CHEMISTRY

The researchers are sorted into research areas. In chemistry we distinguish between Theoretical, Biological, Analytical, Organic, Nucleic Acid and Medicinal Chemistry. Researchers from physics and pharmacy also offer projects within chemistry.

Theoretical Chemistry

Biological Chemistry

Environmental Chemistry

Organic Chemistry

Nucleic Acid Chemistry

Medicinal Chemistry

Supervisors from other research areas

You can find a description of these researchers in the designated catalogue.

Associate Professor Erik D. Hedegård

Topics: Theoretical chemistry, inorganic chemistry, bio-molecules, and enzymes

SDU

Focus of the group

See also https://erikh.gitlab.io/group-page/

- Development of theoretical methods for transition complexes
- Development of theoretical methods for (metallo)enzymes and chemistry in solution
- Theoretical / computational investigations of enzyme mechanisms and metal-containing drugs

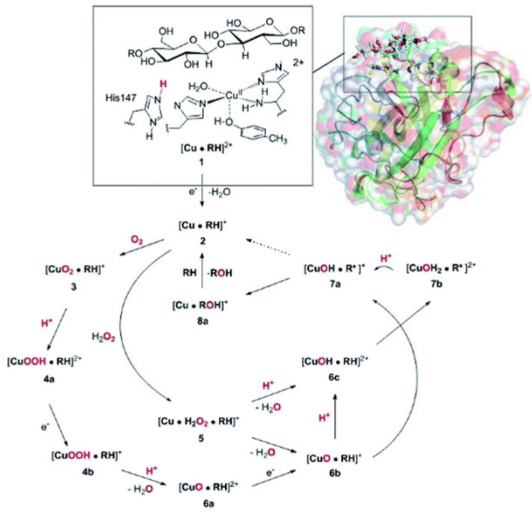
***Examples** of systems we currently investigate (see boxes 1–3):*

1. *Metalloenzymes – mechanism and spectroscopy*
2. *Light-activated chemotherapy*
3. *Bio-mimetic complexes*

1. Metalloenzymes

We employ hybrids of QM and classical methods to investigate LPMOs – a newly discovered class of enzymes used in bio-fuel production

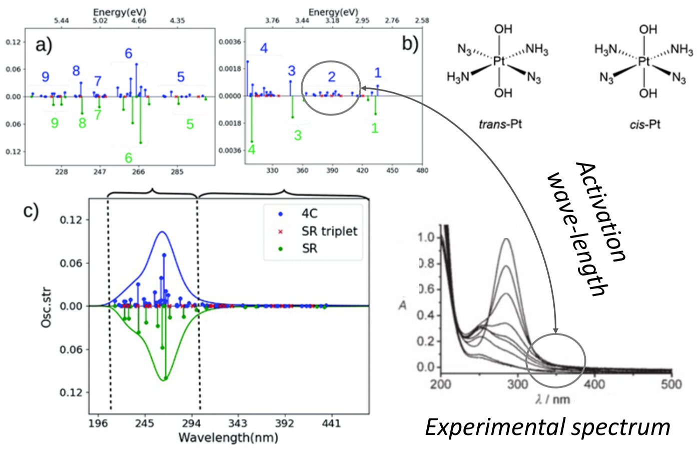
Calculated mechanism (Hedegård & Ryde, Chem. Sci. 2018)



2. Light-activated chemotherapy

We employ relativistic quantum chemical methods to investigate transition metal complexes that can be light-activated into anti-cancer agents

***Blue:** calculated (relativistic, spin-orbit) UV-vis*
***Green:** calculated (relativistic, no-spin orbit) UV-vis*
(Creutzberg & Hedegård, PCCP, 2020)

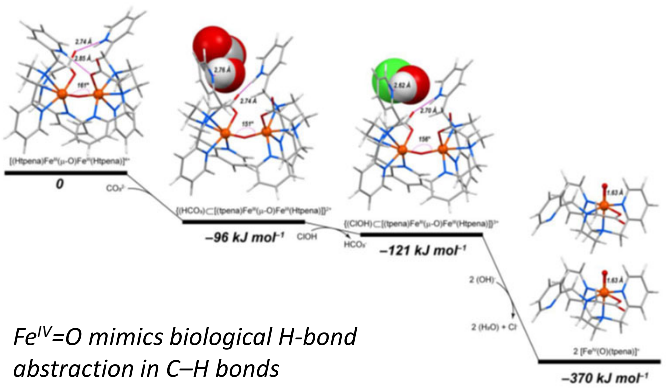


Experimental spectrum

3. Bio-mimetic complexes

In collaboration with experimental groups, we investigate smaller inorganic complexes, mimicking actual enzymes

Calculated mechanism for binding of CO_3^{2-} to an iron-complex, replacement of CO_3^{2-} with HOCl, and formation of Fe^{IV}=O species (McPherson et al. submitted, 2021)



Fe^{IV}=O mimics biological H-bond abstraction in C–H bonds

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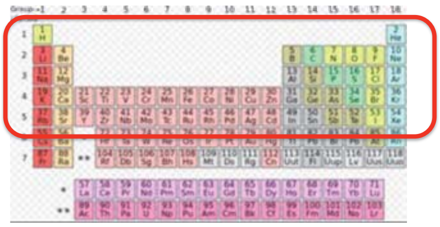
Professor Hans Jørgen Aagaard Jensen

Topics: non-relativistic (DALTON) and relativistic (DIRAC) quantum chemistry; MC-srDFT; 4c EPR and pNMR

SDU

http://daltonprogram.org

Computational quantum chemistry for primarily the *upper* half of the periodic table.

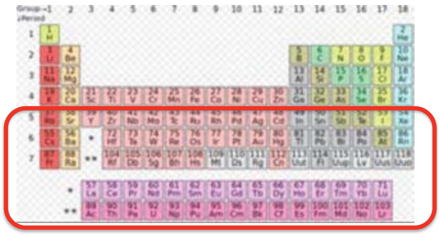


This code is based on the non-relativistic Schrödinger equation.

We develop new, efficient and flexible methods in Dalton, some of them together with Jacob Kongsted. My primary focus is currently on developing the MC-srDFT model described below.

http://diracprogram.org

Computational quantum chemistry for primarily the *lower* half of the periodic table.



This code is based on the relativstic Dirac equation. Relativistic effects are by definition effects which disappear if we artificially increase the speed of light. One example of a relativistic effect is the color of gold: if the speed of light had been the double of what it is, gold would have looked like silver!

We develop new, efficient and flexible metods in Dirac. In 2015 we were chosen by Oak Ridge Naitional Laboratory as one of 13 programs they would hellp optimizie for their supercompter Summit, which was opened for use Jan. 2019 and it is now number 1 in the world.

MC-srDFT – beyond standard DFT

DFT – density functional theory – is today the most used method in computational quantum chemistry. Why? Because DFT often provides sufficiently accurate results without the need of a super computer, in fact many experimental papers are today supplemented with DFT calculations performed on a local work station.

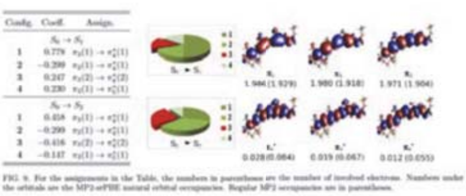
However, there are many cases for which DFT is *not* sufficiently accurate. Examples are typically molecules or processes with a more complicated electronic structure as open *d*-shells of transition metal systems, chemical reactions involving surface hopping, or electronically excited states. These cases are all in principle well described by classical wave function theory (WFT), based on the Schrödinger equation as you learn it in introductory quantum chemistry/quantum mechanics courses. These WFT methods are unfortunately often very expensive, or even unfeasible ☹.

My research idea with MC-srDFT is to combine the best of the two methods, and only use the more expensive WFT when needed. It looks promising ☺

If you want to participate, there are possibilities for projects with method development and implementation; or validation; or applications; or a combination.

FIG. 2. Retinal chromophore.

Example of validation calculations:



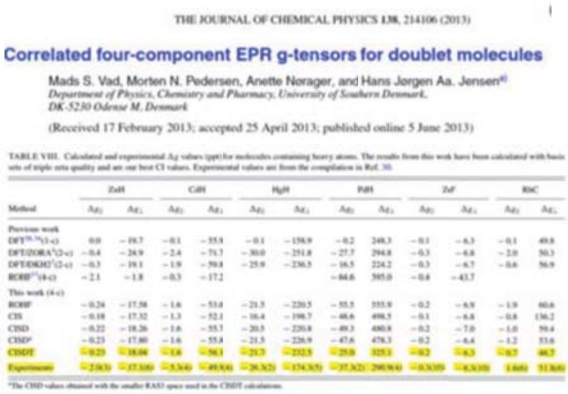
EPR/ESR and pNMR computations

Electron paramagnetic resonance, also called electron spin resonance, is a powerful spectroscopic method for non-singlet molecules as organic radicals and inorganic chemistry involving transition metals with open *d*-shells.

In an EPR/ESR experiment is measured how the electronic structure of the molecule make the g-factor deviate from the value of 2.0023 for the free electron. This deviation is in fact a relativistic effect, so with the pure non-relativistic Schrödinger equation one will always get 2.0023 – not very useful!

My research idea with an EPR/ESR module in Dirac is that using the correct theory for the effect will be the most efficient and most reliable in the long run. This project also looks promising ☺
I hope soon to go on and extend this module to paramagnetic NMR – pNMR.

If you want to participate, there are possibilities for projects with method development and implementation; or validation; or applications; or a combination.



THE JOURNAL OF CHEMICAL PHYSICS 138, 214106 (2013)

Correlated four-component EPR g-tensors for doublet molecules

Mads S. Vad, Morten N. Pedersen, Anette Norager, and Hans Jørgen Aa. Jensen[a]
Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, DK-5230 Odense M, Denmark

(Received 17 February 2013; accepted 25 April 2013; published online 5 June 2013)

TABLE VIII. Calculated and experimental Δg values (ppt) for molecules containing heavy atoms. The results from this work have been calculated with basis sets of triple zeta quality and are our best CI values. Experimental values are from the compilation in Ref. 30.

