antibiotics is acquired mainly by target alterations but in a few cases, the antibiotic chemical moieties are modified; that the primary action of most antibiotics that induce significant local or allosteric conformational alterations is to inhibit functional activities rather than to merely block vital locations; and that most proteins that interact with antibiotics are involved in dynamic aspects of ribosomal function.

Although a precise understanding of all processes associated with antibiotic action is still incomplete, the current findings justify modest optimism and it appears that the elucidation of the common principles, combined with the genetic, structural, and biochemical investigations should lead to structure-based approaches for devising modifications of existing antibiotics as well as in the design of novel potent anti-infective drugs.

Keywords: ribosomes, antibiotics, resistance

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Inhibitors of the Eukaryotic 20S Proteasome Core Particle: a Structural Approach

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The ubiquitin-proteasome pathway is particularly important for the regulated degradation of various proteins which control a vast array of biological processes. Therefore, proteasome inhibitors are promising candidates for anti-tumoral or anti-inflammatory drugs. N-Acetyl-Leu-Leu-Norleucinal was one of the first proteasome inhibitors discovered and has been widely used to study the 20S proteasome core particle (CP) function *in vivo*, despite its lack of specificity. Vinyl sulfones, like Ac-PRLN-vs, show covalent binding of the β-carbon atom of the vinyl sulfone group to the Thr1O$^{\gamma}$ only of subunit β2. However, vinyl sulfones have similar limitations as peptide aldehydes as they have been reported also to bind and block intracellular cysteine proteases. A more specific proteasome inhibitor is the natural product lactacystin, which can be isolated from *Streptomyces*. It was found that this compound forms an ester bond only to the Thr1O$^{\gamma}$ of the chymotrypsin like active subunit β5 due to specific P1 interactions. In contrast to most other proteasome inhibitors, the natural α', β'-epoxyketone peptide epoxomicin binds specifically to the small class of N-terminal nucleophilic (Ntn) hydrolases with the formation of a morpholino adduct.

All previously described proteasome inhibitors bind covalently to the proteolytic active sites. However, as the proteasome is involved in a variety of biological important functions, it is of particular interest to block the CP only for limited time in order to reduce cytotoxic effects. Recently, the binding mode of the natural specific proteasome inhibitor TMC-95 obtained from *Apiospora montagnei* was investigated. The crystal structure revealed that the TMC-95 blocks the active sites of the CP non-covalently in the low nM range.

Keywords: proteasome, ubiquitin, drug design

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Computational Modeling of GPCRS: Insight into the Function of the most Priviledged Drug Targets

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G protein coupled receptors (GPCRs) constitute the largest and most important superfamily of signal transduction membrane proteins known to date. Our study is aimed at understanding, through computational modeling, the molecular mechanisms of GPCR functioning either in their normal conditions or when hit by gain-of-function or loss-of-function mutations. Molecular simulations of the wild type form of luteinizing hormone receptor (LHR) as well as of its spontaneous and engineered mutants were instrumental to infer the structural features, which differentiate the mutation-induced active from the inactive states of this receptor [1]. These features were translated into computational indices instrumental in *in silico* functional screening of novel LHR mutants [1]. Similarly to mutation-induced activation, the interface between the cytosolic extensions of helices 3 and 6 is the target of the structural modifications induced by activating ligands (i.e. agonists). The chemical information transfer from the agonist binding site (on the extracellular side) to the cytosolic domains is mediated by a cluster of aromatic amino acids in helix 6 [1] Computational modeling of the supramolecular organization of GPCRs and their intracellular partners is the current challenge towards a deep understanding of their mechanism of functioning.

[1] Fanelli F., De Benedetti P.G., *Chem. Rev.*, *in press*.

Keywords: GPCR, computational modeling, virtual screening

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Structure-Based Design of New AIDS Drugs: Overcoming Drug Resistance

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Drug resistance is a primary cause of AIDS treatment failure. A multidisciplinary effort [1] led to the discovery of the potent diaryl-pyrimidine (DAPY) nonnucleoside inhibitors (NNRTIs) dapivirine, etravirine, and rilpivirine that are under clinical evaluation. Systematic structural and modeling studies of HIV-1 reverse transcriptase (RT) in complexes with NNRTIs used in the drug design effort revealed different modes of binding for the DAPY inhibitors [2]. The torsional flexibility ("wiggling") of the inhibitors can generate numerous conformational variants and the compactness of the inhibitors permits repositioning and reorientation (translation and rotation) within the pocket ("jiggling"). Such adaptations appear to be critical for the ability of the NNRTIs to retain their potency against a wide range of drug-resistant HIV-1 RTs. Exploitation of inhibitor conformational flexibility can be a powerful element of drug design, especially for the design of drugs that will be effective against rapidly mutating targets.

