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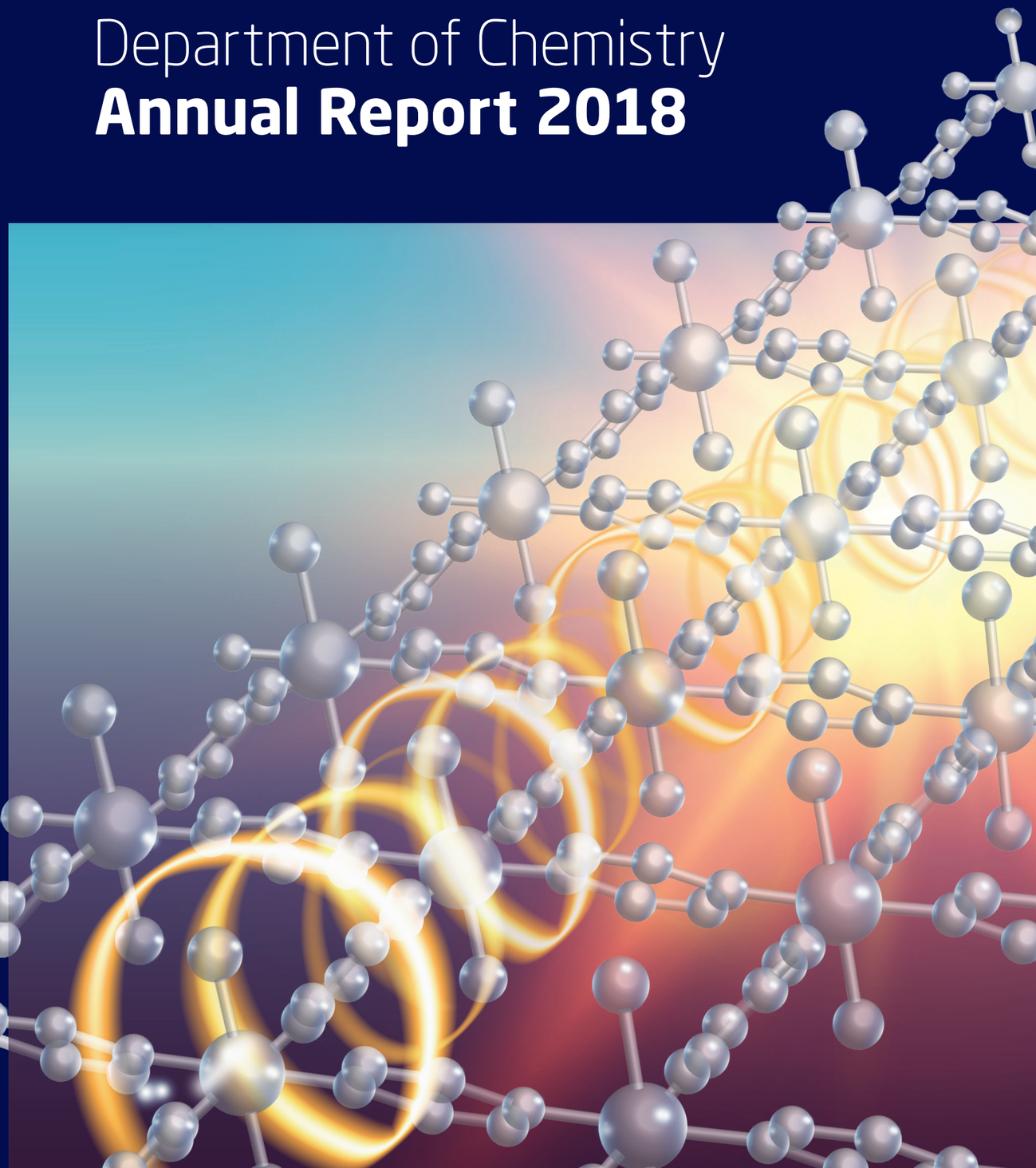
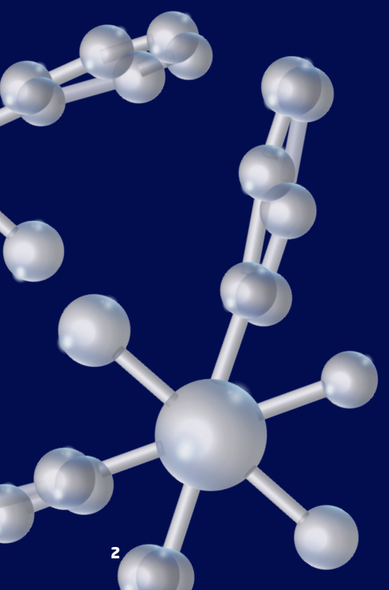
Department of Chemistry
Annual Report 2018



A Department Taking Charge



Content

The DTU Chemistry Management Group 2018 (left to right) Jens Ø. Duus, Inge Halkmann Olsen, Erling H. Stenby, Pernille Harris, and Klaus B. Møller.

Welcome to the DTU Chemistry Annual Report 2018 – a year characterized by new initiatives, innovation, and academic excellence.

Cooperation and innovation in focus

As you can read throughout the report, we prioritize innovation and the development of tomorrow's solutions to climate, health, and energy challenges. One of our new initiatives, Springboard, has already shown great promise in facilitating innovations. We are certain that the Department's research and innovation portfolio will lead to many impactful spin-out companies in the future.

The Department also takes pride in our researchers participating in groundbreaking research networks. Thus, I am extremely excited to see researchers from DTU Chemistry being an integral part of the government designated 'lighthouse' environment SMART. SMART will perform cutting-edge research on atomic structures using the new ESS neutron source – leading the way to new advanced materials.

In 2018, we celebrated the inauguration of DK-OPENSCREEN – a national research infrastructure for chemical biology hosted by DTU Chemistry. This is a testament of our commitment to improve Denmark's competitiveness in the life science sector. I anticipate numerous collaborations with industry and scientists interested in benefitting from this infrastructure and the state-of-the-art compound library located at the Department.

As international cooperation plays an important role in all research activities, I am pleased to see that DTU Chemistry is considered an attractive partner also at the international level. Researchers and companies from all over the world are reaching out to us for close collaboration with our highly competent research groups.

Through significant external funding we have once again been able to initiate projects and develop strong research groups with talents from Denmark and abroad. The Independent Research Fund Denmark, the Novo Nordisk Foundation, and Carlsberg Foundation are just a select few of our funding partners driving the Department's world-class research in materials, life science engineering, etc.

We are always looking for ways to improve already strong research areas and academic excellence. Therefore, I am enthusiastic about the 2019 expansion of faculty to include another professor, associate professor, and senior scientist relocating from DTU Nanotech. They will add expertise to the Department's existing capabilities, especially within polymers and nanotechnology.

I would also like to highlight our focus on safety procedures and occupational health of our employees, which are of utmost importance and continuously evaluated. In addition to complying with applicable laws and regulations, the Department have adopted a series of actions to be followed. In 2018, we started implementing a new digital registration system to further ensure a complete and at all times updated overview of the quantity and location of each of the Department's chemicals. I am extremely proud to see employees on every level taking great responsibility with regards to safety matters.

Educating the next generation of scientists

One of the core tasks at DTU Chemistry is educating and forming the next generation of engineers and researchers.

To my satisfaction, our recruitment strategies are working excellently. The BSc programme Chemistry and Technology continues to attract a very high number of applicants. This has led to an increase in required grade average – securing a very competent group of students. The success also translates to our MSc programme that attracts bachelors from DTU and other universities around the world.

Furthermore, our challenging and inclusive study environment is encouraging students to reach their full potential, proven by the number of individual awards and Honors students graduating our programmes.

2018 was also a productive year at PhD level with 13 PhD students graduating. You can read about their projects in this report. Additionally, a record number of 24 PhD students were enrolled at the Department. I am very proud of our PhD School, as it assists these young scientists to develop through power performance courses, writing workshops, participation in international conferences, and close collaboration with industry.

In conclusion, I see a Department geared to perform research and educational activities at the highest level. At the same time, we work in innovative ways in order to stay competitive and continue to attract talent, address global challenges, and create value to partners within industry and academia. I hope you will enjoy reading this report.

Erling H. Stenby

Faculty – Consolidated and Evolving

Physical and Biophysical Chemistry:
Günther H. J. Peters, Wei Yan, Irene Shim, Niels Engholm Henriksen, René Wugt Larsen, Klaus B. Møller, Esben Thormann, Kasper Planeta Kepp, Sonia Coriani, Pernille Harris, and Kenny Ståhl.

The Department recently recruited heavily with six new young faculty. This has, among other factors, led to an increase in faculty capability – strengthening both research and education at DTU Chemistry.

The research groups at the department are organized in two major sections: Organic and Inorganic Chemistry with Professor Jens Ø. Duus as Head of Section and Physical and Biophysical Chemistry with Professor Klaus B. Møller as Head of Section. Both sections are rapidly evolving in the wake of recent hires and consolidation of research groups. An already strong research area, such as chemical biology, is currently flourishing with new exiting projects and collaborations – giving the Department a boost, e.g. within the field of life science. "We are now in consolidation phase in chemical biology based on the recent recruitments, which – in combination with a historically strong position in the field – allow us to set even more ambitious goals," says Professor Jens Ø. Duus. In addition, Professor Klaus B. Møller stresses the importance of how faculty reinforcement is affecting the educational programmes in a positive manner with new courses in advanced biomolecular, medicinal, and theoretical chemistry and an increased number of PhD students in these fields.

Gaining international reach

Whilst faculty continue to prioritize cooperation with national partners from industry and academia, the international impact is also increasing. Just to mention a few examples; the hiring of Professor Sonia Coriani has established the Department as a powerhouse within development of theory and algorithms related to experiments at international, large-scale facilities. Furthermore, Associate Professor Kira Astakhova is doing forefront research on lipid nanoparticles (LNPs) for delivery of CRISPR gene therapeutics, aiming at treatment of HIV-1 and lung cancer. Her work is done in collaboration with researchers from City of Hope Beckman Research Institute, Stanford Genome Technology Center, and Stanford School of Medicine, Division of Immunology. The internationalization also shows in faculty's hiring of PhDs. Of the 24 newcomers in 2018, 17 were recruited abroad.

Giving the students industry insight

Another focus point for faculty is to actively bridge the gap between students and companies by facilitating BSc and MSc projects offered by industrial partners. The new initiative Company Project Day is a great example of this (pp. 33). Another one is the Open Innovation cooperation with LEO Pharma. Due to this collaboration, chemistry students at DTU will gain access to LEO Pharma's engine room, where they will have the opportunity to work with company researchers and test theory from their studies in practice. Additionally, Assistant Professor Luca Laraia is leading a course that incorporates LEO Pharma Open Innovation. In the course, students can synthesize molecules that are tested for anti inflammatory activity by the Open Innovation platform.

Joining forces on UN goals

Even though it is already an integral part of DTU Chemistry's DNA to induce a better future by creating solutions, inventions, and technological advances, DTU in broad and the Department of Chemistry has now officially adopted the United Nation's 17 goals from 'Transforming our world: the 2030 Agenda for Sustainable Development'. Most of the goals have the common denominator that technology will play a crucial role in solving climate, health, and sustainability issues. The UN goals will act as a platform for the faculty's future work.

New Professor has strong innovative and industrial profile

On 1 June 2018 Esben Thormann was appointed Professor (MSO) in Surface Physical Chemistry. Safe adhesion of ostomy bags to the skin and anti-ice effects at the surface of wind turbine wings are just a few examples of advanced polymer functionalities within the research interest of Esben Thormann. At DTU Chemistry, he has built a research group of around 10 people covering the full range from fundamental research to projects with a high likeliness of industrial application. In recent years, Esben and his group have attracted several huge grants from both industry and independent funds.

Sections

Organic and Inorganic Chemistry

The Section of Organic and Inorganic Chemistry comprises activities within Catalysis and Sustainable Chemistry, Materials Chemistry, and Organic Chemistry. Common themes are the synthesis and characterization of small to very large inorganic and organic molecules. The research areas are homogenous and heterogenous catalysis; gas separation and absorption; development of new materials; conversion of biomass; electrochemistry; bioelectrochemistry; graphene nanoparticles; coordination chemistry; chemical biology; NMR spectroscopy.

Physical and Biophysical Chemistry

The Section of Physical and Biophysical Chemistry comprises activities within pure and applied physical chemistry. It covers both microscopic atomic-level descriptions and the macroscopic thermodynamic approach. Common themes are determination of structure and behaviour of small to medium-sized molecules as well as proteins, and many projects involve spectroscopy, scattering, and computer modelling. The research areas are Biophysical and Biomedicinal Chemistry; IR, THz, and Raman Spectroscopy; High Pressure Phase Behaviour for Oil and Gas Production; Protein and X-ray Crystallography; Polymers and Functional Interfaces; Theoretical, Computational, and Femtochemistry.

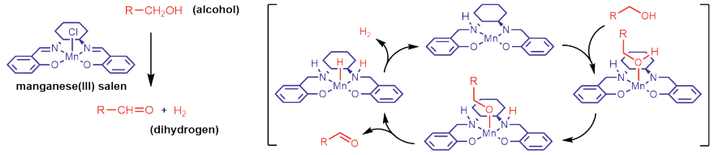
Two new Head of Studies

Since 2010, Professor Klaus B. Møller has held the influential position of being Head of Studies of the BSc programme Chemistry and Technology. In 2018, DTU Chemistry's responsibility and contribution regarding DTU's educations has increased immensely with the appointment of two additional Head of Studies: Professor Mads H. Clausen is responsible for the BSc programme Human Life Science Engineering, and Professor Jens Ø. Duus is now Head of Studies of the MSc programme Applied Chemistry. With three Head of Studies, faculty look forward to obtain an even greater role in securing and shaping the quality of three important study programmes at DTU.

About the study programmes

- Applied Chemistry (MSc) focuses on chemical and biological systems at molecular and nanoscale level, and provides the students a broad knowledge of the design of advanced materials at both theoretical and experimental level.
- Human Life Science Engineering (BSc) educates specialists in discovering, designing, and manufacturing healthy foodstuffs and more effective drug candidates. The programme attaches great importance to using modern, creative forms of teaching, in which theory is combined with hands-on laboratory and computer practicals involving realistic problems.
- Chemistry and Technology (BSc) equips students with knowledge to understand or predict why and how different substances and materials will react in a given chemical process, so they are able to create new, improved products and production methods.

