ISXB6

6TH INTERNATIONAL SYMPOSIUM ON HALOGEN BONDING

20–25 October 2024, Sheraton Riviera Hotel, Srebreno, Dubrovnik, Croatia

Book of Abstracts

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20–25 October 2024, Dubrovnik, Croatia

6th International Symposium on Halogen Bonding

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Dubrovnik, Croatia, October 20 – 25, 2024

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Zagreb, 2024

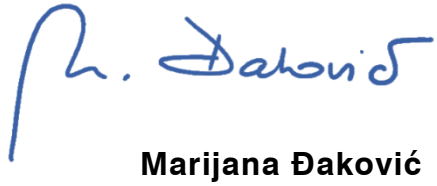
Dear Colleagues and Friends,

It is our great pleasure to invite you to the **6th International Symposium on Halogen Bonding (ISXB6)**, which will be held in **Dubrovnik, Croatia, from October 20–25, 2024**. The symposium will take place at the **Sheraton Dubrovnik Riviera Hotel**, a modern resort located in a secluded beachfront location in the vicinity of the **Dubrovnik Old Town**.

The **ISXB series** of symposia aims to bring together researchers from all over the world who are interested in the fascinating phenomenon of halogen bonding and related interactions, from fundamental principles to applied technologies, covering both experimental and theoretical approaches in various areas of research ranging from advanced materials to medicinal chemistry and chemical biology. The **ISXB6** will feature keynote addresses and invited lectures by internationally renowned experts, contributed presentations, posters, and communications by young and promising researchers. The Symposium will also provide ample opportunities for networking and socializing in a friendly and stimulating atmosphere.

Dubrovnik is one of the most beautiful and historic cities in the Mediterranean, a UNESCO World Heritage Site that offers a rich cultural and artistic heritage, as well as stunning natural scenery. The city is surrounded by medieval walls and fortresses and boasts a wealth of must-visit sites, such as monuments, museums, churches, palaces, and fountains. Dubrovnik is also known for its vibrant nightlife, gastronomic delights, and festivals. During the Symposium you will have chances to explore and enjoy the magnificent city and nearby attractions, such as the city walls, the Rector's Palace, the Dubrovnik Cathedral, the Stradun, the Sponza Palace, and more.

We are looking forward to welcoming you to Dubrovnik and to sharing with you an exciting and memorable scientific and social event!



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KEYNOTE SPEAKERS

Stefan Matile | University of Geneva, Italy

Pui Shing Ho | Colorado State University, USA

Steve Scheiner | Utah State University, USA

Dominik Cinčić | University of Zagreb, Croatia

Arri Priimagi | Tampere University, Finland

Sebastian Riedel | Freie Universität, Germany

Stefan M. Huber | Ruhr-Universität Bochum, Germany

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6th International Symposium on Halogen Bonding

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is organized by

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University of Zagreb Faculty of Science,
Department of Chemistry

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PROGRAMME

SUNDAY, October 20, 2024

17:00 – 19:00 REGISTRATION

MONDAY, October 21, 2024

Chair: Catharine Esterhuysen

9:30 – 9:40	**OPENING OF THE SYMPOSIUM**	
9:40 – 10:20	**KEYNOTE**	**Stefan Matile**: *σ Holes at Work*
10:20 – 10:50	**INVITED**	**Claire Fave**: *Electrochemically Activated Halogen Bonding: from Molecular Recognition to Catalysis*
10:50 – 11:20	**INVITED**	**Claude Y. Legault**: *Investigation of the Activation Modes of Enone Substrates in Halogen-Bonding Catalysis*
11:20 – 11:50	**Coffee break**	

Chair: Catharine Esterhuysen

11:50 – 12:20	**INVITED**	**Yasushi Yoshida**: *Controlling Contiguous Stereocenters by Halogen-bonding Catalysis of Chiral Halonium Salt*
12:20 – 12:45	**ORAL**	**Martin Breugst**: *Applications and Limitations of Iodine Catalysis*
12:45 – 14:30	**Lunch break**	

Chair: Kari Rissanen

14:30 – 15:10	**KEYNOTE**	**P. Shing Ho**: *Twenty Years of Halogen Bonds in Biological Molecules: A Retrospective*
15:10 – 15:40	**INVITED**	**Zhijian Xu**: *The Halogen Bonds in Natural Nucleic Acids System and Halogenated Protein/Peptide System*
15:40 – 16:05	**ORAL**	**Paulo J. Costa**: *How Halogen Anisotropy Modulates the Membrane Permeability of Halogenated Drugs*
16:05 – 16:35	**Coffee break**	

Chair: Kari Rissanen

16:35 – 17:15	**KEYNOTE**	**Steve Scheiner**: *Halogen Bonding to the π-Systems of Polycyclic Aromatics*
17:15 – 17:45	**INVITED**	**Catharine Esterhuysen**: *Probing the continuum of covalent contributions to halogen vs. hydrogen bonds*
17:45 – 18:15	**INVITED**	**Anthony Legon**: *Nucleophilicities of Lewis Bases and Electrophilicities of Lewis Acids Involved in Non-covalent Interactions*

TUESDAY, October 22, 2024

Chair: Mate Erdelyi

9:15 – 9:55	**KEYNOTE**	**Dominik Cinčić**: *Metal-organic Building Blocks in Crystal Engineering of Halogen-bonded Cocrystals*
9:55 – 10:25	**INVITED**	**Susan A. Bourne**: *Metal-NCIs in Mixed Ligand Complexes*
10:25 – 10:55	**INVITED**	**Andrew Docker**: *Exploiting the Macrocyclic Effect for the Stabilization of Halenium(I) Ions*
10:55 – 11:25		**Coffee break**

Chair: Mate Erdelyi

11:25 – 11:55	**INVITED**	**Kari Rissanen**: *The C–I···O–N vs. N–I···O–N Halogen Bonds*
11:55 – 12:25	**INVITED**	**Matic Lozinšek**: *Synthesis of Xe−N and Xe−O Bonded Compounds via σ-Hole Interaction on XeF^+*
12:25 – 12:50	**ORAL**	**Giuseppe Resnati**: *Fluoride anion: Strong Halogen Bond Acceptor*
12:50 – 13:05	**EARLY CAREER**	**Andreia Fortuna:** *Validation of Off-center Point-charge Models to Tackle Halogen Anisotropy*
13:05 – 14:30		**Lunch break**

Chair: Pierre Kennepohl

14:30 – 15:00	**INVITED**	**Mate Erdelyi**: *A new NMR Technique to Characterize Weak Halogen Bonds in Solution*
15:00 – 15:15	**EARLY CAREER**	**Peter Wendt**: *Application of Halogen Bonding for Protein Purification*
15:15 – 15:30	**EARLY CAREER**	**Anita M. Grześkiewicz**: *Halogen··· Chalcogen Interaction in Antimony(III) Complexes*
15:30 – 15:45	**Overview: Giuseppe Resnati:** *Halogen Bonding: Impact and Legacy*	
15:45 – 16:15		**Coffee break**
16:15 – 18:30	**POSTER SESSION**	
18:30 –	**WELCOME GATHERING**	

WEDNESDAY, October 23, 2024

Chair: Pierangelo Metrangolo

9:15 – 9:55	**KEYNOTE**	**Arri Priimägi**: *Halogen-Bonded Shape-Changing Polymer Networks*
9:55 – 10:25	**INVITED**	**Gabriella Cavallo**: *Tuning Materials Properties via Halogen Bonding*
10:25 – 10:55	**INVITED**	**Ie-Rang Jeon**: *Oxidation-induced Activation of Chalcogen Bonding in Tetrathiafulvalene-Based Organic Conductors*

10:55 – 11:25 Coffee break

Chair: P. Shing Ho

11:25 – 11:55	**INVITED**	**Pierangelo Metrangolo**: *Novel Structural Biomaterials through Halogenation*
11:55 – 12:10	**EARLY CAREER**	**Steven van Terwingen**: *What Can We Learn About Halogen Bonds From Electron Diffraction?*
12:10 – 12:25	**EARLY CAREER**	**Arun Dhaka**: *Boosting Halogen Bond Donor Ability of Chloroarenes: a Combined Experimental and Theoretical Study*
12:25 – 12:40	**EARLY CAREER**	**Harry W. Nash**: *Exploring and Predicting σ-hole Interactions in the Cambridge Structural Database (CSD)*

12:40 – 14:30 Lunch break

14:50 –	**EXCURSION AND DINNER**

THURSDAY, October 24, 2024

Chair: Stefan M. Huber

9:15 – 9:55	**KEYNOTE**	**Sebastian Riedel**: *Technical Applications Based on Halogen Bonding: A New Kind of Chlorine Technology*
9:55 – 10:25	**INVITED**	**Tatsuo Kaiho**: *Halogen Bonding and Iodine Industry*
10:25 – 10:50	**ORAL**	**Frank M. Boeckler**: *The Applicability of CF_2X Moieties for Drug Discovery*

10:50 – 11:20 Coffee break

Chair: Zhijian Xu

11:20 – 12:00	**KEYNOTE**	**Stefan M. Huber**: *Noncovalent Organocatalysis with Neutral and Chiral Halogen Bond Donors*
12:00 – 12:30	**INVITED**	**Victor Mamane**: *Chalcogen Bonding Catalysis with Telluronium Cations*
12:30 – 13:00	**INVITED**	**Kazuaki Ishihara**: *Oxidative Dearomative Coupling of Low-Reactive Arenols Using Hypohalite Catalysis*

13:00 – 14:30 Lunch break

Chair: Frank M. Boeckler

14:30 – 15:00	**INVITED**	**Pierre Kennepohl**: *Catalytic Activation via Halogen π-backbonding in Nucleophilic Substitution Reactions*
15:00 – 15:30	**INVITED**	**Yao Wang**: *Catalysis with Nonclassical Weak Interactions*
15:30 – 15:55	**ORAL**	**Jarosław Poznański**: *A Perturbation Approach Leads to a Reliable Estimation of a Halogen Bond Thermodynamic Contribution*
15:55 – 16:10	**EARLY CAREER**	**Markus O. Zimmermann**: Machine Learning Models for Chalcogen Bond Analysis in Protein-ligand Complexes

16:10 – 16:40 Coffee break

Chair: Frank M. Boeckler

16:40 – 17:10	**INVITED**	**Weiliang Zhu**: The Interaction Between Organoflourine and Target Protein
17:10 – 17:40	**INVITED**	**Ayami Matushima**: *Development of a Index to Evaluate Halogen Bonds in Ligand-bound Protein Structures*
17:40 – 17:55	**EARLY CAREER**	**C. Gustavo Mendez**: *Halogen Bonds as Enzymatic Catalysts*
17:55 – 18:10	**EARLY CAREER**	**Maria Winiewska-Szajewska**: *Thermodynamic and Structural Studies on the Binding of Halogenated Ligands by CK2α'. A Halogen Bond Contribution for Different Halogen Atoms.*

FRIDAY, October 25, 2024

Chair: Pierre Kennepohl

9:15 – 9:45	**INVITED**	**Vladimir Stilinović**: *Halogenated Organic Cations as Halogen Bond Donors – Possibilities and Limitations*
9:45 – 10:10	**ORAL**	**Mihails Arhangelskis**: *Computational Prediction of Mechanochemical Reactivity of Halogen-bonded Materials*
10:10 – 10:25	**EARLY CAREER**	**Sibananda G. Dash**: *Optimization of Intermolecular Force-field Parameters for Crystal Structure Prediction of Halogen-Bonded Materials*
10:25 – 10:40	**EARLY CAREER**	**Lavanya Kumar**: *Electronic Structure and Stability of Halogen Bonds with Heavy Pnictogen Acceptors: Insights from Experimental Charge Density Studies and Periodic DFT Calculations*

10:40 – 11:10 Coffee break

Chair: Weiliang Zhu

11:10 – 11:25	**Pierangelo Metrangolo:** *Halogen bondong: Where We Are and Where We Are Going*

Chair: Pierre Kennepohl

11:25 – 11:40	**Announcing ISXB7**
11:40 – 11:55	**Announcing ISXB8**
11:55 – 12:30	**POSTER PRIZES AND CLOSING**

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ORAL CONTRIBUTIONS

EARLY CAREER ORAL CONTRIBUTIONS

POSTER PRESENTATIONS

KEYNOTE SPEAKERS

KL1

σ Holes at Work

Stefan Matile

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The general objective in my group is to integrate principles from supramolecular chemistry, particularly unorthodox non-covalent interactions, into functional systems. The expectation is that offering new ways to get into contact on the molecular level will provide access to new structures and functions that in turn will open new approaches to tackle big questions. In the spirit of the symposium, focus will be on the integration of σ-hole interactions into functional systems. A rich collection of functions will be covered, catalysis from the beginning [1,2] to unpublished results on artificial enzymes that operate with interactions ignored in biocatalysis, on oriented external electric fields in microfluidic devices and in combination with transport across lipid bilayer membranes [3]. Repulsion from σ holes will be covered to access mechanosensitivity, switchable σ holes to image forces in living systems [4], and, if time permits, a hidden dynamic covalent halogen-bonding switch to deliver proteins into cells [5].

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Twenty Years of Halogen Bonds in Biological Molecules: A Retrospective

P. Shing Ho

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The halogen bond was first recognized as a relevant interaction in biological molecules in a study by Auffinger, *et al*. [1] in 2004. This survey of the Protein Data Bank (PDB) identified over 100 examples of halogen bonds, primarily as intermolecular interactions important for recognition of halogenated ligands by their protein targets and as intra- and intermolecular interactions that control the conformation and assembly of halogenated polynucleotides (Fig. 1). In the twenty years since this initial exposé, halogen bonding has become well accepted as distinctive molecular interactions in biomolecular systems, leading to several new lines of research in biology. In this discussion, I will review a number of significant advances in this burgeoning field, including those in medicinal chemistry leading to drug and ligand design; data analyses to further characterize the halogen bond relative to other biomolecular interactions; structure-energy relationships that lead to computational approaches to model halogen bonding; and biomolecular design and engineering to control conformation and stability and, most recently, as enzyme catalysts.

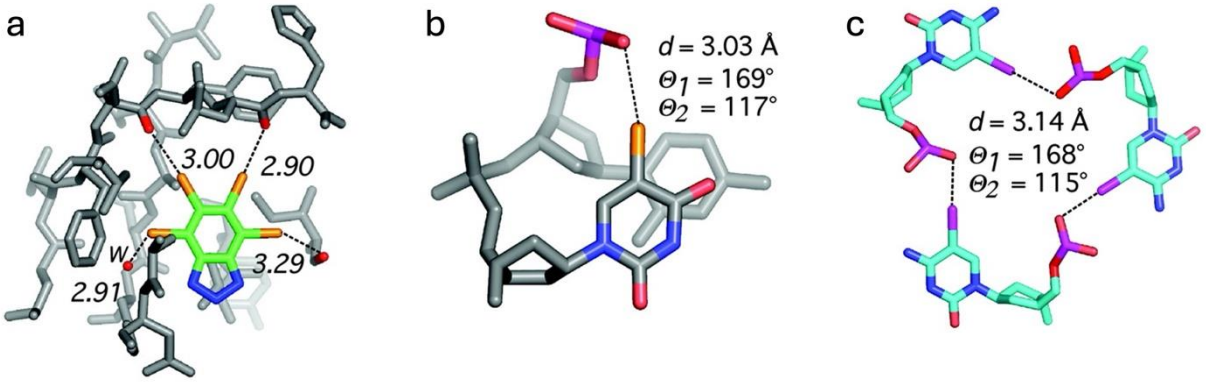

Figure 1. Halogen bonds in a ligand–protein complex (PDB ID 1P5E [2]), a DNA junction (PDB ID 1P54 [3]) and a six-stranded DNA complex (PDB ID 1UE2 [4]) [1].

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KL3

Halogen Bonding to the π-Systems of Polycyclic Aromatics

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The propensity of the π-electron system lying above a polycyclic aromatic system to engage in a halogen bond is examined by DFT calculations. Prototype Lewis acid CF_3I is placed above the planes of benzene, naphthalene, anthracene, phenanthrene, naphthacene, chrysene, triphenyl, pyrene, and coronene. The I atom positions itself some 3.3–3.4 Å above the polycyclic plane, and the associated interaction energy is about 4 kcal/mol. This quantity is a little smaller for benzene, but is roughly equal for the larger polycyclics. The energy only oscillates a little as the Lewis acid slides across the face of the polycyclic, preferring regions of higher π-electron density over minima of the electrostatic potential. The binding is dominated by dispersion which contributes half of the total interaction energy.

Metal-organic Building Blocks in Crystal Engineering of Halogen-bonded Cocrystals

Dominik Cinčić

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Studies on halogen-bonded cocrystals of perfluorinated compounds have mostly focused on organic systems with a variety of organic acceptors involving nitrogen and oxygen atoms [1,2]. The use of halogen bonding to direct the assembly of metal complexes (coordination compounds) as acceptors or donors in cocrystals remains largely unexplored [3]. From the crystal engineering point of view, metal complexes represent extremely intriguing building blocks, they provide a plethora of geometries not normally accessible to organic molecules thus providing a wider range of accessible supramolecular architectures. Our group is focusing on developing halogen bonding as a tool in crystal engineering of multi-component solids through the involvement of new acceptor and donor types, notably the incorporation of metals into halogen-bonded structures. Designing cocrystals with neutral metal complexes as components presents a considerable challenge by both crystallization from solution and mechanochemical methods [4]. This presentation will provide an overview of some of the work related to metal-based halogen-bonded cocrystals that we have pursued recently – evaluation and comparison of halogen bond proclivity of halogenide and pseudohalogenide ligands in metal complexes [5,6] and the potential of metal chelates as halogen bond acceptors or donors in crystal engineering of metal-organic multicomponent solids [7,8].

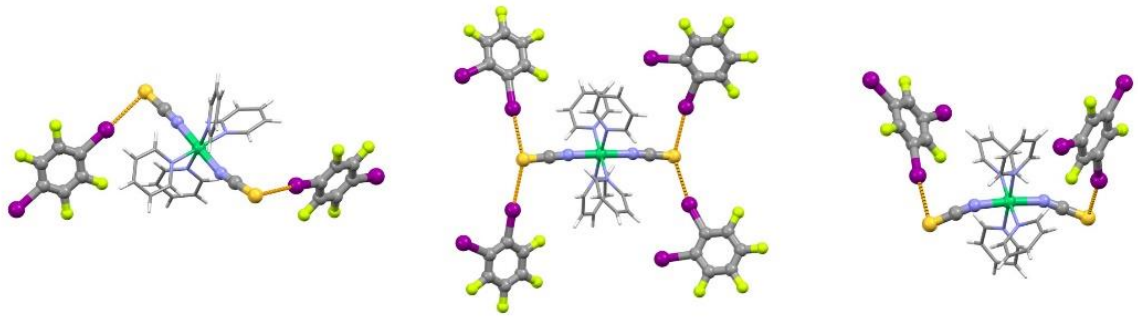

Figure 1. Halogen bonding motifs in cocrystals of $Ni(pyr)_4(NCS)_2$ coordination compound.

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KL5

Halogen-Bonded Shape-Changing Polymer Networks

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Materials that change shape in response to external stimuli are at the forefront of bioinspired materials research, due to the versatility of motions that can be obtained upon proper materials engineering. The motions can be irreversible, like in conventional shape-memory polymers, or reversible, like in, e.g., hydrogel-based or liquid crystal elastomer (LCE) actuators. The shape changes can be triggered with different stimuli, such as light, heat, electric/magnetic fields, or humidity. Out of these, light is a particularly attractive trigger due to its abundance and the precise spatiotemporal control it enables in different environments.

Herein, we present halogen bonding (XB) as a new tool for invoking shape changes in LCE polymer networks. In particular, we utilize XB as supramolecular crosslinks, in combination with permanent covalent crosslinks, to tune the mechanical properties and introduce a new dynamic programming tool via making and breaking the XB crosslinks. Depending on the material design, we achieve either one-way shape memory behaviour when exposed to human body temperature (Fig. 1a),[1] or combination of reversible thermo-responsive shape changes and self-healing in soft elastomeric networks (Fig. 1b).[2] The I···N halogen bond plays a pivotal role in both cases in introducing these functionalities. Our results showcase the promise of XB in expanding the toolbox for designing smart supramolecular constructs with tailored mechanical properties and thermoresponsive behavior, opening up exciting long-term prospects for biomedical tools and microrobotics.