[1] Janssen P.A.J., et al., *J. Med. Chem.*, 2005, *in press*. [2] Das et al., *J. Med. Chem.*, 2004, **47**, 2550.

Keywords: drug design, drug resistance, reverse transcriptase

MS94.30.5

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Evaluation of Docking Results by Diffraction-component Precision Index (DPI)

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Since efficient docking technique can be a powerful tool for the computer-aided drug design, many different approaches to solving the docking problems have been proposed. The reliability of the docking results has not been quantitatively discussed. Relatively subjective criteria have been generally applied to evaluate the docking results so far. The DPI introduced by Cruickshank[1] is 'a good and rough guide' to coordinate precision and can be used to evaluate the reliability of the docking results.

In the docking study the most useful quantity to consider the docking results is an rmsd between predicted and experimental heavy-atom coordinates of the ligand structure. Suppose the standard uncertainty of the observed and predicted molecular model is the same in magnitude and equals to σ, the estimated standard uncertainty of the rmsd between the corresponding atoms in the observed and predicted molecule can be approximated to be $\sqrt{2}\,\sigma$. Therefore the magnitude of the rmsd value can be evaluated using the estimated uncertainty.

We have recently developed a unique docking algorithm named Ph4Dock[2] and the docking results obtained by Ph4Dock were evaluated using DPI. The present study has demonstrated that DPI is a good measure to judge the quality of docking results.

[1] Cruickshank D.W.J., *Acta Crystallogr.*, 1999, **D44**, 583. [2]Goto J., Kataoka R., Hirayama N., *J. Med. Chem.*, 2004, **47**, 6804.
Keywords: protein-ligand docking, DPI, drug discovery

MS95 ADVANCED FUNCTIONAL MATERIALS (INCLUDING MOLECULAR BIOLOGICAL FUEL CELL BATTERY)

Chairpersons: Michele Catti, Dimitri Argyriou

MS95.30.1

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New Approach to Structure Determination of Crystalline Polymer Electrolytes

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Polymer electrolytes consist of salts, e.g. NaI, $LiN(SO_2CF_3)_2$, dissolved in high molecular weight polymers, e.g. poly(ethylene oxide) (PEO). The recent discovery of ionic conductivity in crystalline polymer electrolytes [1] was prompted by the elucidation of the crystal structure of PEO_6:$LiAsF_6$ [2] from powder diffraction data using a simulated annealing technique [3]. This challenged the established view that conduction occurs exclusively in amorphous polymer electrolytes above their glass transition temperature and opened a new avenue in polymer electrolyte research.

Recently we have established even more complex crystal structures of polymer electrolytes, such as PEO_8:$NaBPh_4$ and PEO_4:$ZnCl_2$, using a combination of single crystal diffraction data from a material prepared with a low-molecular weight polymer and powder data from a material with the same chemical composition but synthesized using a high molecular weight PEO. The combination proved to be successful when the individual methods failed to produce a reliable structural model.

We have also discovered polymorphism in PEO_6:$LiAsF_6$ and determined the crystal structure of the new phase. The differences in the crystal structure of the two polymorphs account for the difference in their ionic conductivity.

[1] Gadjourova Z., Andreev Y.G., Tunstall D.P., Bruce P.G., *Nature*, 2001, **412**, 520. [2] MacGlashan G., Andreev Y.G., Bruce P.G., *Nature*, 1999, **398**, 792. [3] Andreev Y. G., Lightfoot P, Bruce P.G., *Chem.Comm.*, **1996**, 2169.
Keywords: polymer electrolytes, ionic conductivity, polymorphism

MS95.30.2

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Magnetic Control of Electric Polarization in Magnetic Oxides with Non-collinear Magnetic Structures

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Recent observations of gigantic magnetoelectric and magnetocapacitive effects in rare-earth manganites, $TbMnO_3$ and $DyMnO_3$ [1,2], provide a novel approach to the mutual control of magnetization and electric polarization in magnetic ferroelectrics. We can control the magnitude and/or direction of the electric polarization vector by the application of magnetic field in these manganites. In comparing the results from the both manganites, we noticed that a characteristic common to the both materials is that they possess modulated magnetic structures with long wavelengths (as compared to the chemical unit cell) which arise from competing magnetic interactions. Ferroelectricity in these materials appears to originate from the competing magnetic interactions which cause lattice modulations through magnetoelastic coupling. In this talk, we show magnetic control of electric polarization in several magnetic oxides with non-collinear magnetic structures, which may provide new route to design magnetoelectrics.

