11th Visegrad symposium on biomolecular interactions

June 20th to June 23rd 2023 at Szidonia Castle

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1 Welcome to the Visegrad Symposium

1.1 Preamble

Welcome to the 11th Visegrad Symposium, a premier scientific conference that brings together researchers from the Visegrad countries and beyond to discuss the latest developments in biomolecular research. We will meet at the marvelous four-star Hotel Szidónia Castle near Sopron (Hungary) from June 20th to June 23rd 2023.

Organized annually since 2011, the Visegrad Symposium is a platform for sharing ideas and establishing interdisciplinary collaborations among researchers using a wide array of scientific approaches. Traditionally, the conference focuses on the application of various computational methods, including bioinformatics, MD & QM simulations, spectroscopy and microscopical techniques in the study of complex biological systems. This year, we would like to broaden the scientific scope and include machine learning and big data science approaches. This year's conference will feature an exciting lineup of invited speakers, poster sessions, and oral presentations, providing a unique opportunity to learn about the latest advances in modeling biomolecular systems and network with leading researchers in the field. Whether you are a seasoned researcher or a student just starting in the field, we invite you to join us for the 11th Visegrad Symposium on biomolecular interactions, where you will have the chance to exchange knowledge, share ideas, and forge new collaborations with colleagues from the Visegrad region and beyond.

A special thanks goes to our sponsor:

Best regards
Christian Schröder

1.2 Conference committees

Organizers

- Christian Schröder (University of Vienna)
- Béla Viskolcz (University of Miskolc)
- Zsófia Borbála Rózsa (University of Miskolc)

Scientific Board

- Babak Minofar (University of South Bohemia)
- Marcin Palusiak (University of Lodz)
- David Reha (University of South Bohemia)
- Christian Schröder (University of Vienna)
- Béla Viskolcz (University of Miskolc)

2 Scientific program

2.1 Schedule

	Tuesday, June 20th	Wednesday, June 21st	Thursday, June 22nd	Friday, June 23rd
09:00 - 09:50		Rudi Ettrich	Oldamur Holloczki	Mohammad Uddin
09:50 - 10:15		Emma Szőri-Dorogházi	Ivan Klbik	Zoltán Mucsi
10:15 - 10:40		Péter Koska	Berna Dogan	Áron Szepesi
10:40 - 11:10		Coffee break	Coffee break	Coffee break
11:10 - 12:00		Alla Sapronova	Ondrej Maršálek	Monika Staś
12:00 - 12:25		Kinga Wzgarda-Raj	Victor Velasco-Berrelleza	András Szabadi
12:25 - 12:50		Agnieszka Rybarczyk-Pirek	Marcin Palusiak	Michael Owen
12:50 - 14:00		Lunch	Lunch	Lunch
14:00 - 14:50	Giorgia Del Favero	Kiattawee Choowongkomon	Justynia Dominikowska	Closing remarks
14:50 - 15:15	Dalma Dojcsak	Pau Reig-Rodrigo	Florian Joerg	
15:15 - 15:40	Timea Gerzsenyi	Milan Melicherčík	Márta Gődény	
15:40 - 16:10	Coffee break	Coffee break	Coffee break	
16:10 - 17:00	Pál Jedlovszky	György Panyi	Adam Buczkowski	
17:00 - 17:25	Marta Hoelm	Nacer Idrissi	Liliana Checińska	
17:25 - 17:50	Chetna Tyagi	Milan Szöri	Ryan Cocking	
18:00 - 20:00	Poster session	Poster session	BBQ	

2.2 Invited speakers

Simulating biomolecular interactions

- Justyna Dominikowska (University of Lodz, Poland)
- Monika Staś (Opole University, Poland)
- Rudi Ettrich (Larkin University, US)

Measuring biomolecular interactions

- György Panyi (University of Debrecen, Hungary)
- Kiattawee Choowongkomon (Kasetsart University, Thailand)

Drug development and diagnostics

- Giorgia Del Favero (University of Vienna, Austria)
- Pal Jedlovszky (Eszterházy Károly Catholic University, Hungary)
- Adam Buczkowski (University of Lodz, Poland)
- Mohammad Uddin (Mercer University)

Biomolecular interaction for green waste management

- Oldamur Holloczki (University of Debrecen, Hungary)

Machine learning and big data

- Alla Sapronova (PetraOS, LLC Bergen, Norway)
- Ondrej Maršálek (Charles University of Prague, Czech Republic)

3 Abstracts of oral contributions

3.1 Tuesday, June 20th

13:30 - 14:00	Opening remarks
14:00 - 14:50	Giorgia Del Favero *Unraveling the secrets of cell motility: from images to -omics with the help of bioinformatics*
14:50 - 15:15	Dalma Dojcsák
15:15 - 15:40	Tímea Gerzsenyi
15:40 - 16:10	Coffee break
16:10 - 17:00	Pál Jedlovszky *Understanding the Molecular Mechanism of General Anesthesia*
17:00 - 17:25	Marta Hoelm
17:25 - 17:50	Chetna Tyagi
18:00 - 20:00	Poster session (odd numbers)

Unraveling the secrets of cell motility: from images to -omics with the help of bioinformatics

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In the body, cells are exposed to a myriad of signals. These originate from cell-cell contact and from the surrounding chemical and physical microenvironment. Despite decades of research, how exactly cells manage to integrate these complex networks remains largely unknown. Along this line, bladder cells perfectly typify these paradigms: on the one side they withstand the everchanging chemical composition of urine and, additionally, constantly adjust to the physical cues stemming from the filling-voiding of the organ. As a drawback of this outstanding plasticity, bladder cancers develop in extremely aggressive phenotypes. Obviously, the elucidation of molecular mechanisms enabling this resilience promises to advance not only basic research, but also to provide valuable knowledge for the development of new therapeutic approaches. Expanding on this, we postulated that the adaptive capacity of bladder cancer cells could be traced back to molecular mechanisms connecting metabolic competence to mechanotransduction. Indeed, it is long known that the morphology of organelles involved in metabolism like mitochondria and endoplasmic reticulum (ER) correlates directly with functional status, however it is also clear that these elements occupy a significant mass within the cells. This makes it plausible that functional changes associated to morphometric rearrangements could also reflect on cell biophysical compliance. Taking advantage of tailored pharmacological interventions, we started to selectively modulate the activity of mitochondria and ER and correlate this with cell motility and response to mechanical stimuli. With this approach we were able to describe a contribution for non-cytoskeletal organelles in the regulation of bladder mechanotransduction and open in this way new perspectives for novel pharmacological intervention.

The Alterations of Serum N-glycome in Response to SARS-CoV-2 Vaccination

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The global pandemic of coronavirus disease 2019 (COVID-19) has affected millions of people worldwide and caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). One of the main strategies to control the pandemic, was the use of vaccination against the SARS-CoV-2 virus, reducing the duration of infection time. Glycosylation is a chemical modification of proteins by the covalent attachment of carbohydrate chains after translation, serving as an important signal in the quality control of protein synthesis. Recent studies suggest that serum glycosylation can be significantly altered in patients after SARS-CoV-2 infection and the analysis of serum N-glycome might be significant in the surveillance of COVID-19. Glycans are complex carbohydrates consisting of multiple monosaccharide units with no fluorophore group requiring multistep sample preparation and high-resolution separation methods for their sensitive and reliable quantitative analysis. One of the most efficient separation technique in quantitative glycomics is the ultra-performance liquid chromatography (UPLC) combined with fluorescence and/or mass-spectrometric detection.

Our goal was analysis of clinical samples to identify potential glycosylation-based alterations in serum samples of SARS-CoV-2 infected and/or mRNA vaccinated patients using ultra-high-performance liquid chromatography (UHPLC).

The anti-SARS-CoV-2 IgG positivity of the samples was determined across the patient groups by anti-SARS-CoV-2 IgG ELISA immunoassay. Glycans from the serum samples were released by PNGase F digestion based deglycosylation followed via fluorescent derivatization and hydrophilic solid phase extraction. Each individual patient samples were relatively quantified by UHPLC with fluorescence detection. Results: Our results suggest the increase of non-fucosylated-sialylated glycan species in both post-COVID and post-Vaccinated patients. In case of the fucosylated and sialylated structures there was no significant increase in response to vaccination while higher fucosylation values were found in post-COVID patients.

In this study, total serum N-glycome was analyzed in patients after SARS-CoV-2 infection and/or after mRNA vaccination in order to identify potential glycosylation based alterations using hydrophilic-interaction liquid chromatography.

Development of manganese ferrite magnetic nanoparticles aided DNA isolation

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DNA isolation is a fundamental and widely used method in molecular biology. Today, in addition to the traditional alkaline lysis method, other affinity column-based and magnetic nanoparticle-based isolation methods are also known. Conventional DNA extraction methods are time-consuming and require chemicals that are harmful to health (e.g. phenol, chloroform). Beyond this, commercially available DNA isolation kits based on affinity columns and magnetic nanoparticles are expensive. At the Institute of Chemistry of University of Miskolc, material scientists create magnetic nanoparticles in a cost-effective way. In this research in-house synthesized $MnFe_2O_4$ nanoparticles were tested in DNA extraction studies. Several applications of manganese ferrite nanoparticles are already known. However, according to the literature, these magnetic nanoparticles have not yet been used for DNA isolation. This work presents a study of bacterial plasmid DNA isolation with $MnFe_2O_4$ magnetic nanoparticles. The aim was to develop a protocol for the extraction of high purity and high amounts of DNA, which is cost-effective and the chemicals used in the process are not harmful to the health of the user. The nanoparticles were first tested for reversible DNA binding, using pure DNA solution, and then investigated for DNA isolation from a complex medium, the bacterial cell lysate. The concentration of the magnetic nanoparticles was adjusted to the volume of the starter cell suspension. The volume of elution fractions to be used in the isolation process and the number of elutions to be performed were also determined, to achieve the most optimal amount of DNA recovery from a unit volume of cells. The presence of DNA in the elution fractions was verified by agarose gel electrophoresis and the concentration of the extracted nucleic acid was determined by UV-Vis spectrophotometry. The quantity of DNA molecules extracted with the $MnFe_2O_4$ nanoparticles is comparable to those extracted with the commercially available cartridge-based kits. Furthermore, the purity of the isolated DNA falls within the appropriate range of the defined values.[1]

References:

[1] Gerzsenyi, T. B., Ilosvai, Á. M., Szilágyi, G., Szőri, M., Váradi, C., Viskolcz, B., Vanyorek, L. & Szőri-Dorogházi, E. (2023). A Simplified and Efficient Method for Production of Manganese Ferrite Magnetic Nanoparticles and Their Application in DNA Isolation. International Journal of Molecular Sciences, 24(3), 2156.

Understanding the Molecular Mechanism of General Anesthesia

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General anesthesia can be caused by various, chemically very different molecules, while several other molecules, many of which are structurally rather similar to them, do not exhibit anesthetic effect, at all. To understand the origin of this difference, and shed some light on the molecular mechanism of general anesthesia, we report here molecular dynamics simulations of the neat dipalmitoylphosphatidylcholine (DPPC) membrane as well as DPPC membranes containing the anesthetics diethyl ether and chloroform, and the structurally similar non-anesthetics *n*-pentane and carbon tetrachloride, respectively. To also account for the pressure reversal of anesthesia, these simulations are performed both at 1 bar and at 600 bar. Our results indicate that all solutes considered prefer to stay both in the middle of the membrane and close to the boundary of the hydrocarbon domain, at the vicinity of the crowded region of the polar headgroups. However, this latter preference is considerably stronger for the (weakly polar) anesthetics than for the (apolar) non-anesthetics. Anesthetics staying in this outer preferred position increase the lateral separation between the lipid molecules, giving rise to a decrease of the lateral density. The lower lateral density leads to an increased mobility of the DPPC molecules, a decreased order of their tails, an increase of the free volume around this outer preferred position, and a decrease of the lateral pressure at the hydrocarbon side of the apolar/polar interface, a change that might well be in a causal relation with the occurrence of the anesthetic effect. All these changes are clearly reverted by the increase of the pressure. Furthermore, non-anesthetics occur in this outer preferred position in a considerably smaller concentration, and hence either induce such changes in a much weaker form, or do not induce them, at all.

