Technical University of Denmark

DTU

Annual Report 2014

Department of Chemistry

Building the Future

The DTU Chemistry Management Group 2014 (left to right) David A. Tanner, Klaus B. Møller, Rasmus Fehrmann, Kenny Ståhl, Charlotte Mondrup and Erling H. Stenby.

Welcome to the DTU Chemistry Annual Report 2014 – a productive year for the Department where we continued to address the demanding challenges through excellence in research, training of highly skilled graduates, and a successful collaboration with industry and academia.

In 2015 we will move into the new DTU Chemistry building with laboratories for research and teaching. This will give access to new state-of-the art facilities and equipment, and also set high standards for the working environment.

The vision of DTU Chemistry is an internationally recognized department for advanced fundamental and applied chemistry that generates and implements ideas to the benefit of a sustainable societal development.

We therefore work hard to ensure the best possible platform for this development. We focus on scientific excellence through people, projects, and results in order to strengthen our position. With a strong brand we believe that DTU Chemistry will attract the necessary resources, ensure recruitment of the best candidates, and strengthen the external cooperation.

The powerful blend of innovative scientists, a strong curriculum, and skilled support units enables DTU Chemistry to meet all these challenges of chemistry for the future, and I am proud to see the dedication of the entire Department.

Nursing Talent attracts Funding

I am also pleased to notice that we are ready to encompass the interest from young scientific talent, not only in terms of providing thrilling intellectual challenges, but also when it comes down to providing them with a physical space from where they can start their new careers.

DTU Chemistry is successful in attracting and nursing scientific talent in a systematic approach to create a focused dialogue with the entire chain of scientific talent from high school over BSc and MSc level and all the way to a PhD degree.

DTU Chemistry takes pride in educating PhD students who go on to exciting careers in industry and academia.

We note with great satisfaction that a steadily increasing part of the new PhD projects are financed from sources outside DTU. Public funds, private companies, and private foundations all take growing interest in our Department. This aids us in carrying out excellent research and proving top level training to our students.

I invite you to let yourselves be inspired by the PhD Defenses 2014 (p. 20) which are projects that contribute to the development of cutting edge science at the Department.

Devoted Scientists' Outreach

The Department gives priority to sharing knowledge. Most of this outreach is done by devoted, individual scientists in their daily contacts with students and external partners. The primary drivers of the direction and development of the research at the Department are the expertise, ideas, and ambitions of our Faculty.

The Department maintains a strong track record in scientific publications. With an increase of 20 % in ISI publications, 2014 was very productive. You can find some of the outstanding results in the articles in this year's report. It is my hope, that existing and new collaborators find inspiration in these articles for new activities together with DTU Chemistry.

For some years now, the Department has held a high level of patenting, and I am pleased to see that a growing number of inventions are taken into industrial use. Some times this is done in cooperation with existing industry, while on other occasions spin-outs are created. Find more information in the Highlights (p. 42) about one actual case which has recently been spun out. Several other potential spin-outs are currently in the incubator stage.

2015 is off to a good start. You can sign up for our Newsletter at kemi.dtu.dk to follow the development at DTU Chemistry during the year. You can also follow our activities on facebook (/DTUKemi) and Twitter (/ErlingStenby).

I look forward to see a unified drive towards excellence at the Department throughout the coming year, and I encourage you to join us.

– Erling H. Stenby

DTU Chemistry Annual Report 2014

PUBLISHER:
DTU Chemistry
Building 207, DK-2800
Kgs. Lyngby, Denmark
Phone: +45 45 25 24 19
E-mail: reception@kemi.dtu.dk
Website: www.kemi.dtu.dk

EDITOR-IN-CHIEF:
Erling H. Stenby, Head of Department, DTU Chemistry

EXECUTIVE EDITOR:
Charlotte Malassé, Special Adviser, Communication, DTU Chemistry

ASSISTANT EDITOR:
Charlotte Mondrup, Deputy Head of Department, DTU Chemistry

TEXT:
Morten Andersen, City Pressekontor, Copenhagen, Charlotte Malassé, DTU Chemistry

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Maria Bundgaard, Mette Hansen, Signe Møller Jørgensen, Bo Sørensen, Anne Frejberg Juhl-Schmidt

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Inorganic, Organic and Physical Chemistry

DTU Chemistry's trademark is scientific expertise founded in fundamental research in applied chemistry. For some years now the research at the Department has been organized into three areas – Inorganic, Organic and Physical Chemistry – each with underlying research groups.

Inorganic Chemistry is comprised of the Center for Catalysis and Sustainable Chemistry and two groups on Nano Chemistry and Metalloprotein Chemistry.

Center for Catalysis and Sustainable Chemistry is focused at catalysis, gas separation and absorption, development of new materials, process design and conversion of biomass. The NanoChemistry Group is focusing on electrochemistry and bioelectrochemistry and has a long track record for applying electrochemical STM (Scanning Tunneling Microscopy). In situ electrochemical AFM (Atomic Force Microscopy) has recently been introduced.
The Metalloprotein Chemistry combines diverse fields such as molecular biology, coordination chemistry, biochemistry, computational chemistry and biophysics.

Organic Chemistry's main areas of focus are Catalysis, Chemical Biology, and Spectroscopy.

The core discipline of Organic Chemistry is organic synthesis with interfaces to biology, medicine and natural products chemistry. Computational chemistry and kinetic/mechanistic studies are also represented, as well as expertise in high-field NMR spectroscopy.

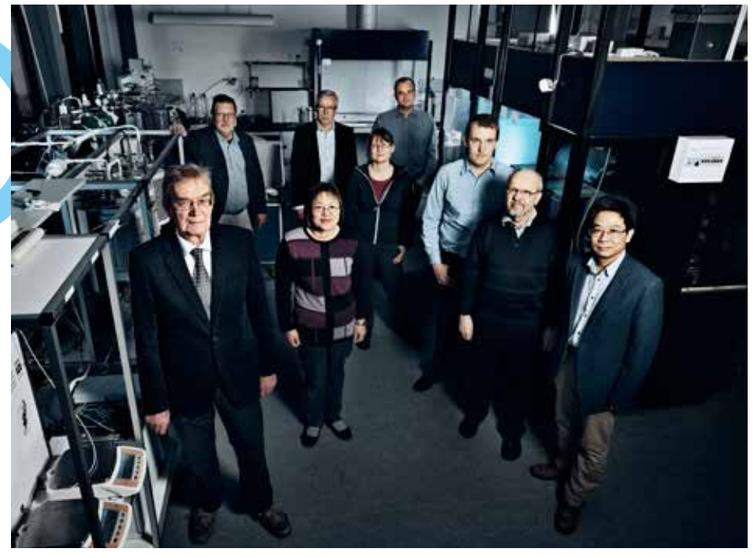
Physical Chemistry comprises activities within pure and applied physical chemistry as well as analytical chemistry. It covers both microscopic atomic-level descriptions and the macroscopic thermodynamic approach. Common themes are the behavior of small to medium sized molecules, and many projects involve spectroscopy and quantum chemical modeling.
The underlying groups are Analytical Chemistry and identification by Raman Spectroscopy; High Pressure Phase Behavior for Oil and Gas Production; Colloid Chemistry; Theoretical, Computational and Femtochemistry; IR- and THz Spectroscopy.

Stronger international profile

DTU Chemistry works hard to ensure the best possible platform to generate and develop ideas to the benefit of a sustainable development. In order to strengthen the research profile and our visibility further, the Department will be organized in two major sections in 2015. One section will cover Physical and Biophysical Chemistry and another section Inorganic and Organic Chemistry. The underlying research groups as described above will consist under the new organization. We invite you to follow the development at kemi.dtu.dk/english/Research

Organic Chemistry
(Top down)
Mads Hartvig Clausen, Professor
Charlotte Held Gotfredsen, Associate Professor
David Tanner, Professor (Section Coordinator)
Jens Øllgaard Duus, Professor
Peter Fristrup, Associate Professor
Robert Madsen, Professor

Inorganic Chemistry
(Clockwise)
Jens Ulstrup, Professor
Jingdong Zhang, Associate Professor
Rasmus Fehrmann, Professor (Section Coordinator)
Hans Erik Mølager Christensen, Associate Professor
Susanne L. Mossin, Associate Professor
Anders Riisager, Associate Professor
Søren Kegnæs, Associate Professor
Jens H. von Barner, Associate Professor
Qijin Chi, Associate Professor



Physical Chemistry
(From left to right)
Günther H. Peters, Associate Professor, Wei Yan, Senior Researcher, Rolf W. Berg, Associate Professor
Irene Shim, Associate Professor, Niels Engholm Henriksen, Associate Professor,
René Wugt Larsen, Associate Professor, Klaus Braagaard Møller, Associate Professor,
Esben Thormann, Associate Professor, Jonas Rosager Henriksen, Assistant Professor,
Pernille Harris, Associate Professor, Kenny Ståhl, Associate Professor (Section Coordinator).
Absent: Jens Enevold Thaulov Andersen, Associate Professor, Kasper Planeta Kepp, Associate Professor.

