4th European NECTAR Conference and Final Action Meeting

Milazzo, February 26th-27th, 2024

BOOK OF ABSTRACTS

COST ACTION CA18202

NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

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The 4th European NECTAR Conference and Final Action Meeting is a two-days meeting, held in Milazzo, organized within the activities of COST Action CA18202 (NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research).

The international conference represents the closing event of NECTAR, of which the University of Messina is also Grant Holder.

This last meeting will keep the format of previous editions (the first Conference was held in Belgrade, the second in Lisbon, and the third in Ljubljana), merging Management Committee (MC), Core Group (CG) and Working Group (WGs) meetings with a classical conference.

This format allows NECTAR's WG members and other eminent scientists to share and disseminate latest results within the scopes of the Action and to rationalize the work done since NECTAR's start.

More than a scientific workshop, the 4th European Conference and Final Action Meeting, represents a moment of joyful reencounter, invigorating in-person scientific discussion and deepened engagement, all this in the outstanding city of Milazzo, with all of its handsome landscapes and unique places.

This book collects the abstracts of main communications from attendees, hoping that it can serve as stimulus for fruitful scientific discussions and future collaborations.

Demetrio Milea (NECTAR Action Chair)

Sofia Gama (NECTAR Vice Chair)

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4th European NECTAR Conference and Final Action Meeting Programme		
	February 26th, Monday	February 27th, Tuesday
8:30 - 9:00	Registration	Registration
9:00 - 9:20	Opening Ceremony	Individual WG Meetings
9:20 - 9:40	OC01 - M. Filella	
9:40 - 10:00	OC02 - M. Meyer	
10:00 - 10:20	OC03 - P. Lubal	
10:20 - 10:40	OC04 - V. Sladkov	
10:40 - 11:00	OC05 - J. Galceran	
11:00 - 11:30	Coffee Break	Coffee Break
11:30 - 11:50	OC06 - D. Griffith	WG1 Summary
11:50 - 12:10	OC07 - S. Potocki	WG2 Summary
12:10 - 12:30	OC08 - F. Binacchi	WG3 Summary
12.30 - 12:50	OC09 - E. Kaya	WG4 Summary
12:50 - 13:10	OC10 - M. Marafante	WG5 Summary
13:10 - 14:30	Lunch Break	Lunch Break
14:30 - 14:50	OC11 - A. Baryłka	Managers Summary and Status of the Action
14:50 - 15:10	OC12 - L. Castellino	
15:10 - 15:30	OC13 - S. Blasco	Core Group Meeting
15:30 - 15:50	OC14 - G. Santonoceta	
15:50 - 16:10	OC15 - M. Sanadar	MC Meeting
16:10 - 16:30	OC16 - T. Trtić-Petrović	
16:30 - 17:00	Coffee Break	Coffee Break
17:00 - 17:20	Poster Session	MC Meeting
17:20 - 17:40		
17:40 - 18:00		Closing Ceremony
20:30	Dinner	

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CONFERENCE PROGRAMME

Monday 26th

8:30 – 9:00	***Registration***
9:00 – 9:20	***Opening Ceremony***
Chairs:	Olga IRANZO – *University of Aix-Marseille – CNRS, France* Carmelo SGARLATA – *University of Catania, Italy*
9:20 - 9:40	**OC01** – To what extent are our equilibrium data unFAIR and how can this be remedied in practice? Montserrat FILELLA – *University of Geneva, Switzerland*
9:40 - 10:00	**OC02** – Scandium(III) hydrolysis and complexation studies with desferrioxamine B Michel MEYER – *University of Burgundy – CNRS, France*
10:00 - 10:20	**OC03** – Thermodynamic and Kinetic Study of Palladium(II) Complexation with 1-methyl-2-mercaptoimidazole (Methimazole) Premysl LUBAL – *Masaryk University, Czech Republic*
10:20 - 10:40	**OC04** – Complexation of selected highly hydrolysable metal ions with organic ligands of environmental and medical interest Vladimir SLADKOV – *University of Paris-Saclay – CNRS, France*
10:40 - 11:00	**OC05** – Free gallium (III) determination with AGNES (Absence of Gradients and Nernstian Equilibrium Stripping) Josep GALCERAN – *University of Lleida, Spain*
11:00 - 11:30	***Coffee Break***
Chairs:	Tarita BIVER – *University of Pisa, Italy* Slobodan GADŽURIĆ – *University of Novi Sad, Serbia*
11:30 – 11:50	**OC06** – Ga(III) complexes as antimicrobial drug candidates. Solution studies, synthesis and antimicrobial activity Darren GRIFFITH – *Royal College of Surgeons in Ireland, Ireland*
11:50 – 12:10	**OC07** – Mycobacterial Unusual Chaperonin GroEL1 and Its Complexes with Cu(II) and Ni(II) Metal Ions Sławomir POTOCKI – *University of Wroclaw, Poland*
12:10 – 12:30	**OC08** – How essential is the choice of method to evaluate the equilibrium constant? The case of Ag(I)-anthracenyl biscarbene/DNA system Francesca BINACCHI – *University of Pisa, Italy*
12:30 – 12:50	**OC09** – Binding of unconventional Fluorescent Molecular Probes based on peptides conjugates to Serum Albumin and DNA

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	Eric KAYA – *University of Orléans, France*
12:50 – 13:10	**OC010** – A network to define recommended procedures for potentiometric measurements of stability constants Matteo MARAFANTE – *University of Torino, Italy*
13:10 – 14:30	***Lunch Break***
Chairs:	Silvia BERTO – *University of Torino, Italy* Marija Bešter-Rogač – *University of Ljubljana, Slovenia*
14:30 – 14:50	**OC11** – The accurate assessment of the chemical speciation of complex systems: a multi-technique approach Anna BARYŁKA – *University of Bialystok, Poland*
14:50 – 15:10	**OC12** – SpectrApp and PyES, two free tools for soft and hard modelling of chemical systems Lorenzo CASTELLINO – *University of Torino, Italy*
15:10 – 15:30	**OC13** – Microspeciation Analysis with GEMS Salvador BLASCO – *University of Valencia, Spain*
15:30 – 15:50	**OC14** – Can solution equilibria drive the development of pH-responsive drug delivery systems? Giuseppina D.G. SANTONOCETA – *University of Catania, Italy*
15:50 – 16:10	**OC15** – Understanding the coordination behavior of Eu(III) in [P_{66614}][Decanoate] Ionic Liquid Martina SANADAR – *University of Udine, Italy*
16:10 – 16:30	**OC16** – Equilibrium extraction in aqueous biphasic systems based on ionic liquids Tatjana TRTIĆ-PETROVIĆ – *Vinca Institute of Nuclear Sciences, Serbia*
16:30 – 17:00	***Coffee Break***
17:00- 18:00	***Poster Session***
20:30	***Dinner***

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Tuesday 27th

8:30 – 9:00	***Registration***
9:00 – 11:00	***Individual WG Meetings***
11:00 - 11:30	***Coffee Break***
Chairs:	Demetrio MILEA – *University of Messina, Italy* Sofia GAMA – *University of Bialystok, Poland*
11:30 – 11:50	***WG1 Summary*** Olga IRANZO – *University of Aix-Marseille – CNRS, France* Montserrat FILELLA – *University of Geneva, Switzerland*
11:50 – 12:10	***WG2 Summary*** Tarita BIVER – *University of Pisa, Italy* Sławomir POTOCKI – *University of Wroclaw, Poland*
12:10 – 12:30	***WG3 Summary*** Marija BEŠTER-ROGAČ – *University of Ljubljana, Slovenia* Slobodan GADŽURIĆ – *University of Novi Sad, Serbia*
12:30 – 12:50	***WG4 Summary*** Silvia BERTO – *University of Torino, Italy* Carmelo SGARLATA – *University of Catania, Italy*
12:50 – 13:10	***WG5 Summary*** Álvaro MARTÍNEZ-CAMARENA – *University of Strasbourg, France* Emanuele ZANDA – *University of Paris-Saclay – CNRS, France*
13:10 – 14:30	***Lunch Break***
Chairs:	Demetrio MILEA – *University of Messina, Italy* Sofia GAMA – *University of Bialystok, Poland*
14:30 – 15:10	***Managers Summary and Status of the Action***
	Science Communication Elżbieta GUMIENNA-KONTECKA – *University of Wroclaw, Poland*
	Grant Awarding Sofia GAMA – *University of Bialystok, Poland*
	Training Schools Enrique GARCÍA-ESPAÑA – *University of Valencia, Spain*
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Emel YILDIZ – *Cukurova University, Turkey*

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Éva A. ENYEDY –*University of Szeged, Hungary*

Chairs: Demetrio MILEA – *University of Messina, Italy*
Sofia GAMA – *University of Bialystok, Poland*

15:10 – 15:50	***CG Meeting***
15:50 – 16:30	***MC Meeting – part 1***
16:30 - 17:00	***Coffee Break***
17:00 – 17:40	***MC Meeting – part 2***
17:40 – 18:00	***Closing Ceremony***

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Oral Communications

To what extent are our equilibrium data unFAIR and how can this be remedied in practice?

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Scientific research operates on the basis that the results are disseminated through scientific publications. These publications generally do not contain all the original data or do not contain them in a format that is reusable. In some fields, such as medicine, the limitations of the system have been openly acknowledged (e.g., in the words of the European Medicine Agency's former executive director, "relying solely on the publications of clinical trials in scientific journals as the basis of healthcare decisions is not a good idea. Drug regulators have been aware of this limitation for a long time and routinely obtain and assess the full documentation (rather than just publications)" (doi:10.1136/bmj.o102). The need to change this unsatisfactory situation lead, as early as 2016, to the provision of guidelines to improve the Findability, Accessibility, Interoperability, and Reuse of scientific data (doi:10.1038/sdata.2016.18). Since then, many initiatives have emerged and some funding agencies even promote the publication and sharing of data. Examples include the European Union's science funding programme, which already requires almost all data to be FAIR, and the US government's announcement that research articles and underlying data generated with federal funds should be publicly available at no cost by the end of 2025 (doi:10.1038/d41586-022-02820-7). In practice, however, what seems simple and obvious can quickly become difficult to implement. Based on the idea that open science, when properly applied, is synonymous with "pragmatic solutions to understanding, disseminating, scrutinising, and implementing research findings" (doi:10.1136/bmj.p1609) and on the experience gained in this COST action, this communication aims to be a step forward by i) discussing the FAIRness of the sources of equilibrium data, ii) analysing the FAIRness of the publications and results of this COST action (including the so-called "periodic table"), iii) proposing a ready-to-use approach in the case of equilibrium data.

Acknowledgements:

This contribution is based upon work from COST Action CA18202, NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research, supported by COST (European Cooperation in Science and Technology). What is presented in this communication is largely based on what I have learned from managing part of WG1 of this COST Action, as well as working and discussing with its members and Marc Biver, Josep Bonet, Stuart Chalk, Wolfgang Hummel, Peter M. May, Leah R. McEwen and Juan Carlos Rodríguez-Murillo. My deepest thanks to all of them.

Scandium(III) hydrolysis and complexation studies with desferrioxamine B

Michel MEYER,[a] Stéphane BRANDES,[a] Marie-José PENOUILH,[a] Lucas VACHEY,[a] Abbie HASSON,[b,c] Jean-Claude CHAMBRON,[b] Sofia GAMA,[d] Clemente BRETTI,[e] Daniel L. J. THOREK[c]

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Scandium exists only in the trivalent oxidation state in aqueous solutions, with coordination numbers (CN) equal to 3, 6, 7, 8, and 9. Crystal structures containing the $[Sc(H_2O)_x]^{3+}$ (x = 6–9) hydrated cations have been described [1]. Owing to the d^0 electronic configuration and rather small ionic radius (0.745 Å for CN = 6), scandium(III) is a hard Lewis acid sharing some common features with aluminum and lanthanides, among them the high affinity for oxygen donor ligands, but it shows a stronger tendency to undergo hydrolysis and polycondensation reactions even at low pH [2]. The free aqua ion is only stable in acidic solutions (pH < ~2.5), while scandium exhibits an amphoteric character at high pH values. Besides mononuclear $[Sc(OH)_x]^{(3-x)+}$ hydrolyzed species with x = 1–4, olation promotes the formation of polynuclear hydroxides, although clear evidence has only been provided for two species, the $[Sc_2(OH)_2]^{4+}$ dimer and $[Sc_3(OH)_5]^{4+}$ trimer.

In nature, scandium is found as a single, NMR active, isotope (^{45}Sc, I = 7/2) of rather high receptivity (0.302 with respect to ^1H). Although the quadrupolar moment is responsible for line broadening that increases upon symmetry lowering, ^{45}Sc NMR spectroscopy turns out to be a valuable technique for probing the chemical environment as the chemical shifts span a wide range of ca. 350 ppm (from –100 to 250 ppm with respect to $Sc(ClO_4)_3$ in 1 M $HClO_4$ [3].

Over the last decade, the coordination chemistry of scandium(III) has experienced an upsurge in interest, spurred by the possibility to use ^{44}Sc ($T_{1/2}$ = 3.97 h) in positron emission tomography (PET) and the β^- emitting isotope ^{47}Sc ($T_{1/2}$ = 3.35 d) in radiotherapy [3]. Moreover, the possibility to generate in a cyclotron ^{44m}Sc that decays into ^{44}Sc with emission of soft γ rays with a half-life ($T_{1/2}$ = 2.44 d) that is compatible with the pharmacokinetics of antibodies, paves the way towards an *in vivo* $^{44m}Sc/^{44}Sc$ generator. Hence, $^{44/44m}Sc$ together with ^{47}Sc is considered as a most promising radioimmunotheranostic pair in oncology. Radiopharmaceuticals incorporating bifunctional chelators derived from either the octadentate linear $DTPA^{5-}$

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(diethylene-triamine-*N*,*N*,*N*′,*N*′′,*N*′′-pentaacetate) or the macrocyclic $DOTA^{4-}$ (1,4,7,10-tetraazacyclo-dodecane-1,4,7,10-tetraacetate) binders have been tested. However, as efficient radiolabeling of $DOTA^{4-}$ can only be achieved at elevated temperatures, usually above the denaturation point of proteins and thus of antibodies, bioconjugates made thereof are restricted to oligopeptides. Thus, the search for mild-labeling alternative bifunctional chelators that provide in vivo stability is ongoing.

Desferrioxamine B (DFO), the emblematic hexadentate trishydroxamic siderophore excreted by *Streptomyces* bacteria, is an authorized drug for treating iron or aluminum overloads in humans, but is also entitled as the "gold standard" for chelating another positron emitter, $^{89}Zr^{4+}$ [4]. Currently, ^{89}Zr-labeled DFO immunobioconjugates are the only constructs that have been translated for human applications. Our on-going work intends to evaluate the potency of DFO to bind efficiently Sc^{3+} *in vitro* before envisaging *in vivo* tests.

As part of NECTAR working group 1 (task-group *highly hydrolysable cations*) and 2 (task-group *metallophores*) activities, the lecture will focus on three aspects.

- The implementation of ^{45}Sc NMR spectroscopy for investigating the hydrolytic behavior of Sc^{3+} in aqueous media;
- The speciation study of the Sc^{3+}/DFO^{3-} system by combining potentiometric, absorption spectrophotometric, and ^{1}H, ^{13}C, ^{15}N, and ^{45}Sc NMR spectroscopic measurements.
- As some experiments have been carried out in acidic solutions, acid-base properties of DFO have been revisited too. Protonation constants retrieved from the literature or taken from our own work have been analyzed by applying the Specific Ion interaction Theory (SIT), while the proton-assisted hydrolysis kinetics and mechanism of $(DFO)H_4$ was investigated too by UV spectrophotometry and mass spectrometry.

Acknowledgements:

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Thermodynamic and Kinetic Study of Palladium(II) Complexation with 1-methyl-2-mercaptoimidazole (Methimazole)

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The mercapto-imidazole derivatives belong to the group of thyreostatic drugs since they are utilized in medicine for their ability to inhibit the function of the thyroid gland [1] and cause a decreased production of thyroid hormones, therefore such molecules are termed sometimes as antihormones. Some physico-chemical properties of metal complexes (e.g., Pd, Pt, Cu, Zn, Ag, etc.) [2-4] have been studied due to their possible biological activity. In addition, it was described oxidative dissolution ability in dichloromethane and water of the methimazole–iodine system towards palladium in powder [4].

The acidobasic and complexing properties of 1-methyl-2-mercaptoimidazole (*Methimazole*, *Tapazole*) with Pd(II) ion were investigated under experimental conditions close to physiological ones (I = 0.10 M NaCl, t = 25 °C) by molecular absorption spectroscopy in UV region, solvent-extraction technique and glass-electrode potentiometry. It was proved by theoretical methods (LFER and quantum chemical calculation) and experimentally by ^{1}H and ^{13}C NMR spectroscopy that the ligand is preferred to be in a thion form, and the proton dissociation is taking place on nitrogen atom. Using the glass electrode potentiometry, the complexation of Pd(II) ion by *methimazole* ligand is taking place without participation of protons. The best chemical model considers $[Pd(HL)]^{2+}$, $[Pd(HL)_2]^{2+}$ and $[Pd(HL)_3]^{2+}$ complex species, whose stability constants were also found from spectroscopic and capillary zone electrophoretic measurements. The metal complexes are decomposed at –log $[H^+] > 7$, where probably an uncharged palladium(II) hydroxide is formed. The formation kinetics of palladium(II) complex with *methimazole* was studied in perchloric and hydrochloric acids (I = 1.00 M, t = 25 °C) and the found rate constants and activation parameters are consistent with literature values determined for the reactions of Pd(II) ion with thiourea derivatives. The rate constants differ by two orders of magnitude in both media, which can be assigned to a lower tendency of dissociation chloride ion from the $[PdCl_4]^{2-}$ complex species than water molecule from the $[Pd(H_2O)_4]^{2+}$ ion.

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Complexation of selected highly hydrolysable metal ions with organic ligands of environmental and medical interest

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The interest for the speciation of metal ions is steadily growing. This subject is not only valuable for fundamental science, but is also of practical importance in industry, environmental geochemistry, medicine... [1]. To model the speciation of metal/ligand systems in different media, it is imperative to know the chemical equilibria and associated equilibrium constants. The situation is more complicated for highly acidic metal cations, which start to hydrolyze at low pH values and show a tendency to form polynuclear species. Here, we will present the work done in the frame of the NECTAR COST activities, mostly WG-1 and a STSM. We are interested in highly hydrolysable cations, such as V(IV), V(V), Th(IV), and U(IV) and their complexes.

There is a growing curiosity in the study of vanadium because of the potential environmental hazards linked to its increasing use [2]. Although large vanadium concentrations can cause harmful effects on ecosystems, the element seems to play a dual role in environmental systems since it is also considered, at micro concentration levels, as a beneficial element with a range of applications related to human welfare. Vanadium is mainly present in oxidation states +IV and +V in natural waters and soils. Among a variety of possible geochemical processes, complex formation with natural organic matter (NOM) present in the aqueous phase may play an important role in the eventual dispersion of vanadium [3]. The formation of such complexes typically causes significant changes in migration properties of chemical elements in the environment. Here, succinic acid was chosen for complexation studies with V(IV) and V(V), as a simple model of the structurally more complicated NOM [4]. Affinity capillary electrophoresis was successfully used for studying simultaneously the equilibria involving both V(IV) and V(V) [5].

Thorium and uranium are also of interest because of their use in the nuclear industry. The knowledge of their speciation is important for understanding the fate of these elements in the environment and for proposing new decontamination technologies. Moreover, some of their

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isotopes are of potential medical interest for targeted alpha therapy (TAT) applications (^{227}Th, ^{226}Th, ^{230}U) [6]. We will present solution complexation studies of U(IV) and Th(IV) with hydroxamic acid ligands, by using affinity capillary electrophoresis, UV-vis absorption spectrophotometry, electrochemical methods, and quantum chemical calculations (density functional theory (DFT)). Special attention has been payed to equilibrium studies involving original abiotic polyhydroxamic ligands.
Finally, U(IV) hydrolysis will be discussed, as it can play an important role in the complexation equilibria. We will point out some contradictions found in the literature. Obviously, U(IV) hydrolysis is currently still a matter of debate and is not fully understood, although a better knowledge of that system could help us understand the hydrolytic behaviour of other highly radiotoxic tetravalent actinides.

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Free gallium (III) determination with AGNES (Absence of Gradients and Nernstian Equilibrium Stripping)

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Gallium equilibrium speciation is of interest in environmental studies and in medical research. The knowledge of the free fraction (i.e. the hexaaquo cation) of Ga (III) in a natural water or in a growth medium is relevant for the Free Ion Activity Model (FIAM), which is hegemonic in ecotoxicology. Currently, there is no commercial ion selective electrode for measuring [Ga^{3+}], so that alternative techniques, such as AGNES (Absence of Gradients and Nernstian Equilibrium Stripping) can be helpful for measurements in a medium. AGNES has been successful in determining Zn, Cd, Pb, Sn and In free ion concentrations in a variety of matrices ranging from wine to seawater or nanoparticle dispersions [1-2]. In the case of Ga, AGNES results can also be used to distinguish between competing complexation models by comparing of the conflicting predicted gallium concentrations from the different models with the specific measured [Ga^{3+}] provided by AGNES.
The presentation will show how the electrodic irreversibility of the couple Ga^0/Ga(III) can be overcome with a suitable calibration strategy. The successful checking of equilibrium conditions will be shown, as well as suitable deposition potentials and times. The impact of hydrolysis will be discussed. AGNES results for mixtures of Ga with phthalate will be compared with predicted concentrations from existing complexation models.

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Ga(III) complexes as antimicrobial drug candidates. Solution studies, synthesis and antimicrobial activity

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There is an urgent need to develop novel antibiotics as antimicrobial resistance (AMR) is reported to be one of the leading causes of death worldwide. Multi-drug resistant pathogenic infections were associated with approximately 4.96 million deaths annually in 2019, with 4.95 million of these being directly associated with microbial AMR. The antimicrobial properties of metals have been well known for centuries, with many metal-based compounds playing important clinical roles as therapeutics and diagnostic agents.[1]

Microbes have a high demand for Iron (Fe) as it plays a vital role in DNA synthesis and oxygen metabolism. To satisfy this high requirement pathogenic microbes produce Fe-scavenging molecules known as siderophores, which sequester Fe from their extracellular environment and the hosts innate Fe transporting proteins. Consequently, siderophore Fe uptake systems can therefore be targeted as an antimicrobial strategy to enhance the uptake of antimicrobial cargos. Cefiderocol for example is a new FDA approved drug belonging to a new class known as siderophore drug conjugate's (SDC's) that hijack the bacteria's own Fe acquisition system to internalize a cephalosporin antibiotic. Furthermore iron chelators are also well-known to exhibit antimicrobial activity as iron withdrawal strategies can be employed to target microbes. Gallium (Ga) in its +3 oxidation state, Ga(III), is an effective Fe(III) mimic, since they have a similar size and the same charge. Significantly, Ga(III) is redox inert under physiological conditions and therefore cannot be reduced. It consequently inhibits critical physiological Fe redox activity and in turn Ga(III)-substituted proteins disrupt important metabolic pathways. Fe, for example, is found as a co-factor in numerous important enzymes such as oxidoreductases, which play roles in electron transfer, DNA synthesis and oxidative stress.[2]

Solution equilibrium studies were carried out for a series of siderophore analogues and corresponding Ga(III)-complexes. In particular, pKa values were determined for a series of catechol-based ligands, 2,3 DHBA, aminochelin and azotochelin and a series of Kojic acid-based ligands. Stability constants were also measured for their corresponding Ga(III) complexes. Overall, a series of Ga(III) complexes with catecholate and kojate derivatives has been

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successfully designed, synthesized and fully characterized. Progress to date in relation to the investigation of antimicrobial activity of the aforementioned complexes will also be reported.[2-3]

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[3] Unpublished results.