Quantum chemical study of the β-CD complexation ability towards antihistamine drug loratadine

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Loratadine (LOR) is an effective second-generation antihistamine drug widely used to treat antiallergic conditions. Although LOR is classified as a safe medication, some adverse effects may occur, especially headaches or vomiting due to the drug's anticholinergic effects [1]. According to the biopharmaceutics classification system (BCS), LOR is a class II drug, which means that it is characterized by good permeability but extremely low water solubility [2]. The latter is highly pH dependent as LOR is a weak alkali, which is the main reason of its poor bioavailability. The improvement of the latter is urgently needed, especially for elderly patients who have problems with insufficient gastric acid secretion. For this purpose, various formulations of LOR have been developed such as nanoemulsions, which indeed, improve solubility but their drug-loading efficiency is too low [3]. The listed above pharmaceuticals problem can be overcome by using highly water-soluble drug carrier, which by forming a complex, will be able to improve LOR properties. One of the most widely used carriers characterized by the high-water solubility is β-cyclodextrin (β-CD).

In this lecture the results obtained from the theoretical analysis performed for the β-CD:LOR complex (1:1) will be presented, with emphasis on the most stable structures and the corresponding complexation as well as the interaction energies. According to the M06-2X-D3/6-31G(d,p) results, β-CD forms a very stable complexes with the lowest complexation energy ca. -49.1 kcal/mol. The theoretical results, especially NMR chemical shifts will be compared with the experimental ones.

Acknowledgments:

Part of calculations has been carried out using resources provided by Wroclaw Centre for Networking and Supercomputing (http://wcss.pl), grant No. 443.

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[1] R.F. Orzechowski, D.S. Currie and C.A. Valancius. *Eur J Pharmacol.* **04** (2005), 257-64.

[2] M. El-Hammadi and N. Awad. *AAPS PharmSciTech* **13** (2012), 53–8.

[3] O. Sarheed, D. Shouqair, and K. Ramesh *Int J Pharm* **576** (2020), 118952.

Accelerated molecular dynamics: modeling fungal peptaibols and their interaction with lipid membrane models

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The use of enhanced sampling techniques in molecular dynamics (MD) simulations to facilitate the folding of peptides and proteins is a relatively new approach which has quickly gained momentum in recent years. One such technique, namely accelerated molecular dynamics (aMD) introduced by Hamelberg et al. [1], can make accessible different intermediate states visited during peptide folding by lowering the energy barrier between them. In other words, the dynamic path from the unfolded state to all intermediates and finally to the near-native state is "flattened" by introducing a non-negative boost to the potential. This approach has been applied by Miao et al., [2] to elucidate the native structures of fast-folding small peptides from their unfolded states.

The molecule, Alamethicin (Alm F30/3), chosen in this study belongs to the class of fungal peptaibols that are 7-20 residue long, non-ribosomally synthesized, amphipathic molecules showing interesting membrane perturbing activity. It is important to elucidate the structure and dynamics of such peptaibols due to their potential antimicrobial effects and future application. In this study, we parameterized the constituent non-standard amino acid residues and constructed the unfolded primary structure of Alm F30/3 to be simulated using aMD simulation for its comparison with the X-ray crystallography-based 3D structure available from the Protein Data Bank (1AMT). The aMD simulation parameters were optimized on the Alm F30/3 system. The calculation of convergence revealed that 1 μs long aMD simulation with slightly aggressive boost parameters is sufficient to obtain the complete conformational ensemble of peptaibols.

Consequently, we tested the accuracy of aMD technique to simulate Alm F30/3 hexamer ion channel embedded in a lipid bilayer mimicking bacterial cell membrane and under an applied electric field. The presence of peptide channel clearly introduced disorder to the membrane as shown by the lipid SCD parameter. The average pore radius value was comparable to the experimental values reported by Abbasi et al., [3]. We also observed that the N- and C-termini of the pore undergo high fluctuation and correlates with the hinge-like movement of peptaibol chains around their central region. We conclude that aMD can be successfully applied to model all-atom representations of bilayer membranes and their interaction with peptaibols.

References:

[1] D. Hamelberg, J. Mongan, J. A. McCammon. *J Chem Phys* **120** (2004), 11919-11929.

[2] Y. Miao, F. Feixas, C. Eun, J. A. McCammon. *J Comp Chem* **36** (2015), 1536-1549.

[3] F. Abbasi, J. Alvarez-Malmagro, Z. Su, J. Leitch & J. Lipkowski. *Langmuir* **34** (2018), 13754-13765.

3.2 Wednesday, June 21st

9:00 - 9:50	Rudi Ettrich *Computational Modeling of 3′-Phosphoadenosine 5′-phosphosulfate Synthase Papss*
9:50 - 10:15	Emma Szőri-Dorogházi
10:15 - 10:40	Péter Koska
10:40 - 11:10	Coffee break
11:10 - 12:00	Alla Sapronova *AI/ML Methods Application to Optimize Molecular Modeling*
12:00 - 12:25	Kinga Wzgarda-Raj
12:25 - 12:50	Agnieszka Rybarczyk-Pirek
12:50 - 14:00	Lunch
14:00 - 14:50	Kiattawee Choowongkomon *Computer-aided Drug Discovery: From Small Compounds to Protein Inhibitors against Tyrosine Kinase of EGFR for cancer therapy*
14:50 - 15:15	Pau Reig-Rodrigo
15:15 - 15:40	Milan Melicherčík
15:40 - 16:10	Coffee break
16:10 - 17:00	György Panyi *Molecular interactions between ion channels and peptide toxins: advantages and limitations of electrophysiology*
17:00 - 17:25	Nacer Idrissi
17:25 - 17:50	Milán Szöri
18:00 - 20:00	Poster session (even numbers)

COMPUTATIONAL MODELING OF 3'-PHOSPHOADENOSINE 5'-PHOSPHOSULFATE SYNTHASE PAPSS

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The sulfur nucleotide PAPS (3'-phosphoadenosine 5'-phosphosulfate) is the universal sulfuryl donor of the cell. In mammals 3'- phosphoadenosine 5'-phosphosulfate Synthase (PAPSS), using ATP, converts biochemically inert inorganic sulfate to the metabolically active PAPS. It is a bi-functional enzyme and catalyzes the formation of PAPS in two sequential steps [1] In the first step, inorganic sulfate reacts with ATP to form APS and pyrophosphate. The resulting phosphoric-sulfuric anhydride bond has high energy that is the chemical basis of sulfate activation. The second step is catalyzed by the kinase domain of PAPSS and involves the reaction of APS with ATP to form PAPS and ADP. The proper function of PAPSS is essential for normal physiology in the human being. As the ubiquitous sulfate donor in most biological systems, the product of the enzyme, PAPS, plays an essential role in ECM formation, embryonic development and biomolecule secretion. PAPSS has also been shown to be involved with the pathophysiology of a number of diseases and deficiency in human results in osteochondrodysplasias or defective cartilage and bone metabolism as evidenced in the clinical condition of the recessively inherited, spondyloepimetaphyseal dysplasia (SEMD). Using a combination of molecular docking, homology modeling, and molecular dynamics simulations in combination with experimental work we try to understand how the three dimensional structure of PAPSS determines the enzyme function, focusing on the roles of specific amino acid residues [2] /overall structures on the dynamics of the enzyme in aqueous solution and the related quaternary arrangements of the enzyme. Results are discussed that give a realistic picture of the enzyme activity.

References:

[1] Venkatachalam, K.V. IUBMB Life **2003**, 55, 1–11

[2] K.V. Venkatachalam K.V., Ettrich R.H. *Biochemistry and Biophysics Reports* **2021**, 28, 101155

Added value of biological tests in advanced material design

Emma Szőri-Dorogházi[1], Timea Gerzsenyi[1], Gergely Szilágyi[2], Karina Kecskés[1], Julie Mallouhi[1], Anikó Jordán[1], Béla Viskolcz[1]

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Designing new materials involves more than just controlling their physical and chemical properties. The interactions of these materials with biological systems also play a crucial role in their applications. Conducting tests to assess antimicrobial properties, toxicity, bacterial retention capacity, and other biological characteristics helps guide the development of these materials and select the most suitable ones for specific applications. Through these endeavors, our research group makes significant contributions to the creation and advancement of new materials, as well as the overall development of materials.

Recent developments have been made in the field of titanium-silver alloys, which are used as implant materials. We have characterized antibacterial properties of the material, and the selection of optimal alloys was performed accordingly.

Similarly, polyurethane foams (PUF) with antibacterial properties have proven advantageous for various applications, such as mattresses. In this context, a recently developed polyurethane foam containing natural zeolite coated with silver nanoparticles was subjected to antibacterial activity testing. The widespread use of PUF generates a significant amount of waste, highlighting the importance of its (bio)degradation after use. Degradation can potentially lead to the formation of ecotoxic compounds, which can hinder further biodegradation processes. In our laboratory, we have developed a monitoring system utilizing bacteria and plants to assess the toxicity associated with PUF degradation.

The environmental challenges in developing countries are not limited to solid waste but also extend to contaminated water sources, posing significant risks. To address this issue, a cost-effective and efficient water filtration system is crucial. In our research, we have evaluated the bacterial retention capacity of newly developed zinc oxide-cellulose hybrid and titanium oxide-based hybrid membranes, which hold promise for water filtration applications.

DNA isolation plays a crucial role in health diagnostics, molecular, and microbiological research. Solid phase extraction (SPE) utilizing magnetic nanoparticles is a widely applied technique for this purpose. In our study, newly designed in-house magnetic nanoparticles were evaluated for their suitability in DNA isolation, and optimal conditions for their application were determined. Subsequently, the purified DNA can be employed as a template in qPCR assays, utilizing both conventional and newly developed fluorescent dyes. The objective of this research is to develop potential new dyes for qPCR reactions that offer comparable or enhanced sensitivity compared to existing ones.

Detection of esterase production of Bacillus strain in shake flask fermentation

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Biodegradation of synthetic polymers eg.plastics could be an ecofriendly and sustainable way to eliminate the plastic waste instead of depositing it in landfills or combustion. The bottleneck of plastic degradation is the hydrolytic process of synthetic polymers into monomeric compounds which can get across into the microbial cell wall and can be metabolized and transformed it into biomass, carbon-dioxide and water. Hydrolytic processes depend on the activity and amount of the hydrolytic enzymes produced by different microbes. Therefore, the first step toward microbial hydrolysis of plastics is screening of microbes derived from soils for production of esterases and lipases.

In recent work *Bacillus subtilis, and Bacillus velenzis* strains were screened in shake flask fermentation for producing hydrolytic enzymes using *1% tributyrin as an esterase substrate* in Luria Bertani medium. After 24 hours of incubation significant pH drop have been detected, which indicated that butyric acid was liberated from the tri-ester tributyrin. Bacilli were unable to grow at pH 5 which was indicated by lower biomass production (OD600) related to tributyrin free control fermentation.

Equivalent results have been obtained with a non-characterized microbial Bacillus consortium. Furthermore, in this case microaerophilic (without shaking cultures) have been tested to tributyrin hydrolysis. In such conditions there were only slight and transient pH drop have been detected. These data may indicate that lack of aeration may inhibit production of esterases, which results in lower concentration of butyric acid than in aerobic condition.

These experimental data suggest that application of tributyrin can be a suitable sensitive method for detection of esterase production directly in fermentation medium.

AI/ML Methods Application to Optimize Molecular Modeling

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The work is centered on the transformative potential of artificial intelligence (AI) and machine learning (ML) in refining the field of molecular modeling. One critical question set the stage: "How can AI and ML methodologies revolutionize precision and efficiency in molecular modeling?" Drawing on advanced ML techniques, particularly convolutional neural networks (CNNs) and graph neural networks (GNNs), application in predicting molecular properties and behaviors will be demonstrated.

