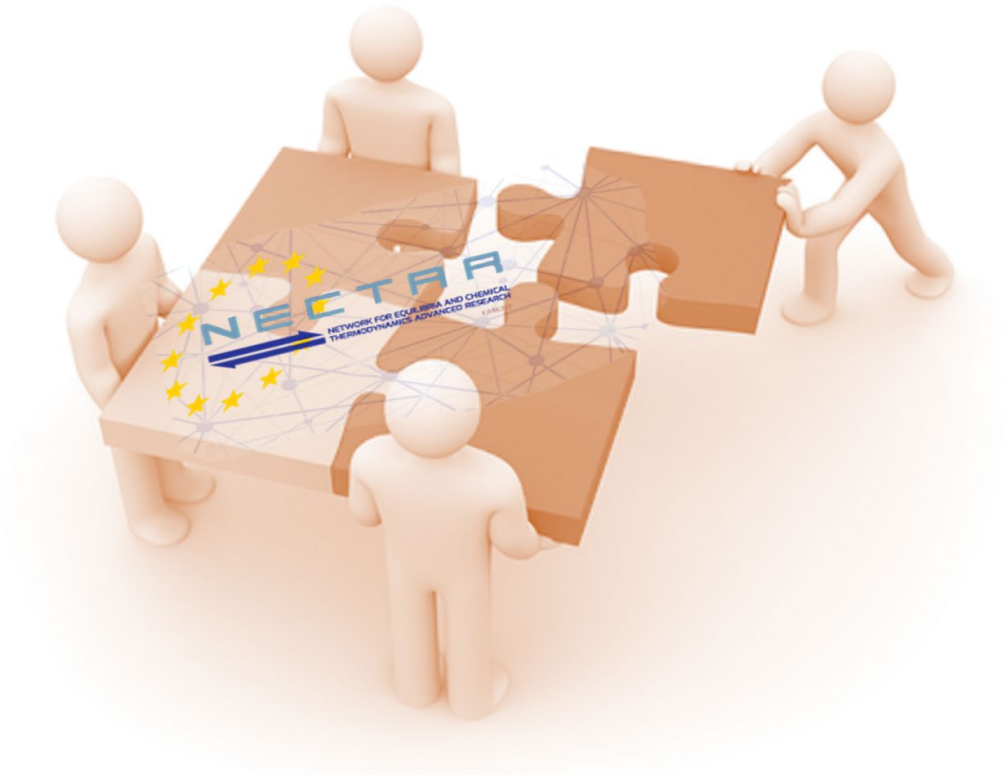
NECTAR's Spring Web-meeting

25th-26th March 2021

BOOK OF ABSTRACTS



COST ACTION CA18202, NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research

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It has been one year since all COST-NECTAR members have met to discuss science. The covid-19 pandemic has prevented the organization of traditional conferences.

Some working groups have met regularly but kept isolated from each other. A larger event is needed to share the findings since the last NECTAR conference. The NECTAR's Spring Web-meeting 2021 will be two informal afternoon dedicated to share and discuss the activities and results from all NECTAR working groups and NECTAR members.

Please bring your own food and drinks, and enjoy the discussion!

Isabel Cavaco

This contribution is based upon work from
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Program

Thursday, 25th March 2021

14:00	**Opening Ceremony**

14:05	***WG1: NECTAR for Challenging Cations – State of the Art*** ***Montserrat Filella (WG1 Leader)*** ***Olga Iranzo (WG1 co-Leader)***
	Preliminary studies of vanadium and sulfide/polysulfide system **Elvira Bura Nakić** (Rudjer Boskovic Institute, Croatia)
	Hydrolytic equilibria of gallium ions - a necessity in coordination studies of novel DFO E analogues complexes for infection imaging **Andrzej Mular** (University of Wroclaw, Poland)
	U(IV) hydrolysis: can we study it by spectrophotometry and potentiometry? **Vladimir Sladkov** (Lab Physique 2 Infinis Irène Joliot-Curie, France)
	State of art and advances on the definition of Fe^{3+} hydrolysis **Demetrio Milea** (Università degli Studi di Messina, Italy)
	DISCUSSION

14:45	***WG2: NECTAR for Challenging Ligands – State of the Art*** ***Petr Hermann (WG2 Leader)***
	Polydentate ligands (TG1) – State of the Art **Petr Hermann** (Charles University in Prague, Czech Republic)
	Metal - DNA Interactions (TG2) – State of the Art **Tarita Biver** (Università degli Studi di Pisa, Italy)
15:00	Zincophore metal binding sites: from solution equilibria to metal transport in human pathogens **Denise Bellotti** (Università degli Studi di Ferrara, Italy)
	Development and investigation of novel anticancer thiosemicarbazones and their copper complexes **Eva A. Enyedy** (University of Szeged, Hungary)

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	Transition metal complexes of Schiff base ligands as selective G-quadruplex DNA binders. **Gianluca Farine** (Università degli Studi di Palermo, Italy)
	New and ready biodegradable phosphonates **Stephan Liebsch** (Schimmer & Schwarz Mohsdorf GmbH & Co. KG)
	Luminescent Sensor Based on Ln(III) Ternary Complexes for NAD(P)H Detection **Přemysl Lubal** (Masaryk University, Brno, Czech Republic)
	Strong complexes bearing labile ligands: challenges in catalysis with supported metal complexes **Matteo Savastano** (University of Florence, Italy)
	Metal-enhanced antimicrobial peptides from marine creatures **Adriana Miller** (University of Wroclaw, Poland)
	DISCUSSION