Mycobacterial Unusual Chaperonin GroEL1 and Its Complexes with Cu(II) and Ni(II) Metal Ions

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The mammalian immune system's response to mycobacterial infection is the increase of various metal ion concentrations in phagosomes to a toxic level [1, 2]. Mycobacterial GroEL1 chaperonin is an essential component of a response to toxic Cu(II) levels [3]. Understanding the process of metal homeostasis is necessary to overpower multidrug-resistant *M. tuberculosis*.
In this project, we present the properties of GroEL1 His-rich C-terminus as a ligand for Cu(II) and Ni(II) ions. We studied the thermodynamic properties of seven model peptides: Ac-DKPAKAEDHDHHHGHAH and its 6 His mutants in the pH range 2-11. The exchange of each single His to Gln residue did not disrupt the ability of the ligand to provide 3 binding sites for Cu(II) ion. Despite the most possible preference of Cu(II) ion for the His9-His13 residues (Ac-DKPAKAEDHDHHH-), especially the His11 residue, the study shows that there is not only one possible binding mode for Cu(II). This phenomenon may be important for the GroEL1 function – if the single mutation occurs naturally, the protein would be still able to interact with the metal ion. However, when the excess of Cu(II) ions is present, single mutations can impact the ability to form polynuclear species [3]. In the case of Ni(II) complexes, we noticed that similarly to Cu(II)-complex, the presence of Lys5 residue significantly increases the stability of the system. The impact of His mutations was also examined and carefully studied with the use of NMR spectroscopy. His9 and His13 are the crucial residues for Ni(II) binding (Figure 1), whereas His12 has minimal relevance in complex formation [4].

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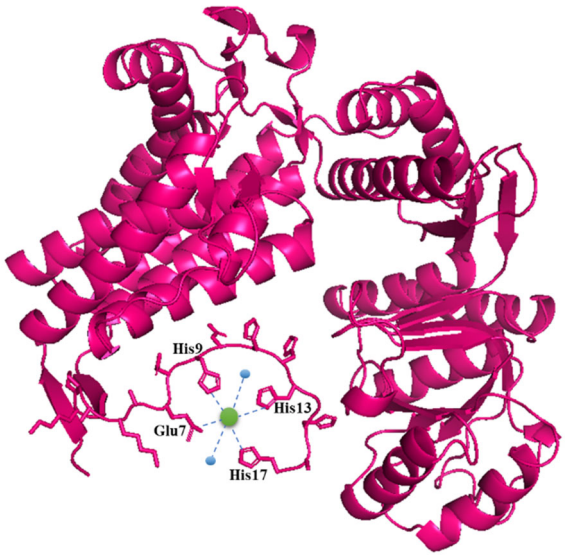

Figure 1. Proposed coordination sphere for Ni(II)-Ac-KPAKAEDHDHHHGHAH complex at pH = 7.1. Green dot: Ni(II) ion, blue dots: water molecules. The structure of the GroEL1 protein is based on simulation by Phyre2. Figure was generated using PyMOL.

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How essential is the choice of method to evaluate the equilibrium constant? The case of Ag(I)-anthracenyl biscarbene/DNA system

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How to efficiently and robustly find the value of a binding constant between a small molecule and a nucleic acid? The connected calculations appear in many papers as some easy routine. Instead, the procedure to extract numbers from experiments deserves many tricky aspects, which may turn our values random [1]. This problem is at the basis of the task of one of sub-groups (TG2) of the Working Group 2 (WG2) of NECTAR COST Action.
In this contribution, fully correlated with the work of WG2-TG2 – "Biosubstrates binding", we have studied the interaction of a nucleic acid-intercalator ($[Ag(BIA)_2]^+$, Figure 1) to natural DNA from the calf thymus (CT-DNA, B type). We did spectrophotometric and spectrofluorometric titrations under different salt content conditions. They were analysed using one-wavelength equations or multi-wavelength software (HypSpec®) to extract binding constants data. We will comment on the numbers obtained, their dispersion, and how the latter influences the discussion of salt dependence in the frame of the Record's theory [2].

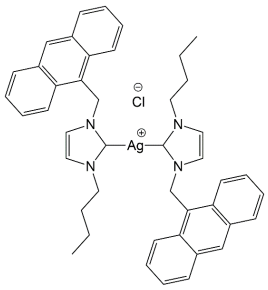

Figure 1. Molecular structure of bis(1-(anthracen-9-ylmethyl)-3-butylimidazol-2-ylidene) silver chloride, $[Ag(BIA)_2]Cl$

Acknowledgements:

This contribution is based upon work from COST Action CA18202, NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research, supported by COST (European Cooperation in Science and Technology).

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Binding of unconventional Fluorescent Molecular Probes based on peptides conjugates to Serum Albumin and DNA

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The development of fluorophore-peptide conjugates (fluorophore + one or more 6kDa peptides called affibodies) for targeting cancer cells represents one of current research topics in our group. In addition to the study of interactions between affibodies and cellular receptors, it is also essential to understand the interactions between the fluorophore alone or the fluorophore-containing linkers and surroundings biomolecules such as proteins and DNA.

The STSM was thus focused on spectrophotometric investigations of binding (intercalation, adsorption) of our unconventional molecular probes, previously synthetized in our lab, to DNA or to BSA as a model protein. In case of interaction, the aim was to quantitatively determine the stability constants. It is worth to notice that such fluorescent molecules have been rarely investigated for this purpose.

The related titrations were thus performed using LS55 Perkin-Elmer spectrofluorometer for fluorescence experiments, and a Perkin Elmer Lambda 35 UV-vis spectrophotometer for absorbance experiments. This work enabled us to characterize absorption and emission spectra of our 5-6 fluorophores (with or without linker). A quantitative treatment of binding curves provides information about the affinity [1,2]. Interestingly, the binding is more pronounced with DNA than with BSA, which is rather encouraging for our applications taking place in cytoplasm. The obtained results are of importance for optimizing experimental conditions for an efficient detection of fluorophore-conjugates in flow cytometry analyses and confocal microscopy of cancer cells, and will be discussed during the presentation. The use of complementary biophysical techniques (i.e., fluorescence anisotropy) is envisaged to corroborate our analysis in the future.

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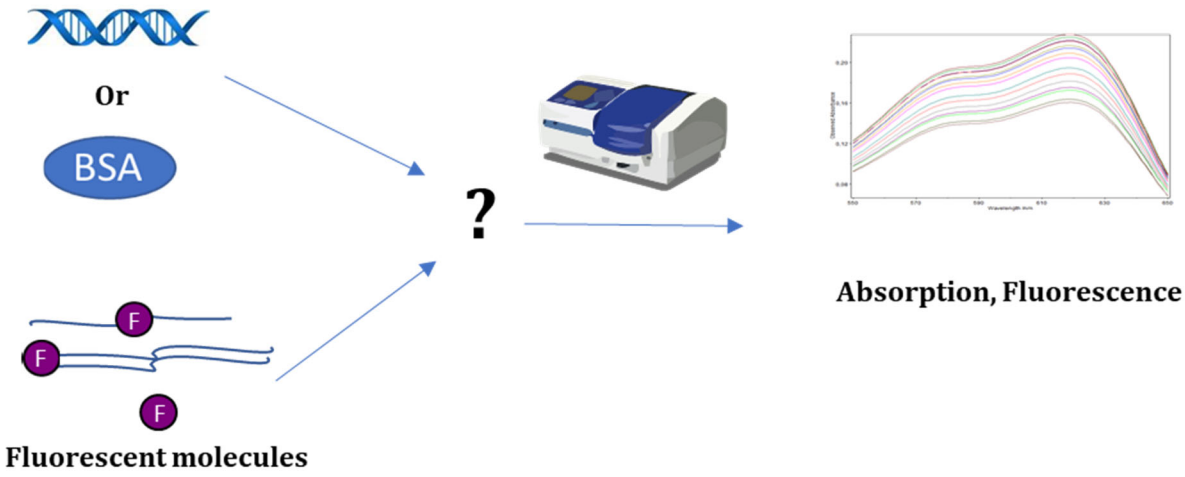

Scheme: Principle of spectrophotometric analysis of binding interactions between fluorescent molecules and biomolecules

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A network to define recommended procedures for potentiometric measurements of stability constants

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The determination of reliable formation constants for metal complexes in aqueous solution is a fundamental step to define the behavior of a chemical system. The experimental path that leads to determination of values of the stability constants is as important as challenging.

Several experimental and theoretical aspects need to be considered when the experiments and the calculations are done, and the workflow needs to be carefully planned.In 1987, *Braibanti et al.* [1] published some recommended procedures for testing the apparatus and techniques for pH-metric determination of stability constants of metal ion complexes by means of the "Nickel-Glycine Project".

In the context of the NECTAR COST Action 18202, and inspired by the pioneering work of *Braibanti et al.,* different laboratories active in the field of stability constants measurements, from several European countries, worked together to enlarge and refresh the view on potentiometric measurements. Recommended procedures for potentiometric determination of equilibrium constants of metal ion complexes with polydentate ligands were described summarizing the know-how and experience of the involved laboratories. The laboratories were involved in the measurement of the formation constants in a real system to obtain an inter-laboratory comparison.

A well-known system was chosen as case of study: Zn(II) as metal ion and H_4edta (EDTA) as ligand were considered. H_4edta possesses incredible features to test the analytical procedure for the calculation of stability constants. The ligand is widely used in most of the laboratories, is commonly available at high level of purity and appears in different protonation states along a wide pH range.

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The involved laboratories agreed on several aspects concerning the experimental work: from the preparation and standardization of the reagents to the instrumental details adopted during the measurements. The experience of the involved researchers leads to description of the recommendations that need to be followed in order to successfully determine the equilibrium constants of polydentate ligands and their metal ion complexes. Besides the pure experimental aspects regarding the use of suitable reagents and their manipulation, the importance of (*i*) well designing the experiments, (*ii*) proper electrode calibration and (*iii*) good data treatment were highlighted.

The different laboratories worked on the Zn(II)–H_4edta system determining the protonation constants of the ligand and the formation constants of the metal complexes following an established experimental plan. The concentration levels of the tested compounds were previously decided, and the instrumental parameters were similar in all the involved laboratories. The experimental details adopted were common. KCl was chosen as background electrolyte and ionic strength was fixed at 0.1 mol·dm^{-1}. KOH and HCl were used as strong base and acid, respectively., The ligand dipotassium salt ($K_2H_2EDTA{\cdot}2H_2O$) was used as ligand source and standardization procedure of both the ligand and the metal ion solutions were adopted.

The obtained constants values were compared between them and with the literature data to stress any weakness in the workflow. The results were used to estimate the uncertainty of the constants, and to assess the repeatability and reproducibility of the measurements.

Acknowledgements:

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The accurate assessment of the chemical speciation of complex systems: a multi-technique approach

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In the past two to three decades, a growing interest in techniques intended for chemical speciation studies has been observed since it is known that both the bioavailability and toxicity of a particular element in a specific environment are strictly linked to its chemical form. Research in biochemistry and toxicology has revealed that, for living organisms, the chemical form or the oxidation state in which a particular element is released into the environment is of paramount importance, along with the quantities involved. Hence, to glean insights into the behavior of the specific component (metal or ligand) in the environment, especially interacting with living organisms, it becomes essential to obtain a distribution of its individual chemical and physical forms, as it is well established that the determination of total concentration fails to offer adequate details for an understanding its behavior.

Such a complex problem necessitates a suite of techniques that captures all relevant interactions of an element (or molecule) with all other components of a given environment/system and allows the determination of the thermodynamic parameters of these processes. In order to evaluate the chemical speciation of the metal ion of interest in the presence of strong ligands in real aqueous systems, such as, for example, biological fluids, the knowledge of metal ion coordination equilibria may be crucial. Potentiometry and UV-Vis spectrophotometry, followed by computer data analysis, have long been regarded as the most accurate methods to determine binding affinities of metal complexes as they provide universally applicable stability constants in solution. However, investigating more complex systems (e.g., ligands with several different binding sites, very strong chelators, unconventional conditions, multicomponent solutions, etc.) has introduced new challenges and questions for solution chemists. Consequently, complementary techniques and/or approaches are becoming even more necessary to get further insights, for example, on the nature of species effectively formed, their structure, and reactivity.

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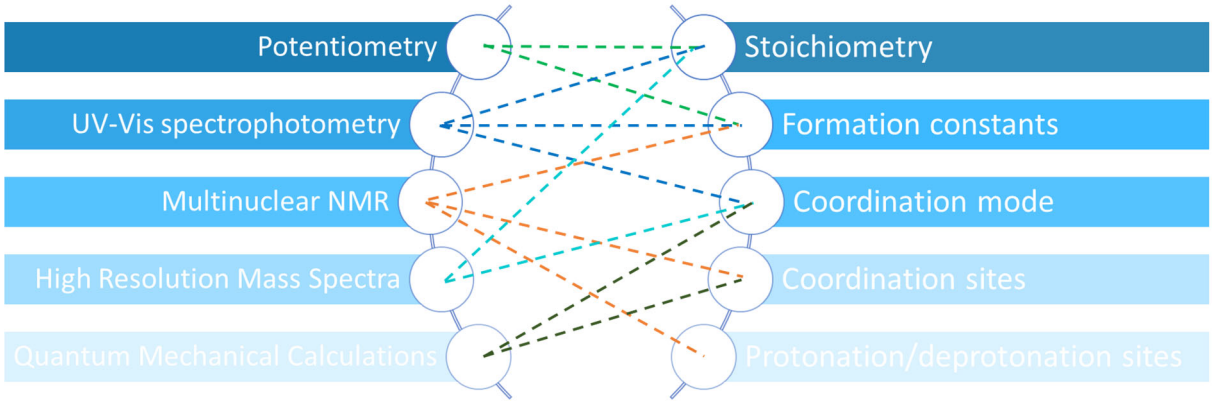

This communication aims to highlight the importance of the use of a multi-technique approach for accurate assessment of chemical speciation of complex systems. Several examples will be shown to demonstrate how these techniques and approaches have been exploited to complement potentiometric and/or spectrophotometric results to solve some issues related to the assessment of the chemical speciation of exceptionally complex systems. In particular, the results relative to the binding ability of some multi-hetero-dentate ligands (namely natural and synthetic metallophores) towards metal cations of relevance will be discussed.

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SpectrApp and PyES, two free tools for soft and hard modelling of chemical systems

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We live in an age in which information is becoming more and more relevant. Data is the source of information, and nowadays, we can acquire, store and sort huge amounts of data. Although the amount and the quality of acquired data alone are extremely important, their correct treatment can make or break the outcome of a research program. The idea is to extract from the data models that can help to make better, more accurate and explainable decisions.

The concept of "building models" from data can usually take two forms. *Soft modeling*, often synonymous with data-driven or empirical approaches, relies on flexible algorithms to capture intricate relationships within complex systems. In contrast, *hard modeling* employs mechanistic principles, emphasizing a detailed understanding of underlying physical and chemical processes.

The synergistic use of both modeling approaches can be an important tool available to researchers, particularly because each technique has its strengths and weaknesses. *Soft modeling* techniques demonstrate an unprecedented capacity to discern complex patterns and relationships. However, the interpretability and transferability of these models to deterministic physical events can be challenging. On the other hand, *hard modeling* approaches offer a more intuitive representation of physical phenomena but may falter in the face of complex, non-linear systems. The application of such techniques, usually associated with the necessity to dive into the endeavor of tackling programming, statistics and linear algebra, can pose a barrier for day-to-day research projects, due both to the time required to master these interdisciplinary requirements and the amount of work to develop the tools required for the job.

To address these challenges, we argue that the dedicated development of custom-tailored IT tools is extremely important for researchers in the field, not only for their convenience of use, but also by providing a unified platform for model development and validation. With this work, we aim to showcase two of these tools.

SpectrApp[1] aims to be a one-stop solution for small to mid-sized soft modeling problems, with chemical and analytical systems as its core targets. It provides tools for loading, cleaning and

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manipulating datasets coming from different sources. Guiding the end-user through the so-called “best practices” when dealing with data-driven problems, such as rationally sound pre-processing steps, exploratory analysis of the feature space and correct application of chemometrics algorithms. It is available both as a web application, hosted on a UniTO server accessible free of charge, and as an installable application that can be run locally on the user's machine.

PyES[2] is a released software, available for all major operative systems, for the computation of species concentration at thermodynamic equilibrium. By defining the composition of a chemical system and the equilibrium constants that regulate its evolution, it is possible to compute the concentration of all the species present in different conditions. Recently, the groundwork for implementing routines for the refinement of the constants themselves from potentiometric experimental data has been laid down, with the intention of including other experimental procedures as data sources as well.

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Microspeciation Analysis with GEMS

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The determination of protonation constants is a task of major importance in Chemistry.[1] For polyprotic species, with more than one protonation centre, there are several protonation constants which contain information about the degree of protonation but not on where the protons are located within the structure of the molecule. The resolution of the microspeciation can sometimes be useful, but it is not an easy task because not all analytical techniques convey information about the individual protonation sites. Usually, NMR titration data is the preferred tool for the job because a correspondence can be assigned between the nucleus that is shifting and the centre that is being protonated in each step.[2-4] We have carried out NMR titration of a set of three azamacrocycles. The we use a new tool called GEMS,[5] a piece of software which implements Cluster Expansion Techni-ques[6,7] and Symmetry Simplification[8] and allows the fitting of the protonation microconstants and the resolution of the microspeciation. We present the proto-nation scheme of these azamacrocycles and validate the results obtained with additional techniques.

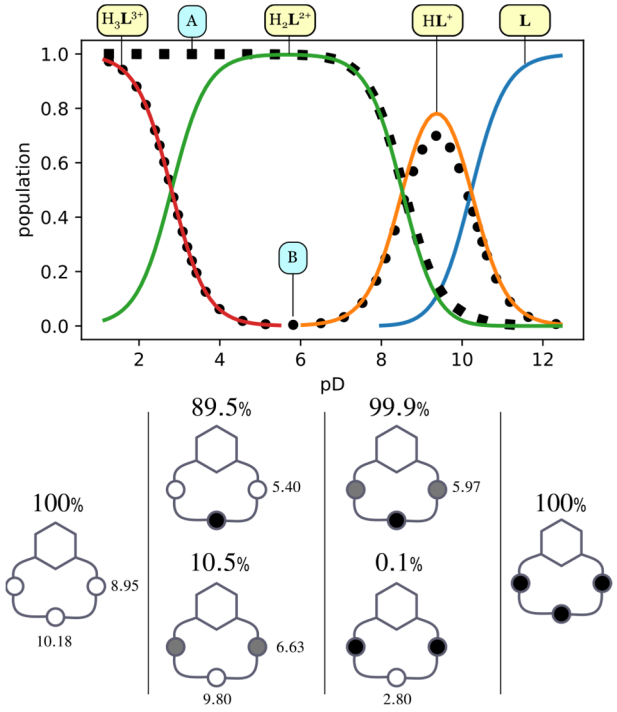

Figure 1: Microspeciation of the 3, 6, 9-triaza-1-(1, 3)-benzena-cyclodecaphane. (Top) Species distribution (solid line) and protonation centres population (marks). (Bottom) protonation microconstants and microspecies population.

Acknowledgments:

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Can solution equilibria drive the development of pH-responsive drug delivery systems?

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In the search for a strategy to overcome the intrinsic limitations of several drugs (low solubility, poor permeability, and short biological half-life) which can affect their efficacy and/or induce toxicity, the past decades have witnessed many efforts in developing nanocarriers to deliver many and varied classes of payloads. [1]
Stimuli-responsive systems gained particular interest in getting through the shortcomings in the targeted delivery of drugs as they allow *"on-demand"* processes that account for the tailored site- and time-controlled release of therapeutics by the *"smart"* recognition of the altered surrounding microenvironment of a specific pathology. [2]
Although rarely considered, the affinity of a drug for a specific carrier plays a pivotal role in understanding its binding and release ability. At the same time, the thermodynamic fingerprint of this interaction provides fundamental insights into the mechanisms of the binding processes which are essential for developing successful drug delivery systems. [3-5]
Within this framework, we propose the detailed thermodynamic analysis of the equilibria occurring in solution as a key strategy for designing and developing stimuli-responsive drug delivery systems. This approach was used to prepare pH-responsive carriers by exploiting the non-covalent assembling of selected model drugs (quercetin, Que and methotrexate, MTX), pH-sensitive molecule (poly(acrylic acid), PAA) and metal ions of biological interest (Cu^{2+}, Zn^{2+} and Co^{2+}) (**Figure 1**). [6]

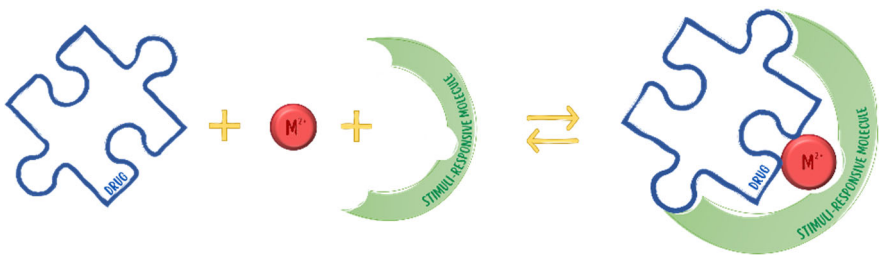

Figure 1. Schematic representation of the metal-coordinated assembly formation

The accurate study of the assembly formation, which relies on the acid-base properties of the polymer and drug functional groups as well as their complexing ability towards metal ions, implies that all the chemical equilibria involving the system components have to be considered. To this aim, the binding features and the thermodynamic parameters for the interaction of the drugs (Que or MTX) towards the metal ions and PAA as well as of the metal ions with PAA were

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investigated in aqueous solution at 25 °C and pH 7.4 through UV-Vis spectrophotometry and isothermal titration calorimetry (ITC). The detailed analysis of the solution equilibria permitted the development of Que or MTX-based assemblies containing Cu^{2+}, Zn^{2+} or Co^{2+} and PAA for potential anticancer and/or antimicrobial applications. The stabilization properties of these systems and the controlled release of the model drugs under pH control were investigated in solution (UV-Vis) and at the solid-liquid interface (quartz-crystal microbalance, QCM-D). [7]
The importance of the metal ions in the assembly formation was further proved by preparing a poly-lysine(PLys)-based system containing MTX by exploiting the electrostatic interactions between the anionic groups of the drug and the positively charged moieties of the polymer at pH 7.4. The affinity of MTX towards PLys as well as the pH-sensitive release of the drug were investigated both in solution and at the interface by UV-Vis, ITC and QCM-D experiments.
Finally, envisaging a possible biological application of these delivery systems, the ability of the MTX-based assemblies to interact with human serum albumin (HSA) was explored both in solution and at the interface.
Overall, this work highlighted how solution equilibria and their accurate analysis can be fruitfully used in the design and development of effective stimuli-responsive drug delivery systems. This research perfectly fits the activities of the Working Group 2 and 4 of the NECTAR-Cost Action CA18202 dealing with the study of systems containing structurally complex molecules and the determination of thermodynamic parameters and analysis.