Organic and Inorganic Chemistry:
Jens Ø. Duus, David Tanner, Susanne Mossin, Robert Madsen, Hans Erik Mølager Christensen, Charlotte Held Gotfredsen, Søren Kegnæs, Anders Riisager, Rasmus Fehrmann, Jingdong Zhang, Mads H. Clausen, Qijin Chi, Kasper Steen Pedersen, Sophie Beeren, Katrine Qvortrup, Luca Laraia, Kira Astakhova, and Martin Nielsen.



In 2018, the Robert Madsen Group at DTU Chemistry discovered a cheap manganese(III) salen complex able to catalyze (de)hydrogenations. This constitutes the first example of a manganese(III) catalyst for releasing dihydrogen.

Making Metal Catalysis Affordable

Transition metal catalysis has revolutionized organic chemistry and will be instrumental for providing food and energy to the growing global population. However, the current state-of-the-art solutions are too costly for these large-scale applications.

Almost like a magic touch, transition metal catalysis has entered organic chemistry, allowing reactions which were previously either extremely slow or simply impossible. Not only has this development been recognized with the chemistry Nobel prizes of 2001, 2005, and 2010; the implications for industry and society as such are large. As the global population continues to grow while fossil resources become exhausted, finding efficient ways to convert renewable feedstock into food, chemicals and fuel will be imperative. However, the current solutions rely mainly on expensive transition metals such as palladium or platinum.

"Presently, almost all really important transformations are catalyzed by precious elements. These metals have been the cornerstone of the field and responsible for much of the fundamental understanding of metal catalysis. Unfortunately, they are also extremely expensive," says Professor Robert Madsen, DTU Chemistry.

Consequently, his group has embarked on a quest which will make the cheaper elements in the contingency of transition metals available.

Russia and South Africa dominate

Metal-catalyzed transformations are used around the globe every day for preparing pharmaceuticals, agrochemicals, vitamins, functional materials and many other applications. Obviously, a wide range of industrial corporations are keen to see their costly catalysts replaced by cheap ones. However, the benefits are far from only of an economic nature. The precious elements necessary in current solutions are only available in low quantities, and more than 80 per cent of the annual production comes from just two countries, Russia and South Africa.

"Thus, a key area of chemistry is based on precious metals with a very limited and potentially uncertain supply," notes Robert Madsen. "It is therefore fair to say, that research aiming to develop Earth-abundant metals for homogeneous catalysis and elucidation of their reaction pathways is a substantial contribution to preserving our present-day standard of living."

Strive to understand the mechanism

Two of the metals in focus are manganese and zinc. As both these elements are abundant and produced for other purposes, they are cheap. The current market price for both manganese and zinc is around 2 USD pr. kg – as compared to 37,900 and 28,700 USD pr. kg for palladium and platinum respectively.

"It is important for us not only to develop new and cheaper catalysts. We are also keen to understand the mechanisms, meaning the reactions at the molecular level. This kind of understanding will provide a framework for rational decisions on which efforts are likely to lead to further improvements of the catalysts. We are not fans of the trial-and-error approach," says Professor Robert Madsen.

"Typically, the cheaper alternatives do not follow the same mechanisms as the expensive platinum group metals do. This provides challenges, but is also very interesting from a scientific point of view, as we need to develop an entirely new basis for our work to succeed."

In 2005, the group of Robert Madsen began developing benign catalytic procedures on alcohols and aldehydes by using ruthenium, iridium, and rhodium catalysts. In 2017, the group moved into novel catalysts based on Earth-abundant metals for dehydrogenating alcohols with the release of dihydrogen, i.e. $R\text{-}CH_2OH \rightarrow R\text{-}CHO + H_2$.

"The carbonyl compound thus formed can be converted into other functional groups in the same transformation. This is an extremely competitive field and a hot topic in modern catalysis," notes Robert Madsen.

Discovered a unique reactivity

Especially manganese catalysed (de)hydrogenations have received huge attention over the past two years. However, all the initial catalysts were expensive manganese(I) complexes stabilized by carbon monoxide ligands. In 2018, the group at DTU Chemistry discovered a cheap manganese(III) salen complex able to catalyze the same transformation. In addition, the mechanism was elucidated and shown to involve the ligand. This constitutes the first example of a manganese(III) catalyst for releasing dihydrogen. In unpublished work, the group has also shown that a manganese(III) porphyrin complex catalyses the same transformation although the mechanism is not known.

"These discoveries show that manganese(III) complexes with tetradentate ligands display a unique reactivity in reactions with dihydrogen – something previously completely unknown," according to Robert Madsen.

Other recent achievements by Robert Madsen and his colleagues are zinc oxide catalyzed dehydrogenation of primary alcohols into carboxylic acids, and manganese-catalyzed cross-coupling of aryl halides and Grignard agents.

Professor Robert Madsen
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Why do Transition Metals Catalyze so well?

In order to comprehend why transition metals are especially well suited as catalysts, it is useful to recapitulate how atoms are built. Starting with the simplest element, hydrogen, with one proton and one electron, the atom number of the chemical basic elements increase by one each time a proton is added to the atom's nucleus. Each extra proton is counterbalanced by an additional electron. The electrons orbit the nucleus and are organized in shells. While the inner shell (the K shell) holds just two electrons and has no sub-shells, the subsequent shells further away from the atom's nucleus have sub-shells.

Beginning with the third shell (the M shell) a sub-shell named the d-shell, capable of hosting up till 10 electrons, appears. For the transition metals, the d-shell is not filled. This feature allows for one or more electrons from other compounds to reside temporarily in the d-shell. By "lending" electrons to the transition metal, these compounds will be able to engage in chemical reactions more easily. In other words, the transition metal acts as a catalyst, speeding up reactions between other compounds. If the process is designed correctly, the transition metal will later release the borrowed electrons again and thus, having regained its original condition, be ready to perform the same task over and over again.

Depending on the specific context, the definition on which chemical basic elements are classified as transition metals may vary slightly. In the context of catalysts for organic synthesis the relevant elements are three groups of eight; the first group ranging from titanium (atom number 22) to cupper (no. 29), the second group from zirconium (no. 40) to silver (no. 47) and finally a group from hafnium (no. 72) to gold (no. 79). As one of these elements - technetium (no. 43) - is an artificial compound which would be highly impractical to use, the total number of transition metals available as catalysts for organic chemistry synthesis is 23. It should be mentioned that many basic elements with higher atom numbers have partly filled d-shells, but as these are all radio-active they are not relevant for this purpose.

Shaping the Digital Chemist

No less than 14 PhDs have begun their work and training in a European network on computational spectroscopy with strong DTU Chemistry participation.

As synchrotron radiation sources, free-electron lasers, and other advanced facilities become available, there is a growing need for computational chemistry.

"It is simply not possible to interpret results from advanced spectroscopy intuitively. You will need corresponding models and software tools," explains Professor Sonia Coriani, DTU Chemistry. She heads a key work package in a new European training network (ETN) for computational spectroscopy. With 14 new PhD students hired, the network is set to shape the digital chemists of tomorrow.

"Education and training of students or early-stage researchers in this field is not part of any standard curriculum, neither in chemistry nor physics. This is in clear contrast to the increasing importance of computational spectroscopy," says Sonia Coriani.

Of the 14 young researchers, two – Torsha Moitra and Daniil Fedotov – are employed at DTU Chemistry with Sonia Coriani as their supervisor and Klaus B. Møller, Professor in Physical Chemistry at the department, as their co-supervisor. The two professors are also co-supervising Postdoc Shota Tsuru, employed at the department through DTU's H.C. Ørsted COFUND programme.

In 2018, the group's activities included a 3-month stay by Professor Henrik Kock, SNS & NTNU, as Visiting Professor at DTU Chemistry – funded by a grant from the Otto Mønsted foundation.

Model before you measure

The initiative is named COSINE (COmputational Spectroscopy In Natural science and Engineering). Sonia Coriani heads the work package on modeling of advanced spectroscopies while Klaus B. Møller contributes with his experience from computer simulation of chemical dynamics and interpretation of ultrafast X-ray scattering experiments.

"Scattering and spectroscopy are very different techniques, but they are alike in the sense that they both yield indirect information about the probed molecules. This implies that before you do your experiment, you need to have a model. There is just no way of working your way backwards from an experimental result," says Klaus B. Møller.

Both professors have extensive experience from large-scale facilities abroad. And with the experience of the seven European academic partners and associated industrial partners included, the network covers a wide range of techniques. Examples are Near-Edge X-ray Absorption Fine Structure for ground and excited states, Resonance Raman Optical Activity, Resonance Inelastic X-ray Scattering, and Photo-Electron Spectroscopy.

Importantly, the network also offers specific training on programming and use of High-Performance Scientific Computing resources, both locally and through the PDC Center for High Performance Computing of Kungliga Tekniska Högskolan in Stockholm.

Predict the properties of new molecules

Both in her own research and in the COSINE project, Sonia Coriani focuses on excited electronic states.

DTU Chemistry is strongly represented in the Marie-Sklodowska-Curie European Training Network COSINE with PhD students Daniil Fedotov and Torsha Moitra, and professors Klaus B. Møller and Sonia Coriani.

"User-friendly software packages for ground-state chemistry already exists, but similar solutions for excited states are lagging behind," she points out.

Over the last two decades it has become possible to model molecular ground-state properties on the computer with high accuracy. This enables chemists to predict the properties of new molecules virtually. Thereby a huge number of molecules can be pre-screened on computers prior to synthesis, avoiding costs. It is also easily tested whether a proposed change in the structure of a molecule, a particular substitution for example, can be expected to give the desired effect. This approach to design of molecules with specific properties – like molecules with low optical band gaps, high or low electron affinities or ionization potentials – is gaining momentum in both academia and industry.

"The ultimate goal of computational spectroscopy is, similarly, to be able to predict excited-state properties and spectra of real-life molecular species in gas and condensed phases, and to be able to study light-triggered reactions on the computer," says Sonia Coriani.

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How we adjust to sunlight

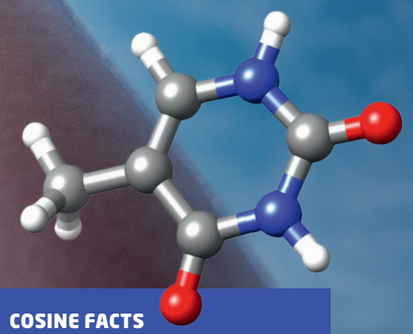
A recent joint project with experiments executed at the XFEL facility in California illustrates the scope of computational spectroscopy. The subject was thymine, which is a key DNA component. The thymine molecules were first excited by an UV laser pulse and then probed with a time-delayed X-ray pulse. This is an example of what is known as pump/probe spectroscopy.

"Based on computational spectroscopy tools we were able to explain the experimental results found by our American partners and identify the population of the electronic excited states involved in the de-excitation process," says Professor Sonia Coriani.

The experiment shows how the excited electrons in thymine release a major part of their newly acquired energy in just a few pico-seconds (1ps = 10^{-12} s).

"This ultrafast internal conversion is actually a vital mechanism, which contributes to explain why our DNA is surprisingly resistant to the destructive potential of UV radiation from the Sun," comments Professor Klaus B. Møller.

This example shows how computational spectroscopy can increase fundamental understanding in the field of photo-biology. Other applications where light-triggered reactions are important can be found in emerging scientific and technological fields dealing with optically active materials, organic opto-electronics, photo-medicine, and photo-catalysis.



COSINE FACTS

Beneficiaries:
UHEI, KTH, LMU, SNS, SDU, ENSCP, DTU

External Partners: Elettra Sincrotrone Trieste; Electromagnetic Geoservices ASA; EXACT Lab SRL; NVIDIA GmbH; DELL S.p.A; Bio Tools Inc.; PDC Center for High Performance Computing; UNITS

Total budget: EUR 3.7 million

DTU budget: 580,000 EUR

Webpage:
https://sites.google.com/site/itncosine

Opening the Door to Hybrid 2D Materials

For the first time, an organic and inorganic hybrid 2D material has been synthesized that combines the desirable properties of being electrically conductive and magnetic. The achievement marks the dawn of a new class of materials with possible applications in quantum computing.

Since the first synthesis of graphene in 2004, hundreds of 2D materials have been synthesized. However, the novel material chromium-chloride-pyrazine (chemical formula $CrCl_2$(pyrazine)2) is based on a truly groundbreaking concept. While the other known 2D materials are all inorganic – just like graphene – chromium-chloride-pyrazine is an organic/inorganic hybrid material. This allows for highly tunable properties which is advantageous in a range of possible applications, not least in future quantum computers.

An international team led by Assistant Professor Kasper Steen Pedersen, DTU Chemistry, has synthesized the new material.

"This marks a new type of chemistry, in which we are able to replace various building blocks in the material and thereby modify its physical and chemical properties. This cannot be done in graphene. For example, one can't choose to replace half the carbon atoms in graphene with another kind of atoms. Our approach allows designing properties much more accurately than known in other 2D materials," says Kasper Steen Pedersen.

A quantum revolution awaits

In principle, a 2D material has a thickness of just a single molecule and this often leads to properties very different from those of the same material in a normal 3D version. Not least the electrical properties will differ. While in a 3D material, electrons are able to take any direction, in a 2D material they will be restricted to moving horizontally through the chemical bonds.

Chromium-chloride-pyrazine is a layered material. Strictly speaking, it is not a 2D material in itself, but a precursor for a 2D material.

Besides the electrical properties, also the magnetic properties in chromium-chloride-pyrazine can be accurately designed. This is especially relevant in relation to the quantum revolution, promising much more powerful computers and improved electronics.

"Almost all other known 2D materials are non-magnetic in their pristine forms, hampering their use in emerging technologies relying on the quantum spin of transported electrons. Examples are spintronics, magneto-electrics, and multi-ferroics. While in normal electronics, only the charge of the electrons is utilized, also their spin – which is a quantum mechanical property – is used in spintronics. This is highly interesting for quantum computing applications. Therefore, development of nano-scale materials which are both conducting and magnetic is most relevant," Kasper Steen Pedersen notes.

How to tune magnetic properties

Recent years have seen vast efforts in semiconductors doped with transition metals. It is generally believed that such materials will be suited for spintronic applications due to their near-total spin polarization. However, the precise distribution of metal ions has so far proven difficult to control, and spatially low-dimensional systems have not been obtained.