15:45	***WG3: NECTAR multicomponent solutions and complex matrices – State of the Art*** ***Slodoban Gadžurić (WG3 Leader)***
15:50	A calorimetric study of the alkali COSAN salts' self-assembly in aqueous solutions **Žiga Medoš** (University of Ljubljana, Slovenia)
	Acidity constants of zwitterionic ionic liquid **Nikolett Bagany** (University of Novi Sad, Serbia)
	Thermodynamic study of the micellization process of functionalized surface-active ionic liquids task-specific for extraction of technologically critical elements **Tatjana Trtić-Petrović** (University of Belgrade, Serbia)
	Interactions of pharmaceutically active ionic liquids with DNA and BSA **Aleksandar Tot** (University of Novi Sad, Serbia)
	Thermodynamic studies of interactions in aqueous solutions of ionic liquids based on the local anesthetic drugs and salicylic acid **Jovana Panić** (University of Novi Sad, Serbia)
	DISCUSSION

16:25	**Coffee Break**

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16:35	***WG4: NECTAR Tools, Services and Facilities – State of the Art*** ***Aleksandar Cvetkovski (WG4 Leader)***
16:40	An open source software for potentiometric data analysis **Silvia Berto** (University of Turin, Italy)
	Spectrapp: an open source software to interpret spectroscopic data using chemometric strategies **Eugenio Alladio** (University of Turin, Italy)
	DISCUSSION

17:00	***Overview of STSM*** ***Matteo Tegoni (STSM Manager)***
17:05	Synthesis of bioinspired metallopeptides and study of their catalytic properties in oxidation reactions **Silvia Gentili** (University of Parma, Italy)
	New efficient chelators for Zr-89 radiometal: design, synthesis and thermodynamic properties **Yuliya Toporivska** (University of Wroclaw, Poland)
	Complexation of V(IV) and V(V) with succinic and oxalic acid in aqueous acid solutions using affinity capillary electrophoresis **Lucija Knežević** (Rudjer Boskovic Institute, Croatia)
	DISCUSSION

17:30	***Guidelines on outreach activities*** ***Elzbieta Gumienna-Kontecka (SC Manager)***

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Friday, 26th March 2021

15:00	***Working Group Leaders Round Table*** **WG1 – Montserrat Filella** **WG2 – Petr Hermann** **WG3 – Slodoban Gadžurić** **WG4 – Aleksandar Cvetovski** **WG5 – Isabel Cavaco**

16:30	***Management Committee Meeting***

18:00	***Closing Ceremony***

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WG1

NECTAR for highly hydrolysable (HHC) and/or low-valence state (LVC) cations

Preliminary studies of vanadium and sulfide/polysulfide system

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The facile formation of thiometalate ions [$MO_xS_{4-x}^{n-}$; x=0-4; M=Mo(VI), As(V), W(VI), Sb(V), Re(VII)] containing the metal in its highest oxidation state has been demonstrated repeatedly within aqueous solutions involving the corresponding oxyanion and hydrogen sulphide. Such transformations are well-known to affect the solubility and mobility of thiometalate-forming metals [e.g. 1-2]. The formation of $MoO_xS_{4-x}^{2-}$ (x=0-4) seems to control Mo solubility in anoxic environments [3]. Increased As concentration in groundwater appears to result from formation of $AsO_xS_{4-x}^{3-}$ (x=0-4) and/or $AsO_xS_{3-x}^{3-}$ (x=0-3) [2].

Although V also has the potential to form of thiovanadate ($VO_xS_{4-x}^{3-}$; x=0-4) and thiovanadite ($VO_xS_{3-x}^{3-}$; x=0-3) soluble complexes, available literature on V oxoanions and their behaviour in aqueous hydrogen sulphide solutions is sporadic. An early spectrophotometric study of vanadate (VO_4^{3-}) and hydrogen sulphide solutions indicated the formation of $VO_xS_{4-x}^{3-}$ only at pH >10 [4]. Wanty and Goldhaber (1992) offered evidence of vanadyl ion (VO^{2+}) reduction at near neutral pH [5].

Here, novel chromatographic data is presented for neutral to mildly alkaline solutions initially containing VO_4^{3-} and aqueous sulphide. Data indicate VO_4^{3-} reduction with polysulfides as the main oxidized product in test solutions. Chromatograms suggest $VO_xS_{3-x}^{3-}$ formation, while in accordance with previous studies, no evidence of $VO_xS_{4-x}^{3-}$ formation is found. We also note the formation of unidentified colloidal solids in these same V + S solutions. Precipitates obtained from pH 6.5 solutions are brown; those formed in pH 8.5 solutions are white. Preliminary XAFS data suggest mildly alkaline precipitates contain V(III).

References:

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Hydrolytic equilibria of gallium ions - a necessity in coordination studies of novel DFO E analogues complexes for infection imaging

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As properties of elements and compounds depends mainly on their interactions in a given system, coordination chemistry, molecular modelling and drug design relays strongly on thermodynamic study of chemical equilibria. Hydrolytic equilibria is a vital part of metal coordination chemistry and in the case of highly hydrolysable metals such as iron and gallium, strongly influence solution thermodynamics. As a part of WG1 – 'NECTAR for highly hydrolysable (HHC) and/or low-valence state (LVC) cations', we were concerned with hydrolysis of gallium ion. We have collected and critically reviewed available data on Ga(III) hydrolysis.