An essential part of the presented work focused on the process of AI models' training: we will show that ML models can compete with traditional methods in terms of prediction accuracy but demonstrate significantly higher speed and computational efficiency. This aligns with [1] evaluation of machine learning applications in materials design and discovery, reinforcing the utility of ML algorithms for delivering much faster yet accurate results.

The work will demonstrate how ML can be used for computing potential energy surfaces (PES) that describe the potential energy of a collection of atoms in terms of the positions of the atoms. The density functional theory (DFT) is commonly used to investigate the electronic structure of multi-electron systems. ML can help optimize DFT calculations, yielding results faster and more efficiently. Thus, ML can be used to construct accurate PES and understand chemical reaction dynamics and molecular behavior.

The work demonstrates how fast ML could shape the future of molecular modeling by employing the adaptability of ML algorithms: a feature of the algorithms to semi-independent adaptation and improvement.

With the potential to amplify molecular modeling, applying ML methods is expected to permeate various fields. These include but are not limited to drug discovery, materials science, and environmental research, signifying a significant step forward in these critical areas.

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X-ray studies of three 3,6-bis(pyridin-2-yl)-1,2,4,5-tetrazine cocrystals - an unexpected molecular conformation stabilized by hydrogen bonds

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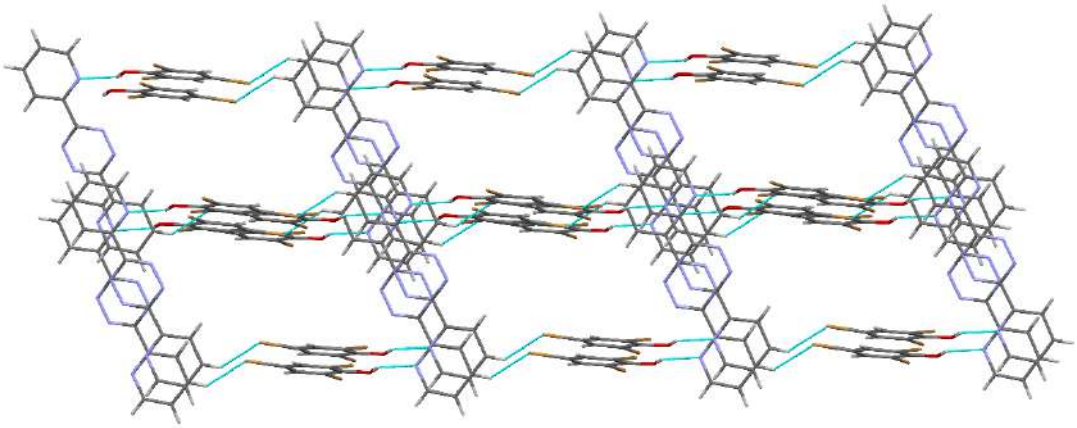
The 1,2,4,5-tetrazines belong to the class of nitrogen heterocyclic compounds [1]. Substitution with four N atoms (–N) of the methenyl groups (–CH) of the six-membered benzene ring results in a strong electron deficiency, i.e., there are four acceptor atoms in the aromatic ring. The properties of the *s*-tetrazine moieties can be modified by substitution at the 3- and 6-positions of the ring [2].

The results of the *X*-ray structure analysis of three novel 3,6-bis(pyridin-2-yl)- 1,2,4,5-tetrazine cocrystals are presented. Special attention is paid to a conformational analysis of the title tetrazine molecule in known crystal structures. Quantum chemistry methods are used to compare the energetic parameters of the investigated conformations. A structural analysis of the hydrogen and halogen bonds with acceptor aromatic tetrazine and pyrazine rings is conducted in order to elucidate factors responsible for conformational stability [3].



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Trithiocyanuric acid – an effective co-crystal coformer

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Co-crystal can be defined as a thermodynamically stable solid state object built from separate chemical components. Co-crystals are becoming more popular due to the relatively easy method of controlling their composition and because of their various applications as energetic materials, luminescent polymorphs or solids of special optical properties. From the viewpoint of structural chemistry, the architecture of co-crystals can be created through various non-covalent interactions, ranging from very strong, such as classic hydrogen bonds, to weak , such as van der Waals interactions. Therefore, various intermolecular interactions are receiving much interest because of role in molecular packing and crystal structure design.

In our work, potential intermolecular synthons of trithiocyanuric acid (hydrogen, halogen, chalcogen bonds, stacking and T-shape interactions) were analysed on the base of X-ray diffraction studies [1,2]. Combination of these results with quantum-chemical calculations let us provide interesting insight into the crystal structure and allow for a versatile analysis and description of sulphur non-covalent interactions. In particular analysis of MEP surfaces indicated electrophilic and nucleophilic regions of the trithiocyanuric molecule. In turn, QTAIM approach allowed for the classification of all types of investigated non-covalent contacts as typical closed-shell interactions.

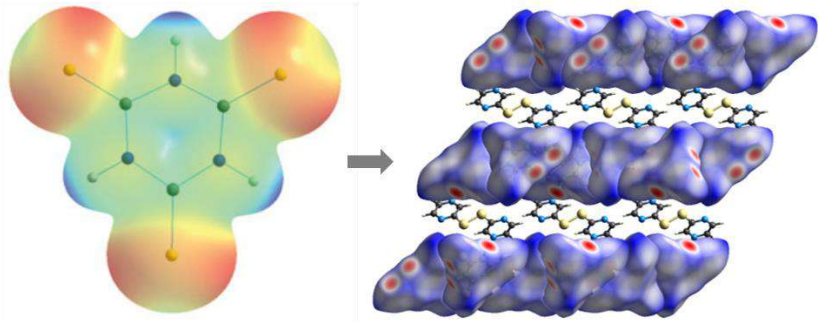

Figure. Electrostatic potentials mapped on the 0.01 au molecular isosurface of trithiocyanuric acid electron density (left). Coloured scale corresponds to values ranging from −0.015 (red) to +0.21 au (blue). Crystal packing of molecules in the structure of trithiocyanuric 2,2'-dithiobispyrazine cocrystal (right). Trithiocyanuric acid molecules are presented with opaque molecular Hirshfeld surface mapped with coloured scale of d_{norm} parameter. Red areas resemble intermolecular contacts of distances shorter than the van der Waals separation.

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Computer-aided Drug Discovery:
From Small Compounds to Protein Inhibitors against Tyrosine Kinase of EGFR for cancer therapy

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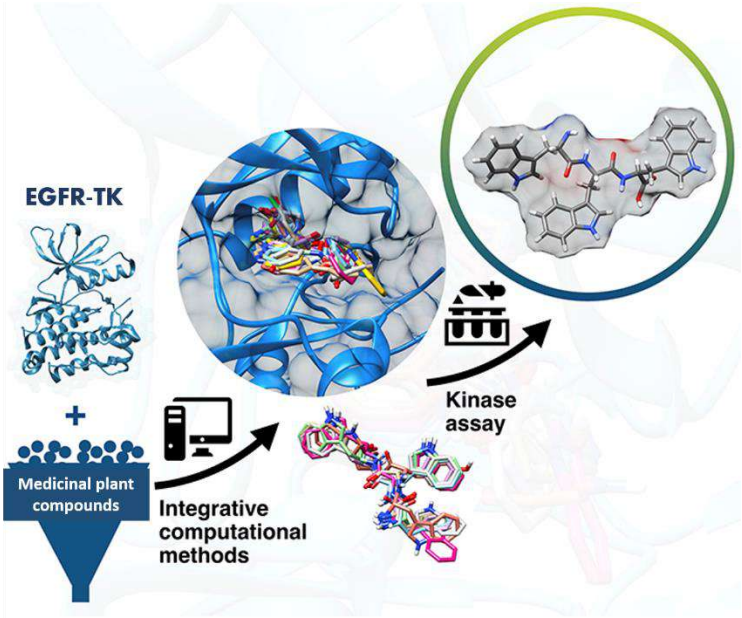
ABSTRACT

Computational studies are an essential part of research in Biochemistry today. The goal of theoretical investigation of biochemical processes is to gain a deeper insight into the molecular mechanism behind the process of study. It can further be used to predict the results of experiments. Protein Bioinformatics is a useful technique to understand biochemical processes of proteins on various levels including protein modeling, protein docking, and protein molecular dynamics. In our group, we focus on the anticancer targeted protein, the epidermal growth factor receptor (EGFR). This protein plays a crucial role in cellular signaling pathways that regulates key functions, especially proliferation. The EGFR abnormalities have been associated with several types of human cancer. Nowadays, there are cancer-treated drugs that inhibit the activity of tyrosine kinase (TK) domain of EGFR – a signaling part of this protein. However, each drug specifically treats with each cancer type and some tumor patients have resisted to those drugs. A discovery of better new efficient inhibitors is extremely needed. The virtual screening of medicinal plant compound databases against EGFR-TK have been used to discover new inhibitors. These compounds were tested on enzymatic inhibiting assay and non-small cell lung cancer cells, A549.



Electrochemical Characterization of Sargassum extracts for Potential Green Corrosion Inhibitors

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Introduction:

Sargassum, a type of seaweed, has become a significant problem on coastlines worldwide, causing environmental and economic damage. It is also considered a waste product[1]. Meanwhile, corrosion is a major issue for many industries, with significant economic and environmental consequences [2]. Current corrosion prevention methods often involve the use of toxic chemicals that can have adverse effects on the environment and human health [2]. Therefore, there is a need for more environmentally friendly corrosion prevention solutions.

Results:

We conducted electrochemical characterization of various types of Sargassum extracts under different potential windows and observed their interaction with the surface and oxygen molecules involved in corrosion. Our results suggest that during the corrosion processes on the surface, the Sargassum extracts could alter the potential involved, and the biomolecules present in the extracts may play a significant role in this process.

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Will chloroquine be able to treat malaria again?

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Since malaria remains the most prevalent parasitic disease, solution of its suppression is a long-term problem. Over the course of several decades, this solution was the drug chloroquine, but later the resistance to this drug appeared. The main cause of malaria resistance is considered the PfCRT protein, the structure of which was determined in 2019. Mutated resistant versions of this protein render treatment ineffective - the generally accepted hypothesis is that the protein transports drug molecules out of the vacuole.

Using molecular dynamics, structural and functional changes of the PfCRT protein influenced by individual mutations and their combinations in selected resistant strains of Plasmodia are described. The effect of structural changes in the PfCRT protein induced by the binding of probable natural substrates (peptides formed by the splitting of heamoglobin) is also studied. In conclusion, the results of the influence of mutations on the ability to transport the drug through the membrane are presented.

Molecular interactions between ion channels and peptide toxins: advantages and limitations of electrophysiology

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Inhibition of the Kv1.3 K^+ channel, which is predominantly expressed in effector memory T cells (T_{EM}), results in selective immunosuppression in animal models of TEM-mediated autoimmune diseases (e.g. multiple sclerosis, rheumatoid arthritis). Prominent among Kv1.3 inhibitors are peptides isolated from the venom of certain organisms, they achieve far greater Kv1.3 affinity (inhibit Kv1.3 in ~pM concentrations) and selectivity than small-molecule inhibitors (e.g. PAP-1 [15]) as they to contact a larger surface area in the vestibule of the channel pore [16].

My laboratory, in collaboration with Prof Possani has identified one of the highest affinity (Kd = 3pM (!)) and selectivity (~1500-fold over other channels) Kv1.3 inhibitor peptide, Vm24 [17, 18]. Vm24 has a great potential in suppressing TEM activation in vitro [19], in addition, Vm24 also suppressed delayed-type hypersensitivity in rats, where TEM cells are responsible for the pathology [17]. Other high affinity Kv1.3 inhibitor peptides were engineered to increase Kv1.3 selectivity. Among these, HsTx1[R14A][20] was generated in the laboratory of Prof. Norton, and the N17A/F32T analogue of anuroctoxin was designed in my laboratory - in this latter case the substitutions increased 16,000-fold the Kv1.3 selectivity. ShK-186 (dalazatide) is a KV1.3-selective analogue of ShK (a peptide derived from the sea anemone S. helianthus) that has been shown to be efficacious in rat models of EAE and pristane-induced arthritis [6, 8, 21].