As an alternative approach, Kasper Steen Pedersen and his colleagues were inspired by so-called reticular molecule-based metal-organic framework (MOF) chemistry. Here, the synthetic engineering of inorganic and organic modules leads to a range of possibilities for tuning both the physical properties and anisotropy of the chemical bonding in a 3D crystalline solid. Further, reports from other groups had shown promise for the isolation of novel 2D materials. These could either be structured as single sheets or as van der Waals heterostructures. For many 2D materials, the individual sheet is very strong in itself, but when stacked, the binding force between two layers is weak. The sheets are only held together by the van der Waals interaction, which is far weaker than covalent chemical bonds. This might sound like a problem, but in relation to spintronics and similar applications, it is actually an advantage. Since the interactions between the layers are weak, it will only require a small external change – for instance switching a weak magnetic field on and off – to tune the properties back and forth.

To introduce strong electronic and magnetic communication between spin carriers in such coordination solids, extensive electronic delocalization is essential. Indeed, record high electrical conductivities have been obtained in 2D coordination solids of ditopic or polytopic conjugated organic ligands and transition metal ions due to strong π-d conjugation between the ligand and metal ion orbitals.

"However, all of these materials are non-magnetic. We therefore turned our attention to a possible new type of 2D materials, where both magnetism and electronic conductivity could be tuned."

Time to investigate stability

Soon, the focus became the simple pyrazine ligand. This common ditopic ligand is found in thousands of crystallographically characterized coordination networks.

Published in the prestigious journal Nature Chemistry, September 2018, the group was able to present the isolation and characterization of a structurally simple layered coordination solid, chromium-chloride-pyrazine, which exhibits both long-range magnetic order and high 2D electronic conductivity.

In addition to quantum computing, chromium-chloride-pyrazine may be of interest in future superconductors, catalysts, batteries, fuel cells, and electronics in general.

Still, companies are not ready to produce the material right away, Kasper Steen Pedersen emphasizes:

"This is fundamental research. Since we are suggesting a material synthesized using an entirely novel approach, a number of questions remain unanswered. For instance, we are not yet able to determine the degree of stability of the material in various applications. However, even if chromium-chloride-pyrazine should for some reason prove unfit for the various possible applications, the new principles behind its synthesis will still be relevant. This is the door to a new world of more advanced 2D materials opening up."

Assistant Professor Kasper Steen Pedersen
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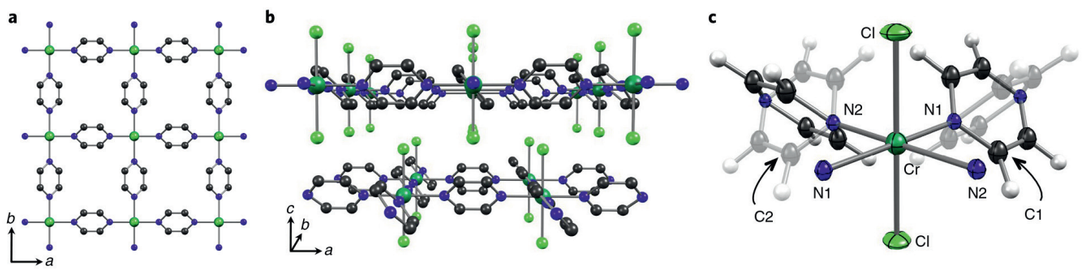

Structure of CrCl2(pyz)2. a) Fragment of the layered structure shown along the Cl–Cr–Cl. b) Perspective view of the staggered stacking of the layers perpendicular to the c direction. c) Thermal ellipsoid plot drawn at 80% probability level showing the positional disorder of the pyrazine rings (dark/light colour). Dark green, Cr; light green, Cl; blue, N; dark grey, C. Hydrogen atoms have been omitted in a and b for clarity.

Making the Leap

Assistant Professor Katrine Qvortrup has developed a new type of chemical linker with great potential. Multiple drug conjugates using the linker already lies ready in a freezer at DTU Chemistry.

A new initiative will help researchers at DTU Chemistry to generate market-ready innovations. After just one year, the initiative is creating results; a novel enzyme-cleavable linker with great medical perspectives is on steady course towards strong patents and multiple drug applications.

Converting research into actual innovations can be somewhat of a challenge. Concerns about patents, which partners to team up with, and how to optimize test phases can be difficult to keep an overview of.

That is why DTU Chemistry, in 2018, initiated an innovation concept called Springboard.

At Springboard meetings, Department researchers can pitch innovative ideas and get direct feedback from industry partners.

“Springboard is a setup that guides researchers in the most efficient direction in terms of innovation. We link directly to the industry and have board members with many years of innovation experience who can advise researchers on every step of the way – from idea to product,” says Innovation Leader Thomas N. Kledal.

The Springboard currently consists of external board members Mads Laustsen, CMO at Symphogen, and Ole Bitsch-Jensen, Senior Partnership Manager at Coloplast. DTU Chemistry’s management and Innovation Officers Anders Riisager, Jane Pedersen and Thomas N. Kledal are also part of the board.

The external board members have signed confidentiality agreements, so Springboard participants are able to discuss research projects in details – without holding back information.

Thomas N. Kledal stresses that Springboard is not an isolated initiative, but a part of the Department’s overall innovation portfolio.

Linker in demand

At the first Springboard, one of the presenters was Assistant Professor Katrine Qvortrup.

The Qvortrup Group at DTU Chemistry has developed a novel enzyme-cleavable linker technology for efficient and target-specific drug delivery. The flexibility in the design of the cleavable linker allows application in many different disease areas, including metabolic diseases, viral infections, and cancer.

According to Katrine Qvortrup, the chemical linker is able to release a wide variety of drugs, including alcohol-, amine-, and thiol-functionalized drugs. It is also very stable in plasma, which minimizes the drugside effects.

Even though the linker itself has great pharmaceutical potential, Katrine Qvortrup is convinced that Springboard acts as an important hub of knowledge when trying to commercialize an invention.

”Springboard evaluates your research through industrial glasses, so they know what to emphasize, throughout the entire innovation process. They give advice on which specific products your research is going to be held up against, and this is important to know in order to convince investors,” says Katrine Qvortrup.

Due to Springboard advices and the versatility of the linker, Katrine Qvortrup is already collaborating with multiple companies and research units.

Antag Therapeutics, for instance, are interested in the linker’s ability to target metabolic diseases by drug release in plasma at a controlled, predetermined rate. ADCendo and Rigshospitalet want to test the linkers in antibody drug conjugates, e.g. for breast cancer treatment. The company Synklino produces drugs treating viral infections, which make the company interested in phosphatase-cleavable linkers, since phosphatases are upregulated in viral infections. The highly modular design of the linker ensures that it can easily be modified to match the specific application, including enzyme and cleavage rate.

“In each of these collaborations, I need to have an overview of how to make the drug design process as efficient as possible, and Springboard offers a roadmap for this,” says Katrine Qvortrup.

Creating a stronghold

When your research has great application potential, patience can be the hardest virtue.

”As a young researcher, you want to see the research published,” Katrine Qvortrup points out. However, when it comes to developing new medicinal drugs, there is a long way from basic research to production, and if you move too fast on a patent, it will most likely be weak.

“One of my main discussions with the Springboard was; what experiments do I need to conduct in order to secure the strongest patents – for all of the linker’s applications. They emphasized the importance of securing patents on full conjugates, not only the linker, because a patent on the linker alone would be vulnerable regarding drug development,” says Katrine Qvortrup.

This has led to more extensive testing of the modified linkers, creating a vast amount of preliminary data on specific medicinal drug conjugates.

Within a few months, in vitro experiments will be conducted at Finsen Laboratory at Rigshospitalet. The next steps in testing are already being talked through with the Phase I Unit at Rigshospitalet.

“As soon as we have strong in vitro data, we will apply for patents. Our patents will consequently be much stronger, benefitting both industrial partners and The Qvortrup Group,” she says.

Data led to spin-off project

In addition to the two Springboard events in 2018, the board offers ongoing correspondence and follow up meetings.

“It is key element to follow up on what has been discussed at the Springboard event itself. Innovation work does not stop, when the researcher steps out the door. It has to become a more integrated, natural element in the research process,” Innovation Leader Thomas N. Kledal says.

A correspondence with Mads Laustsen, CMO at Symphogen and external Springboard member, led Katrine Qvortrup to see existing data in a new light.

“Mads Laustsen asked if my group and I could develop a novel method to attach selective compounds on antibodies, due to market demands from the industry. We already had a lot of preliminary data on a new method, but did not recognize the true value of it. Now we do,” she says.

According to Katrine Qvortrup, the Springboard feedback regarding the novel method, at the follow up meeting, helped qualify her grant applications even more – one of them leading to a DKK 4.4 million grant from the Carlsberg Foundation.

“Funds are an essential driver of elevating your research. Therefore, having sparring partners with inside knowledge of the market and what investors look for is quite valuable for scientists,” she says.

Innovation Leader Thomas N. Kledal
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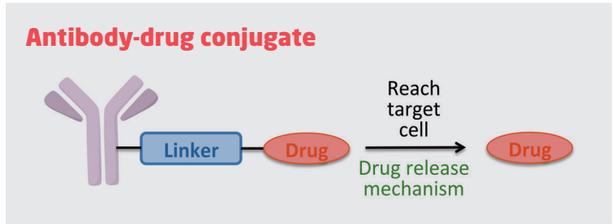

Antibody-drug conjugates (ADCs) are comprised of three parts; a monoclonal antibody, a cytotoxic agent (the ‘drug’), and a structural moiety that joins the two together, the ‘linker’.

– Current linker technologies suffer from plasma instability, inefficient drug release, and limited selectivity.

– Katrine Qvortrup linker technology: Highly modular design – ease of synthesis and expeditious optimization of properties, incl. solubility, stability, enzyme-lability, selectivity, and release-rate.

Exploring the Quantum Mechanics of Life

Capture, transport, and release of oxygen in the body is managed by one single molecular system. This is possible thanks to a delicate mechanism allowing fast and reversible modification of electron spins.

It is common knowledge that our blood transports oxygen. But only recently it has transpired that this vital biological function is based on a delicate mechanism based on the electron spin properties of the key molecule involved, the protein hemoglobin.

"The extraordinary property of hemoglobin is not so much its ability to bind oxygen, but rather its ability to bind and release oxygen quickly and reversibly with a small free energy difference as required for oxygen transport. Such fast, reversible oxygen binding is not commonly seen in chemistry. Life as we know it directly relies on the almost miraculous quantum mechanical properties of this single molecular system," says Professor Kasper Planeta Kepp, DTU Chemistry.

Given the extreme importance of the biological mechanisms involved in oxygen transport, the group at DTU Chemistry is obviously not alone in the field. However, the group has uniquely addressed the heme system across all its organization levels from fundamental quantum mechanics of individual atoms to the full protein structures and all the way up to studying cells and physiological implications of heme modifications, e.g. in diving whales and seals.

How iron captures oxygen

Hemoglobin is a so-called metalloprotein with iron (Fe) inside the protein directly involved in the oxygen binding. Besides the fact that iron is abundant on Earth, this element has several other attractive properties. Iron has a moderate effective nuclear charge, borderline Lewis acid properties, and is not too oxo-philic, nor too thio-philic and thus routinely forms complexes with a variety of ligands. Further contributing to flexibility, iron exists in several oxidation states.

Moreover, once associated with other atoms the richness and modest energy separations of the various electronic configurations of the d-orbitals of iron produce high degrees of freedom and spin-crossover properties. In other words, iron is uniquely suited for the highly flexible task of capturing, transporting, and releasing oxygen.

In hemoglobin, the iron atom is situated in a part of the molecule termed heme. Heme is a coordination complex consisting of an iron ion coordinated to a porphyrin ligand. Porphyrins are macrocyclic organic compounds. When iron(III) binds to porphyrin ligands in a weak ligand field, it produces a highly paramagnetic state having a half-filled d-shell with only spin-forbidden d-d transitions. In a stronger ligand field, however, rich transitions are offered. This is also the case for iron(II) complexes in both weak and strong ligand fields.

Bringing color to the world

Porphyrins have large ring-shaped structures. They typically absorb strongly in the visible region of the electromagnetic spectrum and are thus colored.

"Our ancestors largely associated the red color of blood with courage, war, danger, and suffering. Incidentally, similar transitions within the porphyrin-derived chlorophylls are responsible for the green color of plants, associated with nature, life, and hope. Thus, it is fair to say that electronic transitions in porphyrins have had vast cultural consequences," notes Kasper Planeta Kepp.

On the technical side, recent findings published by the group of Kasper Planeta Kepp at DTU Chemistry describe the spin crossover process of iron in complete detail, while another paper in the same journal introduces the first way to quantify oxo-philicity. These studies among many others have contributed to the overall understanding of the fundamental mechanism of oxygen transport in living organisms.

According to the current consensus, the iron-oxygen ($Fe\text{-}O_2$) bond largely results from so-called back-bonding. Here, electrons move from an atomic orbital of one atom to an appropriate symmetry anti-bonding orbital on a ligand. In other words, electrons from iron are used to bond to the ligand.

Making forbidden binding possible

Still, forming the iron-oxygen bond is only the first step in the function of hemoglobin as an oxygen transporter. The really big question is: How does the heme system facilitate fast and reversible binding of O_2, considering the spin-forbidden nature of this process?

To understand the answer to this question, one needs to take a closer look at the oxygen (O_2) molecule. O_2 has a triplet ground state with two unpaired, parallel-spin electrons. Inconveniently, the first excited singlet state lies far above this ground state in terms of energy (approx. 1 eV). The unpaired electron density of the π^* orbitals is reluctant to react with organic molecules, partly because of the low spin-orbit coupling of the involved atoms and partly because of the high energy of excited singlet oxygen species on the potential energy surfaces (PES) of oxidation reactions, which prevent reaction even if the spin-orbit coupling were moderate. In 2004, Kasper Planeta Kepp and his Ph.D. supervisor Ulf Ryde computed the first fully relaxed PES for O_2 binding to heme and showed spin-forbidden ligand binding to be mainly facilitated by allowing the spin states to be close in energy at dissociation and association. This remarkably produces a broad crossing region, maximizing crossover probability.

"This mechanism, referred to as the "broad crossing mechanism" remains a useful design principle for spin-forbidden ligand binding to transition metals," Kasper Planeta Kepp concludes.

Optimized by evolution

The close-lying spin states of hemes occur not only in hemoglobin, but also in various states of heme enzymes. Amazingly, the balance between spin state energies and back-bonding leads to a dual ability of heme to function either as an oxygen transporter (at low back-bonding) or an oxygen activator (at high back-bonding), enabling both the transport (in globins) and use (in heme enzymes) of oxygen in the molecular infrastructure of oxygen-based life forms.