We are particulary interested in gallium because this metal presents set of suitable properties for medical applications. ^{67}Ga and ^{68}Ga are two isotopes fitting nuclear medicine. The first one is a source of pure γ radiation widely used as single photon marker for the presence of inflammation and malignancy, and with 3.3 days of half-life allows it to be prepared in advance and transported on vast distances. The second one, positron emitting with half-life of 67.7 min is suitable for PET nuclear imaging without exposing the patient to unnecessary radiation, and can be prepared from ^{68}Ge/^{68}Ga portable and efficient generator. [1, 2]

The first generation of gallium imaging agents were not specific. They mostly targeted secondary symptoms of disease such as increased blood flow, vascular permeability, activated endothelial cells or polymorphonuclear cell migration. In an attempt to find more specific radiotracers we are currently investigating group of microbial metabolites called siderophores - iron-specific chelators recognized by specific bacterial transporters, representing one of few fundamental differences between bacterial and mammalian cells. Microbial Fe transport system seems to be a perfect target for specific diagnostic and therapeutic agents but there are no isotopes of Fe with suitable decay properties for nuclear imaging. Thanks to its similarity in coordination properties, Ga(III) can successfully mimic Fe(III) in its complexes and biological systems. [3, 4]

In our approach to simplify native siderophore structure, leaving intact only motifs necessary for efficient chelation and microbial recognition, we have designed a series of 6 analogues of siderophore desferrioxamine E. During our studies of Ga(III)-DFO E analogues we have implemented previosuly collected data on Ga(III) hydrolysis in our coordination models.

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U(IV) hydrolysis: can we study it by spectrophotometry and potentiometry?

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This work has been performed in the frame of WG 1 topic "NECTAR for highly hydrolysable (HHC) and/or low-valence state (LVC) cations". The literature data [1-8] on U(IV) hydrolysis and on UO_2 solubility has been examined. The difficulties due to the slow kinetics of solid phase formation (UO_2) and U(IV) stability on air for chemical equilibrium studies have been pointed out. The majority of works on U(IV) hydrolysis has been performed by spectrophotometric method. The limitations of spectrophotometry and potentiometry for U(IV) hydrolysis studies will be discussed in this communication.

References:

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State of art and advances on the definition of Fe^{3+} hydrolysis

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Iron is one of the essential nutrients required by almost all living organisms, and it is involved in a wide number of biologically and environmentally relevant processes. Fe^{3+}, one of iron's most common oxidation states, it's a relatively strong Lewis acid, undergoing strong hydrolysis even at low pH. The formation of hydrolytic species, including sparingly soluble (oxo-)hydroxides, deeply affects Fe^{3+} speciation in aqueous solution in a very wide pH range. Furthermore, depending on Fe^{3+} analytical concentration, several polynuclear hydroxo-species may also be formed, other than "colloidal" aggregates. To make things even more complex, one must also consider that some of these species have very slow formation kinetics, influencing real Fe^{3+} speciation, as well as the reliability some published results. As a consequence of this, the correct definition of the acid-base behaviour of Fe^{3+} is one of the most debated themes among solution chemists, not only in terms of stability of species formed, but also concerning their nature. In this contribution, an attempt is made to analyse main literature findings on this topic, with the aim of giving a series of references and tools (*i.e.* equations) to derive a comprehensive and reliable dataset of Fe^{3+} hydrolysis (and solubility) constants to be used in a wide range of conditions (ionic media, ionic strengths, temperatures, analytical concentrations).

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WG2

NECTAR for strong and/or multifunctional ligands, macromolecules, polyelectrolytes

Zincophore metal binding sites: from solution equilibria to metal transport in human pathogens

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The assimilation of metal nutrients from the host environment is an important factor for the onset and progression of infectious diseases. Zn(II) ions, in particular, are crucial for the virulence and survival of both pathogen and human cells, being indispensable for the expression and function of many enzymes. Interestingly, the Zn(II) uptake mechanism is one of the major differences in the metabolism of human and pathogen cells, thus it represents a promising drug-target for specific and selective treatments [1].

Pathogens compete with the host organism in order to acquire zinc and meet their physiological metal nutrient demands. An efficient zinc recruitment is therefore achieved by means of specialized zinc-binding proteins and molecular systems which capture the metal ion from the host environment forming stable complexes [2, 3]. A deep knowledge of the properties, structure and action mechanisms of these extracytoplasmic zinc chelators (zincophores) can be a powerful tool to design new therapeutic strategies against the antibiotic and/or antifungal resistance [4].

As a first step, it is essential to obtain information about thermodynamics and coordination chemistry of the involved systems, in order to point out the most effective metal binding sites and to elucidate the dynamics behind the metal transfer. Indeed, a relatively high metal binding affinity is crucial to ensure the acquisition process in an environment rich of competitive systems and thermodynamic studies may help clarifying this aspect. An outstanding example is given by the characterization of the zinc-binding sites of the periplasmic protein ZinT, expressed by *Escherichia coli* and *Salmonella enterica* [5].

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Development and investigation of novel anticancer thiosemicarbazones and their copper complexes

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3-Aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine) is the most prominent representative of the thiosemicarbazone (TSC) compound family, and it has been studied in *ca.* 30 phase I and II clinical trials in both solid and haematological tumours [1]. The mechanism of action of Triapine is strongly related to its ability to form highly stable and redox active iron complexes. On the other hand, interaction with cellular copper ions has been recently associated with the mechanism of action of TSCs, at least for a subgroup of the nanomolar-active compounds. Additionally, numerous copper(II) complexes of TSCs with improved anticancer activity compared to the corresponding ligands were also reported. Structural modifications of the TSC scaffold have a strong influence on the various physico-chemical properties, and as a consequence, on the anticancer activity.

Our aim is to develop more effective and safer TSCs and their copper(II) complexes, and to reveal relationship between the solution chemical properties (*e.g.* lipophilicity, pK_a of the ligands, stability and structure of the complexes), the redox behaviour of the copper(II) complexes and their cytotoxic activity. The fruitful and complementary collaboration of our research groups has resulted in the development and characterization of numerous promising thiosemicarbazone compounds, and the published achievements [2,3] will be presented in the lecture.

