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Keywords: metal-organic polymer, scandium, supramolecular

MS31.P25

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Inhibition of MMP-1, 3, and 13 by Same Inhibitor – Structure Based Design Study

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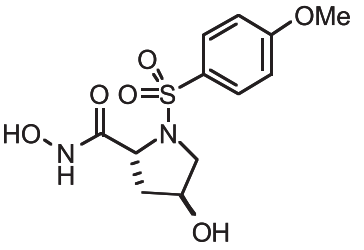
Matrix metalloproteinase (MMP) inhibitors are potential therapeutic agents for various diseases including cancer and osteoarthritis. Recent data from clinical trials with MMP inhibitors indicate that there is a great need for selective inhibitors. X-ray crystallography [1], [2], [3] has been used as a tool to help understand specific binding interactions of inhibitors to various MMPs. Large conformational changes have been noted when comparing the structures of the active MMP-3 catalytic domain and the one inhibited by a hydroxamic acid inhibitor. Both soaking and co-crystallization methods were used to generate the MMP-3/ inhibitor complex crystals for data collection. The same inhibitor has also been co-crystallized with MMP-1 and MMP-13. Comparisons of the structures of three inhibited enzymes, MMP-1, 3, and 13 show that MMP-3 and 13 are extremely similar. There are major differences in the binding pockets, especially in the S1' pocket between MMP-1 and MMP-3/13. These structural studies have helped design more selective inhibitors that can be used as therapeutic agents with improved safety profile.



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Keywords: osteoarthritis, drug, design

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Understanding the Phases of DNAN

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Dinitroanisole (DNAN) is a key insensitive munition melt-phase ingredient that is currently featured in several melt-pour formulations developed by the U.S. Army. Current interest in DNAN has arisen due primarily to its ability to provide a less sensitive melt-cast medium than TNT, allowing for the development of less sensitive melt-cast formulations.

It is known in the literature that crystalline DNAN exists in two phases, A and B, that melt at 96(1)°C and 87(1)°C respectively. During this study, a third phase (C) was observed during a variable temperature study of the low melting point sample. It has also been observed that a spontaneous phase transition of B to A occurs under ambient conditions. Each phase has been isolated and detailed crystallographic studies of the three phases have been done, as well as some theoretical energy calculations. The transition from B to C is reversible and straightforward due to the ordering of a disordered nitro group at low temperature. The transition from B to A is far more complex, requiring a large molecular rotation of DNAN molecules.

Keywords: phase transition

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Regioselective deacetylation based on teicoplanin-complexed Orf2* crystal structure

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Lipoglycopeptide antibiotics are more effective than vancomycin against MRSA as they carry an extra aliphatic acyl side chain on glucosamine (Glm) at residue 4 (r4)[1]. The biosynthesis of the r4 N-acyl Glc moiety at teicoplanin (Tei) or A40926 has been elucidated, in which the primary amine nucleophile of Glm is freed from the r4 GlcNac pseudo-Tei precursor by Orf2* for the subsequent acylation reaction to occur[2]. In this report, two Orf2* structures in complex with -D-octyl glucoside or Tei were solved. Of the complexed structures, the substrate binding site and a previously unknown hydrophobic cavity were revealed, wherein r4 GlcNac acts as the key signature for molecular recognition and the cavity allows substrates carrying longer acyl side chains in addition to the acetyl group. On the basis of the complexed structures, a triple-mutation mutant S98A/V121A/F193Y is able to regioselectively deacetylate r6 GlcNac pseudo-Tei instead of that at r4. Thereby, novel analogs can be made at the r6 sugar moiety.

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Keywords: regioselective, glycopeptide antibiotic, deacetylase.

MS31.P28

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Crystal structure of T-H protein complex of the glycine cleavage system

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Aminomethyltransferase, a component of the glycine cleavage system termed T-protein, reversibly catalyzes the degradation of the aminomethyl moiety of glycine attached to the lipoate cofactor of H-protein, resulting in the production of ammonia, 5,10-methylenetetrahydrofolate, and dihydrolipoate-bearing H-protein in the presence of tetrahydrofolate (THF). Several mutations in the human T-protein gene are known to cause non-ketotic hyperglycinemia. Previously we determined the

crystal structure of human T-protein with folate cofactor and provided the insight into the molecular basis of the disease-causing mutations. Here we present the crystal structure of *Escherichia coli* T-protein in complex with dihydrolipoate-bearing H-protein and 5-methyltetrahydrofolate (5-CH_3-THF): a complex mimicking the ternary complex in the reverse reaction. The structure of the complex shows a highly interacting intermolecular interface limited to a small area and the protein-bound dihydrolipoyllysine arm inserted into the active site cavity of the T-protein. Among the residues contributing to the interface, invariant Arg292 of the T-protein plays a key role in the complex assembly and probably in recruiting the aminomethyllipoyllysine arm to the active site of T-protein. It has been speculated that the aminomethyltransfer reaction from aminomethyllipoate of H-intermediate to THF is initiated by the direct attack of the methylene carbon atom by the nucleophilic N5 or N10 atoms of THF bound to T-protein accompanying the release of ammonia. However, the distances between the tip of the dihydrolipoyllysine arm and the methyl carbon atom of 5-CH_3-THF observed in the complex structure suggests the presence of an intermediary mediating the transfer reaction rather than the direct interaction. The hydrogen bond network surrounding the S8 atom of the dihydrolipoyllysine including invariant Asp96, Asp97, Asn113, and Arg223 of T-protein suggests that the reversible transfer of the methylene group between the lipoate and tetrahydrofolate should proceed through the electron relay-assisted iminium intermediate formation. Based on the structural observations together with mutational analyses, we propose a possible mechanism for T-protein catalysis. The structure also provides novel insights in understanding the disease-causing mutations, in addition to the disease-related impairment in the cofactor-enzyme interactions presented previously.

