge density, materials science

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Charge Density Studies of Ultra High Resolution Protein Structures

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The recent advances in synchrotron radiation and crystallogenesis methods have bought bio-crystallography in a context favorable to subatomic resolution protein structures. At this resolution, electron density reveals fine details related to the deformation of the valence electron density due to chemical bonding and intermolecular interactions. A spherical atom model of electron density does not allow to take into account these features in the refinement. However, in small molecules charge density studies, the Hansen & Coppens [1] multipolar model is commonly used, and allows the asphericity of the atomic electron density to be parameterized and quantified against experimental data.

Here we will show how charge density studies principles can be applied with the software MoPro [2] on protein structures obtained at subatomic and atomic resolution, using specific methods like the multipolar parameter transferability from our experimental database [3]. We will also present derived electrostatic properties based on the multipolar formalism and computed on high resolution Human Aldose Reductase – inhibitors complexes [4] of pharmacological interest.

[1] Hansen N.K., Coppens P., *Acta. Cryst.*, 1978, A**34**, 909-921. [2] Jelsch C., Guillot B., Lagoutte A., Lecomte C., *J. Appl. Cryst.*, 2005, **38**, 38-54. [3] Jelsch C., Pichon-Pesme V., Lecomte C., Aubry A., *Acta. Cryst.*, 1998, D**54**, 1306-1318. [4] Howard E. et. al., *Prot. Struct. Funct. & Gen*., 2004, **55**, 792-804.

Keywords: charge density, protein structure, very high resolution

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Hypervalency – Experimental Charge Density Uncovers a False Concept

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Recently we synthesised and experimentally determined the charge density in molecular species containing so-called hypervalent central atoms. In those compounds formally the amount of valence electrons at the central atom exceeds the number of eight. Typical text book examples are SiF_6^{2-}, PF_6 or SO_3. Historically 3d orbitals are employed to explain the valence expansion and the generate sp^3d or sp^3d^2-hybrid-orbitals. However, the promotion of a phosphorus 3p electron to the d-orbital 16 eV are required but only 1 to 5 eV received by each covalent bond. Theoretical chemistry uncovered hypervalency as a false concept long time ago.[1] We investigated the phenomenon in terms of experimental charge density and topological analysis[2] of the hexacoordinated silicon complex $[F_2Si\{O(Me_2NN)\ CPh\}_2]$, the lithiumiminophosphoranate $[(Et_2O)Li\{Ph_2P(CHPy)(NSiMe_3)\}]$, and the sulfur triimide $S(N^tBu)_3$.[3]

[1] a) Rundle R. E., *J. Am. Chem. Soc*., 1947, **69**, 1327; b) Kutzelnigg W., *Angew. Chem*., 1984, **96**, 262, *Angew. Chem. Int. Ed. Engl*., 1984, **23**, 272. [2] a) Hansen N. K., Coppens P., *Acta Crystallogr*.,1978, A**34**, 909 ; b) Bader R. F. W., *Atoms in Molecules: A Quantum Theory*, Oxford University Press, Oxford, 1990. [3] a) Kocher N., Henn J., Gostevskii B., Kost D., Kalikhman I., Engels B., Stalke D., *J. Am. Chem. Soc*., 2004, **126**, 5563; b) Kocher N., Leusser D., Murso A., Stalke D., *Chem. Eur. J*., 2004, **10**, 3622; c) Leusser D., Henn J., Kocher N., Engels B., Stalke D., *J. Am. Chem. Soc*., 2004, **126**, 1781.

Keywords: hypervalency, topological analysis, sulfur

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Measurements of Electron Densities in Solids

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This talk reports the recent progress in the measurement of electron densities in inorganic crystals and its significance for our understanding of bonding and electronic structure [1]. The talk is organized in two parts. The first part first emphasizes the importance of accuracy in experimental structure factors for electron density mapping and the challenge of studying inorganic crystals, which is then followed by an introduction of the convergent beam electron diffraction technique for accurate structure factor measurement. The second part of the talk reports the study of electron density in several inorganic crystals of materials interest with focus on transition metals and ions. Comparison between experiment and theory will be made to highlight the significance of experimental electron density and the need for further study. The talk will be concluded by looking into future challenges and opportunities in materials science for crystallography.

* The talk is based on work performed in collaboration with B. Jiang, M. Kim, M. O'Keeffe and J.C.H. Spence. The work was supported by NSF and the author thanks DOE BES for supporting his current research.
[1] Zuo J.M., *Reports on Progress in Physics*, 2004, **67**, 2053-2103.

Keywords: electron density, electron diffraction, crystal electronic structure

MS49.27.5

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Orbital-wise Decomposition of Magnetic Compton Profiles and Spin Moments in UGe_2

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The uranium ferromagnet UGe_2 has drawn much attention because of possible coexistence of superconductivity and ferromagnetism [1].

We have measured the spin-polarized electron momentum density distributions (magnetic Compton profiles) of UGe_2 using the synchrotron-based magnetic Compton scattering technique. The spin moment of UGe_2 has been determined as -1.15 μ_B at 10 K with an applied magnetic field of 0.5 T. Compared with the saturated magnetization of +1.40 μ_B, we have determined the orbital moment at +2.55 μ_B.

The magnetic Compton profiles are decomposed into partial profiles by fitting with the U-5f atomic profiles with different magnetic quantum number *m*. From the fitted results, we estimated the orbital moment at +2.90 μ_B. It gives a slightly higher value since this estimation does not take account of the partial quenching of the orbital moment due to hybridization.

We also found that the shape of the magnetic Compton profiles depend on temperature, indicating the spin-polarized, ground-state wave-functions vary with temperature.

