COSY COST ACTION

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TRAINING SCHOOL

EXPLORING CONFINED ENVIRONMENTS WITH POLYMERS, IONIC LIQUIDS, AND DEEP EUTECTIC SOLVENTS

Predicting Emerging Applications through Modeling and Advanced Experiments

BOOK OF ABSTRACTS

COST Training School

Exploring Confined Environments with Polymers, Ionic Liquids, and Deep Eutectic Solvents: Predicting Emerging Applications through Modeling and Advanced Experiments

COST action CA21101

Iași, 8 – 9 May 2025
Romania

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Timetable of the COST Training School 2025

Exploring Confined Environments with Polymers, Ionic Liquids, and Deep Eutectic Solvents: Predicting Emerging Applications through Modeling and Advanced Experiments

8 – 9 May 2025, Iași, Romania

DAY 1 - Thursday, 8 May 2025

- 08:30 – 09:00 | Registration and Welcome Coffee
- 09:00 – 09:15 | School Opening
- 09:15 – 10:15 | Lecture: **Introduction to ionic liquids**
  - *Aatto Laaksonen,* Stockholm University, Sweden
- 10:15 – 11:15 | Lecture: **QM/MD and NMR characterization of ionic liquids**
  - *Kestutis Aidas*, Institute of Chemical Physics Vilnius University, Lithuania
- 11:15 – 11:45 | Coffee break
- 11:45 – 12:45 | Lecture: **Force field parameters and challenges in ionic liquids simulations**
  - *Francesca Mocci*, Cagliari University, Italy
- 12:45 – 14:30 | Lunch break
- 14:30 – 15:30 | Lecture**: Theoretical and experimental characterization of nanoparticle enhanced ionic liquids for heat exchange applications**
  - *Alina Minea,* Gheorghe Asachi Technical University of Iasi
- 15:30 – 16:30 | Coffee break / Poster session
- 16:30 – 18:30 | Practical training: **Calculation of NMR parameters of ionic liquids by QM/MM**
  - *Kestutis Aidas*, Institute of Chemical Physics Vilnius University, Lithuania

DAY 2 - Friday, 9 May 2025

- 09:00 – 10:00 | Lecture: **Theoretical modelling and/or experimental characterization of IL/DES and confinement effects**
  - *XiaoYan Ji,* Lulea University, Sweden
- 10:00 – 11:00 | Lecture: **Harnessing Polymer Science for Effective Gene Therapy Solutions**
  - *Dragoș Peptanariu,* Petru Poni Institute of Macromolecular Chemistry, Iasi, Romania
- 11:00 – 11:30 | Coffee break
- 11:30 – 12:30 | Lecture: **Medical applications of ionic liquids**
  - *Lenuța Profire,* Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania
- 12:30 – 14:00 | Lunch break
- 14:00 – 15:00 | **Lecture: Development of force field parameters for the simulation of ionic liquids**
  - *Sonja Grubisic*, Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Serbia
- 15:00 – 15:15 | Coffee break
- 15:15 – 17:00 | Practical training: **Ionic liquids simulations**
  - *Francesca Mocci,* Cagliari University, Italy
  - *Tudor Vasiliu,* Petru Poni Institute of Macromolecular Chemistry, Iasi, Romania
- 17:00 – 18:30 | Coffee break / Poster session
- 18:30 – 19:00 | Award for best poster and Closing remarks

Lecture Abstracts

Exploring Confined Environments with

Polymers, Ionic Liquids, and Deep Eutectic Solvents:

Predicting Emerging Applications through Modeling and Advanced Experiments

8 – 9 May 2025, Iași, Romania

Introduction to Ionic Liquids

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The meaning "Ionic Liquid" is well-defined for those of us who study them experimentally or theoretically, as well as why they can be applied across a very wide range of areas from engineering to pharmacology. For rest of us it may sound like a "liquid with ions" with no good explicit definition. The most common way to introduce ionic liquids is to start with crystals of table salt, NaCl, composed of sodium and chloride ions. However, it becomes liquid (molten salt) first after we heat it to over 800C. But if we change the Na^+ to an organic, bulky and asymmetrical molecule carrying a charge +1, the melting point can quickly drop to below 100C. Why? While the ions of NaCl can quickly without any problem find a cubic packing held together with strong and symmetrical ionic interactions, 1-Ethyl-3-methylimidazolium chloride, for example, melts at 77C, and is an example of an ionic liquid (IL). You may also think that ILs are rare in Chemistry, so it may surprise you that the possible number of different ionic liquids by combining existing and hypothetical cations and anions is order of 10^{17}. So it is like a huge Lego-like universe with a nearly infinite number of combinations of blocks [1]. This makes them to ultimate designer systems in Chemistry with continuously growing number of applications spanning all areas. Among many properties they have wide electrochemical windows, are thermally and chemically stable with virtually no vapor pressure. And all this is so far about neat ionic liquids. When you start to add co-solvents, the application space literally explodes [2]. That this School is about ionic liquids, and to their related Deep Eutectic Solvents (DES) in constrained environments, for example at surfaces or in pores, opens yet another super powerful application area, apart from ILs and DESs being green solvents, replacing the common and polluting organic solvents. Here we give a short introduction to ILs, their highly attractive properties and put them at work. Everything comes with a cost because ILs and DESs are the most complicated systems on molecular level as they apply all possible interactions in concert. This makes them highly challenging systems to model requiring accurate models [3] and long simulations. Also, they are not homogeneous as liquids and have long-range structural long-living correlations. They are the true benchmark systems for computational chemists.

REFERENCES

[1] Yong-Lei Wang, Bin Li, Sten Sarman, Francesca Mocci, Zhong-Yuan Lu, Jiayin Yuan, Aatto Laaksonen, and Michael D. Fayer. 2020, Microstructural and Dynamical Heterogeneities in Ionic Liquids, *Chemical Reviews*, 120, 5798−5877 https://dx.doi.org/10.1021/acs.chemrev.9b00693

[2] Chunyan Ma, Aatto Laaksonen, Chang Liu, Xiaohua Lu, and Xiaoyan Ji, 2018, The Peculiar Effect of Water on Ionic Liquids and Deep Eutectic Solvents, *Chemical Society Reviews*, 21, 8685-8720 https://doi.org/10.1039/C8CS00325D

[3] Yonglei Wang, Xiaoyan Ji, Francesca Mocci and Aatto Laaksonen, 2024, The development of hierarchical ion models and multiscale modelling of tetraalkyl-phosphonium and imidazolium ionic liquids, in *Comprehensive Computational Chemistry*, (Eds. M. Yáñez & R.J. Boyd), Elsevier, pp 674-691, Volume 3, ISBN: 978-0-12-823256-9, https://doi.org/10.1016/B978-0-12-821978-2.00131-8

QM/MD and NMR Characterization of Ionic Liquids

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Molecular dynamics (MD) simulations combined with the quantum mechanics/molecular mechanics (QM/MM) models have proven to be a powerful computational technique for accurate predictions of electronic properties of extensive molecular systems. MD simulations are employed to sample the phase space of molecular system of interest under specific thermodynamic conditions, and then QM/MM calculations of electronic properties are performed where the central part of the molecular system is described by an electronic structure method and the rest of the system is modelled by a classical force field. In this presentation, we will give a brief informal introduction to the fundamentals of the nuclear magnetic resonance (NMR) spectroscopy. The general modelling scheme based on classical MD simulations and QM/MM models for electronic response properties will be presented. The bulk of the presentation will be devoted to the discussion of our recent successes in describing the structural and NMR properties of ionic liquid (IL) systems using this integrated MD-QM/MM scheme based on classical MD simulations and density functional theory.

Aiming to scrutinize intermolecular organization in aqueous mixtures of choline lysinate, [Cho][Lys], IL, the dependences of the ^{1}H NMR chemical shifts and diffusion coefficients on their composition were measured [1]. To rationalize experimental findings, extensive MD simulations and linear-response QM/MM computations of NMR shielding constants were performed. Analysis of MD trajectories reveals that extent of intermolecular contacts between cations and anions intensifies with the increasing content of the IL in the mixture. Moreover, the tendency of choline cations and the side chains of lysinate anions to self-aggregate was observed as well, leading to the formation of a continuous, highly polar domain composed of choline cations and the carboxylate groups of lysinate anions, as well as a less polar domain formed by the side chains of the anions in IL-rich mixtures. Under these circumstances, isolated water pockets are found to be situated at the interface of the polar and nonpolar ionic domains. The dependences of the measured diffusion coefficients on the composition of the mixture reveals the existence of two dynamical regimes – fast and slow regimes below and above molar fraction of the IL of 11%, respectively. Results of MD simulations suggest that – at this specific molar composition of aqueous [Cho][Lys] mixture – continuous water network ceases giving way to the continuous structure of ionic domains being formed. The QM/MM results for the ^{1}H NMR chemical shifts of aqueous IL mixtures generally agree well with experimental findings and corroborate structural results. The prominent upfield shift of the NMR signal of protons in fast exchange with the rising content of the IL was successfully rationalized [1].

In another recent study, relative ^{1}H NMR spectra of neat 1-butyl-3-methyl-imidazolium tetrafluoroborate, [C_4mim][BF_4], IL and its aqueous mixtures have been computed with the near-quantitative accuracy for the first time, with root-mean square deviation of 0.2 ppm with respect to the measured spectra [2]. The computational approach is based on classical MD simulations and linear-response QM/MM models. Theoretical predictions confirm that ^{1}H NMR spectrum of imidazolium cations is virtually independent of the composition of aqueous ionic liquid mixtures, despite considerable changes to the structure of the first solvation shell around the imidazolium ring induced by the increasing content of water were observed [2].

In the third example, the aim of the study was to dissect the nature of intermolecular interactions leading to the improved solubility of antidiabetic drug molecule glibenclamide in an aqueous solution of the choline tryptophanate, [Cho][Trp], ionic liquid [3]. To this end, experimental ^{1}H and ^{13}C NMR measurements and computational modelling employing classical MD simulations and combined QM/MM models were carried out. Samples of glibenclamide dissolved in water and in an aqueous mixture of [Cho][Trp] were scrutinized both experimentally and computationally. MD simulations revealed that the constituent ions of the ionic liquid condensed around the drug molecule pushing water

molecules away. Nevertheless, virtually no specific hydrogen bonding interactions between glibenclamide and the ions were formed. The hydrotropic activity of the [Cho][Trp] ionic liquid thus occurs through the formation of dynamic aggregates between the solute and the ions, which screen the hydrophobic glibenclamide from polar water molecules. Experimental ^{1}H NMR measurements have shown that the largest changes in chemical shifts were registered for protons in the benzene rings of glibenclamide, implying that these are the main sites of interaction with the ions of the ionic liquid – a conclusion well-corroborated by the results of MD simulations. The good qualitative agreement between the computational QM/MM-based and experimental NMR spectra of glibenclamide in an aqueous solution and in aqueous mixture of [Cho][Trp] provides support to the structural results [3].

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REFERENCES

[1] Sipavičius Einaras et al., (2025) "Intermolecular organization in aqueous mixtures of choline lysinate studied by NMR and molecular dynamics/quantum mechanics". *Phys. Chem. Chem. Phys.*, submitted.
[2] Sipavičius Einaras et al., (2025) "Towards accurate modelling of ^{1}H NMR spectra of ionic liquids: the case of [C_4mim][BF_4] and its aqueous mixtures". *Chem. Phys. Lett.*, submitted.
[3] Murnikova Žyginta, Klimavicius Vytautas, Mocci Francesca, Laaksonen Aatto, Aidas Kęstutis, (2025) "On the mechanism behind the enhanced solubility of glibenclamide in aqueous ionic liquid solution". *J. Mol. Liq.*, 422, 127153. DOI https://doi.org/10.1016/j.molliq.2025.127153

Force field parameters and challenges in ionic liquids simulations

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Molecular Dynamics (MD) simulations enable the investigation of structure and dynamics across a wide range of molecular systems, offering direct insight into intermolecular interactions and their temporal evolution with a resolution far beyond that of current experimental techniques, particularly in the liquid state. Understanding molecular-level organization and dynamics, and how these are influenced by external conditions or molecular modifications, is essential for the in-depth interpretation of experimental data and the rational design of systems with tailored properties for a broad range of applications, including pharmaceuticals, biotechnology, and industrial processes.

With high-performance computing platforms and increasingly efficient algorithms, force field-based simulations can now be applied to systems of ever-growing size. On specialized supercomputing architectures, simulations have reached scales involving hundreds of millions of atoms. On the other hand, simulations of systems containing tens of thousands of atoms can be routinely performed on standard laboratory workstations (costing only a few thousand euros), achieving microsecond timescales within just a few days. However, the results of the simulations are meaningful only when the employed force fields are well tuned for the system under examination, and careful validation of the results is always necessary.

Simulating ionic liquids (ILs) presents particular challenges, primarily due to their strong long-range Coulombic interactions, related to their ionic character, and short-range dispersion interactions, which arise from the presence of aromatic moieties and alkyl chains [1].

In this lecture, after a brief introduction to the concept of force fields, I will discuss several issues encountered in the simulation of ILs and other charged systems, along with solutions adopted by the modeling community. Emphasis will be placed on both successes and challenges in modeling structural, thermodynamic, and dynamic properties, using a variety of case studies [1–5]. Particular attention will be given to the role of atomic charges, comparisons to experimental data and higher-level calculations, and strategies to enhance agreement [2,6–8]. Critical aspects such as charge scaling, parameter transferability, and the implications of fixed-charge models on properties like density and diffusion will be discussed.

REFERENCES

[1] Wang YL, Li B, Sarman S, Mocci F, Lu ZY, Yuan J, Laaksonen A, Fayer MD, (2020) "Microstructural and Dynamical Heterogeneities in Ionic Liquids". Chemical Reviews, 120(13), 5798–5877. https://doi.org/10.1021/acs.chemrev.9b00693

[2] Frömbgen T, Blasius J, Dick L, Drysch K, Alizadeh V, Wylie L, Kirchner B, (2024) "Reducing Uncertainties in and Analysis of Ionic Liquid Trajectories". In: Molecular Dynamics Simulations and Reaction Rates, Comprehensive Computational Chemistry, Volume 3, edited by Laaksonen A, Mocci F, Ruud K; series editors Yáñez M, Boyd RJ. Elsevier, pp. 692–722. https://doi.org/10.1016/B978-0-12-821978-2.00097-0

[3] Engelbrecht LdV, Cibotariu N, Ji X, Laaksonen A, Mocci F, (2025) "Deep Eutectic Solvents Meet Non-Aqueous Cosolvents: A Modeling and Simulation Perspective─A Tutorial Review." Journal of Chemical & Engineering Data, 70(1), 19–43. https://doi.org/10.1021/acs.jced.4c00505

[4] Mariani A, Engelbrecht L, Le Donne A, Mocci F, Bodo E, Passerini S, (2021) "Disclosing the Hierarchical Structure of Ionic Liquid Mixtures by Multiscale Computational Methods." In: Joseph A, Mathew S (Eds.), Theoretical and Computational Approaches to Predicting Ionic Liquid Properties, Elsevier, pp. 1–67. https://doi.org/10.1016/B978-0-12-820280-7.00014-0

[5] Engelbrecht LdV, Ji X, Carbonaro CM, Laaksonen A, Mocci F. (2022) "MD simulations explain the excess molar enthalpies in pseudo-binary mixtures of a choline chloride-based deep eutectic solvent with water or methanol." Frontiers in Chemistry, 10, Article 983281. https://doi.org/10.3389/fchem.2022.983281

[6] Lengvinaitė D, Kvedaraviciute S, Bielskutė S, Klimavicius V, Balevicius V, Mocci F, Laaksonen A, Aidas K, (2021) "Structural Features of the [C4mim][Cl] Ionic Liquid and Its Mixtures with Water: Insight from a 1H NMR Experimental and QM/MD Study." The Journal of Physical Chemistry B, 125(48), 13255–13266. https://doi.org/10.1021/acs.jpcb.1c08215
[7] Goloviznina K, Gong Z, Costa Gomes MF, Pádua AAH, (2021) "Extension of the CL&Pol Polarizable Force Field to Electrolytes, Protic Ionic Liquids, and Deep Eutectic Solvents." Journal of Chemical Theory and Computation, 17(3), 1606–1617. https://doi.org/10.1021/acs.jctc.0c01002
[8] Velez, C., Acevedo, O. (2022) "Simulation of Deep Eutectic Solvents: Progress to Promises." WIREs Computational Molecular Science, 12, e1598. https://doi.org/10.1002/wcms.1598

Theoretical and experimental characterization of nanoparticle enhanced ionic liquids for heat exchange applications

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Ultrahigh-performance cooling is one of the most vital needs of many industrial technologies. However, inherently low thermal conductivity is a primary limitation in developing energy-efficient heat transfer fluids that are required for heat exchange applications.