"The spin-forbidden binding of heme has been the subject of substantial evolutionary optimization as this step could otherwise be slow and rate-limiting. However, the broad crossing regions are probably still required to facilitate fast reactions. In my opinion, the most important reactivity gain lies in the facilitation of spin inversion by the broad crossing region caused by close-lying spin states that accelerate binding rates by orders of magnitude."

In conclusion, fundamental quantum mechanics, in the form of the controlled spin-forbidden binding of O_2 to heme, has played a dominant role in the evolution of life.

"Without the porphyrin ring, it is hard to imagine how life as we know it could have existed. We now know that all the three defining features of photo-sensitizing, electron transfer, and spin crossover are present within the very same porphyrin ring. The binding of O_2 to heme is a truly quantum mechanical phenomenon with vast consequences for life on this planet!"

Unveiling the effects of oxygen-doping

The research of Kasper Planeta Kepp has also been important in relation to anti-doping. New emerging technologies aim to circumvent doping rules by increasing oxygen availability to cells during exercise by modifying the nature of oxygen. A well-known method is oxygen-deficient preconditioning, which increases the amount of hemoglobin in the blood to maintain the amount of bound oxygen, and which leads to increased oxygen delivery once performing at normal oxygen levels. The same effect is observed during and shortly after a trip to the mountains where oxygen pressures are lower.

Another, much-used class of emerging methods is so-called 'singlet oxygen' methods. Kasper Planeta Kepp has functioned as consultant for the World Antidoping Agency in its efforts to evaluate these methods.

"At the current stage, any athletic improvement from using these methods can be attributed to the placebo effect, as the singlet oxygen is never delivered to the cells," he comments.

Professor Kasper Planeta Kepp
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PhD

PhD from DTU Chemistry

DTU Chemistry takes pride in educating PhDs at the highest international level. We present a diverse research education in modern chemistry, which contributes to the development of cutting edge science at the department. The goal for all PhD students is to publish in leading journals and participate in leading international conferences during their three year long research education.

PhD ChemClub

The PhD students at DTU Chemistry are strengthening their professional and social network at the Department. They do this through the PhD ChemClub. PhD students run the ChemClub, and they arrange several annual events: PhD Symposium, post-graduate career events with experts from industry and academia, inspiring talks by invited speakers, and social gatherings. We invite interested candidates to have a look at our website kemi.dtu.dk/English, where you can read more about our PhD programme as well as the DTU Chemistry research areas.

Power Performance

Excellent scientists must also be able to communicate their research results efficiently. Therefore, DTU Chemistry offers each PhD student an intensive communication course (1.5 ECTS) to practice their presentation techniques to perfection. A cornerstone in this regard is the annual PhD Symposium at which stakeholders from the industry are invited to attend both oral presentations and a poster session by the Department's PhD students.

Contact us!

In the following pages, you can get acquainted with the DTU Chemistry PhD Defences of 2018. All supervisors invite you to get in touch, if you are interested in the full thesis, in further information, or in a possible collaboration. You are also welcome to contact the Head of the PhD School, Professor Erling H. Stenby, Head of Department, ehst@kemi.dtu.dk

More than a hundred researchers, partners, and PhD students participated in the 2018 PhD Symposium held at Comwell Borupgaard. 38 scientific posters and 12 PhD presentations showed the versatility and great application potential of the research at DTU Chemistry.

In-silico Screening for Anti-cancer Drug Candidates

A few inhibitors of histone deacetylases (HDACs) are already approved for treatment. Through computational chemistry, the project supplies new insight into this new class of anti-cancer drugs.

While DNA (deoxyribonucleic acid) is the molecular basis of genetics, several gene expression changes occur which are not coded in the DNA sequence itself. These are termed epi-genetic changes. As several diseases, including a number of cancers, are linked to epi-genetic changes, vast academic and industrial efforts are directed towards drug candidates which may be able to inhibit specific epi-genetic changes. Using computational methods, the project focuses on histone acetylation, which is an important type of epi-genetic modifications.

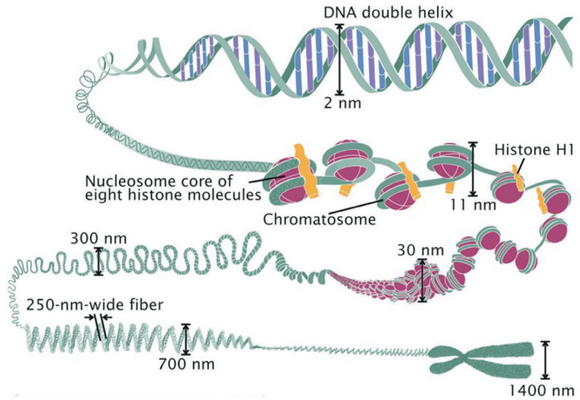
Histone deacetylases (HDACs) are a family of enzymes that contribute to the regulation of DNA expression. Over-expression of certain HDACs has been observed in several types of cancer including gastric, prostate, colon, breast, and cervical cancer. A few HDAC inhibitors have been approved for treatment of various cancers.

In the project, *in silico* studies were carried out to evaluate the binding mode and affinity of a collection of known macrocyclic HDAC inhibitors and their analogues towards class I HDACs. One particularly interesting class of HDAC inhibitors is the macrocyclic peptides and depsi-peptides, which are highly potent and moderately selective, and can be found in nature. The studies in this project confirmed the higher potency of hydroxamate analogues in comparison with their norvaline counterparts, as well as the crucial role of an aspartate in achieving the optimal binding position. Furthermore, the unexpected interaction between aromatic side chains of the inhibitors and the catalytic zinc ion opened a new line of investigation for possible HDAC inhibitors.

Another part of the project focused at class III HDACs, also known as sirtuins. These are NAD+-dependent enzymes with homology to the silent information regulator 2 yeast enzymes. There are seven proteins in the sirtuin family and they all share a conserved 270 amino acid catalytic domain, with variable N- and C-termini. These enzymes have been suggested as therapeutic targets for diabetes, cancer, neurodegenerative diseases and inflammation.

Molecular Dynamics simulations of NADH inhibition of SIRT1, SIRT3, and SIRT5 showed that the addition of a single proton in the nicotinamide ring can induce an important conformational change on NADH, causing misalignment of the nicotinamide amide to the key residues in the C pocket and ultimately resulting in a significant loss of binding affinity. Further, a homology model of SIRT7 was generated. The model includes the secondary structure of both N- and C- termini. The catalytic domain depicts a Rossmann-fold and a Zn^{2+}-binding domain. The termini show a well-defined a-helix organization, essential for the DNA binding. The model is further supported by phylogenetic and structural analyses.

Besides the actual findings, the project contributes to demonstrate that molecular modelling is quickly becoming a go-to approach for efficient, robust and less costly studies.



Chromatin organization.

Ana Rita Colaço
PhD

"In Silico Characterization of Substrate and Inhibitor Specificity of Histone Deacetylases"

Funded by
Lundbeck Foundation and DTU Chemistry

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Christian A. Olsen

Cleavage of Carbon-Carbon Bonds

With applications ranging from energy production to chemical manufacture, cleavage of carbon-carbon bonds in aldehydes and ketones plays a key role in organic chemistry.

The disconnection of carbon-carbon bonds is important in organic chemistry, and generally even more challenging than the formation of these bonds. The project was organized in two parts. In the first part, the focus was the hydroxide-mediated cleavage of carbon-carbon bonds in aldehydes and ketones. The second part involved Ruthenium catalyzed dehydrodecarbonylation of primary alcohols. Both types of reactions result in carbon-hydrogen bonds in place of carbon-carbon bonds.

Hydroxide-mediated cleavage of carbon-carbon bonds in aldehydes and ketones has been known for more than a century. The generated fragments are the carboxylate and various neutral residues such as ketones, nitroalkanes, sulphonyl alkanes, tri-halo-alkanes, and other moieties. The neutral residues are all weak acids (pK_a values between 10 and 40). In the project, toluene residues with a pK_a of about 41, was also cleaved from ketones with hydroxide in generally good yields.

Cleavage of different substituted benzylic ketones and aldehydes promoted by hydroxide sources in various solvent systems were studied to investigate the scope of the reaction and clarify the mechanism. Kinetic data from Hammett correlation plots were compared with theoretical values from density functional theory (DFT) calculations. DFT calculations were also conducted to determine the relative free energies of possible intermediates and transition states.

Dehydro-decarbonylation of alcohols is an attractive reaction based on two individual processes: the acceptorless dehydrogenation of an alcohol and the decarbonylation of the resulting aldehyde. In this transformation, valuable products are formed such as the unfunctionalized organic residue and two gases, hydrogen and carbon monoxide, respectively. The gaseous mixture is also known as synthesis gas ("SynGas") and has many applications ranging from energy production to chemical manufacture.

Rhodium and Iridium complexes have previously been investigated to mediate this process. However, both of these metals have limitations in scope and affordability. Therefore, in this work a cheaper alternative is presented, based on the system $Ru(COD)Cl_2$ and the phosphine P(*o*-tolyl)$_3$ for the dehydrogenative decarbonylation of alcohols.

The reaction was applied to both benzylic and long chain linear aliphatic alcohols. The intermediate aldehyde can be observed during the transformation, which is therefore believed to proceed through two catalytic cycles involving first dehydrogenation of the alcohol, followed by decarbonylation of the resulting aldehyde.

Andrea Mazziotta
PhD

"Cleavage of Carbon-carbon Bonds in Aldehydes and Ketones"

Funded by
DTU Chemistry

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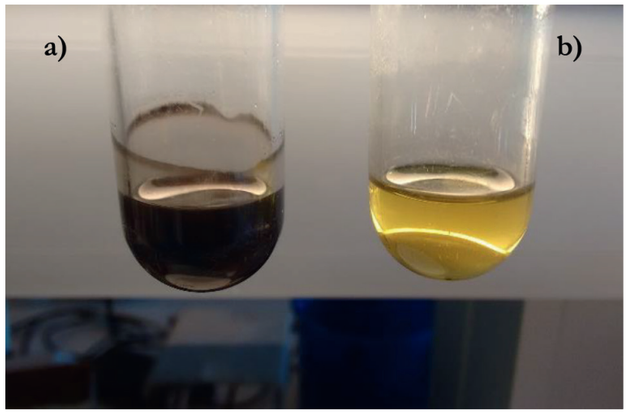

Difference between reactions running with a) 10% of ligand and b) 15 %. The first one show catalyst decomposition responsible for the black color, while the second is clear.

New Tools in Transition Metal Catalysis

Manganese is interesting as a cheaper and less toxic alternative to palladium and other established transition metals as catalysts in organic chemistry.

Transition metals are known to be excellent catalysts in a number of important organic chemistry reactions. While palladium is the most exploited transition metal for the purpose due to its high catalytic efficiency, efforts are directed towards finding other metals which are cheaper and less toxic. The project focuses on use of manganese catalysts in radical coupling reactions.

Catalytic cross-coupling involves a catalyst in the reaction mechanism leading to a repeating catalytic pathway – the catalytic cycle. Dating back to the beginning of the 20th century, the first types of coupling reactions formed the homocoupling product and used stoichiometric amounts of metal. From the early 1970'ies and later on, a number of much more efficient cross-coupling reactions with transition metals as catalysts were found. Especially, palladium was recognized as highly efficient – leading to the 2010 Nobel Prize in chemistry being award to Heck, Negishi, and Suzuki, three pioneers in palladium-catalyzed cross-couplings.

Palladium remains the catalyst of choice in a number of industrial and academic research applications, but the high price of this metal along with toxicity issues has initiated attempts to identify cheaper and less toxic alternatives. The aim of this project was to expand the conditions of the known cross-couplings to include homogeneous manganese catalysts.

Firstly, a procedure for *N*-arylations through a non-cross-coupling mechanism was explored, but found too difficult to control.

Secondly, a Buchwald-Hartwig Catalyzed Cross-Couplings procedure was examined. It was not possible to reproduce findings from the literature. Instead, the reaction was shown to be catalyzed by 10-100 ppm of a copper catalyst. Likewise, it was impossible to reproduce literature findings for a Manganese Catalyzed Stille Cross-Couplings procedure. Instead, the reaction was shown to be catalyzed by 30 ppm of a palladium catalyst.

Further, a Manganese Catalyzed Kumada Cross-Couplings procedure was examined. The scope of this reaction was limited for the electrophile, which was attributed to an aryl radical anion intermediate that was indicated by a clock experiment.

Finally, Dimethyl Zinc Mediated Radical Alkylation of β–Bromostyrenes was investigated. The attempts at a manganese catalyzed Negishi cross-coupling resulted in the discovery of a radical coupling of β–bromostyrenes with ethers and tertiary amines.

Andreas Ahlburg
PhD

"Manganese Catalysis in Radical Coupling Reactions"

Funded by
The Danish Council for Independent Research - Technology and Production Sciences. The project involved an external stay at Haldor Topsøe A/S

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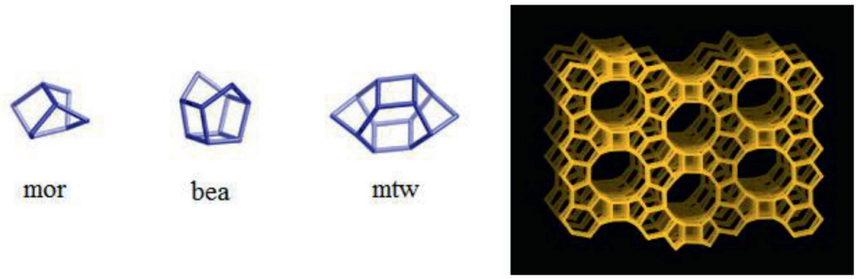


Composite building blocks and framework view adapted from Database of Zeolite Structures.

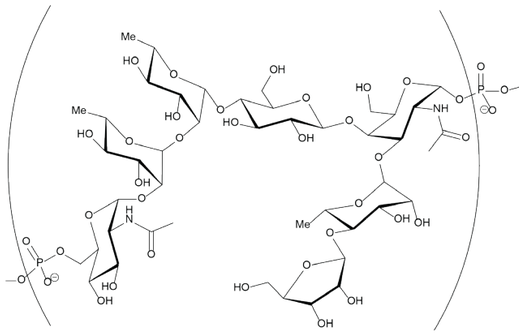
Polysaccharide Structures investigated by NMR

Nuclear magnetic resonance (NMR) spectroscopy is a reliable tool for elucidation of carbohydrate structures important to human metabolism and immune-defense.

In biological life, carbohydrates are perhaps most commonly known for their role as an energy source, but they actually fulfill a broad range of tasks. In order to understand these roles better, knowledge of carbohydrate structures is important. The most reliable tool for this purpose is nuclear magnetic resonance (NMR), which was used in the project to elucidate various carbohydrate structures.