Thermodynamic, local structure and surface properties of N,N-Dimethylformamide – Water System as Seen from Computer Simulations

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The structural and thermodynamic properties of N,N-dimethylformamide (DMF)-water mixtures depend on the peculiar balance of the interactions of the like and unlike molecule pairs, and on the interplay of the van der Waals, dipole-dipole, and H-bonding interactions. In the first step of our investigation, available force fields for N,N-dimethylformamide widely used water models were investigated with respect to their ability to reproduce the experimental thermodynamically data of these mixture. The chosen combination of the fore field was used to investigate in details the N,N-dimethylformamide (DMF)-water mixtures, spanning the entire composition range, at 298 K by molecular dynamics

(i) the locale structure in these mixtures using the nearest neighbor radial distribution as well as the Voronoi polyhedra

(ii) the liquid-vapor interface of these mixtures.

Exploring the Molecular Mechanism of Urethane Linkage Formation and Termination

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Corrected version: Establishing a circular economy for conventional products in the chemical industry poses significant challenges in today's world, encompassing both energy and environmental considerations. In 2018, the global production of plastics reached 359 million metric tons, with Europe contributing 61.8 million metric tons. However, only 32.5% of the 29.1 million metric tons of plastic waste collected in Europe that year was recycled, while the remainder was either landfilled or incinerated for energy recovery. To achieve a circular plastic economy, we must transform the challenge of plastic recycling into an opportunity.

A specific example is the polyurethane industry, which annually requires 6 million metric tons of methylene diphenyl diisocyanate (MDI) as an input material, relying entirely on fossil resources for current production. To explore the potential for achieving a circular economy, it is crucial to understand the energetics and the elemental aspects of urethane production. Therefore, this work aims to demonstrate the energetics of urethane bond formation using modern ab initio calculation techniques, shedding light on the possible intermediates that can be derived from waste polyurethane. The re-activation of used polyurethanes with highly stable urethane bonds, both kinetically and thermodynamically, remains a significant requirement.

This study also seeks to conduct a systematic energetic investigation to assess the thermodynamic feasibility of activating the urethane bond. It will explore targeted chemical activation methods utilizing specific catalysts and investigate the potential for enzyme activity in activating this stable bond.

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3.3 Thursday, June 22nd

9:00 - 9:50	Oldamur Hollóczki *Modeling the effects of microplastics on biomolecular systems*
9:50 - 10:15	Ivan Klbik
10:15 - 10:40	Berna Dogan
10:40 - 11:10	Coffee break
11:10 - 12:00	Ondrej Maršálek *Building robust neural network potentials with active learning*
12:00 - 12:25	Victor Velasco-Berrelleza
12:25 - 12:50	Marcin Palusiak
12:50 - 14:00	Lunch
14:00 - 14:50	Justynia Dominikowska *From weak to strong halogen-halogen interactions*
14:50 - 15:15	Florian Joerg
15:15 - 15:40	Márta Gődény
15:40 - 16:10	Coffee break
16:10 - 17:00	Adam Buczkowski *Dendrimers and CB7 cucurbituril as transporters of selected anticancer drugs*
17:00 - 17:25	Liliana Chęcińska
17:25 - 17:50	Ryan Cocking
18:00 - 20:00	BBQ

Modeling the effects of microplastics on biomolecular systems

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Through the fragmentation of plastic waste, micro- and nanoplastics (MNPs) are formed and distributed through our environment. While these particles have been observed in food, various organisms, and even in human tissues, their impact is still unclear, partly due to the variety of MNPs in composition, size, shape, compounds at their surface (i.e. corona), and partly due to the limitations of analytical techniques to observe them. Molecular modeling offers a structural insight into the interactions of MNPs with biomolecular systems, leading to a deeper understanding of the environmental and health effects of these pollutants.

Molecular dynamics simulations have revealed the fundamental interactions between MNPs and lipid bilayers [1]. In the passing of the MNP through a membrane, the role of the corona was shown. Depending on the composition of the corona, the thermodynamics of the sorption into the bilayer (e.g. a blood-brain barrier model) can be varied significantly. Thereby it is feasible that with the right compounds adsorbed onto the surface of the particle, the passive transmembrane transport through the blood-brain barrier can be thermodynamically and kinetically possible. In agreement, only two hours after mice are fed with food containing environmentally relevant concentration of MNPs, plastic particles appear in their brain tissue just after two hours [1].

When interacting with biomolecules, the composition of the MNP is decisive. Simulations and quantum chemical calculations showed that MNPs can alter the secondary structure of proteins [2, 3]. Depending on the plastic compound, the relative energy between α-helix and β-sheet structures of the same protein can be shifted significantly. While polyethylene was found to stabilize the helix, nylon-6,6 was prone to change the peptide into a β-sheet [2, 3]. Since neurodegenerative diseases may be related to changes in secondary structures of certain proteins, these findings show that further research in the field is essential.

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On the cryoprotective action of dimethylsulfoxide

Ivan Klbik,[1,2*] Milan Melicherčík,[3] Jaroslav Rusnák,[1] Katarína Čechová,[3] Igor Maťko,[1] Ján Lakota,[4,5] and Ondrej Šauša[1,6]

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In the past, an optimization of the cryopreservation protocol for hematopoietic stem cells revealed that effective cryopreservation could be achieved using as low as 2 vol% concentration of the cryoprotectant dimethylsulfoxide (DMSO) [1]. However, further attempts to reduce DMSO concentration, driven by the goal of reducing its toxic effects, have resulted in a dramatic loss of cell post-thaw recovery [1, 2]. The widely held belief that DMSO and similar agents suppress ice formation and stabilize biological membranes against freezing-induced stress was explored by studying model systems consisting of cryoprotective mixtures and liposomes. Employing complementary methods such as calorimetry, positron annihilation spectroscopy, Raman micro-spectroscopy, and atomistic molecular dynamics simulations, we elucidated the concentration-dependent cryoprotective potential of DMSO. Our findings indicate that DMSO's cryoprotection mechanism involves the suppression of eutectic crystallization of sodium chloride naturally present in the cell (freezing) medium. This inhibition can be explained by considering the thermodynamics of mixtures predicting the DMSO-induced lowering of the water's chemical potential, stabilizing it in the liquid phase, and preventing the precipitation of NaCl dihydrate [3]. Additionally, it was demonstrated that DMSO enhances lipid bilayer fluidity in the liquid state but exhibits the opposite effect in the gel state. These membrane alterations impact transmembrane pressure profiles, influencing protein-lipid interactions and possibly affecting the function of membrane proteins.

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Investigating the Conformational Heterogeneity of CCR5 by Molecular Dynamics Simulations

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CCR5 is one of the co-receptors for HIV-1 entry into host cells and is class A GPCR that has vital roles in the immune system and is involved in the pathogenesis of different diseases. Various studies were conducted to understand its activation mechanism including structural studies in which inactive and active states of the receptor were determined in complex with various binding partners. These determined structures provided opportunities to perform molecular dynamics simulations (MD) to analyze conformational changes observed in protein structures at the atomic level. Here, our aim was to investigate the changes observed in the conformation of CCR5 when it is in complex with inhibitor maraviroc (MRV), an approved anti-HIV drug or HIV-1 envelope protein GP120 in comparison to when the receptor was in *apo* form. In our simulations, we considered both ionized and protonated states of ionizable binding site residue GLU283$^{7.39}$ in CCR5 as the protonation state of this residue was considered ambiguously in previous studies. Our simulation results suggested that in fact, the change in the protonation state of GLU283$^{7.39}$ caused interaction profiles to be different between CCR5 and its binding partners, GP120 or MRV. We observed that when the protonated state of GLU283$^{7.39}$ was considered in complex with envelope protein GP120, there were substantial structural changes in CCR5 indicating it adopts more of an active-like conformation. On the other hand, CCR5 when it was in complex with MRV always adopted inactive conformation regardless of the protonation state. Hence, CCR5 displays conformational heterogeneity not only based on its binding partner but also on the state of the protonation state of a binding site residue GLU283$^{7.39}$. This outcome is actually in accordance with some studies that revealed GP120 binding could activate signaling pathways. Additionally, this outcome could also have critical implications for the discovery of novel CCR5 inhibitors to be used as anti-HIV drugs by in silico methods such as molecular docking since consideration of the protonated state of GLU283$^{7.39}$ may lead to the identification of more efficient molecules.

Building robust neural network potentials with active learning

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Machine learning potentials, and neural network potentials specifically, have recently become an enticing way to decrease the computational cost of ab initio simulations. They allow an increase of the length and time scales of simulations by several orders of magnitude while maintaining the accuracy of the ab initio method that they replace. The development of such a potential requires the construction of an appropriate training data set, though, a process that has traditionally been rather tedious and error prone. In this talk, we will introduce an active learning approach that yields robust training sets and associated models while minimizing the need for human intervention and tweaking. We will show how these training sets give rise to models that enable simulations at ab initio accuracy on scales that were previously unavailable. We will also show how in certain cases, we can avoid the need for a reference ab initio trajectory entirely, relying only on a relatively low number of single-point calculations. Finally, we will discuss some promising directions for current and near-future research.

Physical model of supercoiling mediated regulation in synthetic gene circuits

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Current synthetic gene circuits are designed to perform logical functions, mimicking those in electronic circuits [1]. These designs ignore DNA supercoiling, which can affect gene expression as it is intimately related with transcription as it can both up- and down-regulate the expression of distal genes [2]. Our goal is to understand, characterize and harness the potential of supercoiling in regulating transcription in synthetic gene circuits as a novel and powerful component of the next generation of synthetic gene circuits. Here, we introduce TORCphysics, a coarse-grained physical model that predicts the expression profiles of gene circuits in bacteria by simulating transcription-dependent supercoiling under various biological conditions. These expression profiles are suitable for comparison with experimental data. Our results show the interplay between transcription and genomic architecture, highlighting the importance of factors like gene orientation, topological barriers, and promoter sequences. Wetlab experiments in bacteria are underway to validate our results. The insights from our physical model and experiments will inform the development of a computational toolkit (TORC) that will enable the design of genetic circuits that exploit transcription-dependent supercoiling. Once the toolkit is constructed, it will be generalizable to circular DNAs in more complex environments, such as eukaryotic cells.

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Crystal Engineering- our recent attempts of contributing

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Crystallisation is a well known physical process thoroughly observable in the nature. It is also a process being common in laboratory conditions, among others used as one of the methods of chemical compounds purification. This is due to the fact that chemical compounds have a natural tendency to crystallise from the mixture into a separate phase. That fact rises a challenge for those who want to initiate and to effectively carry out the process of co-crystallisation, that is, the crystallisation of a single crystal phase consisting of more than one component. The term co-crystal may cover a various cases of multicomponent crystal phase of which not only a pure two component crystals formed of formally neutral chemical molecules fulfil the definition, but also co-crystals consisting of ions (co-crystalline salts) or solvent molecules (solvates and hydrates).

In this presentation a report of our recent results of various co-crystals synthesis will be given. [1-4] Among others we will show what can be the role of light or what may be the contribution of oxidative factor on the final results of (co-)crystallisation. When, according to our assessment, it was worth of consideration, our analysis was supported by quantum-chemical calculations performed for modle systems being representative for experimental observations.

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From weak to strong halogen-halogen interactions

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Halogen-halogen contacts are widely present in crystal structure. Crystallographers distinguish two types of halogen-halogen contacts [1] differing in mutual spatial arrangement of molecules (Figure 1).