Nanofluids (a more recent term is Nanocolloids) are engineered by suspending nanoparticles in traditional heat transfer fluids such as water, oil, ethylene glycol. Nanofluids (nanoparticle fluid suspensions) is the term that was firstly coined by Choi (1995) to describe this class of nanotechnology-based heat transfer fluids that exhibit thermal properties superior to those of their host fluids.

This new technology, even if its roots are about 30 years old, it is still at the beginning since the most nanocolloids TRL (technology readiness level) is 3-4. Anyway, there is a large debate on literature based on thermophysical properties of nanocolloids, method of approach and validity of applications.

This research is focused on ionic liquids and ionic liquids based nanocolloids. Ionic liquids are entirely made of ions and have the melting point lower than 100°C. The development of room temperature ionic liquids has attracted tremendous interest from researchers and industrial people due to their low melting temperatures (<30°C) which allow these host fluids for INFs to be used in wide range of applications. Ionic liquids exhibit several unique features that allow to develop and synthesize by tailoring of the cation-anion structure for desired physiochemical properties and thus for the targeted applications. As these liquids are not combustible or volatile at ambient conditions and also are recyclable, they are considered as environmental-friendly fluids. Ionic liquids also have extremely low vapor pressure, high thermal stability, as well as high heat capacity, and the combination of these features makes ILs and thus ionanofluids better heat transfer fluids.

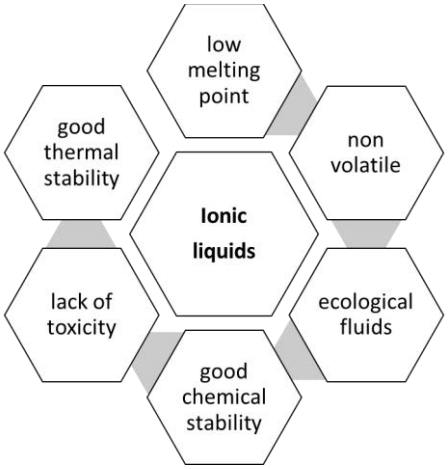

Figure 1 – Ionic liquids properties

Some studies also suggested that, due to their very low vapor pressure preventing them to be cooled by evaporations, ILs can be used for thermal energy storage in an open system. Thus, ionic liquids and their suspensions of nanoparticles (INFs) can be good media for thermal storage systems as well as heat transfer fluids in solar power generation applications.

It was demonstrated that the combination of nanomaterials with ILs show great potential as heat transfer fluids through the enhancement of the thermal properties and heat transfer.

Since the first work on carbon nanotubes (CNT) mixed in ionic liquids (i.e., INFs) reported in 2007, numbers of research works have been performed in this new area of ionanofluids. However, the research on various properties and heat transfer features of these new heat transfer fluids are still at very early stage and some findings are carefully reviewed in later sections.

In terms of real-life applications, few research groups demonstrated that ionanofluids could be very well suited for solar energy applications, especially for the efficient absorption of the solar radiation and for its transmission to heating/cooling systems.
Results on [C2mim][CH3SO3] 1-Ethyl-3-methylimidazolium methanesulfonate ionic liquid revealed that:

- Rheological tests revealed that both IL and INFs have an obvious Newtonian behavior at higher shear rates.
- The viscosity is noticeably rising when nanoparticles mass concentration increase, going up to 250 % for the 10 %wt. of alumina suspended in the pure ionic liquid. Furthermore, the viscosity is diminishing when temperature increase, which is a usual phenomenon for most liquids.
- The assessment of viscosity experimental data versus theoretical equations show that no theoretical model can be appropriate to define the real increase in viscosity of INFs.
- Little to no significant viscosity hysteresis was noticed.
- Specific heat was found to increase with both mass fraction and temperature. However, no agreement with theoretical data was noticed.
- Electric conductivity decreases with nanoparticle addition and increases linearly with temperature.
- Thermal conductivity of the mixtures increases of about 7% for a mole fraction of water of 0.25 and 0.50 and an increase of 23% for a mole fraction of water of 0.75.
- For IoNanofluids, it was observed that the addition of nanoparticles leads to an increase in the thermal conductivity of the dispersions by 1 - 13% depending on the mass concentration of alumina.

Results on [C4mim][BF4] ionic liquid and ionanofluids revealed that:

- The rheological investigation proved that the ionic liquid and low concentrated suspensions with ZnO have Newtonian behavior, while the IL+0.25ZnO has a clear non-Newtonian behavior.
- At ambient temperature, the NEILs viscosity is discreetly increasing with ZnO mass fraction, up to 1.2 % for suspensions up to 1 %wt. ZnO.
- The specific heat is discreetly diminished with the addition of nanoparticles and the temperature influence is moderate.
- The rheological tests confirmed that the suspensions with alumina have non-Newtonian behavior at low shear rates, while at upper shear rates the flow is changed into Newtonian. Plus, viscosity is moderately increasing with NPs concentration
- Specific heat moderately decreases with the alumina addition, while the temperature influence is moderate.
- The viscosity hysteresis for all NEILs is in the same limits as for the base fluid.

As a conclusion, the main application of nanocolloids in heat exchange systems refers to overall energy consumptions decreasing, especially since the heat transfer performance of ordinary fluids is limited due to their low thermal conductivity. Hence, to increase the overall heat transfer performance of a system, a new fluid has to be considered by adding high conductive nanoparticles.

Some gaps can be highlighted and future directions as:

- The development of new heat transfer fluids needs to be intensified and a consistent theory is urgently needed in order to implement new heat transfer fluids in real applications, especially in solar energy.

- Another important topic to be addressed is the report of the thermophysical properties of these new heat transfer fluids, as well as to propose solid correlations to estimate especially the viscosity and thermal conductivity.
- An in-depth study on the relevance of using surfactants is missing.
- Considerably experimental as well as numerical effort is needed to fully understand the behavior of nanocolloids in laminar and turbulent flows.

REFERENCES

[1] A. Minea, Numerical studies on nanoparticle stabilization in ionic liquid medium (IoNanofluids), 30 pages, ch. 5 in Joseph - Theoretical and Computational Approaches to Predicting Ionic Liquid Properties, Editors: Aswathy Joseph, Suresh Mathew, Academic Press Elsevier, ISBN: 9780128202807, 2020.
[2] A. Minea, S.M. Murshed, An insight of ionanofluids flow and heat transfer behavior for solar energy in Nanofluids and their Engineering Applications, ed. K.R.V. Subramanian, Tubati Nageswara Rao, Avinash Balakrishnan, Chapter 11, CRC press Taylor & Francis, ISBN 9781138605268 - CAT# K388492, 2019
[3] AA Minea, EI Cherecheș, Experimental studies on thermal conductivity and heat transfer of 1-Butyl-3-methylimidazolium tetrafluoroborate ionic liquid and its nanocolloids, International Communications in Heat and Mass Transfer 154, 107406, 2024
[4] E.I. Chereches, D. Bejan, A.A. Minea, Experimental on viscosity and isobaric heat capacity of [C4mim][BF4] ionic liquid with MWCNT nanoparticles, Journal of Molecular Liquids 391 (2023) 123214
[5] E.I. Chereches, D. Bejan, C. Ibanescu, M. Danu; A.A. Minea, Experimental investigation of isobaric heat capacity and viscosity for suspensions of alumina nanoparticles in [C4mim][BF4] ionic liquid, Journal of Thermal Analysis and Calorimetry 148 (2023) 8879-8888
[6] E.I. Chereches, A.A. Minea, Experimental study on electrical conductivity of several [C4mim][BF4] ionic liquid based nanocolloids, Nanomaterials, 13(7) 1224 (2023), 10.3390/nano13071224, IF = 5.719.
[7] E.I. Cherecheș, C. Ibanescu, M. Danu, A.A. Minea, Studies on rheological properties and isobaric heat capacity of ZnO - [C4mim][BF4] nanoparticle enhanced ionic liquid, Journal of Molecular Liquids, 121759 (2023), 10.1016/j.molliq.2023.121759, IF = 6.633.
[8] AA Minea, EI Cherecheș, State of the art on the development of 1-Butyl-3-methylimidazolium tetrafluoroborate ionic liquid and its nanocolloids, Journal of Molecular Liquids, 120691, 2022
[9] E.I. Cherecheș, M.I. Cherecheș, A.A. Minea, Analysis of the operating behavior of some mixtures: water, ionic liquid, nanoparticles, BULETINUL INSTITUTULUI POLITEHNIC DIN IAȘI, 67 (71), 2021, Secția ȘTIINȚA ȘI INGINERIA MATERIALELOR, Iasi, Romania.
[10] A. Minea, S. M. S. Murshed, Ionic Liquids-Based Nanocolloids—A Review of Progress and Prospects in Convective Heat Transfer Applications, Nanomaterials 2021, 11(4), 1039
[11] EI Cherecheș, D Bejan, C Ibanescu, M Danu, AA Minea, Ionanofluids with [C2mim][CH3SO3] ionic liquid and alumina nanoparticles: An experimental study on viscosity, specific heat and electrical conductivity, Chemical Engineering Science 229, 116140, 2021
[12] E.I. Chereches, A.A. Minea, Experimental evaluation of electrical conductivity of ionanofluids based on water - [C2mim][CH3SO3] ionic liquids mixtures and alumina nanoparticles, Journal of Thermal Analysis and Calorimetry, (2021), 145 (6), 3151-3157
[13] A.A. Minea, Overview of ionic liquids as candidates for new heat transfer fluids, International Journal of Thermophysics, 41, pp 151, (2020), DOI: 10.1007/s10765-020-02727-3
[14] E.I. Cherecheș, J.I. Prado, C. Ibanescu, M. Danu, A.A. Minea, L. Lugo, Viscosity and isobaric heat capacity of alumina Nanoparticle Enhanced Ionic Liquids: an experimental approach, Journal of Molecular Liquids, 114020 (2020
[15] E.I. Chereches, M. Chereches, A. Alexandru, A. Dima, A.A. Minea, Nanoparticles in ionic liquids: numerical evaluation of heat transfer behaviour in laminar flow, Heat Transfer Engineering, DOI: https://doi.org/10.1080/01457632.2020.1818372 (2020).
[16] E I Chereches, A A Minea, K.V. Sharma, A complex evaluation of [C 2 mim][CH 3 SO 3]–alumina nanoparticle enhanced ionic liquids internal laminar flow, International Journal of Heat and Mass Transfer, 154 (2020) 119674.
[17] E I Chereches, M. Chereches, A A Minea, J I Prado, L Lugo, A numerical approach in the assessment of a new class of fluids performance in laminar flow, IOP Conf. Ser.: Mater. Sci. Eng. 591 (2019) 012044
[18] EI Cherecheș, JI Prado, M Cherecheș, AA Minea, L. Lugo, Experimental study on thermophysical properties of alumina nanoparticle enhanced ionic liquids, Journal of Molecular Liquids 291 (2019) 111332
[19] Minea, A.A., Murshed, S.M.S., A review on development of ionic liquid based nanofluids and their heat transfer behavior, Renewable and Sustainable Energy Reviews, 91 (2018) 584-599

Theoretical modelling and/or experimental characterization of IL/DES and confinement effects

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Thermodynamic and transfer properties of fluids as well as their roles in predicting the performance, e.g., fluid flux, are essential for the technology development, especially those linked to complex fluids, such as ionic liquids. To address this, we have been working on theoretical modeling to predict the thermodynamic properties of complex fluids covering a wide temperature and pressure range, and the theoretical models have been further combined with other theories to describe the transport properties, including viscosity and diffusion coefficient. The models have also been extended to the fluids confined in nano-porous via the combination of the classical density functional theory. The models for describing the properties were further used to describe the flux of nano-membrane, and the comparison with the experimental data shows high prediction capacity. To further promote the model development, the possibility of using artificial intelligence has been investigated, and a framework has been proposed.

Harnessing Polymer Science for Effective Gene Therapy Solutions

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The elucidation of molecular disease mechanisms through breakthroughs in biochemistry and genomics has driven demand for new therapies that address genetic root causes rather than symptoms. Gene therapy, which enables precise therapeutic correction by delivering functional genetic material into cells, has emerged as a pivotal strategy. While viral vectors dominate clinical applications, their limitations-including immunogenicity, insertional mutagenesis risks, and inability to support redosing-have encouraged innovation in non-viral delivery systems. These platforms prioritize biocompatibility, scalability, and tunability for diverse cargoes, from plasmid DNA to CRISPR-Cas9 ribonucleoproteins (RNPs).

Our research group has engineered a suite of modular non-viral vectors based on molecular scaffolds such as fullerene derivatives, flexible cyclic siloxane cores, β-cyclodextrin, or polyrotaxanes [1-4].

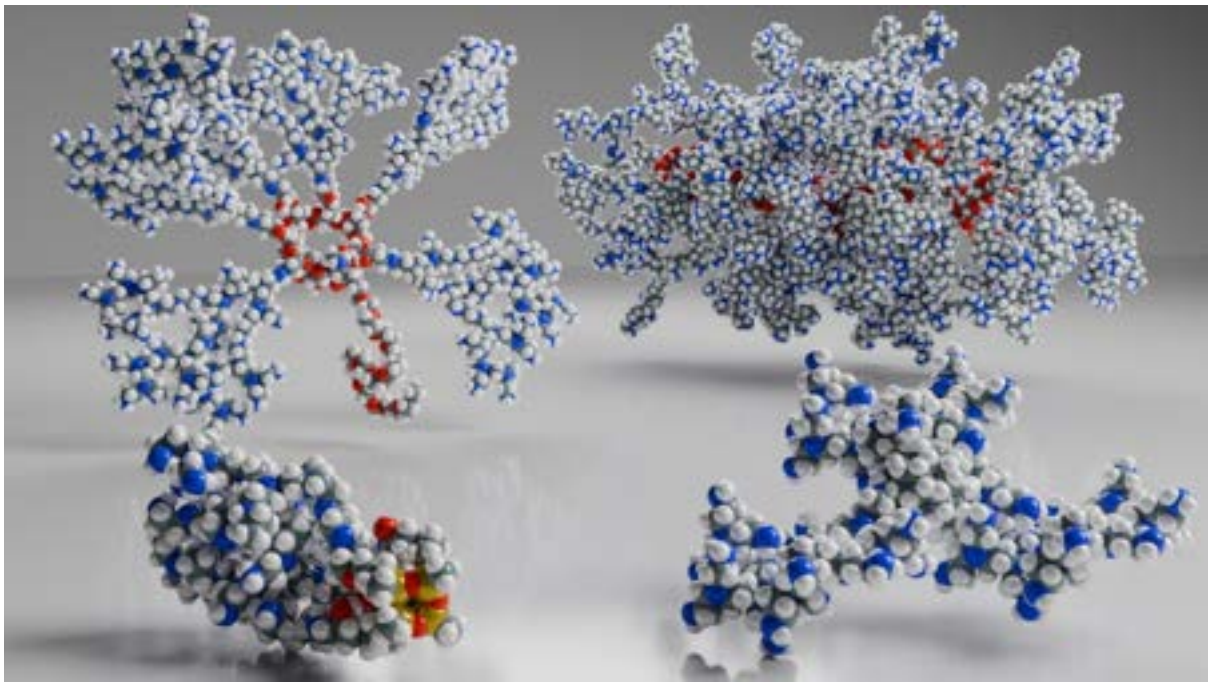

Figure 1 – Nonviral vectors based on cores of fullerene, siloxane, cyclodextrin, polyrotaxanes, and having functional arms of polyethyleneimine and polyethylene glycol. These molecules are capable of electrostatically binding nucleic acids.