	ZnH		CdH		HgH		PdH		ZnF		RhC	
Method	$\Delta g_{\parallel}$	$\Delta g_{\perp}$	$\Delta g_{\parallel}$	$\Delta g_{\perp}$	$\Delta g_{\parallel}$	$\Delta g_{\perp}$	$\Delta g_{\parallel}$	$\Delta g_{\perp}$	$\Delta g_{\parallel}$	$\Delta g_{\perp}$	$\Delta g_{\parallel}$	$\Delta g_{\perp}$
Previous work												
DFT[[illegible]](1-c)	0.0	−19.7	−0.1	−55.9	−0.1	−158.9	−0.2	248.3	−0.1	−6.3	−0.1	49.8
DFT/ZORA[[illegible]](2-c)	−0.4	−24.9	−2.4	−71.7	−30.0	−251.8	−27.7	294.8	−0.3	−6.8	−2.0	50.3
DFT/DKH2[[illegible]](2-c)	−0.3	−19.1	−1.9	−59.8	−25.9	−236.5	−16.5	224.2	−0.3	−6.7	−0.6	56.9
ROHF[[illegible]](4-c)	−2.1	−1.8	−0.3	−17.2			−64.6	595.0	−0.4	−43.7		
This work (4-c)												
ROHF	−0.24	−17.58	−1.6	−53.6	−21.5	−220.5	−55.5	555.9	−0.2	−6.9	−1.9	60.6
CIS	−0.18	−17.32	−1.3	−52.1	−16.4	−198.7	−46.6	498.5	−0.1	−6.8	−0.8	136.2
CISD	−0.22	−18.26	−1.6	−55.7	−20.5	−220.8	−49.3	480.9	−0.2	−7.0	−1.0	59.4
CISD[a]	−0.23	−17.80	−1.6	−55.8	−21.5	−226.9	−47.6	476.3	−0.2	−6.4	−1.2	53.6
CISDT	−0.23	−18.08	−1.6	−56.1	−21.3	−232.5	−25.0	325.1	−0.2	−6.3	−0.7	46.7
Experiment	−2.0(3)	−17.1(6)	−5.3(4)	−49.9(4)	−26.3(2)	−174.3(5)	−37.3(2)	290.9(4)	−0.3(10)	−6.3(10)	1.6(6)	51.8(6)

[a]The CISD values obtained with the smaller RAS3 space used in the CISDT calculations.

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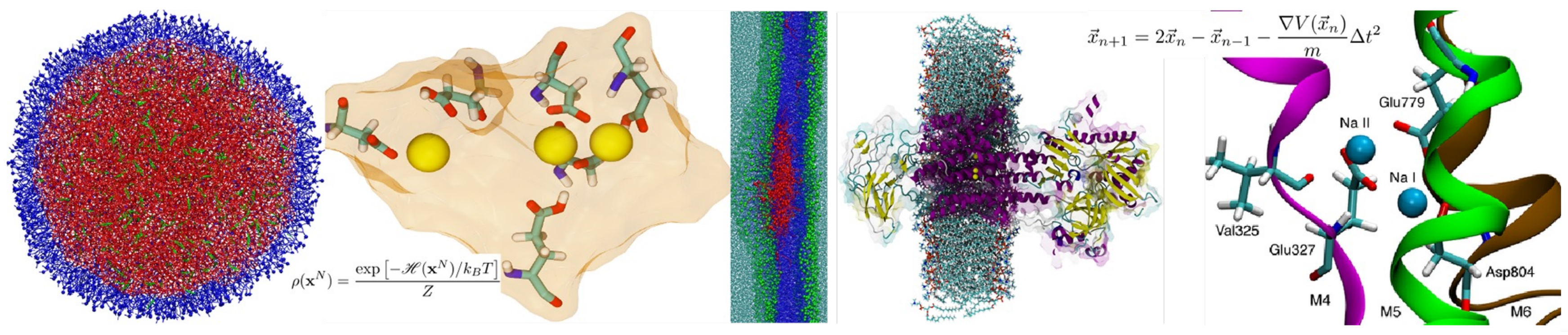
Assoc. Professor Himanshu Khandelia

Topics: Computational Biophysics/Biochemistry
Protein, Membrane Interactions



PHYLIFE
Physical LifeScience
SDU

Overview: Biomolecular Simulations

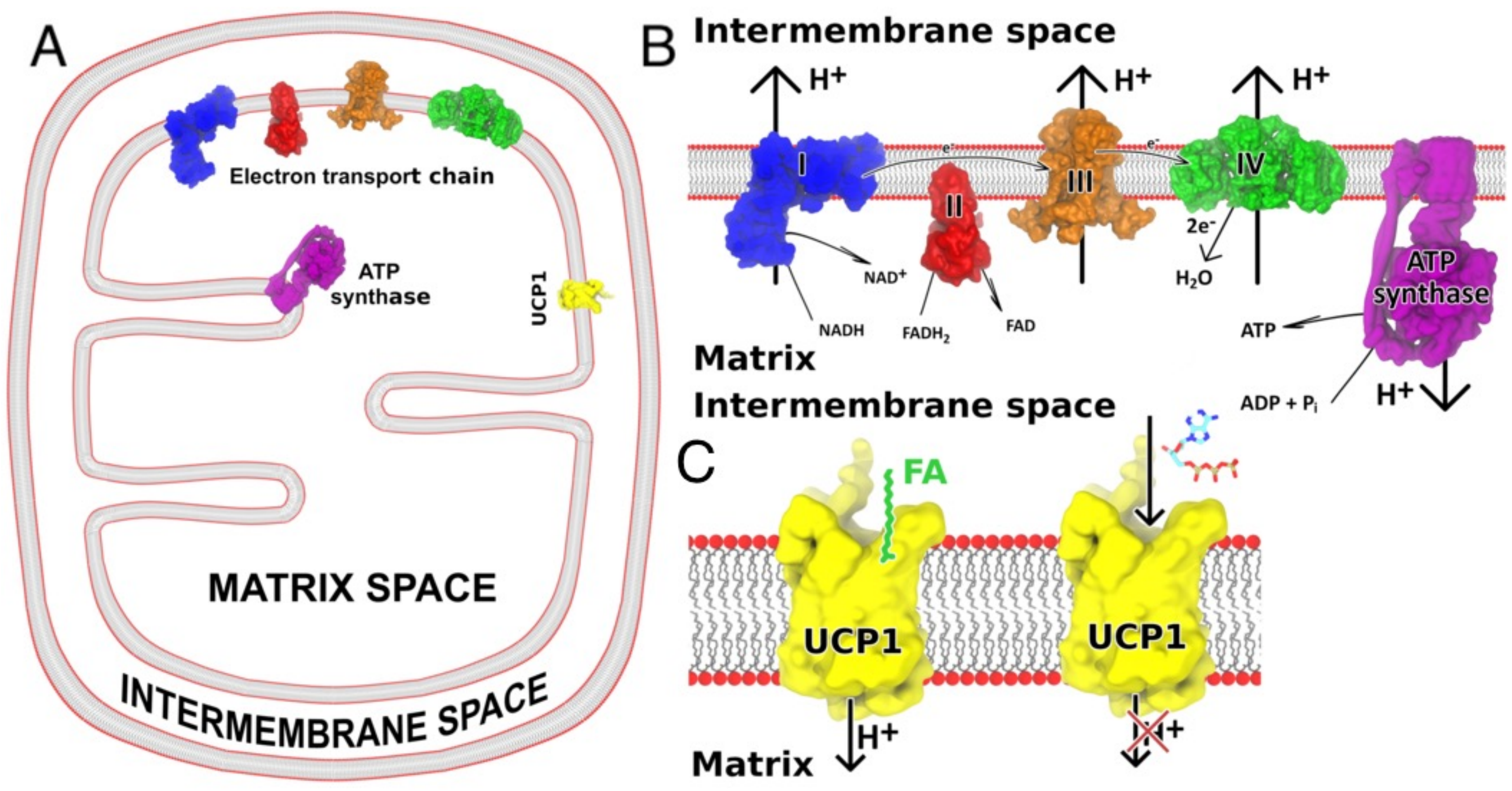
We (PhD1, 3 postdocs + students) use Molecular Simulations to explore a wide range of problem in biological systems, particularly near biomembranes, in **collaboration with experiments**. Examples of topics:

- The physics of biological membranes
- Nanoplastics
- Drug-membrane interactions
- Mechanisms of transport across membranes

We are housed at PHYLIFE: Physical Life Sciences, and use **Supercomputers** for research

EuroHPC Joint Undertaking

Physics, Chemistry
Proton-Coupled Transport

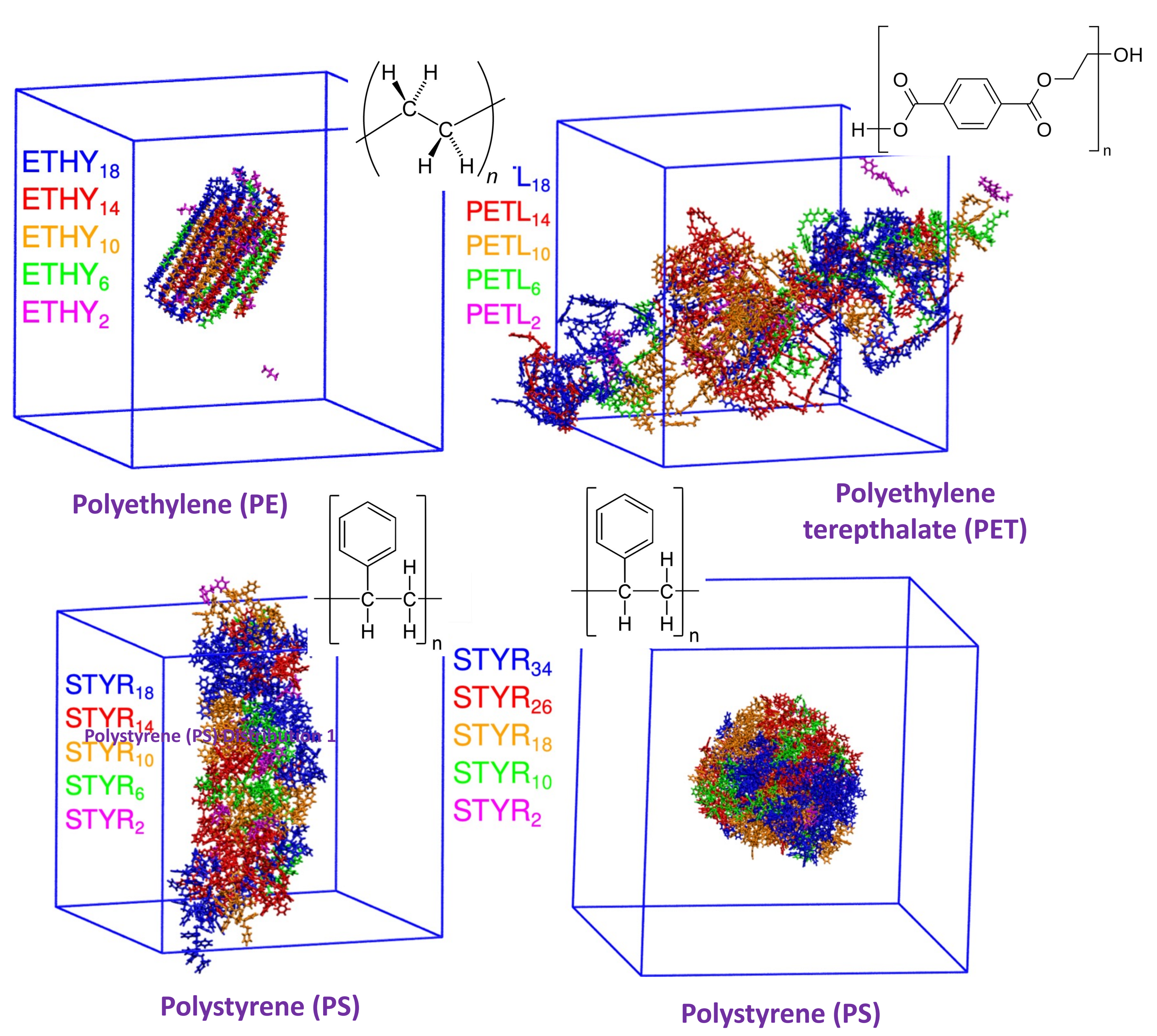


A: mitochondrion B. The electron transport chain establishes a proton gradient C. The uncoupling protein 1 dissipates the gradient to produce heat