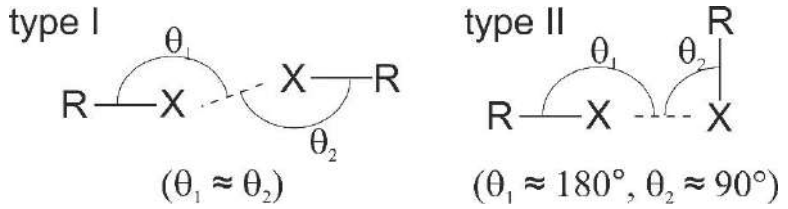

Figure 1. Schematic representation of type I and type II halogen-halogen contacts (X: halogen atom).

Type I halogen-halogen contacts very often are of the van der Waals type but when they are short, they are repulsive. [2] In turn type II contacts are halogen bonds [1] with interaction energies usually in the range of a few kcal/mol. [3] Due to this halogen-halogen interactions are generally considered as weak or at most of moderate strength. But at the same time the halogen bond in the triiodide anion is an example of one of the strongest halogen bonds. [4] Such situation takes place when halide anions play role of a halogen bond acceptor. The methods of computational chemistry allow to study the nature of weak and strong halogen-halogen interactions.

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Protex – a python utility for proton transfer in molecular dynamics simulations

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Protic ionic liquids exhibit great potential as candidates for future battery advancements, mainly due to their non-flammability and the elimination of critical raw materials. These substances can be characterized by their reversible proton transfer, allowing them to form hydrogen-bonded networks, which in turn leads to an increase in conductivity. To explore these properties, a computer simulation was conducted using the model compound 1-methylimidazolium acetate. A newly developed polarizable force field was employed to analyze various mixtures of neutral and charged species. The equilibrium position was determined by considering not only single value properties like density, diffusion coefficients, and conductivity but also the complete frequency-dependent dielectric spectrum. All obtained data were then compared to experimental values.

To overcome the limitation of conventional molecular dynamics simulations, which lack the capability to model bond breaking or formation, a novel open-source program called protex was created. This program allows for the exchange of protons between molecules in computer simulations. With the help of protex, various transfer reactions between molecules can be defined and specified by means of different parameters. This advancement provides a deeper understanding of transport mechanisms and facilitates the interpretation of experimental data. The application of protex to 1-methylimidazolium acetate allowed for the calculation of transport properties, which were then compared to both experimental data and conventional molecular dynamics simulations.

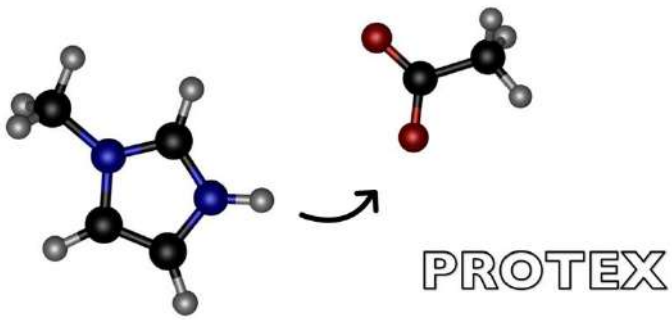

Figure 1: Protex - proton exchange in molecular dynamics simulations

Investigating the Transport of Excess Protons in a Protic Ionic Liquid via Polarizable Molecular Dynamics Simulations using Protex

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Ionic liquids (IL) have been proposed as alternative, non-flammable, electrolytes for batteries. While the conductivity of aprotic ILs is in general too low for this purpose due to their viscosity; protic ionic liquids show a higher conductivity. Protons have a high mobility, and with reversible proton transfers, charge transfer is no longer bound to mass transfer.

In order to investigate the mechanisms and time scales of proton transfer in a protic IL, polarizable molecular dynamics simulations were carried out on a 1-methylimidazolium acetate based system. Excess protons were introduced by the photoacid 8-hydroxypyrene-1,3,6-trisulfonic acid. Extensive research had already been done by our research group on the system, including the development of the polarizable force field, characterization of the equilibrium concentrations of charged and neutral species, as well as proton transfer probabilities in the 1-methylimidazolium acetate IL, and the development of the Python module protex which makes the simulation of proton transfers possible.

In this work, the force field parameters of the photoacid were optimized. Subsequent simulations of the photoacid and the IL in methanol were set up in a way to mimic that of our experimental partners, who investigated the transfer dynamics via pump-probe experiments. Thus, a direct comparison of transfer times, conductivities, etc. was possible. Proton transfer was enabled by protex, using a single topology approach: in regular intervals legible protons were transferred with a certain probability, by changing the parameters of the involved molecules to that of the corresponding (de)protonated species. Only protons within a certain distance to an acceptor were transferred.

Subsequently, radial distribution functions, conductivity and diffusion coefficients were calculated. The calculated transport properties showed a good agreement with experimental values, showing that the force field and protex lead to reliable results. Cases of proton transfer by the Grotthuss mechanism were observed. Examining the radial distribution functions of each pair of species, and the dynamics of the consumption of protonated methanol led to further refinement of protex.

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Dendrimers and CB7 cucurbituril as transporters of selected anticancer drugs

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Supramolecular carriers can improve the effectiveness of medical treatment with toxic drug molecules. Small molecules of anionic drugs, such as 5-fluorouracil, can be bound and transported using macromolecules of cationic PAMAM and PPI dendrimers in aqueous solutions. Molecules of cationic drugs, e.g. gemcitabine hydrochloride may be transported using cucurbituril CB7. The aim of the current study is to evaluate stoichiometry, thermodynamic spontaneity, and binding modes in selected supramolecular systems – poly(amidoamine) (PAMAM) and poly(propyleneimine) (PPI) G4 dendrimers with 5-fluorouracil (5-FU) as well as cucurbit[7]uril (CB7) with gemcitabine hydrochloride (Gem) in aqueous solutions.

The results of isothermal titration calorimetry (ITC) indicate spontaneous binding of 5-FU molecules by cationic PAMAM and PPI G4 dendrimers in aqueous solutions [1]. The equilibrium dialysis results allow to differentiate in both PAMAM and PPI macromolecule two subpopulations of active sites, binding 5-FU molecules with, respectively, higher and lower affinity toward this drug.

ITC results [2], equilibrium dialysis [3] and molecular dynamic (MD) simulations also confirm the spontaneous inclusion of Gem inside CB7 cavity in aqueous solutions. The increase of temperature reduces Gem binding constants with CB7, but even at elevated temperature conditions (up to 50 ° C), the formed supramolecular complex is thermodynamically stable ($\Delta G<0$). Therefore, CB7 may serve not only to transport this drug in living organism but also to stabilize the sensitive Gem molecules during extended storage.

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Hydrogen-bonded polymeric chains in miconazole-drug salts with selected pyridinedicarboxylic acids

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Our study has been motivated by trends in scientific research, in which known medicinal substances are subjected to structural modifications in order to obtain new forms that may have better physicochemical parameters compared to the reference active pharmaceutical ingredient (API). Chemists use various strategies to change the chemical and physical properties of solid-state APIs, the most common practice is the formation of salts, cocrystals, and hydrates/solvates. It is estimated that more than half of the drugs available on the market are just administered in the form of salts [1,2].

As a result of the co-crystallization of miconazole drug (API) with selected pyridinedicarboxylic acids, we obtained two salts: MIC·Py-2,3-DCA·H_2O and MIC·Py-2,6-DCA·H_2O. They exhibit unusual formula. The formal positive charge is on the nitrogen atom of the imidazole moiety, while the assignment of the hydrogen atoms in the formal monocarboxylate anion is not obvious. Despite the transfer of one proton to the miconazole molecule, both carboxyl groups remain partially protonated, because the second hydrogen atom is shared equally between the two acidic groups.

In the crystal structures of the salts analysed, the characteristic mono-periodic polymeric chains are generated by O···H···O hydrogen bonds, where the hydrogen atoms lie at the inversion centre, due to which they are exactly halfway distance between two oxygen atoms (approximately 1.23Å).

The crystal and molecular structures of the miconazole salts with details about hydrogen bonds that are responsible for molecular motifs will be presented in a poster.

The Student Research Grant 2023 (University of Lodz, Poland) is gratefully acknowledged.

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Coarse-grained mesoscale rod simulations of fibrinogen under flow

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The Fluctuating Finite Element Analysis (FFEA) software [1] uses continuum mechanics to model proteins at the biological mesoscale as 3D tetrahedral meshes and 1D elastic rods [2] that deform viscoelastically in response to thermal noise. Tetrahedra additionally experience repulsive excluded volume and attractive surface-surface interactions, neither of which are included in the rod model, but are necessary to describe protein function. Viscous drag is represented as an isotropic force acting on mesh elements due to a stationary background fluid.

Fibrinogen (mass ~ 340 kDa) is a fibrous protein that polymerises into the fibrin network to form a crucial supportive component of blood clots [3]. The effects of shearing flow on fibrin(ogen) are well-documented, but less is known about extensional flow, which is predicted to elongate von Willebrand Factor, another fibrous clotting factor, significantly more than shear. Extensional flow-induced aggregation of antibodies has been demonstrated *in-vitro*, at strain rates typically experienced during pharmaceutical manufacturing [4].

We aim to improve the simulation capability of the FFEA rod model by implementing protein-protein interactions and additional viscous effects, with a view to modeling the aggregation propensity of fibrinogen in physiological and pathological flows. Recent FFEA software developments and *in-vitro* extensional flow experiments are presented.

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3.4 Friday, June 23rd

9:00 - 9:50	Mohammad Uddin *Formulation and Characterization of Ionic Liquid-Containing Melatonin Orally Dissolving Films for Buccal Drug Delivery*
9:50 - 10:15	Zoltán Mucsi
10:15 - 10:40	Áron Szepesi
10:40 - 11:10	Coffee break
11:10 - 12:00	Monika Staś *Isosteric replacement of the amide bond in bioactive peptides*
12:00 - 12:25	András Szabadi
12:25 - 12:50	Michael Owen
12:50 - 14:00	Lunch
14:00 - 14:20	Closing remarks

Formulation and Characterization of Ionic Liquid-Containing (IL) Melatonin Orally Dissolving Films (ODFs) for Buccal Drug Delivery

Dr. Mohammad N. Uddin
College of Pharmacy
Mercer University
Atlanta, Georgia, USA

Insomnia affects 30% of adults worldwide and leads to reduced physical functioning, productivity, and mental health.[1] There are several over-the-counter products currently available to manage insomnia, but many of these have burdensome anticholinergic effects such as constipation, urinary retention, dry eyes and mouth, and cognitive impairment. As such, these medications ae not preferred in pediatric or elderly patients. However, melatonin, an endogenous hormone which regulates the sleep-wake cycle, is an over-the-counter sleep supplement that does not cause anticholinergic effects and is generally well-tolerated by a larger variety of patients.[2] Orally dissolving films (ODFs) are thin, polymer-based films which can be loaded with drug for buccal or sublingual drug delivery.[3] Compared to traditional oral drug delivery, ODFs avoid first-pass effect, have a faster onset of action, do not require water for administration, and can be used in patients unable to swallow oral tablets.[4,5] Because of the necessity for rapid relief of insomnia symptoms, an ODF for buccal or sublingual melatonin drug delivery would be beneficial. Ionic liquids have been studied to enhance dissolution and permeation of drugs in a variety of platforms and could be utilized in ODFs to enhance their effects.[6] A formulation of 2.5 mg melatonin ODFs containing several polymers, including HPMC K4M, Kollidon K90, and polymeric solubilizer SoluPlus, plasticizer PEG 2000, and the ionic liquid DABCO was formulated using solvent-casting method and characterized for several physical properties. A control film without ionic liquid was also characterized. Film weight and thickness of the IL-containing film were uniform (average 24.5 mg ± 1 and 0.052mm ± 0.0009, respectively), indicating drug content uniformity. Tensile strength indicated high film strength (average 11.08 MPa ± 0.68), while film flexibility was lower as indicated by lower folding endurance and percent elongation (average 179 folds and 6.25%, respectively). Drug release studies showed that the ionic liquid reduced dissolution time (p-value 0.01), and indicate an extended-release profile of the drug, with the IL-containing film drug having about 90% dissolved after one hour, and ex vivo permeability studies using pork buccal mucosa also indicated that the ionic liquid enhanced permeation of the film significantly with roughly 43% of the drug permeated in one hour, as compared to 32.3% permeated in the control film (p-value 0.002). An extended-release profile would be helpful in helping patients maintain sleep throughout the night. Melatonin would be a good candidate for IL-containing oral dissolving film delivery to increase patient compliance, safety, and health outcomes.