[1] Saxena S. S. et al., *Nature*, 2000, **406**, 587.

Keywords: spin moment, magnetic Compton scattering, U-5f orbitals

MS50 ENZYMES AND ALLOSTERY

Chairpersons: Alexander Wlodawer, Silvia Onesti

MS50.27.1

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Allostery and Heteroinhibition of Human Thymidylate Synthase

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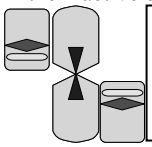
Thymidylate synthase (TS) is a homodimer which shows strong negative cooperativity between subunits. Unique property of human TS (hTS) among TS enzymes it that its active site loop (residues 181-197) can flip 180 degrees producing an inactive conformation [1]. Solution fluorescence studies have shown equilibrium between the active and inactive conformers [2]. We have developed bisphosphonate inhibitors that stabilize the inactive conformation and bind between dimers leading to the formation of hTS tetramers (but not higher oligomers) in solution. These inhibitors show positive cooperativity with antifolate inhibitors used in chemotherapy, which bind only to the active conformer. These data are consistent with a model in which hTS exists preferably as an asymmetric dimer with one subunit in the active conformation of loop 181-197 and the other in the inactive conformation.



Model of hTS homotetramer in which two subunits are connected by bisphosphonate inhibitor stabilizing the inactive conformation and two are inhibited by an antifolate with dUMP.

[1] Schiffer C. A., Clifton I. J., Davisson V. J., Santi D. V., Stroud, R. M., *Biochemistry*, 1995, **34**, 16279. [2] Phan J., Steadman D. J., Koli S., Ding W. C., Minor W., Dunlap R. B., Berger S. H., Lebioda L., *J. Biol. Chem*., 2001, **276**, 14170.

Keywords: chemotherapy, cooperative phenomena, inhibitor and drug design

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Structural Basis for Substrate Channelling of a Fatty Acid β-oxidation Multienzyme Complex

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Many enzymes are organized into multienzyme complex to catalyze sequential reactions termed the channelling mechanism. The purpose of our structural study is to elucidate this mechanism at the atomic level, focusing the fatty acid β-oxidation multienzyme complex from *Pseudomonas fragi*. We have determined two distinct crystal structures of the bacterial multienzyme complex that catalyzes the last three sequential reactions in the fatty acid β-oxidation cycle. The $\alpha_2\beta_2$ heterotetrameric structure shows the uneven ring architecture, where all the catalytic centers of 2-enoyl-CoA hydratase (ECH), L-3-hydroxyacyl-CoA dehydrogenase (HACD) and 3-ketoacyl-CoA thiolase (KACT) face a large inner solvent region. The substrate, anchored through the 3'-phosphate ADP moiety, allows the fatty acid tail to pivot from the ECH to HACD active sites, and finally to the KACT active site. Coupling with striking domain rearrangements, the incorporation of the tail into the KACT cavity and the relocation of 3'-phosphate ADP bring the reactive C2-C3 bond to the correct position for cleavage. The α-helical linker specific for the multienzyme contributes to the pivoting center formation and the substrate transfer through its deformation. This channelling mechanism could be applied to other β-oxidation multienzymes, as revealed from the homology model of the human mitochondrial trifunctional enzyme complex.

Keywords: beta-oxidation, multienzyme complex, three-dimensional protein structure

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Structural Biology of Cytochromes P450

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The mammalian cytochrome P450 enzymes are a family of membrane-associated haem-containing proteins which play a major role in the metabolism and subsequence clearance of numerous and diverse xenobiotics such as drug molecules. CYP3A4 is the most important member of P450 family, responsible for metabolising 50 % of drugs while CYP2C9 metabolises some 15 % of all marketed therapeutics. Both enzymes exhibit non-Michaelis-Menten kinetics, including homotropic and heterotropic cooperativity; to predict the *in vivo* clearance of drugs and drug-drug interactions, a better understanding of P450 allostery is required.

In the last few years, a number of mammalian P450 structures have been determined, including CYP2C9 [1] and CYP3A4 [2], both in unliganded forms and in complex with marketed drugs. These crystal structures provide insights into the principles of substrate binding for these promiscuous enzymes, and the structural basis of P450 allostery.

[1] Williams P.A., Cosme J., Ward A., Angove H.C., Vinkovic D.M., Jhoti H., *Nature*, 2003,**424(6947)**, 464-8. [2] Williams P.A., Cosme J., Vinkovic D.M., Ward A., Angove H.A., Day P.J., Vonrhein C., Tickle I.J., Jhoti, H., *Science*, 2004, **305(5684)**, 683-686.

Keywords: drug-protein interactions, drug metabolism, metalloproteins

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The Structure of Yeast Phosphofructokinase 1

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Phosphofructokinase 1 (PFK) catalyses the ATP-dependent phosphorylation of fructose 6-phosphate (Fru-6P) to fructose 1,6-bisphosphate, one of the principal regulatory steps in glycolysis.

The structure of 12S PFK from *S.cerevisiae*, a product of limited proteolysis of the native enzyme (known as 21S), has been solved at 2.9 Å resolution in complex with Fru-6P. This is the first crystal structure of eukaryotic PFK and one of the largest protein crystal structures known to date in atomic detail (approx. 600 kDa). We have determined the topology of the enzyme, the active site and the binding site of fructose-2,6-bisphosphate (Fru-2,6-P_2), the allosteric effector specific to eukaryotes. Still unknown is the effector binding site for ATP. A detailed interpretation has been carried out of the electron density map. The refined atomic model contains over 5,000 amino