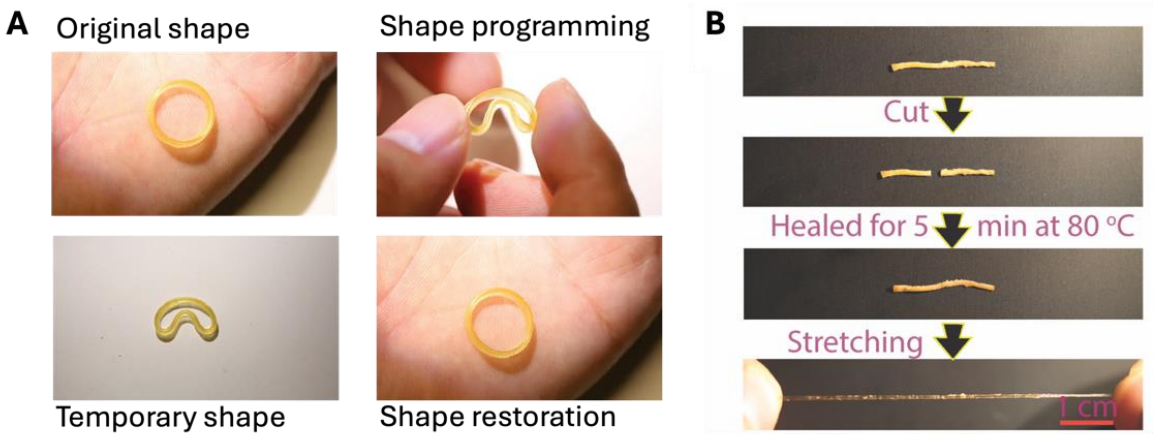

Figure 1. Halogen-bond-driven (a) shape memory effect and (b) self-healing in crosslinked liquid crystalline polymer networks.

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Technical Applications Based on Halogen Bonding: A New Kind of Chlorine Technology

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In recent years, our group has been involved in the study of polyhalogen anions, mainly based on fluorine, chlorine and bromine.[1] Novel synthetic strategies either in ionic liquids or in pure halogens have led to the preparation of several new polyhalogen anions with interesting properties. Halogen bonding is one of the most important aspects for understanding of the bonding situation in such systems. Based on this research, our group has developed new ionic liquids capable of storing elemental chlorine via halogen bonding.[2] Alkyl ammonium chloride salts can be used as safe and sustainable chlorine storage media. The most promising candidate, $[NEt_3Me]Cl$, stores up to 0.79 kg of chlorine/kg of storage material, is easy to prepare and is stable against chlorination for long periods of time. The ionic liquid can also be handled in air. Chlorine release can be achieved by the application of heat or vacuum, or alternatively by the addition of water, etc. The combination of these properties highlights $[NEt_3Me]Cl$ as a suitable storage medium to facilitate the flexibilisation of industrial chlorine production. Since polychlorides can be used for different chlorination reactions, a combined industrial process is envisaged using $[NEt_3Me]Cl$ as a storage medium and the loaded system as a reagent for industrial chlorinations, as shown for example in the synthesis of phosgene.[3-5]

Figure 1. Polychloride based ionic liquids and its chemistry.

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KL7

Noncovalent Organocatalysis with Neutral and Chiral Halogen Bond Donors

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In the last years, a key focus of our research was on the development of halogen- and chalcogen-bonding-based organocatalysis [1]. To this end, a broad variety of multidentate non-covalent interaction donors have been employed, which for halogen bonding comprises neutral fluorinated as well as cationic ones.

While the polyfluorinated halogen bond donors feature several advantages like the absence of (sometimes annoying) counterions, and good solubility in relatively apolar solvents, they are also noticeably weaker Lewis acids compared to their cationic heteroaromatic counterparts. Their modification with further functional groups had also proven to be difficult, but such derivatives have been prepared by now and have been used for the construction of higher-dentate systems [2]. Here, we will introduce a new type of neutral multidentate halogen bond donors, which markedly exceed the Lewis acidity of the previous polyfluorinated ones.

An important current goal of halogen bonding organocatalysis is the realization of enantioselective syntheses. Previously, we had reported a chiral variant of a bis(iodo-imidazolium)benzene halogen bond donor, which however only achieved low to moderate enantioselectivity in a Mukaiyama aldol reaction. Here, we present the second generation of this catalyst, which now allows a highly enantioselective transformation [3]. Importantly, several control experiments indicate that halogen bonding is decisive for substrate activation and enantioinduction.

In addition, we will introduce an alternative approach to perform enantioselective reactions via halogen bonding catalysis which relies on the use of chiral counterions.

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INVITED SPEAKERS

IL1

Electrochemically Activated Halogen Bonding: from Molecular Recognition to Catalysis

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In the field of supramolecular chemistry, halogen bonding (XB), a non-covalent interaction, has been extensively studied during the past 20 years.[1] Among potential applications of XB in solution, molecular recognition [2,3] is now well documented while organo-catalysis is growing rapidly and is currently under active investigation. Some recent examples illustrate the high potential of XB in this field.[4] However, activation and detection of XB in solution by electrochemical techniques remain almost absent in the literature and is limited to anion recognition.[2,5] In our group, we explore the potentiality to tune and control the strength of XB when electrochemically changing the oxidation state of the XB donors. In fact, tuning the strength of a redox active XB donor via a reversible electrochemical reaction should change its affinity towards XB acceptors. In this presentation, I report first how the concept of electrochemical activation can be generalized to many redox systems such as tetrathiafulvalene or ferrocenyl derivatives as XB donors in solution in the field of molecular recognition. In a second part, several results will confirm all the relevance of combining redox activation of XB for organo-catalysis (CO2 reduction, Ritter type reaction, dehalogenation).

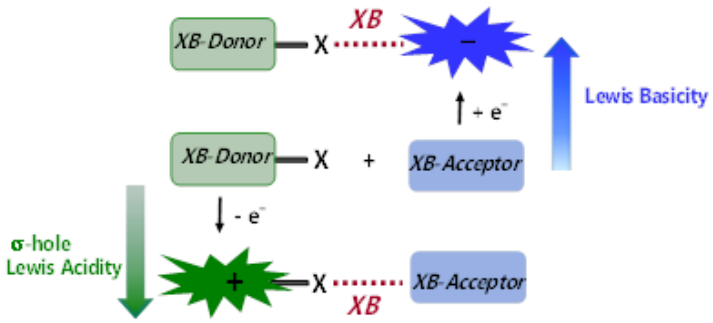

Figure 1. Electrochemical redox-switching of non-covalent halogen bonding interaction.

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Investigation of the Activation Modes of Enone Substrates in Halogen-Bonding Catalysis

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In recent years, the impact of halogen bond donors on catalysis has been increasing, and their development is highly active. Specifically, numerous iodine-based halogen bond donors have been created and used to promote various reactions. Their accepted mode of activation is by coordinating the carbonyl groups of substrates. We found evidence with computational data suggesting an alternative activation mode could be utilized for unsaturated carbonyl substrates through direct π-complexation. Our calculations also indicate that solvent polarity could influence the preference of the activation mode, leading to a possible switch in the mechanistic manifold through solvent variation. These findings could significantly affect the development of the next generation of halogen-bond donor catalysts.

IL3

Controlling Contiguous Stereocenters by Halogen-bonding Catalysis of Chiral Halonium Salt

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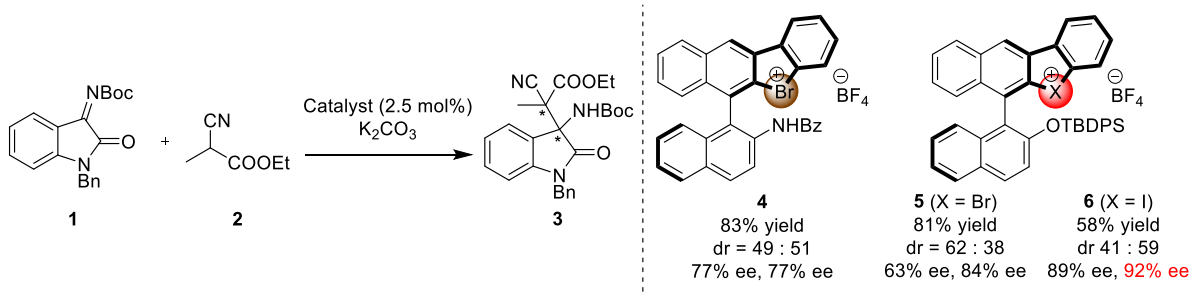
Halogen-bonding have been applied to the wide range of chemistry in these decades, although, their successful application in asymmetric catalysis is still rare [1]. We have focused on the halogen-bonding of halonium salts, and developed achiral and chiral halonium salts and their chemistry so far [2]. In this presentation, I would like to discuss about our recent work on chiral halonium salt catalysis, especially on controlling contiguous stereocenters.

The Mannich reaction of imine **1** with cyanoester **2** was conducted in the presence of our chiral halonium salt **4** under basic conditions, which produced corresponding adduct **3** in good yield with 77% ee for both diastereomers. Because the stereoselectivity of the present reaction was not satisfactory, we have tried to develop new catalyst. This time, we have turned our attention to control the sreteoselectivities of products not by hydrogen-bonding, but by bulkiness of the chiral catalyst. Catalyst **5** and **6** with OTBDPS group was prepared from NOBIN in several steps, and applied it in asymmetric Mannich reaction. Although, bromonium salt **5** provided **3** in moderate diastereoselectivity with 84% ee for minor one, iodonium salt **6** gave the better outcome to form **3** in 41:59 diastereomeric ratio and 92% ee for major one. In this presentation, I would like to show the more details and the generality for the reaction.



Scheme 1. Chiral halonium salt catalyzed asymmetric Mannich reaction with cyanoester.

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The Halogen Bonds in Natural Nucleic Acids System and Halogenated Protein/Peptide System

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In PDB survey, no XBs are formed between noncovalent ligands and natual nucleic acids (NAs). Through statistical database analysis, quantum-mechanics/molecular-mechanics (QM/MM) optimizations, and energy calculations, we find that XBs formed between natural NAs and noncovalent ligands are primarily underestimated and that NAs can serve as XB acceptors to interact with noncovalent halogen ligands. Finally, through energy calculations, natural bond orbital analysis, and noncovalent interaction analysis, XBs are confirmed in 13 systems, among which two systems (445D and 4Q9Q) have relatively strong XBs. In addition, on the basis of energy scanning of four model systems, we explore the geometric rule for XB formation in NAs.

Current studies on XBs in drug design mainly focus on the interactions between halogenated ligands and target proteins, lacking a systematic study of naturally existing and artificially prepared halogenated residue XBs (hr_XBs) and their characteristics. We conducted a computational study on the potential hr_XBs in proteins/peptides using database searching, quantum mechanics calculations, and molecular dynamics simulations. XBs at the protein–peptide interaction interfaces are found to enhance their binding affinity. Additionally, the formation of intramolecular XBs (intra_XBs) within proteins may significantly contribute to the structural stability of structurally flexible proteins while having a minor impact on proteins with inherently high structural rigidity. Impressively, introducing halogens without the formation of intra_XBs may lead to a decrease in the protein structural stability.

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IL5

Probing the Continuum of Covalent Contributions to Halogen *vs*. Hydrogen Bonds

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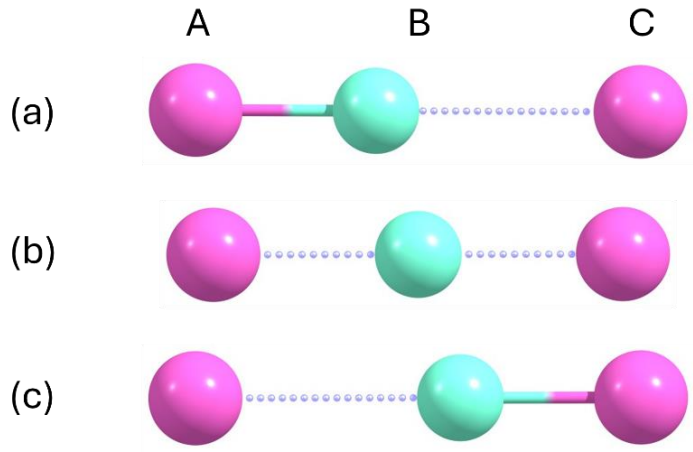
Although hydrogen and halogen bonds were both originally described as primarily electrostatic in origin, many studies have subsequently shown that there may be a large covalent contribution that aids in stabilising the interactions,[1,2] though this has been contested in the case of hydrogen bonding.[3] The covalency of the interaction may also vary; consider the system shown in the figure below where bond A–B may be regarded as changing from covalent in (a) to noncovalent in (c), with (b) corresponding to an intermediate case where large covalent contributions lead to a strong, symmetric complex. Within this continuum, the nature and properties of the bond/interaction change. In addition, the covalent contribution to the interaction may be influenced by a variety of factors, such as the type of interaction (e.g. halogen vs hydrogen bond), the nature of the donor and acceptor molecules involved and the substituents on both of these that may affect the electronic properties of the interacting atoms. For instance, the continuum of halogen bonds formed between differing electrophiles and DABCO as the halogen bond acceptor has been reported.[4] In this presentation, the role of these factors on the covalent nature of a range of different hydrogen and halogen bonds is probed systematically using a variety of computational methods.



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Nucleophilicities of Lewis Bases and Electrophilicities of Lewis Acids Involved in Non-covalent Interactions

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It has been shown [1] that equilibrium dissociation energies D_e of complexes B⋯A involving various types of non-covalent interaction can be described by the equation $D_e = N_B.E_A$, in which N_B is a *nucleophilicity* assigned to the Lewis base B and E_A is an *electrophilicity* assigned to the Lewis acid A. Thus, graphs of D_e (calculated *ab initio*) versus N_B or E_A should be straight lines through the origin. Examples of the application of this equation to various types of non-covalent interaction will be discussed.

It will be shown that D_e (for series of complexes B⋯A in which B is varied but A is fixed) are directly proportional to the minimum values σ_{min}(B) of the molecular electrostatic surface potentials (MESP) of the monomers B (*i.e.* the region of most negative potential of B). Likewise, there is an accurate direct proportionality between D_e and the maximum values σ_{max}(A) (most positive region) of the MESP of A for series B⋯A in which A is varied but B is fixed. These observations lead to definitions of a *reduced nucleophilicity* $\mathit{И}_B$ [2] and *reduced electrophilicity* Ξ_A [3], respectively. It will be demonstrated that the value of $\mathit{И}_B$ is a property only of the atom of B directly involved in the non-covalent interaction and is independent of the remainder of B. Likewise Ξ_A is a property of the atom of A directly involved in the B⋯A interaction. Moreover, the equilibrium dissociation energy D_e of the complex B⋯A may then be predicted (with reasonable accuracy) from σ_{min}, σ_{max}, $\mathit{И}_B$ and Ξ_A values of the molecules B and A, (*i.e.* from properties of the individual molecules only [4]).

The concepts introduced here will be illustrated by examples of hydrogen-bonded B⋯HX and halogen-bonded B⋯XY complexes, including the effect on nucleophilicities caused (a) by inductive effects of different groups attached to B [5] and (b) by substituting first-row atoms in B by second-row analogues. Additionally, novel types of tetrel-bonded complexes B⋯H_3MX (M = Si, Ge, Sn; X =H, F, Cl, CN) and B⋯MS (M = Ge, Sn) [6] will be considered.

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IL7

Metal-NCIs in Mixed Ligand Complexes

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Non-covalent interactions (NCIs) between metal and halogen atoms influence molecular and material stability and reactivity, facilitating the creation of new materials with specific properties and enhancing our understanding of molecular recognition [1]. Interactions between metals and halogens form two types of polar NCIs:semi-coordination bonds (sXBs) or halogen bonds (XBs), depending on the electron-rich and electron-deficient regions involved, with distinct electrophilic or nucleophilic characteristics [2].

A series of mixed-ligand silver(I) compounds containing benzoate (OBn) and neutral pyridyl ligands offers insight into various metal-involved interactions [3]. We assessed metal$^{+}\cdots$metal^{+}, metal$^{+}\cdots C_{aromatic}$ and metal$^{+}\cdots$ X (where X=Br or I) interactions in crystal packing, using quantum theory of atoms in molecules (QTAIM) and natural bond orbital (NBO) analysis. The strength of these interactions followed the the order $Ag^{+}\cdots I(C) > Ag^{+}\cdots Ag^{+} > Ag^{+}\cdots Br(C) > Ag^{+}\cdots(C)_{aromatic}$. Bromine and iodine substituents enhance stability via $Ag^{+}\cdots X(C)$ sXBs.

Crystal packing analysis of compounds with and without halogen substituents will also be presented to highlight the differences in molecular conformations and geometries observed.

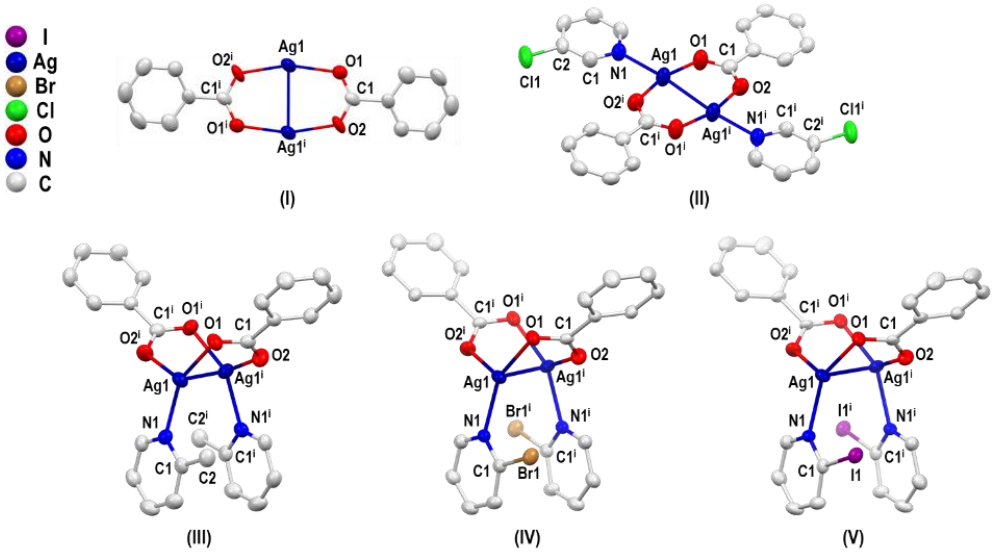

Figure 1. Crystal structures of compounds **I-V** with atom labels. Ellipsoids drawn at 50% probability level.

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Exploiting the Macrocyclic Effect for the Stabilization of Halenium(I) Ions

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Halenium ions (X^+) are highly reactive electron deficient species and are prevalent transient intermediates in halogenation reactions.[1] Characterisation of these species is remarkably challenging and still in its infancy,[2] with the most common approach to sequester reactivity through the formation of pyridine (Py) coordination complexes; $[(Py)_2X]^+$. Herein , we present the first example a macrocyclic stabilization effect for halonium species. Exploiting a series of bis-pyridine macrocycles we demonstrate the endotopic complexation of a Br(I) cation, impressively facilitating the isolation of bench stable of 'Br^+ NO_3^-' species. Extensive structural comparison with Ag(I) and Au(I) analogues provide insightful information concerning similarities and stark contrasts in their coordination behaviors. Furthermore, we also demonstrate solution phase chemical ligand exchange of Br^+ cations between acyclic and macrocyclic donor ligands.

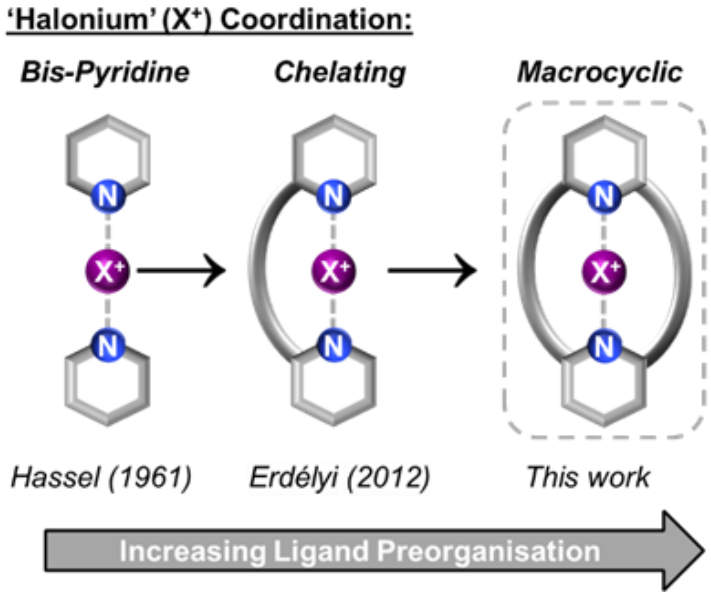

Figure 1. Cartoon representation of design conception.