Solute transport in mitochondrial solute carriers is often coupled to proton transport along a pH gradient. Disruption is linked to metabolic and obesity-related disease

Nanoplastics (Physics, Chemistry)

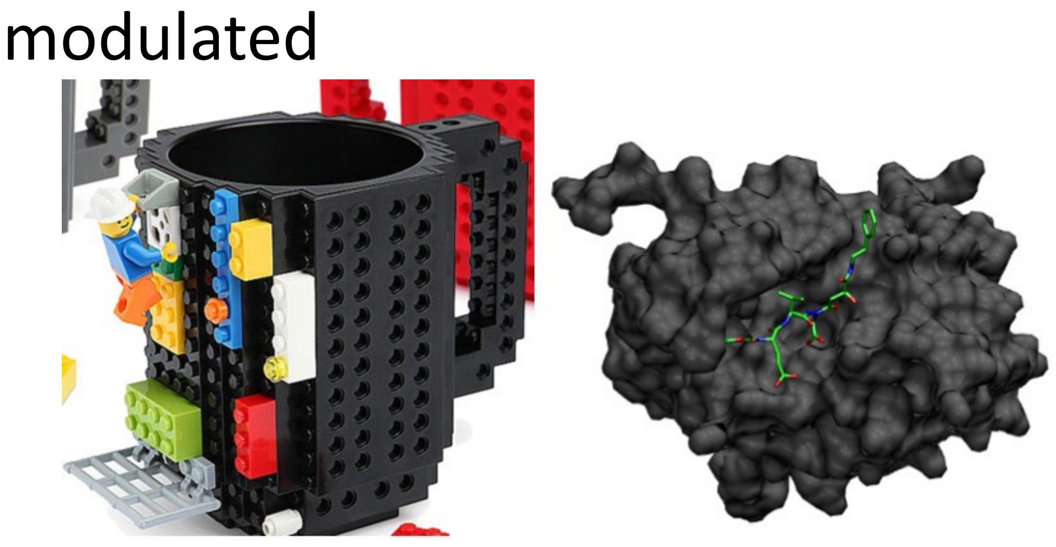
Most research on nanoplastics focusses on > 50 nm particles. What do < 50 nm particles look like? How can they be removed from water? How do they interact with biological systems?



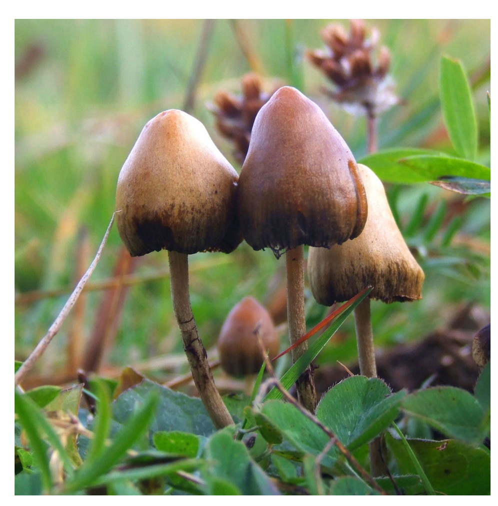
Self-assembly simulations of Nanoplastics

Chemistry, Pharmacy
Protein-Drug Interactions

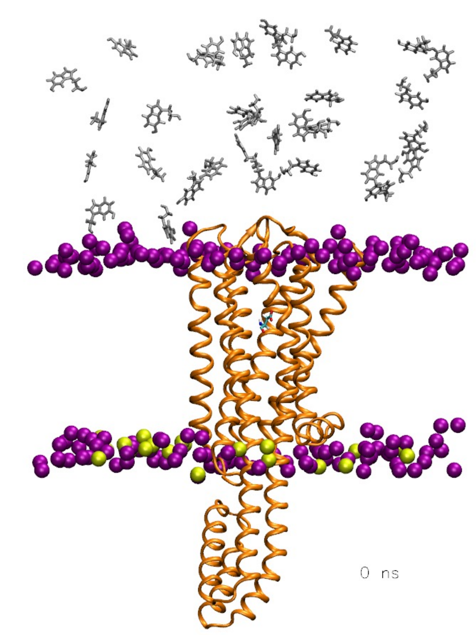
What are the molecular forces which determine the specificity and affinity of drugs to protein targets? How are these forces modulated



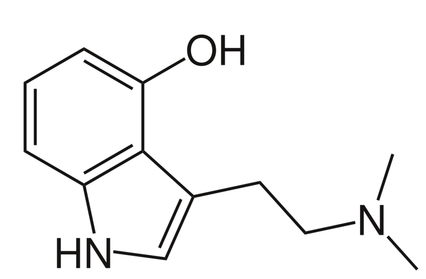
Physics, Chemistry, Pharmacy
Magic Mushrooms



How does the active component of magic mushrooms cause hallucinations?



We also work with Other GPCRs



Psilocin

novo nordisk fonden   LUNDBECKFONDEN   VILLUM FONDEN

web: hkgroup.sdu.dk   email: hkhandel@sdu.dk

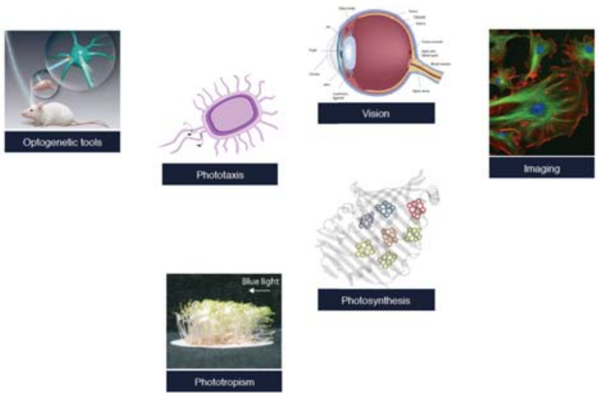
Professor Jacob Kongsted

Topics: Computational and Theoretical Physics, Chemistry and Biology

SDU Syddansk Universitet

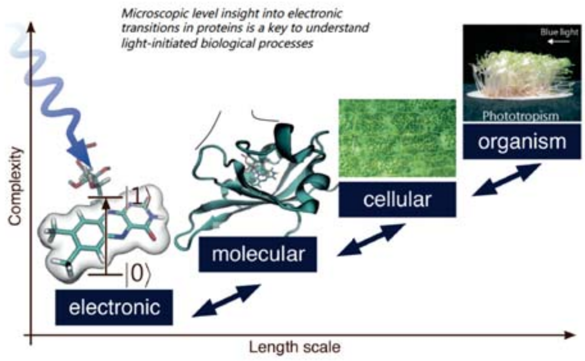
Light-driven biological processes

We develop and use theoretical and computational methods to study light-controlled biological processes such as photosynthesis, optogenetics etc. Our aim is to understand and develop functional biological materials at an atomistic level.



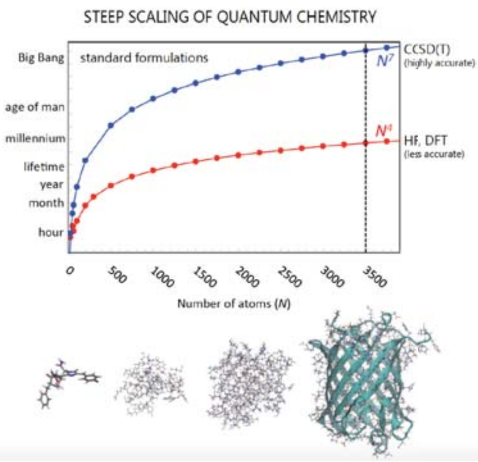
Development and applications of multiscale strategies

We develop and use multiscale strategies to rationalize biological functions. Our strategy is based on a hierarchy of methods based on either quantum or classical principles.



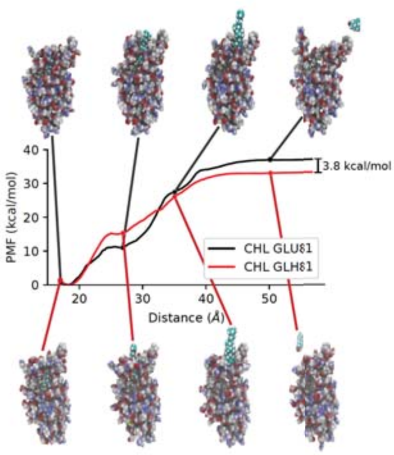
Method development within computational quantum chemistry

We develop novel computational methods and procedures within quantum chemistry aimed at being able to perform calculations on very big molecular systems. Our developments are focused around quantum embedding methods.



Computational medicinal chemistry

We develop and use computational procedures aimed at understanding the function of drug-like molecules at the atomistic level. In particular we study binding processes between macro-molecules and drugs.



email: kongsted@sdu.dk

Associate Professor Changzhu Wu

Topics: **Enzyme Catalysis and Protein Chemistry**

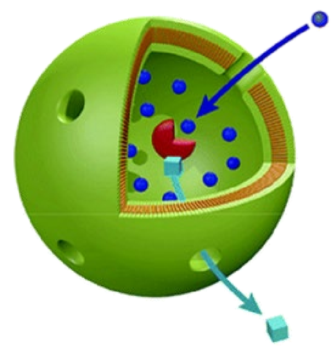
Who?

www.wugroup.sdu.dk

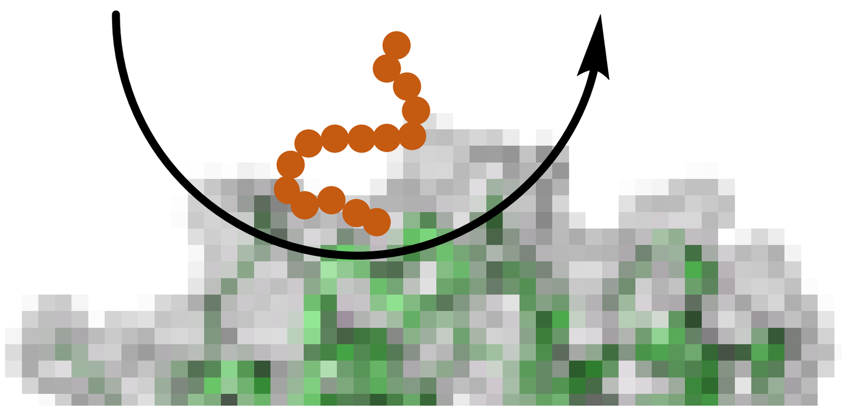
Enzyme Catalysis & Protein Chemistry

What?