Acknowledgements:

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Understanding the coordination behavior of Eu(III) in [P_{66614}][Decanoate] Ionic Liquid

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Ionic liquids (ILs) have emerged as a promising alternative to conventional organic solvents in the liquid-liquid extraction of metal ions from waste streams due to their unique properties, including negligible vapor pressure, good thermal stability, wide electrochemical windows, and intrinsic high conductivity [1,3]. Hydrophobic quaternary phosphonium ([P_{66614}]$^+$) ILs have shown a good performances in meta ions separations on the lab scale and potential for upscaling as they are relatively less expensive than other ILs families[4].

In this study, we focused focus on trihexyl(tetradecyl)phosphonium decanoate, ([P_{66614}][Dec]) (Figure 1), notable for its convenient recycling and reuse, in addition to the environmentally friendly decanoate anion. This ILs has proven effective in selectively extract and lanthanide(III) ions [5] and separate them from other transition metals.

However, the nature of the extracted Ln(III) ions is not clear. To achieve a deeper understanding of this aspect we employed luminescence spectroscopy to characterize the coordination of Eu(III) in [P_{66614}][Dec]. This spectroscopic technique, has been shown to provide useful information on the coordination environment around the emitting Ln(III) ion in ILs [6].

The results of the study provide insights into the coordination mode and contribute to the understanding of the metal-ligand interaction in the context of liquid-liquid extraction processes. Furthermore, the impact of various environmental factors, such as temperature and timing, on the coordination behavior of Eu(III) in [P_{66614}][Dec] was systematically explored. The insights gained were not only crucial for expanding fundamental understanding of IL coordination chemistry but also offering valuable information for future developments in metal ion recovery from waste streams.

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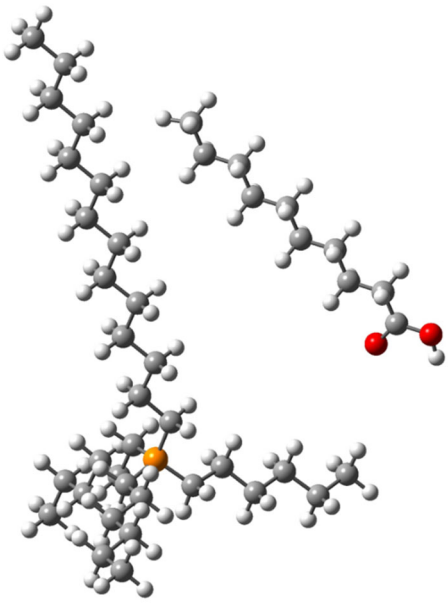

Figure 1. Graphical representation of $[P_{66614}][Dec]$.

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AM&MS acknowledge the University of Udine for the fellowship funded through the European Union – NextGenerationEU - MSCA Grants D.M. 737/2021.

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Equilibrium extraction in aqueous biphasic systems based on ionic liquids

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Ionic liquids (ILs) are organic salts that exist in the liquid phase at temperatures < 100 °C and there are up to 10^{18} possible candidates for this group of compounds. By using different ions arrangements it is possible to design ILs to fit the requirements of a certain application which is the most important feature of ILs. Furthermore, ILs can be tailored to exhibit minimal toxicity or significantly reduced toxicity when compared to traditional organic solvents. As potent and designed solvents with adjustable physical and chemical properties, ILs find successful application in extraction processes, serving as both solvents and task-specific extractants simultaneously. Moreover, extraction procedures can be optimized to yield extraction mixtures with over 95% water content [1].

The equilibrium extraction process in ABS involves the partitioning of solutes between the two immiscible phases at thermodynamic equilibrium. This partitioning is driven by the differences in the physicochemical properties of the solutes and the composition of the biphasic system. The two phases create a unique environment where selective extraction and separation of target compounds can occur, offering advantages over traditional liquid-liquid extraction methods. Factors influencing equilibrium extraction in ABS include the choice of phase-forming components, their concentrations, and temperature [2].

In this study, the effects of ILs structure and the composition of ABS on the equilibrium extraction of the selected textile dyes Orange II (4-(2-Hydroxy-1-naphthylazo)benzenesulfonic acid sodium salt, OII) and Remazol brilliant blue R (1-amino-9,10-dioxo-4-[3-(2-sulfonatooxyethylsulfonyl)anilino]anthracene-2-sulfonate disodium salt RBBR) have been studied.

Firstly, the building of ABSs based on the symmetric imidazolium ILs: 1,3-dibutylimidazoliumdicyanamide and bromide ([bbim][DCA], [bbim][Br]), and ○ 1,3-diethylimidazolium dicyanamide and bromide ([eeim][DCA] and [eeim][Br]) combined with phosphate salt was investigated (Figure 1). ABS based on [bbim][DCA] shows the best properties e.g. the largest biphasic area, and exceptionally low amount of salt (~2%) is required to induce two phases.

Secondly, the effect of ILs on the extraction of the targeted textile dyes was investigated. In all investigated ABSs, the dyes preferentially migrated into the upper IL-rich phases. Obtained distribution ratios ranged between 218 and 394 for RBBR, and from 345 to 703 for OII. distribution ratios for both dyes decrease in the following order [bbim][DCA] > [bbim][Br] > [eeim][DCA] > [eeim][Br].

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The driving forces which govern the partition behavior of selected dyes are the hydrophobicity of the ILs, π-π and Coulombic interaction between IL and dye molecules, and salting-out effect of inorganic salt. The binding energies of IL-cation/IL-anion and IL-cation/dye interactions are also calculated in order to further explain the distribution of dyes in the IL-ABSs. The more negative ΔG_{bin} values and a higher number of non-covalent interactions were obtained for the interactions between symmetrical IL cations and OII in comparison with RBBR. Considering that the molar volume of OII is lower, it can easily approach to IL-cation and establish stronger non-covalent interactions than RBBR which readily explain generally higher distribution values of OII.

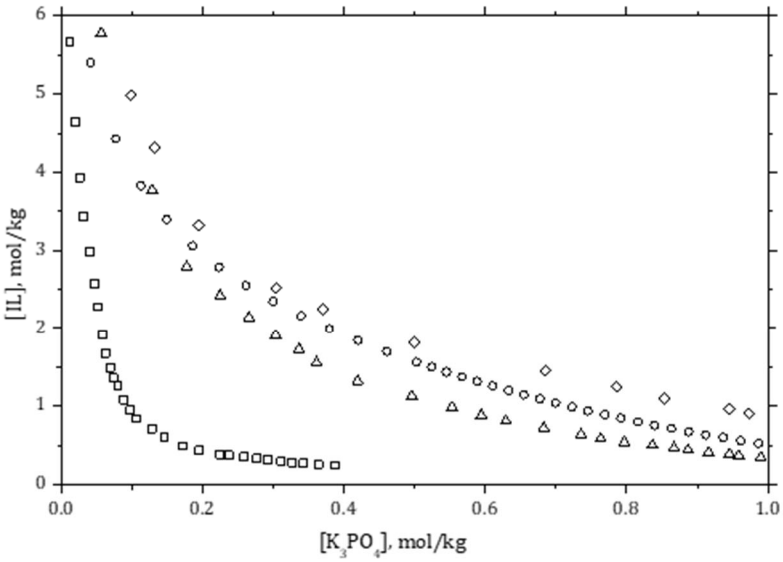

Figure 1. Binodal curves of the studied ABS {IL + K_3PO_4 + H_2O} based on ILs at 296.15 K and 0.1 MPa. Legend: □ [bbim][DCA], Δ [bbim][Br], ○ [eeim][DCA] and ◊ [eeim][Br].

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Poster Communications

Transition metal complexes of Schiff base ligands as G-quadruplex DNA binders

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In the search of DNA-binding molecules with preferential affinity toward G-quadruplex (G4) compared to double-helical DNA, we have recently designed and synthesized several Schiff base complexes of transition metal ions.[1-3] The DNA binding has been studied by using both experimental and computational approaches. Some of these metal compounds have shown *in vitro* biological activity against human cancer cell lines, that was related to the inhibition of the DNA properties. Besides the important role of the metal ion in determining the DNA-binding strength, the nature of aromatic ring on the N,N' bridge of the Salen scaffold (Fig. 1a) and of positively charged side chains allow to opportunely tune the DNA-binding properties of the resulting metal complexes. In this context, we have recently found that a Cu^{2+} Salphen-like complex (Fig. 1b) shows interesting catalytic activity for the selective epoxidation of styrene. Since analogous transition metal complexes are also effective and selective G4-DNA binders, we are currently investigating the possible catalytic oxidation of guanine DNA bases into 8-oxoguanine, and how this may affect the G4-DNA structure and stability.

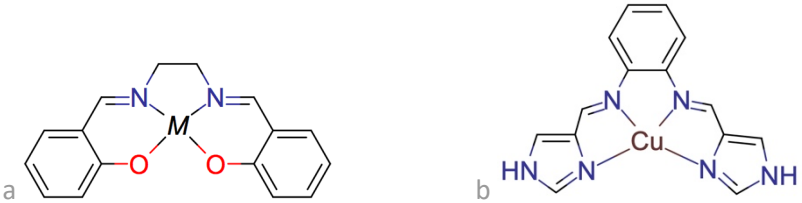

***Figure 1**: Structure of a generic Salen metal complex (a) and of a Cu^{2+} Salphen-like complex (b)*

Acknowledgements:

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Proton binding characterization of Dissolved Organic Matter extracted from natural river systems

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The global carbon cycle supports current and future life on Earth, with dissolved organic matter (DOM) acting as a key bioactive carbon reservoir. Carbon cycle and thus climate, can be altered due to the mobilization of the DOM carbon pool, which depends on the DOM physicochemical characteristics.

Dissolved organic matter is formed of structurally complex and poorly defined compounds with a size range <0.2/0.7 µm. This diversity on the chemical composition of DOM has large implications on its accumulation, fate, physicochemical properties, and thus binding behaviour. The direct analysis of marine DOM has proved difficult due to its low concentration, especially in open-ocean environments (<1 mg DOM/L). Thus, DOM physicochemical analysis is challenging and usually requires pre-concentration and isolation techniques.

Despite the DOM inherently heterogeneity and complexity, carboxylic acids are nevertheless one of the main chemical functionalities in its structure followed in a smaller proportion by phenolic compounds. Thus, DOM possesses fundamental acid-base properties, which can be investigated [1-4].

Two distinct systems located in Spain were selected as study sites:

1) The Ebro River, its delta and plume into the Mediterranean Sea.

2) The Mero River, the Coruña (Burgo) Ría (NW of Spain) and its outflow into the Atlantic Ocean.

Preliminary results of the DOM proton binding capabilities are presented in this meeting together with other ancillary data collected during the sampling process.

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From biological systems to metal-binding tools: the case of polyhistidine peptides

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In biological systems, and in particular in proteins and peptides, there is only a relatively small number of potential metal ligands, corresponding to specific amino acids sidechains, and/or the amino and carboxylic ends of the sequence. Polyhistidine peptides have been reported to form relatively strong interactions with transition metal ions, mostly thanks to the imidazole ring of the histidine sidechain. Not surprisingly, many metal-binding proteins contain polyhistidine domains able to form metal complexes. The position of histidine residues, however, may affect the metal binding ability of the system [1].

In this work we take advantage of nature, and we investigate the HTHEHSHDHSHAH sequence of the N-terminal domain of YrpE protein, a zinc-binding system of *Bacillus subtilis* [2]. The fragment contains seven alternated histidines separated by only one amino acid. Comparing its Zn^{2+} and Cu^{2+} binding affinity with that of other His-rich peptides can therefore highlight its potential as metal chelator and unravel functional details about its bioactivity. Nevertheless, the information obtained by solution equilibria studies (Figure 1) is also useful for other purposes, e.g. immobilized metal ion affinity chromatography (IMAC), where purification of recombinant proteins is based on the metal interaction with hexa-histidine (His6-tag, -HHHHHH-), alternated histidine-glutamine and histidine-asparagine tags, or other natural derived polyhistidine tags [3].

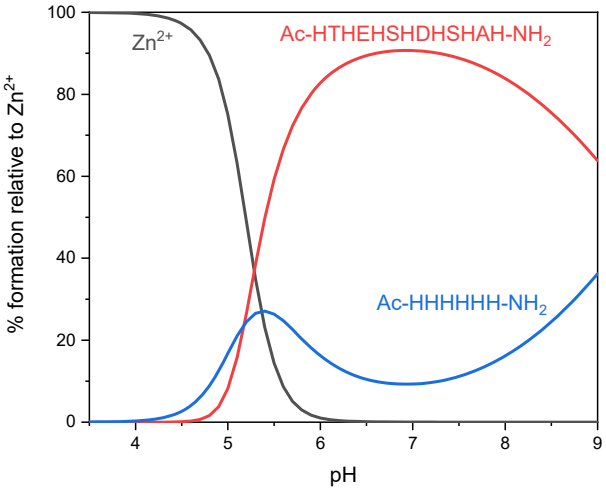

Figure 1. Competition plot for a solution containing Zn^{2+}, Ac-HTHEHSHDHSHAH-NH_2 and Ac-HHHHHH-NH_2 at equimolar amounts. The plot is based on the determined thermodynamic constants and describes the formation of the binary metal complexes with each component at different pH values.

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Potentiometry and spectroscopic techniques have been employed to describe the complex-formation equilibria and coordination chemistry of the formed species. Our thermodynamic results revealed that the YrpE domain HTHEHSHDHSHAH forms more stable metal complexes than other His-rich domains of the same protein family. Moreover, the studied $(\text{-XH-})_n$ motif proved to be more effective than the His6-tag in binding zinc ions, ideally opening the way to various applications aimed at sensing and trapping metals.

Acknowledgements:

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When hard modelling needs some help: case study 2- Chemometric-assisted investigation of Albumin interaction with sulfonephthalein dyes

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Hard models such as speciation modelling represent the most powerful tool for a chemist to describe and predict the behaviour of compounds in different environments, but their development might become extremely laborious and time-consuming when complex systems are under investigation involving different species and experimental conditions or even heterogeneous systems.

In all these cases, the application of soft modelling strategies, such as chemometric tools for experiment planning (Design of Experiments, DOE) [1,2] and data analysis (MultiVariate Analysis, MVA) [3,4], can provide valuable help in extracting information about the systems from the raw data, despite their complexity and in rationalizing the ongoing processes.

In this investigation, we applied chemometric tools to rationalize the interaction between albumin and five different halogen-containing sulfonephthalein dyes with different protonation constants [5]: bromophenol blue (BPB, $\log K_a$=3.75), bromocresol green (BCG, $\log K_a$=4.42), chlorophenol red (CFR, $\log K_a$=5.74), bromocresol purple (BCP, $\log K_a$=6.03) and bromothymol blue (BTB, $\log K_a$=6.72). The investigation focuses on evaluating the effect of this interaction on dyes spectral features, taking into account also the pH and ionic strength-dependent behaviour of both albumin and dyes. [6-8] Firstly an informative set of experiments has been designed testing, for each dye, four different buffered pH values (3.5, 6.0, 7.5 and 9.0) and two ionic strength conditions (native and after the addition of NaCl 0.5 M). An example of the UV-Vus spectra acquired is reported in Figure 1a.

Secondly, the UV-Vis spectra are submitted to Principal Component Analysis to rationalise the ongoing processes and highlight and explain the observed differences between dyes, pH values and ionic strength conditions. An example of the obtained score plots is reported in Figure 1b.

After qualitative investigations, the following step involves albumin quantification relying on the interaction with the selected dyes. In this case, for each set of dye and conditions, a dedicated regression model is developed and validated by Partial Least Square regression and the analytical performances are compared to identify the best experimental conditions for quantification purposes.

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Finally, the detection of albumin relying on the colour-changing mechanism shown by sulfonephthaleins dyes can be exploited in the development of colorimetric sensors for the detection and quantification of this important protein.

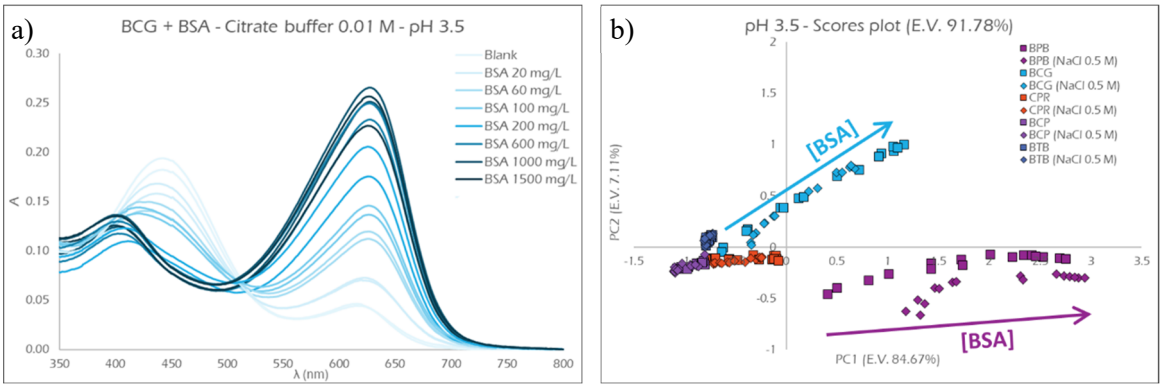

Figure 1: UV-Vis spectra of BCG (10μM) in citrate buffer 0.01 M at pH 3.5 upon addition of BSA (0-1500 mg/L) (a); score plot built on the first two principal components for PCA models built on UV-Vis spectra of BPB, BCG, CPR, BCP and BTB, at native or buffered I (NaCl 0.5 M), registered at pH 3.5

Acknowledgements:

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Artificial catalytic copper proteins based on the Spy technology. When the peptide's tail matters!

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Metalloproteins promote several of the most complex biomolecular processes in Nature. The design of new metalloproteins is therefore of interest in the field of the development of new efficient biocatalysts which can carry out reactions that are not relevant for biological systems but are important for applications in bio- and nanotechnology.[1] In the redesign of metalloproteins one of the major challenges is the introduction of metal binding sites in specific position of the construct, here makes possible by the "Trojan-horse" strategy. A peptide, bearing a metal site, interacts with a protein anchoring a metal site to the protein. Here we present a new copper protein designed using the SpyCatcher/SpyTag construct.[2,3]
The SpyCatcher construct is a β-barrel protein (Fig. 1, blue) which binds covalently an oligopeptide called SpyTag (Fig. 1, green) through the formation of an isopeptide bond between an Asp and a Lys residues.

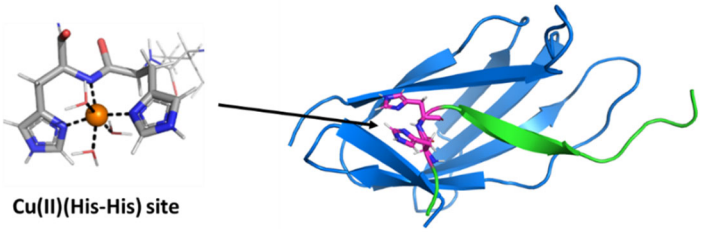

Figure 1: Representation of the SpyCatcher/SpyTag adduct. SpyCatcher is represented in blue, SpyTag is represented in green. The His-His copper binding site is represented in magenta.

Despite a short sequence of 5 amino acids, called consensus sequence (IVMVD), presents in the SpyTag is recognized as the key for SpyCatcher/SpyTag recognition and therefore the isopeptide bond formation with the consequent formation of the complex SpyComplex/SpyTag, there are no evidence concerning the role of the positively charged tail of the SpyTag.
Through a computational study and a mass spectroscopy study we now know that the positively charged tail of the SpyTag peptide plays a crucial role in the SpyTag/SpyCatcher complex recombination and it cannot be neglected in the next SpyTag sequence design (Fig. 2).

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Moreover, we have studied different SpyTag peptides, bearing a His-His site, to specifically direct copper binding to these sites. SpyTag and SpyCatcher were independently fully characterized by absorption, CD, fluorescence and potentiometry.

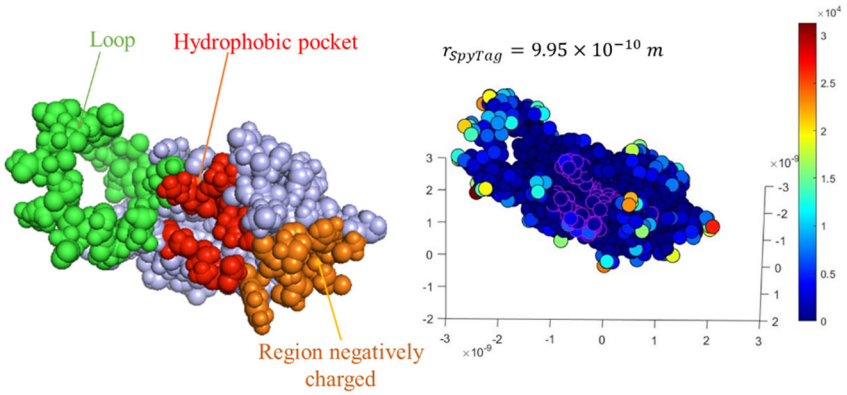

Figure 2: Left: Representation of the SpyCatcher. Loop is represented in green, hydrophobic pocket (where the SpyTag forms the isopeptide bond with the SpyCatcher) is represented in red and tail is represented in orange. Right: Simulation of collision frequency between SpyCatcher and SpyTag.