Important Drug Discovery Tool

As alkaloids are known to exert a wide variety of pharmacological effects, they have long been of great interest for numerous drug discovery projects. In a modern variation on a classical theme, a century-old chemical reaction for the synthesis of alkaloids has now been improved.

Morphine, cocaine, caffeine, nicotine, and ephedrine – all "household names" – are members of the alkaloid family, a group of naturally occurring compounds containing nitrogen atoms. Besides these well-known examples, a large variety of other alkaloids exist. Many of these occur in nature, while others are synthetic, typically produced as drug candidates inspired by the structures of biologically active natural products. Therefore, it is good news for drug developers that a group at DTU Chemistry has improved a key reaction for the synthesis of alkaloids.

In the classical reaction, discovered in 1911 by Amé Pictet and Theodor Spengler, an amine (for instance tryptamine) will undergo ring closure after condensation with an aldehyde to give important precursor molecules (for instance THBCs, tetra-hydro-β-carbolines) for the synthesis of alkaloids. Usually, a strongly acidic catalyst is employed and the reaction mixture is heated to promote the overall process. "The original Pictet-Spengler reaction can be highly efficient – or else it would not be still in use – but it has its drawbacks, since the heating and especially the strong acid represent rather harsh reaction conditions. Simple molecules can survive, but if you are looking to create more complex alkaloids, with more delicate chemical structures, you need a milder regime," says Professor David Tanner, DTU Chemistry.

Offers mild conditions

The new process produces 1,2,3,4-tetrahydro-β-carbolines (TBHCs) relying on the use of two chemically compatible catalysts, which are a ruthenium hydride complex and a Brønsted acid, respectively. The process is so-called tandem catalysis, meaning that both catalysts can simply be added to the reaction mixture in the same reaction vessel from the outset. Neither catalyst will interfere with the job of the other, as the effect of the Brønsted acid catalysis will set in only after the ruthenium hydride catalytic process has created the relevant compound for the other catalyst to work on.

"In other words, the synthesis can be performed as a one-pot process," David Tanner underlines. "We are not the first to create a milder alternative to the original Pictet-Spengler reaction, but we do think that the simplicity and user-friendliness of our solution is unique. For instance, our catalyst system is highly stable to air exposure and does not require work under glove-box conditions." A further advantage of the new process is that, in contrast to the traditional reaction, it does not require the use of aldehydes as starting materials; the aldehydes required for the classical Pictet-Spengler reaction can sometimes be difficult to synthesise, and can also be quite unstable compounds. The modern variant uses alternative and more stable starting materials which are easy to produce.

"Also, the new reaction offers attractive possibilities for the total synthesis of structurally very intricate organic compounds, relying on the rapid generation of molecular complexity," says David Tanner. "The art and science of total synthesis involves the development of synthetic methods which can efficiently transform simple starting materials into complex products."

From the simple to the complex

In technical terms the process can be summarized as a ruthenium hydride / Brønsted acid catalyzed tandem isomerization / N-Acyliminium cyclization sequence for the synthesis of tetrahydro-β-carbolines. This means that three discrete chemical reactions can be carried out in a single laboratory operation, without the need to isolate and purify intermediates, thus increasing molecular complexity in a straightforward fashion.

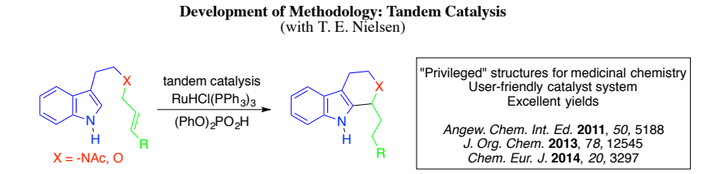
The year 2011 was not only the International Year of Chemistry, but also the 100-year anniversary of the Pictet-Spengler reaction. The group at DTU Chemistry celebrated both events with a modern, milder version of the classical Pictet-Spengler reaction based on the experience in the Organic Chemistry area within novel catalytic techniques relying primarily on transition metal complexes. The idea was the brainchild of Professor Thomas E. Nielsen (now at Novo Nordisk), who suggested a ruthenium-catalyzed tandem sequence which efficiently transformed simple tryptamine derivatives into indolizinoindoles via N-acyliminium intermediates. "The project fitted well with the overall objective of our research, which can be summarized as finding ever more efficient ways to get from simple molecules to complex ones, which is an ongoing quest for synthetic organic chemistry," David Tanner recalls.

"I was privileged to take part in the further development of the concept, in collaboration with Thomas E. Nielsen and some other exceptionally gifted younger colleagues."

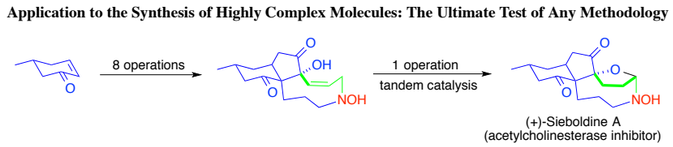
A superior solution

Two recent scientific publications present the current status of the work. The first article was published in the Journal of Organic Chemistry (JOC), 2013, presenting the tandem catalytic process. The second article, published in Chemistry, A European Journal, 2014, describes the synthesis of oxacyclic scaffolds (analogues of Pictet-Spengler products which contain oxygen atoms instead of nitrogen) via isomerization / cyclization of allylic ethers by employment of the same two catalysts. Together, the two articles confirm that the methodology can now be considered practically viable.

"First and foremost the process is relevant to fundamental research, and is of most interest to our colleagues in academia and in the drug discovery departments of the global pharmaceutical industry. These are the people who are faced with synthesis of the complex alkaloid precursors which our process is especially well suited for. However, in the long run it could well be imagined that the process will also be relevant for production of pharmaceuticals," says David Tanner.



Tandem catalysis: 3 consecutive steps, in the same reaction vessel (i.e. only 1 laboratory operation)



Tandem catalysis allows a synthesis of (+)-Sieboldine A, consisting of 9 laboratory operations
Current "best in class" requires 24 operations

Published article

The text is based on the scientific article published in *JOC* (The Journal of Organic Chemistry).

You can download it as a pdf by scanning the QR-code below.

Next step ...

"Objectively, the process is superior to the traditional Picter-Spengler reaction, but of course we cannot expect everybody to adopt it just like that. Only time will tell."

While the methodology is now ready-to-use, the group will continue its efforts. Amongst other tasks, the aim will be to improve the diastereo- and enantio-selectivity of the reaction.

CONTACT

Professor
David Tanner
Organic Chemistry
dt@kemi.dtu.dk

When Atoms mine for Gold

Novel nanochemistry techniques control the stereochemistry of self-assembled monolayers (SAMs) of small molecules. This is good news for basic research in the field, and also for future development of catalysts for renewable energy and other applications.

Not only humans are keen to dig for gold, sometimes atoms are as well. Exploiting a phenomenon known as "atomic gold mining" an international effort led by the NanoChemistry group at DTU Chemistry has solved a tricky problem.

Self-assembled monolayers (SAMs) promise great advantages in a number of fields such as catalysis, sensing and other nanoscale device function. Composed of small molecules, the SAMs are ultra-thin, meaning they change the behavior of the surface without altering the electronic carrier structure underneath. Further, the required amount of the material is extremely small, and as the layers are self-assembling they are highly uniform, since errors created by the processing are reduced to a minimum.

Some of the molecules of interest are chiral, meaning they have two forms which – like the human left and right hand - are mirror images of each other but cannot be superimposed onto each other. The two forms are described by the same chemical formula while in fact being differently structured and potentially with different properties.

It is very desirable to have only one of two such chiral forms in a given SAM. This will guarantee uniform surface properties and offer unique selectivity in SAM applications.

Danish-Chinese-Australian effort

A novel set of methods for controlling this so-called stereochemistry in a relevant chiral molecule SAM has been developed in a joint effort by the NanoChemistry Group and Organic Chemistry at DTU Chemistry, Xiamen University, The University of Sydney, University of Technology of Sydney, and Shanghai University. The results have been published in Journal of the American Chemical Society (JACS) 2014.