Immobilization



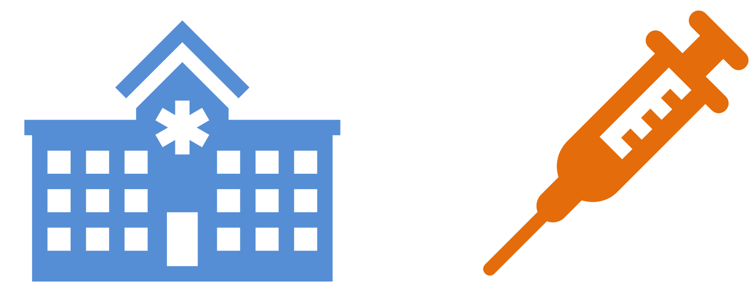
Proteins or enzymes



Chemical modification

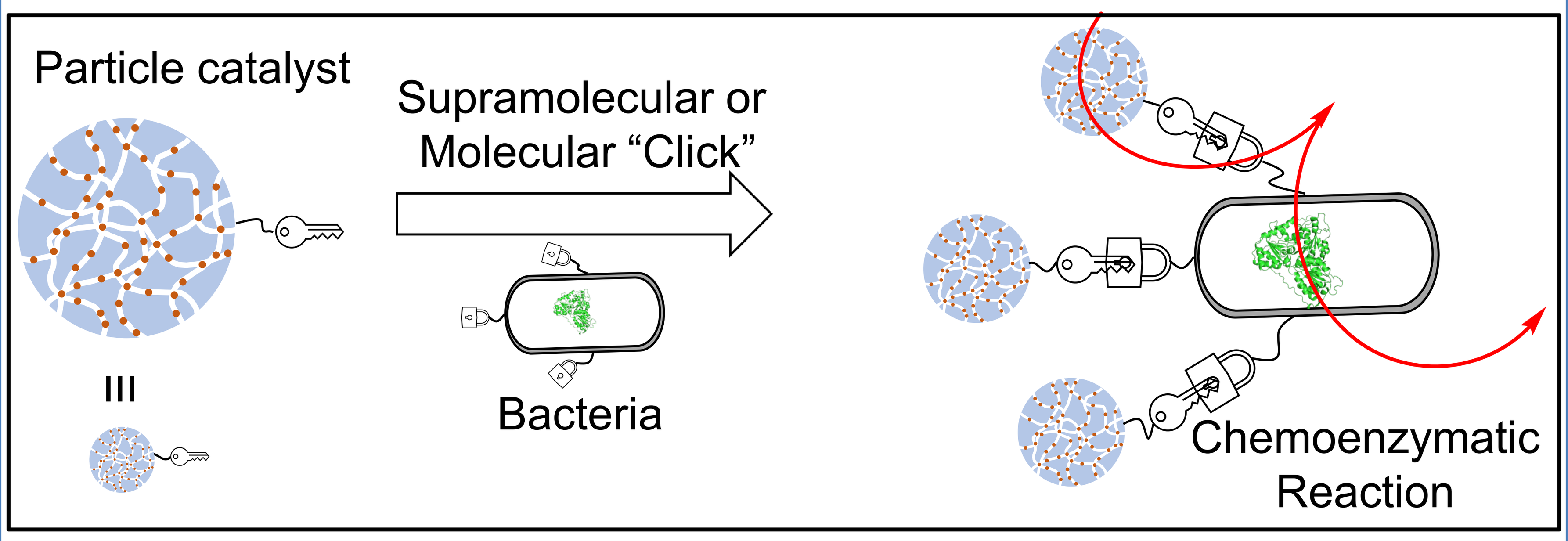
Why?

Industrial Biotechnology



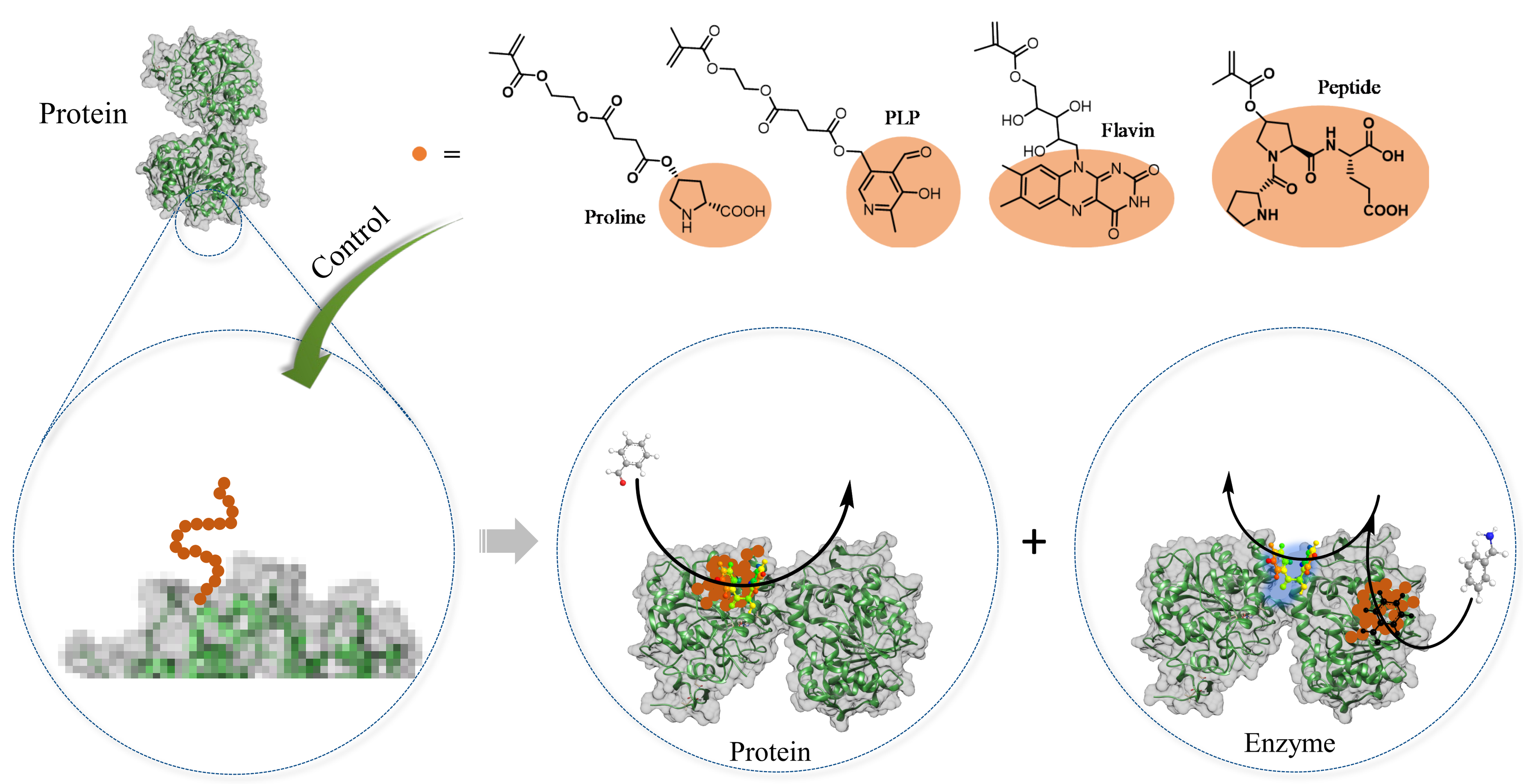
Medical Biotechnology

Project 1. Biohybrid catalysts



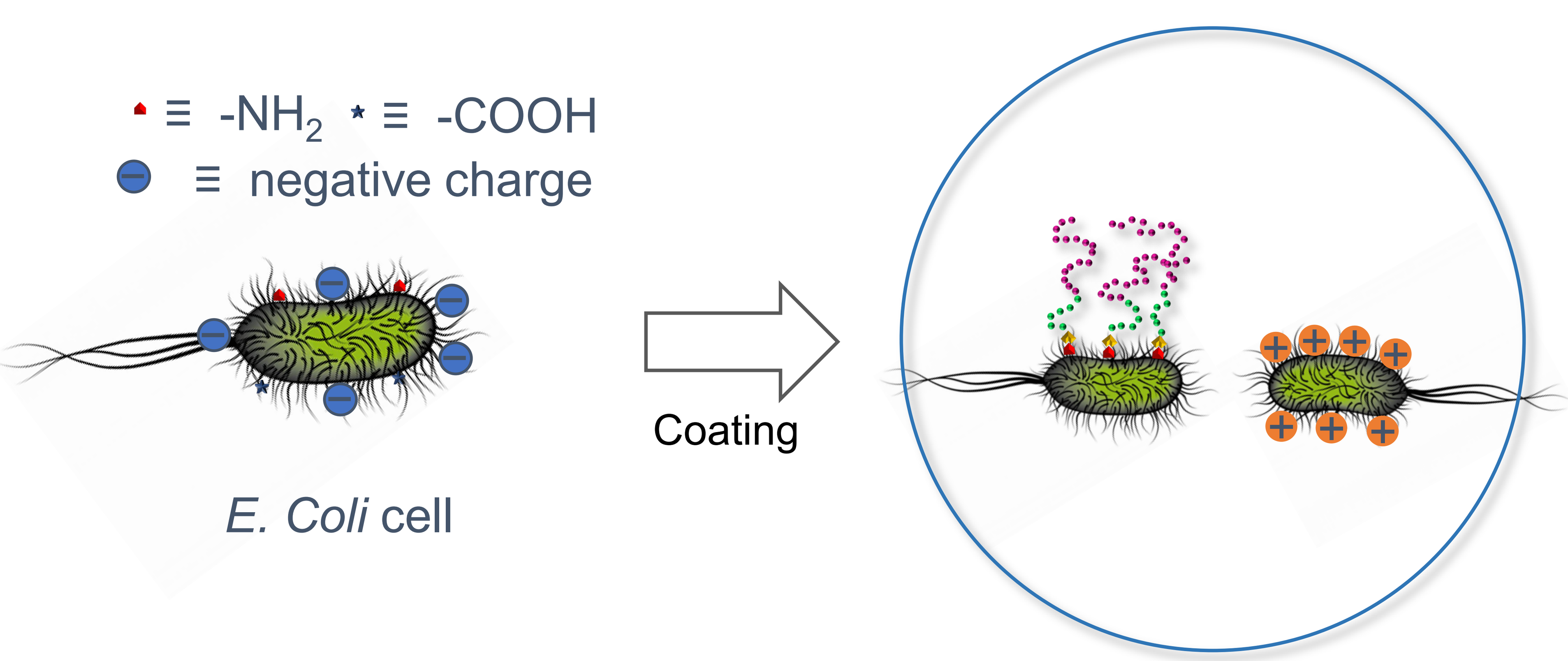
- **Aim**: Combine chemical catalysts with enzymes in bacteria for cascade reaction;
- **Method**: 1) Prepare particles that contain different catalysts, e.g., metal catalysts; 2) modify the catalyst with active molecules; 3) couple the particle with bacteria;
- **Evaluation**: Evaluate the catalytic efficiency.