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This paper provided background information and statistics related to the prevalence of insomnia.

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This paper provided information on the use of melatonin as an over-the-counter sleep agent

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This paper provided information on orally dissolving films and their applications of use.

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This paper highlighted the advantages of orally dissolving films.

5. Sevinç Özakar, R., & Özakar, E. (2021). Current Overview of Oral Thin Films. *Turkish Journal of Pharmaceutical Sciences*, *18*(1), 111. https://doi.org/10.4274/TJPS.GALENOS.2020.76390

This paper provided further information on orally dissolving films and their mucosal permeation.

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This paper provided information on the role of ionic liquids in pharmaceutical applications.

Novel heteroaromatic scaffold as a highly efficient fluorophore derived from the chromophore of the GFP - synthesis, spectroscopy and application

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Fluorescent microscopy became one of the key tools in biology and drug discovery, therefore, the need for brighter and more efficient fluorescent stains is ever growing. While many fluorescent probes have been developed, the used fluorophores remained highly conservative. Although they determine many characteristics of probes, the fluorophores utilized are constrained to only a few examples. For example, in the most commonly used green channel of microscopes, the latter two are available and while they offer many advantages, they are compromised by considerable spectral overlap between their absorbed and emitted light. The small Stokes-shift leads to a large part of the emitted light being filtered out to avoid a high background caused by scattering of the excitation source. Maintaining a high brightness and a high Stokes-shift at the same time is however challenging, requiring novel fluorophores instead just fine-tuning existing ones. In this work we have demonstrated, that compounds based on a novel heterocyclic system, exhibit bright fluorescent intensity (>3×10) and a reasonable Stokes-shift (>70 nm), that eliminates spectral overlap. The presented structure can be considered a conformationally locked GFPchromophore, which results in a green (λ = 465 nm) excitation wavelenght. We present a straightforward, one pot synthesis by utilizing an intramolecular ring closure aided by microwave irradiation. Detailed spectroscopical characterization of the fluorophores are presented and their practical relevance is demonstrated by confocal and two-photon live cell imaging using targeted fluorescent probes built on the chromeno[2,3-d]imidazole system.

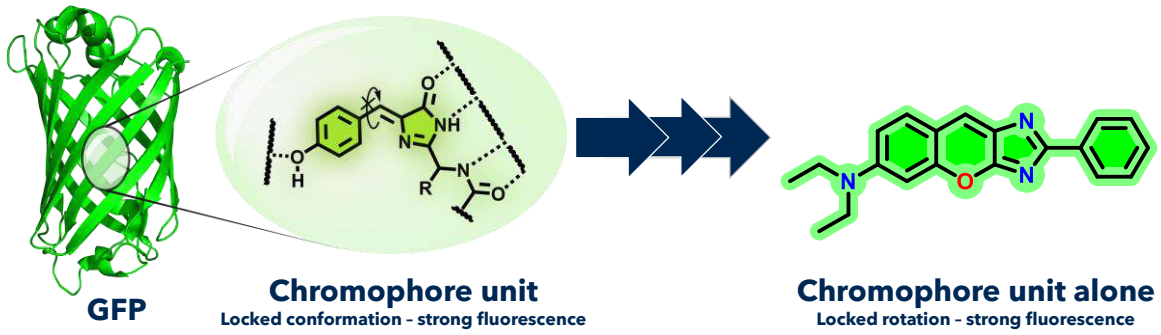

Figure 1 2D structure of the investigated VF dyes

Measuring and altering neural activity in living animals with two-photon microscopy

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For understanding neuronal functions and cellular connections live fluorescent imaging provides an effective tool as it allows the measurement of neurons in function even at *in vivo* condition. The first decade of the century was determined by the development of newer and faster imaging techniques, including 3D imaging and holographic microscopy. Then in the last years the focus turned on the other, as least as important, component of these measurements, towards the functional molecules used. These novel compounds either chemically or genetically produced can both detect or affect neuronal function and can be sensitive to different ions and compounds as well as for membrane potential. Thinking of human brain and the potential brain therapy applications in different brain regions targeting and safety are also important topics of these developments.

We have developed two-photon-specific genetic and chemical sensors for voltage imaging and photostimulation for both *in vivo* and *in vitro* studies. Genetically coded indicators provide specific cell types or brain region-specific targeting and stable expression for up to several weeks, while with chemical compounds we can reach a very high signal-to-noise ratio. With access to the full spectrum of these two types of indicators, or even to the combination of these we will demonstrate kHz range voltage imaging, chemically targeted labeling as well as uncaging and photostimulation.

Isosteric replacement of the amide bond in bioactive peptides

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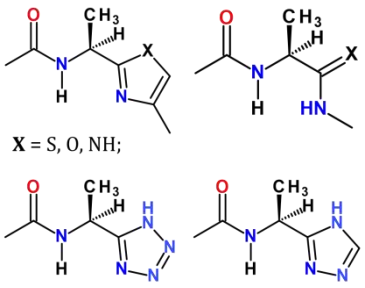
Post-translational modified amino acid residues with azole ring in place of the C-terminal amide bond have been found in numerous natural peptides. Peptides, in which such unique amino acid residues occur, belong mainly to RiPP (*Ribosomally Synthesized and Post-translationally Modified Peptides*) [1-2]. Those peptides reveal antibacterial, antitumor and antimalarial activity. The biological activity and metal-binding properties of proteins and peptides depend on their conformation [3], therefore the conformational screening for series of peptidomimetics inspired by natural residues were performed (Fig.). To get the whole picture of the influence on conformational properties linear analogues of azole rings were also studied.



Presence of azole ring as oxazole, thiazole, imidazole, tetrazole or triazole rings in the main chain of peptide constrains the chain's conformational flexibility, gives opportunity for creating new interactions and protects form proteolytic enzymes. Those properties can be used as biomolecular engineering tools for drug design [4-6].

Conformational studies were performed using theoretical calculations (DFT method) to obtain conformational maps. The solid-state crystal structures of studied amino acid residues were retrieved from the Cambridge Structural Database and the results were compared with the calculations. The results showed that the rings which include only nitrogen and carbon atoms are good candidate of amide bond isosteres because the residues have similar conformational properties and maintain the hydrogen bond pattern.

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Comparison of Computational IR Spectra of Ionic Liquids

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The accurate reproduction of experimental infrared spectra of bulk liquids using molecular dynamics methods remains challenging as most force fields aim to reproduce static properties such as density and radial distribution functions.

To explicitly target molecular vibrations, a genetic algorithm has been developed which uses gas phase quantum mechanics frequencies and normal modes as its input, varying the force constants of bonded parameters to improve the agreement between quantum mechanics and molecular mechanics vibrations.

Using polarizable molecular dynamics simulations, a comparison between different force fields and a machine learning approach is given, highlighting the strengths and shortcomings of each method regarding their ability to reproduce experimental IR spectra.

We find that the higher computational cost of machine learning (recomputing potentials at each geometry) can increase the agreement between simulation and experiment, although smaller system sizes lead to less reliable statistics. When investigating molecules with less common functional groups or atoms not present in the training set of the neural network, the advantages of readily tunable force fields become apparent. In these cases, usually a combined approach leads to the most promising results.

While no single approach emerges as generally superior in all systems, continuing the development of new force fields and machine learning potentials to reproduce IR spectra will help elucidate the structure and dynamics of bulk liquids, allowing the design of new task-specific solvents.

The effect of GM1, GM2, and GM3 gangliosides on Amyloid-β dimers in MD simulations

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Neuronal membranes can enhance or prevent the formation of oligomers of the amyloid-β (Aβ) peptide, the neurotoxic species implicated in Alzheimer's disease. However, the relation between the membrane composition and its effect on Aβ oligomerisation remains unclear. Gangliosides have an important role in brain development, regeneration, and the progression of Alzheimer's disease. The aim of this work is to determine the first step in the description of how gangliosides (sialic acid-containing glycosphingolipids) influence Aβ42 behaviour and characterize the molecular interactions between the Aβ42 dimer and the GM1, GM2 and GM3 gangliosides, as shown in **Figure 1**. We used molecular dynamics simulation in this study.

GM2 reduced the attractive interaction energy between Aβ42 dimers more than GM1 or GM3 did. This was particularly evident in the central polar region of the peptide dimer. These results would suggest that the GM2 seems most likely to act as neuroprotective due to its propensity to destabilize the Aβ42 dimer. However the effect of the ganglioside identity on the secondary structure of the dimer was not significant over the sampled trajectory.

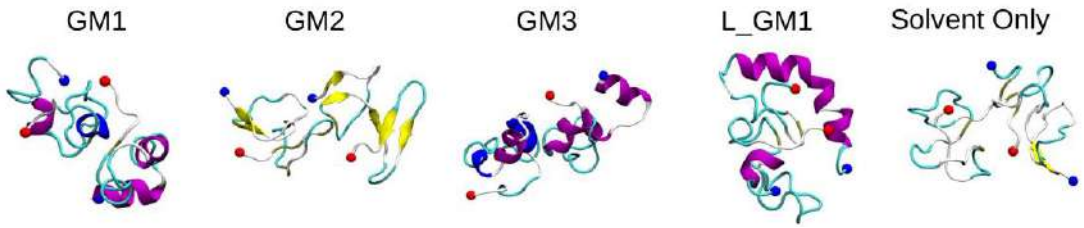

Figure 1. The most representative structures of the Aβ42 dimers in each system as determined by cluster analysis.

4 Abstracts of poster contributions

4.1 Poster session on Tuesday (odd numbers)

P1	Nesreen Alkanakri
P3	Christian Fellinger
P5	Anikó Jordán
P7	Julie Mallouhi
P9	Babak Minofar and David Řeha
P11	Zsófia Borbála Rózsa
P13	Helga Tóth Ugyonka
P15	Marion Sappl

Molecular Dynamics Simulations Of The Proline And Hydroxyproline Of Collagen

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Fundamental aspects of the collagen structure stirred the minds of many scientists throughout the 20th century. Although many of the fundamental questions in this field have not been fully answered, since collagen is not a simple protein, it is difficult to put a generalization about its solubility and how a solvent affects the properties of collagen. However, developing collagen materials that enable resolving practical issues in tissue engineering and regenerative medicine is the focus of significant research nowadays [1]. Molecular Dynamics (MD) Simulations is a technique that can be used effectively to understand macromolecular structure-to-function relationships [2]. To further our understanding of the structure and dynamics of collagen, the influence of hydroxyproline and proline on hexameric and heptameric collagen structures are investigated by using the GROMACS software. We applied the Amber99sb force field to conduct molecular dynamics simulations in triplicate of the collagen fragments over a trajectory of 200 ns. We studied the root mean square (RMS distribution), hydrogen bonds, and solvent accessible surface area (SASA). The results showed proline and hydroxyproline help to stabilize the 3-helix of collagen, hydroxyproline did so more extensively than proline did. Hydroxyproline is responsible for the formation of inter-molecular H bonds and increases the stability of the triple helical, while proline promotes the formation of the intra-molecular H bonds and makes the structure less stable than hydroxyproline.