"Our cooperation with the groups in Australia and China go back 15 years, and we have had several joint publications in prestigious journals. Still, it is always a great pleasure to learn that this article has been accepted," says Associate Professor Jingdong Zhang, DTU Chemistry.

The project was focused on alkanethiols, R-SH. These are molecules with a thiol group (-SH) in one end of a carbon chain and different functional groups in the other end. Alkanethiols adsorb strongly on metals enabling the formation of SAMs. Among several possible metal supports, gold (Au(111)) was chosen since it is highly stable and can be processed into well-defined atomically planar surfaces.

"Alkanthiol SAMs on gold surfaces have come to offer more detailed understanding of the adsorption process than any other surface system. This is due to facile SAM handling and a unique combination of experimental technologies and theoretical computations," Jingdong Zhang explains. "Further, we can use electrochemistry and scanning probe microscopies directly in the chemical media, combined with large-scale electronic structure and molecular dynamics calculations offering structural SAM resolution to the unprecedented level of the single molecule or even atom."

Atomic gold mining

The target molecules of the project were the five butanethiols, each with one thiol group and four carbon atoms. Of these R- and S-2-butanethiol are chiral molecules. They are each other's mirror images, but in fact different molecules.

"The butanethiols display an amazing variety of SAM patterns determined by very subtle surface chemistry and by interactions between the R-groups," Jingdong Zhang remarks.

Adsorption converts thiol (-SH) to a thiyl group (-S·) bound to a gold surface site, Au-S·, which can be a single gold atom or a hollow site between several atoms. This is where the phenomenon "atomic gold mining" comes in. With the exception of one butanethiol, the bulky tertiary butanethiol, which is able to bind directly on a flat surface, the molecules adsorb by digging out surface gold atoms. Hereafter, they bind sideways to the mined gold atom, R-S-Au-S-R.

"The chiral butanethiols open new perspectives. They are the first case for thiol-binding at the same time to mined gold atoms and on the planar surfaces," Jingdong Zhang comments with enthusiasm. "Binding also induces new chiral centres in both the gold surface and the binding sulfur atoms, in addition to the molecular 2-C chiral centre. As a result a "collective" chirality in whole SAM domains arises, leading to the amazing outcome that chiral domains can arise from achiral molecules, and achiral domains from chiral molecules."

The results offer a new level of understanding of the molecular adsorption process.

"They will help to understand a wide range of chemical, electrochemical, and spectroscopic phenomena," according to Jingdong Zhang.

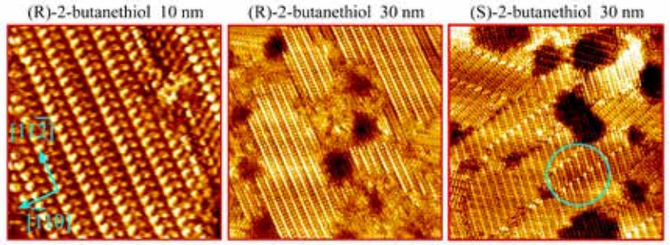
Looking for biofuel catalysis applications

A possible field of application is heterogeneous catalysis in relation to renewable energy, for instance from bio-fuels. Recently, Jingdong Zhang received funding for a project on chemical production of 3D graphene biocatalysts for enzymatic biofuel cells. While the grant is not directly related to the SAM-study published in JACS, Jingdong Zhang hopes to find ways to apply the new nanochemistry findings:

"It is very important for us, as for DTU in general, that fundamental and applied research go hand in hand. Fundamental research is essential to push things to the next level, and applied research is the way we can bring value back to the society which has supported our research. Doing this through applications in clean energy which is highly desirable for society would be really beautiful."

The project on graphene biocatalysts for enzymatic biofuel cells has been granted 0.9 million EUR by the YDUN-program (Younger women Devoted to a University carreer) of the Danish Council for Independent Research.

Besides catalysis, the group's research on SAMs has potential applications for a number of new synthesis strategies for metallic nanostructures and chemical graphene in chemical and pharmaceutical production and research.



In situ STM images of SAMs of chemisorbed (R)-2-butanethiol and (S)-2-butanethiol in 25 mM KH_2PO_4.

Published article

The text is based on the scientific article published in *JACS* (Journal of the American Chemical Society).

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Next step ...

The NanoChemistry Group's research on SAMs (Self-assembled monolayers) has also potential applications for a number of new synthesis strategies in chemical and pharmaceutical production and research.

CONTACT

Associate Professor
Jingdong Zhang
Inorganic Chemistry
jz@kemi.dtu.dk

New Paths towards combatting Alzheimer's Disease

Coupling clinical data with bio-chemical analysis has allowed DTU Chemistry to reveal molecular mechanisms behind the neuro-degenerative disorder. The implications to the field could be substantial.

Attempts to cure or at least halt Alzheimer's disease - the major neurodegenerative disease affecting millions of people worldwide – have so far been largely unsuccessful. But research at DTU Chemistry opens a new door of hope.

Previous drug candidates have been ineffective, because the mechanism behind this wide-spread neuro-degenerative disease has been wrongly perceived. A research group led by Associate Professor Kasper P. Kepp has combined information at the molecular level with genetic profiles of Alzheimer's disease patients. This unique approach has brought about a new understanding with large implications to the field.

"Unfortunately, we have to conclude that a number of recent and current drug candidates will never be successful because they target the wrong phenotypes. Continuing on this path will only give patients false hope and impose economic loss on shareholders and society as such. But the good news is that the direction can now be changed so that future drug candidates with substantially improved prospects can be developed," says Kasper P. Kepp.

Some of the new findings have just been published in the journal Dalton Transactions of The Royal Society of Chemistry, with Kasper P. Kepp and Postdoc Manish K. Tiwari, DTU Chemistry, as authors.

The key peptide

Alzheimer's disease patients typically suffer from impaired memory, gradual decline of cognitive abilities, and personality changes. The disease is strongly linked to aging and mostly occurs sporadically. However, about 5 % of patients have inherited the disease risk. These cases are known as Familial Alzheimer's Disease (FAD). FAD cases are generally more severe and the disease on-set is earlier, in some cases down to 40-50 years of age.

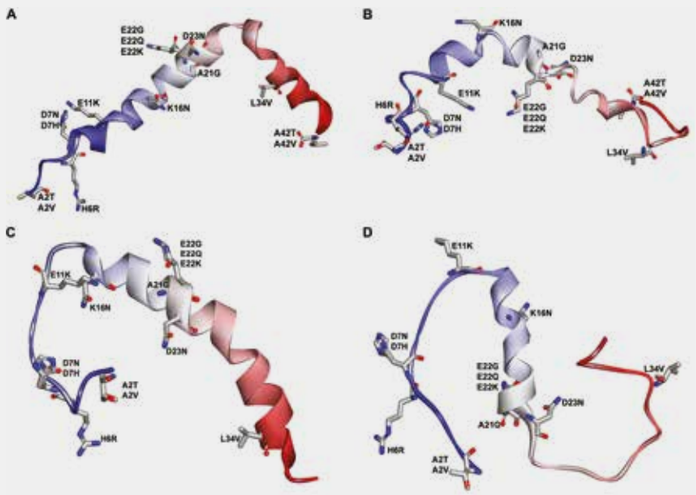
The relation between FAD and other cases of Alzheimer's has been a puzzle to researchers in the field. Some have assumed that two different mechanisms, and thus in reality two different diseases were in play. However, the DTU Chemistry group is working with a new hypothesis that at the molecular level the exact same phenomenon is occurring, only to a higher degree in the FAD cases.

It has been known for decades that the brains of Alzheimer's patients contain extracellular deposits of senile plaques consisting of the peptide β-amyloid (Aβ). The peptide is a cleavage product of a protein found in the membrane of the brain cells, namely Amyloid Precursor Protein (APP).

Plaques alone do not cause the disease

It has been assumed that the build-up of these plaques was closely linked to the disease – in other words that the brain would only be able to tolerate this build-up to a certain level.

As a logical consequence of this perception, several drug candidates by major pharmaceutical companies have been designed to limit the build-up of Aβ in the anticipation that this would cure or at least halt the progression of Alzheimer's. However, this has not happened, while at the same time the patients have suffered side-effects. Furthermore, quite often,



Wild-type and mutant structures of Aβ42 and Aβ40. (A, B) The NMR structure of wild-type Aβ42 (PDB codes 1IYT and 1Z0Q) and their 15 superimposed computational structures of Aβ42 mutants. (C, D) The NMR structure of wild-type Aβ40 (PDB codes 1BA4 and 2LFM) and their 13 superimposed structures of Aβ40 mutants. The mutant residues are shown in stick-model. The peptide's secondary structure is shown with blue N-terminus and red C-terminus (the figure was generated using Discovery Studio (DS) 4.0 visualizer).

a pathological examination will reveal vast plaques without the deceased patient ever having experienced symptoms of Alzheimer's.