Project 2. Artificial enzymes



- **Aim**: Artificial or semisynthetic enzymes
- **Method**: 1) Prepare active organocatalysts; 2) conjugate the catalysts to protein or enzymes as active polymer;
- **Evaluation**: 1) Characterize the conjugate; 2) evaluate the catalytic efficiency.

Project 3. Cell coating for biotechnology



- **Aim**: Protech cells for biocatalysis
- **Method**: 1) graft polymers from cells surfaces; 2) coat cells using charge or chemical reactions;
- **Evaluation**: 1) characterize the system; 2) evaluate the catalytic efficiency

Ref.: Wu et al., *Nature Communications*, 13, 3142

Homepage: www.wugroup.sdu.dk email: wu@sdu.dk

Professor Christine J. McKenzie

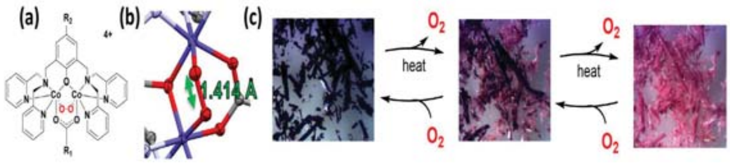
Metal-organic, Bioinorganic and Green Chemistry

SDU
Syddansk Universitet

Industrial processes are far from achieving enzyme-like selectivity, atom- and energy-efficiency. We synthesize new metal-organic compounds with *biomimetic* active sites with one aim being discovery of new technologies for alleviating the emission of Greenhouse (CO_2, CH_4) and toxic gases (NO_x) from anthropogenic activities.

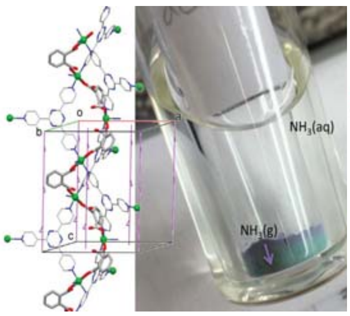
Solvent-free reactions

Just like the gas processing enzymes, small molecules are *chemi*sorbed by our new metal-organic materials. Reactions include reversible gas binding and toxic gas capture and conversion.

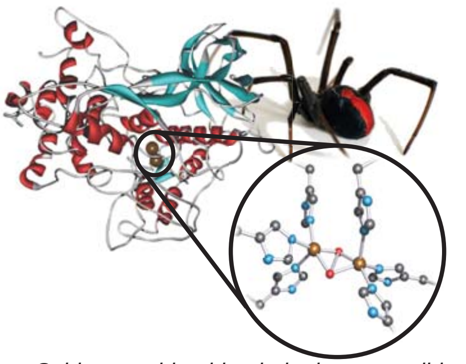


(a) *Active site structure of a material that grabs O_2 from air*
(b) *Section of X-ray structure showing the chemisorbed O_2*
(c) *Visible color changes on sorption and desorption.*

QR-code for Youtube Video:



Copper "metal-organic framework" that can reversibly bind NH_3.

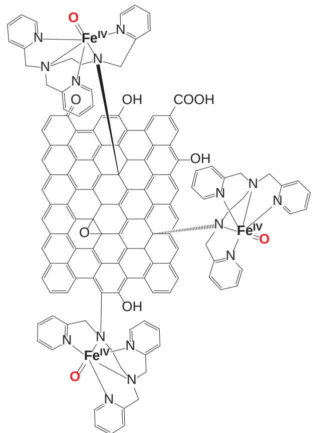


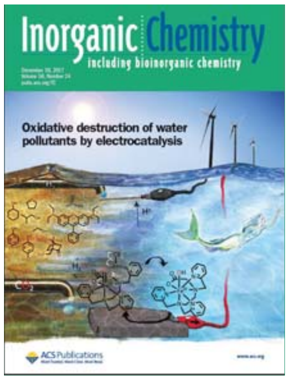
Spiders are blue-blooded - they reversibly bind O_2 at the dicopper site of hemocyanin.

Catalysis

Using our high-valent non-heme iron complexes we are developing a new electrocatalytic technology for the *total mineralization* of organic pollutants (e.g. pesticides) in contaminated water.

The next step is immobilization of the catalysts of on electrode materials e.g. graphene.



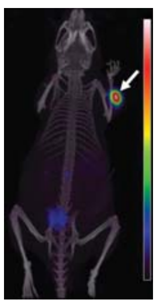


Collaboration with the Water Research Center, University of New South Wales, Sydney, AUS.

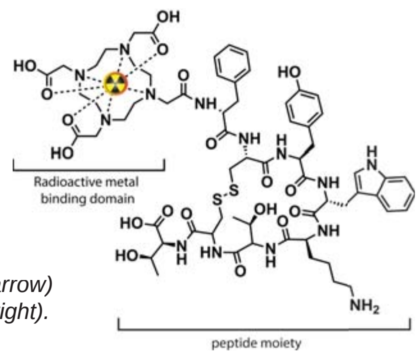
Single crystal X-ray crystallography
Co-supervisor Adjunkt prof. Vickie McKee

Radiotheranostics

Auger Electron Emitters (AEEs) hold great promise in targeted radionuclide therapy for cancer. Short decay paths means cell destruction can occur without extensive damage to surrounding tissues. We are synthesizing ligands for the *in vivo* transport of AEEs, 119-antimony (^{119}Sb) and 58m-cobalt (^{58m}Co). Sister isotopes (^{117}Sb, ^{55}Co) can be used for diagnostics.



PET/CT image of AR42J tumor (arrow) in mouse using a ^{55}Co complex (right).



Collaboration with Assoc. Prof. Helge Thisgaard at OUH-nuclear medicine

web: http://mckee.sdu.dk/cjmck/home.html email: mckenzie@sdu.dk

Professor Frants R. Lauritsen

Topics: Analytical environmental chemistry, portable instrumentation, dynamics of chemical and biological systems

Membrane Inlet Mass Spectrometry

Membrane inlet mass spectrometry (MIMS) is a special type of mass spectrometry that makes it possible to monitor chemical and biological processes in real time and all kinds of samples being gaseous, liquid or solid can be analyzed directly for volatile organic compounds without sample preparation.

MIMS principle and typical applications

On-site measurement of off odours from pig manure

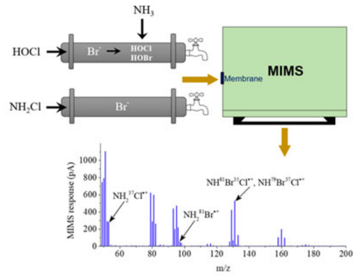
Ground water characterization at a nuclear power station

Online monitoring of trihalomethanes in swimming pools at Gladsaxe Sportscenter

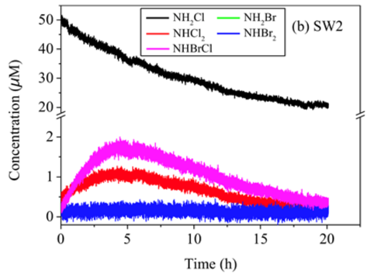
Disinfection of water and the derivative formation of disinfection byproducts

Experimental setup to investigate disinfection of surface water using chlorination (OCl^- or chloramination).

As part of the disinfection chemistry chloramines are transformed into more reactive bromamines



A typical kinetic experiment showing the disinfection of surface water and the associated transformation of monochloramine into dichloramine and bromchloramine



Science of the Total Environment 751 (2021) 142303

Hot Cell MIMS

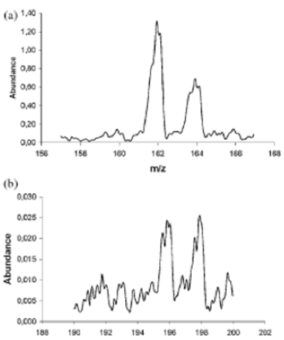
In hot cell MIMS solids can be analysed directly for their content and liberation of chemicals to the surroundings. This makes it possible to evaluate the dangers associated with physical contact to the materials.

EXAMPLE: Direct analysis of soil from a factory site in Sweden that was heavily contaminated with herbicides (2,4-D and 2,4,5-T in particular) also known as agent orange. For analysis a spoonful of contaminated soil was simple dumped into the MIMS as is.

Picture of the contaminated site

Waste sampling. Half masks was needed because of the odour.

Mass spectrometric verification of the presence of the two precursors to 2,4-D and 2,3,5-T



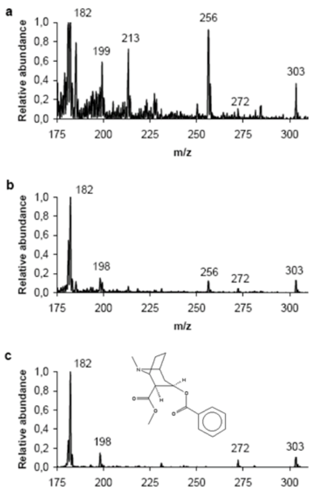
Rapid Communications of Mass Spectrometry 22 (2008) 2234–2240

Analysis of drugs

In addition to environmental samples the hot cell MIMS technique can also be used for direct analysis of active compounds in plant materials and for detection of counterfeit medicines.

EXAMPLE: Leaves from a plant analysed as is reveals its origin and content of cocaine

Coca plant



Direct analysis of leaves

Micro extract in methanol

Cocaine standard

Analytical Chemistry 81 (2009) 4010-4014.