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IL9

The C–I···O–N *vs.* N–I···O–N Halogen Bonds

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Data mining is the process in which certain specific information is extracted from existing large data sets to discover systematic patterns or parameter modulations. In crystallography data mining[1] normally means the use of large crystallographic databases, such as the Cambridge Structural Database[2] (CSD) and Inorganic Crystal Structure Database[3] (ICSD) for extraction of geometrical parameters, *viz.* bond distances, angles, interaction distances (*e.g.* hydrogen and halogen bonds) etc. Our research interest has been focused on the studies of weak non-covalent intermolecular, *viz.* supramolecular interactions as the driving force in complex formation, self-assembly and molecular recognition, especially in the solid-state by single crystal X-ray diffraction (SCXRD). The lecture will highlight some of our recent studies on N-I···O-N and C-I···O-N halogen-bonded systems, using unusually large set of in-house SCXRD.[4-7]

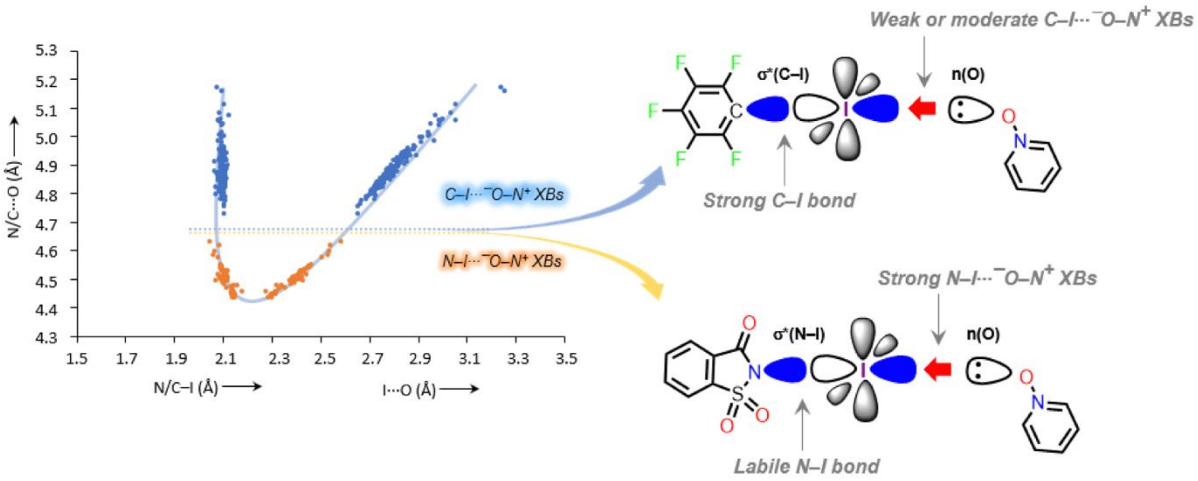

Figure 1. The experimental bond parameter correlations of C–I···⁻O–N⁺ and N–I···⁻O–N⁺ halogen bonds.[7]

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Synthesis of Xe–N and Xe–O Bonded Compounds *via* σ-Hole Interaction on XeF^+

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Noble-gas bonding interactions are an interesting subclass of σ-hole interactions [1,2], which are responsible for the formation of a variety of fascinating adducts [3] and complexes [4], thereby enriching the diversity of xenon and krypton compounds. The XeF^+ cation, which is isoelectronic with IF, is a strong Lewis acid and exhibits a large σ-hole on the xenon atom [5] (Figure 1). This feature can be exploited for the synthesis of xenon compounds containing Xe–N [6] and Xe–O bonds [7]. A suitable oxidatively resistant Lewis base (L) must have an ionization potential higher than the estimated electron affinity of XeF^+ (10.9 eV) to form the $[LXeF]^+$ adduct cation. In this work, a selected XeF^+ salt was reacted at low temperatures with carbamoyl fluoride, H_2NCOF, resulting in the formation of a rare Xe–O-bonded adduct cation, $[H_2NC(F)OXeF]^+$. Moreover, in a similar reaction with cyanogen, NCCN, the first bis-coordinated adduct cation $[FXeNCCNXeF]^{2+}$ was isolated. This species undergoes a rearrangement resulting in the formation of $[XeNC(F)C(F)NXe]^{2+}$, a cation featuring an unprecedented C=N–Xe bonding modality and a pronounced σ-hole on the xenon atom, which can be utilized to prepare compounds with an N–Xe–N linkage.

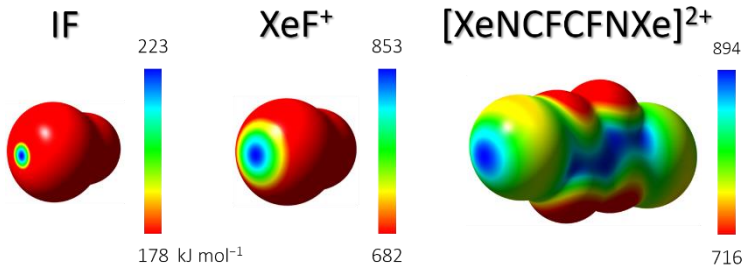

Figure 1. Molecular electrostatic potential surfaces of IF, XeF^+ and $[XeNC(F)C(F)NXe]^{2+}$ (isovalue of 0.001, top 20% of the positive range).

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IL11

A New NMR Technique to Characterize Weak Halogen Bonds in Solution

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Halogen bonds are typically weak, and hence easily form and break. In solutions, they are present in association-dissociation equilibria with only a small fraction of the interaction partners being present in their halogen bonded form, whereas most are dissociated. The weakness of halogen bonds, and non-covalent forces in general, makes their detection in dilute solutions cumbersome. Accordingly, standard spectroscopic techniques are often incapable of their reliable characterization, and often even of their detection.

I present a new strategy that expands the current boundaries of the NMR characterization of weak interactions in solution, and demonstrate its scope by the characterization of weak (Ka < 10 M^{-1}) intermolecular halogen and hydrogen bonds in a dilute (2 mM) solutions. This is an impossible feat when applying a standard NMR titration. I show that this new strategy is universally applicable to the geometric and thermodynamic characterization of any type of non-covalent interactions in chemistry and biology, independent of context.

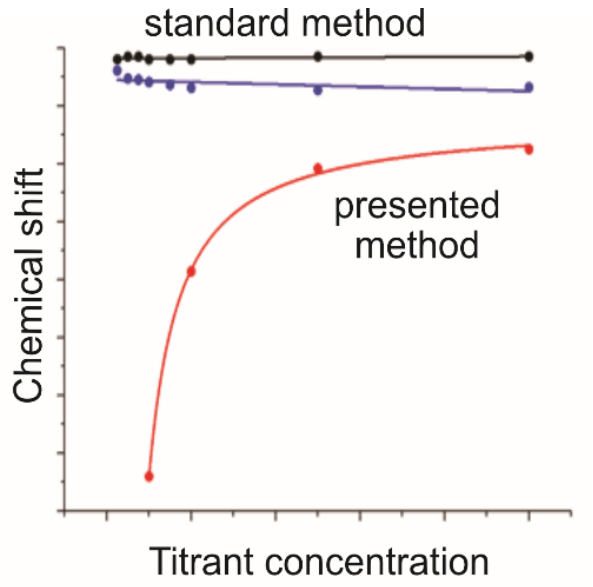

Figure 1. Comparison of the sensitivity of the standard chemical shift perturbation (NMR titration) technique with the novel strategy presented in this talk for characterizing a weak halogen bond in a dilute solution.

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Tuning Materials Properties *via* Halogen Bonding

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In recent years halogen bonding (XB) has found widespread applications in materials science. This is because of its unique features, which cannot be easily met by other noncovalent interactions.[1] First of all, the anisotropic distribution of electron density in covalently bound halogen atoms allows the formation of highly directional interactions both with nucleophiles (XB through the σ-hole) and electrophiles (at the negative belt perpendicular to the covalent bond formed by the halogen). This high directionality, together with the tunable interaction strength enabled by the halogen atom selection, makes the XB an effective tool for controlling the self-assembly of molecular building blocks and fine-tuning their functional properties. Moreover, the frequent presence of fluorinated segments in the XB-donor not only boosts interaction strength, but also increases the hydrophobicity of the final supramolecular adducts, giving protection against humidity and boosting material stability. Further, the bare size of halogen atoms may significantly alter the light-emitting properties of halogenated dyes and is beneficial for constructing all-organic solid-state phosphorescent materials.

In this lecture we will highlight some of our recent studies on XB- functional materials, ranging from liquid crystals [2] to perovskites [3] and we show how XB strength and directionality, coupled with the segregation tendency of perfluoroalkyl and alkyl chains, might open the way to several new possibilities for structure control as well as for the tuning of functional properties.

Acknowledgements. We acknowledge the financial support from the MUR, project SHINE (PRIN2022, no. 20225SYHXM).

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Oxidation-induced Activation of Chalcogen Bonding in Tetrathiafulvalene-based Organic Conductors

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The ability to control intermolecular interactions in organic charge transfer donor-acceptor (D-A) salts is crucial owing to the critical role of molecular organization in their conducting properties.[1] Earlier efforts in this direction include the functionalization of tetrathiafulvalene (TTF) molecules with hydrogen bonding (HB) donor groups.[2] In parallel, iodine atoms have been also introduced as a peripheric substituent of TTF, to promote intermolecular halogen bonding (XB) interactions.[3] The charge transfer materials conceived through these strategies show intriguing structures highlighting the packing of D and A molecules influenced by HB and XB interactions. Nevertheless, none of them shows metallic conductivity, implying a challenging aspect.

In this presentation, I will discuss our efforts in this direction by introducing chalcogen bonding (ChB) interactions within TTF-based charge transfer salts. Radical salts of the $TTF(SeMe)_2$ derivatives with bromide shows highly linear Se···Br^- ChB interactions, demonstrating the efficient σ-hole interaction of Se through redox-active TTFs.[4] Upon co-crystallization with $TCNQF_2$, the obtained 1:1 salt (Figure 1) shows original packing of the donor and the acceptor molecules, each organized into segregated stacks, through ChB interactions between Se atoms of the donor and N atoms of $TCNQF_2$. Due to the segregated packing and a partial charge transfer, the compound shows metallic conductivity at ambient temperature.[5] Furthermore, the 3D coupling of the modulations in different stacks brought by ChB likely led to a metal-to-insulator transition at rather high temperature compared to other known 1D charge transfer salts.

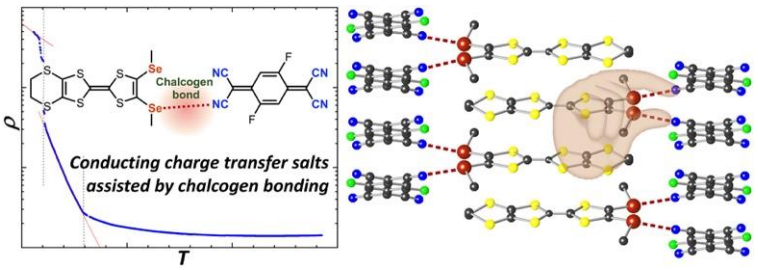

Figure 1.

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Novel Structural Biomaterials through Halogenation

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Although many modifications of peptide sequences have been utilized to tune their self-assembly behaviour, halogenation has rarely been pursued. The advantage of the introduction of halogen atoms on peptide motifs lies in the fact that halogenation is a minimal structural modification, which, on the other hand, induces a large difference in the peptide supramolecular behaviour as a consequence of the variety of noncovalent interactions given by halogens [1].

In this lecture, I will show how the halogen bond can be used to promote the molecular self-assembly of peptides. We have applied this new supramolecular concept to the augmented fibrillation of amyloidogenic peptides [2] and the control of their nanostructures (Figure 1) [3]. The obtainment of a novel unnatural amino acid functioning as strong halogen-bond donor has allowed to engineer the hydrophobic cavity of an amyloid fibril. Our results prove that selective halogenation of an amino acid enhances the supramolecular organization of otherwise unstructured biologically-relevant sequences. This method may develop as a general strategy for obtaining novel structural biomaterials through peptide halogenation [4].

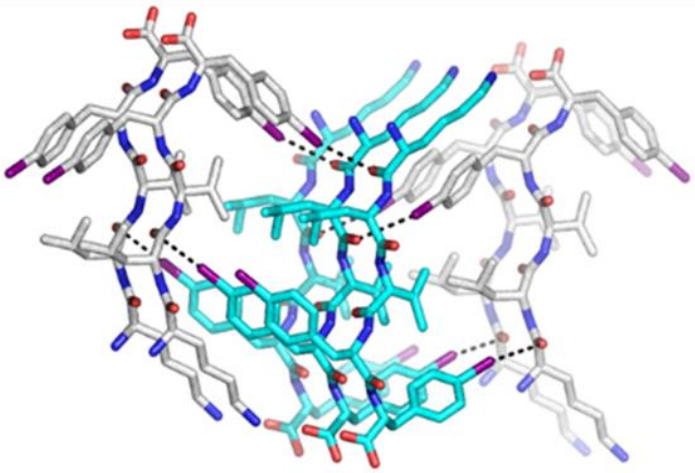

Figure 1. Steric zipper motif formed by KLVF(I)F(I) showing halogen bonds with the carbonyl oxygens.

Acknowledgement. The project KARATE (grant no. 2022-0437) funded by Cariplo Foundation is gratefully acknowledged.

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IL15

Halogen Bonding and Iodine Industry

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Halogen bonding (XB) has attracted a great deal of attention in life and material science in the past decade [1]. In this paper, we would like to review and discuss about iodine production and applications from the viewpoint of XB chemistry.

1. Iodine Production and XB

In Japan, iodine is produced from natural gas brine. Iodine production and recycling methods are a blowing-out process and an ion exchange resin process. XB plays an important role for an ion exchange resin process [2].

2. Inactivation Effects of Iodine on SARS-CoV-2 and XB

Iodine has a wide range of antimicrobial action against bacteria, fungi, and viruses. In this study, we examined the inactivating effect on severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) of different forms of iodine, including free iodine, iodide ion, and polyiodide ion, which are the main constituents of iodine-based disinfectants. The results indicate that although iodide ion is not involved in the inactivation of SARS-CoV-2, iodine complex and polyiodide significantly contribute to the inactivation [3]. The action mechanism of iodine is closely related to XB (Figure 1).

3. Synthesis of XB catalyst and XB donor non-natural amino acid

Perfluoroiodobenzene derivatives are strong XB donors (Figure 2). We would like to report about the synthesis of XB catalysts and XB donor non-natural amino acids [4].

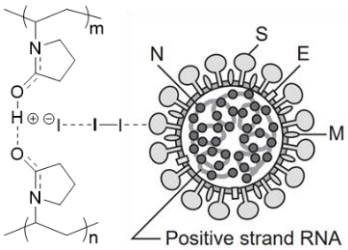
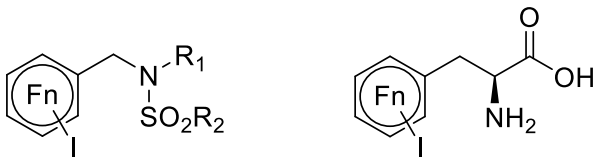


Figure 1. Disinfectants and XB



1 2

Figure 2. XB Catalyst (1) and XB donor non-natural amino acid (2)

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Chalcogen Bonding Catalysis with Telluronium Cations

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The chalcogen bond (ChB) is a non-covalent interaction (NCI) involving electrophilic chalcogen atoms, in analogy to the halogen bond (XB) involving halogen atoms. These two interactions are due to the attraction between a nucleophilic entity (Lewis base) and an electrophilic region, called σ-hole, located on bonded halogen or chalcogen atom, at the opposite of the σ-bond bound and coinciding with the σ* orbital. The energy of these NCIs are based on electrostatic, charge transfer and dispersion. The number of σ-holes on an atom generally depends on its valency. Thus, a monovalent halogen has one σ-hole while divalent chalcogen atoms have two σ-holes. Although comparable to hydrogen bonding (HB) in terms of strength, XB and ChB on the other hand are highly directional. This interesting property has recently allowed the exploitation of ChB in many applications and more particularly in organocatalysis. As with XB, the strength of ChB depends on the polarizability of the chalcogen atom (S<Se<Te) and therefore chalcogen interactions involving tellurium are the strongest. Tellurium derivatives are therefore very promising for applications based on σ-hole interactions. This presentation will focus on the latest results from our laboratory involving cationic derivatives of tellurium, the telluroniums, which have three σ-holes and which have proven to be very effective in many catalytic reactions (Figure 1) [1-5].

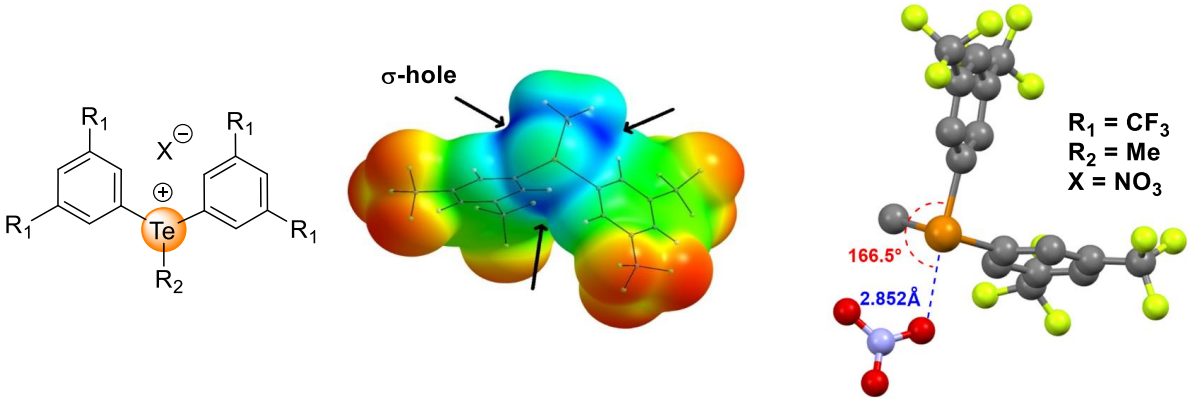

Figure 1. Telluronium salts.

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Oxidative Dearomative Coupling of Low-Reactive Arenols Using Hypohalite Catalysis

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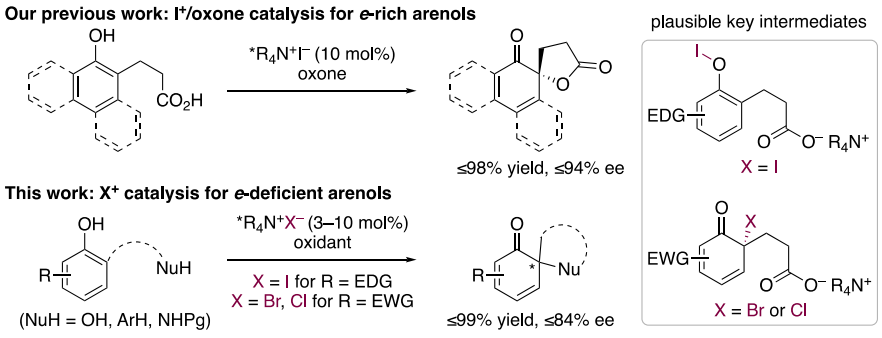
The dearomatization of arenes, which are readily available planar molecules, is a powerful method for the construction of complex three-dimensional molecular skeletons. Several strategies for dearomatization reactions have already been developed [1]. Among these, the dearomatization of electron-rich arenes such as arenols can proceed under relatively mild conditions due to their reduced resonance-stabilization energy. Especially 2,4- or 2,5-cyclohexadienones are important building blocks for the synthesis of natural products and bioactive compounds. The oxidative dearomatization of arenols has been developed as a conventional method for synthesizing cyclohexadienone skeletons [2]. To date, many elegant strategies for catalytic asymmetric dearomatization (CADA) reactions of arenols have been developed using transition-metal or organocatalysis [1,3]. Recently, we have developed high-performance hypoiodite catalysis for the oxidative dearomatization of arenols [4]. However, the substrate scope of I^+/oxone catalysis has been limited to electron-rich arenols, which are relatively reactive, and no reaction was observed for low-reactive phenols that bear electron-withdrawing groups (EWG). Based on the characteristics of each halogen, here, we have developed a hypohalite, especially hypobromite, catalysis for the oxidative dearomatization of phenols of low reactivity by tuning the reaction conditions (e.g., oxidant and solvent). Notably, we have expanded the reaction scope to include inter- and intramolecular dearomative C–O, C–N, and C–C coupling reactions. In addition, we have achieved the first enantioselective hypobromite catalysis for oxidative dearomative coupling reactions. Interestingly, we found that the reaction mechanism might differ depending on the specific halide used in the catalyst system [5].



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Catalytic Activation *via* Halogen π-backbonding in Nucleophilic Substitution Reactions

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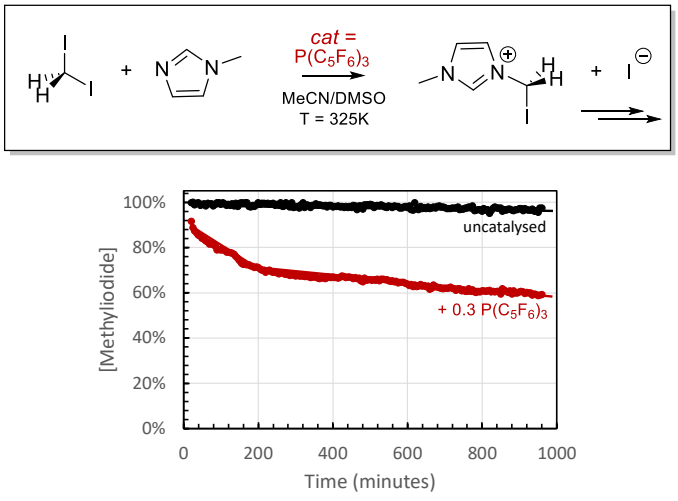
The role of halogen bonding (XB) in chemical catalysis has largely involved using XB donors as Lewis acid activators to modulate the reactivity of partner Lewis bases. In a recent computational study, we explored a more uncommon scenario, where a Lewis base could potentially modulate reactivity via a spectator halogen bond interaction.[1] In certain cases, we observed that σ-donors that could also act as π-acceptors might lower the barrier in S_N2 reactions by redistributing electron density in the very electron rich five-coordinate transition state.