"Our findings strongly suggest that it is not the amount of Aβ in itself which triggers the disease. The amounts observed for variants of this peptide simply do not correlate with disease tendency of patients having these variants. Instead, Aβ can assume a number of different forms and properties of which only some are pathogenic," Kasper P. Kepp explains.

The group has found that, as a rule of thumb, the more disordered the structure of the peptide is, the more pathogenic will it tend to be. Furthermore, a strong correlation seems to exist between the disease and the water affinity of the peptide surface: A hydrophobic surface relates to disease, whereas a hydrophilic surface doesn't.

Keen to cooperate with pharma industry

The project benefits from the recent possibility of retrieving data from genetic profiling of Alzheimer's disease patients. The group has extracted its clinical data from a range of published clinical papers and from the international database on Alzheimer's and related diseases AD & FTD Mutations Database, where data from the sequencing of a little over 200 Alzheimer's patients are currently found. These data were compared with similar data from patients without the disease – that is, persons with "sound" forms of Aβ.

Unfortunately, the findings can't be translated directly into efficient anti-Alzheimer's drugs. "We have to remember that the main cause of the disease is aging, which again causes several changes in the bio-chemical processes of the brain. These changes are complex and are likely to occur no matter what we do – you can't cure aging. However, it is likely that drugs can be found which will delay or partly offset the tendencies leading to Alzheimer's. Also, this is yet another reason for recommending people to do exercise, both physically and mentally – by for instance solving Sodoku puzzles etc. Complex late-onset human diseases need to be tackled by a multitude of strategies, and medicine is only one of them."

The group is, however, keen to cooperate with the pharmaceutical industry based on the new findings, Kasper P. Kepp underlines:

"We will be able to carry out some of the basic design of drug candidates which may address the identified pathogenic structures of Aβ. But for taking these candidates into detailed design and further into clinical trials we will need participation from an industry partner with the necessary experience. Using existing compounds with drug-like and safe properties but with the special properties that we have found to be important for targeting Alzheimer's would speed up drug development."

Published article

The text is based on the scientific article published in *Dalton Transactions*.

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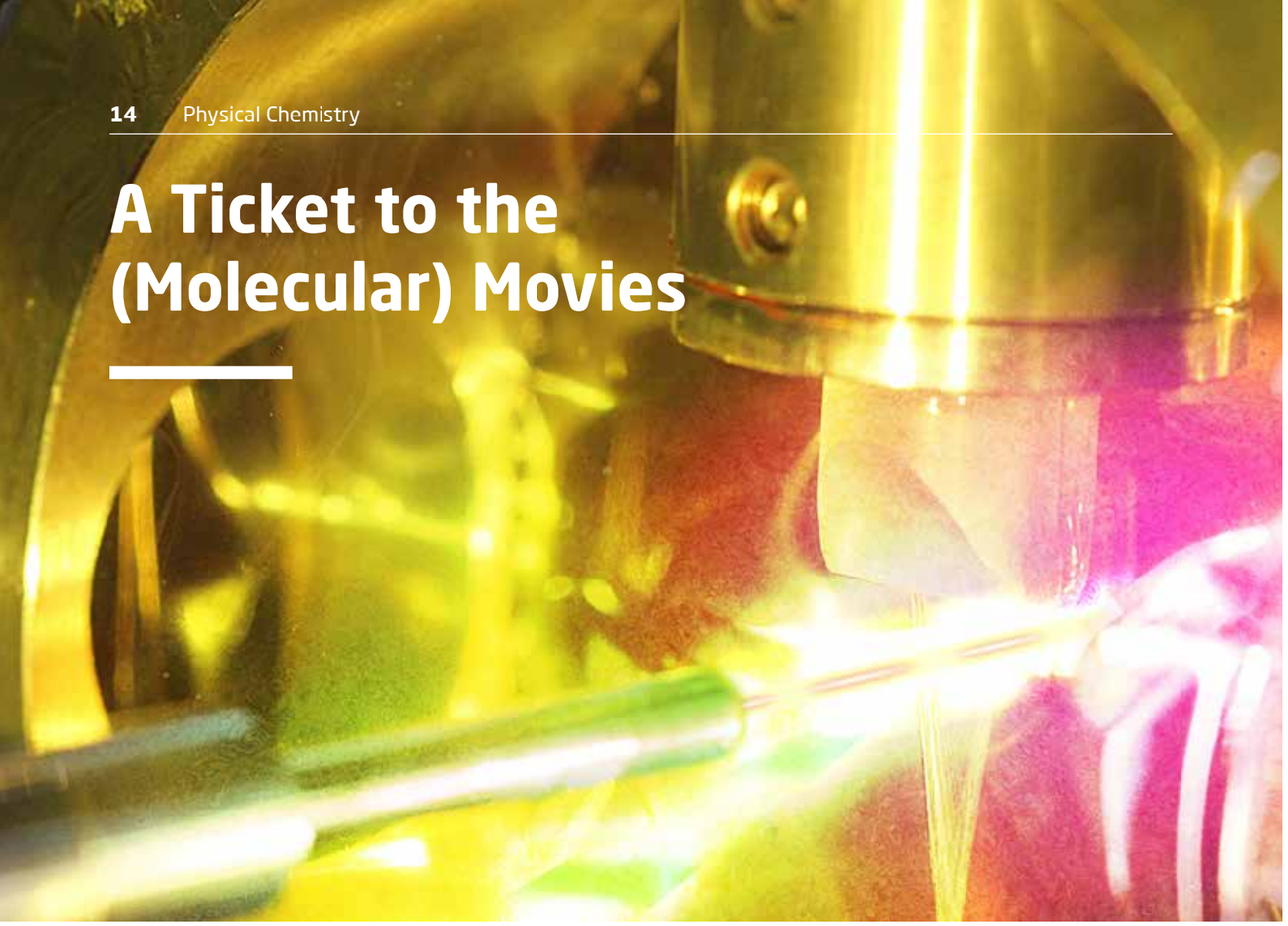
Next step ...

To take the drug candidates into detailed design and clinical trials the research group at DTU Chemistry welcomes the participation from the pharmaceutical industry.

CONTACT

Associate Professor
Kasper P. Kepp
Physical Chemistry
kpj@kemi.dtu.dk



A Ticket to the (Molecular) Movies

Beam time is in high demand at the exclusive international facilities able to "film" on the femtosecond scale which applies to chemical reactions. A successful DTU modeling tool opens the doors.

Certain molecules are able to absorb light and use it internally to break or make chemical bonds. A team of scientists from DTU Chemistry and DTU Physics has successfully used advanced computer simulations to describe how one such molecule absorbs light, leading to a different structure of the complex and to a further dissipation of the energy. The findings were accepted for publication by the Journal of Physical Chemistry Letters, one of the most prestigious journals of the field. Further has the modeling tool, which made the accurate description possible, proven to be a ticket to an exclusive world of cutting edge science.

"We are not the first to observe this type of phenomena in a molecule. What is so special about the study is the amount of statistical information we have been able to generate. Our article contains about ten times more dynamic information compared to other articles. This enables us to not only "see something", but also to perform large evidence-based simulations, which establish the prevalence of the various states of the molecule," says Associate Professor Klaus B. Møller, DTU Chemistry.

The new tool developed by scientists from DTU Chemistry and DTU Physics builds on Quantum-/Molecular-Mechanical (QM/MM) Direct Dynamics. It describes excess excitation energy dissipation via dynamic changes in molecular structure, vibrations and solvation.

Filming a chemical reaction

Traditionally a chemical reaction is described by an equation which features the reactants on the left hand side and end products to the right. This picture is, however, simplified as even simple reactions involve a set of sub-reactions so complex that it would take vast amounts of modelling and computer calculations to describe them. But recently advanced international facilities has been built in which it is possible to "film" chemical reactions using X-rays.

A chemical reaction can be compared to a football game in the sense that only in a fraction of the total time consumed will the events that are most important to the spectator – the actual scoring of goals – take place. The vast majority of time is used for getting the conditions for scoring a goal in place. Once the conditions are right, it will only take seconds to score the football goal – and in parallel; the transformation of a molecule takes just a few hundred femtoseconds (one femtosecond is 10^{-15} second). Hence the field has been dubbed femtochemistry.