These substrates are functionalized with cationic polyethyleneimine (PEI) branches via a two-step synthesis: initial core activation followed by PEI conjugation. This design capitalizes on electrostatic nucleic acid binding while incorporating hydrophobic domains (e.g., siloxane, fullerene) which are known to enhance membrane interaction [5].

Recently, other research groups demonstrated that cyclodextrin-based polyrotaxanes-threaded with PEG axles and modified with diethylenetriamine and cystamine groups enable efficient Cas9 RNP delivery [6].

Similarly, PEI600-β-cyclodextrin conjugates achieve 30% transfection efficiency in mesenchymal stem cells with minimal cytotoxicity, outperforming conventional PEI25kDa as was proven by another research team [7].

The non-viral vectors also support ligand conjugation (e.g., targeting peptides) to improve cell specificity. The ability to add targeting elements such as peptides to the cargo-complex significantly enhances the precision, and effectiveness of therapeutic delivery. Peptides, due to their small size, structural flexibility, and high specificity, can be designed to selectively bind to receptors or other markers uniquely expressed on the surface of target cells, such as those found in tumors or specific organs.

ACKNOWLEDGEMENT

This work is supported by European Union's Horizon Europe research and innovation programme under grant agreement No 101086667, project BioMat4CAST (BioMat4CAST - "Petru Poni" Institute of Macromolecular Chemistry Multi-Scale In Silico Laboratory for Complex and Smart Biomaterials).

REFERENCES

[1] Uritu CM, Calin M, Maier SS, Cojocaru C, Nicolescu A, Peptanariu D, et al. Flexible cyclic siloxane core enhances the transfection efficiency of polyethylenimine-based non-viral gene vectors. *Journal of Materials Chemistry B*. 2015;3(42):8250-67. DOI: 10.1039/C5TB01342A

[2] Uritu CM, Varganici CD, Ursu L, Coroaba A, Nicolescu A, Dascalu AI, et al. Hybrid fullerene conjugates as vectors for DNA cell-delivery. *Journal of Materials Chemistry B*. 2015;3(12):2433-46. DOI: 10.1039/C4TB02040E

[3] Dascalu AI, Ardeleanu R, Neamtu A, Maier SS, Uritu CM, Nicolescu A, et al. Transfection-capable polycationic nanovectors which include PEGylated-cyclodextrin structural units: a new synthesis pathway. *Journal of Materials Chemistry B*. 2017;5(34):7164-74. DOI: 10.1039/C7TB01722G

[4] Ardeleanu R, Dascalu AI, Neamtu A, Peptanariu D, Uritu CM, Maier SS, et al. Multivalent polyrotaxane vectors as adaptive cargo complexes for gene therapy. *Polymer Chemistry*. 2018;9(7):845-59. DOI: 10.1039/C7PY01256J

[5] Falanga A, Bellavita R, Braccia S, Galdiero S. Hydrophobicity: The door to drug delivery. *Journal of Peptide Science*. 2024;30(5):e3558. DOI: https://doi.org/10.1002/psc.3558

[6] Taharabaru T, Kihara T, Obata A, Onodera R, Wen Y, Li J, et al. Cyclodextrin-based tailored polyrotaxanes for highly efficient delivery of the genome-editing molecule. *Carbohydrate Polymers*. 2024;323:121443. DOI: https://doi.org/10.1016/j.carbpol.2023.121443

[7] Tong H, Wang C, Huang Y, Shi Q, Fernandes JC, Dai K, et al. Polyethylenimine600-β-cyclodextrin: a promising nanopolymer for nonviral gene delivery of primary mesenchymal stem cells. Int J Nanomedicine. 2013;8:1935-46. DOI: 10.2147/ijn.S43074

Medical Applications of ionic liquids

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Ionic liquids (ILs) are a class of chemical compounds with significant applications in organic synthesis, including heterocyclic synthesis, alkylation, oxidation, and dehydration reactions, owing to their exceptional solvent, reagent, and catalytic properties [1]. In addition to their versatile reactivity, ILs are considered environmentally friendly and have been shown to enhance enantioselectivity in the synthesis of various active pharmaceutical ingredients (APIs). ILs exhibit a range of biological activities, notably antimicrobial, antitumoral, and antioxidant effects. These properties make them promising candidates for pharmaceutical and biomedical applications. In drug delivery, ILs offer key advantages, particularly in the development of polymer-based delivery systems and novel pharmaceutical formulations known as API-ILs. For instance, ILs serve as excellent solvents for a variety of biomolecules, including proteins, DNA, and polysaccharides, facilitating their processing into films, microspheres, and nanoparticles [2].

Furthermore, ILs have demonstrated considerable potential in the functionalization of ionogels, as new advanced materials with tailored properties [3].

The choice of administration route for IL-based formulations depends largely on the physicochemical characteristics of the API (e.g., melting point, molecular weight, polarity, solubility), its pharmacokinetic profile, and the intended site of action [2]. ILs have been explored as promising biopharmaceutical agents and formulation components to address challenges associated with various delivery routes, including intravenous, oral, topical, and transdermal systems [4]. Additionally, ILs have shown potential in the development of analytical biosensors, which exhibit high efficiency in detecting biomarkers, therapeutic agents, and organic molecules [5].

In summary, ILs hold substantial potential in biomedical applications. However, further research is needed to better understand their supramolecular architecture, assess their toxicity, and ensure their long-term stability for clinical use.

REFERENCES

[1] Zhuo Y, Cheng HL, Zhao YG, Cui HR, (2024) Ionic Liquids in Pharmaceutical and Biomedical Applications: A Review. *Pharmaceutics*, 16, 151. DOI:10.3390/pharmaceutics16010151.

[2] Pedro SN, Freire CS, Silvestre AJD, Freire MG, (2020) The Role of Ionic Liquids in the Pharmaceutical Field: An Overview of Relevant Applications. *IJMS*, 21, 8298, DOI:10.3390/ijms21218298.

[3] Manasa C, Basavanna V, Ningaiah S, (2022) Ionic Liquid-Based Hybrid Materials: Ionogel Review. *Biointerface Res Appl Chem*, *13*, 391. DOI:10.33263/BRIAC134.391.

[4] Jadhav NR, Bhosale SP, Bhosale SS, Mali SD, Toraskar PB, Kadam TS, (2021) Ionic Liquids: Formulation Avenues, Drug Delivery and Therapeutic Updates. *J Drug Deliv Sci Technol*, *65*, 102694. DOI:10.1016/j.jddst.2021.102694.

[5] Curreri AM, Mitragotri S, Tanner EEL, (2021) Recent Advances in Ionic Liquids in Biomedicine. *Adv Sci*, *8*, 2004819. DOI:10.1002/advs.202004819.

Development of force field parameters for the simulation of ionic liquids

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Ionic liquids (ILs) exhibit distinctive physicochemical properties—such as negligible vapor pressure, high thermal stability, and tunable solvation capabilities—that make them attractive for diverse applications in energy storage, catalysis, and sustainable chemistry. Accurately modeling ILs, particularly in condensed phases and aqueous environments, requires precise treatment of medium- and long-range intermolecular interactions, including electrostatics, van der Waals forces, and polarization effects. The sensitivity of IL behavior to small changes in force field parameters presents a major challenge in molecular simulations, highlighting the importance of developing specialized and validated force fields.

This lecture presents recent progress in the development of force fields specifically tailored for IL systems, with emphasis on key methodological challenges such as capturing strong electrostatic interactions, accounting for conformational flexibility, and improving the representation of polarization [1-3]. Parameterization strategies—including those based on experimental observables and high-level quantum mechanical (QM) calculations—are discussed, along with approaches for validating these models against thermophysical properties such as density, diffusion coefficients, and viscosity.

As a case study, we highlight our recent work on the 1-decyl-3-methylimidazolium chloride (DMIMCl) ionic liquid (Figure 1), both in its neat form and in aqueous mixtures. Non-bonded parameters were optimized within the AMBER force field framework and validated against experimental density measurements at multiple temperatures, as well as diffusion data from the literature. These refined parameters also enable enhanced sampling of IL dynamics and improve the predictive accuracy of quantum mechanics/molecular mechanics (QM/MM) calculations of NMR observables, such as ^{35}Cl chemical shifts, which are crucial for understanding the mesomorphic behavior of these systems.

In addition, we evaluate the transferability of the developed parameters to mixed IL-solvent systems. This involves further QM analysis of ion-solvent clusters to better capture specific solvation effects and ensure robust performance across diverse environments.

Overall, the presented force field (FF) development contributes to predictive modeling and the rational design of novel ionic liquids (ILs), enabling their application in advanced technologies through accurate and computationally efficient simulations.

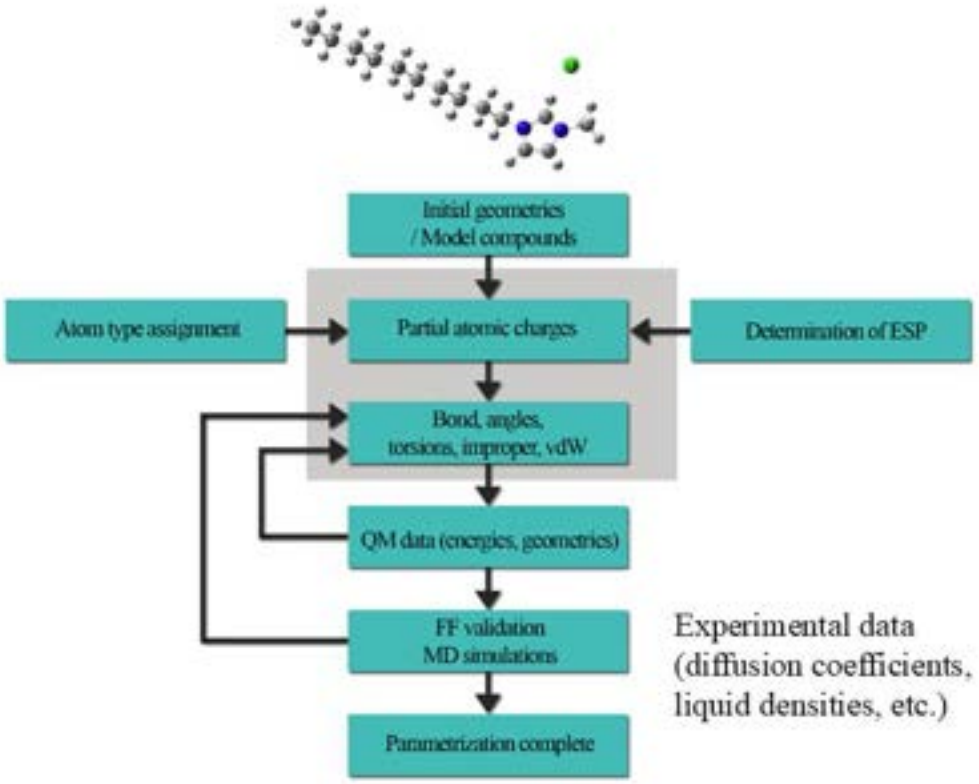

Figure 1 – Schematic representation of the force field fitting procedure using experimental data. The chemical structure of 1-decyl-3-methylimidazolium chloride (DMIMCl), the model ionic liquid used for force field development and validation, is also shown. This structure highlights the amphiphilic nature of the cation, featuring a long hydrophobic alkyl chain and a polar imidazolium headgroup, paired with a chloride anion. The molecular characteristics of DMIMCl make it an ideal candidate for studying ion–ion and ion–solvent interactions in both neat and mixed systems.

REFERENCES

[1] Goloviznina K., Gong Z., Pádua A. The CL &Pol polarizable force field for the simulation of ionic liquids and eutectic solvents. Wiley Interdisciplinary Reviews: Computational Molecular Science, 2022, 12 (3), pp.e1572. 10.1002/wcms.1572 hal-03365754.

[2] Zhiping Liu, Shiping Huang, and Wenchuan Wang, *Phys. Chem. B* 2004, 108, 12978-12989, https://doi.org/10.1021/jp048369o.

[3] Bagno A., D'Amico F., Saielli G., *Chem. Phys. Chem.*, **8**, 2007, 873, 10.1002/cphc.200600725.

ABSTRACTS

OF

POSTER PRESENTATIONS

Exploring Confined Environments with

Polymers, Ionic Liquids, and Deep Eutectic Solvents:

Predicting Emerging Applications through Modeling and Advanced Experiments

8 – 9 May 2025, Iași, Romania

Correlation between the structural properties of multifunctional copper-lanthanide (Cu_4Ln_4, Ln=Dy, Er and Y) clusters

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Heterometallic complexes that combine copper and lanthanide ions are of great interest due to their unique optical, catalytic, and magnetic properties. The 3d electrons of copper and 4f electrons of lanthanides combine to give rise to magnetic properties below a specific temperature, making them useful for data storage [1]. The magnetic moment of the atoms in the material can affect the electronic energy levels, which can in turn affect the absorption spectrum of the material. As a result, the optical absorption spectrum of these materials can be greatly influenced by their magnetic properties [2, 3].
We have synthesized $Cu_4Ln_4(vanox)_6(Hvanox)_2(NO_3)_4(\mu\text{-}HOMe)_2]\cdot 6MeOH$ $\{Cu_4Ln_4\}$ (Ln= Y, Dy and Er), which crystallize in the Pbca space group[3]. The octanuclear complexes shown here can be seen as built from $\{CuLn(vanox)(Hvanox)\}^{2+}$ units, in which Cu is equatorially-coordinated by two oxime nitrogens and two phenoxo oxygens while Ln is lying in a pocket formed by two phenoxo and two methoxy oxygens. All eight metals are coplanar within 0.077 Å in Cu_4Dy_4. The recorded absorbance peaks of $\{Cu_4Dy_4\}$ are at 370, 480, and 690 nm. The exchange interaction between the 3d electrons of copper and the 4f electrons of Dy causes a shift in the band gap of the $\{Cu_4Dy_4\}$ cluster.

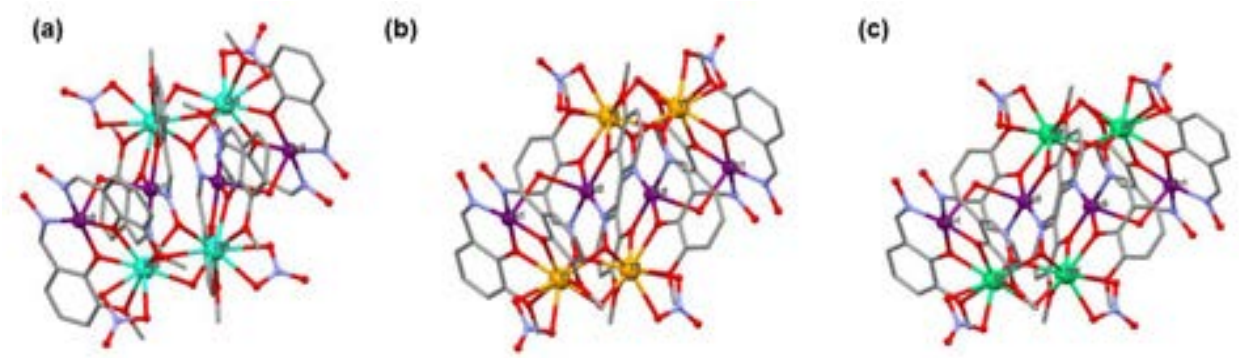

Figure 1 – Crystal structure of Cu_4Dy_4, Cu_4Y_4 and Cu_4Er_4

REFERENCES

[1] D. N. Woodruf; *et al. Chem. Rev.;* **2013**; 113; 5110−5148.
[2] P. Kumar; *et al. Appl. Phys. A.;* **2016**; 122; 740-751.
[3] I. A. Kühne; *et. al, Chem. Commun.;* **2014**; 50; 1882-1885.