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Binding Affinity Prediction Based on Pharmacophores

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We present a rapid method for the prediction of various binding affinity measures (pKi, pKd, ΔG) for protein-bound ligands. The computational efficiency of our method largely relies on the quantification of non-bonding ligand-receptor interactions by pharmacophore-based (LigandScout)[1] GRAIL[2] scoring functions which were extended for a more accurate characterization of H-bonding interactions. Combining the calculated GRAIL scores, Van der Waals and electrostatic interaction energies, and a receptor-independent ligand fingerprint yields a fixed-length descriptor which serves as input for the training of machine learning models and later affinity predictions.

Employing the developed descriptor, different machine learning models were trained and evaluated using data from the PDBbind database[3]. The results showed that some of these models achieved comparable accuracy to existing scoring functions while significantly increasing the prediction speed. Additionally, we ensured compatibility with GRAIL maps and efficient GPU acceleration techniques, further improving the prediction speed down the line. This will allow for efficient scanning of large databases within a reasonable time frame.

By elaborating the first possible steps towards a fast and accurate method to predict binding affinity based on structure-based pharmacophore models, our approach promises to streamline workflows within the early drug discovery process.

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Polyuretane Biodegradation from a Bioinformatic Point of View

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Polyurethane (PU) and other polymers play a crucial role in our daily lives, but the accumulation of polyurethane waste in our environment, such as water and soil, is a significant concern. While various waste management methods exist, biodegradation is not widely employed. Biodegradation offers advantages such as complete mineralization of plastic throughout the process and minimal energy requirements. However, there are drawbacks, including the potential generation of hazardous chemicals during degradation and the premature breakdown of the polymeric product. Microorganisms have been extensively studied for their ability to degrade polyurethanes. Over time, certain organisms have developed the capability to break down these materials as an energy source. For this purpose, microorganisms require specific enzymes, including esterase, urease, and lipase, with lipase believed to play a significant role. In this study, all available bacterial esterase sequences were collected and their homology were analyzed by using BLASTp and AliView. Among them, esterases with known 3D structures were selected as host molecules for molecular docking. Model urethanes were prepared using GaussView 6.0 software, and their structures were optimized at the B3LYP/6-31G(d,p) level of theory using the Gaussian 09 software package. Subsequently, these optimized molecules were docked to carefully chosen esterases. The protein structures were also prepared before studying their interactions with the model urethanes. Once the protein and ligand structures were ready, the AutoDock Vina software was employed to carry out standard molecular docking procedures. The structural and energetic aspects of the interactions between the enzymes and model urethanes were assessed, and the different complexes were compared. By combining the results of sequence analysis and molecular docking, we gain a deeper understanding of polyurethane biodegradation. However, further analysis is still required to fully harness the potential of microorganisms in polyurethane waste management.

Ecotoxicological Assessment of Polyurethane Foams: Impacts on Mustard Seeds and Bacterial Model Organisms

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Polyurethane (PU) is a highly versatile polymer with a wide range of forms, from rigid or flexible foams to elastomers. They can be utilized in a wide range of products, including paints, coatings, elastomers, insulators, elastic fibers, and foams[1]. PU foams are especially important as part of various convenience products. PU products often end up in landfills where toxic compounds may be released when the material is severely damaged by either human activity or microbial attacks[2]. As a result, the ecotoxicological assessment of PU foams is critical. In this study, five PU foam samples with different isocyanate indices (0.8, 0.9, 1.0, 1.1, and 1.2) were prepared and tested for toxicity, while toxic foam has been used as a reference. Two test organisms, *Sinapis alba* (white mustard) and *Escherichia coli* (non-pathogenic bacterial model organism) were successfully applied and toxicity tests applicable for examining PU-derived substances were developed. Regarding *Sinapis alba* test, the presence of the sample with the highest isocyanate index (NCO-1.2) significantly reduced root length by 9.8% compared to the control. In the bacteria test, it was observed that the samples containing NCO-1.1 and NCO-1.2 had the lowest colony numbers in case of the autoclaved *E. coli* condition. While in the case of non-autoclaved+*E. coli* condition NCO-1.1 had the lowest colony number ($4.1\times*10^8$ CFU/ml). All in all, two protocols were developed and successfully applied in the ecotoxicological assessment of PU foams.

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The effect of crowding agents on the structure and function of biomolecules

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The cellular environment contains large amounts of macromolecules. None of them is present in high concentration, but overall, the environment is crowded, because macromolecules occupy about 40 % of the volume of the cells. Proteins are frequently studied in aqueous solutions without the presence of other macromolecules both in vitro and in silico. However, including these crowding agents is required for a realistic description, because they influence the overall stability of proteins, preference of more compact conformations, enzyme kinetics, etc. We have focused on citrate synthase (CS) which activities are influenced by crowding and because of its two conformations. The study was performed by means of molecular simulations in aqueous solutions of dextran, polyethylene glycol, and other crowding agents. Furthermore, we have utilized QM/MM calculations in order to study the effect of the crowding agents on the kinetics of CS enzymatic reaction. The results of the study and their critical comparison with experimental data have a potential to provide a deeper understanding of the effects of crowding agents on the structure, stability, and activity of the enzymes. We have analyzed the detailed spatial and time-resolved picture of CS - glucose interactions and observed large flexibility of the substrates in the active site of CS. We have found that the glucose slightly modulates citrate synthase flexibility and the presence of glucose at the protein surface does not exhibit strong saturation.

Computational investigation of radioactive Sr^{2+} and Ca^{2+} complexation

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Industrial activities release various heavy metal ions into the ecosystem, which are known to have a significant polluting effect on the environment and are particularly toxic to humans. Because of nuclear power plant operations, nuclear weapon tests of the past and catastrophes, a considerable amount of radioactive strontium (^{90}Sr) and cesium (^{137}Cs) were released into the environment. Radioactive strontium is one of the most dangerous isotopes in terms of its physiological effects considering its ability to replace calcium in the skeleton [1]. Searching for a chelating agent that can be used for the removal of this ion is crucial for nuclear safety and sustainable development of nuclear energy.

In this study we investigate the chelate effect of the compounds (7,16-bis-malonate)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-bis-malonicacid (XI) [2] and 5-[bis(carboxymethyl)amino]-3-(carboxymethyl)-4-cyanothiophene-2-carboxylic acid (ranelic acid) on alkaline earth metal cations, namely Calcium (Ca^{2+}) and Strontium (Sr^{2+}). Structural and bonding characteristics of the complexes to the ions have been explored by the highly accurate hybrid density functional (DFT) B3LYP/def2-TZVP theory calculations [3], [4] in aqueous SMD polarizable continuum model. [5]. Molecular dynamics (MD) simulations have also been carried out to further study the two complexes. A comparison between DFT and various force field parameters have been made with the goal of obtaining the most precise cation-complex structures. Based on our calculations accurate force fields were chosen that give comparable data to the DFT results.

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Adsorption of HCN on Amorphous Ice under Interstellar Conditions

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The adsorption of hydrogen cyanide (HCN) on low density amorphous (LDA) ice is investigated under interstellar conditions by grand canonical Monte Carlo (GCMC) simulations. HCN is known to be present in the interstellar medium, and its reactivity on icy surfaces might lead to the spontaneous formation of several building blocks of large biomolecules, such as proteins and nucleic acids. Thus, for example, adenine is formally a pentamer of HCN, and such an oligomerization reaction can occur under interstellar conditions, given that the local concentration of HCN is large enough. A potential mechanism of such HCN enrichment is its adsorption on LDA ice, known to cover the surface of comets and interstellar dust. To investigate the problem of HCN adsorption, we have performed a set of GCMC simulations, in which we have systematically varied the HCN chemical potential, and calculated, as its function, the number of adsorbed molecules. This way, we determined the adsorption isotherm at three different temperatures, namely, at 50 K, 100 K, and 200 K. To distinguish between the HCN molecules that are dissolved in bulk LDA ice, those forming the first molecular adsorption layer, and those belonging to outer adsorption layers, the Identification of the Truly Interfacial Molecules (ITIM) method [1] has been used, as implemented in the freely available Pytim software [2]. We have found that a considerable fraction of the HCN molecules are dissolved in the bulk LDA phase, however, while the adsorption becomes stronger, the dissolution becomes weaker with decreasing temperature. Thus, while adsorption of HCN is an exothermic, its dissolution is an endothermic process. To characterize the adsorption layer, we have calculated the density profile of the adsorbed molecules, as well as the orientational and binding energy distributions of the first layer HCN molecules. Our results reveal that adsorbed molecules prefer to stay more or less parallel with the ice surface, and their stay is stabilized by up to 2 hydrogen bonds with the surface water molecules and their HCN neighbors.

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Computational dielectric spectroscopy of amino acids in saline solutions

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The objective of this investigation was to ascertain the distinct ion-induced influences on the dielectric behavior of amino acids in saline solutions, in line with the Hofmeister series. The impact of cations was studied by examining various concentrations of potassium, sodium, and lithium chloride. Simultaneously, the effect of anions was scrutinized through the analysis of potassium bromide, chloride, and iodide. Three particular amino acids—arginine, lysine, and serine— displayed significant variations in aqueous solutions as a function of the salt and their concentrations in the experimental data. The computed spectra were juxtaposed against the experimental spectra obtained from our colleagues at the Max Planck Institute in Mainz. Furthermore, we undertook supplementary analyses to investigate the underlying causes of the ion-specific effects.

Simulations were executed using OpenMM, incorporating a modified version of the Amber-ff14SB. Given the absence of default zwitterions in this force field, they were introduced manually, employing the standard protein-ff14SB force field constants for the amino acids. The charges for the atoms were computed utilizing ACPYPE. This force field is superior to the classical CHARMM force field which shifted the peaks of dielectric spectra to lower frequencies due to clustering. The water model SPC/E shows excellent dielectric behavior. However, the corresponding ion parameter parametrized for SPC/E overestimate their impact on the amino acids at high concentrations. Thus, the SPC/E model was paired with the ion force field originally parametrized with respect to the TIP3P water model. Subsequently, the TIP3Pfb force field for the ions was employed, owing to its force balanced model and notable agreement with experimental dielectric data.

The ion specific effects are mostly pronounced for cations, chaotropic cations as lithium show stronger effects on the dielectric behavior as kosmotropic cations as potassium. Significant anionic effects could not be determined.

4.2 Poster session on Wednesday (even numbers)

P2	Mazin Saad Almarashi
P4	Béla Fiser
P6	Magdalena Małecka
P8	Calvin Mathiah
P10	Zsófia Borbála Rózsa
P12	Dalal Thbayh
P14	Hadeer Waleed
P16	Francesca Goudou-Rosnel

Coarse Graining-

Investigating the Hydrodynamic Properties of Co-Polymers for Drag Reduction in Water

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Hydrophobically modified associating polymers were investigated because they have been shown to be effective drag-reducing agents in aqueous solutions. These polymers form weak links that can reform after degradation, protecting the backbone from fast scission. [1]

To gain insight into the system the BMW-water [2] model was chosen as solvent, which uses a modified Born-Mayer-Huggins Potential for non-bonded interactions. The Polymers were parametrized by force matching atomistic simulations to this functional form and adapting the parameters to reproduce experimental radii of gyration for the pure polymers.

The experimental systems are computationally not accessible using our methods, therefore a series of smaller systems were extrapolated to obtain the radius of gyration and optimize the force field to the experiment.

Following this step we aim to gain insight into to distribution of the hydrophobic modifications on the polymer backbone and the association-energies of multiple chains in solution. Thereafter using these to calculate, which flow rates this polymers are usable as drag reducing agents without backbone scissions.

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Interaction of DNA with Polycyclic Aromatic Hydrocarbons

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Polycyclic aromatic hydrocarbons (PAHs), usually generated during incomplete combustion of organic materials, are toxic molecules present in the environment [1,2]. Their harmful effect on human health and other living organisms is a hot topic in the scientific community, knowing their mutagenic effects caused by their interaction and reaction with DNA leading directly to cancer. Although many different types of PAHs exist, 16 molecules were selected by the US Environmental Protection Agency (EPA) to describe the effect of all of them [1,2]. In this work, molecular docking was used in order to get a better understanding of how PAH molecules interact with DNA. After noticing that all of the PAHs chosen by the US EPA are planar, 11 non-planar molecules were also selected in order to see how linearity affects their interaction with DNA. The results showed that the best fitting planar PAH molecules were the dibenz[a,h]anthracene and indeno[1,2,3-cd]pyrene, both of them established strong interactions with DNA and therefore, potentially the most toxic molecules. Furthermore, within the set of non-planar species benzo(a)perylene had the highest binding affinity. The results show that there is a preference in terms of PAH binding toward specific regions of DNA.