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Influence of methyl salicylate as an additive on structural organization and caffeine solubility

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Caffeine is a widely used psychoactive substance that belongs to the group of xanthine alkaloids. It acts as a stimulant for the central nervous system, cardiovascular system and metabolism. Caffeine can be found as an ingredient in coffee, black and green tea, as well as soft and energy drinks, sports supplements for fat burning, anti-aging creams, anticellulite creams, shampoos for hair loss, etc. [1]. Caffeine presents a challenge for creating concentrated solutions or storing it at lower temperatures due to its low solubility in water. The body's ability to absorb caffeine depends on its solubility in water and self-aggregation. Caffeine is considered limitedly soluble in water due to the self-association and aggregation of caffeine molecules by hydrophobic interactions [2]. Our research aims to determine caffeine solubility and the structural organization of its molecules in solvents suitable for wide use in the previously mentioned industries. One of the molecules that meet both criteria is methyl salicylate. Usually, it is used as a fragrance and as a flavouring agent in mouthwash in low concentrations [3]. However, in higher concentrations, methyl salicylate is used as a topical analgesic for muscle pain [4].

The present study analyzed experimental data from solubility, volumetric, viscosimetric measurements and computational simulations to understand caffeine aggregation properties in methyl salicylate. At lower temperatures, the solubility of caffeine in methyl salicylate is 69% higher than in water, while at higher temperatures, the solubility is 7% lower. The dissolution of caffeine in methyl salicylate occurs with heat absorption and an increase in the order of the system. The results noted in volumetric and viscosimetric measurements indicate that caffeine self-aggregation does not happen in the presence of methyl salicylate (Figure 1.). Molecules of methyl salicylate form a clathrate-like structure around the one caffeine molecule. Negative values of the S_v coefficient, as a result of the reduction of the apparent molar volumes of the system with an increase in the concentration of caffeine, indicate weak interactions between caffeine molecules in the methyl salicylate solution. Obtaines *B*-coefficients from viscosity measurements for caffeine in methyl salicylate had positive values and decreased with the temperature increased, which is a consequence of the breakdown of the solvent's clathrate-like structure. According to the molecular dynamic simulations, interactions between caffeine and

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methyl salicylate molecules occur through hydroxyl groups of methyl salicylate and carbonyl caffeine groups.

The study offers clear instructions on how the biocompatible solvent methyl salicylate improves solubility and prevents caffeine self-aggregation, making it ideal for topical and transdermal caffeine delivery in the pharmaceutical and cosmetic industries.

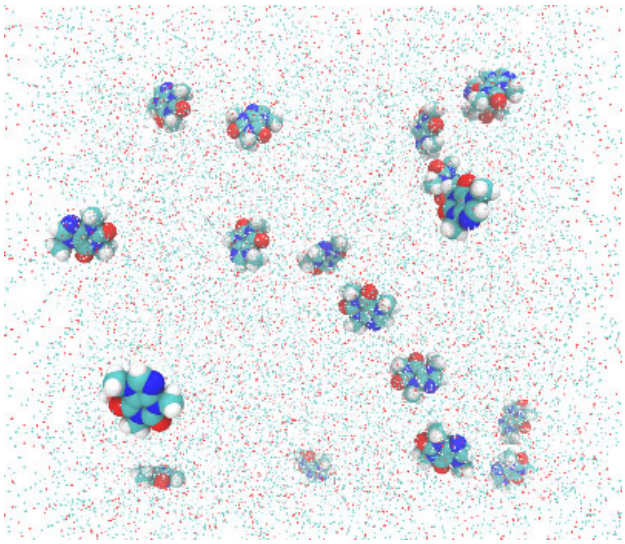

Figure 1. Visual representation of caffeine organisation in methyl salicylate solution.

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Automated spectrophotometric titrations *vs* pH : Better results and time-saving

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The determination of the protonation constants of ligands and of the stability constants of their metal complexes is at the heart of the NECTAR COST Action. When the ligands contain chromophoric groups, these determinations can be achieved by spectrophotometric titrations *vs* pH. The quality of the results relies, among other factors, on the number of pH values (and thus on the number of spectra) recorded and of the reproducibility of the titrations. Manual titrations are very experimenter dependent and time consuming. Improving reproducibility while saving time to the experimenter can be achieved by automating the system. We will present the coupling and interfacing of a potentiometric titrator (Metrohm Titrando 804 driven by Tiamo 2.5 software) with an UV-Visible spectrophotometer (Agilent Cary 60 driven by Cary Win-UV software) equipped with an external fiber-optic quartz absorption probe that allows to carry out completely automated spectrophotometric titrations vs pH. In addition to ensuring good reproducibility, this system also allows important time-saving.

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La(III) hydrolysis in aqueous solution at 298.15 K

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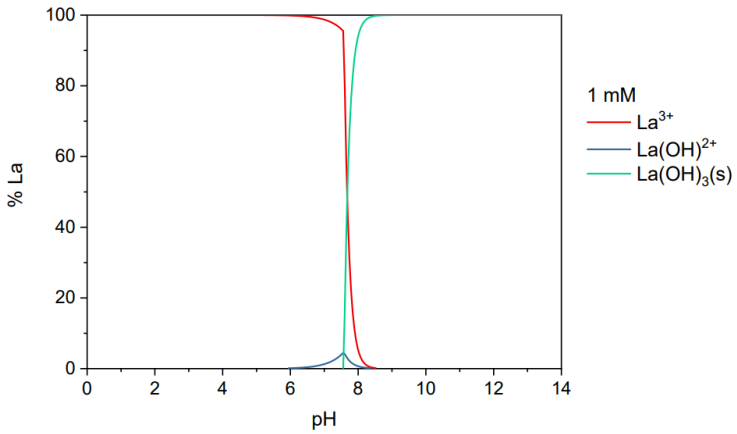
Lanthanum is often used in various electronic devices, such as catalysts, batteries, and optical devices. The extraction of lanthanum typically involves several steps, including mining, beneficiation, and chemical processing that can be complex and environmentally challenging due to the presence of radioactive elements in some ores. Therefore, to overcome this, recovery process in aqueous solution is the key to eliminate the pollution issues. For this reason, the knowledge of its acid-base properties is fundamental to understand La^{3+} behavior in aqueous solution. Literature analysis [1-5] revealed limited data and notable disparities on this subject, highlighting concerns regarding both the characteristics and stability of hydrolytic species of La^{3+}. This underscores the need for additional dedicated experiments to gain a more comprehensive understanding. For this reason, some experimental data at 298.15K were performed in NaCl and $NaClO_4$ at different ionic strength (0.1 to 1 mol dm^{-3}) and at different concentration of La^{3+} (0.5 to 2 mmol dm^{-3}).



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Determination of acidity constant of carboxyl-functionalized ionic liquds

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Ionic liquids (ILs) have gained significant attention in recent years due to their unique properties and environmental benefits. ILs are also known as "designer solvents" defined as organic salts with melting point below 100 °C. Unlike traditional volatile organic solvents, which can pose health and safety risks and contribute to air pollution, ionic liquids have low vapor pressure, wide liquid range, excellent chemical and thermal stability. Because of these excellent features, ionic liquids are widely used as solvents in organic, inorganic and material synthesis, biocatalysis and cellulose dissolution [1].

In this work, carboxyl-functionalized ionic liquids with different cations, $[C_1COOHmim]^+$, $[C_2COOHmim]^+$, $[C_1COOHetim]^+$ and $[C_2COOHetim]^+$ were synthesized. The characterization of the newly synthesized ionic liquid was performed by recording the IR and NMR spectra. The acidity constant for these carboxyl-functionalized ionic liquids were determined experimentally applying potentiometric method. In this technique, a glass electrode is used to measure the pH of the solution, while a reference electrode provides a stable potential. The ionic liquid is titrated with a standard base solution, and the potential changes are recorded as the pH changes [2].

For one of these ionic liquids with $[C_2COOHmim]^+$ cation, the acidity constant was determined experimentally and also by computational simulations, and the result was compared with the acidic constant of propanoic acid.

Acknowledgements:

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Towards the complementarity of solution equilibria and solid state studies in hydroxypyrones complexes

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Hydroxypyrones, as kojic acid (5-hydroxy-2-(hydroxymethyl)-4-pyrone, KA), are natural compounds which show a versatile chelating properties. Most of their derivatives exhibit low toxicity, therefore good biocompatibility, making them ideal candidates for the development of novel chelating agents in the fields of Bioinorganic and Medicinal Chemistry.

Three KA derivatives (named S1, S2, S3), synthetized according to a very easy and cheap method, joining the chelating properties of the pyrone molecules and those of polyamines, are here presented.

Firstly, they have been studied by solution methods, showing their coordination ability towards Fe^{3+}, Al^{3+}, Cu^{2+}, and Zn^{2+} and the effect of different length of the linker in the metal ion complexation.

With the aim to investigate their recognition patterns with different first-row transition metal ions, the second effort has been devoted to pursuing the crystallization and solving the crystal structure such complexes in solid state, by the use of single crystal X-ray diffraction, for a solution vs solid state comparison and to decipher the supramolecular structure of such systems and rationalize novel chelating strategies and targets for this versatile ligand.

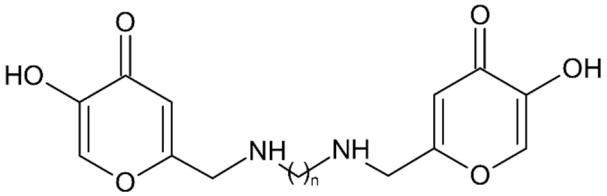

Figure 1: Kojic acid derivatives structure: S ligands where n = 2 in S2, n = 3 in S3 and n = 4 in S4.

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The removal of hydrocarbons from bilge water by biochar from *Posidonia oceanica*

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New biochar obtained by pyrolysis of *Posidonia oceanica*, a marine plant widespread in the Mediterranean Sea, was tested as adsorbent material of hydrocarbons from bilge water. The normal operations carried out on the boats during navigation generate wastewaters, namely bilge water, composed by potential pollutants of different origins and types: oily fluids, lubricants and greases, cleaning fluids and other wastes that accumulate in the lower part of the vessel [1,2]. Low concentration of this kind of pollutants can compromise the life of animals and plants of aquatic ecosystems [2]. The current legislation provides that they can be discharge directly into the sea if the concentrations of some components are below the expected limits. In particular, regarding oil/hydrocarbons contamination, the current regulatory limit is 15 mg L^{-1} of total hydrocarbons. Here we have characterized and tested biochars obtained from bio-oil production waste: adsorption experiments were carried out with the not activated biochar and with two chemically activated biochars by means of acid or alkali treatments. Moreover, a commercial activated carbon (Filtrasorb400) has been used for comparison purpose. Synthetic bilge waters were prepared following reference standards [3] containing MGO (marine fuel) and SDS (sodium lauryl sulfate). Batch adsorption isotherms were carried out without ionic medium and at different concentrations of NaCl in order to evaluate the effect of salinity on the adsorption ability of adsorbent materials. The same adsorbents were tested by column experiments. A bench pilot system was built, and breakthrough curves were obtained changing amount of adsorbent material in column, flow rate, initial MGO and surfactant concentrations. Several instrumental techniques (turbidimetry, TOC, HPLC-FLD) have been used to measure surfactant and hydrocarbon concentrations in experimental samples.
The experimental data were fitted with Langmuir, Freundlich and Sips models and important considerations were made on the breakthrough curves of column experiments.

Acknowledgements:
This contribution is based upon work from COST Action CA18202, NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research, supported by COST (European Cooperation in Science and Technology).

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Looking for Zn(II) complexes of cytokinin derivatives

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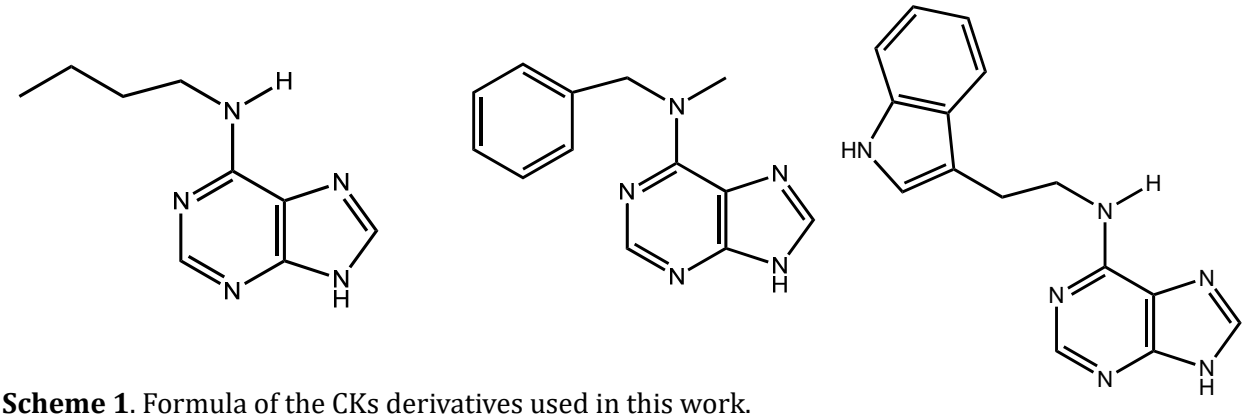
N6-substituted adenines are interesting substrates due to their cytokinin (CK) activity, i.e. play a central role in the regulation of the plant cell cycle [1]. Moreover, metal complexes involving N6-modified-nucleobase derivatives have been already reported as important approaches to achieve the optimal pharmacokinetic and pharmacodynamic characteristics of potential metallodrugs [2]. Herein we report the synthesis and solid state characterization of three Zn(II) complexes containing the synthetic CKs AdeC4 (N^6-alkyl-aminopurine), BAPC1 (N^6-benzyl-N^6-alkyl-aminopurine) and Ade-Triptamine (see Scheme 1)



Scheme 1. Formula of the CKs derivatives used in this work.

Acknowledgements:

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Antiproliferative fused indole derivatives and their copper(II) complexes: anticancer activity, solution studies and interaction with DNA

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Natural alkaloids latonduines and related multiring systems, such as indolobenzazepines, exhibit good antiproliferative activity [1]. The indole moiety, which is also present in vinca alkaloids, is the common structural component of the fused heterocycles shown in the Figure. Potent inhibition of tubulin polymerization has been reported for related structures [2]. Indolo[3,2-*c*]quinolines are known to induce apoptosis in cancer cells. These planar molecules most probably intercalate into DNA and inhibit topoisomerase I/II [3,4]. One of the main obstacles to develop more effective and more bioavailable agents is the limited aqueous solubility of the basic structure of these molecules. This issue can be addressed by the introduction of metal chelating sites into the molecule, since complex formation with metal ions fundamentally affects the charge, solubility and lipophilicity of a ligand. A series of compounds containing the indole unit fused to a bicyclic *N-heterocycle* and completed with a metal ion chelating function was syntesized together with their copper(II) complexes (Figure). The ring size of the N-heterocycles was increased systematicaly (from quinoline to benzazonine). The compounds with larger ring size, in contrast to the planar indoloquinoline platform, have a bent structure, which probably affects the mechanisms of action of these compounds. The attachment of morpholine, known as a pharmacophore moiety, can improve the pharmacological profile of a drug candidate.

Hereby, we present the results obtained on the *in vitro* anticancer efficacy, aqueous stability, solubility and lipophilicity of a series of indoloquinoline, indolobenzazepine, indolobenzazocine and indolo benzazonine derivatives and their copper(II) complexes [5,6]. Furthermore, stability in human blood serum and DNA binding of selected compounds were assayed as well. For the most promising compounds the biological studies covered apoptosis induction assay, profiling for cellular kinase inhibition, monitoring of ROS production, mitochondrial damage and double strand breaks in DNA. Solution chemical characterization and DNA binding studies were implemented by UV-vis spectrophotometry, steady-state and time-domain fluorescence spectroscopy.

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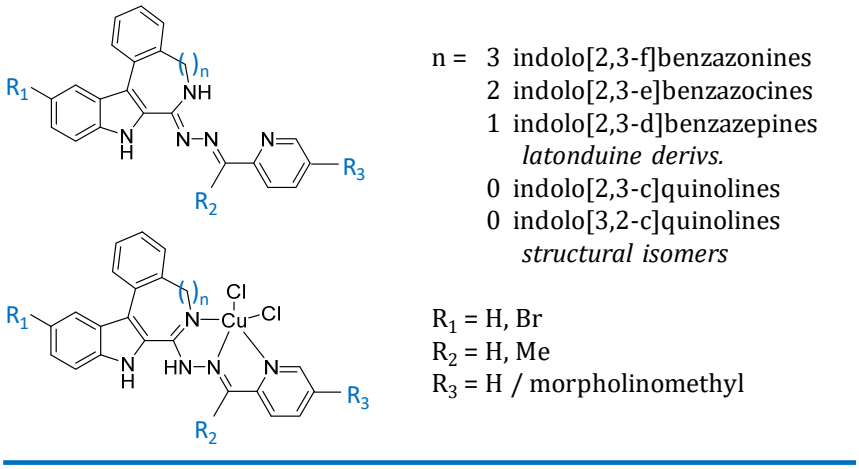

Figure. General structure of the studied ligands and their copper(II) complexes.

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Modulation of the anticancer and solution chemical properties of 8-hydroxyquinolines and oligopyridines via metal complexation

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The serious side effects and drug resistance associated with anticancer drugs still motivate the design and development of novel compounds that possess improved efficacy and selectivity. Numerous chemotherapeutic approved or potential drugs contain metal-chelating pharmacophores that act by complex formation with endogenous metal ions. Moreover, the intrinsic anticancer and physico-chemical properties of these organic compounds can be further fine-tuned by bioconjugations and/or metal complexation. Since, the metallodrugs may possess improved pharmacokinetic properties, such as improved aqueous solubility, optimized lipophilicity or serum protein binding. Particular derivatives of 8-hydroxyquinolines (8HQs) and oligopyridines, containing (*N*,*O*) and (*N*,*N*) donor sets, respectively, demonstrate significant anticancer activity based on *in vitro* assays [1,2].

8HQs exhibit strong chelation ability for various metal ions, and their broad pharmacological activity was reported. Substituents on the heterocyclic scaffold affect the pK_a values, the metal-binding ability as well as the anticancer properties. Mannich bases with methylamine R7 substitution display unique anticancer activity against multidrug-resistant cells [1], while the presence of a coordinating amine/imine moiety at R2 position can result in the tridentate binding of the ligands affecting the bioactivity [3-5]. In our collaborative work, Schiff-base derivatives were developed featuring hydrazone, morpholine or piperidine moieties alongside their reduced counterparts. Based on our solution speciation and structural studies, it could be concluded that these ligands form stable complexes with copper(II) and zinc(II) ions, which showed significant cytotoxic activity [3-5]. The bidentate 8HQs are able to form stable and cytotoxic complexes also with $[Rh(\eta^5\text{-}C_5Me_5)(H_2O)_3]^{2+}$ [2] and $[Ru(\eta^6\text{-}p\text{-cymene})(H_2O)_3]^{2+}$ organometallic cations [2,6], however, the bioactivity is strongly affected by the substituents on the 8HQ scaffold and the type of the co-ligand. In our collaborative work, the biological activities of a series of Ru(η^6-*p*-cymene) complexes of bidentate ligands, including a 8HQ derivative, were evaluated to reveal correlations with their stability and reactivity in aqueous media [6].

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The bidentate oligopyridines such as 2,2-bipyridine and 1,10-phenanthroline also form stable and cytotoxic Ru(η^6-*p*-cymene) and Rh(η^5-C_5Me_5) complexes. Molecular hybridization is an efficient tool to obtain even more active compounds. We have combined 2,2-bipyridine bearing (*N*,*N*) donor set with a lipophilic sterane backbone, and their Ru(η^6-*p*-cymene), Rh(η^5-C_5Me_5) and $Re(CO)_3$ complexes were synthesized and tested for their cytotoxic activity. The comprehensive solution studies revealed the formation of highly stable complexes with a more favorable hydrophilicity profile in comparison to the ligands, and the Ru(η^6-*p*-cymene) complexes exhibited strong cytotoxic activity against prostate cancer cells.
In the oral presentation, our most important collaboration achievements obtained within the COST Action (NECTAR) will be presented focusing on the relationship between the solution chemical properties and biological activity.

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A novel rigidified HBED-based class of chelators for radiopharmaceutical applications

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Advances in nuclear medicine, have spurred a growing interest not only in emerging radionuclides but also in new ligands that can address the stringent demands of metal chelation in nuclear medicine. In fact, the choice of the chelator is a crucial aspect for the development of a radiopharmaceutical as it ensures safe biological transport of the metal. While macrocyclic ligands provide kinetic inertness due to their rigid binding sites, they demand harsh labeling conditions due to slow binding kinetics. Conversely, non-macrocyclic ligands offer faster radiolabeling under milder reaction conditions but may undergo in vivo decomplexation due to their flexible structure and milder inertness. Among these non-macrocyclic ligands, HBED [1] stands as one of the most promising coordinating agents for Ga^{3+}, forming a high thermodynamically stable complex ($\log\beta_1$ = 38.51) [2]. In the present study, new constrained HBED-based chelators have been synthesized by exchanging the *en* chelating site with DACH (diammine cyclohexane) moiety. The synthesized chelators are hexadentate and the coordination motive can be tuned in term of hard/soft character changing the ligating groups (N_xO_y x+y = 6). Among them, N,N′-Di(2-HydroxyBenzyl)-(1,2-Cyclohexanediamine)-N,N′-Diacetic acid (HBCD, Figure 1) demonstrated high affinity for Ga^{3+}. The kinetics of the complexation reaction and the thermodynamic stability of metal complexes were investigated in solution by both NMR and UV-vis spectroscopy.

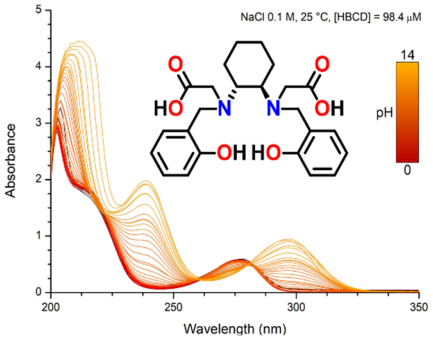

Figure 1. Structure of HBCD, with its UV-Vis absorption spectra registered at different pH values.

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A Novel Biphenol-based Bis-macrocyclic Fluorescent Receptor Able to Bind and Sense Zn(II) and Amino Acids

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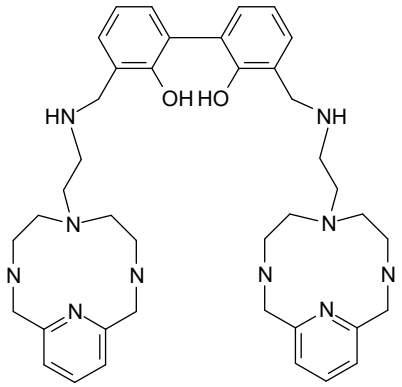
A new fluorescent ligand based on two macrocyclic pyridinophane units connected as side arms to a 2,2'-biphenol moiety was synthesized. The ligand was studied in aqueous solution and potentiometric and spectrophotometric data revealed a dual binding capacity of ligand **L**, being able to strongly interact with both metal ions and anions. Notably, the ligand exhibits fluorescence under acidic pH conditions, and intriguingly, its emission undergoes to complete quenching upon the binding of Zn(II) ions. Molecular dynamic calculations were performed with the aim to elucidate the unusual phenomenon of fluorescence quenching upon coordination with Zinc metal ion. In-depth solution studies were conducted to explore the ligand binding properties towards both anions and amino acids. The results underscored the ligand's capability to form stable complexes with L-Aspartic, L-Glutamic, Succinic, and Glutaric acids. Notably, these interactions exhibit distinct selectivity, dependent on the pH conditions, thereby providing valuable insights into the intricate binding behavior of ligand **L** with these species.