The new advanced facilities are able to generate X-ray pulses so short that processes at this incredibly small time scale may be seen.

The three main facilities of interest to the DTU team are the Linac Coherent Light Source (LCLS), operated by Stanford University, USA, the Japanese X-ray laser system SACLA, and the soon-to-open European facility, XFEL, in Hamburg, Germany.

"Any result will be first of its kind"

Postdoc Asmus Ougaard Dohn, DTU Chemistry, has been involved in experiments at both LCLS and SACLA during his recently concluded PhD project. The experiments included the Iridium-containing complex which is the basis for the Journal of Physical Chemistry Letters article.

"It is a real privilege to work at such cutting edge facilities," Asmus Ougaard Dohn remarks. "It is a privilege and a challenge: We more or less need to build the analytical tools from scratch, to achieve results. But almost every result we get will be the first of its kind."

The studied complex is $[Ir_2(dimen)_4]^{2+}$. This binuclear Iridium-containing complex was chosen mainly for two reasons. Firstly, it is a large complex containing heavy atoms with a high number of electrons, which makes it easier to observe and get statistically viable results. Secondly, it has been studied by several other groups, including collaborators at Stanford University. This provides a background for validating the results.

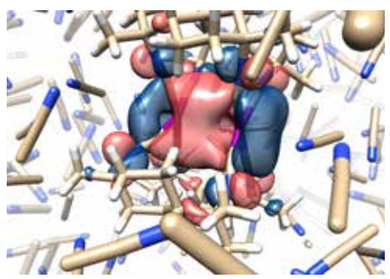
Even though the complex had been studied by several other groups, the DTU-scientists were able to provide new insight. The molecule was believed to exist in two main distinct states, but the study revealed a previously unknown third state. The group has dubbed this the "breathing" state, as here the molecule alters its structure periodically, much like a person breathing. Another new insight feature involves the relation between the molecule and the solvent utilized. Traditionally the solvent is not seen as a part of the experiment but here the dissemination of energy from the complex to the solvent was followed closely. Surprisingly, the solvent was seen to stabilize the molecule leading to a longer period of concerted motion – in contrast to the general assumption.

Relevant to solar cell applications

While these discoveries have credited the team in the academic world, it is still a long route to practical applications.

"Molecular absorption of light and the precise resulting distribution of energy are in fact of interest to a number of applications. One of these would be solar cells. It is very likely that an improved understanding of such processes can lead to significantly better photovoltaic cells. However, the Iridium-containing complex which we studied will never be seen in such cells. It is a model molecule with mainly basic scientific importance," says Asmus Ougaard Dohn.

"We are enthusiastic about the four beam time sessions we will have in 2015 and also by the fact that several international groups have invited us to take part in their projects. In other words, they invite us to do calculations based on their experiments because they know we can contribute," notes Klaus B. Møller.



Snapshot of a simulation made with the new theoretical tool developed by the DTU-scientists. The molecule in the middle is treated with quantum mechanics, under the influence of the classically described solvent particles.

Published article

The text is based on the scientific article published in *The Journal of Physical Chemistry Letters.*

You can download it as a pdf by scanning the QR-code below.

Scan to see molecular movies:

Next step ...

The scientists from DTU Chemistry are enthusiastic about their four beam time sessions in 2015. Also, the group has been invited by several international groups because they can contribute to do calculations based on others experiments.

CONTACT

Associate Professor
Klaus B. Møller
Physical Chemistry
klaus.moller@kemi.dtu.dk

X-rays Aid Production of Industrial Enzymes

Analysis of an enzyme produced by Novozymes in large-scale as a detergent ingredient, confirms that X-ray powder diffraction (XRPD) is highly relevant for protein-producing industries.

When your shirt has a sauce stain the enzyme Savinase in your washing powder chops up the proteins in the stain. This is an important first step, which allows the water and other detergent components to remove the tricky substance. By doing so Savinase – with the scientific name Bacillus lentus subtilisin – also helps the environment and protects the climate, as before the application of enzymes to washing powder, such stains could only be washed away at high temperatures, leading to shorter life of the textiles and to higher energy consumption. Therefore it is good news that a technique nursed by Associate Professor Pernille Harris and her group at DTU Chemistry is able to aid in the everyday production of Savinase.

The technique X-ray powder diffraction (XRPD) allows for fast characterization of the product. Just like all other proteins, Savinase can assume a variety of crystal structures, so called polymorphs. Depending on the actual production conditions, the distribution of polymorphs will vary.

"The collaboration has proven that the XRPD technology can provide Novozymes with a molecular insight into the complex biological process fluids," says Sune Jacobsen, Senior Manager at Novozymes – the world's leading producer of industrial enzymes.

Know your precipitation

It takes about an hour to set up the analytic procedures, and you obtain the results right away.

"This is fast enough for use in everyday production," says Industrial Postdoc Christian G. Frankær, who divides his time between DTU Chemistry and Novozymes.

Novozymes prefers to keep the details confidential on which exact distribution of Savinase polymorphs that would be ideal. But in general terms it can be stated that certain structures are better suited for the production flow than others. First of all the different structures correspond to different precipitation behavior.

"Controlling precipitation in the various steps in the production is key for Novozymes in order to run an efficient production. As precipitation can be beneficial at certain steps in the production the contrary is also true. In other words you want to control your precipitation, and getting the right distribution of polymorphs is a key feature," explains Associate Professor Pernille Harris, DTU Chemistry. "The point is that we have been able to show that XRPD is a good practical tool in this context".

XRPD is a standard method used in many types of industry. An example is characterization of the distribution of sand, clay and pebbles in soil for the building industry. However, characterization of protein structures is complicated as proteins are large molecules. Over the years, the group at DTU Chemistry has developed a number of software and analytical tools which has improved the accuracy of XRPD for protein characterization purposes greatly.

A highly representative method

Results from XRPD studies of Savinase have recently been published in the journal Acta Crystallographpica, the International Union of Crystallography. Christian Frankær, Pernille Harris, and Associate Professor Kenny Ståhl, all DTU Chemistry, co-authored with several Novozymes researchers and members of a group at University of York, UK.

"The article is a scientific landmark. We hope that it will spur further interest from industry," Pernille Harris says. "What we have done on Savinase is equally relevant to all other proteins. Many other proteins are manufactured both by Danish and foreign companies, and this is generally believed to be a rising trend."

For some years the prime technique for establishing the polymorphs of produced proteins has been single-crystal macromolecular crystallography (MX).

"MX will give you much more detailed information about the structure compared to XRPD. But MX will cost you a lot more time, it may also involve sending your samples to synchrotrons, and last but not least the results are probably not representative," says Christian Frankær.

Relevant in optimizing production

The problem with MX is that it requires large crystals – as indicated by the phrase macro-molecular. It is by no means given, that when you pick the largest crystals in your samples, you will get a representative picture.

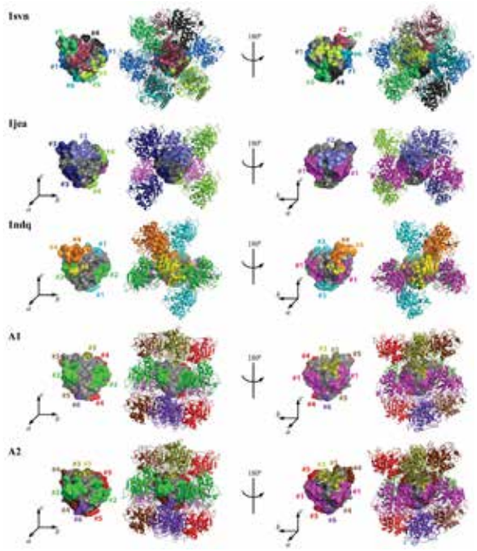
Pernille Harris points to the example of diamonds, which are a polymorph of carbon.

"Suppose you want to characterize the content of your coal mine, and you do that by looking at a few diamonds found in the mine. Similarly, you can get a false picture, if you try to fine-tune the production of an enzyme based on characterization of the largest crystals."

Pernille Harris and Christian G. Frankær admit that convincing industry about the attractive features of the method is not straight-forward.

"Industry is used to a development whereby science can help in looking at their products in ever finer detail. This is not the case here," says Pernille Harris, elaborating:

"On the contrary, MX and other techniques can give you much better detailing. The point is that XRPD is relevant not so much to the R&D people in industry, but rather to the process development and production optimization people. It will give you fast results, which are fully representative for your product. In other words, you get information, which you can actually use to optimize your processes. Once this is realized, we hope to see several new joint projects."