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

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Cationic transition metal compounds of N_2O_2 and N_4 tetradentate Schiff base ligands, have been recently designed and synthesized as selective G-quadruplex DNA binders.

The DNA binding with both double-helical and G-quadruplex DNA has been investigated by the combination of experimental and computational approaches [1, 2]. The effect of the solution ionic strength has also been monitored, highlighting that counterion screening of the electrostatic attraction between the negatively charged phosphate groups of DNA and of the positively charged metal complexes, reduces the DNA-binding by increasing the ionic strength conditions.

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New and Ready Biodegradable Phosphonates

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A new class of water-soluble complexing agents bearing two methylene phosphonate moieties and a number of carboxylate functional groups has been discovered recently [1]. Surprisingly, and contrary to all known phosphonate based complexing agents, the representatives of this new group show when tested for their biodegradation potential under the conditions laid down in the Technical Guidance document for OECD 301A and OECD 301F excellent biodegradation values and can be classified as readily biodegradable.

The synthesis of the new substances is based on the reaction of Alkali salts of iminosuccinic acid derivatives with 2-Chloroethylaminobis(methylenephosphonic acid). The Alkali salts of the iminosuccinic acid derivatives are readily prepared by adapting the published synthesis [2, 3] starting from maleic acid anhydride, α-amino acids and alkali hydroxide with slight modifications to optimize yield, type and quantity of by-products.

The second partner, 2-Chloroethylaminobis(methylenephosphonic acid), is synthesized according to the protocol of Moedritzer and Irani [4]. Using such approach, an ethylendiamine skeleton with a mixed set of substituents is formed. Strict pH and temperature control of the aqueous reaction medium is essential to achieve a selective transformation to the new complexing agents and to avoid hydrolysis of the reactive phosphonate.

Complexometric titrations show the potential of the new substances to act as strong complexing agent.

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Luminescent Sensor Based on Ln(III) Ternary Cmplexes for NAD(P)H Detection

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The Ln(III) complexes of macrocyclic ligands are used in medicinal chemistry, *e.g.* contrast agents in MRI or radiopharmaceutical compounds, and in diagnostics using fluorescence imaging. This contribution is devoted to a spectroscopic study of Ln(III) ternary complexes consisting of macrocyclic heptadentate DO3A and bidentate 3-isoquinolinate (IQCA) ligands (see **Figure**). IQCA serves as efficient antenna ligand leading to higher quantum yield and Stokes shift (250-350 nm for Eu, Tb, Sm, Dy in VIS region, 550-650 nm for Yb, Nd in NIR region) [1]. The shielding - quenching effect of NAD(P)H on the luminescence of Ln(III) ternary complexes was investigated in detail and this phenomenon was utilized for analytical determination of this compound [1]. This general approach was verified on an example of enzymatic reaction when the course of ethanol transformation catalyzed by alcohol-dehydrogenase (ADH) was followed by luminescence spectroscopy which can be utilized for selective and sensitive determination of ethanol concentration and/or ADH enzyme activity [1]. This new analytical method can be used for another enzyme systems coupled with NAD(P)H / $NAD(P)^+$ redox pair.

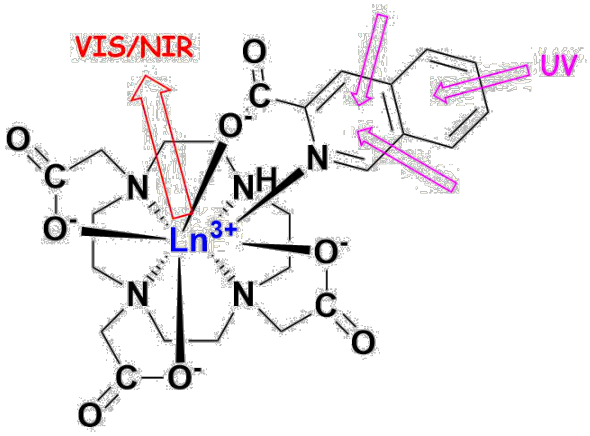

Figure. The ternary Ln(III) complexes with DO3A macrocyclic and IQCA ligands

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Strong complexes bearing labile ligands: challenges in catalysis with supported metal complexes

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The ideal prerequisites for a metal complex to be effectively used in catalysis surely include high thermodynamic stability and kinetic inertness towards demetallation. At the same time, ancillary/liable/fast exchangeable ligands, leaving thermodynamically and kinetically activated position(s) in the metal cation's first coordination sphere, are required for catalyst effectiveness and cycling abilities. This general picture results in the search of a perfect balance, where the complex is stable enough to remain unaltered under reaction conditions yet activated enough to display significant catalytic activity. Here we discuss some ongoing studies and past experiences (Figure 1), with CNTs-supported Pd(II) metal complexes catalysts for Sonogashira cross-coupling and oxygen reduction reaction, showing how different ligands' types (linear, tripodal, macrocyclic) come with their own pros and cons.

