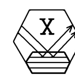

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Friday, March 15, Session VI

L20

INHIBITORS OF GLUTAMINYL CYCLASES AGAINST ALZHEIMER`S DISEASE

P. Kolenko[1,3], B. Koch[2], S. Schilling[2], J.-U. Rahfeld[2], H.-U. Demuth[2], M. T. Stubbs[3]

[1]*Institute of Macromolecular Chemistry AS CR, v.v.i., Heyrovského nám. 2/1888, 162 06 – Prague 6, Czech Republic*
[2]*Probiodrug AG, Weinbergweg 22, 06 120 Halle (Saale), Germany*
[3]*Institut für Biochemie und Biotechnologie, Martin-Luther Universität, Kurt-Mothes-Straße 3, 06 120 Halle (Saale), Germany*
petr.kolenko@gmail.com

N-terminal formation of pyroglutamate (pGlu) is catalyzed by glutaminyl cyclases (QCs) [1,2]. This form of post-translational modification is observed on numerous bioactive peptides. Formation of pGlu-amyloid has been also linked with Alzheimer`s disease [3-5]. Inhibitors of human QCs are currently the subject of intense development and testing [6,7].

We have currently solved crystal structures of two isoforms of QCs from *Drosophila melanogaster* [7]. Comparative study of structures of human, murine, and insect QCs from the PDB [8] allowed us reasonable evaluation of various binding modes of inhibitor PBD150. Structural observations are in concert with our inhibition studies.

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L21

REACTION MECHANISM OF RU(II) PIANO-STOOL COMPLEXES; UMBRELLA SAMPLING QM/MM MD STUDY

Zdenek Futera, Jaroslav V. Burda

Department of Chemical Physics and Optics, Faculty of Mathematics and Physics, Charles University, Ke Karlovu 3, 121 16 Prague 2, Czech Republic

Biologically relevant interactions of piano-stool ruthenium(II) complexes with ds-DNA were explored by hybrid QM/MM computational technique. The whole reaction mechanism is considered in three step: hydration of $[Ru^{II}(\ ^{6}\text{-benzene})(en)Cl]^{+}$, binding of resulting aqua complex to DNA and final intra-strand cross-link formation between two neigboring guanosines. Free energy profiles of all reactions are explored by QM/MM MD umbrella sampling approach where the Ru(II) complex is described by DFT and remaining part by General Amber Force Field (GAFF). For that purpose, our own software was developed, which couples the Gaussian and Amber programs. Calculated free energy barriers of Ru(II) hydration as well as DNA binding process are in good agreement with experimentally measured rate constants. Following this method-justification step, possibility of cross-link formation is investigated and one feasible pathway leading to Ru(II) guanosine-guanosine cross-link with synchronous releasing of the benzene ligand is predicted. The cross-linking is exergonic process with energy barrier lower than for initial binding to DNA.

L22

CH- INTERACTION BETWEEN CARBOHYDRATES AND AROMATIC MOIETIES: ELECTRON DENSITY ISSUE

S. Kozmon[1,2], R. Matuška[1,2], J. Koča[1,2]

[1]*CEITEC – Central-European Institute of Technology, Masaryk University, Kamenice 753/5, 625 00, Brno, Czech Republic*
[2]*National Centre for Biomolecular Research, Faculty of Science, Masaryk University, Kamenice 5, 625 00, Brno, Czech Republic*

Former studies of the CH- đ interactions [1,2] between carbohydrates and aromatic moieties were focused on exploration of interaction energies in complexes of selected carbohydrates (-D-glucopyranose, -D-mannopyranose and -L-fucopyranose) with benzene and naphthalene as simplest representatives of aromatic amino acids side chains. These studies provided complex insight into the nature and strength of carbohydrate-aromatic CH- interaction as well as its additivity with respect to total number of đ-electrons interacting it the aromatic system. The next logical step in complex study of CH- interaction is to study the influence of electron density in the aromatic system to the total interaction energy of the carbohydrate-aromatic complex.