Molecular dynamics simulation of mussel adhesive proteins

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Marine organisms like mussels exhibit remarkable underwater adhesion, attributed mainly to the presence of the amino acid 3,4-dihydroxyphenylalanine (L-DOPA) within Mussel Foot Proteins (MFPs) (1). This study aims to perform coarse-grained molecular dynamics (CGMD) simulations of multiple levodopa-containing MFPs, using a version of the MARTINI3 force field, specifically designed for disordered biological macromolecules (2). Particular focus will be placed on understanding the role of protein aggregation and liquid-liquid phase separation (coacervation) in adhesion (3), (4). The study will investigate how L-DOPA and pH influence protein coacervation and assess the adhesive properties when substituting L-DOPA with chemically similar species, including phenylalanine, tyrosine, and TOPA (3,4,5-trihydroxyphenylalanine). Additionally, this study will explore the effect of adding phosphoserine, a typical amino acid utilized by other organisms such as barnacles, sandcastle worms, and freshwater caddisfly larvae to achieve DOPA-free underwater adhesion (5). Ultimately, the goal is to elucidate the fundamental principles of wet adhesion at the molecular and mesoscopic level, providing critical insights for developing bio-inspired adhesives applicable in medical surgeries, underwater construction, marine engineering, and wearable biomedical devices.

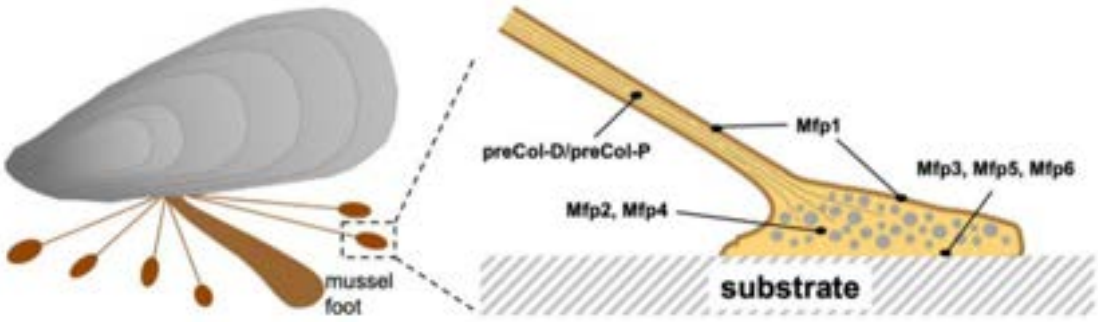

Figure 1 – The mussel byssus and foot proteins. Taken from the permission of (5).

References

[1] The molecular mechanisms underlying mussel adhesion. Cao, Yiran Li and Yi. 11, 2019, Nanoscalte Advances, págs. 4246-4257.

[2] Improving Martini 3 for Disordered and Multidomain Proteins. F. Emil Thomasen, Francesco Pesce, Mette Ahrensback Roesgaard, Giulio Tesei, and Kresten Lindorff-Larsen. 4, s.l. : Journal of Chemical Theory and Computation, Vol. 18.

[3] Polymer Adhesion: Seeking New Solutions for an Old Problem. Raos, Guido and Zappone, Bruno. 23, s.l. : Macromolecules, 2021, Vol. 54.

[4] Hydrogen-bonds mediate liquid-liquid phase separation of mussel derived adhesive peptides. Qi Guo, Guijin Zou, Xuliang Qian, Shujun Chen, Huajian Gao & Jing Yu. 2022, Nature Communications, Vol. 3, pág. 5771.

[5] Marine-inspired polymers in medical adhesion. Diederik W.R. Balkenende, Sally M. Winkler, and Phillip B. Messersmith. 2019, European Polymer Journal, Vol. 116, págs. 134-143.

Relationship Between Optical and Structural Properties of Nitrogen-doped Carbon Dots.

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Carbon Dots (CDs) are a novel class of luminescent carbon-based nanomaterials that have attracted increasing attention due to their unique photoluminescent properties, low toxicity, chemical stability, and biocompatibility. Typically quasi-zero-dimensional, these nanoparticles exhibit a hybrid sp^2/sp^3 carbon core and a surface enriched with oxygen- or nitrogen-containing functional groups, offering great potential for applications ranging from bioimaging to optoelectronics.

In this study, we present a combined experimental and theoretical investigation of nitrogen-doped CDs synthesized from citric acid and urea in a 1:1 molar ratio.
The optical properties were characterized via UV-Vis absorption, steady-state photoluminescence, and time-resolved photoluminescence measurements.

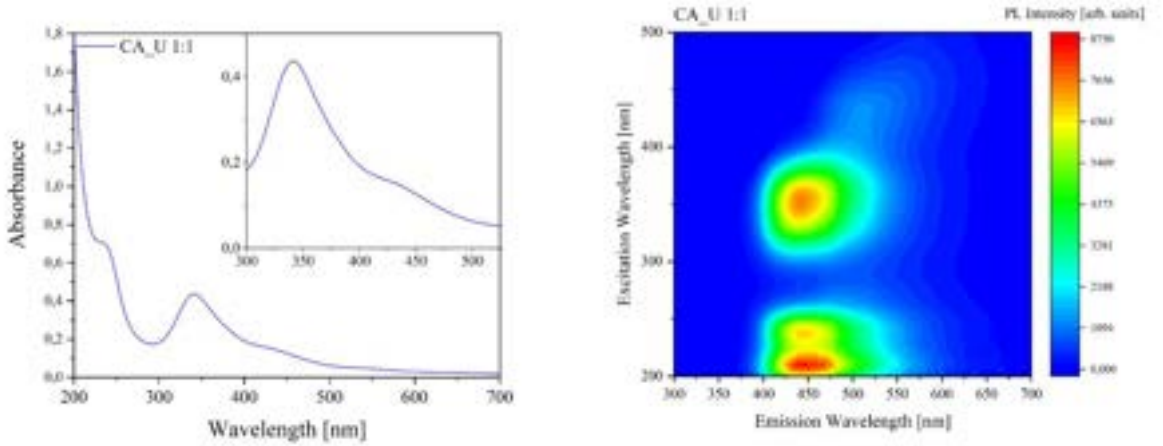

Figure 1 – UV-Vis optical characterization of the CDs obtained from citric acid and urea precursors with a 1:1 molar ratio**.**

To complement the experimental findings, molecular dynamics simulations were performed using GROMACS 2023.4 on the LUMI supercomputer. Two representative CD models were constructed: a pure CD functionalized with hydroxyl groups, and a nitrogen-doped CD featuring surface amine groups and graphitic nitrogen, simulating the 1:1 synthesis ratio. Structural characterization was carried out by analyzing the density distribution and the radius of gyration. The layer density distribution was measured to determine the distance between layers, and the radius of gyration was used to study the evolution of the system's compactness.
We further explored the interaction between these CD models and key fluorophores such as citrazinic acid, citrazinic acid amine and citrazinic acid amine amide. This multiscale approach offers insights into the structural and photophysical behavior of CDs, shedding light on the role of nitrogen doping and functional surface groups in tuning their emission properties.

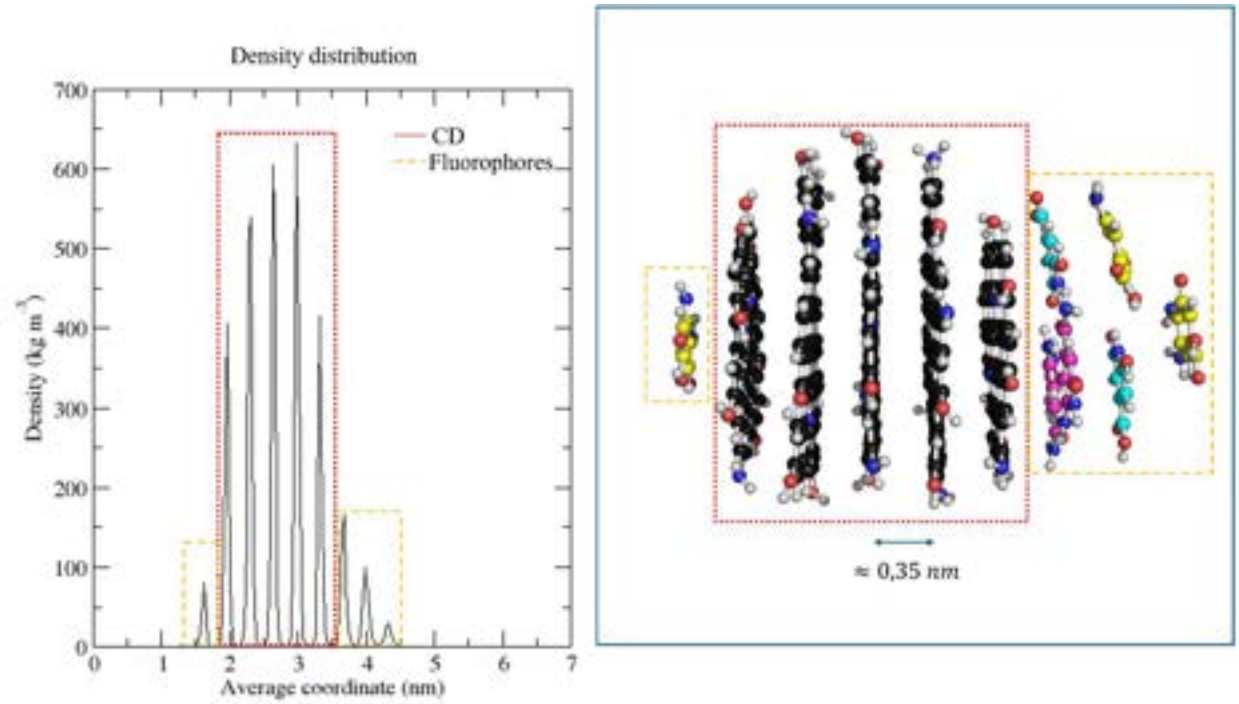

Figure 1 – Plot of the layer density distribution of the nitrogen-doped CD with amine groups on the surface along with the fluorophores citrazinic acid-like

Molecular Dynamics Investigation of Lignin Behavior in Deep Eutectic Solvents

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Human activities have increased greenhouse gas emissions, accelerated global warming, and intensified pollution, while non-renewable natural resources are rapidly depleting. Environmental degradation and the depletion of natural resources require an urgent shift towards sustainable solutions aligned with nature's principles. In this context, biomass stands out as a key renewable resource capable of replacing fossil resources in the production of energy, materials and chemicals [1-2].

Lignin, a major component of lignocellulosic biomass, is the second most abundant biopolymer after cellulose on Earth, and it is the one that provides rigidity and protects the plants. In chemical aspects, lignin is composed of three main types of phenylpropanoid units: p-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol. These monomers are interconnected by ether and carbon-carbon bonds in a complex and heterogeneous 3-dimensional network that has limited efficient utilization, despite the huge potential for sustainable pharmaceutical and chemical applications. Conventional extraction methods, such as sulfate and sulfite processes, are energy-intensive and polluting, requiring environmentally friendly alternatives [1-2]. Given these circumstances, deep eutectic solvents (DESs) are emerging as a promising environmental solution. They are usually composed of a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA), which interact extensively through hydrogen bonds, resulting in a eutectic mixture with a markedly decreased melting point compared to that of the pure components. Due to their excellent solubilization properties, low toxicity and the possibility to be obtained from renewable sources, DES are increasingly used in biomass processes. For the efficient valorization of lignin, DESs, in particular those based on choline chloride (ChCl) and lactic acid (LA), represent a promising option due to their ability to disrupt hydrogen bonding networks and facilitate the cleavage of ether linkages and C–C bonds [1,3].

However, DESs are complex molecular systems, and their optimization requires a deep understanding of their dissolution mechanisms. Molecular dynamics (MD) simulations serve a crucial role in investigating lignin-DES interactions at the atomic level, enabling rapid screening, reducing experimental failures and the development of novel solvents [3].

The present study employs MD simulations to investigate the interactions between ChCl:LA DES at different concentrations and lignin dimers and trimers, in order to grasp the molecular behaviors underlying lignin dissolution. Simulations show that the hydrogen bond network within DES, in particular the interactions between the HBA and lignin functional groups, play a key role in lignin solubilization. The LA preferentially forms hydrogen bonds with the γ-OH groups of lignin, and a higher concentration of this component suggests a more efficient dissolution of lignin.

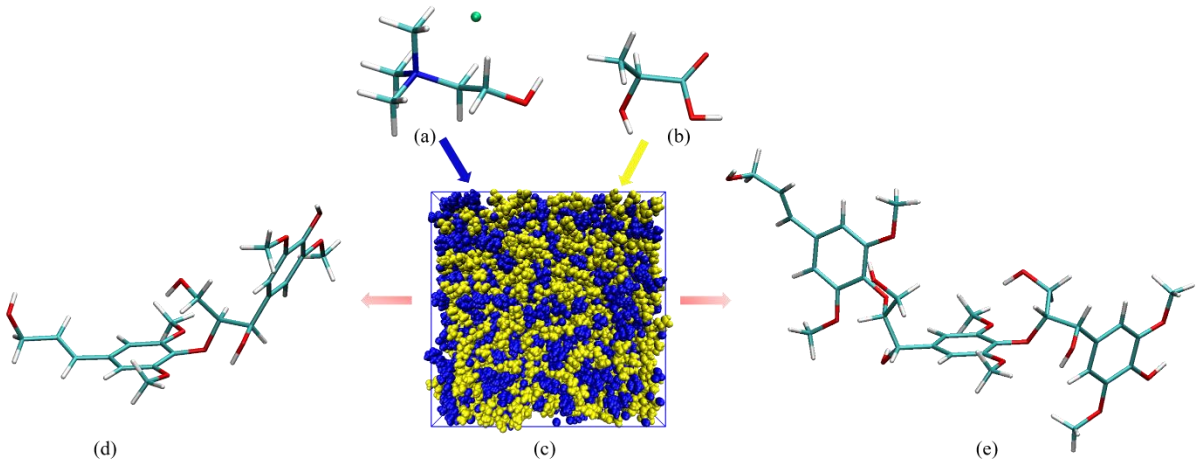

Figure 1 – Molecular structures used in this study: choline chloride (a), lactic acid (b), simulation box containing the deep eutectic solvent (c), and model lignin compounds – dimer (d) and trimer (e).

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This work is supported by European Union's Horizon Europe research and innovation programme under grant agreement No 101086667, project BioMat4CAST (BioMat4CAST - "Petru Poni" Institute of Macromolecular Chemistry Multi-Scale In Silico Laboratory for Complex and Smart Biomaterials).

REFERENCES

[1] Guo Y., Xu L., Shen F., Hu J., Huang M., He J., Zhang Y., Deng S., Li Q., Tian D., (2022) "Insights into lignocellulosic waste fractionation for lignin nanospheres fabrication using acidic/alkaline deep eutectic solvents". *Chemosphere*, 286, 131798. DOI https://doi.org/10.1016/j.chemosphere.2021.131798

[2] Chen H., Wang A., Yan C., Liu S., Li L., Wu Q., Liu Y., Liu Y., Nie G., Nie S, Yao S., Yu H., (2023) "Study on the solubility of industrial lignin in choline chloride-based deep eutectic solvents". *Sustainability*, 15, 7118. DOI https://doi.org/10.3390/su15097118

[3] Pan X., Liu Y., Ma Z., Qin Y., Lu X., Feng X., Shao Q., Zhu Y., (2024) "Molecular insight into the mechanism of lignin dissolution in acid choline chloride–based deep eutectic solvents". *Journal of Molecular Liquids*, 406, 125123. DOI https://doi.org/10.1016/j.molliq.2024.125123.

Integration Of Scattering Data Into Molecular Dynamics Via On-the-fly Structure Factor Refinement

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Molecular Dynamics (MD) simulations are widely used to explore the structural and dynamical properties of molecular systems. However, inaccuracies in the force fields and inadequate sampling of the phase space often limit their accuracy in reproducing real-world structures. The introduction of direct constraints from experimental data would enhance the usefulness of MD simulations as a tool to interpret those data, especially on complex materials such as ionic liquids.

To bridge this gap, a method is being developed to incorporate scattering data (X-ray, neutron, or both) directly into MD simulations. Inspired by the Empirical Potential Structure Refinement (EPSR) approach [1]—which employs reverse Monte Carlo techniques to refine structural models against experimental data—our method aims to retain the temporal evolution of the system, a key limitation in EPSR. To achieve this, we introduce an additional biasing term into the MD potential, which generates fictitious forces that guide the system toward configurations consistent with the experimental structure factor.