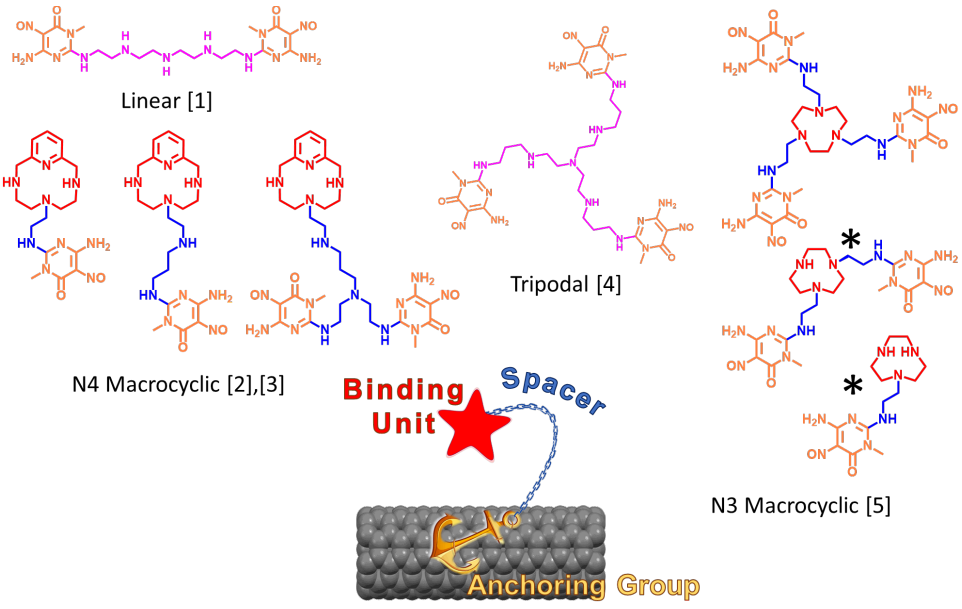

Figure 1. Some of our ligands and general scheme of CNT functionalization.

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Metal-enhanced antimicrobial peptides from marine creatures

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In recent years, a severe increase of infections caused by drug-resistant pathogens increases drastically. [1] Antimicrobial peptides (AMPs) are a group of molecules with confirmed antibacterial, antifungal and/or antiviral activity. Their natural occurrence, low cytotoxicity and minimal pathogenic resistance make them potential treasure-troves for new antimicrobial agents. [2, 3] As a part of WG2: NECTAR for strong and/or multifunctional ligands, macromolecules, polyelectrolytes, we focus on peptides, which antimicrobial properties were enhanced by the coordination of metal ion. In this presentation, two peptide families, isolated from marine creatures are discussed. Our research focuses on finding and understanding the relationship between metal coordination ability, structure and biological activity of mentioned metal-AMP complexes.

Clavanins are alpha-helical, histidine-rich cationic peptides, derived from tunicates (*Styela clava*). There are five types of those peptides - clavanin A- E which consist of 23 amino acids, with four (or in clavanin D - three) histidine residues. [4] Interestingly, in case of the clavanin C, coordination of Zn(II) ion resulted in the improvement of MIC (minimal inhibitory concentration) for numerous pathogens.

Piscidins are 22-residue, cationic, alpha-helical peptides, isolated from the mast cells of striped bass. All discussed members of this family – piscidin 1, 2 and 3 – contain characteristic C-terminal ATCUN-motif, which is the reason of their high affinity towards Cu(II) ions. [5] In our work, preeliminary studies show that the coordination of Cu(II) improves the antimicrobial activity of piscidins.

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WG3

NECTAR for multicomponent solutions and complex matrices

A calorimetric study of the alkali COSAN salts' self-assembly in aqueous solutions

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Self-assembly of amphiphilic ions and molecules is a well-known and extensively studied process with widespread application.[1] The process in aqueous solutions is usually entropy driven due to the release of water hydrating the non-polar parts into the bulk.

Metallacarboranes, such as the $[3,3'\text{-}Co(C_2B_9H_{11})_2]^-$ anion or also known as the COSAN anion (see Figure), are boron cluster compounds containing metal cations (for example, Co, Ni, and Fe) sandwiched by two dicarbollide clusters. The COSAN anion has a low charge density, which leads to specific interactions such as the hydrophobic/chaotropic effect. Therefore, alkali COSAN salts are also regarded as amphiphilic compounds.[2]

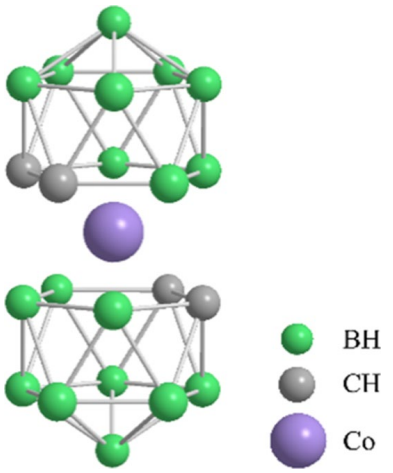

Figure. Structure of the COSAN anion.

In our recent publication isothermal titration calorimetry (ITC) was used to study thermodynamics of COSAN aggregation with Li^+, Na^+, K^+ as the counterions and of the acid HCOSAN. The effects of added salt and acetonitrile were further examined.[3] With the improvement of the ITC data interpretation, the thermodynamic parameters as well as the average aggregation number and the degree of counterion binding can be reliably determined.[4]

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Acidity constant determination of zwitterionic ionic liquid

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Abstract: Ionic liquids have been recognized as environmental benign alternative to volatile organic solvents [1]. They are also known as "designer solvents" defined as organic salts with melting point below 100 °C [2]. They have many attractive attributes, such as low vapour pressure, low flammability, a wide liquid range and excellent thermal and chemical stability [3-4]. Zwitterionic ionic liquids (Zw-ILs) are structurally very similar to conventional ionic liquids, except that the positive and negative charges reside on the same molecule. These ionic liquids are used as enhanced solvents for cellulose dissolution while maintaining low toxicity and biocompatibility [5-6]. For the first time, the zwitterionic ionic liquid, 1-carboxyethyl-3-methylimidazolium chloride, [C_2COOHmim][Cl], was synthesized. The characterization of the newly synthesized ionic liquid was performed by recording the IR and NMR spectra. The acidity constant for this Zw-IL was determined experimentally applying potentiometric method. The results were compared with the acidity constant of propanoic acid. From these results, it can be noted that introduction of imidazolium ring in the structure of propanoic acid, instead of terminal hydrogen decrease acidity of ionic liquid.