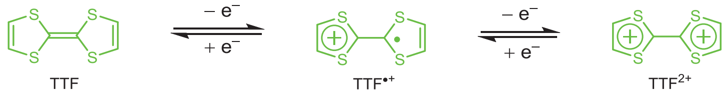
email: frl@sdu.dk

Professor Jan O. Jeppesen

Topics: Organic Chemistry, Supramolecular Chemistry, Analytical Chemistry and Tetrathiafulvalene

SDU
Syddansk Universitet

Tetrathiafulvalene (TTF)

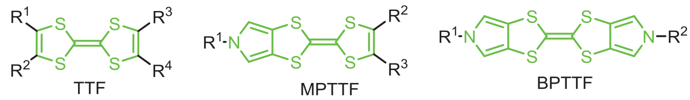


Tetrathiafulvalene's (TTF's) Properties

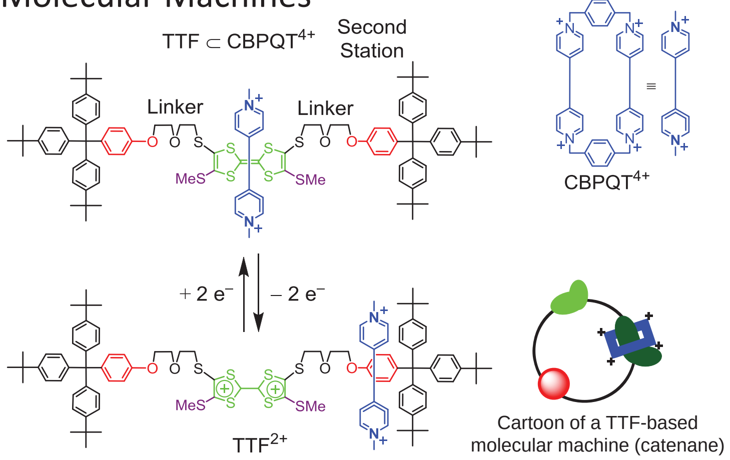
- Strong electron donor
- Readily oxidised in a stepwise and reversible manner to $TTF^{\bullet+}$ or TTF^{2+}, either chemically or electrochemically
- 3 oxidation states (TTF, $TTF^{\bullet+}$ and TTF^{2+}) easily distinguished using spectroscopy
- Stable under most synthetic conditions, allowing incorporation into larger systems – see below

TTF-Derivatives

- Various substituents can be added to TTF to build useful molecules
- Pyrrolo annelated TTFs, monopyrrolo-TTF (MPTTF) and bispyrrolo-TTF (BPTTF), are often used to avoid isomerism
- MPTTF and BPTTF have comparable properties to TTF but different positions to connect to other groups – this can be helpful when designing new molecules



Molecular Machines



Cartoon of a TTF-based molecular machine (catenane)

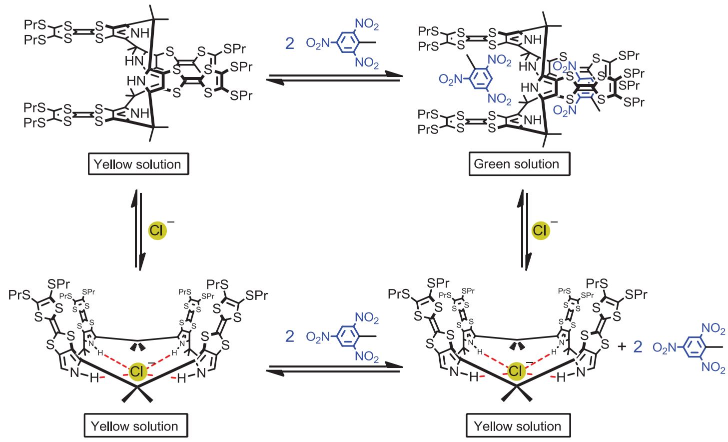
Advantages of Using TTF

- TTF is an electron donor which can interact (complexate) with cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$) which is an electron acceptor
- Allows preparation of interlocked systems: rotaxanes (linear) and catenanes (cyclic)
- Oxidation of TTF destroys the interaction between TTF and $CBPQT^{4+}$ and induces a movement

Challenge

- Design of systems capable of using the induced movement to perform unidirectional motion (linear or rotary)

Molecular Sensors –TetrakisTTF-calix[4]pyrrole



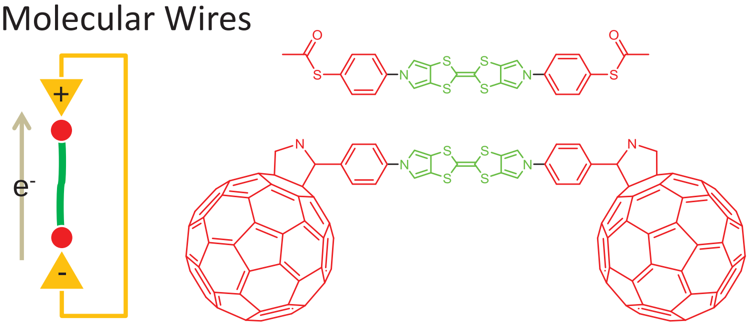
Advantages of Using TTF

- tetrakisTTF-calix[4]pyrrole binds nitrated benzene derivatives (e.g. trinitro-toluene (TNT)) – can be used to detect explosives
- Distinct, easily visible colour change when TNT binds to tetrakisTTF-calix[4]pyrrole – helpful for use in devices

Challenges

- Chloride anions bind stronger than TNT to tetrakisTTF-calix[4]pyrrole and disrupts sensing behaviour (see above)
- TNT binds only to the 1,3 alternated configuration (top) – can this be locked?

Molecular Wires



Advantages of Using TTF

- TTF's redox properties can be used to add switching behaviour to wires
- BPTTF allows for highly conjugated molecular wires – this improves conductance

Challenges

- Improve solubility of wires so conductance studies can be done
- Find good anchoring groups for different electrodes (e.g. gold or graphene)

Jeppesen, J. O.; Becher, J. *Eur. J. Org. Chem.* **2003**, 3245–3266
Andersen, S. S.; Share, A. I.; Poulsen, B. L. C.; Kørner, M.; Duedal, T.; Benson, C. R.; Hansen, S. W.; Jeppesen, J. O.; Flood, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 6373–6384
Nielsen, K. A.; Cho, W. S.; Jeppesen, J. O.; Lynch, V. M.; Becher, J.; Sessler, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16296–16297
Solano, M. V.; Della Pia, E. A.; Jevric, M.; Schubert, C.; Wang, X.; van der Pol, C.; Kadziola, A.; Nørgaard, K.; Guldi, D. M.; Nielsen, M. B.; Jeppesen, J. O. *Chem. Eur. J.* **2014**, *20*, 9918–9929.

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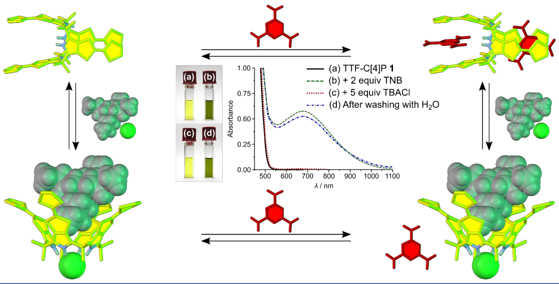
Assistant Professor Steffen Bähring

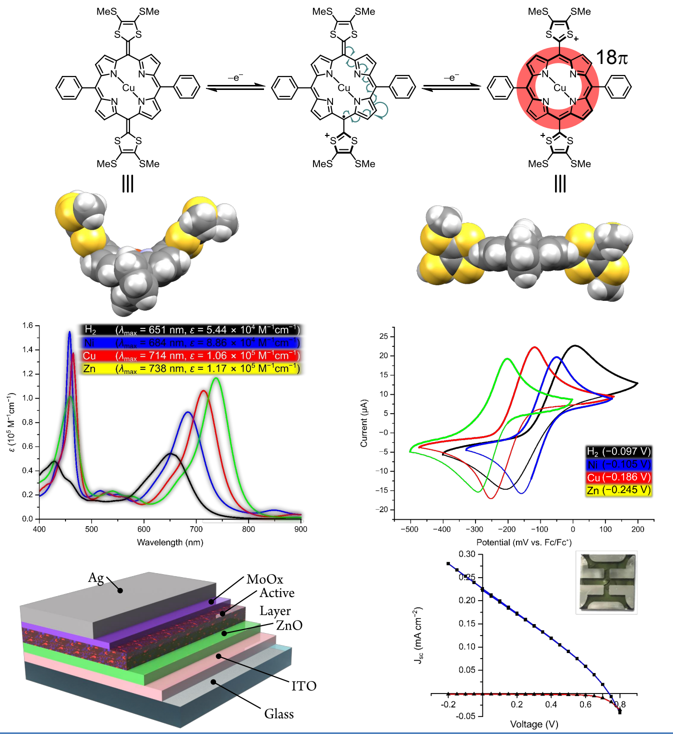
Topics: Supramolecular Chemistry and Synthetic Organic Chemistry

Supramolecular Chemistry

The area of Supramolecular Chemistry covers non-covalent interactions between molecules to assemble larger ordered structures. The non-covalent nature of these structures makes them highly sensitive towards external stimuli, which can be exploited in e.g. sensors and electron-transfer processes.
Tetrathiafulvalene is a highly electron-rich molecule that functions as a π-electron donor. This has made it ideal as a building block in Supramolecular Chemistry and the sensing of explosives (e.g. TNT) and Buckminster fullerenes.

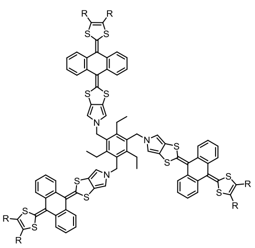


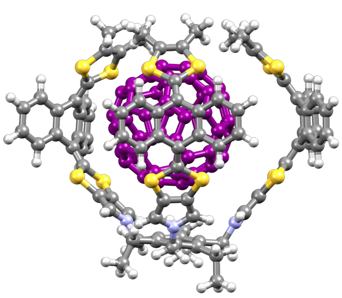
Organic Solar Cells

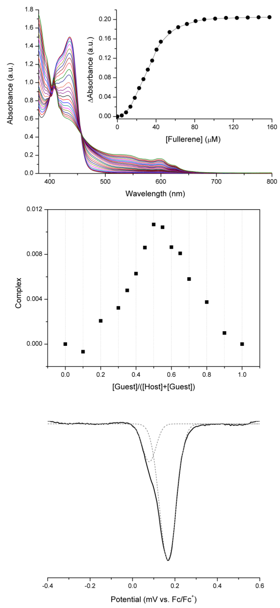


Fullerene Receptor

B. Sc. Project Jesper Tversted. Synthesis and investigation of extended tetrathiafulvalene receptor for fullerene by computational modelling, NMR, absorption, ITC, CV and transient spectroscopy.

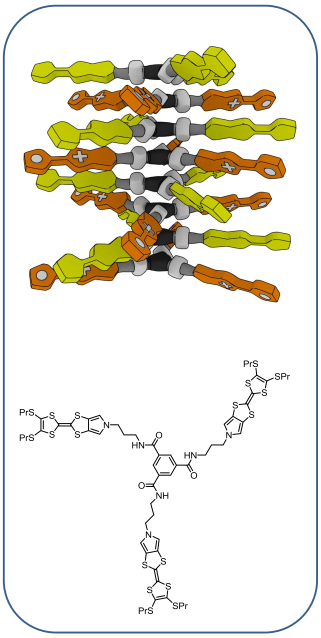


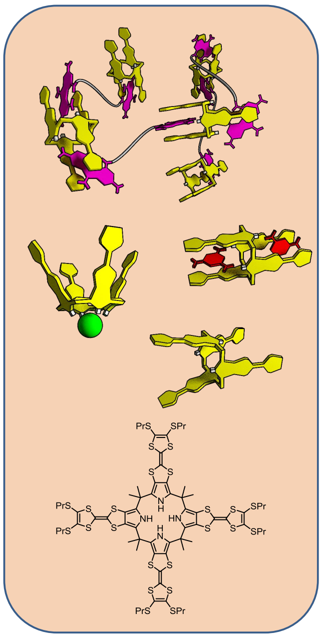




Supramolecular Polymers

Concentration and temperature dependent polymerization of TTF-monomers investigated by absorption spectroscopy, NMR, AFM and DLS.