Crystal packing in five B. lentus subtilisin crystal forms.

Published article

The text is based on the scientific article published in the journal *Acta Crystallographica.*

You can download it as a pdf by scanning the QR-code below

Next step ...

"The collaboration project has proven that the XRPD technology can provide Novozymes with a molecular insight into the complex biological process fluids."

Sune Jakobsen,
Senior Manager,
Novozymes.

CONTACT

Associate Professor
Pernille Harris
Physical Chemistry
ph@kemi.dtu.dk

A New Catalyst for an Ancient Bulk Chemical

Zeolite recrystallization allows synthesis of extremely efficient gold nanoparticle catalysts. This could revive one of the oldest processes in chemical industry, namely production of acetaldehyde from ethanol. The principle may apply to a range of new catalysts.

In itself it is no great achievement to produce acetaldehyde. The annual global production of this bulk chemical with numerous applications is well above 1 million tonnes. However, research groups at DTU Chemistry and the Max-Planck-Institute für Kohlenforschung have managed to oxidize ethanol effectively and selectively into acetaldehyde by use of a novel type of zeolite catalyst with encapsulated gold nanoparticles.

"This is likely to be a favourable, green alternative to the so-called Wacker process, which dominates the world's current production of acetaldehyde. And hopefully this is just the beginning. This type of catalyst will in principle apply to a range of other reactions," says Associate Professor Søren Kegnæs, DTU Chemistry.

"On top, the materials have been well studied by advanced electron microscopy with help from DTU Cen."

Rise of the gold nano-particles

A few decades ago it came as a surprise to many, when gold nanoparticles were shown to be active and selective catalysts for several oxidation reactions with molecular oxygen despite the unreactive nature of bulk metallic gold. Since then many groups have sought to find the best practical solutions on how to make catalysts with gold nanoparticles.

The Danish-German research groups are at the leading edge of these efforts, as shown by their recent publication of an article in the journal Angewandte Chemie.

While most other attempts to encapsulate metal nanoparticles in zeolites have relied on expensive additives and complex procedures, the new approach is both simple and effective. Crystals of the zeolite silicalite-1 are modified by recrystallization, which creates intra-particle voids and mesopores. The recrystallization was performed in the presence base and a surfactant, which protects the outer surface of the crystals. Since the zeolite crystals are porous, the base will penetrate into the crystals and begin to dissolve them from within. The trick is to stop the process at the right time, when the inner voids have the optimal size. The voids will then be filled with a precursor solution containing a metal salt. In the acetaldehyde project an aqueous solution of $HAuCl_4$ was applied. Further, the material is dried and then reduced under H_2. The confined space provides ideal conditions for preparation of small and disperse gold nanoparticles inside the zeolite crystals.

In other words, the zeolite structure functions as a physical barrier which hinders the nano particles from sintering. In this way they will stay separate, leading to a large inner active catalyst surface which in turn makes the catalyst more efficient and at the same time less exposed to sintering.

A clever way to use bio-ethanol

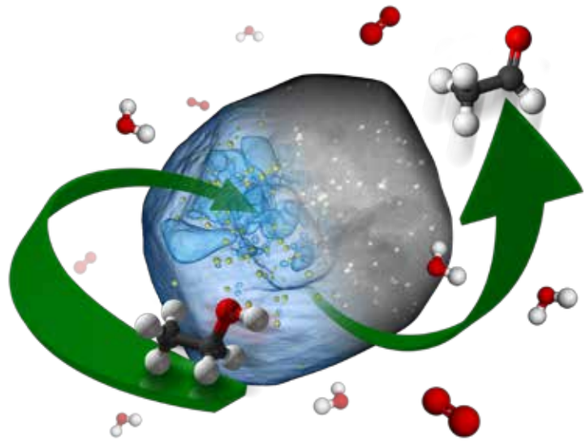
While the researchers were certain they had created efficient catalysts, they also needed to prove it. The choice was to catalyze oxidation of ethanol into acetaldehyde. First described in 1774, acetaldehyde has numerous applications. For instance it can be processed further into acetic acid (known as vinegar in aqueous solution), and it can serve as a precursor for production of vinyl polymer. For several centuries, oxidation of ethanol was in fact the dominant route, but since the beginning of 1960'ies, with the invention of the Wacker process, which oxidates ethylene using a homogeneous palladium/copper system, ethylene has been the primary feedstock.

"We chose the ethanol process, because bio-ethanol receives large attention these years, since it is a renewable resource," Søren Kegnæs explains.

Most interest targets the use of bio-ethanol as a fuel or fuel component, but this has a drawback, since the direct synthesis of ethanol from biomass normally yields ethanol with a 90 % water content.

"If you want to use ethanol as fuel you need to get rid of the water content, which will cost you a rather high amount of energy. It would thus be interesting to find an alternative use of the bio-ethanol in which a high content of water is not a problem. This is the case for the production of acetaldehyde," notes Søren Kegnæs.

"Also, this revival of ethanol as source for production of acetaldehyde has some benefits in comparison with the use of ethylene, since ethylene is produced from crude oil which is a non-renewable resource."



An artistic representation of the catalyst based on results from STEM microscopy. The figure also shows how bioethanol diffuse into the porous zeolite and gets converted into acetaldehyde on the encapsulated gold nanoparticles.

Strong Danish-German cooperation

DTU has patented the new type of catalysts.

"We hope that industry will be interested in cooperation on this," says Søren Kegnæs.

At the time of this interview the article on the novel zeolite catalyst has just been published in Angewandte Chemie. It is thus too early to evaluate the impact.

"My feeling is that this very article will not in itself be enough to have industry call us and inquire about cooperation. But recently we have had another article on design and synthesis of advanced nanoparticle catalysts accepted by Angewandte Chemie, so we are getting closer," Søren Kegnæs remarks.

He further emphasizes the cooperation with the Max-Planck-Institute initiated in early 2013. The cooperation was made possible by a grant from the Danish Council for Independent Research (FTP).

"The cooperation takes place in a very open atmosphere, with a high degree of sharing ideas and having students visit for shorter or longer periods of time."

Published article

The text is based on the scientific article published in *Angewandte Chemie*.

You can download it as a pdf by scanning the QR-code below.

Next step ...

This is likely to be a favourable, green alternative to the so-called Wacker process, which dominates the world's current production of acetaldehyde.

DTU has patented the new type of catalysts. Associate Professor Søren Kegnæs and his group hope that industry will be interested in cooperation on this.

CONTACT

Associate Professor
Søren Kegnæs
Inorganic Chemistry, CSC
skk@kemi.dtu.dk

PhD from DTU Chemistry

DTU Chemistry takes pride in educating PhD's 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.

Excellent scientists must also be able to communicate their research results efficiently. DTU Chemistry offers each PhD-student an intensive communication course to practice presentation techniques with focus on rhetoric, voice control, attitude, appearance, and efficient formulation of key messages. 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 postersession by the Departments PhD-students.

In the following you can witness the diverse PhD Defences 2014 with topics ranging from basic research to projects made in collaboration with industry as well as projects leading to start-up companies. Within the projects you will find a QR-code leading you to the full thesis, and we welcome you to contact the supervisor for further information, inspiration and possible collaboration.

Anti-cancer Drugs Based on Epigenetic Modulation (I)

Desmethyl azumamide analogs are promising candidates for inhibition of histone deacetylases (HDACs), which are key substances in gene expression.

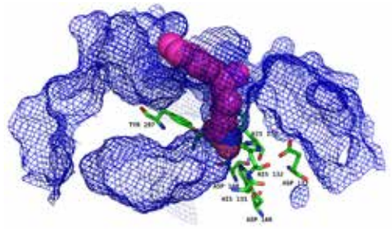
Alex R. Maolanon, PhD

"Synthesis and Evaluation of Desmethyl Azumamide Analogs"

Histone deacetylases (HDACs) are key substances in regulation of gene expression, which is a fundamental life process. While all genetic information is stored in DNA, and the same DNA is present in all cells, not all genes will actually be expressed in all cells. The actual gene-expression is regulated by a number of processes called epigenetic mechanisms. HDACs play an important role in one of these mechanisms. They function as "erasers", which remove certain modifications. Aberrant epigenetic processes have been associated with various forms of cancer, and HDACs have therefore become targets for new types of anticancer drugs. So far, two HDAC inhibitors have been approved by the American food and drug administration (FDA), and several compounds are in clinical trials. The thesis investigates a group of possible HDAC inhibitors, namely analogs of natural products called azumamides.