L

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The Italian Ministero dell'Istruzione dell'Università e della Ricerca (MIUR) (project 2017EKCS35) is gratefully acknowledged for the financial support.

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Binding Properties of a New Chiral Bis-Urea-Based Cage Receptor for Anions

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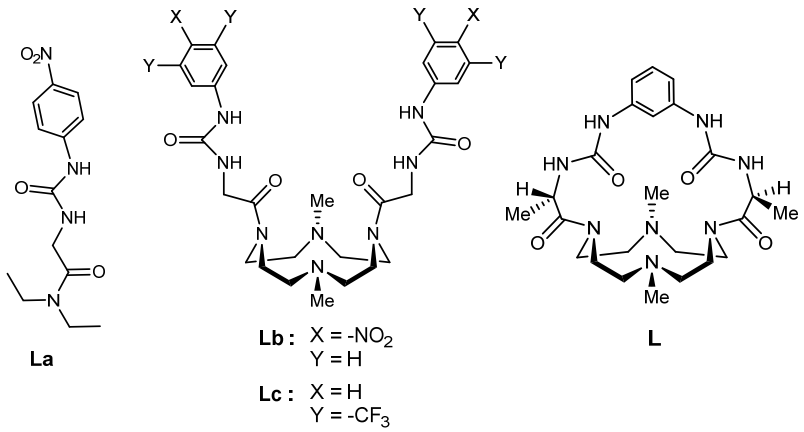
The synthesis and characterization of a novel bis-urea-based cage receptor for anions (3S,15S)-3,15,20,25-tetramethyl-1,4,6,12,14,17,20,25-octaazatricyclo[15.5.5.17.11]octacosa-7(28),10-diene-2,5,13,16-tetraone (**L**) is reported. The main objective was to obtain a macro-bicyclic ligand based on the 1,7-dimethyl-1,4,7,10-tetraazacyclododecane scaffold, already exploited in the previously synthesized similar ligands **Lb** and **Lc**, in which two urea-based units are appended to the polyamine macrocyclic base as side arms. [1, 2] The high degree of structural organization observed in these ligands, compared to the simplest receptor **La**, [1] due to the cooperation of side arms in the binding of acetate (AcO^-), prompted us to increase the preorganization of the system by connecting the two urea-based side arms with a phenyl unit. The results of the ^1H NMR studies carried out on **L** in DMSO-*d6* - 0.5% D_2O solution showed the ability of **L** to interact with anionic guests (**G**), in particular with the spherical Cl^- and the V-shaped AcO^- as well as with more complex carboxylate anions, such as sodium norfloxacin (Nor^-). The results of solution studies together with the solid-state analysis of three structures obtained are in accord with the hydrogen bonding formation between urea hydrogen atoms and the anionic guests (NH···**G**).



Scheme 1. Structures of ligand **L** and its parent compounds **La-c**.

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Critical literature survey on thermodynamic data of Ga(III) acid-base properties

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Gallium is widely employed in plenty of fields, being crucial in many industrial and technological, as well as medical, applications [1,2]. This widespread use, together with its limited availability, concurred to include Ga(III) in the list of the *Technologically Critical Elements* (TCEs) [1]. As such, its recovery is important for the reutilization in all these applications. Many Ga properties and applications, as well as some recovery processes, take place in aqueous solutions, in which Ga is present as trivalent Ga species. Being Ga^{3+} a hard Lewis acid, it undergoes strong hydrolysis in aqueous solution, which deeply affects its chemico-physical parameters and reactivity. Consequently, its speciation is dominated by the formation of several hydrolytic species, both mononuclear and polynuclear, with different stability. The knowledge of its acid-base properties is thus fundamental to understand Ga^{3+} behavior in aqueous solution. Within the activities of Working Group 1 (WG1 – NECTAR for highly hydrolysable (HHC) and/or low-valence state (LVC) cations) of COST ACTION CA18202 (NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research), a literature survey on Ga^{3+} hydrolysis has been carried out. In this contribution, the results of a critical analysis of available thermodynamic data (including solubility) and an attempt of their rationalization are reported. Significant discrepancies were found concerning both the nature and the stability of hydrolytic species of Ga^{3+}, suggesting the necessity to perform further dedicated experiments in different conditions, in order to define a correct speciation model [3-7].

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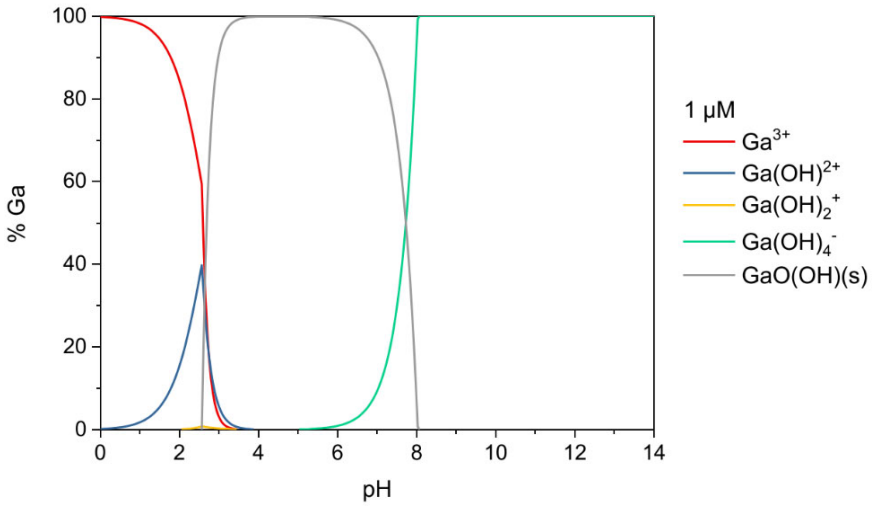

Figure 1: Distribution diagram at T = 298.15 K and at I = 0 mol dm^{-3}. c_{Ga} = 1 x 10^{-6} mol dm^{-3} [8].

Acknowledgements:

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Artificial Siderophores for Molecular Imaging Applications

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Under iron-deficient conditions most aerobic microorganisms secret low molecular-weight, highly specific iron(III) chelating compounds – siderophores, which actively transport ferric ions into the cells via specific receptors in the microbial membranes [1]. The difficulties in synthesis of structurally complicated natural siderophores has directed the siderophore research towards biomimetic chemistry, aiming at mimicking or reproducing the function of the natural product rather than its detailed structure. This approach allowed us to diversify the arsenal of biologically active siderophore-type molecules, introduce additional desired chemical and/or physical properties, and provide means to identify general motifs governing an interplay between structure and function in biological activity [1-4].

Taking into account, that siderophores are absent in the host cells, they are tempting targets for microbial imaging; ^{68}Ga is positron emitters that that is well recognised for molecular imaging applications using positron emission tomography (PET) [5]. Of the evaluated siderophores, ^{68}Ga-ferrioxamine E (FOXE) and its close biomimetic analogues were shown as the most promising for possible applications in PET imaging of *S. aureus* [4]. Currently we are working on other bacterial (*P. aeruginosa*) and fungal (*A. fumigatus*) species, to better understand the *in vivo* speciation and differences in the biological recognition and uptake of these artificial siderophores.

On the other hand, desferrioxamine B (DFO) is currently the most commonly used chelator to radiolabel biomolecules with 89Zr [5]. However, its *in vivo* stability has proven insufficient, and transchelation has been observed. Our Zr(IV) – DFO solution studies provided information on the actual chemical form of the complex in biological media, and this can contribute to a better understanding of the *in vivo* speciation and differences in the biological activity of this and other chelators [6, 7].

Overall, proposed derivatives may hold potential as inert and stable carriers for Fe(III), Ga(III) and Zr(IV) ions for diagnostic medical applications. They could also allow identifying critical

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microbial compartments in which siderophores accumulate and thus illuminate key targets for specific drugs against bacterial/fungal diseases.

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Binding of Small Molecules and Metallic Complexes to DNA: A Methodological Approach

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During the NECTAR COST Action, the activities of the working group 2 were focused on elaborating standardized protocols for the determination of binding affinities.[1] Several model systems were carefully considered, but finally we have decided to investigate and benchmark a simple and well-known binding of EtBr to DNA. Nevertheless, other molecular systems remain of interest in terms of interactions.

In this contribution we critically review binding interactions between DNA (intercalation, minor groove binding, aggregation) and small ligands or molecules, with a particular interest in organic ligands (EtBr, porphyrines) and metallic complexes (Pt, Ru, Co) (Scheme 1). These compounds are often used as imaging, diagnostic or therapeutic agents, and therefore an accurate determination of their binding affinity to DNA may play a crucial role for their further applications. In this context we focus on reviewing strategies and experimental methodologies used for measuring binding affinities for the above-mentioned systems, on contrary to a recent review focused on structural aspects.[2] Moreover, different computational tools for the data treatment will be discussed. Finally, this work will allow to draw general recommendations to guide new users in this field and potentially indicate further development of different tools.

This collaborative work is a part of deliverables provided by WG2 of NECTAR.

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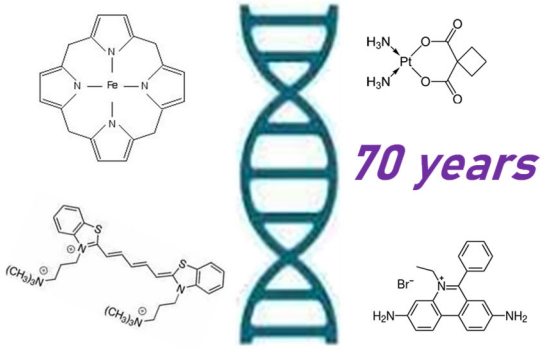

Scheme 1. Small molecules interacting with DNA.

Acknowledgements:

This contribution is based upon work from COST Action CA18202, NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research, supported by COST (European Cooperation in Science and Technology).

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Copper Removal from Aβ Peptide: fine-tuning ligand design to control Cu(I) speciation and lessen Cu-Aβ toxicity

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Alzheimer disease (AD) is the most common neurodegenerative disease in the elderly [1] and it is characterized by β-amyloid peptide (Aβ) deposits in the brain constituting the senile plaques [2]. The causes of AD are still not clearly identified but several evidences highlight the involvement of metal ions in its pathogenesis and indeed it has been shown that Aβ peptide possesses the ability to bind Cu, Zn and Fe [3, 4]. When bound to Aβ peptide, Cu do keep the propensity to produce reactive oxygen species (ROS) and these ROS contribute to the overall increase of the oxidative stress linked to the development of the disease [3].

Many therapeutic approaches are currently developed to aid fighting against AD, one of them targeting the redox active Cu ions. A large range of chemical families has been investigated to remove Cu (mainly Cu(II)) from Aβ including multi-targeting drugs [5-7]. Along this research line, we recently reported the use of a phenanthroline-based peptide like ligand (L1) [8] which is able to withdraw Cu(II) and Cu(I) from Aβ and redox silence it (Figure 1) even in the presence of Zn [9]. However, strikingly, the desired effect of preventing ROS production is lessen in the presence of excess of L due to the formation of the species $Cu(I)(L1)_2$ during the redox cycle (Figure 1, [9]). Our current endeavor is the optimization of L to obtain a new generation of phenanthroline-based peptide ligands capable of preventing the formation of the undesired $C(I)(L1)_2$ species. In this communication we will present our advances towards this goal highlighting how speciation and redox chemistry are crucial players.

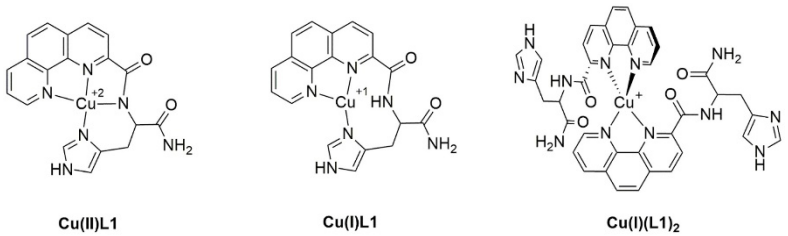

Figure 1. Chemical structure of the Cu(II)L, Cu(I)L and $Cu(I)L_2$ complexes.

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DNA and BSA binding mode of selected vanilin-based aza-heterocycles

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Pharmaceuticals can interact with DNA and circulating protein in various ways, and these interactions are critical considerations in drug development, pharmacology, and toxicology. Understanding these interactions is crucial for drug development and personalized medicine. It's important to note that while many pharmaceuticals target DNA for therapeutic purposes, unintended interactions or side effects may also occur. Furthermore, many drugs directly bind to DNA. Examples include certain chemotherapeutic agents like cisplatin, which forms covalent bonds with DNA, causing DNA cross-linking and interfering with cell division. Research in this area continues to evolve, and ongoing studies aim to deepen our understanding of these interactions for the development of safer and more effective treatments. Biologically active molecules (tetrahydropyrimidines and pyrido-dipyrimidines) that are developed in our group were subjected to various experimental techniques (DSC, UV/Vis and fluorimetric titration, and agarose gel electrophoresis) in order to examine of their binding mode with DNA and albumin. [1-3]

Acknowledgements:

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Solubility of ellagic acid in the targeted ionic liquid, natural eutectic solvent and polymers

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Ellagic acid (EA) is a bioactive polyphenolic compound naturally occurring as a secondary metabolite in various fruits (pomegranate, raspberries, blackberries, strawberries,) and nuts (walnuts, hazelnuts, acorns, chestnuts, pecans). EA is the precursor of the active compound Urolithin A, which results from the transformation of ellagitannins by the gut bacteria. EA is attracting attention due to its antioxidant, anti-inflammatory, antimutagenic, and antiproliferative properties [1]. Furthermore, EA has also been well-documented for its antiallergic, antiatherosclerotic, cardioprotective, hepatoprotective, nephroprotective, and anticancer properties. Due to a wide range of biological effects of EA, edible plants containing this phytochemical belong to functional foods that promote health and may reduce the risk of disease. The main limitation of the EA, which needs to be resolved for them to be applied as efficient pharmaceuticals/supplements, is their poor bioavailability due to their low aqueous solubility. Therefore, solubility is a crucial challenge for scientists who aim to increase the bioavailability of the EA. Micellar solubilization of highly hydrophobic compounds with surface active ionic liquids (SAIL), natural deep eutectic solvents (NADES) and polymers is one of the approaches for increasing of bioavailability of these compounds. This study aims to investigate the solubility properties of EA in different systems which include polymers, biodegradable ILs and NADES [2].

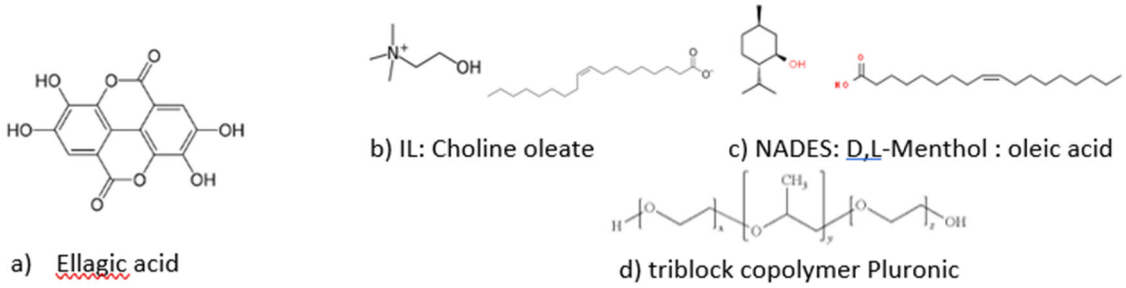

Figure 1. Structure formula of (a) ellagic acid; (b) Choline oleate IL; (c) NADES: D,L-Menthol: oleic acid; and (d) triblock copolymer Pluronic.

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The following compounds were used for the investigation of EA solubility: SAIL – choline oleate; NADES: D,L-Menthol: oleic acid in 1:1 ratio; and triblock copolymer Pluronic R17 (Figure 1b-d). SAIL (choline oleate) is synthesized through acid-base titration of oleic acid with choline hydroxide. After synthesis, water is removed via lyophilization. NADES is synthesized by mixing equimolar concentrations of D,L-Menthol and oleic acid at 55°C, 1 h with constant stirring and without the addition of water.

The solubility of EA in water is remarkably low (< 10 μg mL^{-1}), as is the case with methanol and ethanol (≈ 600 μg mL^{-1}). However, it has been found that EA exhibits significantly enhanced solubility (≈ 10 mg mL^{-1}) in the synthesised SAIL and polymer matrices.

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Solution equilibrium studies on 8-hydroxyquinoline reduced Schiff bases and their complexes with essential metal ions

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The 8-hydroxyquinoline (8HQ) scaffold is mentioned in the literature as a privileged structure in medicinal chemistry, since 8HQs can have a wide range of applications, including in anticancer therapy [1,2]. Based on the literature, the biological activity of 8HQs shows a correlation with their complex formation ability [2]. Mannich bases of 8-hydroxyquinolines which were substituted by a methylamine subunit in position 7 are reported to possess high potency against multidrug-resistant human cancer cells [3]. 8HQs which contain this subunit in position 2 can coordinate metal ions via three donor atoms (*N*,*N*,*O*). Representatives of this type of derivatives were synthetized by the combination of 8HQ-2-carbaldehyde with amines containing morpholine or piperidine moieties yielding 8HQ Schiff bases [4]. These compounds along with their copper(II) and zinc(II) complexes demonstrated significant anticancer activity on malignant melanoma cells [4]. However, these Schiff bases have low aqueous solubility, and are prone to hydrolytic decomposition in water due to the presence of the C=N bond [4].

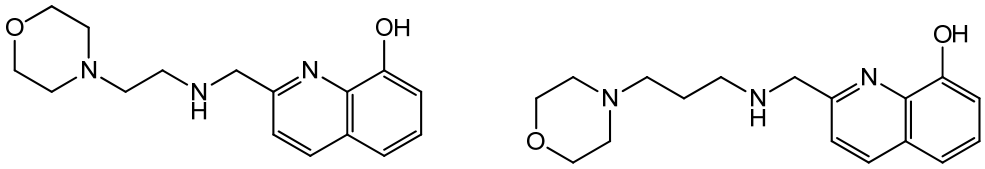

Chart 1. Chemical structure of the studied new 8-hydroxyquinoline reduced Schiff bases.

Herein, we aim to synthetize and characterize two new 8HQ-based reduced Schiff bases bearing a morpholine moiety (Chart 1) which have been reduced to prevent hydrolysis. Upon the reduction the ligands become hydrolytically stable, however, this chemical modification may alter the solubility, lipophilicity, metal chelating properties as well as the cytotoxic activity. Therefore, we explore the solution chemical properties of the new HQs including their complexation with various metal ions. The lipophilicity of ligands was determined by *n*-

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octanol/H_2O partitioning, and their proton dissociation processes were characterized using pH-potentiometry, UV-visible and ^1H NMR spectroscopic titrations. The complex formation equilibria with essential metal ions, namely Cu(II), Fe(III), Fe(II), and Zn(II) were studied by UV-visible spectrophotometric titrations, and in the case of Zn(II) ^1H NMR spectroscopy was also applied to confirm the complexation speciation. Titrations with Fe(II) ions were conducted under strictly controlled anaerobic conditions in a laboratory glove box. For the iron and copper complexes, cyclic voltammetric measurements were performed to monitor the redox properties. The cytotoxic activity of the ligands were assayed in chemosensitive and multidrug resistant cell pairs along with the coincubation with Zn(II), Cu(II) and Fe(III) ions.

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Solution study of cytotoxic platinum(II) complexes with 1-(benzofuran-2-yl)-2-(1H-1,2,4-triazol-1-yl)ethenone

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Chemotherapy is one of the leading pillars of cancer treatment. Nevertheless, therapy results are often unsatisfactory to patients. Additionally, according to observations and prognoses, there is a growing tendency in cancer occurrence. For that reason, platinum-based drugs currently used in anticancer therapy require constant improvements.

From the historical point of view, Cisplatin (CDDP) was the first platinum-based anticancer agent and it has been in use up till now to treat various types of human cancer.[1,2] Unfortunately, side effects resulting from its toxicity.[3,4] Overcoming these clinical drawbacks in cisplatin-based chemotherapy poses a challenge in the process of more effective and less toxic platinum-based anticancer drugs development by modification of its coordination sphere.

As a part of research in this area we synthesized two new platinum(II) complexes with 1-(benzofuran-2-yl)-2-(1H-1,2,4-triazol-1-yl)ethenone (bfte) of the general formula *cis*-[$PtCl_2(bfte)_2$] **(1)** and *cis*-[$PtCl_2$(bfte)(dmso)] **(2)** (Fig. 1). The complexes have been synthesized and fully characterized by an elemental analysis and spectroscopic methods (^1H, ^{13}C, ^{15}N NMR).

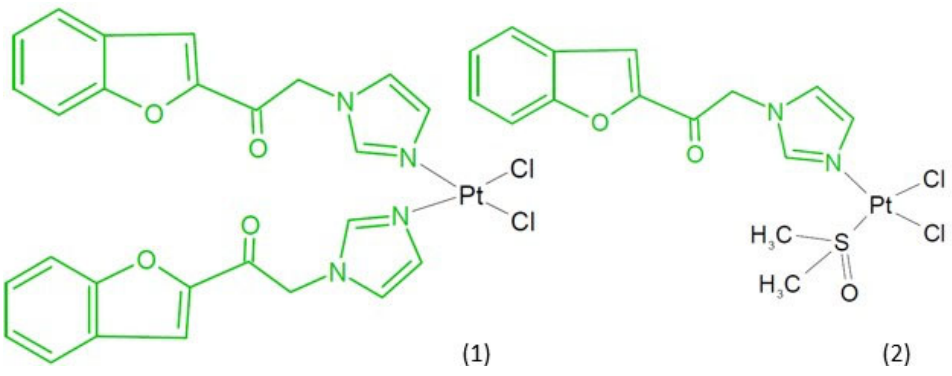

Figure 1. Structural formulas of coordination platinum(II) compounds **(1),** and **(2)**.