Carbohydrates are highly complex molecules. They can be branched and derivatised, making them optimal for specific recognition. This specificity is instrumental in numerous biological processes, for instance in metabolism when a given enzyme will hydrolyze a specific carbohydrate, but not others. Other examples involve the function of the immune-defense, and also the mechanisms used by pathogens to hide from attacks from the immune-defense.

NMR spectroscopy relies on the alignment, or polarization, of nuclear spins when subjected to a magnetic field and the subsequent manipulation of these spins. The outcome of these spin manipulations are then measured using a radio-frequency module. Carbohydrates primarily consist of hydrogen, carbon, and oxygen. NMR is ideal for obtaining data on the positions of hydrogen and carbon in the molecular structure. Both elements have abundantly occurring isotopes (^{1}H and ^{13}C respectively) with precisely the spin necessary for NMR detection.



Repeating unit structure of the capsular polysaccharide from Streptococcus pneumoniae serotype 7C.

Firstly, the capsular polysaccharide of *Streptococcus pneumoniae* was studied. As this polysaccharide is responsible for much of the bacteria's virulence, understanding the structures of the polysaccharide from different serotypes can improve the understanding of the pathogen. The structure of a novel serotype in serogroup 7 was elucidated.

Secondly, *Inonotus obliquus* – commonly known as the chaga mushroom – was investigated. This fungus has been used in Eastern European folk medicine to treat a variety of symptoms. It contains several polysaccharides of medicinal interest. These were extracted and purified, and different structural trends were determined.

A third branch of the project focused on β–Lacto-globulin, which is a major protein present in dairy products. Little is known about its ability to bind carbohydrates. Several polysaccharides were fragmented into oligosaccharide mixtures and characterized to be used for binding studies.

Further, human milk oligo-saccharides (HMO's) were investigated. HMO's are complex, and during synthesis via transglycosylation several products can be formed, making the structural determination troublesome. Here, the transglycosylation products of three different β–acetyl-glucosaminidases using lactose as acceptor were identified.

Finally, dissolution dynamic nuclear polarization was used to increase the sensitivity of single scan solution 13C-NMR. The method is able to increase sensitivity with up to four orders of magnitude, and using a doubly isotopically labelled β–galactopyranoside the *lacZ* β–galactosidase was investigated. Previously undescribed short-lived transglycosylation products of the enzyme were observed, and by using a kinetic model the hydrolysis and transglycosylation rates were determined.

Christian Kjeldsen
PhD

"Structural Elucidation of Polysaccharides and Investigations of Enzymatic Synthesis of Oligo-saccharides using NMR Spectroscopy"

Funded by
The Novo Nordisk Foundation

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Better Calculation of Chemical and Phase Equilibria

The project presents a new set of algorithms which are demonstrated to be effective for complicated systems in chemical industry and oil recovery.

Simultaneous calculation of chemical and phase equilibria (CPE) is highly relevant in the chemical industry, in oil and gas production, and in geochemistry. The project presents a new set of algorithms which are demonstrated to be robust and effective even for complicated systems.

CPE calculations are essential in demanding simulations of industrial processes. The applications include reactive distillation, heterogeneous organic synthesis, fuel synthesis from renewable feedstocks, and oil and gas production. Such calculations are also useful in association equation of state models, since association can be regarded as a type of reaction.

One class of CPE methods are the stoichiometric. While these are more intuitive, they are known to be less effective for systems involving many reactions. As complex challenges are the focus of this project, thus a non-stoichiometric approach was chosen.

The proposed solution is a hybrid of two different non-stoichiometric approaches and is therefore named "the combined method". The first of the two methods, the Lagrange multipliers method, successive substitution is employed to solve a modified set of equations originating from the Lagrangian conditions at the minimum. The second method, the modified RAND method, one of the Lagrangian conditions is linearized around the current estimate of mole numbers. Composition derivatives of fugacity or activity coefficients are utilized to achieve quadratic convergence.

Combining the two methods improves robustness and efficiency. The Lagrange multipliers method is used for the first iterations of successive substitution, and the modified RAND method for final second-order convergence. The combined algorithm has several advantages including a smaller system of equations (fewer variables), less sensitivity to initial estimates, the same treatment for all components and all phases, and the ability to monitor the decrease in Gibbs energy in the modified RAND step to guide convergence.

The combined method was applied to vapor-liquid, liquid-liquid, and vapor-liquid-liquid equilibrium of ideal as well as non-ideal systems for acid/alcohol esterifications, alkene/alcohol etherifications, hydration, hydrogenation, and isomer preparation. Additionally, predictions were made for the more complex transesterification of two individual triglycerides with methanol, which entails five chemical reactions and can result in one-, two-, or even three-phase equilibrium. Finally, CPE calculations were attempted for electrolyte systems, and the equilibrium solution was obtained for aqueous mixtures of electrolytes in contact with a vapor and a solid phase. As the method is robust to the presence of a solid phase, the algorithms are applicable even to more complicated geological systems with an electrolyte aqueous phase and multiple solids.

In summary, the method proved applicable all the way from simple one-reaction ideal systems to highly non-ideal electrolyte mixtures with speciation reactions and solids. Both algorithms were able to converge to the equilibrium solutions. Considering CPU time and the reasonable number of iterations, the method is demonstrated to be efficient and robust.

The project also involved a small study on dimethyl ether (DME) phase equilibrium modeling.

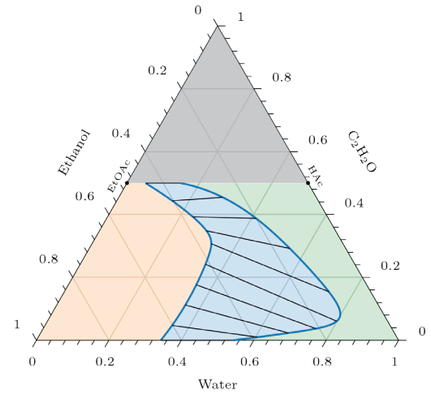
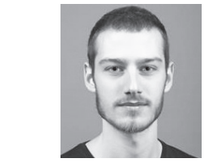


Figure 4.6: Ternary diagram of elements in acetic acid/ethanol esterification at 355 K and 1 atm [binodal curve (—), tie lines (—), VLE region (▭), vapor region (▭), liquid region (▭), infeasible region (▭), HAc (acetic acid), EtOAc (ethyl acetate)].



Christos Tsanas
PhD

"Simultaneous Chemical and Phase Equilibrium Calculations with Non-stoichiometric Methods"

Funded by
DTU Chemistry.
Co-sponsored by the Danish Hydrocarbon Research and Technology Centre (DHRTC)

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Platform Chemicals for Renewable Polymers

Catalytic reactions for removal of oxygen from bio-based raw materials are needed to obtain platform chemicals mimicking those used today.

With the inevitable exhaustion of fossil resources, finding renewable bio-based alternatives becomes increasingly important. A major challenge when employing biomass as a renewable resource is the natural high abundance of oxygen. Therefore, catalytic reactions for oxygen removal are needed to obtain platform chemicals mimicking those used today. The project is mainly focused on synthesis of renewable precursors for production of polymers.

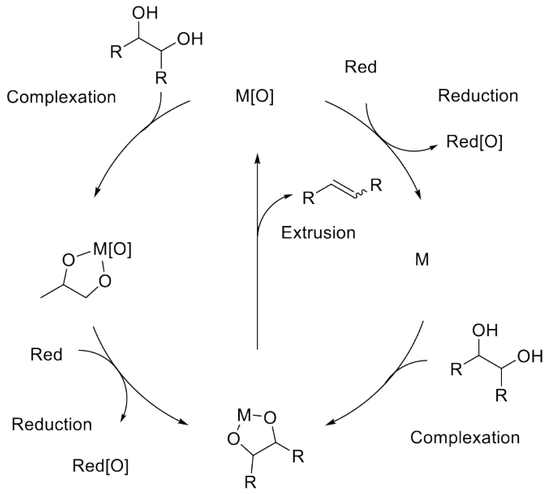
In relation to renewable materials, it is desirable to use non-edible biomass, meaning cellulose, hemicellulose, and lignin. A vast amount of reactions have been developed aiming to turn these compounds into either known chemical compounds or novel bio-based building blocks. In both cases, catalysis is fundamental for maintaining efficient and renewable reactions.

When optimizing a given type of catalytic reaction, it is necessary to know the intricate mechanism of the system. This can be determined through experimental studies, such as Hammett studies, or by utilization of labelled compounds. However, it may instead be possible to elucidate the catalytic mechanisms through advanced computational quantum mechanical studies, avoiding the need for laboratory experiments.

In the first part of the project, two reactions for oxygen-removal from biomass were investigated; the deoxy-dehydration and the hydro-deoxygenation reactions. The former was studied using both vanadium and rhenium catalysts, whereas the latter was performed using a molybdenum catalyst. Further, density functional theory (DFT) was applied for elucidation of the intrinsic mechanisms of the reactions. This led to discovery of new types of mechanisms for both reactions, explaining differences in reactivity compared to what was reported in the literature for similar systems.

The second part of the project focused on the utilization of bio-based platform chemicals for synthesis of novel thermo-set polymer materials. Here, the diallyl furan-2,5-dicarboxylate monomer was tested through a plethora of different cross-linking techniques. This monomer is of high interest due to being derived from allyl alcohol and the bio-based building block 2,5-furan-dicarboxylic acid, the latter being a possible replacement for phthalates. The studies led to various new materials, along with new methods for determinations of molecular weights of branched polymer systems, by examining the intrinsic growth patterns of hyper-branched polyester systems.

Summing up, the project has contributed to further development of methods for production of bio-based platform chemicals.



Generally accepted mechanism for the catalytic DODH reaction.

Daniel Bo Larsen
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"Development and Utilization of Bio-based Platform Chemicals for Renewable Materials"

Funded by
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Tomatoes inspire future Bio-polymers

Synthesis of polymers found in the skin of tomato fruit provides insight into fundamental natural mechanisms.

Polymers which are produced from biomass rather than fossil raw materials are emerging as a new class of materials. Here, it is interesting to study polymers already present in plants. The project provides new insight into the structure and function of the plant polyester cutin which possesses several properties that are suitable for the polymer industry.

Plants maintain their structure through the formation of a rigid extracellular structure, namely, the plant cell wall. The cell wall is covered by a protective layer, the cuticle. Acting as a skin for the plant, the cuticle is a primary barrier against mechanical stress, pests, microorganisms, UV light, and other types of stress. The cuticle is a lipophilic composite material made of organic soluble compounds referred to as cuticular waxes, embedded in a polymeric scaffold named cutin.

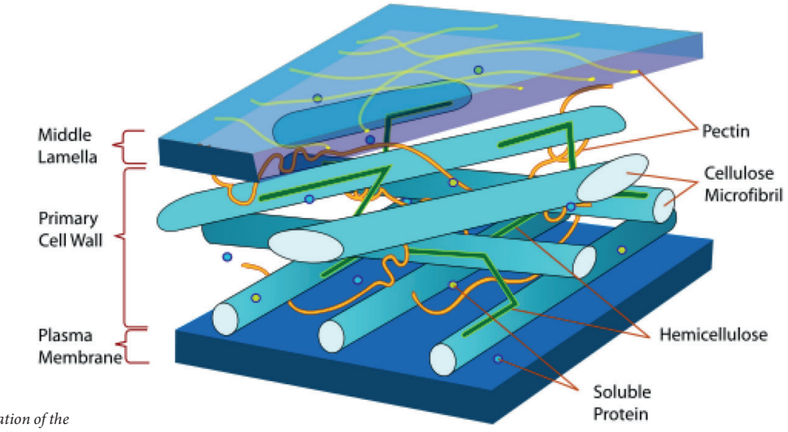
Understanding the bio-information of cutin is important both for fundamental biology and for industrial applications. Despite the fact that the monomeric composition of cutin has been thoroughly studied in the past, not much is known about its three-dimensional structure. Tomato fruit has a high cuticle density, making it easier to obtain samples.

Up to date, very little is known about cutin synthases (CUS) enzymes, their selectivity, their tertiary structure and their mechanism of action

The synthesis of a cutin monomer, a deuterated derivative of this monomer, as well as five other 2-MHG derivatives was accomplished. All these compounds have been synthesized to be used in CUS1-mediated polymerization to gain more information on CUS1 selectivity and mechanism of action. Additionally, the use of one of these compounds as a CUS1 ligand in co-crystallization experiments was initiated.

Further, four 2-MHG derivatives in which the *sn*-2 glyceryl moiety was substituted by other small alcohols were synthesized. The subsequent enzymatic assays showed that CUS1 present activity towards fatty acid esters different than 2-MAGs including the product of the migration of the glyceryl moiety to one of the primary hydroxyls, 1-MHG.

Finally, the interaction between CUS1 and its substrates through the formation of hydrophobic tunnels was investigated by the formation of CUS1 mutants through site-directed mutagenesis. Also, the investigation of several Arabidopsis GDSL mutants as potential suberin synthase was initiated through the production and characterization of knockdown mutants via RNA silencing.



Representation of the primary cell wall

Gauthier Mike L. Scavée
PhD

"Synthesis and Investigation of the Bio-polymerization of Cutin Monomers and Derivatives"

Funded by
The Novo Nordisk Foundation and DTU Chemistry.

The project involved extensive cooperation with the group of Professor Jocelyn K. C. Rose, Cornell University

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Photoinduced Molecular Dynamics in Solution

A novel modelling strategy for simulating the structural dynamics of complex molecular systems in solutions is presented.

Photocatalytic processes are highly relevant in both academic research and in a range of industrial applications. In recent years, new powerful X-ray facilities have made it possible to observe these processes in real time. Such experiments do not provide direct insight, but need to be accompanied by extensive modelling and theory. Especially photocatalytic processes taking place in solution are challenging to monitor, as photocatalytic complexes tend to undergo structural modifications or change the solvent in which they are embedded. In the project, a novel modelling strategy for simulating the structural dynamics of complex molecular systems in solutions was developed.

Being able to observe the dynamics of the chemical bond in real time is one of the greatest achievements of physical chemistry. Nuclear vibrational motion unfolds on a very short time scale, the femtosecond time scale (1 fs = 10^{-15} s). Previously this was out of reach, but over the last three decades femtosecond X-ray scattering measurements have emerged. In the project, experiments were carried out as part of an experimental campaign at the Linac Coherent Light Source (LCLS) X-ray Free Electron Laser (XFEL) of Stanford University, USA.