Keywords: Protein_complex, Catalytic_reaction

MS31.P29

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Molybdenum Oxide/Bipyridine hybrid materials: synthesis, structure and catalytic studies

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The chemistry of Mo(VI) is very important in industrial and biological systems [1, 2]. Monomeric complexes of the type $[MoO_2X_mL_n]$ (X = mono/dianionic ligand, L = neutral ligand) have been shown to be active catalysts, or catalyst precursors, for homogeneous epoxidation of non-functionalized olefins. Recently we found that $[MoO_2Cl_2(bipy)]$ (bipy = 2,2'-bipyridine) can produce a molybdenum(VI) oxide-based hybrid material [3] which can be used as an heterogeneous catalyst.

The molybdenum oxide/bipyridine hybrid material $\{[MoO_3(bipy)][MoO_3(H_2O)]\}_n$ can be isolated as a microcrystalline powder, in yields of 72-92%, from the reaction of $[MoO_2Cl_2(bipy)]$ in water using three distinct methods: hydrothermal (100ºC, 19h), reflux (120ºC, 4h) and microwave (120ºC, 4h).

The crystal structure of this hybrid material was determined from synchrotron X-ray powder diffraction data. The material is composed of two distinct neutral one-dimensional polymers: an organic-inorganic polymer, $[MoO_3(bipy)]_n$, and a purely inorganic chain, $[MoO_3(H_2O)]_n$; the two are interconnected by O-H···O hydrogen bonding interactions.

The material is a moderately active, stable, and selective catalyst for the epoxidation of *cis*-cyclooctene at 55 ºC with *tert*-butylhydroperoxide (*t*BuOOH, 5.5 M in decane or 70% aqueous) as the oxidant. Within the process, biphasic solid-liquid or triphasic solid-organic-aqueous mixtures are formed, and 1,2-epoxycyclooctane is the only reaction product. When *n*-hexane is employed as a co-solvent and *t*BuOOH(decane) is the oxidant, the catalytic reaction is heterogeneous in nature, and the solid catalyst can be recycled and reused without loss of activity. For comparison, the catalytic performance of the precursor $[MoO_2Cl_2(bipy)]$ was also investigated. The FT-IR spectra of the solids recovered after catalysis indicate that the discrete complex transforms into the organic-inorganic polymer $[MoO_3(bipy)]$ [4] when the oxidant is *t*BuOOH(decane) and compound $\{[MoO_3(bipy)][MoO_3(H_2O)]\}_n$ when the oxidant is 70% aqueous *t*BuOOH.

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Keywords: dioxomolybdenum(VI), catalysis, olefin-epoxidation

MS31.P30

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Structural and functional analysis of rRNA methyltransferase from *Staphylococcus aureus*

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Ribosomal RNAs (rRNAs) are modified post-transcriptionally to generate variety of nucleotides required for fine tuning of ribosomes. In *Escherichia coli*, m2G 2445 of 23S rRNA is produced by *Ec*RlmL (ribosomal large subunit methyltransferase L), which possesses two methyltransferase domains. In *Staphylococcus aureus*, these two domains are separated two proteins, *Sa*RlmL-N and *Sa*RlmL-C. Here we present crystal structure and RNA binding study of *Sa*RlmL-N and *Sa*RlmL-C.

SaRlmL-N and *Sa*RlmL-C were expressed in *E.coli* and purified by Ni-affinity chromatography and size exclusion chromatography. Crystals were obtained by using vapor diffusion method and X-ray diffraction data were collected at BL41XU SPring-8, Harima, Japan and PF BL-17A, Tukuba, Japan. crystals of *Sa*RlmL-N *Sa*RlmL-C belong to space group $P2_1$ with cell dimensions (*Sa*RlmL-N: a = 52.5, b = 107, c = 77.2 Å, β = 100° ; *Sa*RlmL-C: a = 95.8, b = 91.7, c = 103 ∓, β = 93.9−). structures were solved by molecular replacement with the program *Morlep*.

Structure of *Sa*RlmL-N contains methyl donor, *S*-adenosyl-methionine (SAM) in methyltransferase domain. SAM binding pocket is connected to vast cleft which is charged positive and surrounding residues are highly conserved. RNA binding experiments were performed using *in vitro* transcribed RNA fragment including Guanine 2445. Formation of *Sa*RlmL-N and RNA fragment complex was confirmed by size exclusion chromatography. This result indicates that *Sa*RlmL-N may serve as m2G 2445 methyltransferase in *S. aureus*. ased on the structur and RNA binding study, we propose the RNA binding model of *Sa*RlmL-N.

Structure of *Sa*RlmL-C is composed three domains: NTD, EEHEE and MTase, and is similar to *Ec*RlmI with different intermolecular