The first step involves implementing the on-the-fly calculation of radial distribution functions (RDFs) at each MD timestep for water boxes of increasing size. An alternative strategy involves the direct calculation of the structure factor [2]. These methods are being implemented and tested within the Tinker [3] molecular dynamics package, selected for its simplicity and ease of customization.

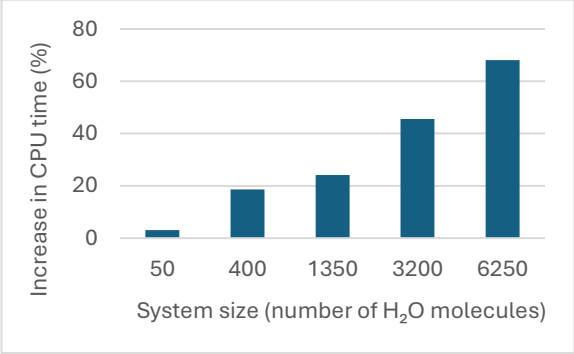

Figure 1 – Increase in computational cost due to the on-the-fly calculation of the H–H radial distribution function

REFERENCES

[1] Soper, A. K. (2001). Tests of the empirical potential structure refinement method and a new method of application to neutron diffraction data on water. Molecular Physics, 99(17), 1503–1516
[2] Liu, H.; Paddison, S. J. Direct Calculation of the X-Ray Structure Factor of Ionic Liquids. Phys. Chem. Chem. Phys. 2016, 18 (16), 11000–11007.
[3] Rackers, J.A. et al. (2018) 'Tinker 8: Software tools for molecular design', Journal of Chemical Theory and Computation, 14(10), 5273–5289.

Comparative Molecular Dynamics Simulations of Human Telomeric G-Quadruplexes: Evaluating Ligand-Induced Stabilization of Parallel and hybrid Topologies

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DNA in the cell nucleus is mostly found in a double helix shape. However, there are also other secondary structures, like G-quadruplexes, which are very important for biological functions. G-quadruplexes (G4s) are involved in controlling gene activity and in DNA replication. One way to stabilize the formation of G-quadruplexes is by introducing ligands that can bind to G4s and help keep their structure stable.

In a previous study, we investigated the effect of a porphyrin-based ligand 4-[2-[10,15,20-tris[1-(2-amino-2-oxoethyl)pyridin-1-ium-4-yl]-21,24-dihydroporphyrin-5-yl] pyridin-1-ium-1-yl]acetamide (p11b), on the stability of the human telomeric G4 structure with parallel topology (PDB: 1KF1, sequence: 5(AGGGTTAGGGTTAGGGTTAGGG)-3), using molecular dynamics (MD) simulations. The results from the simulations with 1KF1 showed that the G-quadruplex without the ligand has a greater tendency to unfold compared to the system in the presence of the ligand [1].

In this study, we extend our analysis to another topology of the human telomeric G-quadruplex structure, focusing on the hybrid topology adopted in the PDB structure 143D, which has the same sequence of 1KF1. The objective is to verify whether the system is stabilized or destabilized in the presence of the ligand. MD simulations were performed using the OL15 [2] force field for the DNA and GAFF [3] for the ligand, with solvation modeled using the SPCE water model.

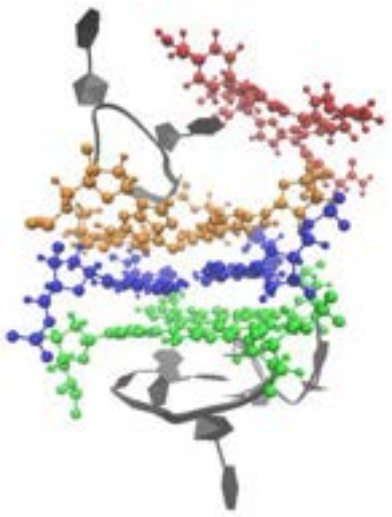

Figure 1 – Graphical representation of 143D with ligand using a different color for each loop and tetrad (Color code: first quartet, orange; second quartet, blue; third quartet, green; loops, grey.)

Simulations were conducted at both room temperature (300 K) and elevated temperatures (500 K, 525 K, and 550 K), maintaining constant pressure and temperature (NPT ensemble) at room temperature and constant volume and temperature (NVT ensemble) at high temperatures. The purpose of the high-temperature simulations was to determine the stabilizing or destabilizing effects of the ligand: if the complex's denaturation temperature is higher than that of the G4 alone, the ligand is considered to stabilize the G4; if lower, it implies a destabilizing effect [4,5,6]. RMSD analyses over simulation time were used to monitor structural integrity and detect denaturation events.

Preliminary results suggest that the ligand stabilizes the parallel topology but not the hybrid topology. These findings partially align with experimental observations (manuscript in preparation), which indicate a destabilizing effect of this ligand on the hybrid G-quadruplex.

REFERENCES

[1] Satta G., Trajkovski M., Cantara A., Mura M., Meloni C., Olla G., Dobrovolná M., Pisano L., Gaspa S., Salis A., De Luca L., Mocci F., Brazda V., Plavec J. and Carraro M. (2024) "Complex Biophysical and Computational Analyses of G-Quadruplex Ligands: The Porphyrin Stacks Back". Chemistry – A European Journal, 30(69), e202402600. 10.1002/chem.202402600.

[2] Zgarbová M., Šponer J., Otyepka M., Cheatham T. E., Galindo-Murillo R. and Jurečka P. (2015) "Refinement of the Sugar-Phosphate Backbone Torsion Beta for AMBER Force Fields Improves the Description of Z- and B-DNA". Journal of Chemical Theory and Computation, 11(5), 1487-1499. 10.1021/acs.jctc.5b00716.

[3] Wang J., Wolf R. M., Caldwell J. W., Kollman P. A. and Case D. A. (2004) "Development and testing of a general amber force field". Journal of Computational Chemistry, 25(9), 1157-1174. 10.1002/jcc.20035.

[4] Todde G., Hovmöller S., Laaksonen A. and Mocci F. (2014) "Glucose oxidase from Penicillium amagasakiense: characterization of the transition state of its denaturation from molecular dynamics simulations". *Proteins*, 82(10), 2353. 10.1002/prot.24596.

[5] R. Day, B. J Bennion, S. Ham, V. Daggett (2002) "Increasing temperature accelerates protein unfolding without changing the pathway of unfolding". *J Mol Biol*, 322, 189. 10.1016/s0022-2836(02)00672-1.

[6] Mulliri S., Laaksonen A., Spanu P., Farris R., Farci M., Mingoia F., Roviello G.N. and Mocci F. (2021) "Spectroscopic and In Silico Studies on the Interaction of Substituted Pyrazolo[1,2-a]benzo[1,2,3,4]tetrazine-3-one Derivatives with c-Myc G4-DNA". International Journal of Molecular Sciences, 22(11), 6028. https://doi.org/10.3390/ijms22116028

Towards the formation of biofuel precursors by heterogeneous catalysis: The case of aldol condensation on Ru metal.

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The challenges of depleting fossil fuel reserves and their impacts on the environment have inspired substantial research into the efficient production of renewable biomass fuels and chemicals over the past decade.

An emerging strategy for biomass production is the formation of C-C bond by heterogeneous catalysis of aldol condensation of bio-based target molecules such as acetone, furfural and 5-hydroxymethylfurfural (HMF).[1] This approach can produce larger organic compounds such as the C13 furanic adduct 1,5-di-2-furanyl-1,4-pentadien-3-one (referred to as: FAF) , which can be transformed to high-quality diesel fuels by further hydrogenation.[2] However, the molecular level understanding of the reaction mechanisms at the catalysts for the selective production of diesel is still scarce.[3] For remediation, we treat the reaction of formation of FAF through aldol condensation on the most stable phase (0001) of Ru-based catalysts, targeting thus understanding the reaction mechanism for the large hydrocarbon production.[4]

Gas phase computations showed that there are 30 different possible conformations of FAF molecules. However, when these molecules were impregnated on to the Ru(0001) surface, they are found to stabilize through FAF O-Ru (Ru(0001)), and FAF C-Ru (Ru(0001)) bonding with very few varietry of conformations (i.e., parallel, tilted, parallel+vertical and diagonal conformers) in contrast to the gas phase data. We show that this is due to the chemical adsorption of these FAF conformers on the Ru active sites of the Ru(0001) slab and the subsequent electron and charge transfer induced on adsorbed FAFs.

The calculated lowest interaction distances between the FAF O-Ru (Ru(0001)) and FAF C-Ru (Ru(0001)) vary from 2.01 Å to 2.54 Å and 2.10 Å to 2.22 Å, respectively. In addition, the total energies of these 30 different FAF at the Ru-slab clearly show that several FAF confromers exhibit similar patterns and also strongly stabilized via the above-mentioned chemical bonding with the metal slab.
This screening allowed us to identify the most stable configuration of the FAF@Ru slab among the 30 possible conformers (identified from the gas phase). This screening not only reduces the computational costs but also significantly drop the activation energies, i.e. energy requirements, for the production of longer-chain hydrocarbons. Besides, the Neuged elastic-band calculations will be carried out to examine the in-depth reaction mechanism.

In particular, we are looking to determine the kinetically determining step. Also, machine learning methods will be used to find the activity relationship between the major intermediate and the Ru catalyst by using the accuracy plot of the regularized Model. Obviously, this goes through the identification of the corresponding transition states and reaction barriers on Ru metal and products. Our work will suggest the most prominent catalyst for the efficient bio-fuel production with less energy barrier and cost.

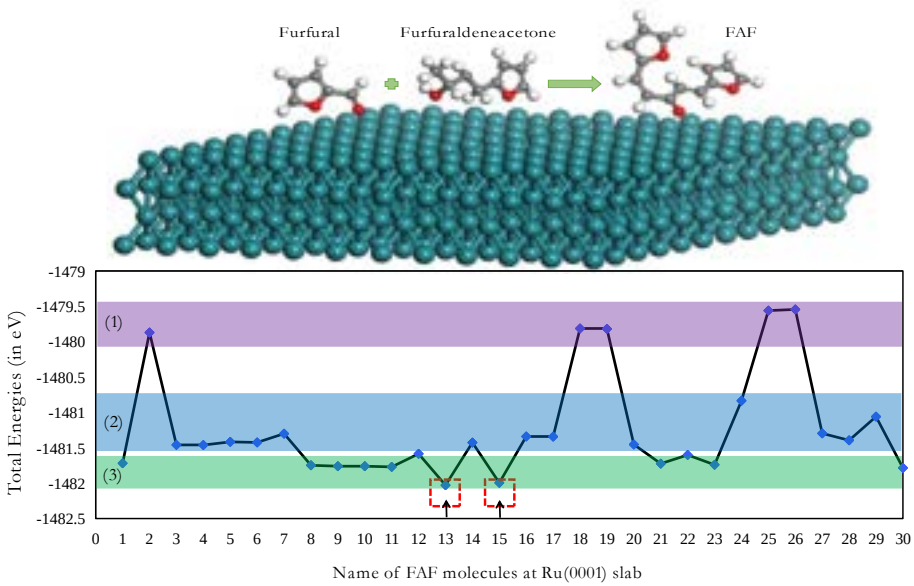

Figure 1 – Biomass production at the Ru metal surface

REFERENCES

[1] X. Kong, X. Wei, L. Li, Z. Fang, H. Lei, Production of liquid fuel intermediates from furfural via aldol condensation over La2O2CO3-ZnO-Al2O3 catalyst, Catalysis Communications, 149, 106207. 10.1016/j.catcom.2020.106207

[2] V. Korolova, O. Kikhtyanin, E. Grechman, V. Russo, J. Warna, D. Y. Murzin. D. Kubicka, Kinetics of furfural aldol condensation with acetone, Catalysis Today, 423, 114272.10.1016/j.cattod.2023.114272

[3] E. F. William, B. K. Tomas, B. Jonas, Catalytic conversion of ethanol to 1,3-butadiene on MgO: A comprehensive mechanism elucidation using DFT calculations, Journal of Catalysis, 346, 78-91. 10.1016/j.jcat.2016.11.042

[4] M. M. Kauppinen, E. N. Słap, J. L. G. Escobedo, R. L. Puurunen, K. Honkala, Computational insight into the selectivity of γ-valerolactone hydrodeoxygenation over Rh(111) and Ru(0001), 751, 122624.10.1016/j.gee.2024.05.004

Water Confined In Ionic Liquid Matrices – Insight From A ^{1}H Experimental And QM/MD Study

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Room-temperature ionic liquids are organic salts that remain liquid at or near room temperature and are widely studied due to their low vapor pressure, high conductivity, thermal stability, and excellent solvent properties. Their versatility stems from the vast range of possible cation-anion combinations, allowing for tailored applications. However, pure ionic liquids are rarely used, as they are highly hygroscopic and readily absorb moisture from the air. To enhance their properties, they are often mixed with conventional solvents, highlighting the importance of understanding how molecular solvents influence their behavior.

In this study, we investigated the structural and spectroscopic properties of 1-butyl-3-methylimidazolium chloride ([C4mim][Cl]) and its mixtures with water at varying concentrations. Experimental ^{1}H NMR spectroscopy revealed a non-monotonic dependence of water proton chemical shifts on water content in the mixture. To explain this phenomenon, we applied an integrated approach combining classical molecular dynamics (MD) simulations with quantum mechanics/molecular mechanics (QM/MM) calculations based on density functional theory.

An integrated approach based on molecular dynamics simulations and combined quantum mechanics/molecular mechanics models has proven to be a powerful technique for accurate predictions of electronic properties of extensive molecular systems. MD simulation protocols are employed to sample the phase space of molecular system of interest. Then, QM/MM calculations of electronic properties are performed where the central part of the system is described by an electronic structure method and the rest of the system is described by the static multipole distribution.

Our results showed that the increasing chemical shift of water at low water concentrations is driven by the formation of strong hydrogen bonds between chloride anions and water molecules. The proliferation of these strongly hydrogen-bonded complexes explains the elevated chemical shifts observed when the water molar fraction in the mixture is low. As the water content increases, the prevalence of such complexes decreases, resulting in lower chemical shifts. Moreover, water molecules not directly interacting with chloride anions—i.e., those trapped within the ionic liquid matrix—exhibit significantly lower shifts compared to those in pure water. The simulated ^{1}H NMR spectrum of neat [C4mim][Cl] showed good agreement with the experimental data (Fig. 1). [1]

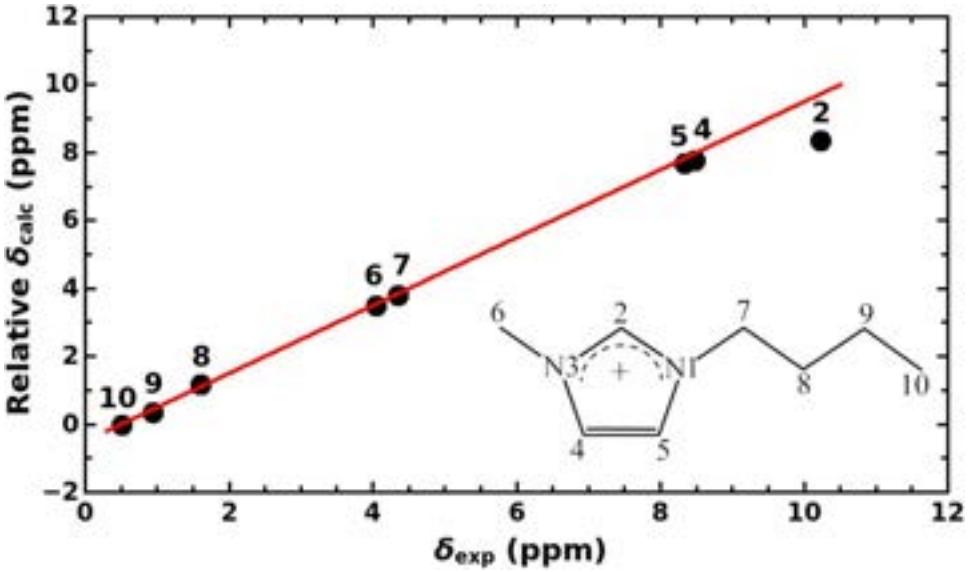

Figure 1 – Calculated relative versus experimental ^{1}H NMR spectrum of neat [C4mim][Cl] IL at 298 K. The unit line is drawn to facilitate the comparison between calculated and measured chemical shifts: points above the unit line indicate the overestimated chemical shift and vice versa. Atom numbering in the C4mim^{+} cation is included as an inset.