Azumamides are an interesting type of HDAC inhibitors. These macrocyclic compounds are able to interact with a variety of amino acids on the surface near the binding site. The interactions can be used to obtain selectivity for specific HDAC isozymes. Further, the azumamides are potent HDAC inhibitors, and since they possess a relatively weak zinc-binding group, the activity must come from interactions with the large "cap group".

Aromatic substituents in cyclic peptides were explored, with the most challenging modifications being introduced in the β–amino acid residue. Six azumamide analogs were synthesized, all with the methyl group removed from the 2-position of the β–amino acid. Different amino acids were investigated as well as modifications to the unsaturation in the side chain. The key step in the synthetic route was a cross-metathesis on a vinyl amino acid building block, which could be readily obtained from commercially available L-aspartic acid. An optimized position for the cyclization was found, which led to a significantly improved yield.



TSA (magenta, space filling model) bound to histone deacetylase-like protein (PDB: 1C3R). Amino acids involved in the deacetylation are shown as sticks.

The azumamide analogs were tested against a number of HDAC enzymes. Minor changes in activity were observed among the analogs. However, removal of the methyl group had a significant impact relative to the natural products. Compounds containing a phenylalanine and a trans olefin in the side chain were slightly less potent.

Investigations by NMR and computational techniques were performed in collaboration with the laboratories of Charlotte H. Gotfredsen and Peter Fristrup at DTU Chemistry, and these revealed that the 3D-structures of the azumamide analogs were similar to the natural compounds. Although a conclusion was not found, the preliminary docking results indicate favorable lipophilic interaction with the methyl group in the azumamides.

Largazole is another macrocyclic natural product with HDAC inhibitory activity. The compound contains a thioester functionality in the side chain, which is presumably hydrolyzed before interaction with the HDAC enzymes. To mimic the prodrug nature of largazole, compounds containing a thiol were designed as it was hypothesized that acylation with different lipids could generate compounds with improved cell-penetrating properties. A desmethylated azumamide analog containing a thiol side chain was synthesized.

CONTACT

Supervisor:
Christian A. Olsen, now Professor at University of Copenhagen
cao@sund.ku.dk

Funded by:
The project was funded by the Lundbeck Foundation. The project was related to the PhD study of Jesper Villadsen.

Scan the QR-code and get the thesis as a pdf.

Catalysis in Sustainable Chemistry

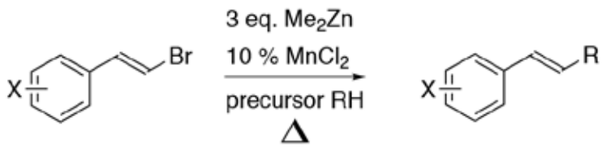
An atom-economical way of synthesizing esters by dehydrogenative coupling of primary alcohols, catalyzed by a ruthenium complex is presented.

The concept of "atom economy" in chemistry was introduced by Trost in 1991. The basic idea is to maximize the share of reactant atoms that can be found in the end product(s), thus minimizing waste. In practice this often depends on catalysts which assist by arranging the atoms during the process. Efficient catalysts therefore play a key role in sustainable chemistry. More specifically, a number of transition metals have proved to be highly efficient catalysts. The thesis investigates two classes of transition metal catalyzed reactions with large practical applications, and one sequence of mainly theoretical importance. The last few years have seen a steep rise in the interest in dehydrogenative reactions in the scientific literature. These reactions are atom-economical in the sense that the only redundant atoms are hydrogens which are cleaved off, producing molecular hydrogen as the only byproduct. The thesis presents a new atom-economical way of synthesizing esters by dehydrogenative coupling of primary alcohols, catalyzed by a ruthenium NHC complex. Esters are produced industrially on a very large scale.

The proposed reaction is catalyzed by the ruthenium N-heterocyclic carbene complex RuCl2(IiPr)(p-cymene). The optimal reaction conditions were found to be 2.5 mol % of the carbene complex, 4.5 mol % of PCy3 and 10 mol % of KOH in refluxing mesitylene. The substrate scope was shown to include a range of different straight-chain and branched primary alcohols, which reacted to give the corresponding esters in moderate to excellent yields. Condensation of diols also proceeded well, giving the corresponding lactones in good yield. Preliminary investigations confirm that the reaction is dehydrogenative. A catalytic cycle is proposed.

Another area of high attention is the idea of replacing palladium with alternative catalysts. Palladium is a highly efficient catalyst in many contexts, but is unfortunately both expensive and toxic, which limits its use for a number of catalytic applications. Finding cheaper and less toxic alternatives is highly desirable. The thesis presents a new method for formation of styryl derivatives by reaction of ether and hydrocarbon radicals with β–bromostyrenes. The best conditions were found to involve addition of three to four equivalents of Me_2Zn to a solution of β–bromostyrene, using the radical precursor as solvent, in the presence of 10-12 % of MnCl2, and refluxing overnight by the presence of air. A simple acidic workup and purification by chromatography gave the products in moderate to good yield.

Finally, a new member of the family of [5]-phenylenes, named Anti Zigzag-[5]-phenylene, was synthesized and characterized. The molecule was synthesized in ten steps, of which six steps had not been performed before, and six new compounds were isolated and characterized. The molecule is primarily of theoretical interest. Its complex synthesis underlines the unrivaled capacities that can be achieved by practical application of transition metal catalyzed reactions.



Amanda Birgitte Sølvhøj, PhD

"Transition Metal Catalyzed Reactions for Forming Carbon-Oxygen and Carbon-Carbon Bonds"

CONTACT

Supervisor:
Robert Madsen
rm@kemi.dtu.dk

Funded by:
The project was funded by DTU.

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Modeling of Transient Molecular Changes

A Direct Dynamics model was developed to represent the processes exhibited in molecular complexes of significant size and intricacy.

Asmus Ougaard Dohn, PhD

"Transient Changes in Molecular Geometries and How to Model Them"

This thesis was granted the Springer Thesis Award by the international scientific publisher Springer.

CONTACT

Supervisor:
Klaus B. Møller
Klaus.moller@kemi.dtu.dk
Niels Engholm Henriksen
neh@kemi.dtu.dk

Funded by:
The project was funded by the Lundbeck Foundation and DTU Chemistry.

Scan the QR-code and get the thesis as a pdf.

Light-induced chemical processes are accompanied by molecular motion at the femtosecond time scale. Uncovering this dynamical motion is central to understanding chemical reactions on a fundamental level. The thesis focuses on the excess excitation energy dissipation via dynamic changes in molecular structure, vibrations and solvation. The studies are necessary for understanding data from X-ray Free Electron Laser (XFEL) experiments, which have become possible at new international large-scale facilities.

Working towards discovering the nature of the chemical reaction entails scrutinizing molecular systems of increasing size and complexity, which again motivates the need for development of new theoretical tools.

The main part of the work concerns the development of a Direct Dynamics model which combines the quantum mechanical description of Density Functional Theory (DFT) with the classical Molecular Mechanical method to represent the processes exhibited in molecular complexes of significant size and intricacy. The term Direct Dynamics arises from the notion that the atomic motion is simulated by directly calculating the classical forces on the nuclei, influenced by the explicitly calculated electronic density of the Quantum Mechanical part of the system. The resulting atomic motion is collected into trajectories which can be analyzed to reveal information about the transient changes.

The method was employed to simulations of two transition metal complexes in solution, to uncover their energy dissipation channels, and how they are affected by the solvent. The main complex studied was [Ir2(dimen)4]2+. In this bi-metallic Iridium complex, excited state bond formation results in a large Ir-Ir contraction with oscillatory behavior. Implementation of the modeling tool reproduced the experimentally observed metal pinching oscillation. Further, the experimentally obtained model was improved by analyzing the pinch, twist, and breathing modes in relation to the solvent. The system proved interesting, since the coherence lifetime was actually increased by solvation, since the solvent (acetonitrile) can block the Intramolecular Vibrational energy Redistribution (IVR), which would cause de-coherence.

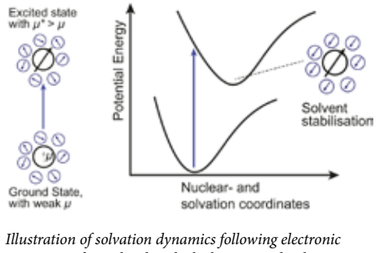


Illustration of solvation dynamics following electronic excitation of a molecule, which changes its dipole moment.