We report experimental evidence that demonstrates that appropriately selected electron-deficient phosphines accelerate the rate of substitution reactions in diiodomethanes (see Scheme 1). Although the final product in these reactions involves double-substitution, the first step is rate limiting allowing us to effectively track the process effectively. With appropriate modelling,[2] the rates of substitution have been evaluated and we demonstrate that the predicted rate enhancement is observed experimentally. The implications of these findings – and the limitations of applying such a strategy more broadly – will be discussed.



Scheme 1. Initial reaction rates for nucleophilic substitution of diiodomethanes in the presence and absence of an electron-deficient phosphine.

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IL19

Catalysis with Nonclassical Weak Interactions

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Catalysis based on nonclassical weak interactions has been demonstrated to be an important synthetic platform capable of addressing reactivity and selectivity issues.[1] The research in Wang's group at Shandong University was focused on catalysis with nonclassical weak interactions (Figure 1).[2] They developed general chalcogen and carbon bonding catalysts, and elucidated their bonding properties and mechanisms. Two catalysis approaches including "chalcogen-chalcogen bonding catalysis"[3] and "chalcogen···π bonding catalysis"[4] were developed. The unique catalysis properties of these two modes were demonstrated by a range of reactions. Carbon bonding catalysis was achieved and its universality was demonstrated.[5] The strategy of "carbon-bonding metal catalysis" was established. These research works have expanded the capabilities of weak interactions.

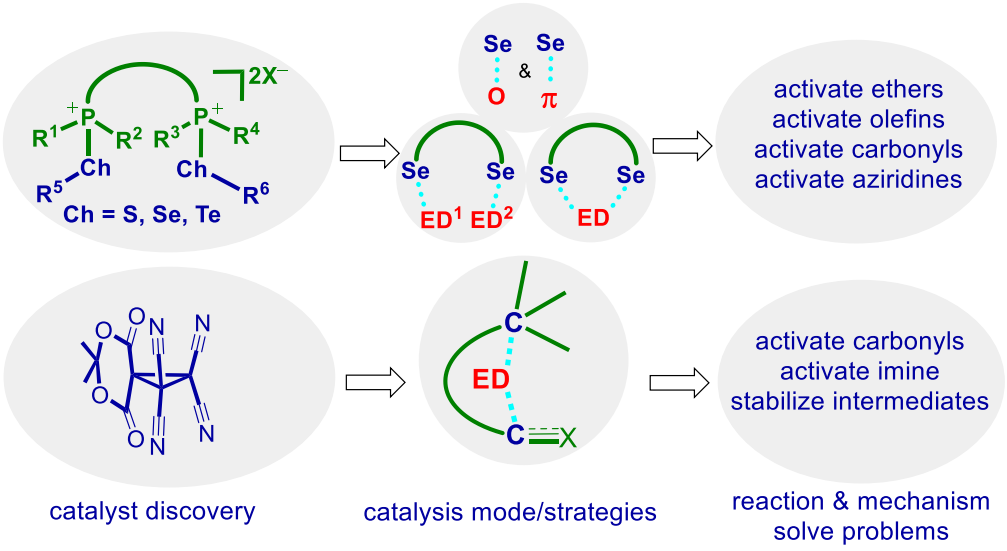

Figure 1. Catalysis with nonclassical weak interactions in Wang's group

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The Interaction Between Organoflourine and Target Protein

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Fluorination of organic compound is frequently used in medicinal chemistry. However, the exact effect of the substitution on bioactivity is still controversial. This speak focuses on the effect of the –CF3 substitution on bioactivity and the interaction mechanism between F atom and protein.

A statistc survey based on 28,003 pairs of compounds showed that 9.19% substitution of –CH3 by –CF3 could increase the biological activity by at least an order although the replacement of –CH3 with –CF3 does not improve bioactivity on average. PDB survey revealed that –CF3 prefers Phe, Met, Leu and Tyr, while –CH3 prefers Leu, Met, Cys and Ile. Further QM/MM calculations for 39 –CH3/–CF3 pairs of protein-ligand complexes revealed that the –CH3/–CF3 substitution does achieve a large energy gain in some systems, although the mean energy difference is subtle. The –CF3 substitution on the benzene ring could be particularly effective at gaining binding energy. The maximum improvements in energy achieved -4.36 kcal/mol by QM/MM calculation. Moreover, energy decompositions from MM/GBSA calculations showed that the large energy gains for the –CH3/–CF3 substitution are largely driven by electrostatic energy or the solvation free energy. We also investigated the possible effect of the interaction between F atom and protein by the adjacent atoms. These findings should be useful for understanding the interactions and binding contributions of fluorine atom to target protiens.

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IL21

Development of a Index to Evaluate Halogen Bonds in Ligand-bound Protein Structures

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Inter- and intra-molecular interactions are essential for protein folding and ligand–receptor interactions. Halogen bonds were known in the organic chemistry field in the 1950s; however, it was not until the early 2000s that halogen bonds were analyzed in biomolecules [1]. Halogen atoms are rarely observed in biomolecules. The only exception is thyroid hormones. However, drugs and toxic environmental chemicals contain halogen atoms, which are essential for their interaction with biomolecules [2]. The strength of halogen bonds is elucidated by the stabilization energy of the ligand-receptor complex; however, receptor proteins are composed of many atoms, and the whole structural calculation requires a high cost. Therefore, more practical methods are needed to accelerate molecular design and drug discovery. We propose a coordinate clipping strategy appropriate for performing the first principal calculation of a protein crystal structure using the DV-Xα method. We used a nuclear receptor, estrogen-related receptor γ, as a model for calculation, to which the well-known environmental chemical bisphenols bind. We assessed the appropriate region for the calculation, and evaluated the halogen bonds by analyzing the covalent bond located at the opposite side of the halogen bonds. We concluded that clipping nitrogen atoms at the *i-1* position in the main chain is beneficial for calculating protein structures. Here, we defined a new index of halogen bonding or non-covalent interactions by DV-Xα evaluation (HIVE index) to evaluate the halogen bonds in biomolecules [3].

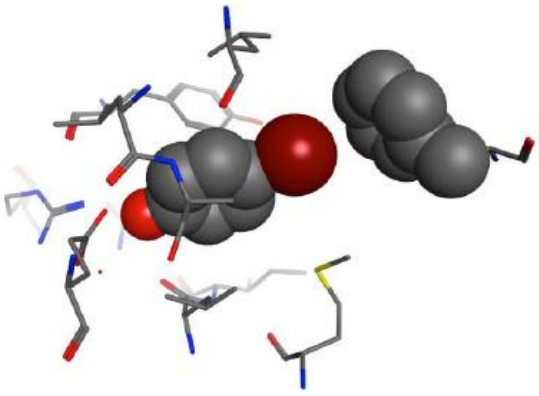

Figure 1. Halogen bond found in estrogen-related receptor γ

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Halogenated Organic Cations as Halogen Bond Donors – Possibilities and Limitations

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The key feature which enables halogen atoms to act as halogen bond donors is the is presence of an area of depleted electron density (σ-hole).[1] Therefore, all strategies aimed at design of new halogen bond donors rely on increasing the positive potential on the halogen atom – be it by addition of electron withdrawing substituents on the hydrocarbon skeleton (most commonly fluorine, as in perfluorinated iodo and bromo-hydrocarbons), binding the halogen to a carbon atom involved in a multiple bond or an electronegative heteroatom, or by using hypervalent halogen compounds. There is, however, another approach for ensuring a large positive electrostatic potential on halogen atom: making the halogen atom a part of a positively charged species.[2]

Here we will present a systematic study of both the possibilities and the limitations of using halogenopyridinium (X-Py) cations as halogen bond donors. A combined experimental and computational study of cations derived from mono-halogenated pyridine derivatives (*o*-, *m*- and *p*-; chloro, bromo and iodo) both by protonation and *N*-methylation has shown that while the halogen atom in cations exhibits a considerable increase in the ESP of the halogen σ-hole, X-Py cations have not shown to be superior to the commonly used neutral halogen bond donors, as the halogen σ-hole is generally not the most positive site on the surface of the cation.[3] In spite of this, cations derived not from iodo- and even bromopyridines form halogen bonds with remarkable consistency with a variety of acceptors, and even in presence of competing halogen bond donors, making them reasonably reliable halogen bond donors for synthesis of halogen bonded materials.

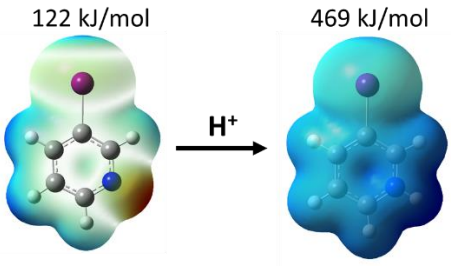

Figure 1. Increase of electrostatic potential on iodine σ-hole upon protonation of 3-iodopyridine.

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OVERVIEW

Halogen Bonding: Impact and Legacy

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The halogen bond developed as an important and powerful tool in fields as diverse as chemical catalyses, functional materials, the binding of small molecules to proteins.

Even more important, it paved the way to the understanding and fruitful use of many other interactions formed thanks to the anisotropic distribution of the electron density in bonded atoms. In this way it allowed for the development of a taxonomy of chemical interactions. This seminal role will be briefly discussed.

ORAL CONTRIBUTIONS

OC1

Applications and Limitations of Iodine Catalysis

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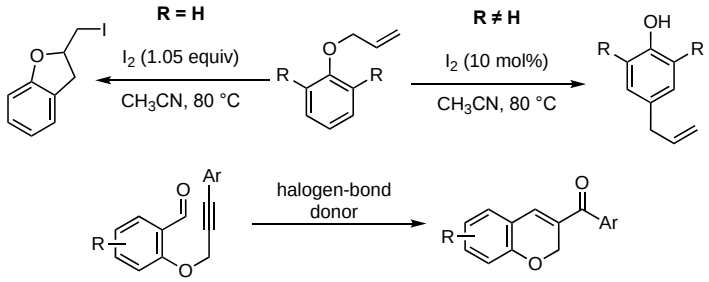
Molecular iodine is a highly efficient catalyst for different transformations under very mild reaction conditions [1]. We were recently able to show that the origin of its catalytic activity in Michael additions, Nazarov cyclizations, and Diels-Alder reactions is a halogen-bond activation [2]. In contrast, an iodonium activation is active in the closely related carbonyl-olefin metathesis [3].

However, most substrates are structurally similar and typically feature carbonyl groups that interact with the catalyst. Furthermore, they do not include functional groups that could potentially react with iodine. We will now report on the catalytic activities of molecular iodine in reactions involving aryl vinyl ethers or alkynes [4,5]. We will discuss spectroscopic and computational studies together with experimental investigations and provide insights into the reaction mechanisms and, thus, highlight applications and limitations for halogen-bond catalysis by iodine.



Scheme 1. Application of iodine catalysis in the [3,3]-sigmatropic rearrangements (top) and of halogen-bond donors in the carbonyl-alkyne metathesis (bottom).

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How Halogen Anisotropy Modulates the Membrane Permeability of Halogenated Drugs

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Halogenated compounds can interact with proteins through halogen (XBs) and halogen bonds and hydrogen bonds (HBs) [1] owing to the σ-hole formed on the opposite side of the X atom along the R–X bond axis. Using Molecular Dynamics (MD) simulations, our Lab recently suggested that these interactions can play a role in ligand-membrane interactions trough the formation of XBS with both phosphate and ester oxygen acceptors from the phospholipids, the main component of biological bilayers [2]. However, the potential effect on permeability coefficients remains unclear. In this communication, we will disclose the recent advances in the study of membrane-ligand interactions mediated by XBs. By means of molecular MD simulations combined with umbrella sampling, along with the inhomogeneous solubility-diffusion model (ISDM) and a ranking score based on the difference between the maximum and minimum free energies (ΔGranking), we will show how XBs affect the permeability of six commercial halogenated drugs - diazepam, bromazepam, clonidine, metolazone, furosemide, and amiodarone – whose experimental values are known. These results highlight the potential importance of XBs in drug permeation and provide a robust methodology for future studies.

Acknowledgments. FCT: SFRH/BD/146447/20119 (AF), UIDB/04046/2020 (DOI: 10.54499/UIDB/04046/2020) and UIDP/04046/2020 (DOI: 10.54499/UIDP/04046/2020) to BioISI, 2021.00381.CEECIND (DOI: 10.54499/2021.00381.CEECIND/CP1650/CT0004) to PJC. EU: project TWIN2PISPA - Twinning for Excellence in Biophysics of Protein Interactions & Self-Assembly (GA 101079147). BioISI: BioISI Projects 2024.

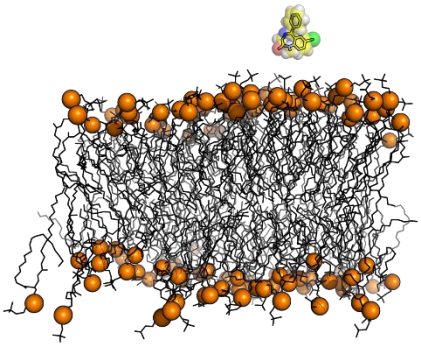

Figure 1. A drug about to interact with a phospholipid bilayer.

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Fluoride Anion: Strong Halogen Bond Acceptor

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Many structures have been reported wherein iodide anions act as halogen bond (HaB) acceptors against haloperfluorocarbons, effective halogen bond donors. The number of structures decreases for bromide anions and even more for chloride anions and it is very minor for fluoride anions. Assuming that this behavior might be related to the strong tendency of fluoride anions to exist as hydrated species, we pursued obtaining halogen bonded cocrystals wherein fluoride anion act as the HaB acceptors by exploiting the strong nucleophilicity of fluoride anions in anhydrous conditions. We will describe here how 18-crown-6 (K.2.2.2), potassium fluoride, and mono- or di-iodoperfluoroalkanes self-assemble into tricomponent cocrsystals wherein anhydrous fluoride anions are present (Fig. 1). Structural aspects of the obtained cocrystals (Fig. 2) will be discussed and a comparison with analogous systems formed by chloride and iodide anions [1] confirm that the fluoride anion is an extremely good donor of electron density.

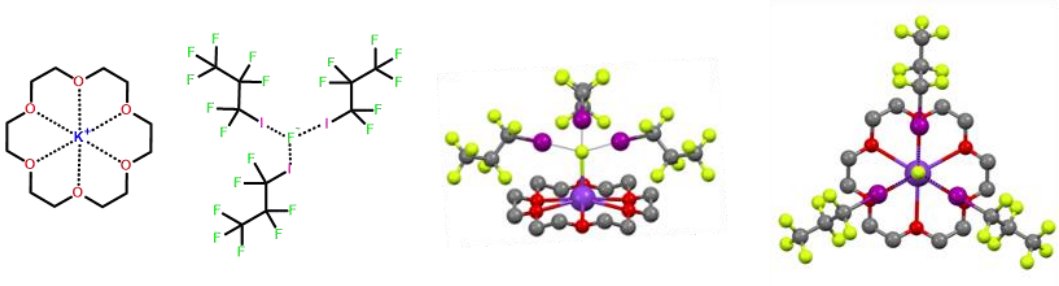

Figure 1. Structural formulas (left) and two partial views after orthogonal directions (mid and right) of the salt K.2.2.2/KF/1-iodo-heptafluoropropane.

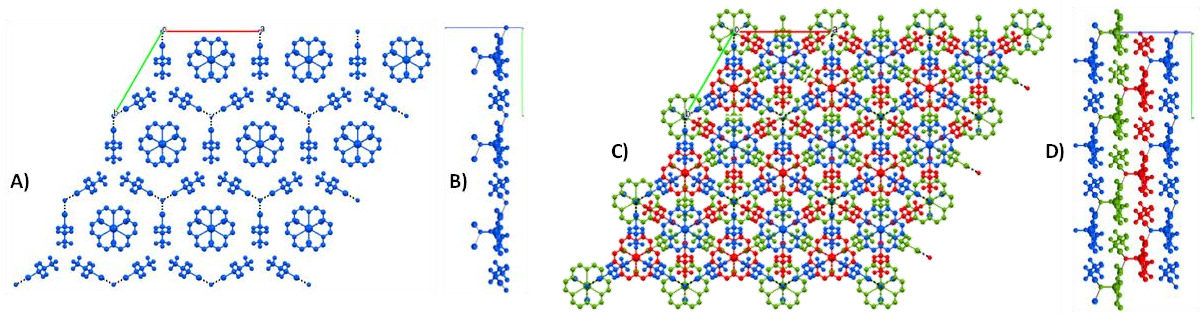

Figure 2. Representation, along crystallographic c (A) and C)) and a (B) and D)) axes, of one (A) and B)) and three (C) and D)) layers present in the crystal packing of K.2.2.2/KF/1-iodo-heptafluoropropane.

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The Applicability of CF_2X Moieties for Drug Discovery

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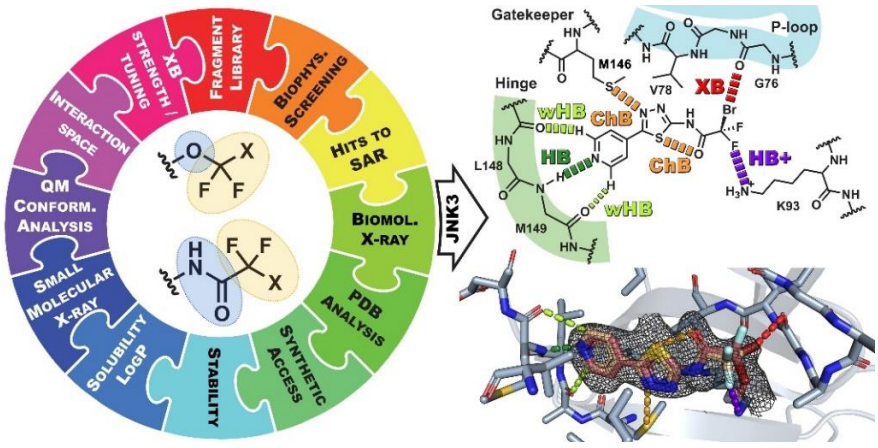
Since Emil Fischer coined the "lock-and-key principle" in 1894 [1], engineering specific molecular recognition has become one focus of attention for medicinal chemists, as the "guild of therapeutic key makers". Directional molecular interactions are at the heart of their tool kit. Halogen bonds have been added just recently and sparked great interest for unconventionally addressing protein binding sites [2-5]. For reasons of stability, halogenation of aromatic rings appeared to be the only logical way to construct halogen bonds in medicinal chemistry. Thus, they were confined to the two-dimenional plane of the (hetero)aromatic scaffold. Overcoming this limitation, we have shown that replacing one fluorine atom in the popular CF_3 moiety by chlorine, bromine or iodine can integrate strong halogen bonds into a network of interactions, maintain reasonable stability, and add CF_2X moieties to the medicinal chemists' arsenal of tools [6,7]. For halogens, it's the blend that makes the difference!



Scheme 1. Conceptualization of studies characterizing halodifluoroacetamide and halodifluoromethoxy moieties. Evidence for usability in drug discovery by engaging in unconventional binding modes is provided through fragment **23** binding to c-Jun N-terminal kinase 3 (PDB ID: 8BZP). Molecular recognition is based on halogen bonding, chalcogen bonding, cation···fluorine interactions and weak and regular hydrogen bonding.

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A perturbation Approach Leads to a Reliable Estimation of a Halogen Bond Thermodynamic Contribution

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Our extensive long-term study on the thermodynamic contribution of halogen bonding to the free energy of protein-ligand interactions has led to significant findings. We have used a model system of binding variously halogenated benzotriazole derivatives by the catalytic subunit of protein kinase CK2 (CK2α). This model system was selected due to the abundance of CK2α structures with halogenated heterocyclic ligands accessible in the Protein Data Bank.[1] We have brought the relative share of particular types of interactions to the forefront, demonstrating that the dominant factor is the balance between hydrophobic and electrostatic interactions, which drives a ligand's binding affinity and the orientation in the complex.[2–6] We have demonstrated that the contribution of the direct interaction between the halogen atom and the electron-density donor remains minor in the tested system.

The most significant challenge we have identified is the unbiased estimation of the impact of introducing a halogen atom into the ligand. This complexity arises from the hard-to-control effect of changes in the free ligand's solvation and alterations in the electron density caused by introducing such an electronegative substituent.

We have experimentally applied the small perturbation method to thermodynamic measurements to overcome this issue. As a perturbation, we tested how controlled small changes in the environment (pH, solvent isotopic effect, buffer composition, single point mutations in the target protein) or minute changes in the structure of the ligand (mainly swapping the type of halogen atoms in a series of isostructural compounds) affects the binding affinities determined by Microscale Thermophoresis or Isothermal Titration Calorimetry.

The collected thermodynamic data and the corresponding structural data allowed us to estimate the contribution of Br-to-Cl replacement at ~ 2 kJ/mol.

