mechanisms implying periplasmic protein activity (e.g. alkaline phosphatase) and metabolic activity (e.g. sulfate reducing bacteria) will be reviewed.

Keywords: biomineralization, carbonate formation, polysaccharides

MS93.30.3

Acta Cryst. (2005). A**61**, C118

Nano-scale Studies of Processes on Crystal Surfaces in Aqueous Solutions

Guntram Jordan[a], Kirill Aldushin[a], Wolfgang W. Schmahl[b], [a]*Inst. f. Geol., Mineral. u. Geophys., Ruhr-Universität, Bochum, Germany.* [b]*Dept. f. Geo- u. Umweltwiss., LMU, München, Germany.* E-mail: guntram.jordan@rub.de

At the crystal-water interface a large diversity of processes takes place which influence or even control environmental conditions. Among these processes are sorption, growth, dissolution, formation of surface complexes or metastable phases by leaching, repolymerization, or precipitation. For a detailed understanding of these processes, factors and properties such as the stability of metastable phases or structural frameworks need to be taken into account.

Hydrothermal atomic force microscopy has been used for nano-scale in-situ investigations of crystal surfaces in aqueous solutions [1-3]. The method can provide insights into the molecular mechanisms and kinetics of solid-liquid interface processes. The results stress that especially for processes taking place at silicate-water interfaces the consideration of the stability of metastable states and structural influences is very important. In contrast, mechanisms of processes at interfaces like the carbonate-water interface although largely unsolved rather seem to comprise sequences of less numerous steps.

[1] Aldushin K., Jordan G., Fechtelkord M., Schmahl W.W., Becker H.-W., Rammensee W., *Clays Clay Minerals*, 2004, **52**, 432. [2] Aldushin K., Jordan G., Rammensee W., Schmahl W.W., Becker H.-W., *Geochim. Cosmochim. Acta*, 2004, **68**, 217. [3] Jordan G., Higgins S.R., Eggleston C.M., Knauss K.G., Schmahl W.W., *Geochim. Cosmochim. Acta*, 2001, **65**, 4257.

Keywords: surfaces and interfaces, AFM, silicates

MS93.30.4

Acta Cryst. (2005). A**61**, C118

Hydrothermal Preparation of TiO2: AC Composite Crystalline Particulates

A. K. Subramani[1], K. Byrappa[1], R. Dinesh[2], K. M. L. Rai[3], S. Ananda[3], M. Yoshimura[2], [1]*Departmant of Geology, University of Mysore, Manasagangotri, Mysore –6.* [2]*Materials Research Laboratory, Tokyo Institute of Technology, Nagatsuta, Midori, Yokohoma - 226, Japan.* [3]*Departmant of Chemistry, University of Mysore, Manasagangotri, Mysore –6.* E-mail: byrappak@yahoo.com

A highly active, monodispersed designer crystalline nano-particulate TiO_2 has been impregnated onto the activated carbon surface under mild hydrothermal conditions (<250^{0}C, P~40 bars) which finds the application as photocatalyst. Conventionally TiO_2 is prepared through solid state reactions, etc; further the hydrothermal impregnation of such particulates onto the surface layers of activated carbon has not been carried out either to. The hydrothermal technique provides an easy and one-step method to obtain monodispersed and well crystallized desired products and also eliminates the high temperature firing or pyrolysis required by the other methods. In the present study various hydrothermal experimental parameters like the starting precursors, mineralizers, temperature, etc., were taken into consideration for the impregnation experiments. The as-prepared catalyst composite was characterized by various techniques like XRD, SEM-EDX, PALS, BET and FTIR. The XRD results showed the persisting nature of anatase phase of TiO_2 deposited on the activated carbon surface. The BET and FTIR results reveal an optimum (TiO_2 to AC ratio) conditions for the impregnation. The PALS results further confirmed that TiO_2 is impregnated onto the surface and wider pores (macro- and mesopores) of the activated carbon and the micropores do not play a significant role as far as the TiO_2 impregnation is concerned. The results of the study finally revealed that TiO_2 could be effectively impregnated onto the activated carbon surface layers under mild hydrothermal conditions and such a designer crystalline particulate composite is highly useful for the environmental issues such as degradation of hazardous organics/wastes, treatment of effluents, air purification and so on.