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Thermodynamic study of the micellization process of functionalized surface-active ionic liquids for extraction of technologically critical elements

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Extraction is the most commonly used method for metal separation. The main disadvantage of classical liquid-liquid extraction is the use of volatile, highly flammable and harmful to the environment and humans organic solvents. Ionic liquids (ILs) are salts with a bulky organic cation that are poorly coordinated which results in their distinguishing properties such as low melting point and vapour pressure, high thermal, chemical and electrochemical stability. ILs have been used as alternative solvents mainly due to their tailoring ability and the possibility of designing IL with specific features for a particular task (so-called task-specific ILs).

This study aims to investigate the thermodynamic properties of the micellization process of functionalized, surface-active ILs for extraction of targeted technology-critical elements belonging to lanthanides (La and Nd). These elements are important part of batteries, permanent magnets, computers, smartphones etc. We have designed task-specific ILs which consist of a chelate anion which is responsible for metal ion complexation and N,N-dialkylimidazolium cation responsible for the micellization process. Chelate anions (diethylenetriaminepentaacetate $[DTPA]^-$ and lactate $[Lac]^-$) have been selected based on their affinity to form complex with trivalent lanthanides cation (Ln^{3+}) e.g. stability constants (express as logβ) of Ln and DTPA ranging from 18.0 to 22.8 depending on ionic strength of solution . Also, Ln^{3+} can form a complex with 1-3 lactate anion and corresponding constants for Nd ranging from log β 2.7 to 6.0 at 25 °C and ionic strength of 1.05 mol kg^{-1} $NaClO_4$. N,N-dialkylimidazolium cation has been designed to be surface active. It has been shown that the micellization properties, as well as the shape of micelles, were altered by changing the alkyl chain length and the nature of the counterions. For the proposed study, we will synthetized 1-dodecil-3-methylimidazolium $[C12mim]^+$ with lactate and DTPA as the counterion. The thermodynamic properties of the micellization process will be determined by isothermal titration calorimetry (ITC).

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Interactions of pharmaceutically active ionic liquids with DNA and BSA

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Interactions between synthesized ionic liquids (procainium salicylate, procainium ibuprofenate, lidocainium salycilate and lidocainium ibuprofenate) and DNA and BSA were investigated using a theoretical and experimental approach. The information about the binding of ionic liquids with anesthetic and anti-inflammatory properties to DNA and BSA was obtained for the first time. From DFT calculations, the useful descriptors for each ionic liquid were calculated (ion-pair binding energy, strength, and number of non-covalent interactions in ionic liquid, *AlogP*, electrostatic potential, dipole moment, chemical reactivity, and hardness). The optimized structures were further docked to BSA and DNA and interpreted using binding energy and docking score values. The structures with the lowest energy were further refined using molecular dynamic simulations, to investigate the effect of hydration on binding constants and the binding mode of ionic liquids towards receptors. The obtained theoretical results were further correlated with experimental data obtained from fluorescence quenching experiments.

The obtained binding constants from computational results are in good correlation with experimental results (the relative standard deviation is less than 2%). From both theoretical and experimental results, it was obtained that procainium based ILs have stronger affinity to interact with DNA and BSA than lidocainium based ILs. The molecular docking study reveals that the preferable mode of interactions with DNA is intercalation in the minor grove region for all investigated ILs. Moreover, the lidocainium based ILs have a stronger tendency to interact with DNA through hydrogen bonding than procainium. Concerning the interactions with BSA, all ionic liquids interact with BSA predominantly through hydrophobic interactions. The procainium obtained stronger binding due to the existence of π-π interactions.

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Thermodynamic studies of interactions in aqueous solutions of ionic liquids based on the local anesthetic drugs and salicylic acid

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Ion-ion and ion-solvent interactions have been investigated in the aqueous solutions of two drug-based ionic liquids, lidocaine salicylate and procaine salicylate. Lidocaine and procaine were used as a cation in ionic liquids and represent local anaesthetics with two different types of functional groups, an amide and ester type, respectively. A detailed insight into the ion's interactions along with the structure-making/structure-breaking tendency of ionic liquids have been retrieved through the perusal of calculated parameters from volumetric, viscosity and conductivity measurements, and discussed from the view of the difference in cation structures. The obtained experimental results are supported by the theoretical investigation of aqueous solutions using molecular dynamic simulations.

The obtained values of hydration number suggesting slightly better hydration properties of procaine salicylate. From molecular dynamic simulations it was seen that although they have almost the same hydration number, there is a significant difference in the organization of water molecules around cations. The reason for the difference in the rates of water organisation may occur due to the difference between the amide and ester functional group and the side groups attached to the benzene ring. This is a consequence of better hydration of the aromatic part of procaine, but the difference is significantly compensated by more pronounced hydrophobic hydration of the aliphatic part of lidocaine. Also, association constant values of procaine salicylate are higher than lidocaine salicylate, indicating the stronger cation-anion interactions in ionic liquid with procaine as a cation. Calculated association constants proved that ionic liquids association constant could be used as a good predictor of lipophilicity as well as an indicator of the enhanced permeability and topical delivery.