REFERENCES

[1] Lengvinaite D., Kvedaraviciute S., Bielskute S., Klimavicius V., Balevicius V., Mocci F., Laaksonen A., Aidas K., (2021) "Structural Features of the [C4mim][Cl] Ionic Liquid and Its Mixtures with Water: Insight from a ^{1}H NMR Experimental and QM/MD Study". *The Journal of Physical Chemistry B*, 48, 13255–13266. https://doi.org/10.1021/acs.jpcb.1c08215.

Effects of UV exposure on polyvinyl alcohol solutions: optical birefringence and LC alignment in cast and mechanically modified films

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New method, based on physical processes, to modify the PVA thin films to control the Liquid Crystals (LCs) orientation is proposed. The concept is that using UV irradiation of PVA solutions followed by mechanically modification of the obtained film the optical anisotropy, adhesion and alignment of LCs will be enhanced. Our previous studies reveal that PVA thin foils with improved anisotropy, without deteriorated physical and chemical properties are obtained when the PVA aqueous solutions were MW [1] or UV irradiated. Fine or deeper grooves/striations appeared along the stretching direction [2], the films become unidirectionally anisotropic [3] and the adhesion and alignment of LCs are improved.

In this study, the films obtained from 10- and 20-minutes UV irradiated PVA solutions were modified by different new strategies including rubbing, stretching, and scratching with sandpaper. The mechanical modification of PVA films was realized through 3 different approaches: 1. Stretching; 2. Rubbing followed by stretching; 3. Scratching of surface followed by parallel stretching. For the stretching procedure, the polymer film was subjected to a controlled tensile force, at an elevated temperature of 42-45 ^{0}C, to elongate it along one axe. This process aligns the polymer chains in the direction of acting force, enhancing the structural order, optical anisotropy, and surface characteristics of the films [3]. Stretching degree was expressed as the ratio of the semi axes of an ellipse in which a circle drawn on the polymer foil degenerates. The rubbing was performed prior fully drying of samples in one single direction and one single turn with a rigid tooth network like a hair comb [4]. The surface of the polymer films was scratched with low roughness sandpaper. A single turn scratching was performed with a speed of 3 mm/s , keeping a constant contact with the surface of polymer. This new rubbing method, combined with scratching with sandpaper and stretching of PVA films, constitutes a novel and original preparation procedure of alignment layers (Als) for LCs.

The results were evidenced by using ATR-FTIR spectra analysis, contact angle measurements, optical microscopy images, and induced optical birefringence measurements using polarization ellipse method [5]. The adhesion and cohesion interactions between the modified surface of PVA and LCs was evaluated using contact angle technique. Polarized optical microscopy was used to evidence the orientation of LC at the surface of modified PVA films. Parameters as exposure time, stretching degree and roughness of the sandpaper were discussed regarding the used approach to achieve optimal orientation of nematic molecules at the surface of PVA for LC biosensor applications.

The effects of stretching and rubbing processes on the films obtained from UV exposure of PVA solutions were discussed in terms of induced optical birefringence, surface polarity, free energy of hydration and surface morphology. The alignment of LC molecules was analysed, and the contribution of UV exposure and the modification strategy on LC behaviour was considered.

The interplay between UV exposure time and stretching degree reflects how chain structure develops. 10 minutes of UV exposure enhances chain order via intramolecular H-bonding, optimizing birefringence at moderate stretch, $\gamma = 1.5$. At higher stretching degree, $\gamma = 2$, the structure may be overstretched, losing some advantage. Crosslinking appeared for 20 minutes irradiated sample creates stiff films. At $\gamma = 1.5$, this rigidity limits alignment, but at $\gamma = 2$, the crosslinks sustain alignment under greater strain, overtaking the 10-minute sample. These results suggest that short time UV exposure of PVA aqueous solution (10 minutes), where the intramolecular H-bonds dominate, enhance optical birefringence only for moderate stretch, where order can be preserved. Long term UV exposure (20 minutes), where crosslinking appears, and the polymer matrix is more structured can be used to obtain films with high anisotropy when these are elongated for higher stretching degree.

Rubbing and scratching procedure of UV exposed samples decreased the polarity for $\gamma = 2$ and increased it for $\gamma = 3$.

The proposed method to pattern the surface of PVA substrate modify the surface morphology. Relatively uniform microgrooves or striations appeared along the direction of the applied force. The deepness and the distance between the formed structures depend by the applied procedure. Stretching the films after patterning process induced an orientation of the polymer chains along the bdirection of deformation force proved by the thinning of the microgrooves, and by the smoothing of the surface with stretching degree. The contrast between bright and dark states revealed that rubbing before complete drying and scratching with sand paper of polymer surface can improve the uniformity of LCs orientation. Further stretching of scratched PVA films creates additional surface anisotropy, and this improves LC orientation, when stretching degree is increased from 2 to 3.

REFERENCES

[1] Nechifor C.-D., Aflori M., Dorohoi D.-O., (2019), "Anisotropy of Thin Foils Obtained from Microwave-Irradiated Poly(Vinyl Alcohol) Aqueous Solutions",*Polymers* 11: 1072-1084. 10.3390/polym11061072

[2] Barzic A. I., Albu R. M., Stoica I., Nechifor C.-D., Avadanei M. I., Dimitriu D. G., Dorohoi D.- O., (2023), "Birefringent polyvinyl alcohol layers as retardation components for display devices", *Polym. Adv. Technol*. 35: 1-11. https://doi.org/10.1002/pat.6196

[3] Ward, I.M. (1997) Structure and Properties of Oriented Polymers. 2nd Edition, Chapman and Hall, London. https://doi.org/10.1007/978-94-011-5844-2

[4] Nechifor C.-D., Postolache M., Albu R. M., Barzic A. I., Dorohoi D.-O., (2019), "Induced birefringence of rubbed and stretched polyvinyl alcohol foils as alignment layers for nematic molecules", *Polym. Adv. Technol*. 30 2143–2152. https://doi.org/10.1002/pat.4647

[5] Postolache M., Dimitriu D. G., Nechifor C.- D., Condurache Bota S., Cloșca V., Dorohoi D.- O., (2022), "Birefringence of Thin Uniaxial Polymer Films Estimated Using the Light Polarization Ellipse" *Polymers* 14 1063-1074. 10.3390/polym14051063

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Reactive collisions between electrons and cations at extreme energy

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The Multichannel Quantum Defect Theory (MQDT) has been employed in computing cross sections and Maxwell rate coefficients for electron-driven reactions involving molecular cations. The provided collisional data are useful in the kinetics modeling of cold plasma physics and of various cold ionized media of fundamental and applied interest. Rotational and vibrational transitions and dissociative recombination rate coefficients, an extension of our previous studies [1-2] and outline several important features, like isotopic and resonant effects are presented for H2+ , HD+ and D2+.

For the fusion plasma edge, cross sections and rate coefficients have been produced for BeH+ [4,7], BeD+ [5] and BeT+ [6] cations suitable for the modeling of the kinetics in fusion plasmas, in devices with beryllium based main chamber materials, such as ITER and JET. The isotopic effects demonstrate the quasi-independence of the rate coefficients on the isotopologues, if they are represented with respect to the vibrational energy of the target, at a given electron temperature. The energy of the incident electron is below and above the dissociative threshold, 2.7eV.

REFERENCES

[1] O. Motapon N. Pop, F. Argoubi, J. Zs Mezei, M. D. Epee Epee, A. Faure, M. Telmini, J. Tennyson, and I. F. Schneider (2014), "Rotational transitions induced by collisions of HD+ ions with low-energy electrons" *Phys. Rev. A* 90, 012706.

[2] M. D. Epée, J. Zs Mezei, O. Motapon, N. Pop, I. F. Schneider, (2016), "Reactive collisions of very low-energy electrons with H2+: rotational transitions and dissociative recombination", *MONTHLY NOTICES OF THE ROYAL ASTRONOMICAL SOCIETY*, 455, 27

[3] M. D. Epee´ Epee, O. Motapon ; Pop N.; Iacob F ; Roueff E ; Schneider IF; Mezei JZ, (2022). " Dissociative recombination and rotational transitions of D_2^+ in collisions with slow electrons", *MONTHLY NOTICES OF THE ROYAL ASTRONOMICAL SOCIETY*, 512, 424–429

[4] S.Niyonzima, S.Ilie, Pop N., J.Zs.Mezei, K.Chakrabarti,V.Morel,B.Peres,D.A.Little,K.Hassouni, Å.Larson, A.E.Orel, D.Benredjem, A.Bultel, J.Tennyson, D.Reiterl, I.F.Schneider, (2017), "Low-energy collisions between electrons and BeH^+ in the edge of fusion plasmas: cross sections and rate coeffcients for all the vibrational states of the ion", *Atomic Data and Nuclear Data Table*, 115-116, 287-308

[5] S Niyonzima, Pop N., F Iacob, Å Larson, A E Orel, J Zs Mezei, K Chakrabarti, V Laporta , K Hassouni, D Benredjem, A Bultel, J Tennyson , D Reiter ,I F Schneider, (2018), "Low-energy collisions between electrons and BeD "*Plasma Sources Sci. Technol.* 27, 025015

[6] N. Pop, Iacob F ; Niyonzima S; Abdoulanziz A; Laporta, V; Reiter D ; Schneider IF; Mezei, JZ (2021)., "Reactive collisions between electrons and BeT+: Complete set of thermal rate coefficients up to 5000 K" *Atomic Data and Nuclear Data Table*, 139, 101414

[7] E. Djuissi,, J. Boffelli, R.Hassaine,, N.Pop, V. Laporta, K. Chakrabarti, M.Ayouz , A.d Bultel, J. Zs. Mezei, and I. F. Schneider (2024), "Reactive collisions between electrons and BeH+ above dissociation threshold" *Phys. Chem. Chem. Phys*., 26, 18311-18320.

Computational Study of a Human Papilloma Virus G-Quadruplex

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Human Papillomaviruses' (HPVs) are among the most common sexually transmitted infections and are associated with the development of head and neck, skin and anogenital cancer, including cervical cancer, which remains one of the most significant global health challenges [1].

In this study we investigate the stability of a G-Quadruplex present in HPV type 52, a strain frequently detected in patients with vaginal cancers and precancerous lesions [2]. The aim is to identify molecules capable of stabilizing this G-quadruplex conformation in viral DNA, thereby inhibiting replication and paving the way for novel antiviral therapeutic strategies.

G-quadruplex (G4) are DNA structures stabilized by eight Hoogsteen hydrogen bonds between G-quartet-forming base, by coordinated metal ions in the central cavity of the G-quadruplex structure and through the ordered stacking of coplanarly aligned aromatic moieties. They play a significant role in various cellular processes and show high potential for application. G-quadruplexes' formation in the promoters of several genes has been demonstrated to affect their expression and indicates that G-quadruplexes can act as transcriptional regulators [1] and, for this reason, they are considered promising targets for drug development [3].

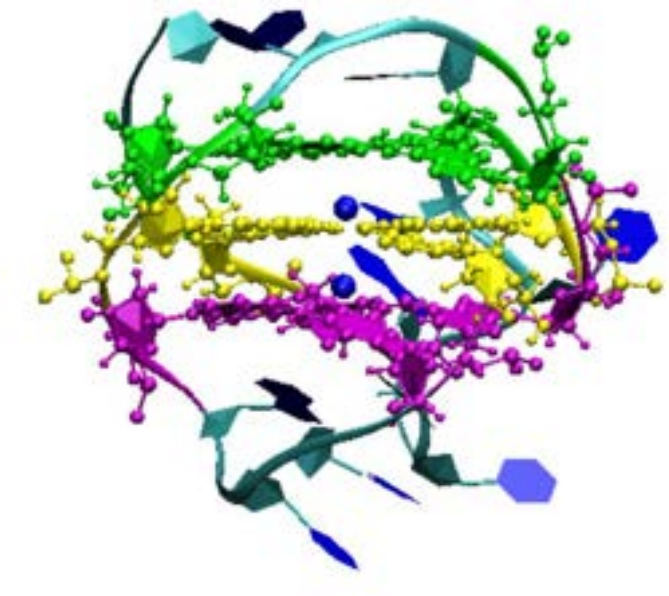

Figure 1 – Graphical representation of 5O4D with two sodium ions (blue) in the channel. 5O4D features three tetrads (colored from top to bottom in green, yellow and magenta) and three loops.

The three-dimensional G4 structure we use in this study was retrieved from RCSB Protein Data Bank (DNA PDB 5O4D). We have selected one of the 10 different conformations it contains proceeding to evaluate its stability through molecular dynamics methods. In order to compare the stabilizing effect on structural stability of potassium ions, previously studied [4], with sodium ions, we use the latter ion in this simulation.

The simulated system comprises a G4 structure, modeled with the OL15 force field, immersed in a 150 mM NaCl aqueous solution, using the SPC/E water model and the Joung and Cheatham parameters for the ions. Two ions were manually added in the core channel of HPV G4 (Figure 1). We plan to extend the study by also employing different force fields to compare the results obtained.

After the creation of the simulation box, the system was equilibrated with two energy minimization runs, followed by six runs of Molecular Dynamics (MD) of 10ns length, imposing restraints on the G4 and channel ions, of decreasing strength, until complete removal in the last run. The Production Phase was of 1 μs length at 300K (constant temperature) with no restraints. We analyzed the results evaluating Root Mean Square Deviation of the quadruplex during the MD trajectories and found that the HPV G4 is very stable at 300 K, reaching its equilibrium and stability at 300K.

As a future goal, we aim to run more MDs at higher temperatures to better evaluate G4 stability with and without a ligand. Employing temperatures higher than those typically used in experimental settings

has proven effective in accelerating the denaturation process, allowing it to occur within the timescales accessible to MD simulations [3,4,5]. Previous research has shown that such temperature increases do not affect the overall denaturation pathway [5].

This study is part of the development of new strategies to target viruses, by the rational design of G-quadruplex-targeting molecules capable of stabilizing the G4 structure.

REFERENCES

[1] Tlučková, K.; Marušič, M.; Tóthová, P.; Bauer, L.; Šket, P.; Plavec, J.; Viglasky, V. Human Papillomavirus G-Quadruplexes. *Biochemistry* **2013**, *52* (41), 7207–7216. https://doi.org/10.1021/bi400897g.

[2] Wang, M.; Liang, H.; Yan, Y.; Bian, R.; Huang, W.; Zhang, X.; Nie, J. Distribution of HPV Types among Women with HPV-Related Diseases and Exploration of Lineages and Variants of HPV 52 and 58 among HPV-Infected Patients in China: A Systematic Literature Review. *Human Vaccines & Immunotherapeutics* **2024**, *20* (1), 2343192. https://doi.org/10.1080/21645515.2024.2343192.

[3] Mulliri, S.; Laaksonen, A.; Spanu, P.; Farris, R.; Farci, M.; Mingoia, F.; Roviello, G. N.; Mocci, F. Spectroscopic and In Silico Studies on the Interaction of Substituted Pyrazolo[1,2-a]Benzo[1,2,3,4]Tetrazine-3-One Derivatives with c-Myc G4-DNA. *International Journal of Molecular Sciences* **2021**, *22* (11), 6028. https://doi.org/10.3390/ijms22116028.

[4] Orrù M.; "Studio Computazionale Di Un G-Quadruplex Virale e Delle Sue Interazioni Con Potenziali Ligandi"; Bachelor thesis; University of Cagliari, 2021/2022; Relator: Mocci F.