The NMR parameters unambiguously confirmed the square-planar geometry of Pt(II) in a solution with two monodentate N-ligands and two chloride ions in *cis* position (1), and

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monodentate one N-donor ligand, one S-donor molecule of dmso, and two chloride ions in *cis*
position.
The obtained platinum(II) complexes exhibit lower toxicity and affinity to glutathione in comparison with Cisplatin. Thus there is a possibility that they can more effectively avoid the mechanism of drug resistance associated with binding to this tripeptide Additionally those platinum(II) compounds show higher lipophilicity (**(1)** = 1.12, **(2)** = 0.94) than Cisplatin (-2.53), which may result in better permeability through cell membranes in passive transport. Preliminary biological studies have shown that complex **(1)** has higher *in vitro* cytotoxicity towards bladder cancer cells from the CRL1472 (IC_{50} = 7.72 µM), T24 (IC_{50} = 8.95 µM) and HBCLS (IC_{50} = 6.51 µM) lines, as well as lower toxicity towards healthy cells isolated from ureters from the SV-HUC line (IC_{50} = 14.00 µM) compared to Cisplatin (IC_{50} = 22.01 µM; 21.98 µM; 13.58 µM respectively). The highest *in vitro* cytotoxicity of compound (1) caused us investigate the mechanism by which this compound affects cancer cells. This search began with examining the interaction with DNA by intercalation. For this purpose, two experiments were performed: spectrophotometric titration and fluorescent titration. No significant changes were observed in the measured spectra, suggesting that the compound does not interact with DNA in an intercalating manner.

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On the rare-earth metal ions adsorption onto biochars of dead *Posidonia oceanica leaves*

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Rare earth elements (**REE**) belong to the list of critical raw materials, i.e. the list of materials whose recovery is considered strategic from the European Community.[1] Adsorption is recognized as one of the most attracting recovery technique, in particular when the adsorbents employed become from waste platforms.[2,3] This contribution presents the results achieved using three biochars obtained from the pyrolysis of dead *Posidonia oceanica*, a marine plant whose leaves accumulate in abundance on the sicilian cost, as adsorbents of rare earth metal ions from aqueous solutions. To this end, thermodynamic and kinetic adsorption experiments were carried out to study the recovery of lanthanum, neodymium and dysprosium ions onto the biochar of *Posidonia oceanica* as it was (**BC**) and after two types of chemical activation, i.e., an acid activation threating the material with phosphoric acid (**BCA**) and a basic activation with potassium hydroxide (**BCB**) in aqueous solution at pH = 5 and t = 25°C. The adsorption of REE ions onto BCA was also studied in $NaNO_3$ 0.1 mol L^{-1} at pH = 3 and pH = 6 to evaluate the effect of pH and of the ionic medium. Chemical and morphological characterization of adsorbents were carried out by SEM-EDX, FT-IR, elemental analysis and nitrogen adsorption/desorption measurements. The REE adsorption was well described by Langmuir isotherm equation. Among the tested adsorbents, the BCA showed the highest q_m value. Moreover, the adsorption capacity decreases with the decreasing of pH and in presence of $NaNO_3$. The adsorption equilibrium was reached within 8 hours. Recycling experiments, using HNO_3 or EDTA 0.1 mol L^{-1} as extractants, were also carried out to test the reusability of the BCA.

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Thermoreversible aqueous biphasic systems for biomolecule recovery from plant

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In separation procedures, the capacity to create reversible transitions between biphasic systems and homogenous solutions is of essential importance [1]. In this particular case, thermo-triggered aqueous biphasic systems composed of Pluronic copolymers and ionic liquids are disclosed here as switchable mono/biphasic systems, and their potential application is further demonstrated through the extraction of parthenolide from plant feverfew (Tanacetum parthenium L. Bip.), (Figure 1a,b). In vitro studies have confirmed the highly selective cytotoxic activity of parthenolide against cancer cells, and the feverfew has been shown to increase the sensitivity of cancerous cells to chemotherapy and radiotherapy.

To study the thermoreversibility of Pluronic-based aqueous biphasic systems, the phase diagrams at 25 °C and 35 °C for the systems composed of water, Pluronic 17R4 and six ionic liquids (ILs) cholinium bitartrate ([Ch][Bit]), cholinium lactate ([Ch][Lac]), cholinium tosylate ([Ch][Tos]), cholinium acetate ([Ch][Ac]), cholinium dihydrogencitrate ([Ch][DHCit]), cholinium dihydrogenphosphate ([Ch][DHP]) were determined. The best results for thermoreversibility and extraction of parthenolide we get with a system composed of Pluronic 17R4 and IL cholinium bitartrate [Ch][Bit] (Figure 1c). Temperature has an influence on the phase separation in these systems, so the increase in temperature enhances the phase separation of these systems, i.e., less amounts of IL and copolymer is needed to accomplish biphasic systems. Under specific thermodynamic conditions, Pluronic-ABS typically has a top phase rich in IL and a bottom phase rich in polymer.

These results lead to the development of a new technique for the extraction of the active pharmaceutical ingredient using green, biocompatible solvents.

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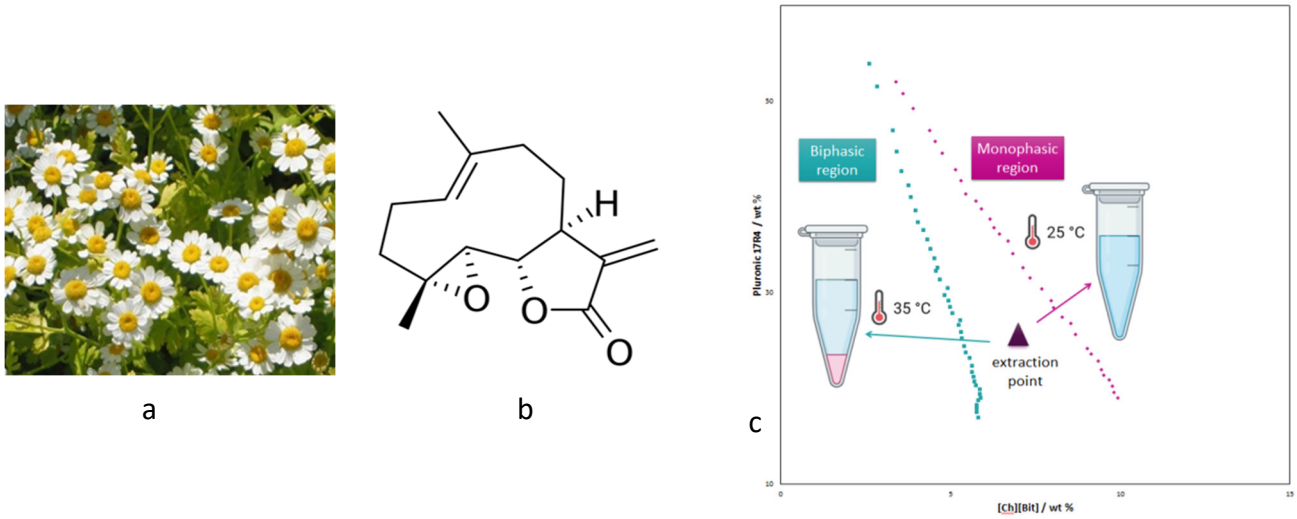

Figure 1. a) Fevefew; b) Structure of parthenolide; c) Binodal curve of the systems composed of Pluronic 17R4 + [Ch][Bit] + H2O at 25 and 35 °C

Acknowledgements:

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When hard modelling needs some help: case study 1.
Chemometric-assisted investigation of functionalized AgNP interaction with heavy metal ions

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Hard models such as speciation modelling represent the most powerful tool for a chemist to describe and predict the behaviour of compounds in different environments, but their development might become extremely laborious and time-consuming when complex systems are under investigation involving different species and experimental conditions or even heterogeneous systems.

In all these cases, the application of soft modelling strategies, such as chemometric tools for experiments planning (Design of Experiments, DOE) [1,2] and data analysis (MultiVariate Analysis, MVA) [3,4], can provide valuable help in extracting information about the systems from the raw data, despite their complexity and in rationalizing the ongoing processes.

In this investigation, we applied chemometric tools to rationalize the interaction between different AgNPs, functionalized with synthetic and natural ligands, and heavy metal ions: this interaction triggers the aggregation of these nanoparticles, leading to peculiar changes in the optical properties. [7] In Figure 1 an example of the naked-eye visible changes in AgNP solution colour upon addition of different heavy metals is depicted.

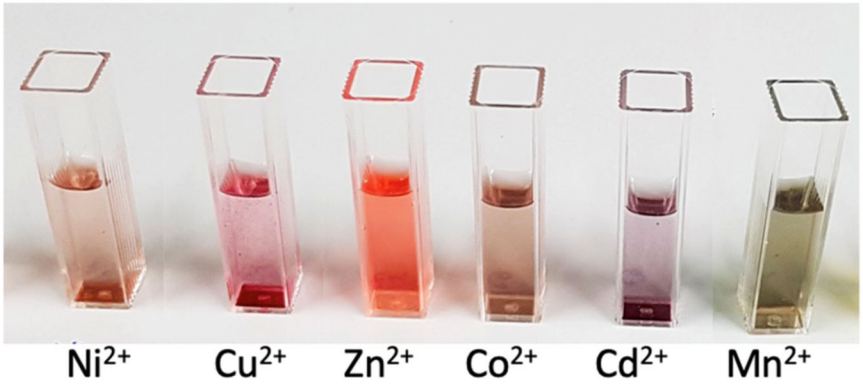

Figure 1: AgNP functionalized with mercaptoundecanoic acid (11MUA) upon addition of heavy metal ions.

Depending on the functionalizing agent, the surface coating density, and other experimental conditions, both the range of explorable concentration of metal ions and the type of cation

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interaction can be tuned, leading to promising sensing systems in solution, both for selective and differential applications.

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Highly stable Lanthanide(III) complexes as potential MRI and NIR imaging probes

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Molecular imaging finds nowadays success in biological and medical applications as it provides a high detection sensitivity and potentially can be targeted to specific tissues or monitor specific functions [1]. Lanthanide(III) complexes find application in many areas of medicine for diagnostics or treatment, for example: radioisotopes in nuclear medicine, MRI contrast agents, luminescent probes for sensing and optical imaging applications [4-6].

In the field of optical imaging, luminescent Ln(III) complexes have advantages in respect to common organic fluorophores, such as: sharp emission bands, large energy differences between excitation and emission bands and long luminescence lifetimes [2,3]. The design of the ligand is essential to tightly complex the metal ion and generate an efficient emission upon excitation through the ligand-to-metal energy transfer mechanism ("antenna effect") [3]. A particularly interesting case is when the light emitted by the Ln(III) ion falls in the NIR region where the biological matrix is transparent. In this context, ligands containing picolinate moieties have characteristics to be considered as potential good antennas for sensitizing NIR-emitting Ln(III) ions [6].

A key requisite of such Ln(III) complexes is the high thermodynamic stability and kinetic inertness needed to avoid the release of the toxic metal ion, as well the loss of function of the complex. Moreover, a high selectivity of the ligand towards Ln(III) ions over bivalent metal ions abundant in biological media (Zn(II), Ca(II)) is required.

In this communication, the results of the solution studies on the complexation of Ln(III) ions with the ligand based on the chiral 1,2-diaminocyclohexane (DACH) motif (Figure 1) are reported. The determination of equilibrium constants for protonation and complex formation for Yb(III), Zn(II) and Ca(II) was carried out by means of potentiometric and UV-VIS spectrophotometric titrations. Also, the complex formation with the Gd(III) ion has been considered as its complex with L has the potential to be an efficient contrast agent for MRI, given its high molecular weight and rigid structure [7].

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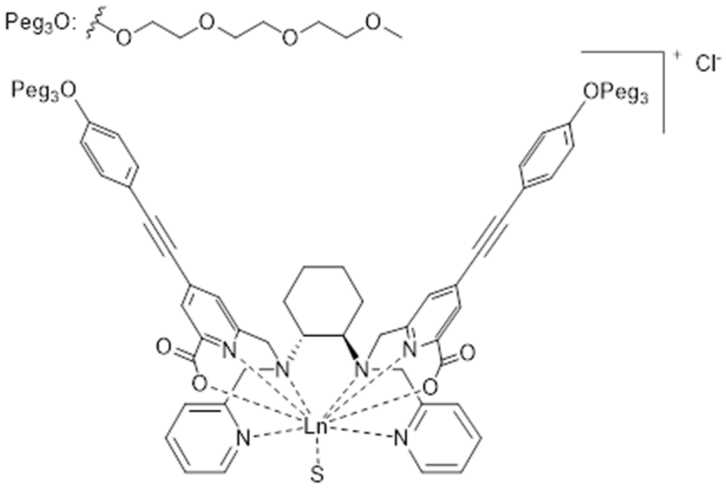

Figure 1. Structure of the ligand **L** reported in this work.

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Adsorption of Pb^{2+} from aqueous solutions on to soy protein microsponges

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Over the past decade, protein-based materials have emerged as promising adsorbents for toxic metal ions in contaminated water [1–3]. In fact, they demonstrate the main characteristics of model adsorbents: i) high availability of raw materials, ii) cost-effectiveness, iii) biocompatibility, iv) high density of binding sites, v) ease of preparation. In this work, we prepared protein microsponges based on soy protein isolate (SPI) and tested them as adsorbents for Pb^{2+} ions. SPI comes from the soybean oil production industry, has an isoelectric point in the pH range 4 to 5, and has two main parts: the trimer, glycoprotein β-conglycinin (7S) and hexameric glycinin (11S) [4]. Microsponges have amyloid-like molecular structures and are prepared by incubating SPI aqueous solutions at high temperatures and at two different pH values (pH 5 and pH 9, close to and far from the protein's isoelectric point, respectively).
Solution conditions for SPI incubation affect the polarity and water accessibility of the microsponges and alter their metal binding affinities. Both SPI adsorbents were characterized by various spectroscopic techniques including microscopy, ATR-FTIR and FLIM analysis, while their adsorption behavior towards Pb^{2+} ions was studied through batch isotherms and kinetic experiments under different experimental conditions. The differential pulse anodic stripping voltammetry (DP-ASV) technique was used to measure the Pb^{2+} ion concentration in the collection solution, and several kinetic and isothermal adsorption models were used to process the experimental data. In addition, lead removal experiments were conducted using column-supported SPI microsponges to analyze the adsorption capacity under dynamic conditions and evaluate the recovery and reuse of the microsponges. SPI microsponges successfully removed Pb^{2+} ions from aqueous environments and also showed high recovery rates.

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Exploring the metal specificity of the bacterial Fe(II) transporter FeoB

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Bacterial resistance to antibiotics has been a growing problem worldwide [1], hence alternative methods of treating bacterial infections are sought. During infection, bacteria need to assimilate transition metal ions from the host environment, such as Fe(II), Mn(II), and Zn(II), which play a key role in pathogenicity and survival and are transported into bacterial cell by specific transporters located in the bacterial membrane. The Feo system, common in both pathogenic and non-pathogenic bacteria, is considered to be the most important bacterial transport system for Fe(II) ions, possibly transporting other divalent metal cations, such as Mn(II) and Zn(II), which are often transported by ferrous iron transporters [2]. Feo consists of three proteins, transmembrane FeoB and cytoplasmatic FeoA and FeoC proteins (Fig.1). The most important is the transmembrane FeoB protein, which transports metal ions from the periplasm to the bacterial cell. The mechanism in which the FeoB protein transports the metal ion is not yet elucidated. Furthermore, the metal-binding characteristics of the protein are also not known. As the transmembrane proteins are very difficult to crystalize in their native state, the crystal of the metal-bound FeoB has not been yet obtained.

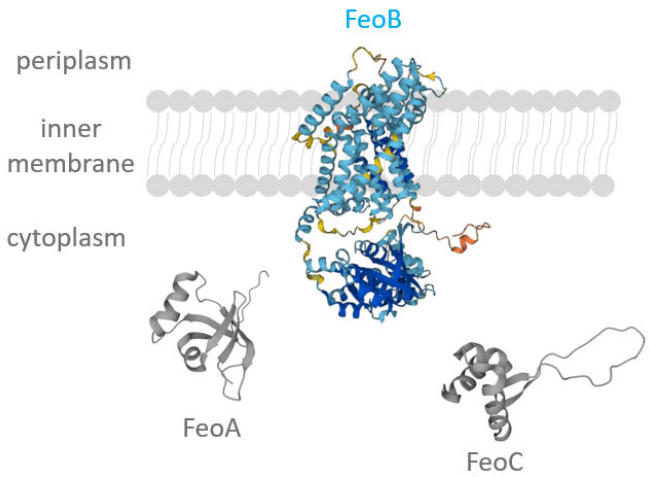

Fig. 1 Scheme of the Feo system. The scheme doesn't show the true relations between the size of the proteins, nor their factual orientation.

Thus, solution studies of the fragments of the FeoB are an alternative way to characterize its' metal-binding properties.

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There are few putative Fe(II) binding sites in the structure of FeoB recognized in the literature. These are for example the Gate 1 and Gate 2 motifs, reminiscent of the yeast iron permease Ftr1p, found in the periplasmic, cytoplasmic, and transmembrane parts of the protein, the Core CFeoB region found in the cytoplasmic insertion between the 4th and the 5th helix, and the ExxE motif located in the cytoplasmic GTP-binding domain. Another potential Fe(II) binding place recognized in the literature could be the C-terminal fragment of the protein, rich in strongly conserved throughout the gammaproteobacterial class cysteine and histidine residues [2,3].
In our research, we have chosen the peptide fragments of the FeoB protein, representing the putative metal-binding sites. Utilizing a variety of physicochemical methods, such as potentiometry, mass spectrometry, NMR and EPR spectroscopy, and molecular dynamics, we have characterized the complex species formed between the chosen peptide fragments and Fe(II), Zn(II), and Mn(II) ions. We characterized the metal-specificity of the fragments and their binding affinity towards divalent iron, zinc, and manganese. This way we have performed a thorough analysis of the most probable metal-binding sites of the FeoB protein, a very valuable input into the topics of the bacterial Fe(II) transport and Fe(II) coordination chemistry [4].

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Evaluation of physicochemical and antimicrobial profile of phosphonium-based ionic liquids with the with medium-chain fatty acids as anions

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The importance of developing effective antimicrobial agents has become more evident recently, and quaternary phosphonium-based ionic liquids with fatty acid anions have shown great potential in this regard. Tetrabutylphosphonium-hexanoate, -octanoate, -decanoate, and -dodecanoate were synthesized as potential antimicrobial ionic liquids. Confirmation of the structure of the synthesized ionic liquids was determined by IR and NMR spectroscopy. Also, the thermal stability was examined by thermogravimetric analysis. Physicochemical characterization was carried out, which included the measurement of density, viscosity, and electrical conductivity in a wide temperature range to understand. It was found that thermal stability, ionicity, and the interactions between the tetrabutylphosphonium ion and the anion depend on the number of carbon atoms of the anion, which is caused by the increase of Van der Waals interactions between the alkyl chains in the homologous sequence.

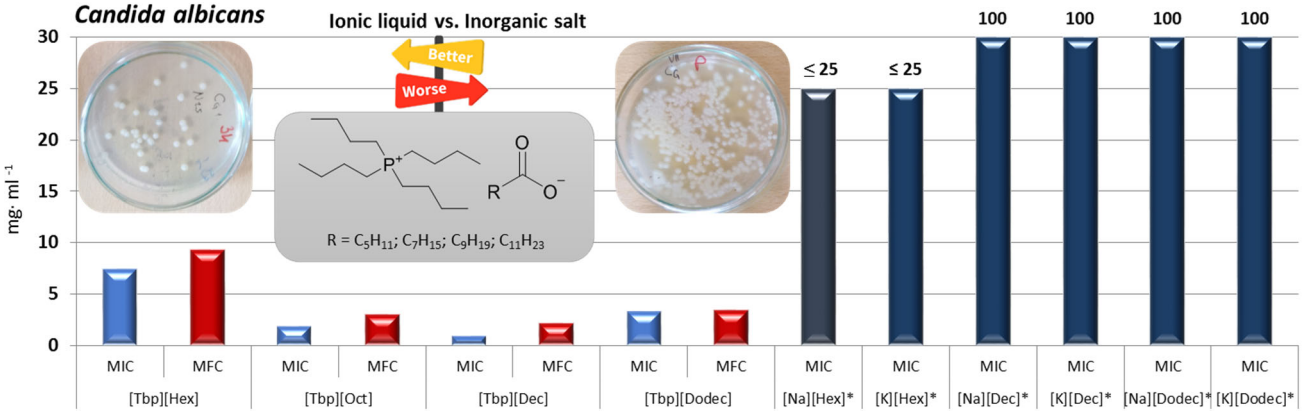

Figure 1. Antimicrobial activity of tested ILs against *Candida albicans*.

The antimicrobial activity against various microorganisms was determined, including three Gram-negative and Gram-positive bacteria, two yeast, and four filamentous fungal strains. Based on the results, ILs were more efficient against Gram-positive than Gram-negative bacteria, whereby the longest-chained anion contributes to the best antibacterial activity. Yeast *Candida guillermondii* and all tested filamentous fungi were most sensitive to tetrabutylphosphonium-decanoate. Research by *Cabezas-Pizaro* et al. [1] used the sodium and potassium salts of medium-chain fatty acids and determined MIC values for *C. albicans*. The

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results indicate that the antifungal activity concerning the mentioned salts increases by using a more voluminous cation, such as the tetrabutylphosphonium cation.

Acknowledgements:

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Improving the thermal and electrochemical stability of lithium-ion battery electrolytes safety

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Lithium-ion batteries (LIBs) are becoming increasingly important for electrifying the modern transportation system and, thus, hold the promise to enable sustainable mobility in the future. However, their large-scale application is hindered by severe safety concerns when the LIBs are exposed to mechanical or thermal abuse conditions. These safety issues are intrinsically related to utilization of highly volatile and flammable organic-solvent-based electrolytes. Improving the thermal stability of electrolytes and the safety of LIBs is one of the imperatives of our investigations.

Starting from rather "facile" electrolyte modifications by replacing the organic and/or the addition of functional electrolyte additives, conceptually new electrolyte systems, including ionic liquids (ILs) are considered. Ionic liquid/organic solvent mixtures [1-3] are investigated as potential optimal electrolytes for lithium-ion batteries that can combine low flammability, good thermal stability and high electrical conductivity.

In this work the 0.5 M solution of LiTFSI salt in ionic liquid 1,3-diethylimidazolium *bis*(trifluoromethylsulfonyl)imide, (C_2C_2imTFSI), was tested as electrolyte for LIBs by using robust anatase TiO_2 nanotube arrays (NTAs) electrode and in parallel the same electrolyte with functionalized additive 1-methyl-3-sulfonatebutylimidazole. That additive is sulfonate-containing zwitterion, which prevents decomposition of electrolyte. Through that, the additive addition is contributing to that the voltage decreases less with the number of cycles. The galvanostatic (GS) testing was performed at room temperature, at current rate 3C (Figure 1). Capacity of TiO_2 NTAs is due to both bulk and surface storage of Li^+-ion, and significantly increases with addition of sulfonate-containing zwitterion (additive). GS experiments demonstrated excellent capacity retention with improved Coulombic efficiency during final cycling at current rate ~3 C.