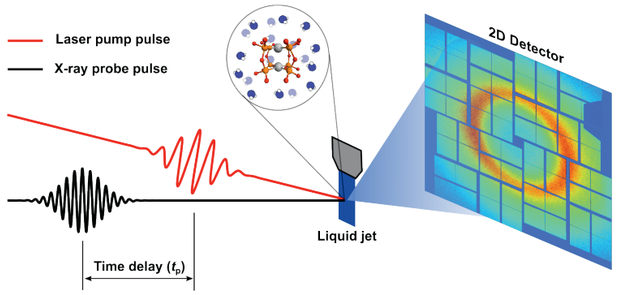
Photocatalytic reactions involving transition metal complexes in solution are popular targets for time-resolved experiments. Apart from their scientific and industrial importance, these systems are attractive to study due to their stability in solution, remarkable photophysical properties, and the presence of electron-rich atoms. However, in order to exploit their structure-function relationships an understanding of the mechanisms behind ultrafast light-induced reactions in complex environments is required. The experiments aimed to elucidate these mechanisms. These novel experiments cover grounds often dominated by complex interplays between vibrational relaxation, solvent effects and electronic couplings. Therefore, solid theoretical and modelling strategies are needed along with advanced computational methods.

In the project, a novel multiscale atomistic modelling strategy for simulating the structural dynamics of complex molecular systems was implemented and applied. The method is based on the direct Born-Oppenheimer Molecular Dynamics propagation of the nuclei and treats solvent effects within a quantum mechanics / molecular mechanics (QM/MM) framework.

Initially, the QM/MM scheme was augmented to include electronic excited states with arbitrary spin multiplicity using a ΔSCF approach.

Further, the photocatalytic diplatinum(II) complex $[Pt_2(P_2O_5H_2)_4]^{4-}$, abbreviated PtPOP, was studied. Owing to its nuclear and electronic structures, PtPOP is the prototype system of choice for photophysical studies within a family of highly photoreactive d^8-d^8 binuclear complexes which can catalytically abstract hydrogen and halogen atoms from different substrates. It was shown how ΔSCF for the first time provided computational evidence that the lowest-lying singlet and triplet excited states have parallel potential energy surfaces along the Pt-Pt coordinate. Also, the synergy between time-resolved experiments and simulations in unravelling the photoinduced ultrafast dynamics of the complex in water was highlighted.

Finally, a step forward was taken in understanding excited-state vibrational relaxation in solution. It was shown that after relaxation, PtPOP does not, as previously believed, retain the symmetry of the ground state; and excess Pt-Pt vibrational energy is first directed towards vibrational modes involving the ligands, while the role of the solvent is to favor intramolecular vibrational energy redistribution in the complex.



Schematical illustration of an optical pump/X-ray probe setup for time-resolved X-ray diffuse scattering (XDS) experiments.

Gianluca Levi
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"Photoinduced Molecular Dynamics in Solution – Multiscale Modelling and the Link to Ultrafast Experiments"

Funded by
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Creation of Carbon-Carbon Bonds

A manganese catalyzed cross-coupling reaction between aryl halides and Grignard agents is promising for green chemistry organic synthesis.

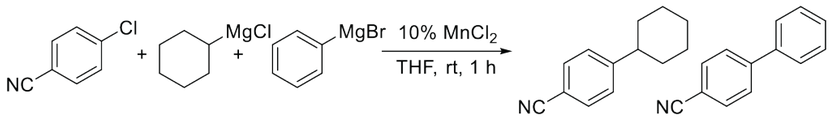
Still more chemists are faced with the task of producing fuel and other chemicals from non-fossil raw materials. Furthermore, they need to improve the sustainability of chemical processes by producing less waste. Catalysis is part of the solution to both problems. The project focusses on manganese catalyzed reactions for creation of carbon-carbon bonds.

Cross-coupling reactions which create a carbon-carbon bond are among the most important reactions in organic chemistry. The main focus of this project is the Kumada cross-coupling reaction which starts from a Grignard agent and an organic halide. When reported independently in 1972 by the groups of Robert Corriu and Makota Kumada, palladium (or nickel) catalyzed cross-coupling reaction was the first to be presented. The Kumada reaction continues to be used in a range of industrial applications such as the synthesis of drugs and manufacture of electronic components.

Palladium is a very versatile catalyst, but has the drawback of being both expensive and toxic. Therefore, finding good substitutes has become of interest. This project presents a $MnCl_2$-catalyzed cross-coupling reaction between aryl halides and Grignard agents.

Aryl chlorides containing a cyano or an ester group in the para or ortho position react smoothly and in good yield. A variety of alkyl- and aryl-magnesium chlorides can be used in this cross-coupling reaction. The cross-coupling is believed to proceed by a SRN1 mechanism, and radical clock experiments were performed to elucidate this pathway. A tri-organo-manganate complex is believed to be formed by the reaction between the organo-magnesium halide and manganese chloride, and it serves both as the nucleophile and the single electron donor. Other mechanistic hypotheses were excluded on the basis of the performed experiments.

An improved protocol was developed for the manganese catalyzed cross-coupling of two aryl-magnesium bromides under an atmosphere of dioxygen. The reaction is performed with a 2:1 ratio between the Grignard reagents and 20 % of $MnCl_2$. When the limiting Grignard reagent undergoes little homo-coupling under the reaction conditions, very good yields of the hetero-coupling product can be achieved. Aryl-magnesium bromides with 4-methoxy, 4-dimethylamino, 4-fluoro, and 4-chloro substituents give high yields in the cross-coupling while heterocyclic Grignard reagents turned out to be poor substrates for the reaction.



Reaction tested in the competitive time study.

Giuseppe Antonacci
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"The Manganese-Catalyzed Cross-Coupling Reaction"

Funded by
The Danish Council for Independent Research - Technology and Production Sciences

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Novel Strategies in Anti-cancer Drug Delivery

Radio-iodinated liposomes have been developed with the aim of maximizing efficacy of local internal radio-therapy and minimizing side effects.

Localized internal radio-therapy offers the advantage of destroying primary solid tumors efficiently. However, it remains a challenge to find the optimal way to deliver the relevant isotopes in the body. The project presents remote loading strategies for incorporation of therapeutic compounds and contrast agents into gels and liposomes.

Radio-therapy is one of the most effective types of anti-cancer treatment. The aim is always to deliver the optimal dose to the tumor and the lowest possible dose to the organ at risk. To that end, local internal radio-therapy has emerged as an alternative to external beam radiation. For instance, brachy-therapy has proven successful in prostate cancer treatment, with very rare toxicity and a ten-year cancer-specific mortality of less than 5 %. This therapy relies on implantation of radioactive seeds nearby the cancer tissue, highlighting the importance of tumor-specific delivery and retention of radionuclides.

Over the last few decades liposomes have been investigated extensively as carriers for drug delivery. Liposomes are spherical, self-assembled structures formed by single or several concentric lipid bilayers with an aqueous phase inside and between the lipid bilayers. This structure enables them to entrap compounds. Several liposome systems are approved for drug delivery.

In the project, radio-iodinated liposomes were developed for radio-therapy and for molecular imaging to enable image guidance in therapy. Further, therapeutic radionuclide loaded injectable in situ forming depots were designed with the aim of minimizing side effects of radio-therapy and maximizing efficacy.

Firstly, the iodinated imaging agent diatrizoate was functionalized with a free amine to enable its remote loading into the stealth liposomes. An efficient remote loading method was developed for loading of liposomes with iodine and its radionuclides. Further, functionalized diatrizoate was radio-labeled with ^{125}I and ^{124}I to optimize the radiolabeling protocol and perform PET imaging. Following radio-labeling of the compound, the ^{124}I-radiolabeled diatrizoate analogue ([^{124}I]ADA) was remote-loaded into the stealth liposomes under optimized loading conditions. These liposomes were evaluated in mice *in vivo* quantifying the bio-distribution by PET/CT scanning. [124I]ADA showed prolonged blood circulation of 19.5 h and low accumulation in the spleen, liver, kidney, and tumor.

Also, injectable *in situ* forming depot formulations for the local delivery of therapeutic β-emitters, ^{177}Lu and ^{90}Y, in the tumor were investigated. A novel approach for brachy-therapy was proposed. ^{177}Lu and 90Y were complexed with hydrophobic chelators to enable their controlled release from the depots or prolonged retention in the depot and tumor, and subsequent cellular internalization. The *in vivo* release of ^{177}Lu was quantified by SPECT/CT imaging, and in vivo therapeutic efficacy of an optimized ^{177}Lu depot was evaluated and tumor growth retardation up to eight days was observed. ^{90}Y depots demonstrated even better anti-tumor efficacy, inhibiting tumor growth for twenty days. Also, the treated mice showed prolonged survival.

Gokce Engudar
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"Remote loading Strategies for Incorporation of Therapeutic Compounds and Contrast Agents into Gels and Liposomes"

Funded by
DTU Chemistry

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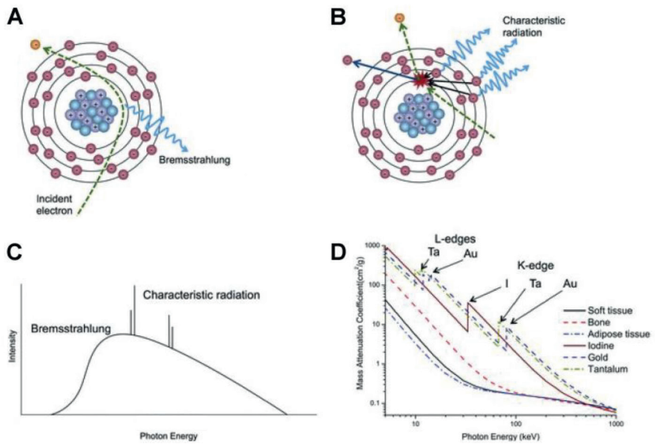


X-ray generation. A) Production of Bremsstrahlung. B) Production of characteristic radiation. C) X-ray emission spectrum showing Bremsstrahlung and characteristic radiation. D) Mass attenuation coefficient of some tissue and heavy elements as a function of X-ray energy.

Mimicking Nature's Polymer Synthesis

The polyesters cutin and suberin play key roles in protecting plants against external stress factors. Synthesizing these natural polymers in the lab is a gateway to new insight.

Plants produce a range of polymers, which are potential sources of renewable and biodegradable plastic. In the project, the approach of a synthesis chemist is applied in order to understand the biosynthesis of cutin and suberin, two of the most abundant natural polyesters, by synthesizing some of their monomers and studying their enzymatic polymerization in vitro.

All living organisms are covered by a layer of polymeric structural components, which defines their boundaries and serve as a barrier towards their environment. In the case of higher plants, especially two polyesters are instrumental in this protective function: cutin, located in the cuticle, which is found in the aerial parts of the plant, and suberin, in the underground parts and wound surfaces. Despite their highly important role in biological life, until recently little was known about the structure and biosynthesis of cutin and suberin.

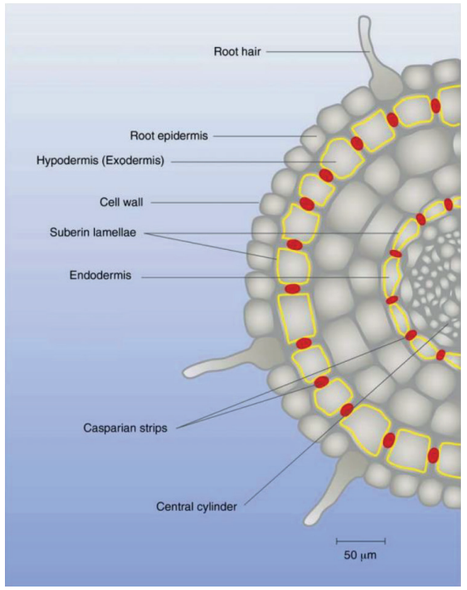
Within the last decade, however, some light has been cast upon the subject. First, the essential role of glycerol-3-phosphate acyltransferases (GPAT) in cutin biosynthesis was discovered. GPATs selectively produce 2-mono-acylglyceryl esters (2-MAG) of fatty acid monomers. The most abundant monomer in tomato fruit (*Solanum lycopersicum*) cutin is 10,16-dihydroxyhexadecanoic acid. Its correspondent 2-MAG, 2-mono(10,16-dihydroxyhexadecanoyl) glycerol (2-MHG) was found in the soluble surface lipids of fruits carrying the cutin deficient 1 mutation.

Later a family of enzymes, the cutin synthases (CUS), were also found. CUS1 has shown in vitro activity towards the polymerization of 2-MHG, strengthening the hypothesis that cutin biosynthesis is extracellular and occurs through a series of transesterification reactions releasing glycerol.

In the project, cutin and suberin monomer derivatives were synthesized. Subsequently, in vitro oligomerization catalyzed by CUS1 was achieved.

Firstly, both deuterium and tritium-labelled 2-MHG were successfully synthesized. The deuterium-labelled molecule was used in oligomerization assays together with 9-hydroxy 2-MHG to study the specificity of CUS1 towards the position of the mid-chain hydroxy group. CUS1 showed equal activity towards both monomers, suggesting that CUS1 is likely to participate in the incorporation of both monomers in cutin. Tritium-labelled 2-MHG could potentially be used to monitor transport and location of the monomer *in planta*.

Secondly, the synthesis and enzymatic oligomerization of 2-MAG derivatives of three fatty acids commonly found in suberin – behenic acid, ώ-hydroxy oleic acid, and octadecanedioic acid – was achieved. The three compounds were successfully synthesized and used as CUS1 substrates in enzymatic assays. The results suggest that enzymes from the CUS or another similar family could be involved in the biosynthesis of suberin.



Transversal section of a root, showing the suberized exo- and endodermis cell walls as well as the casparian strips.

Ignacio Martínez San Segundo
PhD

"Synthesis of Monomers for the Biochemical Investigation of Plant Polyesters"

Funded by
The Novo Nordisk Foundation and DTU Chemistry.
The project involved extensive cooperation with the group of Professor Richard Gross, Rensselaer Polytechnic Institute

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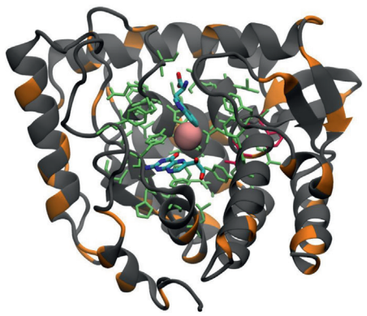
Secrets of a Key Neuro-transmitter

Serotonin is important in both physiological and mental health. Here, new insight into the structure-function relationship of the enzyme tryptophan hydroxylase (TPH) involved in the biosynthesis of serotonin is presented.