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Computational Prediction of Mechanochemical Reactivity of Halogen-bonded Materials

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This presentation will report on the use of computational methods, particularly periodic density-functional theory (DFT) calculations to predict the thermodynamic possibility of solid-state transformations of halogen-bonded materials. The key advantage of using periodic DFT calculations is that the crystal structures are modelled in their entirety, taking into account the energetic contributions of all supramolecular interactions, rather than focusing on just the dominant forces, e. g. halogen- or hydrogen bonding, holding the molecules together.

It will be shown how comparison of the calculated energies of the products and reactants allows us to anticipate, whether a given transformation will be favorable or not, before conducting an experiment. First, interconversions of binary cocrystals,[1] involving exchange of either donor or acceptor components will be explored, with the predicted outcomes of the reactions verified by means of experimental mechanochemical studies. Next, we will turn towards a more complex case of a three-component cocrystal formation, where a wider range of coformer exchange possibilities makes it more difficult to anticipate, which reaction path will be taken by the system.[2]

Throughout the presentation, DFT-calculated reaction energies will be compared with experimental results from the dissolution calorimetry measurements. Such comparisons allow us to validate the accuracy of periodic DFT calculations in predicting the reaction energies and systematically explore the relative performance of different DFT methods in striving to find the most reliable approaches for predicting solid-state reaction thermodynamics of halogen-bonded materials.

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EARLY CAREER ORAL CONTRIBUTIONS

EC1

Validation of Off-center Point-charge Models to Tackle Halogen Anisotropy

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Halogenation is employed in drug discovery to optimize absorption, distribution, metabolism, and excretion properties. Additionally, halogenated compounds can interact with biological targets, such as proteins [1] and membranes [2], through the formation of halogen bonds (XBs) and hydrogen bonds (HBs). However, describing the halogen anisotropy using force fields (FF) is challenging since these typically assign a negative charge to halogens, preventing the formation of XBs in molecular dynamics simulations. To overcome this limitation, the simplest yet efficient strategy relies on off-center point charges (EPs) placed at a given distance from the halogen to emulate the σ-hole. Various EP models have been described in the literature, and while they successfully reproduce protein-ligand geometries and adequately sample XBs, their performance in predicting properties such as hydration free energies (ΔG_{hyd}) remains unknown. Despite optimized halogen radii being provided by us [3] for PBSA calculations, which treat the solvent as a continuum, a proper FF validation requires explicit solvent models. In this study [4], we validated several EP models using alchemical free energy calculations to predict ΔG_{hyd} values for a library of 142 halogenated compounds with known experimental values. The results were compared to those obtained without EPs, when XBs are not possible. By assessing the performance of each EP model, we provide the scientific community with well-validated parameters for halogenated species, which are crucial in computer-aided drug design and biomolecular simulations.

Acknowledgements. FCT: SFRH/BD/146447/20119 (AF), UIDB/04046/2020 (DOI: 10.54499/UIDB/04046/2020) and UIDP/04046/2020 (DOI: 10.54499/UIDP/04046/2020) to BioISI, 2021.00381.CEECIND (DOI: 10.54499/2021.00381.CEECIND/CP1650/CT0004) to PJC. EU: project TWIN2PISPA - Twinning for Excellence in Biophysics of Protein Interactions & Self-Assembly (GA 101079147). BioISI: BioISI Projects 2024.

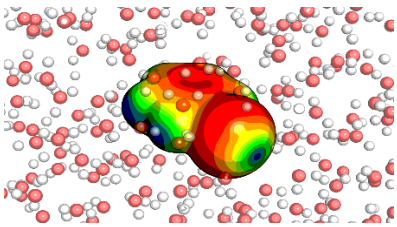

Figure 1. Electrostatic potential of an iodobenzene molecule in water.

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Application of Halogen Bonding for Protein Purification

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Halogen bonding has been successfully applied in catalysis [1] and anion recognition [2]. Recent advancements by our research group have extended the utility of halogen bonding to affinity chromatography, marking the first instance of its application in this field [3]. Affinity chromatography is indispensable for the purification of biomolecules in both academic and industrial contexts, emphasizing its significance in current research.

Studies on halogenopyridinium cations demonstrated their potential as effective halogen bond donors [4]. Our studies focus on the use of iodopyridinium groups immobilized on polyvinylether beads, which act as anchor points on the stationary phase. These iodopyridinium groups function as halogen bond donors, capable of reversible binding and isolating electron-donating molecules such as proteins.

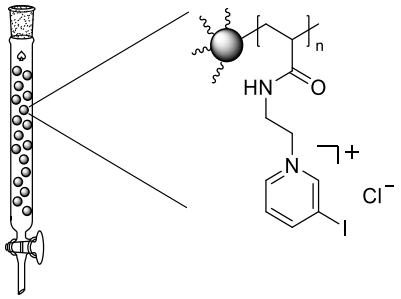

Figure 1. 3-Iodopyridinium groups immobilized on polyamide beads.

This presentation will cover the synthesis of column materials incorporating halogen bond donors and the evaluation of their chromatographic properties. Additionally, we will discuss the separation of various proteins, highlighting the potential of halogen bonding to enhance affinity chromatography techniques.

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Halogen ··· Chalcogen Interaction in Antimony(III) Complexes

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Antimony (III) complexes of aromatic thiosemicarbazones and halogens are mainly investigated due to their potential, cytotoxic and antibacterial activities. However, our primary focus—building on previous findings—was on the single-crystal structure analysis of these complexes due to the interesting structural features they show.

During the case of our studies of a new complex with the formulae {[$SbCl_3$(μ_2-S-acetophenone η^1-S- acetophenone)]$_2$ C_2H_5OH, $2H_2O$, CH_2Cl_2, we have noticed that in one of polymorphic form of this compound very short distance between two antimony atoms is observable (3.92 Å). This encourage us to look more closer to this conntact to find the possible reasons of it. Consequently, we have performed topological analysis using Atoms in Molecules approach and it turns out that one of the causes can be a presence of halogen···chalcogen bonding in the complex core area, as suggested by the presence of the critical point (fig 1) This, quite directional, interaction between sulfur and chlorine atoms has quite high values of Laplacian and electron density at the CP . Moreover, the analysis shows that this interaction is stronger than any other one between two monomers building this dimer, but at the same time - definitely weaker than hydrogen bonds present in the structure. This inspired us to extend the analysis to other analogous compounds from the CDS database. Interestingly, similar halogen···chalcogen interactions are present in each of analogous complexes. Thus, we have performed topological analysis for each of them and the results will be presented.

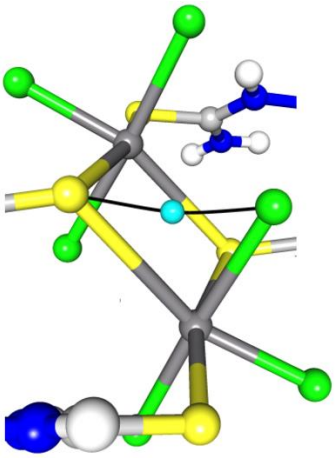

Figure 1. Critical point between sulfur and chlorine atom in complex {[$SbCl_3$(μ_2-S-acetophenone η^1-S- acetophenone)]$_2$

What can we Learn About Halogen Bonds from Electron Diffraction?

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Halogen bonds (XBs) have attracted increasing interest from various scientific fields such as crystal engineering, structural chemistry or biology and material sciences over the last few decades. They arise from the electrostatic interaction of a nucleophilic Lewis base's lone pair with a partially positively charged region of a (mostly heavy) polarized halogen atom. This positively charged region is referred to as the σ-hole. [1] Modern analyses of halogen bonded adducts is commonly carried out by the careful evaluation of the electron density ρ, which is derived either experimentally from a high resolution X-ray diffraction (XRD) experiment or – if the former is not accessible for whatever reason – from ab initio calculations. These calculations are usually carried out with atomic coordinates from XRD experiments. Then, analysis by Bader's Quantum Theory of Atoms in Molecules (QTAIM)[2] is usually carried out.

Since XBs are a directed electrostatic interaction similar to hydrogen bonds, the electrostatic potential (ESP) is of special interest. For the methods described in the first paragraph, the ESP is usually derived from ρ. From a 3D electron diffraction experiment, the ESP is the direct observable of the experiment! Therefore, we herein present the 3D ED structure of PPh4I3, in which the triiodide anion I3 – exists: This anion can be interpreted as the interaction of an iodide with molecular iodine forming an XB (I – I···I – ←−→ I – ···I – I) which is considered to be one of the strongest XBs with an interaction energy of about 180 kJ mol−1 . [3] We also employed our new modeling approach ionic scattering factors (iSFAC)[4] for this molecule, through which we could derive the partial charges of the atoms experimentally.

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Boosting Halogen Bond Donor Ability of Chloroarenes: A Combined Experimental and Theoretical Study

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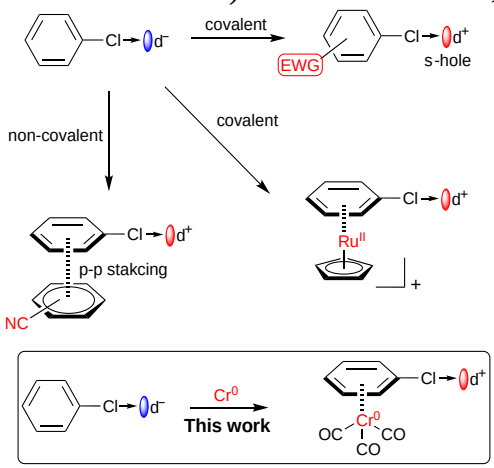
Halogen bonding (XB)[1] has emerged as a promising and versatile tool in the field of molecular recognition, demonstrating successful applications in both solution-state (e.g., catalysis, sensing, anion transportation, and the functioning of biological molecules) and solid-state scenario (e.g., crystal engineering, pharmaceutics, and soft matter).[2] The design of organic solids with targeted molecular functions based on XB has been predominantly realized using more polarizable halogens. These halogens (I and, to a lesser extent Br) tend to form short, highly directional, and importantly, predictable X···Nu contacts. In contrast, less polarizable halogens such as Cl and F present challenges in activation of a sizeable σ-hole and to form predictable X···Nu contacts, limiting their application in supramolecular strategies. Different strategies have been developed in achieving sizeable σ-hole on Cl atom in chloro-arenes as shown in scheme 1.[3] Metal (Cr(0), Mn(I), Ru(II)) π-complexation of arenes is a well-established method known to provide electron-poor arenes with enhanced reactivity. This concept has been recently extended to halo-arenes, involving the η^6-coordination of Ru(II) species to render them excellent XB donors.[4]



Scheme 1. (Non)Covalent approaches in boosting XB donor ability of chloro-arenes.

In this communication, we will discuss a series of neutral Cr(0) coordinated chloro-arenes, demonstrating that their XB donor capability is greater than that of the parent isolated haloarene. These results are substantiated by both experimental (SC-XRD) and theoretical studies (ESP, QTAIM, IRI plots, SPAT analysis). This adaptation further broadens the scope of achieving sizable σ-hole and presents a promising avenue for exploring a new class of σ-hole donors.

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Exploring and Predicting σ-hole Interactions in the Cambridge Structural Database (CSD)

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Halogen bonds, along with chalcogen, pnictogen, and tetrel bonds, are all subsets of σ-hole interactions, involving the interactions of a donor atom covalently bonded to an electron-withdrawing substituent, resulting in the electropositive σ-hole, and an acceptor Lewis base. These interactions are of interest for a wide variety of applications associated with molecular recognition, including in crystal engineering and supramolecular chemistry, catalysis, sensing and biological/medical applications, which have been extensively reviewed.[1]

We have used the Cambridge Structural Database (CSD) to explore the effects of varying donor and acceptor moieties in the solid state on the geometries and prevalence of halogen, chalcogen, pnictogen, and tetrel bonding interactions involving lone-pair Lewis bases. These analyses from crystallographic data were complemented by high-accuracy computational investigations of the nature and directionality of model examples of σ-hole interacting complexes. The calculations provide useful insight into the driving forces behind the strength and directionality of these interactions.

Building upon these studies, a large and diverse database of molecular complexes that engage in σ-hole interactions was constructed, for use for benchmarking computational methods and for training predictive models. This has enabled us to construct and train a machine learning model (ML) on this dataset for computationally inexpensive interaction energy prediction. This model is validated against molecular cutouts of crystal structures extracted from the CSD found to contain σ-hole interacting motifs.

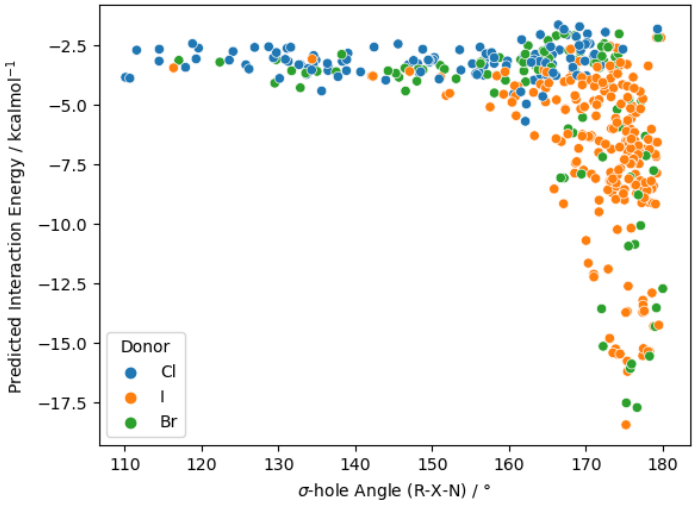

Figure 1. Distribution of ML predicted interaction energies as a function of σ-hole angle from ~500 molecular cutouts from the CSD of halogen bonding motifs to sp^3-hybridised nitrogen, colour-coded by halogen σ-hole donor.

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Machine Learning Models for Chalcogen Bond Analysis in Protein-Ligand Complexes

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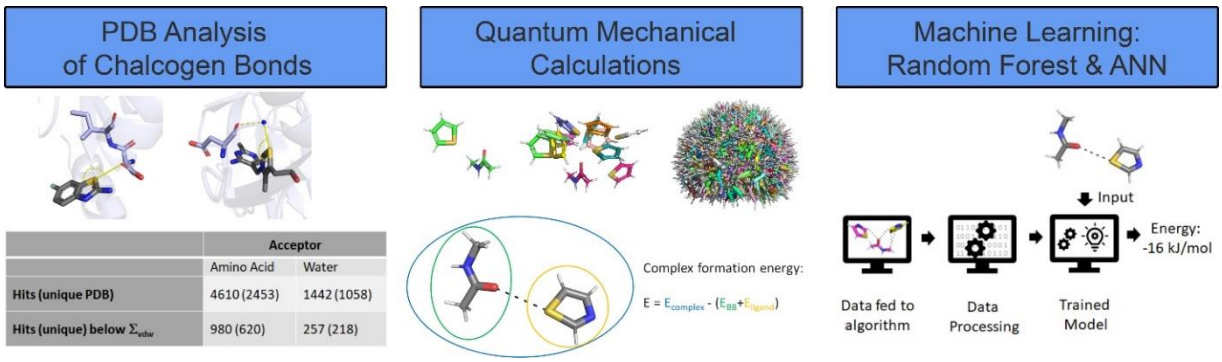
Chalcogen bonds belong to the group of σ-hole interactions [1, 2]. They are highly directional and share similarities with halogen bonds regarding favorable interaction angles and distances [3]. In a protein-ligand complex, chalcogen bonds can either be donated by the protein through the side chains of methionine or cysteine, or by the ligand's sulfur atoms. Extensive analysis of the Protein Data Bank (PDB) showed that more than one third of all sulfur-containing ligands (> 25000 unique PDB entries) engage in a favorable chalcogen bond with an electron-rich region of the protein's binding site such as the carbonyl oxygen of the backbone or a water molecule. This unexpectedly high number of favorable sulfur-protein contacts clearly shows the need of easy and quick ways to quantify this type of interaction.

Based on QM calculations, we developed machine learning models to assess chalcogen bond complexes. Our approach translates interaction geometries into distance-based features, training Random Forest and Artificial Neural Network (ANN) models. Notably, the ANN model showcases promising performance, achieving mean absolute errors below 2% (or 0.5 kJ/mol). The ANN's ability to capture non-linear relationships within the data offers enhanced predictive power, making it a valuable tool for the evaluation of chalcogen bond interactions. With sufficient data, this approach can be applied to other types of interactions. Our next step involves integrating these models into docking programs for virtual screening purposes.



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Halogen Bonds as Enzymatic Catalysts

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DNA processing enzymes utilize metal cations (Mg^{2+}) to catalyze either phosphodiester bond making or bond breaking reactions. In DNA endonucleases, Mg^{2+} catalyzes the cleavage reaction by countering the negative charge of the phosphate backbone, thereby rendering it susceptible to attack from a nucleophilic water. Here, we determine whether the Mg^{2+} cofactor can be replaced by an amino acid with halogen bond (X-bond) potential. Halogen bonds have previously been used to engineer proteins that are more thermally stable[1]. The model system we are using for this investigation is mouse endonuclease G (mEndoG). mEndoG is a Mg^{2+} dependent protein with two DNA binding sites to assist in binding four-stranded DNA junctions. One of these sites (the A-site) has a Mg^{2+} that is active for DNA cleavage. Through genetic code expansion[2], we replaced the Mg^{2+} chelating glutamic acid in this A-site of mEndoG with a synthetic halogenated tyrosine (^{X}Y). The resulting halogenated mutant has a different pH activity profile and maintains higher activity in the presence of the metal chelator EDTA compared to wild type enzyme, supporting the concept of a new class of X-bond catalyzed enzymes (cX-Zymes). The second DNA binding site (B-site) lacks a metallocentre and is inactive, but aids in recognition specificity for junctions. We used this site to explore turning a non-catalytic DNA binding site into a catalytic one by utilizing a halogen bond. A tyrosine residue in the B-site was replaced by a ^{X}Y in an mEndoG construct where the A-site had been inactivated. This halogenated B-site mutant was found to be active in cleaving DNA junctions, indicating that we can create new catalytic centers by introducing halogenated amino acids. We are currently investigating the mechanism of this new catalytic center in the normally inactive B-site of mEndoG.

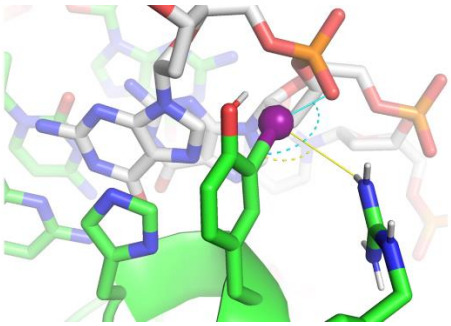

Figure 1. Protein model of halogenated tyrosine in new catalytic center of mEndoG.

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EC9

Thermodynamic and Structural Studies on the Binding of Halogenated Ligands by CK2α'. A Halogen bond Contribution for Different Halogen Atoms.

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Protein kinase CK2 is a serine/threonine protein kinase essential for numerous cellular activities since it may phosphorylate hundreds of proteins in various cell compartments [1]. The main interest CK2 attracts as a target in cancer therapy, although reduction of CK2 also shows antiviral activity [2]. An increasing number of its inhibitors have been reported, a significant number of which are halogenated ligands that bind to the ATP-binding site. Our previous studies on a series of benzotriazole (Bt) derivatives, representing different patterns of halogenation on the benzene ring, revealed that their inhibitory activity reflects their basic physicochemical properties and the binding of variously halogenated ligands is driven by a balance of electrostatic and hydrophobic interactions with a minor contribution of halogen bonding [3, 4].

Changing the model protein from CK2α to its paralog isoform CK2α' resolved the issue of ligand multiposition. In order to correctly measure the halogen bonding contribution, we used a combination of structural (crystallography) and thermodynamic approaches such as isothermal titration calorimetry (ITC) and microscale thermophoresis (MST). We compared ligands with various halogen atom compositions, which barely differed in their primary physicochemical properties, to overcome the predominance of electrostatic and hydrophobic contributions. The structural and thermodynamic data measured for a series of heterogeneously iodinated, brominated, and chlorinated ligands allowed us to estimate the difference in halogen bond energy for these atoms in protein-ligand complexes. This work was supported by the Polish National Science Centre grant 2022/45/N/ST4/02628 and German Research Foundation, grant NI 643/11-1.

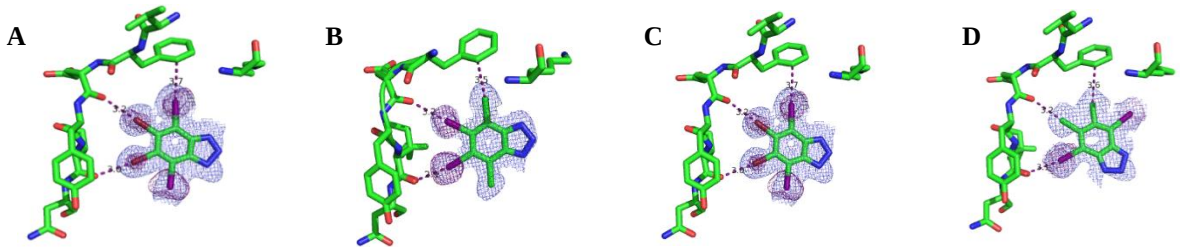

Figure 1. Crystal structure of (A) 5,6-diiodo-4,7-dibromo- (B) 5,6-diiodo-4,7-dichloro- (C) 5,6-dibromo-4,7-diiodo- (D) 5,6-dichloro-4,7-diiodobenzotriazoles in complex with hCK2α'.