[5] Satta, G.; Trajkovski, M.; Cantara, A.; Mura, M.; Meloni, C.; Olla, G.; Dobrovolná, M.; Pisano, L.; Gaspa, S.; Salis, A.; De Luca, L.; Mocci, F.; Brazda, V.; Plavec, J.; Carraro, M. Complex Biophysical and Computational Analyses of G-Quadruplex Ligands: The Porphyrin Stacks Back. *Chemistry – A European Journal* **2024**, *30* (69), e202402600. https://doi.org/10.1002/chem.202402600.

Evaluating Bis-Acridine Orange Dyes for DNA Detection via Umbrella Sampling and qPCR Analysis

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This study explores the interaction between double-stranded DNA (dsDNA) and a newly developed series of dyes (BAO), composed of two acridine orange (AO) units linked by varying molecular connectors.

Understanding these interactions is essential, as environmental factors—particularly confinement within molecular grooves or pockets—affect the conformational flexibility and properties of the dyes. Biochemical assays revealed that BAO dyes outperform the commonly used Eva Green (EG) in qPCR applications.

Molecular dynamics simulations further demonstrated that the dyes adopt diverse conformations within DNA grooves, with the nature of the linker playing a key role in modulating fluorescence behavior.

These results emphasize the value of molecular modeling in the rational design of functional molecules and highlight the promise of BAO dyes for enhanced DNA detection in biochemical contexts.

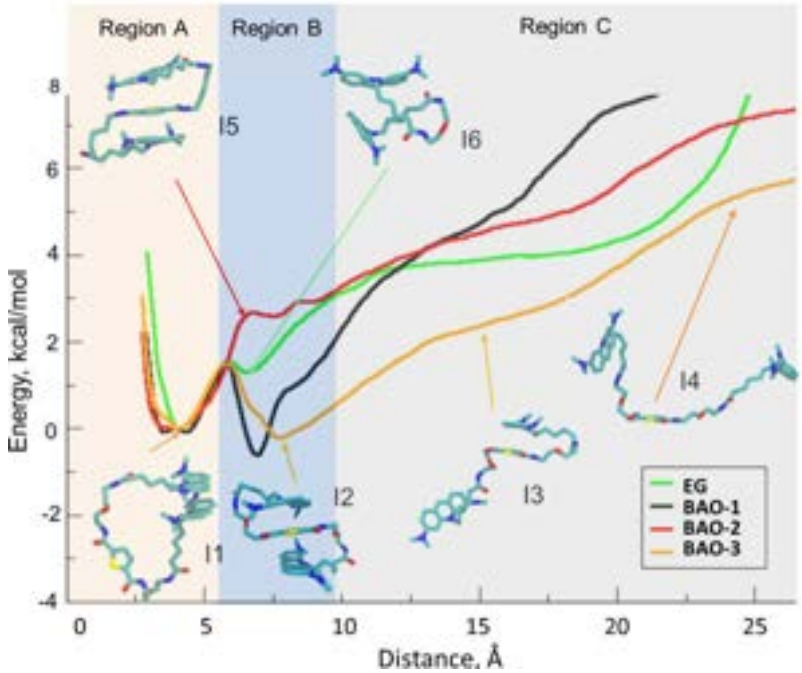

Figure 1 – Potential of mean force (PMF) at varying distance between the two AO moieties.

REFERENCES

[1] Kulyk, O., Krivoshey, A., Kolosova, O., Prylutska, I., Vasiliu, T., Puf, R., Mocci, F., Laaksonen, A., Perepelytsya, S., Kobzev, D., Svoiakov, R., Tkachuk, Z., & Tatarets, A. (2024). Nucleic acid-binding bis-acridine orange dyes with improved properties for bioimaging and PCR applications. Journal of Materials Chemistry B. https://doi.org/10.1039/D4TB01775G.

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Elucidating Viral G-Quadruplex Stability as a Foundation for Antiviral Targeting in Zika and Monkeypox

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G-quadruplexes (G4s) are noncanonical four-stranded nucleic acid secondary structures formed by guanine-rich sequences that stack into planar G-tetrads stabilized by Hoogsteen hydrogen bonding and monovalent cations [1]. Many regulatory genomic regions, including telomeres, promoters, and untranslated regions, contain sequences capable of forming G4s, often referred to as putative G-quadruplex sequences (PQs). G4s play essential roles in viral genome stability, transcription, and replication [2]. While their functions have been extensively studied in human genomes, their presence and regulatory significance in viral genomes, particularly in the RNA genome of Zika virus and the DNA genome of Monkeypox virus, remain largely unexplored. Understanding the structural stability and dynamics of viral G4s could reveal novel regulatory mechanisms and potential antiviral targets. Due to the absence of experimentally resolved three-dimensional structures of viral G4s, we investigated PQ motifs from Monkeypox (MPG4: GGTCTAGGATGAGGATCAGG) and Zika (ZRG4: GGUGGGGGACUGG) viruses using a comparative modeling approach. Structural templates were selected from the RCSB PDB based on sequence alignment and structural similarity to the human telomeric G-quadruplex (PDB: 1KF1) [3] and a GGA triplet motif (PDB: 1OZ8) [4]. Homology screening identified 1KF1 and 1OZ8 as the closest structural matches, which were modified using PyMOL mutagenesis and energy minimization to construct two-quartet G4 models for DNA (MPG4) and RNA (ZRG4). Molecular dynamic simulations were performed to evaluate the structural dynamics and ion stability of the modeled G4s. Amber OL15 [5] and OL3 [6] force fields were used in 1 μs simulations under both Langevin and Berendsen thermostats. Under Langevin dynamics at 300 K [7], both G4s remained structurally stable, maintaining intact G-quartet (GQ) cores, with RMSD values of approximately 4 Å for MPG4 and 1.5 Å for ZRG4 (Figure 1A and 1B). Both systems exhibited stable RMSD oscillations averaging around 1.5 Å, indicating rigidity in the GQ framework (Figure 1A and 1B). The coordinated K^+ ion, essential for neutralizing the negative charge density and maintaining the Hoogsteen hydrogen bonding (HHB) network, remained stably positioned throughout the simulations. In MPG4, the K^+ ion exhibited slightly larger oscillations of about 0.7 Å, reflecting the intrinsic flexibility of the loop regions. In ZRG4, the K^+ ion remained consistently coordinated with only minor displacements of approximately 0.2 Å, suggesting strong interactions with O6 atoms. ZRG4 maintained RMSD values between 2.5 and 3 Å, further supporting stable ion coordination and HHB integrity. In contrast, simulations using the Berendsen thermostat [8] led to substantial RMSD increases and partial destabilization of both G4 models. The Berendsen thermostat's limitations in temperature and pressure coupling led to increased fluctuations and destabilization, whereas Langevin dynamics, with its additional friction and random noise, ensured better structural preservation.

These findings support the structural stability of G4s in the genomes of Monkeypox and Zika viruses, reinforcing their potential regulatory roles in viral gene expression. Additionally, the observed differences between Langevin and Berendsen thermostat simulations highlight the importance of choosing appropriate simulation parameters when modeling G4 structures over extended timescales. This work lays a computational foundation for future studies exploring viral G4s as potential antiviral

targets. Targeting G4s stability with small molecules could provide novel antiviral strategies, with their effect on G4 formation and stability validated through circular dichroism (CD) spectroscopy.

Keywords: Viral G-quadruplexes, Molecular dynamic simulations, OL3

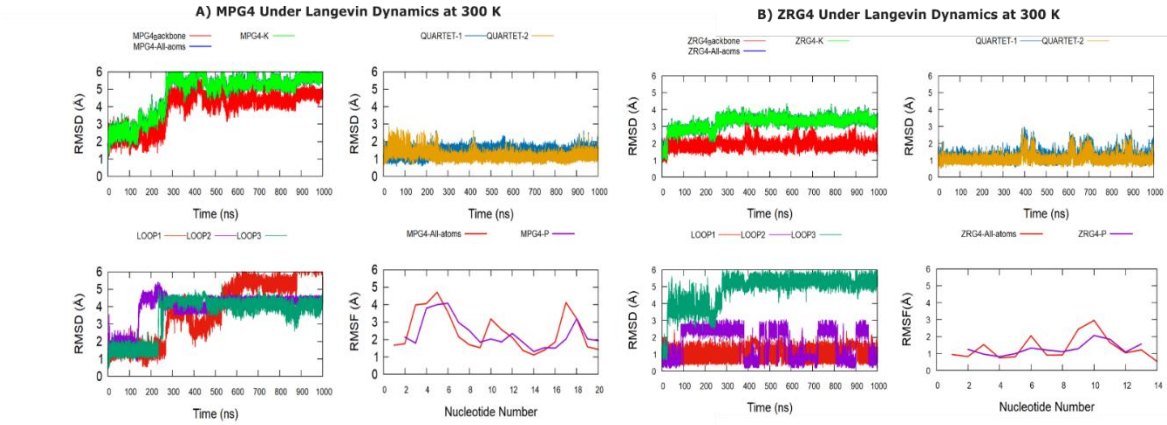

Figure 1 – RMSD and RMSF analyses of MPG4 and ZRG4 G-quadruplexes under Langevin dynamics at 300 K over 1000 ns. RMSD plots show structural deviations of the backbone, all-atoms, K^+-coordinated structures, individual quartets, and loop regions. RMSF plots represent nucleotide-wise fluctuations. MPG4 (A) and ZRG4 (B) display distinct stability and flexibility profiles across simulation time.

REFERENCES

[1] Pathak R, (2023) "G-quadruplexes in the viral genome: unlocking targets for therapeutic interventions and antiviral strategies". *Viruses*, *15*(11), 2216.doi.org/10.3390/v15112216

[2] Rhodes D, & Lipps H J, (2015) "G-quadruplexes and their regulatory roles in biology". *Nucleic acids research*, *43*(18), 8627-8637. doi.org/10.1093/nar/gkv862

[3] Parkinson G N, Lee M P, & Neidle S, (2002) "Crystal structure of parallel quadruplexes from human telomeric DNA". *Nature*, *417*(6891), 876-880. doi.org/10.1038/nature755

[4] Matsugami A, Okuizumi T, Uesugi S, & Katahira M, (2003) "Intramolecular higher-order packing of parallel quadruplexes comprising a G: G: G: G tetrad and a G (: A): G (: A): G (: A): G heptad of GGA triplet repeat DNA". *Journal of Biological Chemistry*, *278*(30), 28147-28153. doi.10.1074/jbc.M303694200

[5] Galindo-Murillo R, Robertson J C, Zgarbova M, Sponer J, Otyepka M, Jurecka P, & Cheatham III T E, (2016) "Assessing the current state of amber force field modifications for DNA". *Journal of chemical theory and computation*, *12*(8), 4114-4127.doi.org/10.1021/acs.jctc.6b00186

[6] Zgarbová M, Otyepka M, Sponer J, Mladek A, Banas P, Cheatham III T E, & Jurecka P., (2011) "Refinement of the Cornell et al. nucleic acids force field based on reference quantum chemical calculations of glycosidic torsion profiles". *Journal of chemical theory and computation*, *7*(9), 2886-2902. doi.org/10.1021/ct200162x

[7] Wu X, & Brooks B R, (2003) "Self-guided Langevin dynamics simulation method". *Chemical physics letters*, *381*(3-4), 512-518.doi.org/10.1016/j.cplett.2003.10.013

[8] Bussi G, Donadio D, & Parrinello M, (2007) "Canonical sampling through velocity rescaling". *The Journal of chemical physics*, *126*(1).doi.org/10.1063/1.2408420

Intermolecular Organization in Aqueous Mixtures of Choline Lysinate Studied by NMR and Molecular Dynamics/Quantum Mechanics

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3rd generation ionic liquids are materials that melt at <100 °C temperatures and are comprised of biocompatible cations and anions resulting in lowered toxicity compared with other ionic liquids (ILs) and expanding its applicability in biological systems. Choline amino acid (ChoAA) ILs are well-known family of 3rd generation ionic liquids, that are used especially for solubilization of various biological molecules, drugs and macromolecules [1-4]. For instance, choline tryptophanate is studied for its capability to enhance the solubility of antidiabetic drug glibenclamide by more than two orders of magnitude in aqueous medium [1-2]. Another important ChoAA IL is choline lysinate ChoLys (see its structure in Fig. 1), which is suggested to be one of the best additives for efficient lignin dissolution in biomass treatment [3].

Peculiar physicochemical properties and solubilization mechanism of ChoAA ILs in aqueous mixtures lies on complex intermolecular structure of ChoAA and water mixtures, ranging from small clusters of water surrounded by IL to intact network of water molecules, with a possible intermediate state – formation of water nanopackets (nanometer scaled clusters of water molecules), which are claimed to be present in ChoLys and water mixtures [3]. Such morphological diversity is caused by propensity of choline and amino acid anions to form various hydrogen bonds [4] and additional intermolecular interactions of charged $-N(CH_3)_3^+$ head of choline and amino acid side chains. Theoretical investigation methods would be best at providing a detailed intermolecular picture of such systems, but all modelling studies may be considered fictitious as long as they are not compared with experimental data.

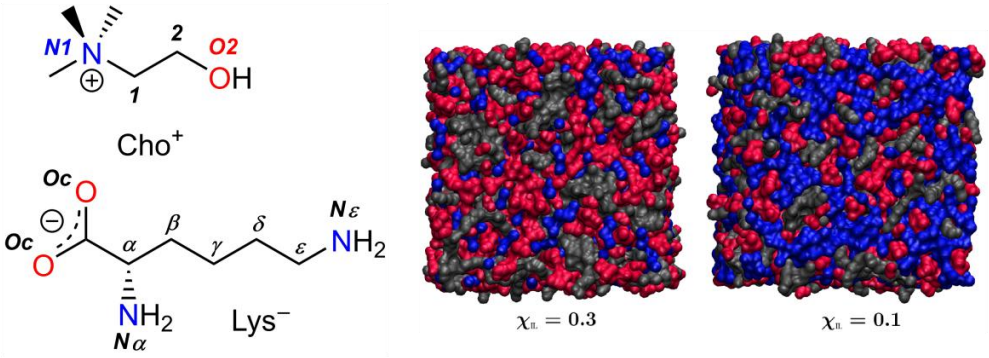

Figure 1 – Left: chemical structure and atomic labels of choline lysinate ionic liquid; right: still-images from molecular dynamics trajectories of choline lysinate:water systems with 0.3 and 0.1 ionic liquid molar fraction, colored by functional group polarity – non-polar moieties are grey, polar moieties are red, water molecules are blue.

We took an integrated computational approach, involving molecular dynamics (MD) simulations and hybrid linear-response quantum mechanics / molecular mechanics (QM/MM) calculations. Using a suitable force-field, MD simulations allow for vast sampling of configurational phase-space and provide information about both intramolecular and intermolecular properties of the system. QM/MM calculations for randomly selected MD trajectory configurations treat a selected ensemble of particles quantum-mechanically (QM subsystem) with others being simplified to point-charges (MM subsystem). Their purpose is to obtain NMR shielding constants – a parameter which can be compared with experimental NMR chemical shifts and ensure validity of computational study.

Six ChoLys:water systems with different ionic liquid molar fraction (χ_{IL} = 0.50, 0.30, 0.10, 0.05, 0.01 and 0.00025) were MD simulated at 298 K with 20 ns NVT equilibration step to obtain 20 ns NVT trajectories using "Amber" software package. Intermolecular structure was characterized by radial distribution functions between various atomic pairs, including N1 and O2 in Cho^+, Oc, Nα and Nε in Lys^- and Ow oxygen atom in H_2O (refer to Fig. 1 for labeling). All these species participate in hydrogen bonding, mostly with Ow in most diluted systems, but carboxylate oxygen Oc becoming a more prevailing hydrogen-bond acceptor in systems with more ionic liquid. It was noticed that choline – $N(CH_3)_3^+$ group acts as a main hydrogen-bond network disruptor in more ChoLys-rich mixtures.
We also investigated aggregation tendencies in these mixtures. From MD trajectories probability distributions of water belonging to cluster of *n* water molecules, ***P(n)***, were calculated. They showed prevalence of small water clusters at χ_{IL} = 0.50, 0.30 systems and continuous water network at χ_{IL} = 0.10 with no signs of larger water nanopockets. Small water clusters tend to lie on interfaces of polar and non-polar domains of the ionic subsystem (as it is shown in Fig. 1) but ionic subsystem breaks apart when water molecules form a continuous network.