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Interactions in the crystaline form of the inclusion complex of cyclodextrin

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Cyclodextrins (CDs) are a group of oligosacharides consisting of D-glucopyranose residues linked by α-1,4 glycosidic bonds, usually containing 6-12 D-glucopyranose units[1]. Cyclodextrins have a toroidal shape with a hydrophobic cavity and a hydrophilic exterior part of different size. The internal hydrophobic cavity leads to the formation of inclusion complexes with guest molecules through non-covalent interactions (van der Walls interaction or hydrogen bond)[2]. Hence CDs are well known in supramolecular chemistry[3] similar to pseudorotaxanes. Inclusion complexes of CDs can enhance aqueous solubility, improve bioavailability, stability, and bioactivity of guest molecules, and even reduce undesirable tastes. For this reason, CDs find their uses in food, pharmaceutical, material, agriculture and chemical industries[4]. Considering the above aspects, there is a great interest in understanding the interactions between gest and host molecules. Therefore we synthesize the complex of α-cyclodextrin with p-aminobenzoic acid, which was characterized by X-ray diffraction.

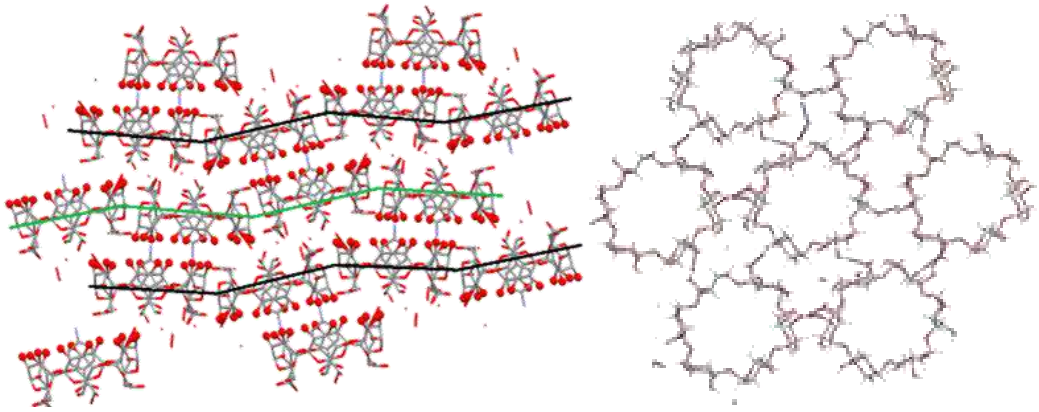

Figure 1. Crystal packing Arrangement for inclusion complexes; on left – ribbons; on right- the cyclodextrin rings on one plane, but stacked perpendicular tot he plane.

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Mechanistic insights into Fdc1 decarboxylase using MD simulations

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The widespread UbiD family of decarboxylases utilise a novel prenylated flavin (prFMN) cofactor to facilitate the reversible catalysis of carboxylic acids to their corresponding alkene and carbon dioxide (CO2). The fungal dimer ferulic acid decarboxylase (Fdc) is the model UbiD member and catalyses the interconversion of cinnamic acid to styrene and CO2. In order to investigate specific unresolved mechanistic features of this reaction, molecular dynamics (MD) simulations were performed on Fdc reaction intermediates. Analysis of an important arginine-leucine distance was used to quantitatively characterise potential active site conformational changes during the Fdc catalytic cycle. A more comprehensive picture of this interesting biochemical reaction may yield information that can inform industrial and biotechnological applications, such as rational enzyme engineering to alter the subtrate scope.

Molecular dynamics simulations of membrane-fluorescent dye interactions

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Membrane voltage changes in electrically excitable cells, such as neurons and cardyomycotes, are an essential part of human life. Voltage imaging with voltage-sensitive fluorophores (or VoltageFluor (VF dyes)) promise a low invasive and high-throughput technique, while enabling the direct observation of membrane potential changes in living systems. VF dyes sense voltage via photoinduced electron transfer (PeT). The transmembrane electric field of the cell changes the rate of electron transfer from the donor to the acceptor, when the membrane is hyperpolarized, the rate of PeT is increased, resulting in quenching of the acceptor, while when the membrane depolarizes, the rate of PeT is decreased, resulting in acceptor fluorescence. [1]–[3]

In this study we have investigated the membrane interactions of two already known (a rhodamine based voltage reporter – RhoVR [4] and a Styryl voltage-sensitive dye, di-4-ANEPPS [5]), and two yet to be tested (UTOAPIA, TA2YN) neuronal cell membrane dyes (**Figure 1**), using 1 µs Molecular Dynamics simulations (MD). The membrane bilayer structure was built based on a liposomal model system, using CHARMM36 force field. Parameters, such as the immediate membrane composition around the VF dye molecules and their orientation inside the membrane - based on which the voltage sensitivity of the dyes were esteemed – were evaluated. Based on our calculations TA2YN is the least promising VF dye out of the investigated structures.

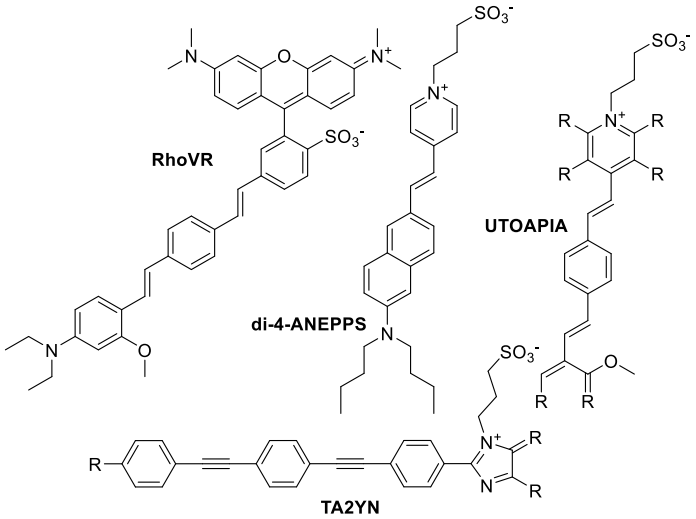

Figure 1 2D structure of the investigated VF dyes

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ANTIOXIDANT ACTIVITY OF EDTA AND IRGANOX AS SYNTHETIC ADDITIVES

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Absract: Antioxidant additives (AAs) have the capability to neutralise free radicals and subsequently stabilize them which will eventually prevent the oxidative damage of the polymeric material. AAs are compounds shielding polymers and plastics from the thermal and photo-oxidative effects arising through normal aging, or combat of free radicals, a surplus of which causes oxidative stress [1]. The antioxidant potential for two synthetic antioxidant additives including ethylenediaminetetraacetic acid (EDTA) and Irganox (Irg) were studied. The geometries of EDTA, Irg, and the corresponding radicals, cations, and anions were optimized by employing the M05-2X and M06-2X functionals in combination with the 6-311++G(2d,2p) basis set in gas phase. Antioxidant potential for these molecules have been studied via using three different antioxidant mechanisms. Bond dissociation enthalpy (BDE), ionization potential (IP) followed by proton dissociation enthalpy (PDE) and proton affinity (PA) followed by electron transfer enthalpy (ETE) values were calculated. Two density functional theory (DFT) methods were used, M05-2X and M06-2X in combination with the 6-311++G(2d,2p) basis set in the gas phase. The results indicated for that EDTA has a higher antioxidant potential than Irg in all mechanisms [2]. These additives can be used to protect polymers and prevent material deterioration caused by oxidative stress.

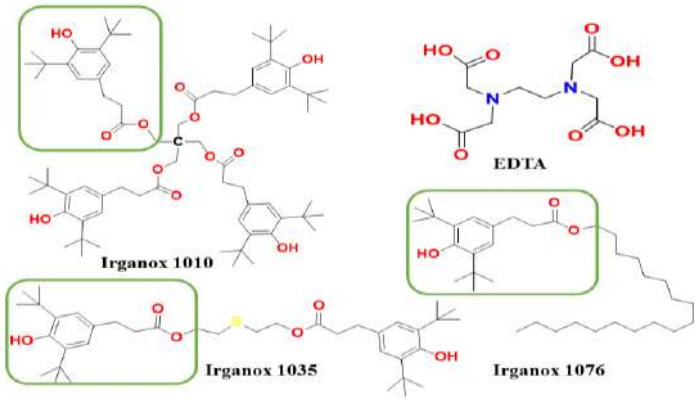

Fig.1 *(2D chemical structure of EDTA and various Irganox types which have the same base unit)*

References:

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Amine Catalysed Urethane Formation – A Combined Experimental and Theoretical Study

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Polyurethanes (PUs) are widely used in different applications, and thus various synthetic procedures including one or more catalysts are applied to prepare them. For PU foams, the most important catalysts are nitrogen-containing compounds. It was developed by Otto Bayer and ranks among the most important breakthroughs in polymer science[1]. As PU is widely used in many applications, and different synthetic procedures are applied to prepare them, therefore catalysts are important in the process of synthesizing the polymer. Catalysis plays a fundamental role in industrial chemical transformations, and can expedite chemical reactions compared to catalyst-free systems[2]. In the current research, the alcoholysis of phenyl isocyanate (PhNCO) using stoichiometric butan-1-ol (BuOH) in acetonitrile in the presence of different cyclic amine catalysts was examined using a combined kinetic and mechanistic approach. The molecular mechanism of urethane formation without and in the presence of cyclic amine catalysts was studied using the G3MP2BHandHLYP composite method in combination with the SMD implicit solvent model. It was found that the energetics of the model reaction significantly decreased in the presence of catalysts. The computed and measured thermodynamic properties were in good agreement with each other. The results prove that amine catalysts are important in urethane synthesis. Based on the previous and current results, the design of new catalysts will be possible in the near future.

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CHLORDECONE AND β-HEXACHLOROCYCLOHEXANE INTERACTIONS WITH FUNCTIONALIZED ACTIVATED CARBON BY MOLECULAR MODELLING AND MOLECULAR DYNAMICS SIMULATION

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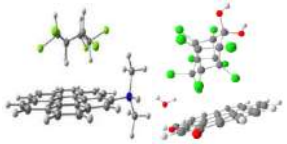
A molecular modeling study of the influence of acidic [1-2] and basic [3] surface groups (SG) of activated carbon (AC) model on chlordecone (CLD) and β-hexachlorocyclohexane (β-HCH) adsorption is presented, in order to help understanding the adsorption process considering pH and hydration effect. A coronene molecule, with the functional groups under study in the edge, were used as a simplified model of AC. Multiple Minima Hypersurface methodology was employed to study the interactions of CLD and β-HCH with SGs on AC using PM7 semiempirical Hamiltonian. A further re-optimization of obtained structures was done for pesticide-AC complexes by means of Density Functional Theory. The Quantum Theory of Atoms in Molecules was used to characterize the interaction types using the Nakanishi criteria. As results, the interactions are governed by dispersive interactions of chlorine atoms of the pollutants with the graphitic surface and by electrostatic interactions with COO^- and O^- acidic groups and water molecules. As conclusion, significant associations of acidic SGs with CLD suggest a chemical sorption at slightly acidic and neutral pH conditions. On the other hand, the interactions of both pollutants with basic SGs on AC are similar with a physisorption process, confirmed also by Molecular dynamics simulation. Finally, an increase in carboxylic SGs content is suggested to enhance CLD and β-HCH adsorption onto AC.

Donor-acceptor interaction



Dispersive interaction

Electrostatic interaction

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