For this reason, we chose established set of selected carbohydrates mentioned above and constructed aromatic systems derivatives with expected increased and decreased electron density in the cycle – namely symmetrical difluoro-, trifluoro- and tetrafluoro-benzene and symmetrical diazine, triazine and tetrazine. All derivatives underwent electron-density evaluation in ring critical points by AIM analysis (MP2/aug-cc-pVTZ), which clearly shows decreasing electron density with respect to the degree of derivatization of fluorobenzenes and increasing electron density with respect to the degree of derivatization by nitrogens in the aromatic ring.With this set of molecules, we repeat the semiempirical SCC-DFTB-D potential energy scan with DFT-D BP/def2-TZVPP interaction energy refinement to identify stationary structures of potential energy surface. Their interaction energy is calculated after geometry optimization at DFT-D BP/def2-TZVPP level. Such level of theory has been previously proved [1] to be sufficient and giving similar results as CCSD(T)/CBS method.

Performed study helps to understand the way how saccharides interact with aromatic amino acid side chains in lectins. More specifically speaking the way, how the substitution of benzene ring in lectins influences the carbohydrate binding potential. Such understanding may be then utilized in tuning the strength of CH- interaction and also for further glyco-force-field refinements.

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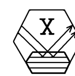

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L23

THYLAKOID MEMBRANE CHARACTERIZATION AND ITS INTERACTION WITH PSBI PROTEIN FROM PHOTOSYSTEM II

Žofie Sovová, Rudiger Ettrich

Faculty of Science, University of South Bohemia in České Budějovice and Institute of Nanobiology and Structural Biology GCRC, CAS, Nové Hrady, sovova@nh.cas.cz

The thylakoid membrane from cyanobacterium *Synechocystis PCC6803* is characterized by means of atomistic and coarse-grained molecular dynamics. Two different compositions reported in the literature are described and potential differences are explored. The major difference between the membranes is found in their phase transition temperatures. Additionally, in the used Martini coarse-grain model the phase transition temperature contains a systematic error. Comparison of atomistic and coarse-grained simulations shows a similar behavior for both kinds of simulations, thus supporting the correctness of our recently published coarse-grain force field parameters.

A structural model of PsbI, a one-transmembrane-helix protein and part of photosystem II, is inserted into the chracterized membrane and its behavior is described. Despite being complexed in photosystem II, PsbI can occur in thylakoid membranes as a single protein. Coarse-grained simulations were used to describe the mutual behavior of a larger number of isolated PsbI in a thylakoid membrane. Througout the simulations, the flexible C-terminal loop does not adopt a stable conformation in isolated PsbI, but it may be stabilized, when the proteins multimerize. We observe a dynamic multimerization of PsbI in the coarse-grained simulations, and describe a tendency to form larger aggregates as the preferable behavior of isolated PsbI in thylakoid membranes.

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L24

STRUCTURAL AND MECHANISTIC PRINCIPLES OF INTRAMEMBRANE PROTEOLYSIS – LESSONS FROM RHOMBOIDS

K. Strisovsky[2], K. R. Vinothkumar[1], H. Sharpe[1], C. Adrain[1], E. Stevens[1], M. Freeman[1]

[1]Medical Research Council Laboratory of Molecular Biology, CB2 2QH, Cambridge, United Kingdom
[2]Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo n. 2, 166 10, Prague, Czech Republic
kvido.strisovsky@uochb.cas.cz

Intramembrane proteases cleave membrane proteins in their transmembrane domains. This is intriguing, since the hydrophobic interior of lipid membranes excludes water and is thus not an ideal milieu for hydrolytic reactions. But intramembrane proteases are very widespread in evolution and those few that have been studied in detail regulate a variety of prominent biological processes including developmental signalling, stress responses, membrane protein quality control, mitochondrial dynamics and apoptosis. Despite their evolutionary ubiquity and biological significance, our mechanistic and structural understanding of these enzymes is limited. There are three catalytic types of intramembrane proteases, their active sites are buried in the lipid membrane and they are all evolutionarily unrelated to the “classical“, soluble proteases. Significant progress has been made in understanding their function during the past few years, but fundamental structural and mechanistic questions are still open. How do intramembrane proteases recognise their transmembrane substrates and how do they achieve specificity? How does water gain access to the membrane-immersed catalytic site? What is the mechanism of the cleavage reaction? Using rhomboid intramembrane serine proteases as a model I will discuss these questions in light of the recent progress in the field focussing on our data that explain important aspects of substrate specificity and mechanism of rhomboids.