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Optimization of Intermolecular Force-field Parameters for Crystal Structure Prediction of Halogen-bonded Materials

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Crystal packing of solids is the key to their physicochemical properties. The desired physiochemical properties can be obtained by tuning the intermolecular interactions and ultimately the molecular packing in the crystal. Theoretical modelling of these molecular solids allows for a better understanding of key material properties such as lattice energy,[1] polymorphism,[2] solubility,[3] and mechanical properties [4]. Both periodic-density functional theory (DFT) and force-field methods are reliable for this purpose. However, the force-field methods offer a preferred alternative when dealing when performing calculations on thousands of crystal structures, with thousands of crystal structures, for instance in the case of crystal structure prediction (CSP), due to the high computational cost of the periodic DFT calculations. The W99 potential developed by D.E. Williams is widely used for CSP of organic molecular crystals containing elements down to the 3rd row of the Periodic table, [5-6] with the latest modifications aimed at improving the description of hydrogen bonding interactions.[7] However, calculating lattice energy becomes more challenging for structures with heavy elements, including those containing halogen bonding interactions.

In this presentation, optimization of W99 force-field parameters for the most susceptible halogen bond donor, iodine, will be reported. The crystal structures of the halogen bonded binary cocrystals will be chosen from the crystallographic database based on the selection criteria like low temperature (<150 K), and high quality (low R-factor and no disorder). Furthermore, we will utilize the experimental sublimation data collected for some of these cocrystals for this specific purpose. The repulsion-dispersion parameters will re-parameterized using the distributed multipoles obtained separately from the gas phase as well as the polarizable continuum model (PCM) model. The newly parameterized force fields will be rigorously validated against a set of co-crystals by obtaining the standard deviation of cell parameters and halogen bond lengths upon lattice energy minimization.

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EC11

Electronic Structure and Stability of Halogen Bonds with Heavy Pnictogen Acceptors: Insights from Experimental Charge Density Studies and Periodic DFT Calculations

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The reliable design of halogen-bonded cocrystals with desired properties depends on a thorough understanding of the energies governing halogen bond formation.[1,2] To analyze the energy (stability) of halogen-bonded cocrystals, we must understand the relationship between energy, geometry and electroninc structure of non-covalent interactions, which can be computed using demsity-functional theory (DFT) calculations. However, DFT results can vary significantly depending on the choice of functional used in the calculations, making it crucial to determine the accuracy of each functional.

Experimentally, understanding the nature of XB interactions between different donor and acceptor atoms involves examining their electronic structure. This is achieved through high-resolution single crystal X-ray diffraction (SC-XRD) measurements, followed by multipole refinement of charge density and interpretation of electron density using Quantum Theory of Atoms in Molecules (QTAIM).[3] In this presentation, I will demonstrate the results of high-resolution XRD measurements on high-quality single crystals involving heavy pnictogen acceptor atoms[4,5] such as phosphorus, arsenic, and antimony (P, As, and Sb). Bond critical point (BCP) analysis will be employed to quantify the charge density within the halogen bonds with various acceptor atoms.

Furthermore, I will discuss the correlations between the magnitude of charge density at the BCPs and the calculated interaction energies, emphasizing the utility of charge density analysis in understanding the stability of halogen-bonded materials. Additionally, an experimental and theoretical correlation of properties at BCPs will be presented. Periodic DFT calculations using different functionals and corrections will be compared with experimental findings. Given that the choice of the computational method significantly impacts the results of the calculations, especially for heavier atoms, this study aims to elucidate reliable methods for DFT calculations and address the associated uncertainties.

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POSTER PRESENTATIONS

P1

Exploring Halogen Bond in Metal Halide Perovskites

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Hybrid organic-inorganic metal halide perovskites (HOIPs) is a class of semiconductors holding a strong potential towards optoelectronic applications (solar cells, LEDs etc). Nevertheless, their environmental and operational stability is not fulfilling, yet, the standards for widespread commercialization. Tremendous efforts have been put on resolving common deficiencies: halogen migration, interfacial reactions, mediocre thermal stability of the organic cations, structural and chemical defects, which contribute to the degradation of the crystalline lattice.

Our approach is targeting both the internal integrity of the HOIPs and the shielding of the exposed surfaces by tuning the electrostatic interactions through halogen bonding (XB). Moreover, this strategy can be expanded to the control of cation-cation interactions within the HOIPs. In the last years, XB-based supramolecular strategies have been implemented to resolve common deficiencies of perovskite-based optoelectronic devices,[1] however little is known about the structure-properties relation. Further, we, recently, shown that halogenation shall expand the available strategies towards phase control of low-dimensional metal halides.[2]

In this context, we design multifunctional organic cations with tunable XB-donating properties to gain access to an atomic/molecular understanding on the self-assembly and properties of crystalline HOIPs. This new supramolecular tool targets the exposed surfaces of the inorganic lattice, rich in undercoordinated halide anions (XB-acceptors), while by tailoring the structure of organic cations, cation-cation XBs enable control over the structure and the photophysical properties of HOIPs.

Acknowledgement. We acknowledge the financial support from the European Union's Horizon Europe research and innovation program, under the MSCA grant agreement No 101059015, acronym HaloCell.

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Halogen Bonding-driven Azobenzene Tautomerism

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Azobenzenes are widely used as photoswitches in light-responsive materials due to their ability to undergo reversible cis-trans isomerisation upon exposure to specific wavelengths of light. In addition, azobenzenes bearing amino or hydroxy groups in para- or ortho-positions show keto-enol tautomerism and can exist as azo (enol) or hydrazone (keto) forms (Figure 1). This tautomerism affects the azobenzene photoisomerisation since cis-hydrazone can rapidly isomerise to trans-hydrazone offering another pathway for thermal cis-to-trans isomerisation.

Tautomerisable azobenzenes show humidity-dependent thermal cis-to-trans isomerisation which has been utilized in humidity sensing [1,2]. Based on computational studies [2], the humidity-sensitivity is attributed to keto-enol tautomerism. Due to the structural differences, the tautomeric forms naturally have different photochemical properties. Interestingly, the hydrazone forms contain keto or imino groups which are expected to be better halogen-bond acceptors than the corresponding hydroxy or (aryl)amino groups of the azo forms. We therefore assumed that halogen-bonding could be used to drive the azo-hydrazone equilibrium towards the hydrazone form which would offer another tool to control the azobenzene photochemistry.

We present results on the computational studies regarding the effect of halogen-bonding on the tautomerism and photochemistry of hydroxy- and aminoazobenzenes. The aim is to design azobenzenes with small enough energy gap between the azo and hydrazone forms to allow cocrystallization in the hydrazone form which is inherently less stable but forms stronger halogen bonds.

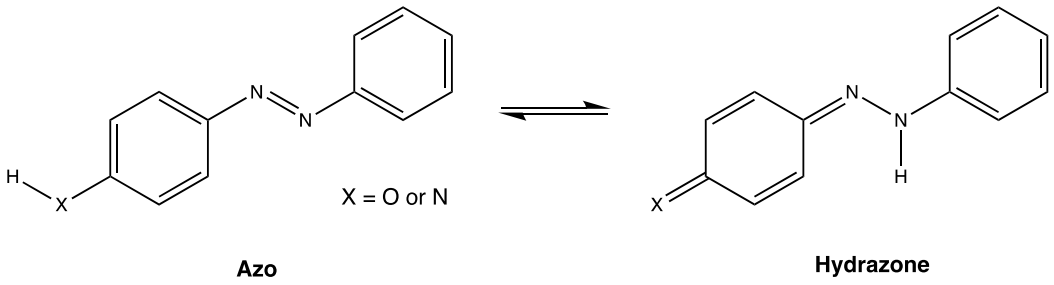

Figure 1. Azobenzene tautomerism showing the azo and hydrazone forms.

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P3

Thioureas – Versatile XB Acceptors

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Besides iodine(I) complexes, our recent research in Jyväskylä has also focused on variety of XB complexes where the sulfur atom acts as XB acceptor [1–3]. Sulfur atom, like oxygen, has two electron pairs in valence *p* orbitals and can accept one, two or even four simultaneous halogen bonds [1,4]. The interest was to study such sulfur acceptors, which do not have a pungent smell and in the most cases thioureas fulfil the criteria. The N–H groups of thioureas are known for their versatile ability to donate HBs [5], which act excellently in anion recognition [6] and in organocatalysis [5,7]. On the other hand the sulfur atoms act as prominent XB acceptors, too [1–3,8].

Around 40 structurally different thioureas, of which half were commercially available, were complexed with five different XB donors in solution in order to get good quality single crystals for X-ray diffraction analysis. The obtained crystal structures of the complexes are discussed together with the most important XB geometries. The Figure 1 depicts a 2:1 XB complex between *N*-methylthiourea and 1,4-diiodotetrafluorobenzene.

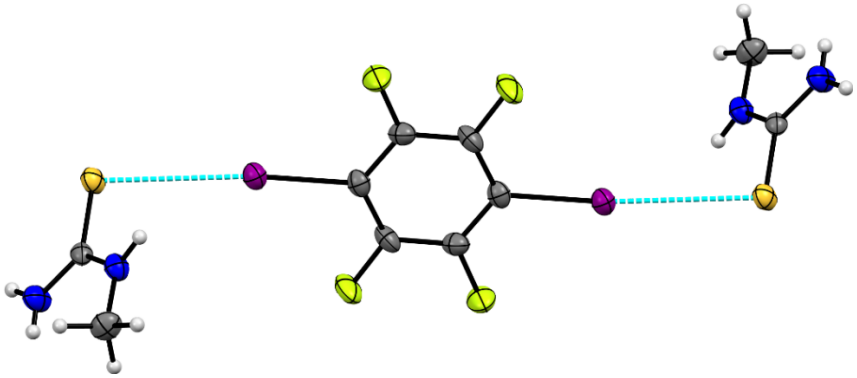

Figure 1. The crystal structure of the 2:1 complex showing the I···S halogen bonds.

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Gold Nanostructure-integrated Conductive Microwell Arrays for Uniform Cancer Spheroid Formation and Electrochemical Drug Screening

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We report gold nanostructure-integrated conductive microwell arrays (GONIMA) that enable both highly efficient uniform cancer spheroid formation and precise electrochemical detection of cell viability. A nanostructured gold on indium tin oxide (ITO) substrate facilitated the initial cell aggregation and further 3D cell growth, while the non-cytophilic polymer microwell arrays restricted the size and shape of the spheroids. As a result, approximately 150 human glioblastoma spheroids were formed on a chip area of 1.13 cm^2 with an average diameter of 224 μm and a size variation of only 5% (±11.36 μm). The high uniformity of cancer spheroids contributed to the stability of electrical signals measuring cell viability. Using the fabricated GONIMA, the effects of a representative chemotherapeutic agent, hydroxyurea, on the glioblastoma spheroids were precisely monitored under conditions of varying drug concentrations (0–0.3 mg/mL) and incubation times (24–48 hours). Therefore, we conclude that the newly developed platform is highly useful for rapid and precise *in vitro* drug screening, as well as for the pharmacokinetic analyses of specific drugs using 3D cellular cancer models.

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P5

New *ortho*-Carborane-based Halogen Bonding Organo-Catalysts

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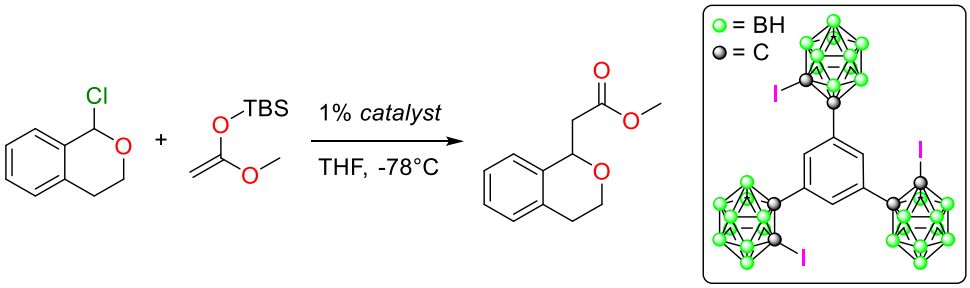
In recent years, halogen bonding (XB) has been thoroughly established as a useful tool in organo-catalysis.[1] By now a wide range of reactions, such as *Diels-Alder*-reactions,[2] *Povarov*[3] and *Nazarov*[4] cyclizations, *Michael*-additions[5] and many more have been catalyzed by the non-covalent interaction[6] of a Lewis-basic substrate and a catalyst bearing positively polarized halogen atoms. Strong polarization of these halogen substituents is commonly achieved by introduction of electron-withdrawing substituents near the halogen substituent, e.g. fluorine, or through introduction of positive charges in the catalyst's backbone. Both approaches come with their own disadvantages though. (Per-) fluorinated materials are persistent pollutants and their environmental and health impact is under scrutiny[7], while charged catalytic systems can suffer from solubility issues or counter-ion exchange, usually reducing reactivity. Pioneering work by *Beau et al*[8] has shown, that C-iodinated (and chalcogenated) carboranes exhibit very pronounced σ-holes. Furthermore, first applications in XB based crystal engineering[9] including carboranes led us to expect reasonable binding – suitable for catalytic application – might also be present in solution.

In this work, we apply ortho-carborane-based catalysts in benchmark halide abstraction reactions, such as the activation of 1-chloro-iso-chromane, in which it surpassed our previously reported neutral syn-substituted fluorinated catalysts.



Scheme 1. Benchmark Test reaction for new XB-catalysts.

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A Combined Halogen- and Chalcogen-Bonding Organocatalyst

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Halogen and chalcogen bonding have been well explored in past decades in supramolecular chemistry, crystal engineering, drug design and biochemistry and in organocatalysis. Our group had developed halogen bond (XB) donors based on the bis-imidazole, bis-benzimidazole and bis-triazole scaffolds which were found to catalyze different reactions namely halide abstraction [1], Michael reactions [2], Diels-Alder cycloaddition [3] etc. Later we developed chalcogen bond (ChB) donors based on bis-benzimidazole and bis-triazole backbone which also catalyzed a wide range of reactions [4].

Until recently, the combination of both XB and ChB in organocatalysis had not been reported. We have constructed a mixed XB-ChB donor system featuring both donor sites [5]. The unsymmetrical backbone consists of a benzimidazolium ring which holds iodine and a triazolium ring which bears tellurium ($\mathbf{3^{R'\text{-}Z}}$). For the very first application, we applied the mixed donor $\mathbf{3^{Oct\text{-}BArF4}}$ in the benchmark Diels-Alder reaction of methyl vinyl ketone and cyclopentadiene. The activity of the mixed system was somewhat similar to the 'pure' XB and ChB donors ($\mathbf{1^{H\text{-}BArF4}}$ and $\mathbf{2^{BArF4}}$). The X-ray crystallographic study of $\mathbf{3^{Bn\text{-}BF4}}$ has depicted the presence of both XB and ChB together in solid state. Iodine and tellurium both showed their corresponding interaction with the fluorine atom of the BF_4 counter-anion.

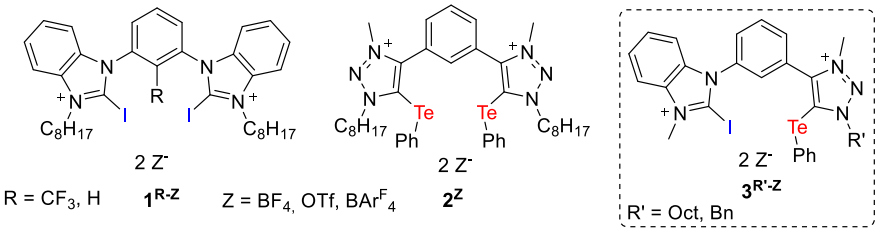

Figure 1. Halogen and chalcogen bond donor systems.

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P7

Evaluation of a Bidentate 'Clamp-Like' Halogen-Bond Donor Motif Based on Iodonium(III) Moieties

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Recently, iodine(III)-compounds have received increased attention as organocatalysts in organocatalysis.[1] It has been proven that the cyclic five-membered diaryliodonium(III) salts (iodolium compounds) are more stable and more Lewis acidic than their acyclic variants or six-membered diaryliodoniums.[2] In 2021, our group reported the first application of bidentate iodine(III)-based XB donor **1**, which exhibited great activity in nitro-Michael reaction, surpassing the arguably strongest iodine(I)-based catalyst.[3] The structure of this thiophene-linked bis(iodolium) barfate is planar and rigid, while the iodine(I)-based donor consists of more flexible motifs.[4]

Within this study, we designed the new 'clamp-like' system **2** that comprises of iodine(III) motifs while featuring a rotational barrier for the preorganization. Providing flexibility to a new bidentate system by connecting cyclic five-membered iodonium(III) moieties to the 1,3-phenylene core we investigated the activity of such a novel system.[5] After confirming the *syn*-conformation of the compound by X-ray crystallography, we evaluated the new XB-donor as a catalyst of a nitro-Michael reaction followed by ^{1}H NMR kinetics.

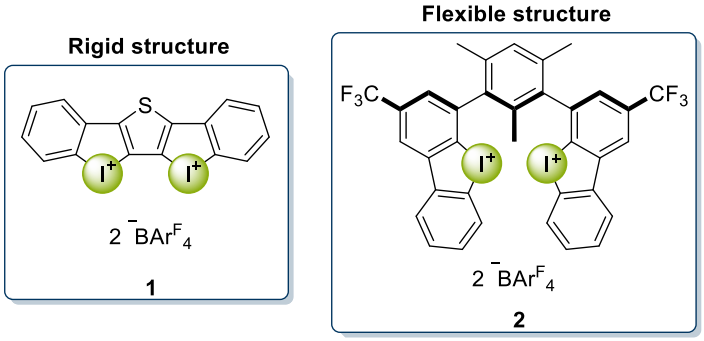

Figure 1. Rigid and 'clamp-like' bidentate iodine(III)-based catalysts.

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Fast Approximation of Halogen-Protein Interactions Using Neural Networks

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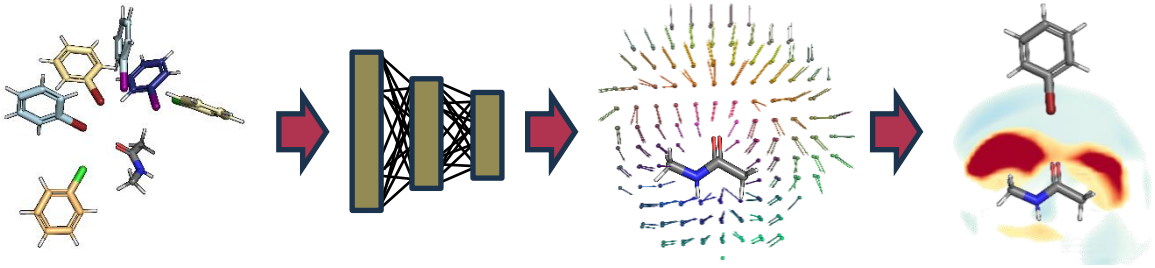
Halogen interactions can be an invaluable tool in structure based drug design due to their highly directional nature which can lead to a greatly increased selectivity[1]. The complexity introduced by this directionality traditionally necessitates a trade-off between runtime and accuracy for scoring functions used in docking programs for high throughput *in silico* screenings[2].

Based on *ab initio* computations at the MP2/TZVPP level of theory between halobenzenes and *N*-methylacetamide, multiple neural network architectures are systematically trained and evaluated for their accuracy and runtime. To achieve runtimes comparable to traditional simple but ultra-fast scoring functions (e.g. ChemPLP[3]), we adapt the networks architecture and training to reflect the common split of slower, receptor-based pre-computation and fast ligand pose evaluation during the actual docking.

The resulting scoring functions are assessed based on their accuracy in reproducing QM-derived results and their improvement of docking outcomes in the PLANTS[3] docking tool.



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P9

Pt–Bi Electrocatalysts Derived from Photoactive Bismuth Oxyiodides

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Hydrogen is one of the most promising energy carriers or storage methods for balancing the intermittency of renewable energy sources, such as photovoltaics and wind power[1,2]. Water splitting is the simplest method for converting renewable energy into hydrogen because it requires only an electrical energy source and abundant water[3]. The durable Pt-based electrocatalysts for glycerol oxidation reaction (GOR) remains challenging because of the inactivation of Pt sites by OH^- absorption under oxidative conditions. In this study, Bi-based Pt was synthesized using Bismuth oxyiodides (BiOI) as a photoactive intermediate for the photoelectrodeposition of Pt. The proposed Bi-based Pt electrocatalysts consisted of PtBi alloy and Pt nanoparticles on a Bi basis. Consequently, it enables the operation in low onset potential for GOR with a high mass activity of 0.3 A mg^{-1} at 0.6 V_{RHE} in alkaline solution.