Dysfunction of the level of serotonin (5-hydroxytryptamine, 5-HT) is associated with a variety of physiological and psychiatric disorders. It is thus highly relevant to investigate tryptophan hydroxylase that consists of two isoforms and catalyzes the first and rate-limiting step in the biosynthesis of serotonin.

Serotonin exerts its function by acting on several different receptors distributed throughout the entire human body. In the peripheral tissues, serotonin acts as a hormone to constrict large blood vessels and regulates platelet adhesion. Serotonin is also found in the intestines. Dysregulation of peripheral serotonin is involved in several conditions including gastro-intestinal disorders, lung fibrosis, carcinoid syndrome, and osteoporosis. In the brain, serotonin is involved in regulating centers that control wakefulness, temperature regulation, blood-pressure regulation, aggressive behavior, and sexual behavior. Disorders such as depression, schizophrenia, autism, and ADHD have been proposed to be linked to serotonin dysfunction.

TPH catalyzes the hydroxylation of tryptophan to L-5-hydroxytryptophan, which is the first and rate-limiting step in the biosynthesis of serotonin. The active form of TPH contains iron(II) and catalyzes tryptophan hydroxylation utilizing 6*R*-L-erythro-5,6,7,8-tetrahydrobiopterin (BH_4) and molecular oxygen. TPH exists in two isoforms. TPH1 is primarily expressed in the peripheral tissues, and TPH2 in the central nervous system. Both isoforms are members of an enzyme family of iron(II)-containing mono-oxygenases.



Of the two isoforms, TPH2 is less characterized in literature due to its inherent instability. To overcome this challenge, three variants of *human* TPH2 were expressed, purified, and examined. Removal of the C-terminal tetramerization domain resulted in sufficient quantities for characterization. Upon further removal of the N-terminal regulatory domain, a significant decrease in rate of inactivation was observed. This observation renders the regulatory domain the main source of instability. To overcome the inherent instability of the regulatory domain, differential scanning fluorimetry was used to identify stabilizing ligands. Analytical gel filtration revealed that in the presence of the regulatory domain, the TPH2 variant resides in a monomer-dimer equilibrium. With the addition of phenylalanine, a significant shift towards dimer was observed explaining the ligand-induced increase in thermo-stability. These results led to the addition of phenylalanine in the purification buffer which significantly increase the purification yields.

Further results demonstrate, that the steady-state kinetic mechanism of the catalytic domain of *human* TPH1 follows a hybrid Ping Pong ordered mechanism. The kinetic study also revealed that the isoforms display very different kinetic properties despite their high sequence identity. TPH1 is substrate inhibited, while TPH2 is not. By scrutinizing the crystal structures of the isoforms, it was found that differences reside in the orientation of a loop lining the active site. Point mutations were conducted within this loop, and significant changes in the kinetic parameters of the mutant TPH1 variants were observed.

Molecular dynamics simulations revealed that the substrate inhibition mechanism occurs through a closure of the BH_4 binding pocket upon tryptophan binding, and that the active site loop is involved in this mechanism by propagating structural changes from the tryptophan binding site to the BH_4 binding pocket.

Crystal structure of human chTPH1 with BH2 and iron (PDB entry: 1MLW) and L-tryptophan (superimposed from chicken TPH1, PDB entry: 3E2T [244]).

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"Characterization of the human tryptophan hydroxylase isoforms"

Funded by
DTU Chemistry

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Hans E. M. Christensen

Theory and Software for Molecular Movies

Modern powerful X-ray sources allow investigation of chemical reactions in real time. The project presents new theory and software code for the purpose.

Recent advances in ultrafast X-ray pulse experiments permit the observation of dynamical changes in atoms and molecules in real time, meaning the femtosecond timescale (1 fs = 10^{-15} s). The analysis of these experiments, however, require an elaborate theoretical framework as well as advanced numerical simulations. The project contributes with both theory and new software code to further development of ultrafast X-ray pulse experiment interpretation.

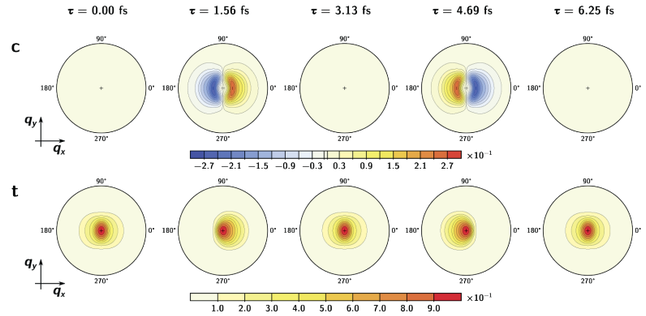
Modern X-Ray Free-Electron Lasers (XFELs) provide extremely intense hard X-ray radiation which makes it possible to conduct experiments with dilute samples of molecules in liquid or gas phase where the intensity of the scattering signal is not enhanced by constructive interference (as in diffraction of X-rays by crystals). Furthermore, the radiation is pulsed and durations of less than 100 fs are currently available, allowing an investigation of structural changes and chemical reactions in real time, since nuclear motion in molecules typically occurs on a timescale of tenths or hundreds of femtoseconds.

In these scattering experiments a target, referred to as the material system, interacts with two subsequent pulses of electromagnetic radiation. The pulses are called the pump and the probe pulse, respectively. The pump pulse excites the material system and thereby induces dynamics such as chemical reactions or relaxation processes. The probe pulse is scattered by the non-stationary material onto a detector. By variation of the pump-probe delay, i.e. the time the probe pulse lags behind the pump pulse, the scattering signal is measured at different points in time. The resulting series of snapshots contains time-resolved information about the dynamics invoked by the pump pulse.

Extracting the desired information from the experimental data is a non-trivial task. In the project, the quantum electro-dynamical description of time-resolved non-resonant X-ray scattering by atoms and molecules in non-stationary states is reviewed. Then, a unified and coherent rederivation is presented. Different contributions to the scattering signal are identified with particular attention to inelastic scattering and to scattering related to electronic coherences. A general analytic solution to one-electron scattering matrix elements of the hydrogen atom is derived. These solutions allow a computationally efficient and mathematically exact evaluation of the X-ray scattering signal of the atom in any non-stationary state.

The analytic solutions are applied to an electronic wave packet of the hydrogen atom. Previously published results that involved numerical integration are reproduced. It is shown that the time-dependence of the scattering signal stems solely from the contributions related to the electronic coherence, whereas the elastic and inelastic signals are independent of time. The effect of the pulse duration on the X-ray scattering signal is revised and explained differently than in the published work. It is shown that the existence of an optimum pulse duration at which the scattering signal displays the strongest time-dependence is entirely due to a restriction on the range of photon energies that are accepted by the detector.

Further, the scattering signal of the hydrogen molecule subsequent to UV excitation from its $X^1\Sigma_g^+$ ground state to its $B^1\Sigma_u^+$ excited state is simulated. This is the first full simulation of two-dimensional time-resolved X-ray scattering patterns of a molecule. All contributions to the scattering signal are evaluated. The separability of the contribution related to the electronic coherence from the total scattering signal is discussed.



Contour plots of the coherence (c) and total (t) time-resolved X-ray scattering patterns dS=d in the qx-qy plane at ve pump-probe delays 'T.

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"Theory and Simulations of Time-resolved X-ray Scattering"

Funded by
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Master Theses 2018

Ahmad Chehaiber
Cobalt-Catalyzed Dehydrogenation of Alcohols

Alexander Søgaard
Catalysis with Liquid Organic Hydrogen Carrier (LOHC) systems

Amalie Nørskov
Chemical sulfation of peptides: Installation of a natural post-translational modification.

Ana Laura Rodrigues da Silva
Methods for Fragment-Based Drug Discovery

Anastasia Antalaki
Fragment-Based Drug Discovery

Camilla Grundvad Toldbod
Synthesis of a natural product-derived compound collection

Charlotte Uldahl Jansen
Design and synthesis of exocholine and derivatives as anticancer agents.

Chinikwa Obayam Edwin
Exploring nucleoside analogues for amplification-free tandem detection of nucleic acid sequences

Clemens Erik Panning
Catalytic conversion of lactic acid ester to plastic monomer

Daniel Nikolaus Rainer
Study of silicic acid polymerization in the presence of transition metals

Daniela Dankova
Development of a synthetic strategy for fluorinated fragments

David Gottlied Bording
Quantum Vibrational Dynamics and X-ray scattering of a Diatomic Molecule: Theory and Computational Simulation

Dorotea Gajdek
Synthesis of porous materials for heterogeneous catalysis

Gurid Kallsberg Kristiansen
Purification and crystallization of tryptophan hydroxylase variants

Gustav Schjær Jensen
Exploring building blocks for the assembly of carbohydrate-based supramolecular polymers

Hang Bian
Investigation of reservoir parameters related to nanocellulose injection in oil reservoir

Ida Slot Arakelian Jensen
Fragment-Based Drug Discovery

Jiaqi Liang
Doping of graphene to synthesize carbon-metal-nitrogen composites as high-performance oxygen reduction reaction catalyst

Jonas Odgaard Petersen
Design and Synthesis of Novel Enzyme-cleavable Linker for Antibody-Drug Conjugates

Julie Bang Nielsen
Characterization of bioactive compounds in NBC00162

Karina Dyrholm Jensen
Analytical results in molecular quantum dynamics

Katarzyna Jadwiga Sniady
Pursuing selective kinase inhibitors using fragment-based drug discovery

Kathrine Schiørring Steen Jensen
Rh-catalyzed asymmetric hydroformylation in biphasic ionic liquid system

Katja Egeskov Grier
Synthesis of photolabile linkers for antibody drug conjugates

Katrine Englund Christensen
Protein Chemical Modification: Sulfation

Kjartan Bjarnov Kaas-Larsen
Development of a pre-catalyst system for low temperature selective catalytic reduction of NO

Klara Trap Kahr
Hydrogen production from alcohols by heterogeneous catalysis

Klaus August Moltved
Theoretical studies of palladium-catalyzed carbonylation in ionic liquids

Laura Aaboe Andersen
Controlled Nucleation in Freeze Dried Protein Formulations

Lisette Prehn Henriksen
In silico and experimental investigations of dimerization of TPH2 ACT domains

Louise Drue Andersen
Analysis of Biological Samples with Surface Enhanced Raman Spectroscopy (SERS)

Mads Holm Jensen
Cellulose conversion with heterogeneous phosphate catalysts in biphasic ionic liquid systems

Máni Dagsson
Synthesis of metal nanoparticles in zeolites

Maria Holm Rautenberg
Synthesis and studies of fatty acid-functionalized GLP-1 analogues

Mathias Thor Nielsen
Synthesis and study of supramolecular systems

Mikkel Burggraaf Buendia
Preparation of pentaerythritol tetrakis(vinyl glycolate) and applications in polymer coatings

Nanna Bo Andersen
Design and Synthesis of aluminum-fluoride (Al18F) prostate-specific membrane antigen (PSMA) ligands.

Oliver Lynggaard Isaksen
In-situ investigations of iron substituted zeolites

Prosper Paidamoyo Mapfumo
Synthesis of a sterol-inspired compound library

Sindri Frostason
Carbon-free anodes for low temperature Aluminium electrolysis

Sofie Slott Enhancing
intra-nuclear uptake of therapeutic RNA using novel bis-functional scaffolds

Stine Skov Møller
Synthesis and investigation of modified peptides for the treatment of food allergy

Stine Stampe Madsen
Novel fluorescent nucleoside analogues for imaging nucleic acids in live cells

Suk Kyu Ko
A molecular dynamics study of the interactions of the glucagon-like peptide 1 (GLP-1) and analogues with the endogenous GLP-1 receptor

Thomas Wammen Sørensen
Synthesis of doxorubicin-functionalized photolabile linkers to antibody drug conjugates

Tianqing Wang
CFD Simulation of Near Wellbore Flow Using Black Oil Description

Yuntian Teng
Experimental Study of Adding Nano-cellulose into the Injection Water for Possible Enhancement of the Oil Recovery

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Publications 2018

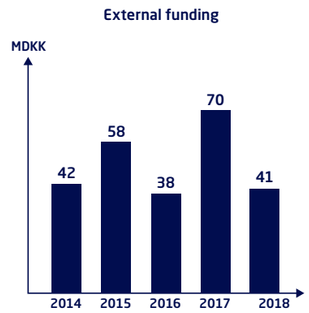
DTU Chemistry has a high performance in the world of chemical science. This is reflected in all the publications produced and published in high impact journals every year. In this Annual Report, you can find examples of some of the Department's exciting results and projects during 2018. The Department has a strong track record in scientific publications and we keep increasing the ISI publications. For a complete list of DTU Chemistry's publications in 2018, please scan the code or visit: kemi.dtu.dk/english/aboutus/publications.

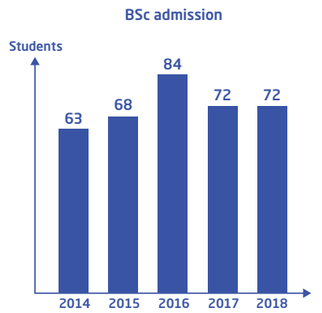
A Leading Research Department

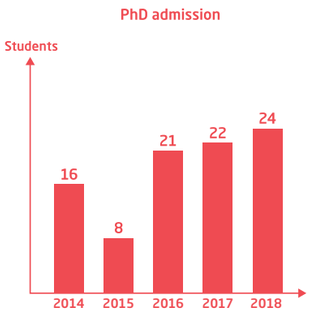
DTU Chemistry focuses on scientific excellence through people, projects, and results in order to stay a leading research department. The Department had a high success rate in applications for external funding in 2018. We are pleased to find that sources outside DTU as public funds, private companies, and private foundations take increasing interest in DTU Chemistry.

DTU Chemistry is still very successful in attracting scientific talent. We keep having a very high number of applicants for the BSc in Chemistry and Technology. Accordingly, DTU Chemistry recently expanded the number of applicants we can accommodate from 66 to 72.

Our research groups are flourishing with new PhD talent. Once again, the Department hired a record number of PhD students.