[1] Kimura T., Goto T., Shintani H., Ishizaka K., Arima T., Tokura Y., *Nature*, 2003, **426**, 55. [2] Goto T., Kimura T., Lawes G., Ramirez A.P., Tokura Y., *Phys. Rev. Lett.*, 2004, **92**, 257201.
Keywords: multiferroics, magnetoelectric effect, non-collinear magnetic structure

MS95.30.3

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Crystal Structure and Magneto-transport Properties of New Cobalt Based Layered Oxides

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The search for new layered cobalt based oxides is very important to discover interesting physical properties as recently illustrated by the discovery of a large thermoelectric power in the metallic phase $Na_{0.5}CoO_2$ [1] and by the report on the superconductivity of the derived hydrated compound $Na_{0.3}CoO_2,1.3H_2O$ [2]. Recent investigations in the Sr-Co-M-O systems (M = Ga, Ti….) by means of transmission electron microscopy techniques have allowed to detect new layered cobaltites. Their structure has been obtained by combining high resolution images and powder X-ray/neutron diffraction data.

Firstly, a new oxide, $(Ga_{1/3}Co_{2/3})_2Sr_2CoO_{6+\delta}$, has been isolated [3]. Its complex structure is described from a modulation vector $q^* = q_1a^* + q_2c^*$. For the as-prepared sample ($\delta\approx0.4$), it can be described in an orthorhombic supercell *Bb2b* (q_1=1/3 and q_2=1) with the unit cell parameters $a=3a_p\sqrt{2}$, $b=a_p\sqrt{2}$ and c=19.2034(4) Å. The layer stacking consists in an intergrowth between a $[SrCoO_3]$ perovskite-type block and a block of triple [AO] layers, $[(SrO)(Co_{2/3}Ga_{1/3}O_{1+\delta/2})(Co_{2/3}Ga_{1/3}O_{1+\delta/2})]$ in which several kinds of GaO_x and CoO_x polyhedra coexist. Low resistivities ($\rho_{300K} \approx 10^{-1}\Omega$.cm) depending on the δ value have been measured whereas a positive thermoelectric power S_{300K} = 30µV/K indicates the presence of holes (Co^{4+}) in the CoO_2 conducting layers. This value can be compared with those observed in the $Na_{0.5}CoO_2$ and the misfit $[(A'_{1-x}Co_y)_{n-2}A_{2+x-y}O_n]^{RS}[CoO_2]_{b1/b2}$ (A'=Bi,Tl.. and A=Ca,Sr..) related cobaltites. Secondly, two hydrated oxyhydroxides have been prepared in air [4]. The structural study coupled to thermal analyses has shown that $Sr_3Co_{1.7}Ti_{0.3}O_5(OH)_2$, xH_2O and $Sr_4Co_{1.6}Ti_{1.4}O_8(OH)_2$, xH_2O are derived from the Ruddlesden-Popper n = 2 and n = 3 members, respectively. The T-dependence of the structure shows upon warming two broad structural transitions from hydrated oxyhydroxides to oxygen deficient RP structures via an anhydrous oxyhydroxide form. The phenomenon of water loss during warming up to 1000°C to obtain the parent RP structures is found to be reversible. The magnetic behavior of these phases is governed by the substituted amount of Ti^{4+} (d^0) for cobalt species : cluster-glass and spin-glass like properties are observed for the hydrated n = 2 and n = 3 members, respectively.

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Keywords: crystal and powder X-ray diffractometry , electron microscopy technique , topotactic transformations

MS95.30.4

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Single-component Molecular Conductor Formed by Electron Transfer between d and π Orbitals

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Recently, research on conducting systems that consist of a single-component molecule has attracted a lot of attention.[1] Herein, we report the crystal structure and electronic properties of novel linear chain rhodium(I,II) mixed-valence complex, $\{[Rh(3,6\text{-DBDiox-}4,5\text{-}Cl_2)(CO)_2]\}_\infty$ (**1**) where 3,6-DBDiox-4,5-Cl_2 is used to indicate the semiquinonate or catecholate form of 3,6-di-*tert*-butyl-4,5-dichloro-