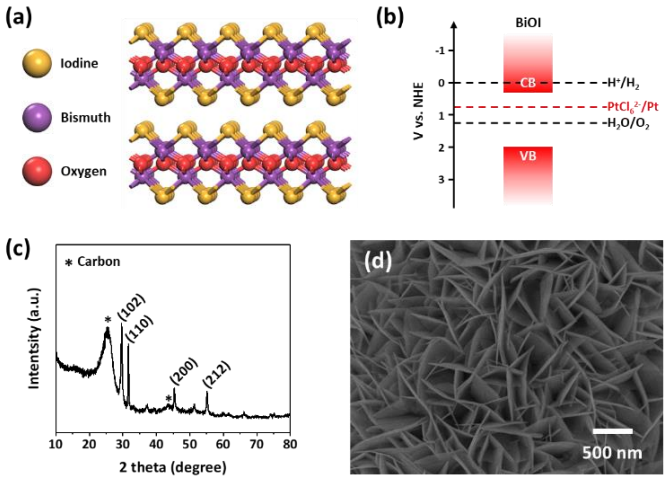

Figure 1. (a) Crystal structure of BiOI and (b) conduction and valence band levels of BiOI. (c) X-ray diffraction pattern and (d) SEM image of the electrodeposited BiOI on carbon cloth.

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Towards Cocrystals with Hexagonal Topology

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Porous materials are one of the research topics in contemporary crystal engineering. Over the years there have been a multitude of reports on metal-organic frameworks (MOFs) and covalent organic frameworks (COFs) [1]. Recently a new area of interest has emerged with the desire to obtain such materials, but stabilized not by strong ionic or covalent bonds, but by somewhat weaker secondary bonding interactions, of which hydrogen bonds (combined with π-stacking) are most exploited. Other interactions, for example halogen bonds (XBs), although less frequently, are also studied and a few papers have already been published [2].

The aim of our research was to obtain cocrystals of neutral components whose crystal structures would have 2D hexagonal topology (analogous to a honeycomb). We chose three symmetric tritopic XB acceptors **tmt**, **tpt** and **Im3**, and a selection of di- and tritopic XB donors, e.g. **tftib** (Figure 1). Cocrystallization of **tmt** with **tftib** from benzene gave crystals with the desired hexagonal topology (Figure 1). The crystal structure contained flat layers with each molecule connected to three others *via* N···I XBs. This is an important result because **tftib** usually forms two such interactions and the third iodine atom remains either uncomplexed or engaged in forming other (weaker) interactions [3]. Benzene molecules perfectly filled the spaces in the crystal lattice facilitating the formation of a honeycomb architecture (Figure 1). Three other examples of such crystal structures will be presented on the poster during the conference.

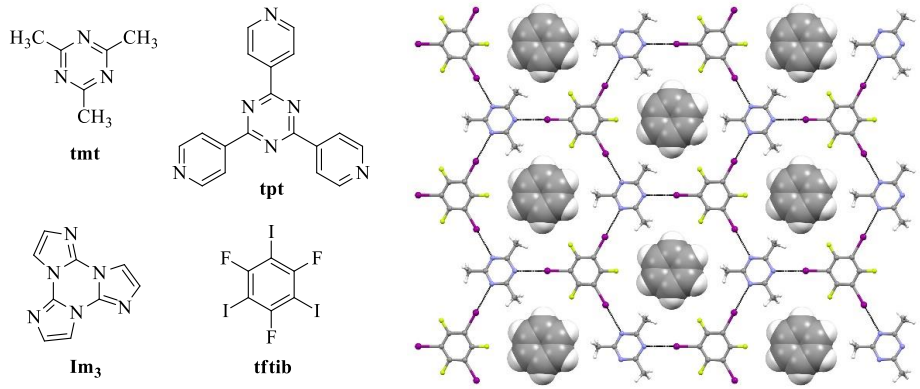

Figure 1. Structures of XB donors and acceptors (left) and crystal structure of **tmt–tftib** (right).

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P11

Investigating the Binding Modes of Halogenated Fragments in JNK2 and JNK3

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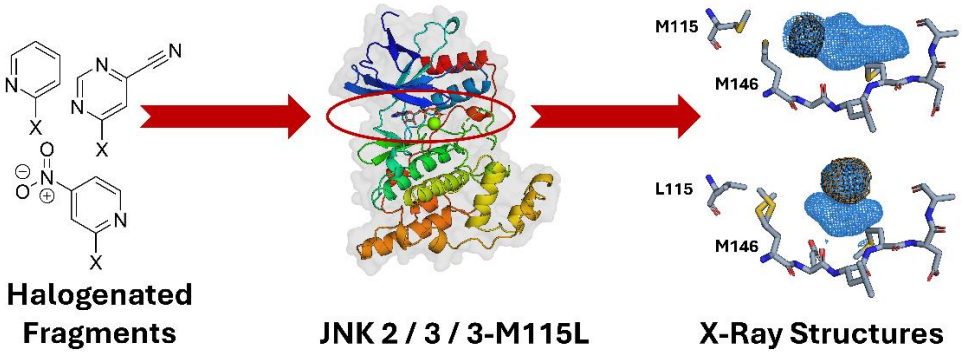
Screening of our previously developed Halogen-enriched Fragment Library (HEFLib) against various targets identified a trend in hits towards compounds with strongly tuned halogen atoms [1,2]. This led to the generation of a new V_{max}-tuned HEFLib. Using STD-NMR, both libraries were screened against the c-Jun N-terminal kinases (JNK) 2 and 3, which share a nearly identical binding site including a gatekeeper methionine (M146). In previous work, we observed a chalcogen bond between M146 and an adjacent M115 in JNK3 [3]. This interaction is precluded in JNK2, due to the naturally occurring leucine residue at the corresponding position. Hits were validated using isothermal titration calorimetry (ITC).

The ITC results indicate a binding preference for JNK2 over JNK3. As crystallization of JNK2 is challenging, we created a JNK3-M115L mutant to test if this would be a sufficient JNK2 model. The binding affinity of the compounds against JNK3-M115L shows an increase when compared to JNK3, but not to the same extent as against JNK2.

Moreover, we obtained multiple high-resolution crystal structures of JNK3 and JNK3-M115L with anomalous signal to unambiguously identify the halogen's coordinates. Within these structures, we observed both halogen and chalcogen bonding with the gatekeeper methionine.

We are currently calculating the binding energy of the obtained crystal structures to better understand the effect of the Met-Met interaction in JNK3 and whether this can explain the selectivity for JNK2.



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Fragment Screening of USP7 with the HEFLib and the V_{max} HEFLib

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Ubiquitin specific protease 7 (USP7), also known as herpes-associated ubiquitin-specific protease (HAUSP), is one of approximately 100 deubiquitinating enzymes (DUB) that removes ubiquitin and protects substrate protein from degradation [1]. It has turned out to be a potential therapeutic target due to its regulation of p53-pathway components, including the oncogene MDM2 and tumour suppressor p53 [2]. USP7 stabilises MDM2 and provides decreased levels of p53 in a normal cell [3,4]. Consequently, inhibition of USP7 leads to MDM2 degradation and ultimately p53 activation [5].

Therefore, we perform fragment screening with our diversity-optimised Halogen-enriched fragment library (HEFLib) [6] and our newly developed V_{max} optimised HEFLib (V_{max} HEFLib) by using the catalytical domain of USP7 (208–560) in biophysical experiments like Differential Scanning Fluorimetry (DSF) and Saturation Transfer Difference-Nuclear Magnetic resonance (STD-NMR). The HEFLib consists of 198 fragments and is characterised by diverse binding motifs. It is not specifically adapted for a certain target protein. Our second screened library is the V_{max} HEFLib currently including 39 compounds and will be extended soon. The focus of this library was to tune the V_{max} value for the employed halogen atom significantly by using electron-deficient scaffolds and electron-withdrawing substituents to foster the potential strength of the resulting halogen bonds. Compounds that exhibited a significant shift in DSF or showed interacting proton peaks in the STD-NMR were further analysed with additional experiments like intact protein mass spectrometry or Ubiquitin-AMC assays. Interestingly, most of the tested compounds show a negative shift in DSF indicating a destabilisation of the protein. At present our main effort is to obtain crystal structures of the modified protein.

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P13

Ternary Halogen-bonded Cocrystals Based on a Werner Nickel(II) Coordination Compound

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In recent years, the design and synthesis of binary cocrystals has been established by utilizing specific intermolecular interactions and therefore the knowledge of supramolecular synthons. However, the targeted synthesis of higher-order cocrystals remains a challenging task, since it is more complex to balance three or more components and to control specific interactions in a crystal [1,2]. According to available structural data in the Cambridge Structural Database, there have been only 10 ternary cocrystals reported so far, formed exclusively by halogen bonds [3]. Those cocrystals are based on small organic molecules which serve as a halogen bond acceptor and two perhalogenated molecules as halogen bond donors.

Herein we report the first study of ternary metal-organic cocrystals based on the Ni–NCS···I halogen bond motif. We have prepared four ternary cocrystals by mechanochemical and solution-based synthesis using a Werner Ni(II) coordination compound, Ni(4-methylpyridine)$_4$(NCS)$_2$ – **1**, and classical perhalogenated halogen bond donors: 1,3-diiodotetrafluorobenzene (**13tfib**), 1,4-diiodotetrafluorobenzene (**14tfib**) and 1,3,5-trifluoro-2,4,6-triiodobenzene (**135tfib**). The prepared ternary cocrystals were compared with three previously synthesized binary cocrystals containing the same halogen bond donors. For all cocrystals, both binary and ternary, dispersion-corrected periodic density-functional theory (DFT) calculations were performed in plane-wave DFT code CASTEP [4]. Isothiocyanate sulfur in **1** proved to be a very good and dependable halogen bond acceptor species capable of forming multiple halogen bonds, enabling the formation of ternary cocrystals via synthon hierarchy or shape-size mimicry approaches.

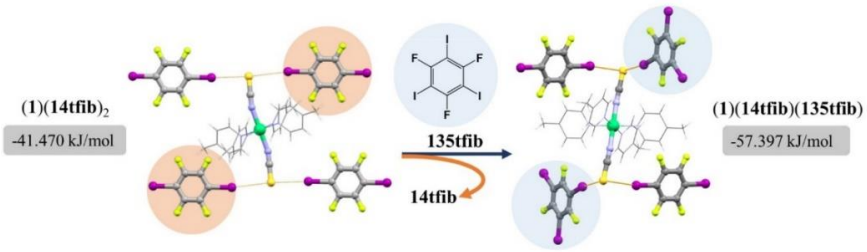

Figure 1. Cocrystal formation energies for (**1**)(**14tfib**)$_2$ (binary) and (**1**)(**14tfib**)(**135tfib**) (ternary cocrystal)

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Utilizing Artificical Neural Networks (ANNs) for the Evaluation of Halogen-π Interactions

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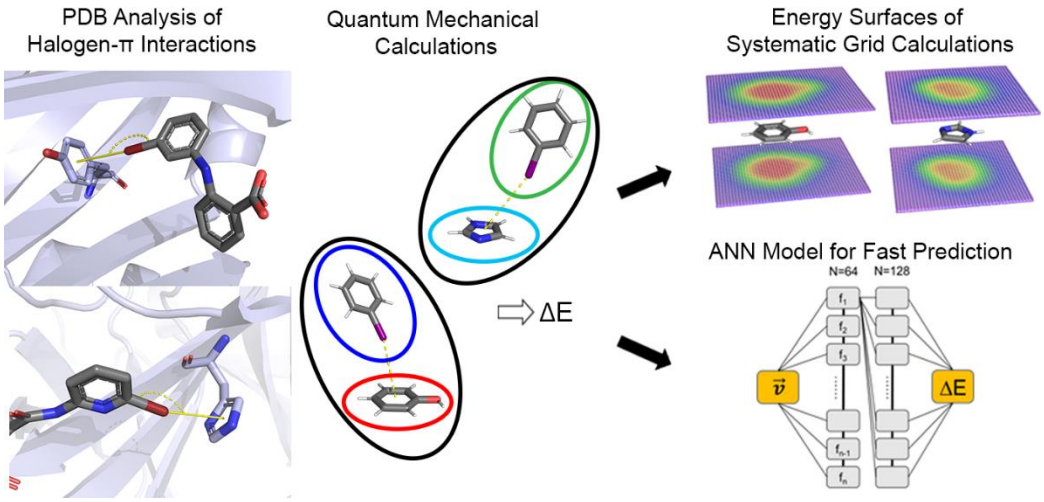
Halogen bonding (XB) has become an important aspect in modern drug design. It has been shown that halogen bonding can yield a beneficial contribution to protein-ligand binding [1,2]. In recent years, we have integrated various QM-derived scoring functions into the drug discovery process, to accelerate the assessment of halogen bond interactions in molecular design [3,4]. While the relevance of π -systems (aromatic side chains of tyrosine, phenylalanine, histidine, and tryptophan) as XB acceptors has been highlighted [5], a systematic assessment of their potential for drug discovery is still pending.

Based on systematic quantum mechanical calculations, we developed machine learning models utilizing ANNs to evaluate these interactions. Their geometries are transformed into distance- and angle-based features used for the training process. Extensive training, hyperparameter tuning, and cross validation enabled our ANNs to accurately predict the energy profiles of halogen-π interactions, achieving errors of less than 0.3% (MSE of 0.02 kJ/mol), offering a robust computational tool for studying these crucial non-covalent interactions.



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P15

Computational Energy Analysis of Halogen Bond Dependent Enzymatic Catalysis

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The use of halogen bonds (XB) in biological systems has revealed exciting new applications for protein design. Previously, we had shown that halogen bonds can be utilized to increase the thermal stability of proteins and to create new protein-protein interfaces [1, 2]. Our recent findings demonstrate that the catalytic magnesium in mouse endonuclease G (mEndoG) can be replaced with a halogenated amino acid to catalyze DNA cleavage. We have shown that incorporating a XB into the active site via 3-halo-tyrosine results in a catalytically active endonuclease, with reduced metal dependence and mechanistic characteristics that are distinct from the wild type enzyme. We have thus demonstrated that a new class of catalytic halogen bond dependent enzymes (cX-Zymes) can be designed with unique and tunable properties.

At this point, we aim to further elucidate the mechanism of halogen bond dependent enzyme catalysis in mEndoG. We are using quantum mechanical calculations to explore in greater detail how the energetic components of noncovalent interaction energies allow halogen bonds to catalyze the DNA cleaving reactions in the active site of the cX-Zymes. Computing the interplay between the halogenated tyrosine and its active site neighbors will establish the energetic foundations for the unique potential of utilizing halogens in protein design.

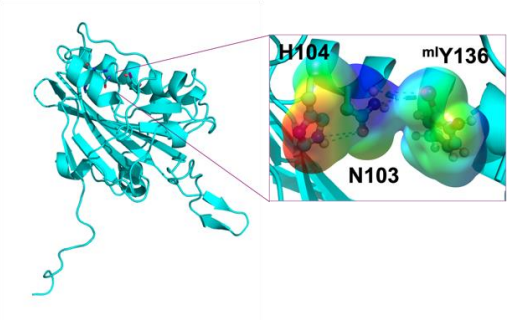

Figure 1. The active site of ^{ml}Y-EndoG, adapted from H97A mEndoG (PDB ID 6NJU, [3]), with QM calculated electrostatic potential (ESP) surfaces mapped to the total density of key active site residues. The map shows surface ESP from -62.8 kcal/mol (red) to 38.1 kcal/mol (blue).

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Inter-anion Chalcogen Bond Interactions

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Non-covalent interactions have been a point of thorough investigation over the last decades. Still, some unexpected properties keep emerging to this day. Recently, the possibility of non-covalent interactions between similarly charged ions has started to gain attention. The existence of such "anti-electrostatic" hydrogen bonding synthons has already been discussed in several theoretical publications[1] and later supported by experimental findings.[2] However, the studies on their halogen (XB) and chalcogen (ChB) counterparts are rather scarce. First theoretical considerations have been put forward in the recent years[3], but the amount of empirical data remains limited.[4]

Herein, we present one of the first examples of inter-anion chalcogen bonding in the solid state. The studied system is based on an anionic cyclopropanide moiety which has been previously utilized in our studies regarding "anti-electrostatic" interactions.[5]

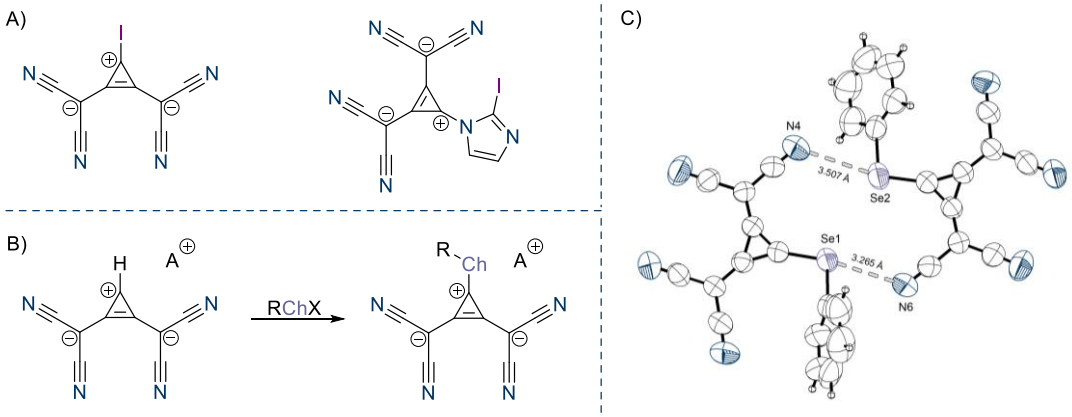

Figure 1. (A): Known "Anti-electrostatic" XB donors. Synthesis (B) and solid-state structure (C) of the novel cyclopropanide-substituted ChB donor.

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P17

Experimental Evaluation of the Thiol Reactivity of Halogen-Enriched Fragments in Drug Design

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Fragment-based drug discovery is a valuable tool for the identification of novel, binding ligands [1]. We conceived a Fragment Library containing a variety of diverse Halogen-Enriched Fragments (HEFLib) to investigate the potential of halogen bonding in the early stages of drug discovery [2-4]. Our investigations with the HEFLib revealed that a higher V_{max}-value, representing a stronger potential for the formation of a halogen bond, correlates with higher hit rates in the screening procedures [2, 3]. It is possible to increase the V_{max}-value of a halogenated fragment by adding electron-withdrawing groups or additional heteroatoms in the aromatic core system [5]. However, the decrease in electron density in the (hetero)arene increases the potential for unintended nucleophilic aromatic substitution reactions (S_NAr). This higher reactivity could lead to reactions with nucleophiles in the biological environment such as glutathione (GSH) or cysteine in proteins (Figure 1), which could result in rapid degradation of the fragment or toxic side effects. Therefore, when working with halogen-enriched fragments (HEF), it is crucial to investigate the boundaries between highly tuned, stable HEFs and promiscuously arylating fragments.

For this purpose, we calculated the V_{max}-values of a series of potentially reactive HEFs. We then experimentally evaluated their cysteine reactivity using an HPLC-UV-based GSH assay. Finally, we compared the experimental S_NAr-reactivities with the QM-calculated V_{max}-values.

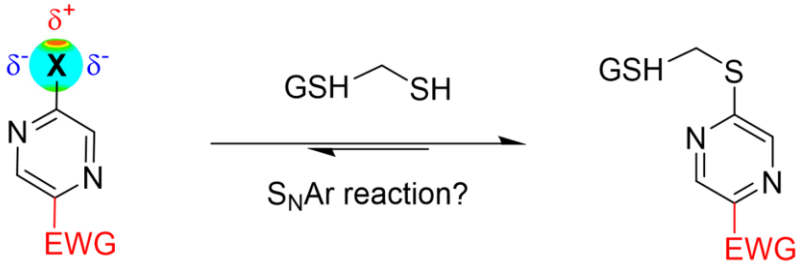

Figure 1. Potential S_NAr-reaction of a tuned halogenated fragment with glutathione.

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Halogen Bonding as a Tool for Assembly of Aromatic Electron Donors and Acceptors

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When aromatic electron donors are in proximity to aromatic electron acceptors, the resulting electron donor-acceptor (EDA) complex can elicit spontaneous charge transfer (CT). Photoexcitation of this CT state can provide access to a rich array of photochemical initiated reactions. Because the π-π stacking attractions between electron rich and electron poor aromatic rings can be fairly weak, the study of CT behavior of these types of EDA complexes in solution can be challenging. One strategy to overcome this is to tether donors and acceptors together via covalent bond or non-covalent interactions in a manner that allows them to interact through space in a predictable fashion. In the current study, we demonstrate several strategies for bringing donors and acceptors together for optimal CT. Covalent bridging and transition metal coordination of properly designed arylene ethynylenes provide access to high concentrations of CT complexes, as evidenced by UV-vis spectroscopy. Current work extends this avenue of study to EDA complexes held together via halogen bond. The directionality of the halogen bond helps bring donor and acceptor components together in a predictable fashion. The lability of the halogen bond interaction—relative to covalent attachment—provides opportunities for donors and acceptors to dissociate after photoexcitation of the CT state.