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WG4

NECTAR Tools, Services and Facilities

An open-source software for potentiometric data analysis

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The progress in the development of an open-source software for potentiometric data analysis will be presented. This work is inserted in the activities of the WG4 of the NECTAR COST Action, the WG devoted to the development of tools, services and facilities for the NECTAR community. The aim of the work that we present herein is the development of a new version of the BSTAC4 software [1-2]. BSTAC4 is a software dedicated to the analysis of potentiometric data developed many years ago [1-2], that shows particularly useful features: *i*) it allows the contemporary optimization of the formation constants, of the components concentrations and of the calibration parameters; *ii*) it can process many titrations together, also conducted at different ionic strengths; *iii*) it can refine the coefficients of the extended Debye–Hückel equation and optimize formation constants at different ionic strengths; *iv*) it is based on a robust mathematical approach. The actual version of BSTAC4 is available for free by a simple request to its authors, but it is not user friendly and it is no longer compatible with actual PC and operating systems. In this line, we are working on the development of a new version maintaining all the good characteristics of the original version but improving its usability. Namely, in the new version, the input pages are interactive and are organized with clear captions in order to help the inexpert users; the titration curves can be uploaded as .xlsx or .cvs files; in the output pages, all the results of the calculations are visible: the concentrations of the species for each titration point, the optimized parameters with the corresponding uncertainties, as well as the results obtained at each iteration are shown. Interactive graphical representations of the results are also included. The development of the new version of BSTAC4 is being done using Python programming language, and is a work still in progress, being the software not yet available. With the aim of sharing this tool among each NECTAR community's member (but not exclusively), the new version will be downloadable for free from the web, as well as usable on own PC without web connection, and the source code will be made available.

This contribution is based upon work from
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SpectrApp: an open-source software to interpret spectroscopic data using chemometric strategies

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SpectrApp is a user-friendly and free-of-charge tool that is currently being developed by the Department of Chemistry of the University of Turin (Italy). The main goal of SpectrApp is the evaluation of spectroscopic data using multivariate data analysis and chemometric strategies. The tool is built under the R Shiny environment, and it is currently available on the website https://www.spectrapp.unito.it (the reference paper describing the features of the app is currently under submission). SpectrApp might be used as a complementary tool to conventional software that treats data by a stoichiometric approach [1], since it involves different techniques related to Multivariate Data Analysis. Therefore, it can be a useful tool for the interpretation of spectroscopic data collected studying equilibria and chemical thermodynamics. At first, users are allowed to upload data in the tool by means of different input files format. It is then recommended that the users evaluate the uploaded data through several graphical approaches such as the univariate, bivariate, and multivariate visualization of the data. Users are then allowed to pre-process the data through different data scaling and data transformation techniques incorporated within the app. Then, Exploratory Data Analysis strategies can be performed on the uploaded and pre-processed data. At the current stage, Cluster Analysis, Principal Component Analysis (PCA), and Multivariate Curve Resolution – Alternating Least Squares (MCR-ALS) have been implemented within the app. Other multivariate modeling approaches can be applied to the data, too. PLS – Discriminant Analysis (PLS-DA) can be used for classification purposes, while PLS – Regression (PLS-R) approach can be exploited for quantification goals. Other methodologies such as Linear Discriminant Analysis (LDA), Quadratic Discriminant Analysis (QDA), Support Vector Machines (SVM), Multiple Linear Regression (MLR), and Principal Component Regression (PCR) are available, too.

Finally, once the user has built the selected model(s), it is possible to predict new samples to evaluate their origin, classification, and/or quantity.

Using Chemometrics and Multivariate Data Analysis might sound scary, but it sensitively helps when dealing with multivariate data. The developed open-source tool will show these approaches can be quickly evaluated even by non-expert users.

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Overview of
Short Term Scientific Missions
STSM

Synthesis of bioinspired metallopeptides and study of their catalytic properties in oxidation reactions

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The work carried out within this STSM is set in the context of the role of metal ions in oxidative stress and neurodegeneration. The study of metal ions/peptide adducts which promote oxidative stress phenomena is of major importance, since these processes eventually lead to the degradation of biological tissues and neuronal death. The main feature of these systems relies on the presence of multiple histidine residues, well-known metal binding sites. This work is focused on the Tau protein, a biomolecule strongly related to Parkinson's Disease.[1]

Recently, our research group examined the stability of Cu(II) and Cu(I) adducts with two peptide fragments which are encompassed in the R1 and R3 repeats of tau.[2] The presence of a tandem of two His residues in the R3 sequence significantly increases the Cu(II)/Cu(I) reduction potential of the copper center by modulating the ligand donor set. By reflection, the catalytic propensity of the adduct in promoting catechol oxidation increases dramatically.

Several neuropeptides, actually, contain other His residues beyond those of the His-His dyad (e.g. β-amyloid). Although much is known about copper/peptides that promote oxidative reactions, the relationship between the catalytic properties and the position of the His residues within the peptide sequence is still far from being fully elucidated [3].

In the framework of COST 18202 Action NECTAR, and during my STSM, I have synthesized four peptides, derived from the tau R3 fragment, that bear a His-His dyad and a third additional His residue located at different positions along the amino acid sequence.

In this communication I will present the design of the different peptides, their synthesis and Cu(II) coordination studies, in view of their study as oxidation catalysts.

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New efficient chelators for Zr-89 radiometal: design, synthesis and thermodynamic properties

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The main objective of my project was to develop novel chelators for non-invasive *in vivo* positron emition tomography's (PET) imaging agents**.** PET requires the injected radiopharmaceutical to be labelled with a positron-emitting radionuclide. Zirconium-89 (^{89}Zr), a positron-emitting radionuclide, possesses excellent physical properties for PET imaging when paired with antibodies, namely, an ideal 78.41 h half-life and low energy positron (β_{avg} = 395.5 keV) [1,2]. A fundamental critical component of radiopharmaceutical is the chelator, the ligand system that binds the radiometal ion in a tight stable coordination complex and then attached to the antibodies, so that it can be properly directed to a desirable molecular target in vivo. Currently, desferrioxamine (DFO) is the chelator most commonly used to radiolabel biomolecules with ^{89}Zr [3]. However, the *in vivo* studies together with DFT calculations, as well as thermodynamic studies performed by us, has proven the stability of Zr-DFO to be insufficient [3-5]. In order to improve stability of Zr(IV) complexes alternative ligands with oxygen-rich donor groups have been tried [1-2].