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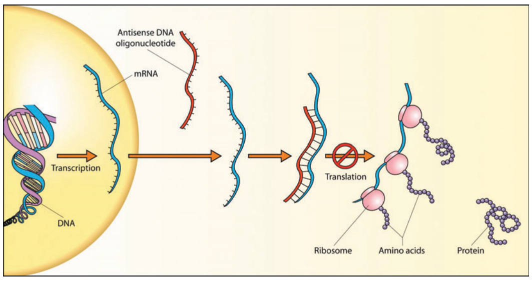
Professor Poul Nielsen

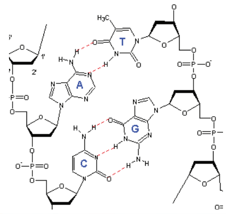
Organic Chemistry;
Synthetic DNA and Medicinal Chemistry towards new antibiotics

DNA therapeutics



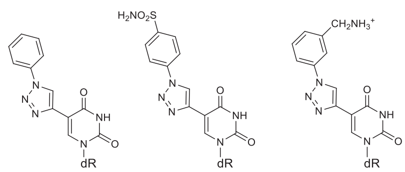
Blocking translation by synthetic antisense DNA

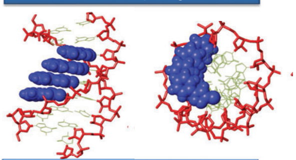
Chemical modification is necessary for improving physiological stability and RNA-affinity



Watson-Crick base-paring

Increasing the aromatic surface leads to π–π-stacking and increased RNA-affinity



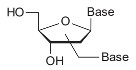


Stacking in major groove

Synthesis by Click Chemistry and incorporation into DNA by using a DNA-synthesizer:

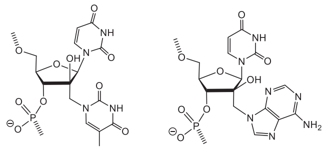
Recent refs: Mick Hornum, Pawan Kumar, Patricia Podsiadly, and Poul Nielsen, *J. Org. Chem.* **2015**, *80*, 9592-9602. Mick Hornum, Alevtina Djukina, Ann-Katrin Sassnau and Poul Nielsen, *Org. Biomol. Chem.* **2016**, *14*, 4436-4447.

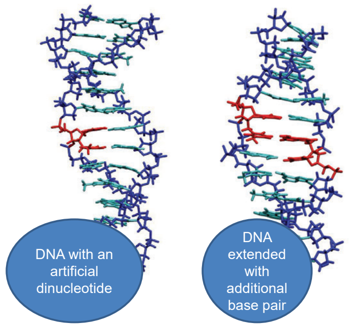
Double-headed nucleotides



Idea: Regocnition of secondary nucleic acid structures. Designing new nucleic acid motifs. Aptamers. Development of Double-coding DNA

Different designs have been approached. This one positions the additional nucleobase in the duplex core for base-pairing

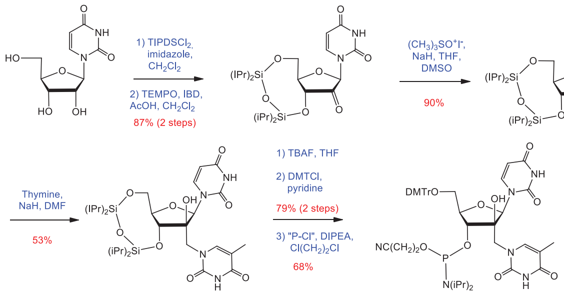




DNA with an artificial dinucleotide

DNA extended with additional base pair

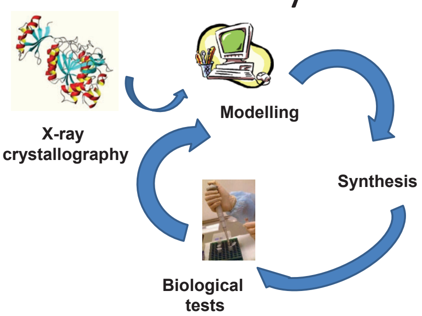
Synthesis:



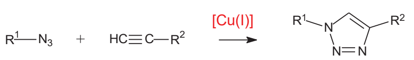
Building block for DNA synthesis

Recent refs: Kasper M. Beck, Pawan K. Sharma, Mick Hornum, Nikolaj A. Risgaard and Poul Nielsen, *Chem. Commun.* **2021**, *57*, 9128–9131. Kasper M. Beck, Linette Ruder, Tine S. Nicolai, Robert L. Pham, Nikolaj A. Risgaard, Mick Hornum and Poul Nielsen, *Eur. J. Org. Chem.* **2021**, 1949–1957

Medicinal chemistry



- with Click Chemistry



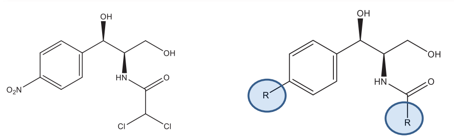
Huisgen cycloaddition with Sharpless-Meldal conditions

Diversity with a simple general reaction. High yields. No side products. Possible in aqueous solution. Used intensively to link complex molecules together.

- towards new antibiotics

Chloramfenicol – a well known antibiotic with side effects

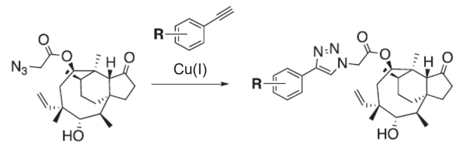
New derivatives are designed based on modelling and synthesized:



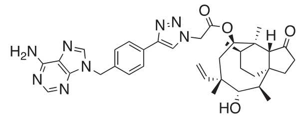
Derivatives are made by simple reactions *e.g.* Click chemistry, Sonogashira coulings, and/ or peptide couplings

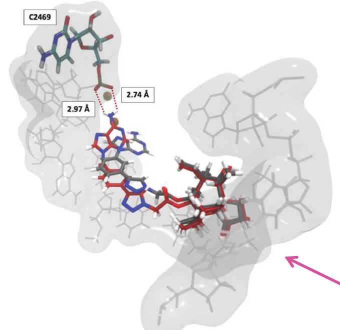
Pleuromutilin – an antibiotic binding to bacterial ribosomes

A click chemistry strategy towards new pleuromutilin conjugates:



Alkynes with a variety of side chains are prepared

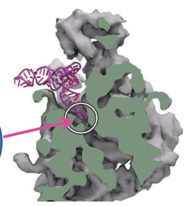




New hit 2019. Excellent activity against MRSA, no human tox.

Intensive work to improve on solubility and pharmakokinetics

The binding site in the ribosome (PTC)



Collaboration with Carsten Uhd Nielsen (FKF), Jacob Kongsted (FKF) and Janne Kudsk Klitgaard (BMB)

Recent ref: Christoffer V. Heidtmann, Faidra Voukia, Louise N. Hansen, Stine H. Sørensen, Brian Urlund, Salli Nielsen, Mona Pedersen, Noor Kelawi, Brian N. Andersen, Maria Pedersen, Peter Reinholdt, Jacob Kongsted, Carsten U. Nielsen, Janne K. Klitgaard, and Poul Nielsen, *J. Med. Chem.* **2020**, *63*, 15693-15708.

https://portal.findresearcher.sdu.dk/da/persons/pouln

email: pouln@sdu.dk

Assoc. Prof. Stefan Vogel

SDU

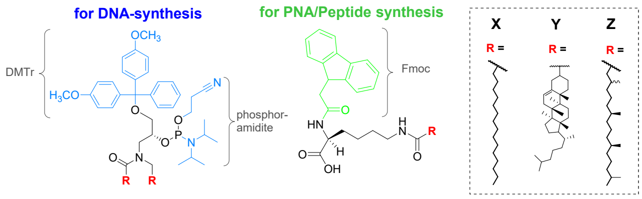
Topics:

Chemistry & Catalysis in Nanoreactors and Liposomal Drug Delivery of DNA & Peptides

Synthesis of Lipid building blocks for automated DNA & Peptide synthesis

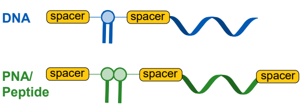
We synthesize lipophilic building blocks for DNA, PNA and Peptides – and incorporate them into oligomers with therapeutic applications.

Anchor building blocks



Lipid-DNA or Lipid-PNA/Peptide conjugates

Design

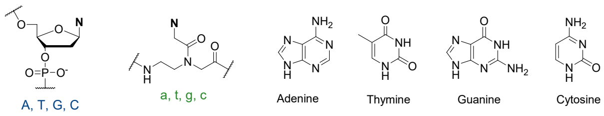


Example Sequence

5'-end T-X-PEG_3-TGT GGA AGA AGT TGG TG 3'-end

N-terminus EE-XX-PEG_{12} ata gtt aca tgc EE C-terminus

DNA-chain | PNA-chain | N = Nucleobases

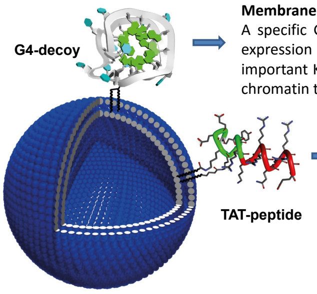


Spacer units PEG_3, PEG_6, PEG_{12} or T (DNA) / E (glutamic acid, peptide)

Ries, O., et al., *Organic & Biomolecular Chemistry* **2015,** *13* (37), 9673-9680; Rabe, A. et al. *Chem Commun* **2017**, submitted.

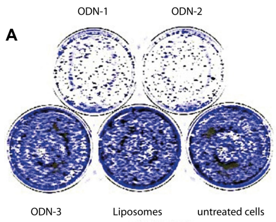
Liposomal platform for targeted drug delivery

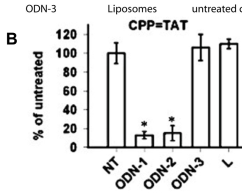
Liposomes allow free variation of payload vs. targeting vector concentrations. Their size controls bio-distribution. Investigation for the treatment of pancreatic cancer:



Membrane-anchored DNA with therapeutic activity. A specific G-Quadruplex (G4) forming sequence can inhibit KRAS expression in mammalian cell. It is called "decoy" as it scavenges an important KRAS transcription factor (MAZ) by mimicking its natural chromatin target.

Membrane anchored cell-penetrating peptide. Cell penetrating peptide aids uptake of the G4 into the cell.