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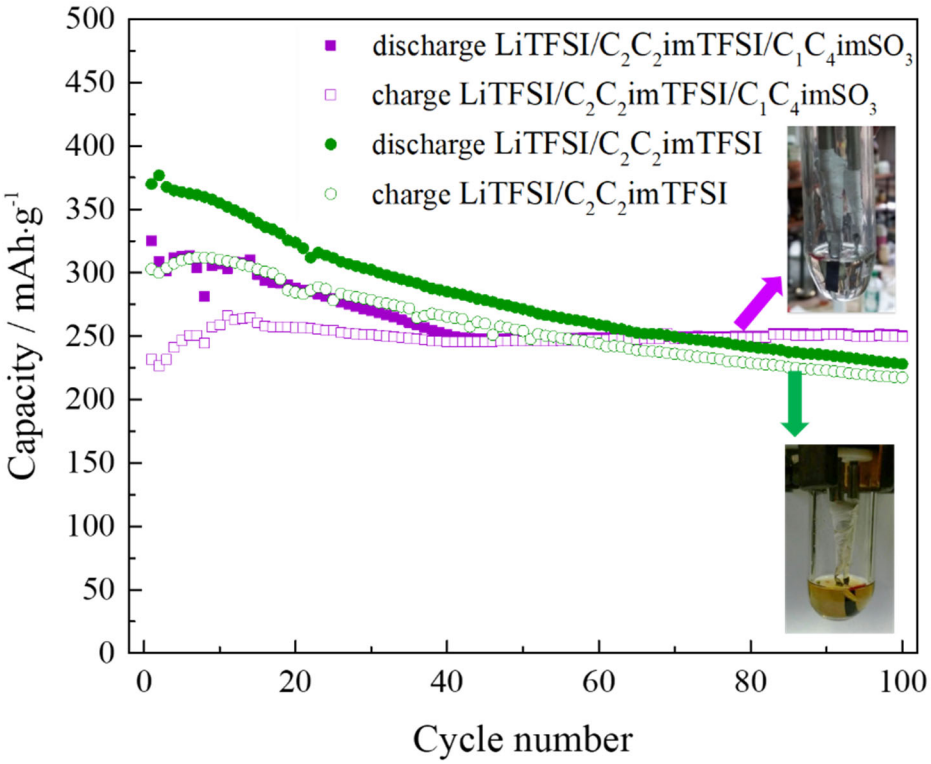

Figure 1. Comparison of galvanostatic discharge/charge performance of anatase TiO_2 NTAs in: LiTFSI/C_2C_2imTFSI electrolyte and LiTFSI/C_2C_2imTFSI/C_1C_4imSO_3 electrolyte.

Acknowledgements:

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Adsorption of Pb^{2+} ions on microplastics dispersed in contaminated waters

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The widespread diffusion of plastic waste in the aquatic environments as well as their effects on animals and humans are among the main research topics of the worldwide scientific community[1,2]. The plastic and bioplastic polymers dispersed in the environment are subject to several degradation processes that cause a high variation of their morphological characteristics and of the size of their particles that can reach the micro and nanometre ranges (MPs, NPs). What most worries the scientific community is that MPs have been found in the food chain and can accumulate in the tissues and organs of vertebrates and invertebrates [1,2]. The dangerousness of MPs can be accentuated by their ability to adsorb pollutants from the surrounding aquatic environment, making them a vehicle of toxic substances in the organism of animals and humans[2,3]. According to the tasks of Working Groups 2 and 3 of NECTAR project, here we report a study on the Pb^{2+} ions adsorption onto MPs of polystyrene (PS), of polystyrene functionalised with carboxylic groups (PS-COOH) and of polylactic acid (PLA). The adsorption capacities and affinities of the three plastic microparticles towards Pb^{2+} ions were studied considering also the effect of the presence of small amount of a surfactant. Differential Pulse Anodic Stripping Voltammetry (DP-ASV) technique was used to determine the Pb^{2+} ion concentration. Electrochemical Impedance Spectroscopy (EIS), Scanning Electron Microscopy with Energy Dispersive X-Ray Analysis (SEM-EDX), ξ Potential and FT-IR measurements were carried out to evaluate the effect of Pb^{2+} ions adsorption on the morphological features and superficial charge of the MPs. The obtained results show a fairly good ability of MPs to adsorb Pb^{2+} ions and a significant effect of the surfactant.

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Organorhenium tricarbonyl complexes bearing (*N,N*) bidentate ligands: synthesis, solution speciation and pharmacological activity

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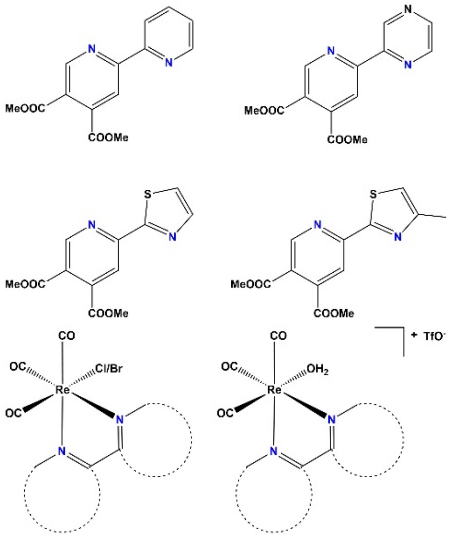
Organorhenium compounds display a diverse array of pharmacological effects, including antiviral and antibacterial properties. Furthermore, tricarbonyl rhenium complexes are widely applied in biological imaging due to their unique luminescent characteristics [1]. Among others, organometallic (mostly Ru, Rh, Ir) complexes have aroused the interest in the field of chemotherapy treatments due to their potent anticancer activity. Recently, as further alternatives, rhenium(I) carbonyl complexes containing the fac-$[Re(CO)_3]^+$ fragment, which contain a bidentate as well as a monodentate ligand (often a halido N-heterocyclic or aqua co-ligand) in an octahedral geometry, are also well-known and widely investigated for their pharmacological activity [2]. Ligands containing aromatic (*N,N*) donor set, such as 2,2'-bipyridine derivatives, are well-known for their strong chelating ability towards various transition metal ions. These bidentate ligands serve as excellent chelating molecules, and particular rhenium tricarbonyl complexes were reported to exhibit strong anticancer and antiviral properties [2-4] including activity against SARS-CoV-2 [3,4]. Herein, the synthesis and study of nine novel rhenium tricarbonyl complexes, containing ligands bearing aromatic (*N,N*) donor atom set as well as a chlorido, bromido or aqua co-ligand (**Scheme 1**) are presented in terms of pharmacological (antitumor and antibacterial) activity and solution chemical properties.



Scheme 1. Chemical structure of the bidentate (N,N) type ligands and their organometallic halido and aqua $Re(CO)_3$ complexes.

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The organometallic rhenium(I) complexes with the halido co-ligand were obtained from the reaction of either pentacarbonylrhenium(I) chloride or pentacarbonylrhenium(I) bromide precursor and the bidentate ligand (**Scheme 1**) in toluene at 120 °C. After the reaction was complete the precipitated complex was collected with vacuum filtration. The aqua complexes were prepared from the chlorido complexes using silver triflate. Reactions were carried out in dichloromethane in the dark. After the reactions were finished the reaction mixtures were filtered through Celite and the solvent was removed on the rotary evaporator. The complexes were then dissolved in a mixture of water and methanol. After time the aqua complex precipitated from the mixture and was collected with vacuum filtration.
UV-visible spectrophotometry as well as ^{1}H NMR spectroscopy were applied to investigate the stability of the complexes in solution at pH = 7.40, in various, biologically relevant matrices such as phosphate buffer, Minimum Essential Medium Eagle (EMEM) and blood serum. Furthermore, the deprotonation processes of the coordinated aqua co-ligand as well as its exchange to chloride ion were also investigated in detail. Based on the stability assays the complex dissociation is negligible in neither case, however, hydrolysis of the ester bonds (R = COOMe) could be observed at pH = 7.40 and in the basic pH range. Considering the determined pK_a values of the complexes, it can be concluded that they are mainly (~80 %) in their aqua form at pH = 7.40 without the formation of mixed hydroxido species. The chlorido co-ligand is able to dissociate in water in a slow ligand-exchange reaction resulting in changes in the charge of the complex and thus have an impact on both the lipophilicity and solubility. The rhenium tricarbonyl complexes displayed no antibacterial activity (MIC >100 μM) and only a weak cytotoxic effect was observed on HeLa, Colo 205 and Colo320 human cancer cell lines.

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Enzyme inhibitors in drug discovery: Modelling the catalytic Zn(II)-binding domain of bacterial metalloproteases

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The rapid growth of multidrug-resistant bacterial species has compelled the World Health Organization to warn about a post-antibiotic era in which current antimicrobial therapeutic strategies would be mostly ineffective against infectious pathogens[1]. Therefore, there is an urgent need to discover novel therapeutic targets and develop antimicrobial drugs with novel modes of action. One appealing avenue for research is the role and regulation of bacterial metalloproteases (MP), a diverse class of proteases that use a metal ion (primarily Zn(II)) to perform hydrolytic reactions. These enzymes play a critical role in the virulence, biochemistry, and pathogenicity of many microorganisms, becoming increasingly viable and worthy of investigation as therapeutic candidates.

Traditional experimental methods for determining enzyme structures and their interactions with inhibitors are often challenging, time-consuming, and expensive. These disadvantages force the scientific community to design models of enzymes for experimental studies [2]. Peptides derived from the binding site of proteins serve as informative protein-mimetics models and are commonly used in drug design to determine the mechanism of metal/inhibitor interactions with the protein and their binding modes [3]. By using peptides being fragments of the catalytic site of chosen bacterial MPs, we determined the stability and geometry of crucial for proteolytic activity Zn(II) complexes, and Cu(II).

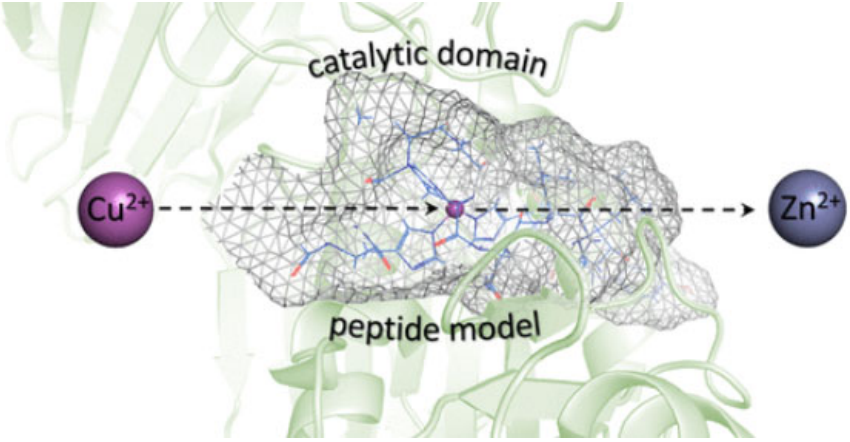

Fig. 1 Schematic representation of the research area.

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This work focused on characterizing the interactions between Zn(II) and Cu(II) ions and the Zn(II)-binding domain of MPs from multi-drug resistant bacteria, namely AprA from *Pseudomonas aureginosa*, CpaA from *Acinetobacter baumanii*, and M10 from *Streptococcus pneumoniae* [4, 5]. The investigation was carried out using potentiometry, MS, NMR, UV-Vis, and CD spectroscopy. The peptide-based study identified the coordination patterns of the Zn(II) and Cu(II) ions in MPs with three histidine imidazole rings and one oxygen from a carboxylate group of glutamic acid (HExxHxxxxxH) for all the studied regions below pH 7. The coordination pattern for Cu(II) complexes changes with increasing pH, as copper coordinates with nitrogen from the peptide backbone. The study found that Zn(II)-binding domains of all MPs have a higher affinity for Cu(II) than Zn(II). This suggests that copper may inhibit the enzymatic activity of MPs by displacing zinc from the binding domain. Additionally, the peptide model of CpaA domain showed greater stability for both Zn(II) and Cu(II) complexes compared to AprA and M10. The non-binding amino acids surrounding the metal ion in CpaA, such as tyrosine, arginine and glutamic acid increased thermodynamic stability of the metal-peptide complex through various intramolecular interactions. These interactions also contributed to the formation of a rare protein structure known as a left-handed polyproline II helix (PPII) in the model of Cu(II)-AprA complexes [4]. This structure is important for the stability and function of various proteins.

The research managed in this work enhances the knowledge of coordination properties of Zn(II) with the catalytic site of bacterial MPs and provides complete physicochemical, structural, and thermodynamic parameters of the model Zn(II)-MPs and Cu(II)-MPs complex, which can be used for experimental studies on MP's active site–inhibitor interaction.

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Adsorption of rare-earth metals on multifunctional materials from various pomaces

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This contribution presents the preliminary results obtained using waste biomasses from the industrial food chain for the preparation of multifunctional materials possibly able to detect, bind and extract, efficiently and selectively, rare earth metal ions from aqueous solutions simulating real matrices. These metals belong to the list of "Critical Raw Materials", *i.e.* the group of materials whose recovery is considered strategic from the European Community. [1]. The use of food-processing industry wastes as second raw materials offers a sustainable and environmentally friendly approach, that could also be useful for the rare earth metals recovery. In particular, the adsorption of neodymium and dysprosium ions in aqueous solution was studied at pH ~ 5 and t = 25 °C using different waste biomasses, such as bergamot pomace (**BP**), olive pomace (**OP**) and grape pomace (**GP**), chemically pretreated at t = 30°C with H_2O and HNO_3 0.10 mol dm^{-3} [2,3]. The materials were characterized employing different analytical techniques. Through the FT-IR ATR spectroscopy [4], it was possible to confirm the presence of functional groups capable of interacting with metals. Potentiometric titrations were performed at t = 25°C and at an ionic strength of 0.10 mol dm^{-3} in $NaNO_{3(aq)}$ to study the acid-base properties of these materials [5]. To evaluate their adsorption capacity, batch experiments were carried out on different solutions containing the metal ions (M^{3+} = Nd^{3+}, Dy^{3+}). The concentration of each M^{3+} was determined by ICP-OES [6]. The results obtained from adsorption experiments show that Langmuir equation was the best fitting isotherm model for **BP**, **OP** and **GP** for the adsorption of rare earth metals. In terms of maximum adsorption capacity, the best performing material was the **BP**. Moreover, release experiments were carried out to assess the potential reuse of these materials. These experiments were conducted using HNO_3 0.10 mol dm^{-3} solution [4]. A graphical schematic representation of the studies carried out is reported in **Figure 1**.

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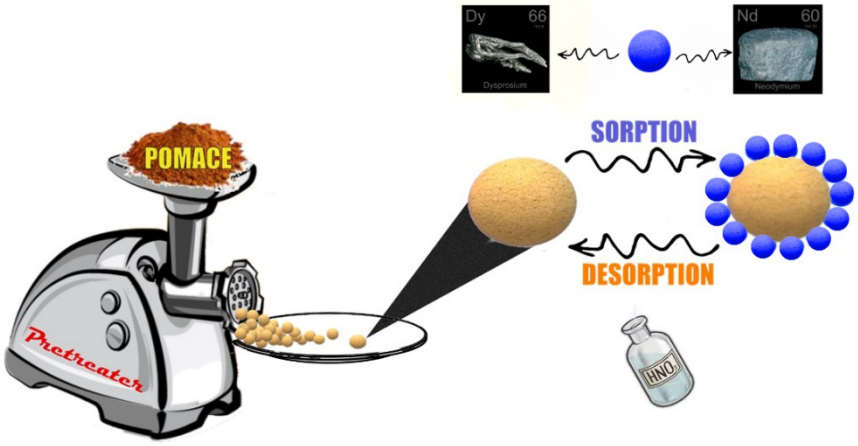

Figure 1: Graphical abstract of the studies performed on pomace.

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Silver(I), gallium(III) and indium(III) solution behaviour in the presence of heterocyclic aromatic carboxylic acids

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Picolinic acid (2-pyridinecarboxylic acid; HPic) is a crucial bioligand whose chemistry has become of big interest by the variety of physiological properties as for example the ability to coordinate with biologically essential metals, forming complexes whose stability constants follow the decreasing order trend: Cu(II) > Fe(III) > Fe(II)> Zn(II) > Mn(II), Mg(II), Ca(II). Furthermore, it has been demonstrated that picolinic acid and its derivatives induce or increase some of the therapeutical properties when it is part of a metal complex, independently if the metal centre is biologically essential or not [1].

Both the ions Ga(III) and In(III) are hard acid cations in aqueous solution, thus with good affinity to ligands containing hard nitrogen and oxygen donor atoms [2]. Despite their non-essentiality in biological systems, similar properties of these ions with essential Fe(III), Ca(II) and Na(I) ions (e.g. ionic radii) allow them to participate in biochemical processes *in vivo* [2,3]. In the present work we have investigated the ability of gallium(III) and indium(III) as potentially active ions with anticancer activity to form complex species with picolinate ions.

On the other hand, five-membered heterocyclic compounds are also in the centre of attention, as many drugs are derived from their structure. Compounds comprising the furan or tetrahydrofuran ring are biologically active and are existent in several pharmaceutical products. Furfurylamine is an intermediate in the diuretic, furosemide. 5-(Dimethylaminomethyl)furfuryl alcohol is an intermediate in the preparation of ranitidine, which is used for peptic ulcers treating. 2-acetylfuran, prepared from acetic anhydride and furan is an intermediate in the synthesis of cefuroxime, a penicillin derivative. 2-Furoic acid (HFu2c) is prepared by the oxidation of furfural. Both furoic acid and furoyl chloride are used as pharmaceutical intermediates [4].

The complex species distribution in dependence of pH values for the Ga(III)-HPic and In(III)-HPic systems were studied by potentiometric and ^{1}H NMR titrations. It is clear that complex species $[Ga(Pic)_2]^+$ and $[In(Pic)]^{2+}$ occur immediately after the ligand addition to the acidified metal(III) nitrate solution (t = 25 °C; I = 0.1 M KNO_3) and their abundance is predominant. The $[Ga(Pic)_3]$ complex is present in the acidic solution in a low abundance and gradually its abundance increases with increasing pH value and becomes dominant from pH 3.5. Its high abundance, above 90%, can be observed in a wide pH range from 4.7 to 6.6. Similarly, $[In(Pic)_2]^+$ complex species abundance increases with the increasing pH and is predominant in the solution

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above pH 4. From NMR titrations experiments it is notable that complexes $[Ga(Pic)_2]^+$ and $[Ga(Pic)_3]$ are not distinguishable. It seems likely that only minor structural differences in the arrangement of the ligands around the Ga(III) ions must occur. Comparing stability constants of the species $[Ga(Pic)_2]^+$ ($\log\beta_{ML2} = 16.23(6)$) and $[Ga(Pic)_3]$ ($\log\beta_{ML3} = 20.86(2)$; ($M = Ga^{3+}$, $L = Pic^-$)) with analogue system for Al(III) [5], we can conclude the formation of more stable gallium(III) complex species [6]. Moreover, Fe(III) forms less stable complex species with picolinate ligand [7,8] than Ga(III) and the stability of Fe(III) and In(III) complex species $[M(Pic)]^{2+}$ and $[M(Pic)_2]^+$ is comparable. For the system Ag(I)-HFu2c, potentiometric data analysis (t = 25 °C; I = 0.1 M KNO_3) resulted in the determination of the stability constant of only one species, i.e., the ML ($M = Ag^+$, $L = Fu2c^-$), $\log\beta_{ML} = 0.59(4)$ [9].
Ga(III) species $Ga(Pic)_3$ and In(III) species $In(Pic)_2$ have been isolated in crystalline form as $[Ga(Pic)_3]\cdot H_2O$ and $[In(Pic)_2(H_2O)(NO_3)]$ and their physico-chemical and biological evaluation has also been studied. Moreover, Ag(I) complex species AgFu2c has been isolated as $\{[Ag(Fu2c)]\}_n$ complex in crystalline form and was fully characterized and tested from antimicrobial and cytotoxic point of view.

Acknowledgements:

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The use of chemical speciation as base on the evaluation of the action of 8-HQA and its Ga^{3+} metal complexes on microbiota radiation related resistance

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Cancer patients submitted to radiotherapy often suffer from severe side effects, which can also arise from imbalance of the normal metabolic pathways. Tryptophan (Trp) is an essential amino acid, with the three major Trp metabolism pathways leading to serotonin, kynurenine, and indole derivatives being under the direct or indirect control of the microbiota. A few gut microbes have been shown to produce kynurenine derivatives and a recent work showed that kynurenic acid provided long-term radioprotection *in vivo* [1]. Furthermore, there is evidence that changes in the plasma metabolome and microbial metabolite levels can be associated with disease progression and severity [2]. This study aims to the understanding of the ability of 8-hydroxyquinoline-2-carboxylic acid (8-HQA, an end product of kynurenic Trp metabolic pathway), and the corresponding 2:1 ligand-to-metal Ga(III) complex $[Ga(8\text{-HQA})_2]^-$ in the protection of different human microbiome bacteria against ionizing γ-radiation.

For this study, the previous knowledge of the chemical speciation of the system 8-HQA/Ga^{3+} is fundamental to know which is the biologically active species. The experimental conditions were also chosen and defined having this as essential starting point.

In this work we will present the detailed chemical speciation of the mentioned system, along with the obtained preliminary results that indicate some evidence of a protective effect against ionizing γ-radiation of the tested compounds in some of the analyzed bacterial strains, with an increase in the D_{10}-value (dose required for 90 % inactivation of the initial population). Furthermore, the compounds' anti-inflammatory activity will be also reported based on the study on RAW264.7 cells (murine monocytes macrophage) and its ability to generate the pro-inflammatory molecule nitric oxide (NO), in presence and in the absence of the evaluated compounds.