Keywords: hydrothermal impregnation, photocatalyst, TiO_2: AC composite

MS93.30.5

Acta Cryst. (2005). A**61**, C118

Crystalline Structure of Biodegradable Polyhydroxybutyrate thin Films

Katsuhito Mori[a], Harumi Sato[a], Hikaru Terauchi[a], Isao Takahashi[a], Yukihiro Ozaki[a], Isao Noda[b], [a]*School of Science and Technology, Kwansei Gakuin University, Japan.* [b]*The Procter and Gamble Company, U.S.A.* E-mail: scbc0010@ksc.kwansei.ac.jp

Polyhydroxybutyrate: PHB and random copolymer, Polyhydroxyalkanoates: PHAs are crystalline biodegradable polyesters. As a substitute for petrochemical materials, the study of biodegradable polymer has attracted considerable attention. Our recent study demonstrated that melting behavior of a new random copolymer, Poly(3-hydroxybutyrate-co-3-hydroxyhexanoate): P(3HB-co-3HHx) showed a sharp contrast with that of PHB. A novel intermolecular interaction successfully explained the results.

As a next step, we are now conducting the X-ray reflectivity (XR) and grazing incidence X-ray diffraction (GIXD) measurements of thin films of PHB and P(3HB-co-3HHx) at various temperatures. The aim of this study is to get information on morphology, crystallinity, and crystal structure in the surface and thin films, which must be crucial for understanding the physical properties peculiar to the surface region and the mechanism of bio-degradation on a microscopic standpoint.

Both PHB and P(3HB-co-3HHx) thin films indicated that the crystallites tend to orient their *b*-axis along the surface normal direction. The present results strongly support the intermolecular interaction along the *a*-axis direction, which was suggested by the previous study on bulk samples. According to Bragg reflection from the near-surface region, surface morphology of PHB is different from that of P(3HB-co-3HHx) even at room temperature. We will also discuss the results of FT-IR spectrum obtained from the thin films.

Keywords: biodegradable polymer, X-ray diffraction, thin film

---

MS94 CRYSTALLOGRAPHIC KNOWLEDGE IN DRUG DESIGN STRATEGIES

Chairpersons: Franck Leveiller, Michele Saviano

MS94.30.1

Acta Cryst. (2005). A**61**, C118-C119

Can Structures lead to Better Drugs? Lessons from Ribosomal Antibiotics

Ada Yonath, *Structural Biology Department, Weizmann Institute.* E-mail: ada.yonath@weizmann.ac.il

Ribosomes, the universal cellular organelles catalyzing the translation of genetic code into proteins, are giant asymmetric riboprotein assemblies with a striking architecture and inherent mobility, enabling their function as ribozymes how place their substrate in stereochemistry suitable for peptide bond formation and substrate mediated catalysis. As the main player in a fundamental cell process, ribosomes are targeted by many antibiotics. Structures of over a dozen antibiotics complexes, obtained by using eubacterial ribosomes suitable to serve as pathogen models at clinically relevant concentrations, showed that although theoretically the giant ribosome offers numerous binding opportunities, ribosomal antibiotics bind to a single or a few binding sites; that most antibiotics interact primarily with riboso mal RNA and cause minor conformational changes; that minute structural differences, scattered in various ribosomal locations, are responsible for antibiotic selectivity; that the properties of the antibiotic-binding modes are dictated by species-specific binding pocket composition and conformation, the functional state of the ribosome, and the drugs chemical nature; that resistance to ribosomal

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

MS94.30.2

Acta Cryst. (2005). A**61**, C119

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

Michael Groll, *Adolf Butenandt-Institut, Lehrstuhl Physiologische Chemie, Butenandtstr. 5, 81377 München.* E-mail: michael.groll@bio.med.uni-muenchen.de

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

MS94.30.3

Acta Cryst. (2005). A**61**, C119

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

Francesca Fanelli[a,b], Pier. G. De Benedetti[b], [a]*Dulbecco Telethon Institute.* [b]*Department of Chemistry, University of Modena and Reggio Emilia.* E-mail: fanelli@unimo.it

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

MS94.30.4

Acta Cryst. (2005). A**61**, C119

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

Kalyan Das[a], Arthur D. Clark Jr.[a], Paul J. Lewi[b], Stephen H. Hughes[c], Paul A. J. Janssen[b], Eddy Arnold[a], [a]*CABM & Rutgers University, New Jersey, USA.* [b]*Janssen Pharmaceutica NV, Vosselaar, Belgium.* [c]*NIH National Cancer Institute-Frederick, Maryland, USA.* E-mail: kalyan@cabm.rutgers.edu

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

Acta Cryst. (2005). A**61**, C119-C120

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

Noriaki Hirayama[a], Junichi Goto[b], Ryoichi Kataoka[b], [a]*Tokai University School of Medicine, Isehara, Japan.* [b]*Ryoka Systems Inc., Urayasu, Japan.* E-mail: hirayama@is.icc.u-tokai.ac.jp

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.