Here I will present the novel hydroxamate chelator (H_4L), which was designed in order to complete the coordination sphere of Zr(IV) by four hydroxamate binding groups, and to take advantage of the stabilizing macrocycle effect upon metal complexation. The solution chemistry of Zr(IV)-H_4L complexes has been investigated and will be discussed in relation to the stability of Zr(IV)-DFO complexes [4]. The detailed speciation studies of Zr(IV) – H_4L system, as the knowledge of the speciation of Zr(IV) complexes, especially at physiological pH, can provide information concerning 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.

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Complexation of V(IV) and V(V) with succinic and oxalic acids in aqueous acid solution using affinity capillary electrophoresis

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Vanadium(V) is a second most abundant trace metal in seawater with characteristic conservative behaviour in open-ocean waters while non-conservative behaviour is reported for coastal waters. There are several possible mechanisms affecting reactivity of V in coastal aquatic systems with the emphasis on deposition of particles, scavenging by terrigenous and/or biogenic material and various adsorption/desorption mechanisms associated with V redox changes [1]. Generally, the distribution of V redox species is controlled by the pH, V concentration, redox potential, ionic strength of the system, chemical composition of natural organic matter and biological activity [2]. Although V(V) is expected to be dominant species in well oxidized marine environments, V(IV) is also previously reported to be present even in surface oxic waters mainly due to its ability to form stable complexes with organic or inorganic ligands in natural waters [1,3,4]. The possible formation of such complexes can greatly influence V mobility and toxicity in the aquatic environment [2].

The complexation of V(IV) and V(V) with carboxylic acids (succinic and oxalic acid) in aqueous acid solutions is investigated. Chosen carboxylic acids served as a proxy for Dissolved Organic Matter (DOM) in order to obtain new information on complexation kinetics and equilibrium conditions of V species interaction with more simple organic ligands. The affinity capillary electrophoresis (ACE) has been used to study complexation of V species with succinic and oxalic acids in perchloric acid aqueous medium on fixed conditions of pH (2.0 and 2.5) and ionic strength maintained at 100 mM by $NaClO_4$ additions. In the case of V(IV) complexes with organic ligands, formation of protonated species is suggested. Conversely, in the case of V(V), deprotonated species are suggested. Novel data set on complexation of V with organic ligands is successfully produced.

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Guidelines on Outreach Activities

Communicating NECTAR COST Action: Guidelines on outreach activities

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Why invest time in communication when I could be doing research? Because, as said by Anne Roe in 1953, "Nothing in science has any value to society if it is not communicated" [1, 2]. Communication is to engage with a wider audience via articles in mainstream newspapers and magazines or TV and radio channels.

Successful communication requires a clear language and attractive scientific subject with results that can catch the media's attention. Thus, it is important to adapt the message to the audience.

HOW TO WRITE A PRESS RELEASE:

What: A release aims to inform about something new that will shortly happen.

Novelty: Is there something new to release about your activity or the study?

Timeliness: Always try to link your story to a current event – what makes the story timely or newsworthy now: climate changes, epidemic flue…Think of the UN days calendar. International days of Cancer, Diabetes etc. It could be the right moment to release your story in the context of International Day of Human Space Flight, World Health Day, World Wildlife Day…

Identify a human interest: How the network or research affect people's everyday life.

Importance of the impact: Story important for the public and how it will affect them.

Fascination or surprise factor: The wow factor. People are always fascinated by space, planets…

Controversy and arguments: Provide an alternate position with a scientific knowledge. Open a debate on a topic.

Local factor helps as media will use it to set the context.

Short and clear: average 350 – 500 words in press release; higher for scientific releases in specialized magazines [1, 2].

- Use the 5 W when you communicate: **WHAT**, **WHO**, **WHEN**, **WHERE** and **WHY**.
- Use ***Hey-you-see-so*** **pyramid** to structure your idea and check

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Hey – Catch the attention
You – Identification
See – Explain
So – Perspective

Hey→ Teaser to catch the reader's eye to bring the attention on the contentand present the story, (headline).

You→Information that makes the article relevant to the reader (relevance and identification).

See→Explain in a few paragraphs the background, the context. Writing about a new a research finding, describe the study and provide some key elements, figures or results.

So→New findings in the end of the article, say something about the impact of the information you are sharing, or you have presented. Outline the prospect of further research in the area [1, 2].

- **Structure - What should be in your press release?**

1. A catchy headline + Picture or illustration.
2. Date and place.
3. Body - content of the story.
4. A final leading to a conclusion or further perspectives.
5. Note to the Editor.

During the presentation several other tips on how to write or spot a good story [3-6] will be given together with the future communication strategy of NECTAR COST Action.

References:

[1] *The Science Communication Manager, A leadership role in all COST Actions*. The COST Association, Brussels, Belgium, **2019**.
[2] *Guidelines for the communication, dissemination and exploitation of COST Action results and outcomes*. The COST Association, Brussels, Belgium, **2017**.
[3] COST Academy 'Media skills training'.
[4] COST Academy webinar 'Present your research with impact'.
[5] COST Academy 'Storytelling training'.
[6] COST Academy 'Mobile video training'.

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IMPORTANT NOTES

From COST Vademecum, May 2020[1]

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Publications funded by COST shall be a direct result of work performed by Action Participants and shall be co-authored by Action Participants representing **at least 3 different Participating COST Full Members / COST Cooperating Members**. Whenever possible, publications should be made available under Open Access licences.

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[1] https://www.cost.eu/wp-content/uploads/2020/06/Vademecum-V8-1-May-20202.pdf

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