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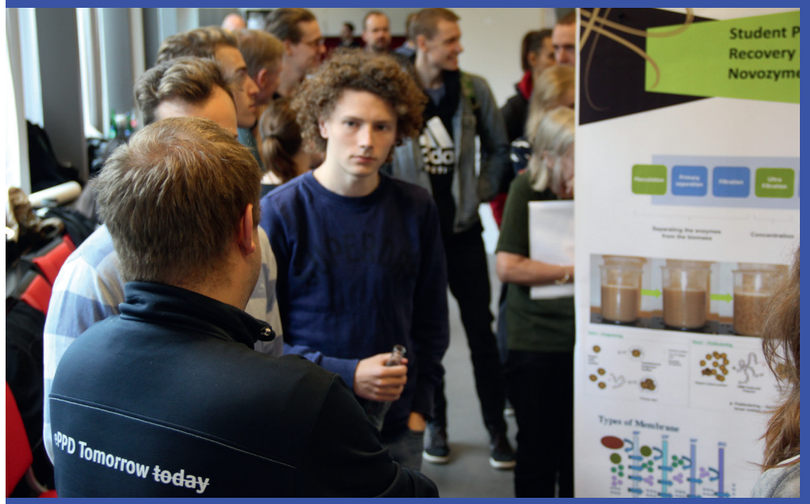


High Tech Summit

DTU Chemistry was responsible for two excellent contributions at High Tech Summit 2018: 'Exploiting advanced research infrastructures at DTU – collaboration and capabilities' with Associate Professor Charlotte Held Gotfredsen as chair and 'How will large scale infrastructures move science and technology forward?' presented by Associate Professor Pernille Harris and Head of Department Erling H. Stenby. DTU High Tech Summit is the leading research-based high-tech event in the Nordic countries. At this summit, companies, researchers, students, and startups meet to find inspiration and create value.

The Inauguration of DK-OPENSCREEN

The national research infrastructure for chemical biology, DK-OPENSCREEN, was officially launched in 2018. In addition to the compound library with room for up to 200,000 substances in total, DK-OPENSCREEN provides a wide range of screening facilities and highly specialized knowledge – e.g. about multi-resistant bacteria and phenotypic screening in cells. According to Professor Mads H. Clausen, Director of DK-OPENSCREEN, the easy access to compounds and screening facilities will boost technological and scientific development and increase Denmark's competitiveness in the life science sector. Both national and international partners, researchers, and representatives from companies were present at the inauguration in October.

Company Project Day

The Department hosted a Company Project Day where industrial partners had the opportunity to present potential projects to students from DTU Chemistry. Haldor Topsoe, Synopsys Denmark, CMC assist, Novozymes, DFM, LEO Pharma, and Aquaporin participated with interesting proposals and interacted with the students. Due to the success of the event, more Company Project Days will be arranged in the future, and DTU Chemistry look forward to seeing even more companies joins.

13th Nordic Femtochemistry Conference

The international conference held in Copenhagen had more than 70 participants from Northern Europe and two keynote speakers from the U.S. Professor Klaus B. Møller from DTU Chemistry was co-organizer of the event.

2018 IEA EOR TCP Workshop & Symposium

Representatives of international energy corporations, authorities, and researchers gathered in Lyngby for the annual IEA EOR TCP Workshop & Symposium to address how more oil and gas can be efficiently produced. Erling H. Stenby, Head of Department at DTU Chemistry and representing Denmark in the Enhanced Oil Recovery (EOR) cooperation, hosted the event.

Open House

The Department is always very active at DTU's annual Open House event. At the information stand, students, faculty, and Head of Studies Klaus B. Møller all answered questions from curious high school students. Around 150 high school students participated in the Department's guided tours, and the effort was not in vain – once again, 72 students were signed up for the BSc programme in Chemistry and Technology.

DTU Chemistry has selected various highlights from 2018 to supplement the articles on pp. 6-15. You can read more at our website kemi.dtu.dk/English/Nyheder, or follow us on linkedin.com/company/dtu-kemi.

Highlights

GRANTS & HONOURS

Carlsberg Foundation

Assistant Professor Katrine Qvortrup from DTU Chemistry received a DKK 4.4 million grant from the Carlsberg Foundation. She has initiated a research project to develop two novel general approaches for the preparation of well-defined bioconjugates. An effective bioconjugation technology has to control both the location and the number of molecules being incorporated in the protein. Current technologies suffer from non-selectivity resulting in heterogeneous product mixtures – that is, variation in the number of molecules incorporated and their locations on the protein. The knowledge gained from this programme should be of considerable value in the design and production of bioconjugates with specific biological and chemical profiles.

Grants from Independent Research Fund Denmark (DFF)

Once again, researchers from DTU Chemistry received a number of grants from Independent Research Fund Denmark (DFF). The following is merely a select few.

Assistant Professor Martin Nielsen received DKK 2.6 million for his research on low-temperature water-gas shift reactions. He will develop benign low-temperature water-gas shift reactions catalyzed by a homogeneous catalyst. Currently, the process is carried out at highly elevated temperatures using heterogeneous catalysis which is problematic for a number of reasons. For example, to render hydrogen fuel cells commercially viable, it is imperative to develop water-gas shift reactions that proceed efficiently at temperatures below 100 °C. Hydrogen fuel cells are considered promising sustainable alternatives to fossil fuels for heat and electricity generation.

Professor Kasper Planeta Kepp received DKK 2.6 million for a DTU/Cambridge project that aimes to halve the uncertainty in predicting protein stability, through computer models. Protein stability is important for the development of effective industrial enzymes and in the chemistry of neurological diseases. The best methods today have an uncertainty of 1 kcal/mol, rendering predictions error-prone. If ½ kcal/mol accuracy is achieved, it enables stronger screening for new proteins and more precise investigations of the relationship between protein stability and diseases.

Professor Esben Thormann received DKK 2.6 million for research in duo functional anti-icing polymeric coatings. The vast majority of research on passive anti-icing surfaces has focused on superhydrophobic surfaces. Esben Thormann's project will focus on passive anti-icing surfaces consisting of more robust and highly hydrophilic polyelectrolyte based films.

Professor Klaus B. Møller – together with Professor Martin Meedom Nielsen from DTU Physics – received DKK 5.9 million to the project 'Trajectories of charge and structural dynamics in functional molecules' – focusing on iron centered molecular spin switches and light harvesters. The research aims to provide a rational basis for optimizing their performance towards applications such as spintronics for high density data storage and light harvesting for solar energy conversion.

Other grants and honours

Postdoc Anders Højgaard Hansen received DKK 1.65 million from the Novo Nordisk Foundation to develop biosynthetic strategies that will lead to better antibody-based drug conjugates for cancer treatment.

Global challenges within energy, the climate, drinking water, health, and food production require research and development of new advanced materials – enter SMART (Structure of Materials in Real Time). SMART will perform cutting-edge research on atomic structures during dynamic conditions at the world's most powerful neutron source, European Spallation Source (ESS), currently being build. As part of the first group, SMART, to be designated as an ESS 'lighthouse' environment by the Ministry of Higher Education and Science, Professor Søren Kegnæs and Assistant Professor Kasper Steen Pedersen from DTU Chemistry have received funding to hire a PhD.

Two young researchers, Xinxin Xiao from China and Shota Tsuru from Japan, have been granted an HC Ørsted COFUND fellowship and will spend the next years at DTU Chemistry advancing their scientific careers.

Reinholt W. Jorck and Hustrus Foundation honour young researchers for outstanding society-relevant research. In 2018, Associate Professor Kira Astakhova was chosen to receive a grant of DKK 300,000 and Jorck's travel grant of DKK 200,000 – a total of DKK 500,000 earmarked research and education.

The Danish Society for Medicinal Chemistry and Chemical Biology (DSMKB) selected former PhD student Jorge Peiró Cadahía to represent Denmark at the contest for the title of European Champion in Medicinal Chemistry in Ljubljana.

PhD Arun Kumar Somavarapu received DTU's 'Young Researcher Award' for the thesis "Structural dynamics and pathogenicity of Aβ and presenilin1 variants: Towards a mechanistic understanding of Alzheimer's disease".

Internationally top-ranked research institutes annually select their best thesis for publication in the scientific portfolio series Springer Theses. In 2018, the choice fell on DTU Chemistry PhD Casper Rønn Hoeck for his work on "Solving a 3D Structural Puzzle". The publication explores how nuclear magnetic resonance (NMR) spectroscopy may be used for spatial structural elucidation of novel compounds from fungal and synthetic sources.

HIGH-IMPACT PUBLICATIONS

A collaboration between the Kramer and Kegnæs groups resulted in a publication in high-impact journal ACS Catalysis. The publication summarizes the current state-of-the-art for applications of metal-containing porous organic polymers (Metal-POPs) as catalysts for synthetic organic chemistry.

While the Coulomb interaction between charged particles dominates the molecular environment, several other interactions are actually present. These interactions are less known, since they are much weaker and therefore not easily observed in experiments. However, by using powerful laser experiments, a Danish team – with PhD student Esben Folger Thomas and Associate Professor Niels Engholm Henriksen from DTU Chemistry – provided surprising new insight into one such mechanism, hyperfine structure-induced depolarization. This led to the publication "Hyperfine Structure-Induced Depolarization of Impulsively Aligned I2 Molecules" which was reported in prestigious Physical Review Letters.

In the publication "Formation of the layered conductive magnet CrCl2(pyrazine)2 through redox-active coordination chemistry" in Nature Chemistry, Assistant Professor Kasper Steen Pedersen and his colleagues present a new 2D material with vast perspectives. Read more about the discovery in the feature article on pp. 10-11.

The production of liquid fuels and fine chemicals often depends on the use of high-pressure excess hydrogen gas, fossil resources, and newly prepared metal catalysts. Lignocellulosic biomass is a promising, renewable alternative substrate for the production of liquid fuels and fine chemicals. An international research team, including Sebastian Meier and Anders Riisager from DTU Chemistry, has developed an efficient process that allows selecting among no less than four valuable chemicals. This innovative process uses renewable ressources, a commercial catalyst, and easy-to-handle hydrogen donor under mild reaction conditions. The work was published in the renowned journal Communications Chemistry, which is part of the Nature Research Journal portfolio.

Kira Astakhova received Jorck's grant for outstanding society-relevant research.

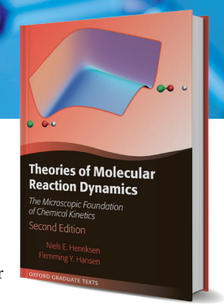
REACHING OUT

DTU ScienceShow is a group of students who deliver a professional science show with entertaining and educational elements from chemistry and physics. DTU ScienceShow is part of DTU's branding and recruiting strategies and locally hosted at DTU Chemistry with Professor Anders Riisager heading the Advisory Board. In 2018, ScienceShow was busy with 90 shows all over Denmark – mainly entertaining high school and primary school students. The show also performed at 'International Children's Science & Mathematics Festival' in India, where the five delegates from ScienceShow were treated as stars.

The Torkil Holm Foundation once again sponsored a huge chemistry symposium with more than 300 chemists from industry and academia. Emeritus Torkil Holm has now turned 95, but he is still an active contributor to the Department.

During the year, 1372 high school students have participated in high school lectures – e.g. Spectroscopy and Identification of Organic substances – by DTU Chemistry.

A new edition of the textbook "Theories of Molecular Reaction Dynamics" was published at Oxford University Press.



The book was written by Associate Professor Niels Engholm Henriksen and Emeritus Flemming Y. Hansen.

SPIN-OUT COMPANIES

ROS Therapeutics was established in 2018 based on technology developed at DTU Chemistry. In July, the company signed a patent license agreement covering prodrugs that upon activation by reactive oxygen species (ROS) release the active moiety – either methotrexate or aminopterin – in inflammatory diseases such as rheumatoid arthritis. Professor Mads H. Clausen from DTU Chemistry has led the development of the early discovery programme and is a co-founder of the spin-out company that aims to create safer and more precise treatment of the forementioned diseases.

Another spin-out established in 2018 is IBIO TECH with Associate Professor Kira Astakhova as Director. The spin-out aims to develop and promote novel diagnostic and therapeutic options for human autoimmune diseases..

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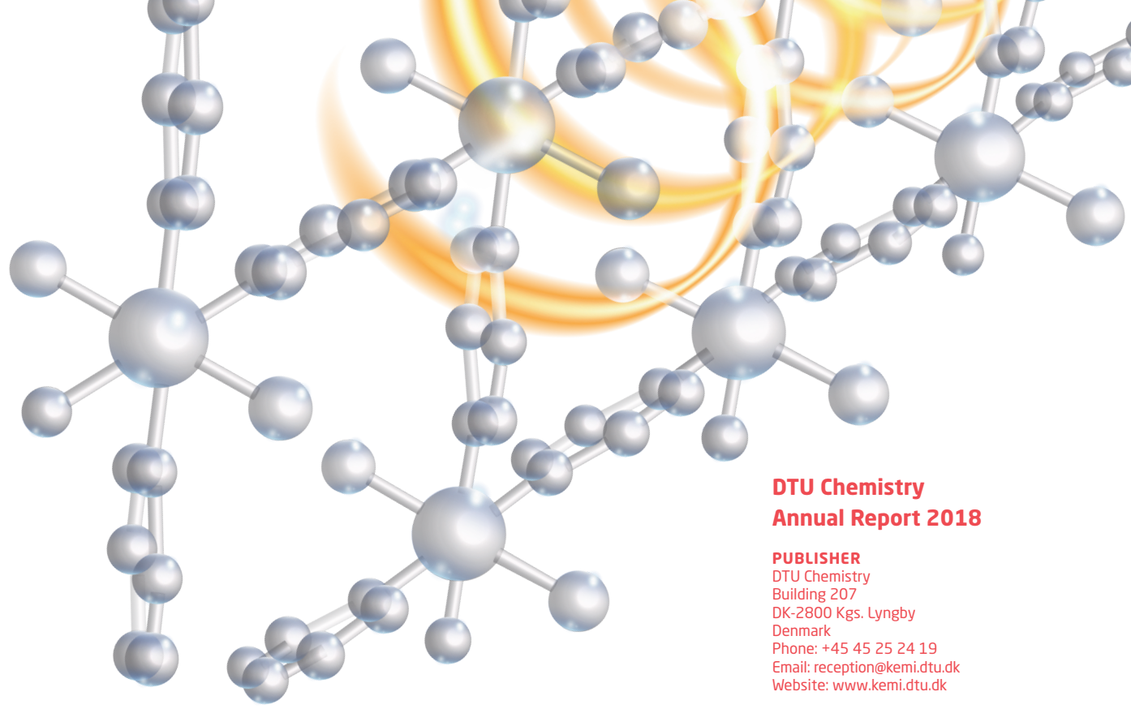

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Annual Report 2018

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