Furthermore, diffusion coefficients of Cho^+, Lys^- and water, obtained both computationally from MD simulations by calculating mean-square-displacement functions and experimentally by ^{1}H NMR DOSY measurements, support the existence of two different dynamical regimes: water network with fast-decreasing diffusion coefficients when IL is added and ionic network with slow-decreasing diffusion coefficients when IL molar fraction is further increased. Percollation point, based on experimental data, is at around χ_{IL} = 0.11.

Finally, shielding constants of H1, H2 (in Cho^+ methylene groups), Hα, Hε (in Lys–) and Hw (in H_2O) were attained by averaging QM/MM calculations results for 100 randomly selected configurations with QM subsystems containing central particle and the part of first solvation shell closest to respective nuclei to be accounted for. A qualitative and quantitative match with experimental ^{1}H NMR spectra was achieved for Hα and Hw protons. Hw were showed to participate in fast proton exchange with both amino groups in lysinate and hydroxyl group in choline. H1 and H2 were quantitatively well-matching with experimental data. Only Hε results were a mismatch, possibly due to force-field imperfections. Thus we deduced that because of mostly accurate NMR calculations, our structural characterization of ChoLys:water mixtures is valid and can be influential in further investigations of physicochemical changes in such systems.

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REFERENCES

[1] Alawi M. A., Hamdan, I. I., Sallam A. A., Heshmeh N. A., (2015) "Solubility enhancement of glibenclamide in choline–tryptophan ionic liquid: Preparation, characterization and mechanism of solubilization". *Journal of Molecular Liquids*, 212, 629-634. 10.1016/j.molliq.2015.10.006
[2] Murnikova Ž., Klimavicius V., Mocci F., Laaksonen A., Aidas K., (2025) "On the mechanism behind the enhanced solubility of glibenclamide in aqueous ionic liquid solution". *Journal of Molecular Liquids*, 422, 127153. 10.1016/j.molliq.2025.127153
[3] Jiang H. J., Miao S., Imberti S., Simmons B. A., Atkin R., Warr G. G. (2021) "Liquid nanostructure of choline lysinate with water and a model lignin residue". *Green Chemistry*, 23, 856-866. 10.1039/D0GC03664A
[4] Gontrani L., (2018) "Choline-amino acid ionic liquids: past and recent achievements about the structure and properties of these really "green" chemicals". *Biophysical Reviews*, 10, 873-880. 10.1007/s12551-018-0420-9

Simulating molecular systems with peculiar fluorescence. A case study of lysine.

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L-lysine is an aminoacid with an aliphatic structure that, despite its lack of aromatic groups manifests a strong peculiar blue fluorescence in solution, dependent of concentration, one of the highest among the 20 aminoacids composing the proteins, comparable to the aromatic ones (L-phenylalanine, L-tyrosine). L-lysine analogues with shorter backbone manifest very weak or no fluorescence at all [1].

For this reason, it's been suspected that aggregation plays a key role in L-lysine fluorescence, directly dependent with the increase in concentration, up to a threshold, influenced by the formation of molecular clusters. The nature of the secondary bonds and intermolecular interactions and the structure of these aggregates is unknown [2]. Computational chemistry has a vital role in investigating these systems, by analyzing different arrangements of L-lysine and their contribution in the theoretical fluorescence spectra and comparing with experimental data.
In a previous study, systems containing L-lysine molecules in water were simulated through the means of molecular dynamics (MD) [3]. We extracted a snapshot from one of these simulations and we initially employed the use of the QM method on a smaller region of the system (involving the closest lysine structures in zwitterionic form, in clusters of 3, 4 and 5 molecules), but the calculation of excited states gave an erroneous result, the structure becomes disturbed when doing optimizations in TD-DFT calculations, due to the initial computational method (classical MD) which is excluding the electron interactions and the lack of molecules in the surrounding vicinity (QM calculations are computationally expensive, especially for systems as large as those simulated through MD), obtaining energies lower than the initial starting structure. To mitigate this problem, we made use, instead, of a hybrid QM/MM ONIOM method as implemented in Gaussian 16, which is performed by setting up two layers of calculations, a high layer using QM (6-311++g(d,p)) and a low layer using MM (AMBER force field) as employed in the study of Langer et al. [4]. This allows for the use of a larger system with a decreased computational cost, while keeping the vicinity intact around the high layer as much as possible. Although having this advantage, the theoretical data is still entirely dependent on how molecules in the layers are selected, especially their number and the degree of separation between the layers strongly influences the convergence which makes the simulation of this system very challenging. One of these simulated systems is illustrated below:

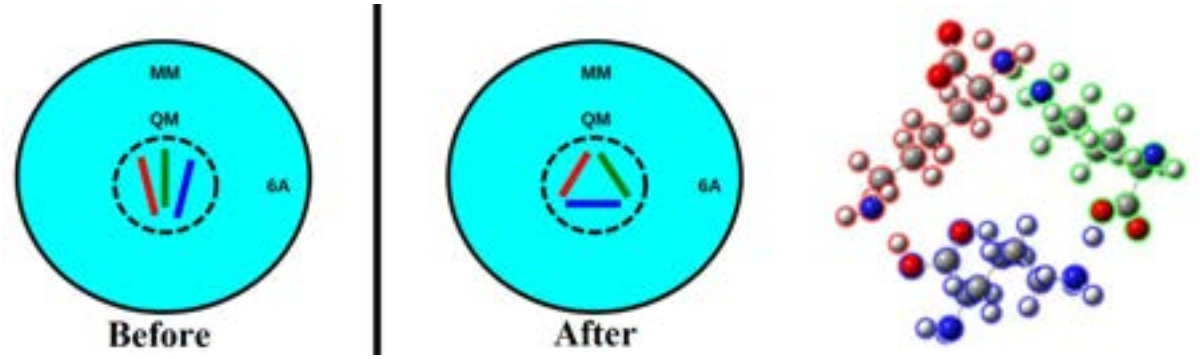

Figure 1 – The schematic structure of a lysine system used for QM/MM simulations, before and after energy minimization with mechanical embedding (system diameter is 6 Å) with an obtained arrangement of 3 L-lysine molecules (right) showing hydrophobic and electrostatic interactions.

REFERENCES

[1] Z. A. Arnon *et al.*, "On-off transition and ultrafast decay of amino acid luminescence driven by modulation of supramolecular packing," *iScience*, vol. 24, no. 7, Jul. 2021, doi: 10.1016/j.isci.2021.102695.

[2] L. de V. Engelbrecht, F. Mocci, Y. Wang, S. Perepelytsya, T. Vasiliu, and A. Laaksonen, "Molecular Perspective on Solutions and Liquid Mixtures from Modelling and Experiment," in *Soft Matter Systems for Biomedical Applications*, L. Bulavin and N. Lebovka, Eds., Cham: Springer International Publishing, 2022, pp. 53–84. doi: 10.1007/978-3-030-80924-9_3.

[3] L. Stagi, R. Farris, L. de Villiers Engelbrecht, F. Mocci, C. Maria Carbonaro, and P. Innocenzi, "At the root of l-lysine emission in aqueous solutions," *Spectrochim. Acta. A. Mol. Biomol. Spectrosc.*, vol. 283, p. 121717, Dec. 2022, doi: 10.1016/j.saa.2022.121717.

[4] M. Langer, T. Hrivnák, M. Medved', and M. Otyepka, "Contribution of the Molecular Fluorophore IPCA to Excitation-Independent Photoluminescence of Carbon Dots," *J. Phys. Chem. C*, vol. 125, no. 22, pp. 12140–12148, Jun. 2021, doi: 10.1021/acs.jpcc.1c02243.

Betaine-Based Drug Delivery Systems

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Drug delivery systems (DDS) are technologies created to transport drugs into or throughout the body. DDS enhance the therapeutic effects of both hydrophobic and hydrophilic drugs and their safety by controlling the rate and place of release and improving their solubility. Furthermore, DDS protect drugs from degradation, ensuring they reach their target within the body.

In recent decades, the field of drug delivery has made significant strides. In particular, the use of biomolecules and bio-derived molecules as drug delivery systems (bio-based DDS) has shown significant potential for improving the effectiveness, safety, and specificity of therapeutic treatments. Additionally, their inherent biocompatibility reduces the risk of adverse immune reactions, thereby enhancing patient safety. [1] Among the bio-based DDS studied intensively in the past years, choline-based DDS have gained great popularity. Choline is a quaternary ammonium salt and an essential nutrient for humans. [2] Choline and some of its derivate, such as phosphatidylcholine, have been used to prepare various ionic liquids and deep eutectic solvents (DES) and combined with long chain carboxylic acids to achieve surface active ionic liquids (SAILs). Some of these SAILs have been used to form micellar systems capable of transporting hydrophilic drugs such as DNA through the skin. [3]

Closely related to choline, glycine betaine (GB) is a non-essential amino acid derived from choline metabolism. GB is a byproduct obtained from the extraction of sugar from sugar beets and is used in the pharmaceutical industry. GB esters have been studied for their surface-active properties and some, obtained via esterification with primary alcohols of varying chain lengths, have been employed n the synthesis of novel ionic liquids [4].

This work presents preliminary results on the synthesis and characterization of SAILs based on long-chain esters of GB combined with carboxylic acids of varying chain length and degrees of saturation such as lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid and linoleic acid (Figure 1).

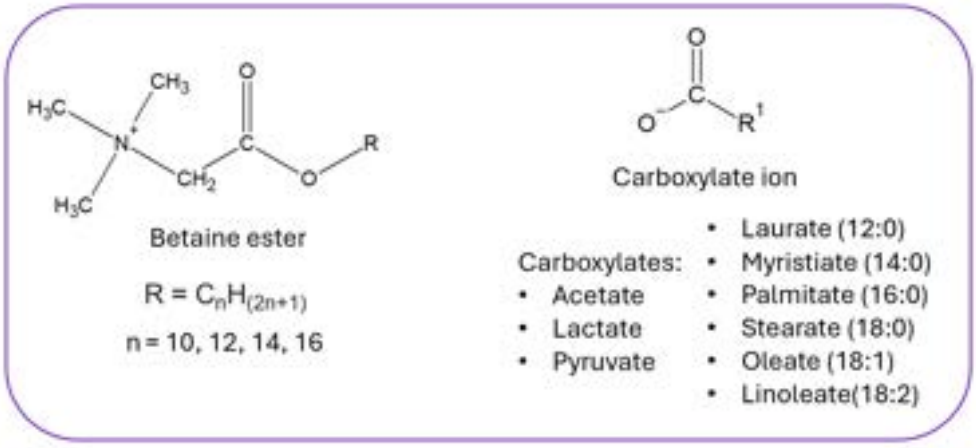

Figure 1 – Carboxylates of GB esters

GB esters have been synthesized from saturated primary alcohols such as 1-decanol, 1-dodecanol, 1-tetradecanol and 1-hexadecanol. These systems are currently being studied using Nuclear Magnetic Resonance (NMR) and Fourier Transform Infrared (FTIR) spectroscopy. The primary aim is to assess the capacity of these SAILs to form micelle and to explore how variations in both the ester and anion chain length and saturation affect their physicochemical properties.

While further studies are needed, these compounds may represent promising candidates for future development in drug delivery or related biomedical applications.

REFERENCES

[1] Srivastav A. K., Karpathak S., Rai, M. K., Kumar, D., Misra, D. P., Agarwal, V., (2023) "Lipid based drug delivery system for oral, transdermal and parenteral delivery: Recent strategies for targeted delivery consistent with different clinical application". *Journal of Drug Delivery Science and Technology*, 85 (2023) 104526. DOI 10.1016/j.jddst.2023.104526

[2] Li X., Ma N.; Zhang L.; Ling G.; Zhang P., (2021) "Applications of choline-based ionic liquids in drug delivery". *International Journal of Pharmaceutics,* 612 (2022) 121366. DOI 10.1016/j.ijpharm.2021.121366

[3] Toyofuku K., Wakabayashi, R., Kamiya, N., Goto M., (2023). "Non-Invasive Transdermal Delivery of Antisense Oligonucleotides with Biocompatible Ionic Liquids." *ACS Applied Materials and Interfaces*, 15(28), 33299–33308. DOI 10.1021/acsami.3c03900

[4] De Gaetano Y., Mohamadou A., Boudesocque S., Hubert J., Plantier-Royon R., Dupont L., (2015) "Ionic liquids derived from esters of Glycine Betaine: Synthesis and characterization". *Journal of Molecular Liquids,* 207 (2015) 60–66. DOI 10.1016/j.molliq.2015.03.016

Development of Indomethacin-Choline Ionic Liquid Using β-Cyclodextrin

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Indomethacin is a nonsteroidal anti-inflammatory drug recommended in rheumatic and arthritic diseases. It is known that long-term treatment could cause side effects such as gastrointestinal bleeding, nausea, abdominal pain, heartburn, headache, edema and others. Given the broad therapeutic applications of indomethacin, understanding its physicochemical properties is crucial, as they significantly influence its bioavailability. Many studies evidenced the chemical instability of indomethacin and the low solubility, being included in the BCS class II drugs [1–3]. The cyclodextrin complexation could be an encouraging approach to enhance solubility, stability and dissolution rates of indomethacin [4].

On the other hand, the use of ionic liquids (ILs) to improve some properties of the drugs is often applied. In the last years many investigations have been focused on development of active pharmaceutical ingredients (APIs)-ILs, especially with choline, based on their advantages such as lower toxicity and higher biodegradability. Choline-based ILs are also suitable for drug delivery, for increasing the skin penetration and could be used as solubility promoters [5].

The aim of the current study is related to the synthesis of indomethacin-choline IL usingβ-cyclodextrin. For comparation, indomethacin-choline IL without ß-cyclodextrin was also prepared. The indomethacin-ILs were characterized by Nuclear Magnetic Resonance spectroscopy (NMR) and Thermogravimetry-Differential Scanning Calorimetry (TG-DSC). Biological evaluation, including antioxidant tests such as antiradical method (ABTS) and Ferric Reducing Antioxidant Power Assay, were also performed.

The results proved the formation of indomethacin-ILs, whose stability increase in the presence of β-cyclodextrin. The evaluation of antioxidant potential showed a better profile for indomethacin-ILs compared with indomethacin and choline. These findings suggest a promising formulation of indomethacin with increased stability and solubility that could be used in various diseases involving inflammation, oxidative stress, or even on neurodegenerative conditions.

REFERENCES

[1] Hipólito-Nájera AR, Del Rosario Moya-Hernández M, Rojas-Hernández A, Gómez-Balderas R, (2019) Interaction of Indomethacin–Cyclodextrins in Water by UV–Vis and ITC. *J Incl Phenom Macrocycl Chem*, *95*, 55–62. DOI:10.1007/s10847-019-00915-9.

[2] Jamrógiewicz M, Józefowicz M, (2021) Preparation and Characterization of Indomethacin Supramolecular Systems with β-Cyclodextrin in Order to Estimate Photostability Improvement. *Molecules*, *26*, 7436. DOI:10.3390/molecules26247436.

[3] Sangiorgi S, Albertini B, Bertoni S, Passerini N, (2025) An Overview on the Role of Ionic Liquids and Deep Eutectic Solvents in Oral Pharmaceuticals. *Pharmaceutics*, *17*, 300. DOI:10.3390/pharmaceutics17030300.

[4] Miranda GM, Santos VOR, Bessa JR, Teles YCF, Yahouédéhou SCMA, Goncalves MS, Ribeiro-Filho J, (2021) Inclusion Complexes of Non-Steroidal Anti-Inflammatory Drugs with Cyclodextrins: A Systematic Review. *Biomolecules*, *11*, 361. DOI:10.3390/biom11030361.

[5] Li X, Ma N, Zhang L, Ling G, Zhang P, (2022) Applications of Choline-Based Ionic Liquids in Drug Delivery. *International Journal of Pharmaceutics*, *612*, 121366. DOI:10.1016/j.ijpharm.2021.121366.

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