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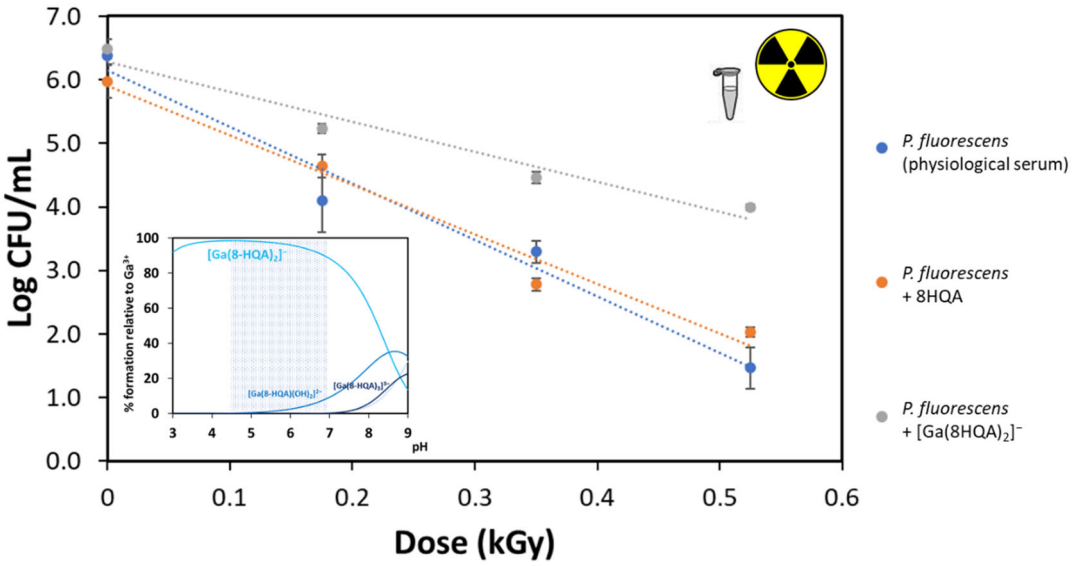

Figure 1. Inactivation kinetics of *Pseudomonas fluorescens* by gamma radiation in physiological serum and in the presence of the compounds, 8-HQA and $[Ga(8\text{-}HQA)_2]^-$. Inset: Distribution diagram of $Ga_pL_qH_r$ species as a function of pH in the Ga^{3+}/8-HQA system ($c_{8\text{-}HQA}$ = 1 mmol dm^{-3}, c_{Ga3+} = 0.5 mmol dm^{-3}).

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Isothermal titration calorimetry for the study of multiple host-guest equilibria: a multi-laboratory exercise

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Solution equilibria are involved in different research fields, including speciation, coordination or supramolecular chemistry, where a complete thermodynamic profile is required to assess the strength and the nature of a chemical interaction. Isothermal titration calorimetry (ITC) is considered a gold-standard technique for the study of binding processes in solution as it allows the simultaneous determination of both the equilibrium constant and the standard enthalpy change values, which means that a complete thermodynamic characterization can be achieved from a single experiment [1,2]. Although widely employed by the scientific community, there is still a lack of good laboratory practices for experimental design and execution as well as data analysis that should be applied to obtain accurate, reproducible and robust results.

Recently, a multi-laboratory benchmark study was performed and a standard operating protocol for examining a simple 1:1 binding process through ITC was proposed [3,4]. However, in the field of solution thermodynamics, there is still a need for guidelines that may help to properly design a calorimetric titration dealing with the formation of multiple species and to accurately analyze ITC data when simultaneous equilibria are occurring. Moreover, an appropriate chemical speciation requires that the exact stoichiometry of each formed species is known rather than relying on the "*n* value" often included as a parameter to be refined in the binding models used by most software.

Within this framework, the activity of the Working Group 2, Task Group 5 (involving research groups from the Universities of Catania, Ferrara, Firenze, Ljubljana, Messina, Strasbourg, Udine and Wroclaw) of the NECTAR Cost Action (CA18202) focuses on a multi-laboratory exercise for the ITC study of a multiple host-guest complex formation. Inspired by a similar supramolecular system [5], *p*-sulfonatecalix[4]arene (C4TS) and decyltrimethylammonium bromide (Dec-Me_3N^+) or decamethonium bromide (Dec-$(Me_3N)_2^{2+}$) were chosen as host and guest model molecules, respectively, able to form 1:1 or 1:1 and 2:1 complexes in aqueous solution (**Figure 1**).

In this work, we present the ITC experiments carried out by the CaSAC Lab of the University of Catania and the related data analysis procedure [6] which enabled the simultaneous refinement of several calorimetric curves obtained at different and carefully defined experimental conditions.

This contribution, along with those from the other research groups of the Task Group 5, will provide the basis for proposing appropriate directions for the experimental design and data refinement when using solution calorimetry for the study of complex chemical equilibria.

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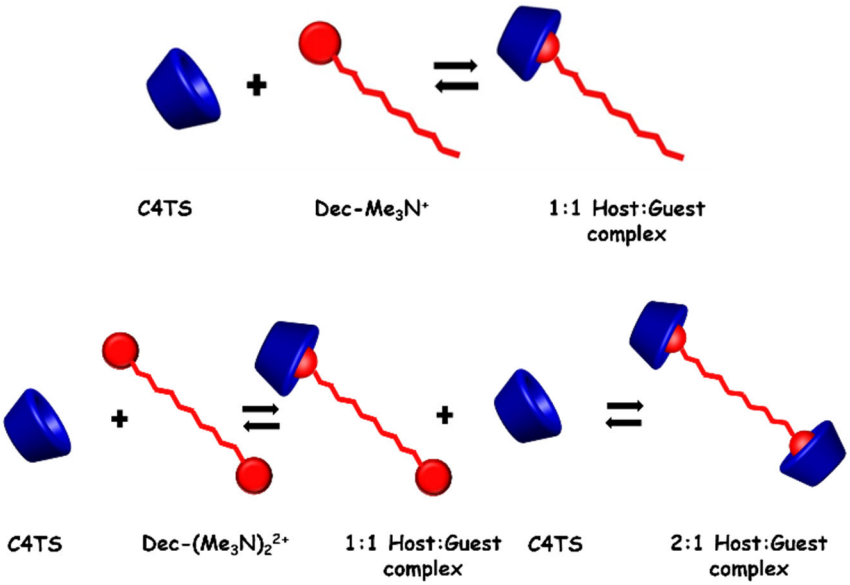

Figure 1. Graphical representation of the investigated equilibria

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8- hydroxyquinoline-2-carboxylic acid (8-HQA) and Ga^{3+}: a metal complex coordination study based on a multi-technique approach

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8-hydroxyquinoline-2-carboxylic acid (8-HQA) is one of tryptophan's metabolites (TrpM). Trp, an essential amino acid, and its metabolites (TrpM) have a fundamental impact on the regulation of immune, central, and gastrointestinal nervous systems as well as on the condition of the intestinal microbiota. A wide range of biological dysfunctions in humans, i.e. depression, schizophrenia, colorectal cancer (CRC), autoimmunity, and neuro-degeneration pathologies, are linked with disruptions in the level of Trp or TrpM. These conditions may result from inflammation and imbalance of intestinal microbiota resulting from an abnormal Trp metabolism. Besides, this process works the other way around – CRC progression affects inflammation that disrupts intestinal microbiota homeostasis, impacting Trp metabolism [1,2]. The amount of dietary metal ions in the organism can also change the intestinal microbiota's balance, quality, and distribution [3].

8-HQA itself was recognized as a siderophore, a small molecule with a high affinity towards iron, produced by microorganisms and plants. A study performed in 2018 by Gama et. al. describes the complex formation between Fe^{2+}, Fe^{3+} cations and 8-HQA [4]. The questions arose as to whether this metal complex could help develop new strategies for manipulating the microbiota or if it could have antimicrobial activity.

In order to fully uncover the potential of Fe^{3+}/8-HQA system, a detailed study on the coordination properties of 8-HQA (one of TrpM) towards Ga^{3+} cation was performed. The explanation for the choice of gallium has many aspects: i) gallium and ferric iron have similar coordination chemistry; ii) 67/68Ga radioisotopes are used as radiotracers in techniques of imaging, as single-photon emission computerized tomography (SPECT) in case of 67Ga, a gamma-emitting isotope, and Positron Emission Tomography (PET) with 68Ga, a positron-emitting isotope. Here, we present a detailed study, based on a multi-technique approach, for the knowledge of a comprehensive set of information necessary to assess the details of the chemical speciation of the Ga^{3+}/8-HQA system. 8-HQA binding ability towards Ga^{3+} has been investigated in KCl(aq) at I = 0.2 mol·dm^{-3} and T = 298.15 K by ISE-H^+ (glass electrode)

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potentiometric and UV/Vis spectrophotometric titrations. Besides studies performed in aqueous solution, it was possible to investigate this system in a solid state, during STSM under the scope of WG2 of the Action. A series of metal-complex syntheses in the solid state was performed, and obtained precipitates were fully characterized by ESI-MS (electrospray ionization mass spectrometry), thermogravimetry (TG), elemental analysis, and IR spectroscopy. In this work, the determined complex formation constants will be presented and discussed, along with the characteristics of the isolated precipitates. A comparison with previous results obtained for the Fe^{3+}/8-HQA system [4] will also be made.

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Application of natural terpene-based solvents as reaction media for Pb(II) complexation during LLE procedure

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Solvents prepared from natural terpenes (menthol and thymol) as H-bond acceptors and series of organic acids (chain lengths from 8 to 18 C atoms), as H-bond donors, previously investigated and characterized [1], were tested as reaction media for liquid-liquid extraction purposes. Due to their high hydrophobicity, they seem to be promising alternatives to conventional (nonpolar and toxic) solvents, since they posses relatively less toxic, less volatile and consequently, more environmentally friendly characteristics [2]. Assuming that the equilibrium is established between solvent and analyte during ligandless procedure, it can be concluded that those nonpolar solvents can efficiently extract nonpolar analytes from the aqueous environment. Previous investigations [3-6] showed a wide range of applications, including their use as solvents in extractions of metal cations, small-molecules and bioactive compounds for food and pharmaceutical applications. In this work, four hydrophobic solvents based on natural terpenes, which showed chemical stability and desirable physicochemical and thermal properties, were chosen as potential reaction solvents in LLE procedure for Pb(II) removal from river sediment samples. Extraction parameters (solvent volume, equilibrium time, pH value) were optimized and chosen solvents were applied. The results showed satisfactory extraction efficiencies in simple, ligandless and fast procedure, followed by low solvent consumption. The best results (>98%) were obtained by the thymol based solvent (Thy:DecA=1:1), but menthol based solvents (Men:DecA=1:1 and Men:OctA=1:1), also showed 97% of effectiveness.

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Recycling of Rare-Earth Magnets through Hydrometallurgical Processes

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Due to the limited availability of primary ore deposits and supply risk, research attention is being drawn towards the recovery of Rare Earth Elements (REEs) from secondary sources [1,2]. Raw materials play a fundamental role in the current and future technologies necessary for achieving sustainable development goals as outlined in the UN 2030 Agenda. Notably NdFeB and SmCo magnets, as secondary solid wastes, are significantly rich in REEs such as Nd, Sm, and Dy [3]. Current hydrometallurgical processes for the recovery of the REEs from aqueous solutions have some interesting advantages, but require the use of significant amounts of toxic volatile organic compounds [4]. Ionic liquids (ILs) have many potential applications since they present many advantages such as negligible vapor pressure, reusability and high thermal stability [5].

In this work, we assess the performance of phosphonium based ILs ($[P_{66614}][Dec]$ and $[P_{66614}][Cl]$ for separation of REEs from other metals from magnets. The versatility of more environmentally friendly IL with decanoate anion at different pH was studied. Moreover, in the acid leaching step, the effects of acid concentration and leaching time were investigated. To complete the recovery process, further separation was proposed using two phosphonium based ILs consecutively, resulting in a high yielding procedure. It was found that bivalent ions are extracted from highly acidic media, while REEs prefers neutral pH in both ILs. After extraction, the water phase was measured by ICP-OES to quantitatively determine metal concentrations and magnet composition.

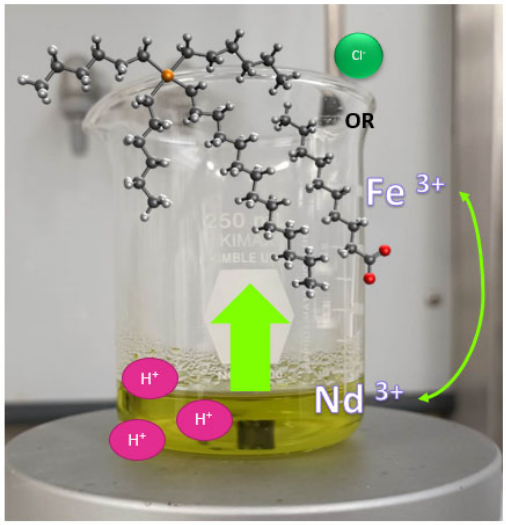

Figure 1. Graphical representation of selective extraction of metals by $[P_{66614}][Dec]$ from acidic media.

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Thermodynamics of energy drinks-taurine and caffeine interactions

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Energy drinks contain two common compounds that are known to have effects on the body - caffeine and taurine. Caffeine is a well-known central nervous system stimulant that can improve alertness, reduce fatigue, and enhance cognitive performance.

Caffeine is found in many sources, including coffee, tea, and energy drinks. In energy drinks, caffeine is often used to promote wakefulness and energy, making it a popular ingredient in these beverages. Caffeine's ability to enhance cognitive performance has been demonstrated in numerous studies, highlighting its effectiveness in improving focus and attention.

Taurine is an amino acid that is naturally produced in the pancreas and is found in high concentrations in the brain, heart, and muscles. Taurine has been associated with several health benefits, including improved athletic performance, reduced muscle damage, and improved insulin sensitivity. In energy drinks, taurine is often added for its supposed ability to enhance physical performance and mental alertness.

Our earlier research showed that the presence of biologically active molecules, such as ATP [1] and salicylate [2], leads to the self-aggregation of caffeine in water. The binding of caffeine molecules into self-aggregates significantly affects its solubility and bioavailability.

Since water molecules surround caffeine and taurine molecules in the human body and energy drinks, it is important to examine how taurine affects caffeine's structural organization in water. This research includes experimental measurements and computational simulations of two systems: taurine water solutions and caffeine in 0.1 mol·kg^{-1} taurine aqueous solution.

The solubility of taurine in water ranges from 85 to 168 g per 1000 g of water in the temperature interval of T = (293.15 – 313.15)K. The presence of taurine in aqueous solutions in a concentration of 0.1 mol·kg^{-1} slightly increases the solubility of caffeine compared to pure water. In both examined systems, enthalpy plays a more significant role than entropy in the dissolution process.

Based on volumetric, acoustic, viscosimetric, and computational studies, it can be concluded that the interactions of taurine with molecules are significant and that taurine acts as a structure-maker in aqueous solutions. The computational simulations indicated that taurine has a hydration number of 6.14 at a temperature of T = 293.15 K. The presence of the SO_3^- group significantly increases the hydration capacity of taurine compared to amino acids.

Caffeine molecules in the solvent 0.1 mol·kg^{-1} taurine aqueous solution do not interact significantly with water or taurine molecules. The positive values of the B-coefficients and their

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increasing with temperature place caffeine in the group of anomalous structure-maker compounds. In the studied system caffeine + 0.1 mol·kg^{-1} taurine aqueous solution, caffeine molecules self-aggregate through π-π interactions (Figure 1). Self-aggregation is a consequence of the dehydrating effect of taurine, which leads to a salting-out effect. The results of this work confirmed that the fragile stability of caffeine molecules in water is relatively easy to break with the addition of polar additives such as taurine and leads to a change in the structural organization of caffeine.

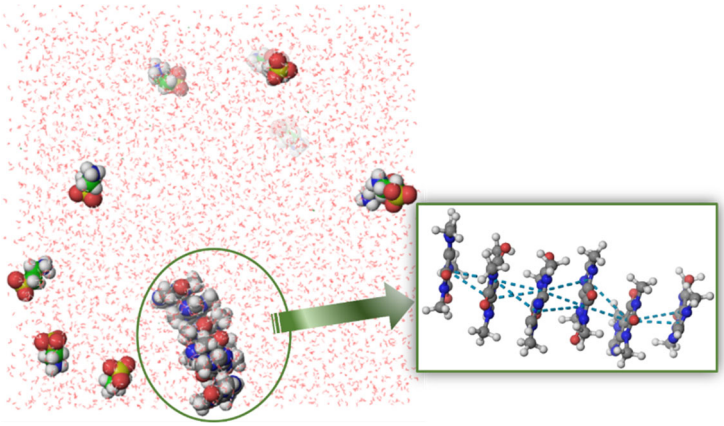

Figure 1. Self-aggregation and π–π interactions between caffeine molecules

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Synthesis and Biological Activity Evaluation of Novel Cu(II) Complexes with Usnic Acid Derivatives

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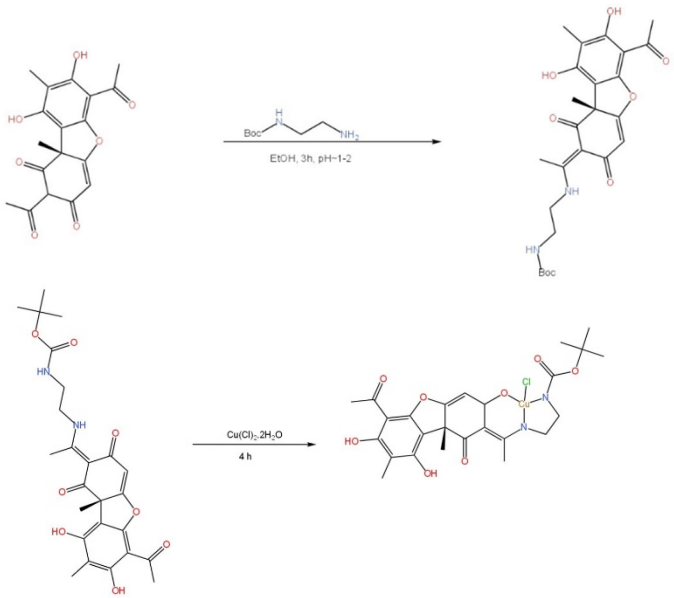
This study primarily aims to synthesize usnic acid derivatives and ensure metal homeostasis by chelating the Cu(II) metal salt with those derivatives. The investigation focuses on their therapeutic properties for Alzheimer's disease, examining their potential to inhibit oxidative stress, anticholinesterase, and to prevent beta-amyloid accumulation.

Three different ligands of usnic acid and their Cu complexes were synthesized according to the reaction outlined in Scheme 1. The synthesis of metal complexes using 1 ligand and Cu(II) salt, along with structure elucidation studies is ongoing.



Scheme 1. The synthesis of compound 1 and its Cu complex [1].

For this purpose, spectroscopic and analytical methods such as ICP, FT-IR, TG, melting point, elemental analysis, and magnetic susceptibility were employed. The results obtained were evaluated in light of literature information, and the most appropriate structural formulas for the ligands and metal complex were suggested.

The acetylcholinesterase (AchE) and butyrylcholinesterase (BuChE) inhibition ability of the Usam-1 ligand was tested using molecular docking and Ellman's method [2]. To further explore

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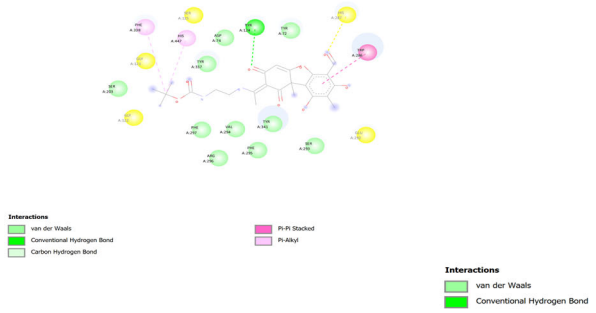
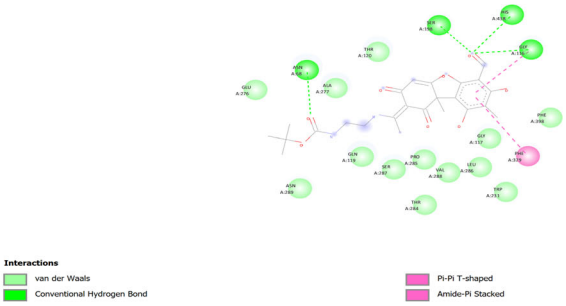
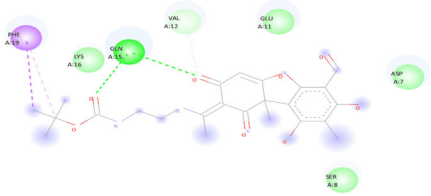
the possible interaction between Usam-1 with AchE, BuChE and beta-amyloid molecular docking simulations were carried out by the AutoDock Vina Tools.
Following AchE docking study, a bond between the amino acid TYR124 in the A chain and 1H was observed, and Van der Waals and pi-pi interactions were noted. The binding energy is -9.7 kcal/mol. The amino acids with which the ligand interacts in the active region can be seen as follows. In the docking study of beta-amyloid, a bond between the amino acid GLN15 in the A chain and 2H was observed. Additionally, a C-H bond with the amino acid VAL12 in the A chain was noted. Van der Waals and pi-pi interactions were observed. The binding energy is -5.4 kcal/mol. According to the BuChE study, a bond between the amino acids SER198, HIS438, GLY116, and ASN68 in the A chain and 4H was observed. Van der Waals and pi-pi interactions were noted. The binding energy is -9.4 kcal/mol. Based on the preceding, it was found that the best result was with acetylcholinesterase.



(A)



(B)



(C)

Figure 1. The binding mode prediction and interaction of compound 1 in the substrate binding pocket of AChE (A), BuChE (B) and beta-amyloid (C).

The synthesis and characterization of the Cu(II) complex with 1, as well as the investigation of its biological effects, are ongoing. In vivo studies are being conducted on rats.

References:

[1] A. Yang, W. Liu, X. Li, W. Wu, X. Kou, R. Shen, **2022**, (1263), 8.
[2] G.L. Ellman, K.D. Courtney, V. Andres, R.M. Featherstone, **1961**, (7), 88–95.

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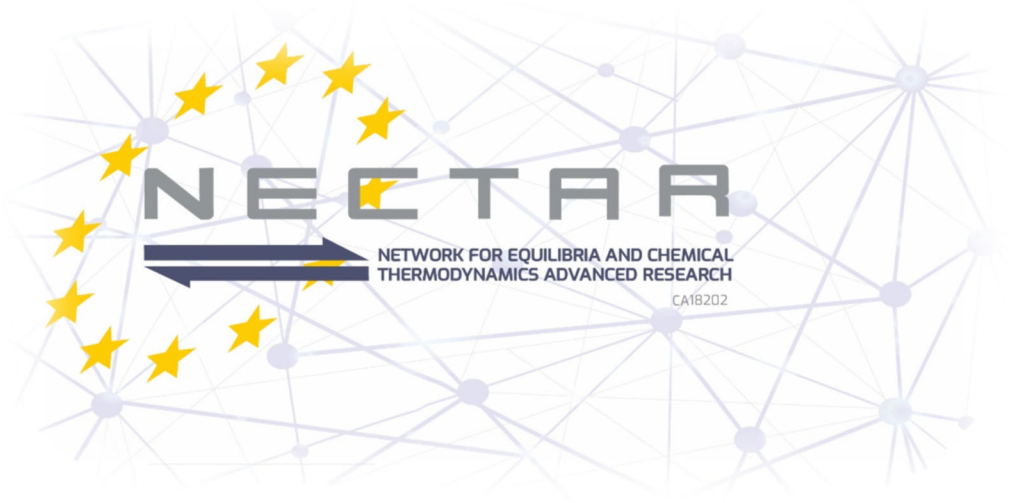

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