P19

Halogen Bond Contribution to the Gibbs Free Energy in a Well-defined Protein-ligand System

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In this work, the catalytic subunit of human kinase hCK2α' and two series of perhalogenated 1-*H*-benzotriazole derivatives are used as models to determine the thermodynamic contribution of a single halogen bond to the Gibbs free energy of binding (ΔG°). Questions concerning the thermodynamic contribution of halogen bonds remain unresolved. Ongoing discussions range from describing halogen bonds as interactions driving ligand binding to completely dismissing their importance.

Our rigorous experimental approach involved introducing small perturbations to a well-described protein–ligand model and observing the effect of these changes on the binding affinity. In the first approach, we obtained derivatives carrying fluorine atoms in the vicinity of bromine (Fig.1). By introducing fluorine, we aimed to increase the electron density anisotropy on bromine atoms, thereby inducing the formation of halogen bonds. However, high-resolution crystal structures obtained for complexes with hCK2α' indicated heterogeneous binding modes within the active site, which made further quantitative analyses impossible. In the second approach, a series of bromo-chloro perhalogenated derivatives with similar hydrophobicity and electrostatic properties were obtained (Fig. 2). Such a series was designed to demonstrate homogeneous binding modes inside the active site of hCK2α', which was confirmed by appropriate crystal structures. The thermodynamic data obtained with the use of microscale thermophoresis lead to the thermodynamic contribution of a single halogen bond to the Gibbs free energy estimated to ~ 2.0 kJ/mol.

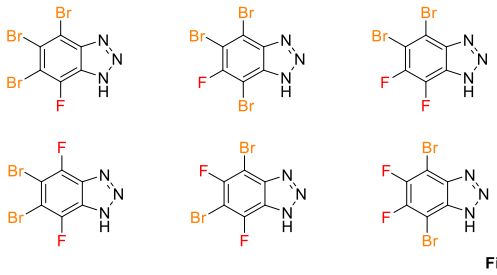

Fig. 1

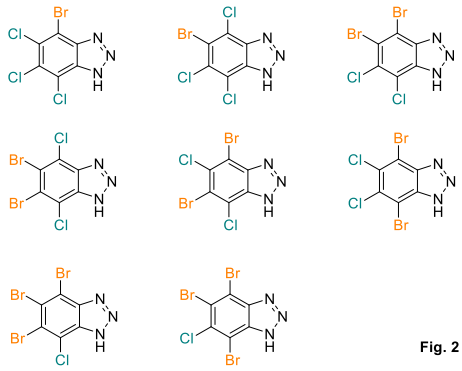

Fig. 2

Acknowledgement. This work was supported by Polish National Science Centre, grant 2022/45/N/ST4/02628 to SK and German Research Foundation, grant NI 643/11-1 to CW

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Lanthanide Coordination Compounds with Isothiocyanate Ligands in Crystal Engineering of Halogen-bonded Cocrystals

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Although crystal engineering initially focused on molecular solids composed of organic synthons, contemporary research increasingly emphasizes metal-organic compounds as building blocks in multicomponent systems. This shift is due to the desirable and tunable magnetic, optical and catalytical properties of systems containing metal ions. [1] It is precisely these properties that elevate *f*-block metals, particularly lanthanides, to prominence.

In this study, we present a new family of halogen-bonded solids, cocrystals containing lanthanide coordination compounds. Our objectives are to explore novel metal-organic cocrystals with lanthanide complexes featuring geometries that are normally not accessible to coordination compounds of a lower coordination number and to evaluate isothiocyanato (NCS^-) ligands as halogen bond acceptors in high coordination number complexes. This follows our previous research on hexacoordinate metal complexes with chlorido ligands as acceptors [2]. The cocrystals were prepared by combining [**Ln**$\mathbf{L}_3(NCS)_3$] coordination compounds (**Ln** = La, Ce, Pr, Nd; **L** = 2,2'-bipyridine or 1,10-phenanthroline) with perhalogenated halogen bond donors. Structural characterization was done using X-ray diffraction (SCXRD and PXRD) and thermal analysis (TG-DSC).

The obtained crystallographic data facilitated an in-depth analysis of the supramolecular architectures present in the systems, revealing different topicities and geometric dispositions of donor and acceptor atoms involved in halogen bonding.

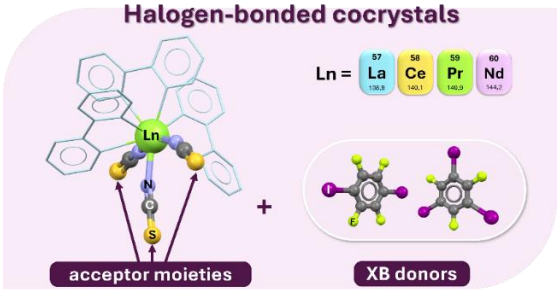

Figure 1. Cocrystallization of lanthanide coordination compounds with halogen bond donors.

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P21

Modular Bidentate Catalysts as a Strategy to Enable Enantioselective Halogen Bonding Catalysis

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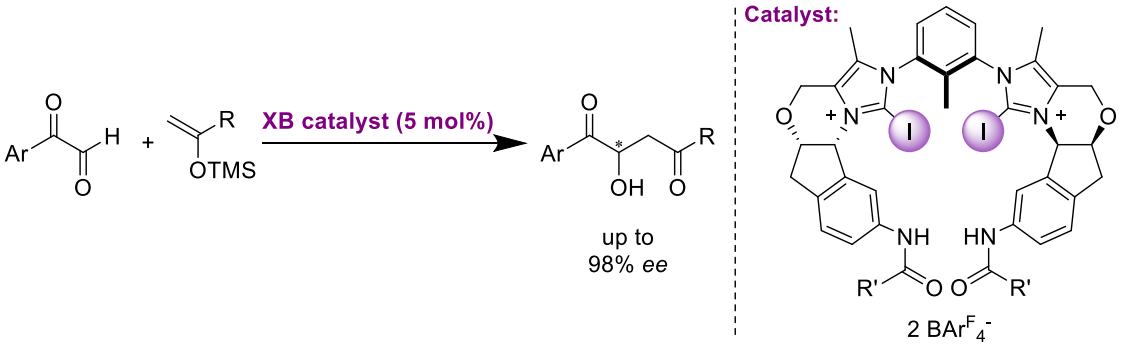
Chiral halogen bonding organocatalysts have already been reported from 2012 on [1]. Most reports on high enantioselectivity were achieved by bifunctional catalysts [2]. Yet the relative importance of halogen bond (XB) is hard to elucidate in these cases, and thus our aim was to develop a proof-of-principle catalyst which acts predominantly through XB. In 2020, our group introduced a chiral bidentate bis(iodoimidazolium)-based catalyst and obtained a modest enantiomeric excess (*ee*) of 33% in a Mukaiyama aldol reaction [3]. Later, the Garcia-Mancheño group achieved a high *ee* of 90% by introducing an iodine substituent into the substrate [4].

Based on the previous studies on the Mukaiyama aldol reaction, we aimed to improve the catalyst system through modular modification to synthesize structurally different catalysts. Various amide-substituted XB donors were thus generated through the derivatization of the catalyst, and this led to an improved *ee* of up to 98% in the Mukaiyama aldol addition to arylglyoxals. We also carried out comparison experiments using non-iodinated species to understand the relevance of XB donors in the catalytic activity and selectivity of the process.



Scheme 1. Mukaiyama aldol reaction catalyzed by chiral XB donor.

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Halogen Bond Architectures in Cocrystals of Organomercury Compounds

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Although there are a number of organometallic compounds in the Cambridge Structural Database used as halogen bond acceptors [1], they account for only 24.4 % (85 data sets) of total halogen bonded multicomponent systems with metal-organic compounds and perhalogenated donors. They mostly correspond to organoplatinum (29 data sets), organogold (16 data sets) and organoantimony compounds (8 data sets). Most of these systems correspond to metals with one or more halide or pseudohalide ligands that are halogen bond acceptors, and include metallocenes, while there are no multicomponent halogen bonded systems containing organometallic building blocks with a pyridine moiety bound to the metal center by a carbon-metal bond.

To address this issue in this work we explore the potential of a simple organomercury building block, bis(pyridin-4-yl)mercury, that has peripherally located pyridyl nitrogen atoms, as a reliable halogen bond acceptor. Using both mechanochemical and solution-based method, we cocrystallized it with selected perhalogenated halogen bond donors: 1,2-diiodotetrafluorobenzene (**12tfib**), 1,3-diiodotetrafluorobenzene (**13tfib**) and 1,4-diiodotetrafluorobenzene (**14tfib**). In total, four cocrystals were obtained and characterized by single crystal X-ray diffraction. Structural analysis revealed that the I···N halogen bond is dominant in the cocrystals, with the overall architecture reliant on the stoichiometry and geometry of the donor used.

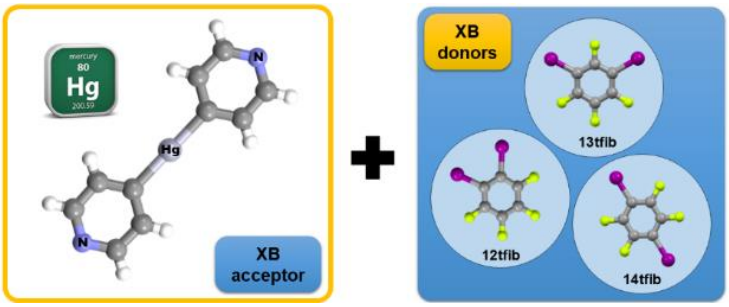

Figure 1. Cocrystals of the (**4-py**)$_2$**Hg** acceptor with halogen bond donors.

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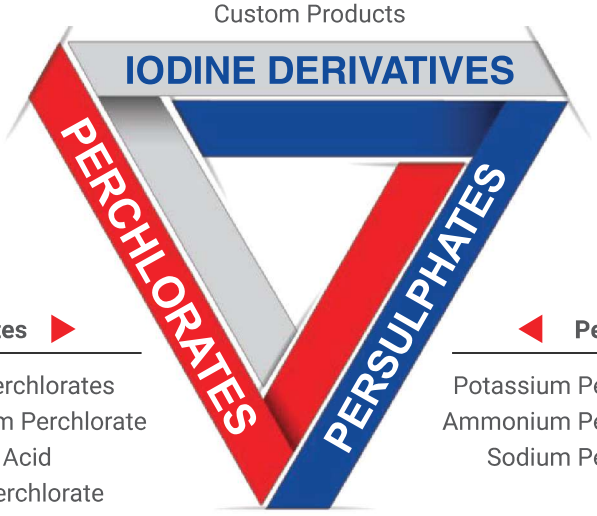

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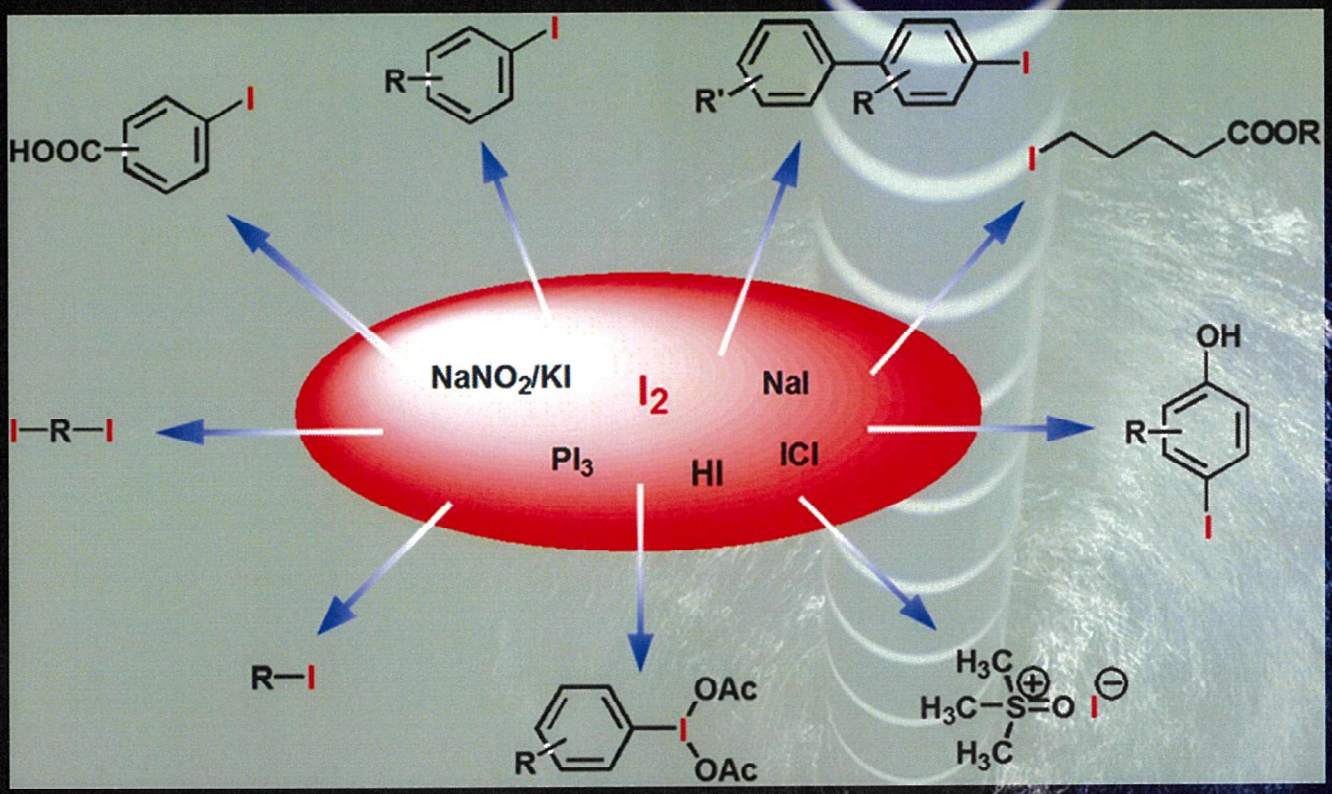

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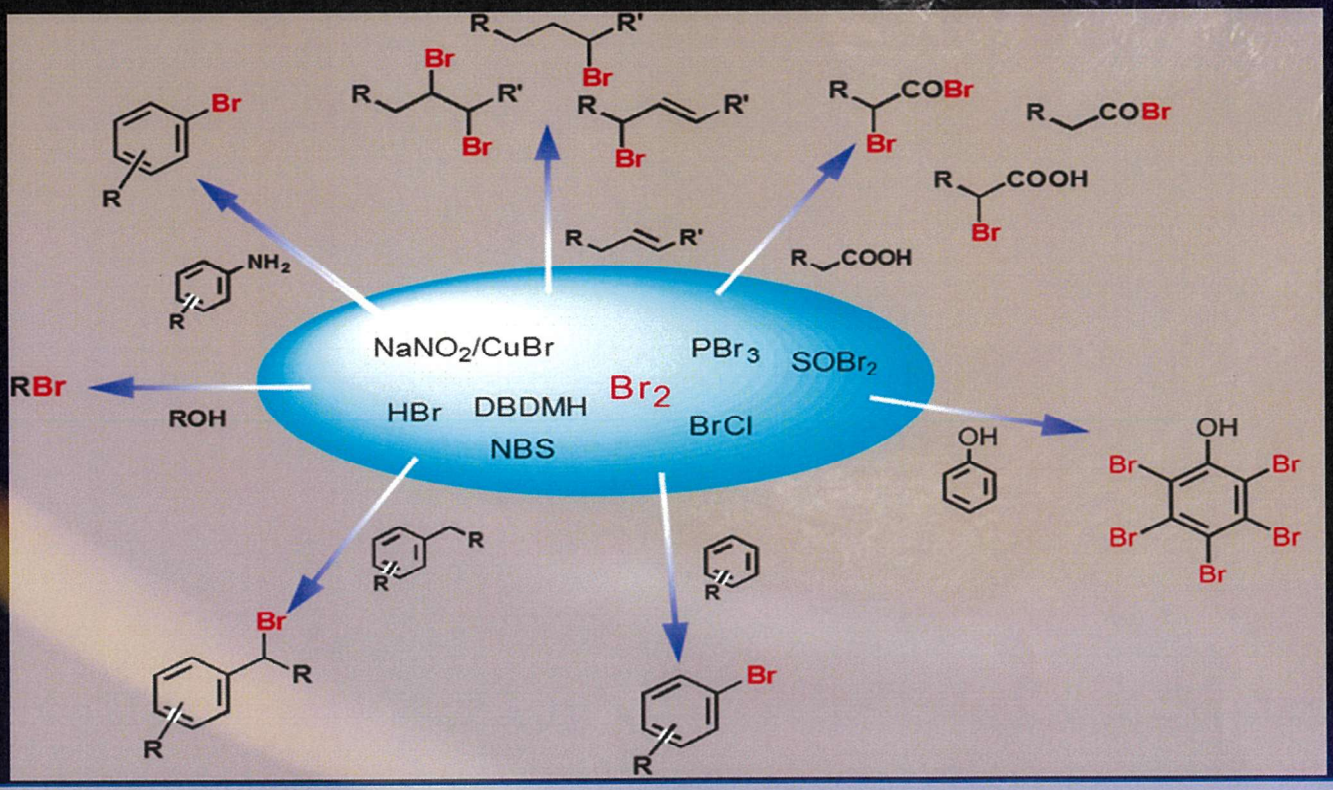

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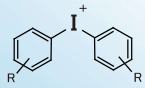
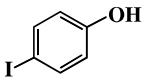




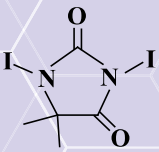
HI

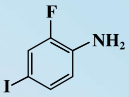
LiI

Iodine compounds

CsI

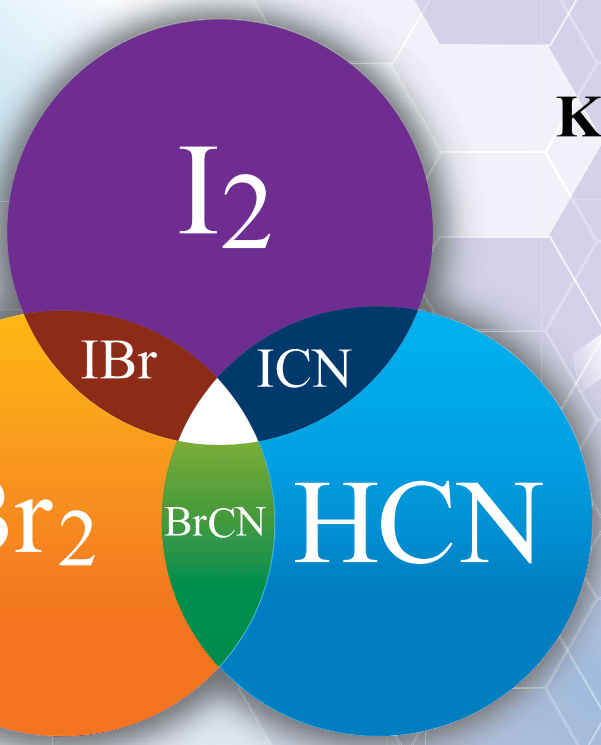
H_5IO_6





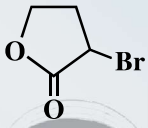
CH_3I

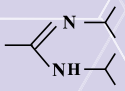
KI

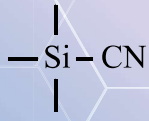


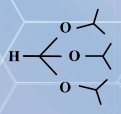
Bromine compounds

Cyano derivatives









Key Reactions

- Cyanation
- Esterification
- Halogenation
- Sandmeyer reaction
- Friedel-Craft reaction
- Hydrolysis
- Pinner reaction
  - Orthoester
  - Amidine
- Heterocycle compound formation
- Suzuki coupling

NIPPOH

NIPPOH CHEMICALS

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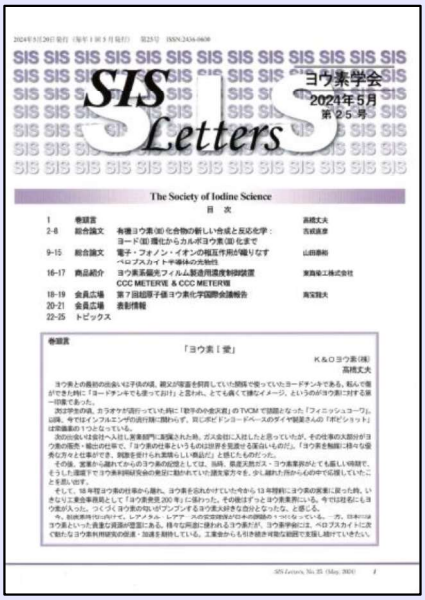
NIPPOH CHEMICALS

ヨウ素学会

SIS the Society of Iodine Science

The Forum on Iodine Utilization was established to contribute the development of Iodine science and industry with the cooperation of the academia, the industry and the government in June 1998. The forum steadily expanded its activities and was reorganized into the Society of Iodine Science (SIS) in July 2007.

The SIS holds the annual symposium, lecture meetings and publishes news letters and books related to iodine. The SIS subsidizes the iodine researches and presents awards each year.



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