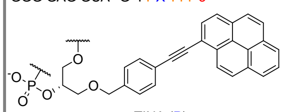


TAT-peptide

HOOC-EEE-XX-YGRKKRRQRRR-E-NH_2

Intercalator-stabilized G4 (ODN1)

5'-GCG GTG TGG GPA AGA GGG AAG APG GGG GAG GCA[L] G[L]TT X TTT-3'



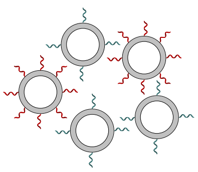
para-TINA (P)

A) Colony formation of Panc-1 cells when treated with liposomes loaded with TAT and ODN-1, -2, or -3 (non-G4), and controls, TAT-Liposomes only (L) and untreated (NT) . B) Histogram showing the percentage of colonies relative to NT.

Cogoi, S., et al., *Scientific Reports* **2016,** *6*, 38468.

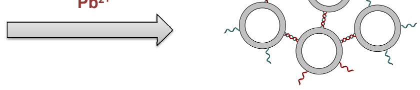
Environmental and Health Diagnostics using Nanoparticle assembly

DNA-encoded liposomes assemble into large aggregates (visible by eye). Assembly can be triggered by binding of a biological target strand for DNA/RNA diagnostics or toxic metals such as mercury (stabilizes T:T mismatch), or lead (stabilizes G-quadruplexes). Non-covalent attachment of lipid-DNA-conjugates to soft nano-particles, like liposomes, is an attractive technology as it needs no surface chemistry.



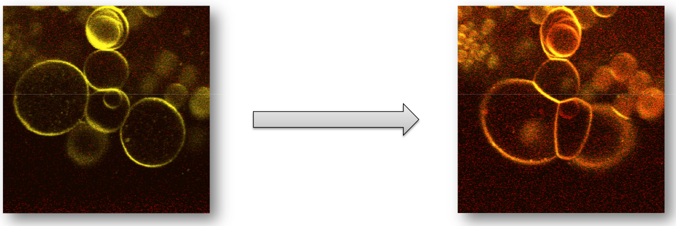
Single Liposomes

Target DNA-sequence or Hg^{2+} or Pb^{2+}



Liposome assembly

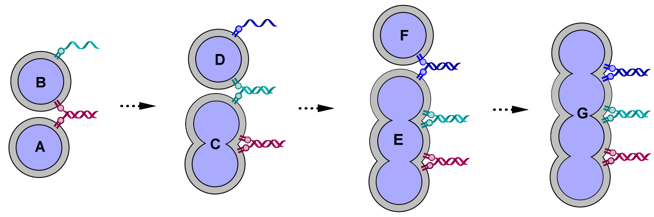
DNA/RNA diagnostics



Jakobsen, U., et al., *Journal of the American Chemical Society* **2008,** *130* (32), 10462-10463;
Jakobsen, U., et al., *Bioconjugate Chemistry* **2013,** *24* (9), 1485-1495; Jakobsen, U., et al., *Org. Biomol. Chem.* **2016,** *14* (29), 6985-6995.

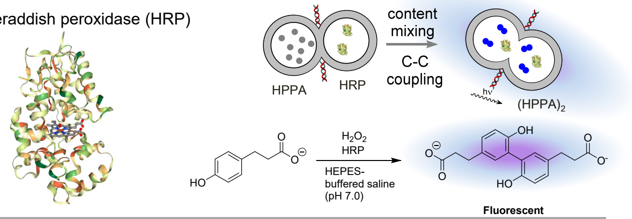
Programmed chemical and enzymatic reactions in liposomes

Liposomes as reaction flasks: DNA-programmed mixing of tiny volumes.

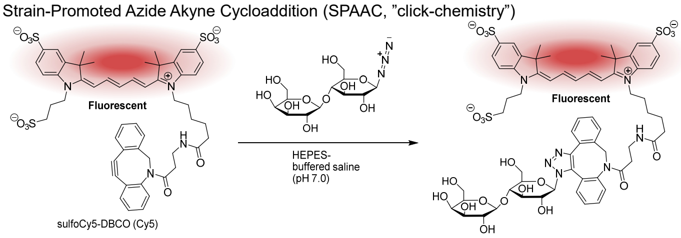


Löffler, P. M. G., et al., *Angew. Chem., Int. Ed.* **2017** (DOI: 10.1002/anie.201703243); Ries, O., et al., *Org. Biomol. Chem.* **2017** (DOI: 10.1039/C7OB01939D)

Horseradish peroxidase (HRP)



Strain-Promoted Azide Akyne Cycloaddition (SPAAC, "click-chemistry")



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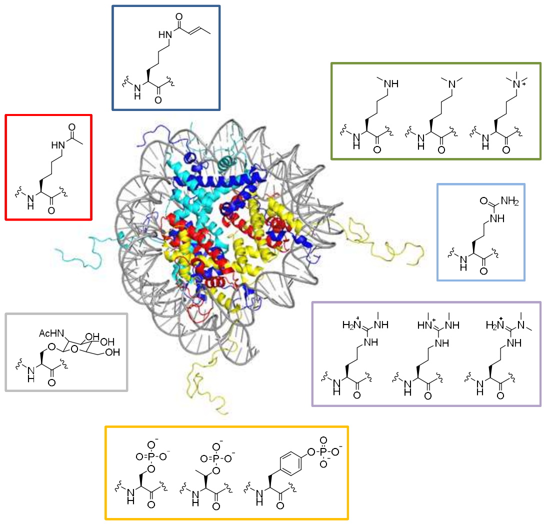
Professor Jasmin Mecinović

Topics: Medicinal Chemistry, Chemical Biology, Organic Chemistry, Bioorganic Chemistry

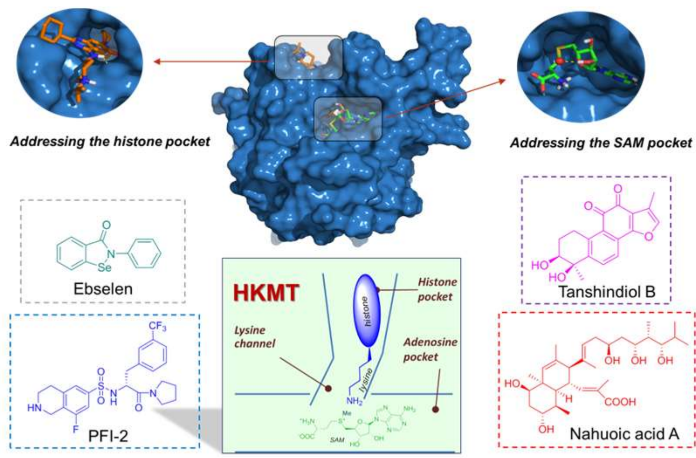
SDU

Chemical Basis of Epigenetics



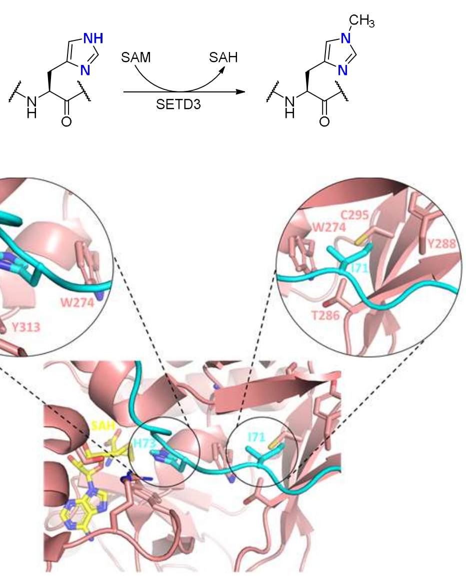
- **Aim**: to unravel the chemical basis of epigenetics
- **Objectives**: to explore diverse posttranslational modifications of histone proteins
- **Approach**: chemical biology and physical-organic chemistry
- **Techniques**: synthesis, peptide chemistry, protein chemistry, enzymology
- **References**: *Nat. Commun.* 2015, 6, 8911, *Commun. Chem.* 2019, 2, 112, *Commun. Chem.* 2020, 3, 69, Commun. Chem. 2022, 5, 27.

Discovery of Epigenetic Inhibitors



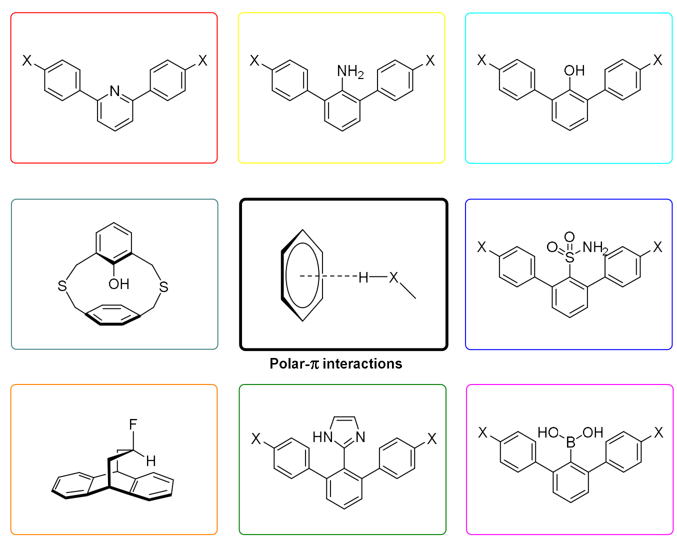
- **Aim**: to develop new epigenetic inhibitors of therapeutic potential
- **Objectives**: to design novel chemical probes for histone-modifying enzymes
- **Approach**: medicinal chemistry
- **Techniques**: synthesis, inhibition assays
- **References**: *ChemMedChem* 2018, 13, 1405-1413, *Bioorg. Med. Chem. Lett.* 2018, 28, 1234-1238, *Org. Biomol. Chem.* 2022, 20, 173-181.

Actin Modifications



- **Aim**: to probe substrate scope and inhibition of actin-modifying enzymes
- **Objectives**: to investigate enzyme catalysis of histidine methyltransferase SETD3
- **Approach**: bioorganic chemistry and chemical biology
- **Techniques**: synthesis, peptide chemistry, enzymology
- **References**: *ChemMedChem,* 2021, 16, 2695-2702, *Org. Biomol. Chem.* 2022, 20 1723-1730. *Protein Sci.* 2022, 31, e4305.

Molecular Recognition



- **Aim**: to probe noncovalent interactions in chemistry and biology
- **Objectives**: to understand interactions between aromatic rings and polar groups
- **Approach**: organic chemistry
- **Techniques**: synthesis, NMR, crystallography
- **References**: *Org. Lett.* 2020, 22, 7870-7873, *Chem. Eur. J.* 2021, 27, 5721-5729, *Chem. Eur. J.* 2022, 28, e202104044, *J. Org. Chem.* 2022, 87, 6087-6096.

email: mecinovic@sdu.dk