Also studied was the effect of solvation on a bi-centred Ru-Co complex. Contrasted to [Ir2(dimen)4]2+ it does not have direct metal-metal interactions, and is believed to have a narrower Ground State (GS) thermal distribution of geometries. However, the structural changes in the complex due to excitation are more subtle. Both specific and non-specific solvation dynamics of the solvent shell around the complex as a consequence of the excited state electron transfer was observed. Use of the developed modeling tool proved capable of recovering several processes which could not be described by purely classical force-field methods.

The project also included participating in experiments on these systems carried out at the LCLS and SACLA XFEL facilities in USA and Japan.

In conclusion, the current limitations of the developed Direct Dynamics method were overshadowed by its efficacy. While many such studies are still confined to interpreting results from single trajectories of few picoseconds, this implementation has shown its efficiency, accuracy and power in the continuing exploration of the world of femtochemistry.

Synthesis of Breast-milk Compounds

The main focus is human milk oligosaccharide (HMO) synthesis based on the motif Galβ1-3/4GlcNAcβ1-3Galβ1-4Glc, which is the core of many HMO's.

For more than a century it has been known that babies fed on breast-milk have lower risk of several diseases compared with bottle-fed infants. While the exact mechanisms are still under debate, this difference has spurred interest in adding key components from human milk to infant formula, which is commonly produced from bovine milk. Human milk contains a range of biomolecules including vitamins, enzymes, proteins, and oligosaccharides. The main focus of the thesis is human milk oligosaccharide (HMO) synthesis while a second and distinct part is dedicated to a protein relevant for future cancer treatment. Both topics are related to carbohydrate and organometallic chemistry.

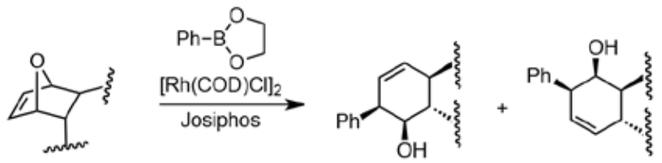
HMO's are the third most abundant component in breast-milk (5-15 g/L). HMO's are composed of five monosaccharide building blocks: galactose (Gal), glucose (Glc), N-acetyl-glucosamine (GlcNAc), fucose (Fuc), and N-acetylneuraminic acid (Neu5Ac). In bovine milk oligosaccharides are less abundant and structurally less complex than HMO.

The synthesis is based on the motif Galβ1-3/4GlcNAcβ1-3Galβ1-4Glc, which is the core of many HMO's. Three distinct HMO's were synthesized: Lacto-N-tetraose, Lacto-N-fucopentaose I, and Lacto-N-neofucopentaose I.

A one-pot strategy was developed for synthesis of the tetrasaccharide backbone core based on the different reactivity of thioglycoside donors and acceptors. Deprotection of the protecting group at the C-2-position on the galactose moiety liberated an acceptor for the fucosylation eventually creating the two linear pentasaccharides Lacto-N-fucopentaose I, and Lacto-N-neofucopentaose I.

The scope of the developed one-pot method was enhanced by 1-4 glucosylations utilizing a glucosamine building block containing two free hydroxyl groups. In addition, pNP-neuraminic acid was synthesized for enzyme activity studies. The enzymes were designed to perform sialyl transfer reactions in HMO's containing neuraminic acid.

The second and distinct part of the thesis describes regio-selective ring opening of enantiopure oxabicycles primarily by use of rhodium catalysts and phosphine ligands. The ring opened products were similar to compounds shown to be potential protein Bcl-XL antagonists, a target for future drugs in cancer treatment. By employing a [Rh(COD)Cl]2 catalyst with a Josiphos ligand, it was possible to perform the ring opening of oxabicycles with ester moieties in good yield and excellent regio-selectivity.



Camilla Arboe Jennum, PhD

"Synthesis of Human Milk Oligosaccharides and Regio-selective Ring Opening of Oxabicycles"

CONTACT

Supervisor:
Robert Madsen
rm@kemi.dtu.dk

Funded by:
The project was funded by The Danish Council for Strategic Research

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Green Synthesis of Nanostructures

Precise structural control of nanomaterials can boost activity and limit the consumption of precious metal catalysts in future technology.

Christian Engelbrekt, PhD

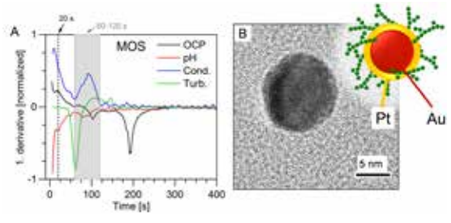
"Green Synthesis and Structural Control of Metal and Mineral Nanostructures"

Nanoparticles already play an essential role as catalysts in energy conversion, e.g. solar energy to electricity, fuel to electricity, and solar to chemical energy, and will become even more important in a future society less dependent on fossil fuels. Precise structural control of nanomaterials is crucial for catalytic efficiency.

Further, it provides the technology to limit the amounts of needed precious catalysts needed, which are known to be efficient, but also expensive and requiring rare raw materials. The thesis presents new fundamental understanding of the formation of metallic nanoparticles and several applications for these in energy technology. Gold (Au) is a very stable metal with well-defined chemistry. Nanoparticles of gold are well suited for several catalytic purposes, and at the same time an ideal model system for studying nanoparticle synthesis. Gold is thus central to all topics in the thesis. Time-resolved chrono-potentiometry, pH, conductivity and turbidity, and ultraviolet-visible light spectroscopy were employed to follow the synthesis of gold nanoparticles under mild reaction conditions, also denoted as "green" synthesis of gold nanoparticles. Several distinct phases were observed. Strong indications of sequential reduction in several identified steps were found and details about ligands and surface immobilized molecules disclosed. This platform is a widely available and facile alternative to traditionally used synchrotron techniques. Structural control lead to the synthesis of both spherical 8-80 nm gold nanoparticles and graphene oxide templated flat, ring-shaped gold nanostructures up to 1 µm in diameter mainly exposing Au(111) facets. A synthesis protocol to produce 8 nm nanoparticles with a gold core and an atomically thin platinum (Pt) shell in one pot was also developed. As platinum is an expensive and scarce raw material, it would be highly desirable if the use of all-platinum catalysts could be replaced by Au core/ Pt shell nanostructures. The catalytic activity of this nanocomposite will be studied in a future project.

In a parallel approach, platinum was alloyed with a cheaper element, namely palladium. Supported palladium-platinum alloy nanoparticles showed promising performance as catalysts in direct methanol and formic acid fuel cells. Further, syntheses of copper mineral nanoparticles were developed. Copper is an abundant element available at a lower cost than most highly efficient catalyst materials. It is important to explore copper-based nanoparticles as catalysts, even if only in niche applications. A buffered synthesis of phase-pure clinoatacamite $Cu_2(OH)_3Cl$ and tenorite CuO was developed. The synthesis of CuO was further optimized. The flat and rod-shaped nanostructures were obtained and used as heterogeneous catalysts for oxidative dehydrogenation reactions. High activity and good reusability was found, and the potential of this system is being explored further in the future.

Finally, a plasmonic photo-electro-catalytic system was prepared to utilize visible light by incorporating gold nanoparticles in titanium dioxide. The composite material showed improved optical properties compared to pure titanium dioxide, and preliminary catalytic tests were promising.



(A) Monitoring AuNP formation. Nucleation is highlighted with grey. (B) High-resolution TEM image and schematic of nanoparticle with a gold core and an atomically thin platinum shell.

CONTACT

Supervisor:
Jingdong Zhang
jz@kemi.dtu.dk
Jens Ulstrup
ju@kemi.dtu.dk

Funded by:
The project was funded by the Lundbeck Foundation and DTU Chemistry.

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Nano-structured Catalysts for Green Chemistry

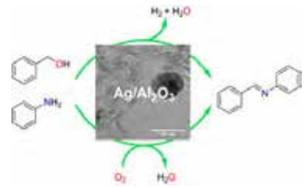
A novel method for the two-step synthesis of amides from alcohols and amines using Au/TiO_2 nanoparticles and base as catalysts is presented.

Catalysis aids the conversion of raw materials into valuable chemicals, materials and fuels in an efficient and environmentally benign manner. Catalytic processes are therefore essential to the industry and to the world economy. Catalysts enhance the rate of chemical reactions, often by many orders of magnitude. Further, catalysts are also important because of their selectivity, i.e. their ability to increase the rate of formation of one particular reaction product relative to other possible, but undesired by-products. In the project, a number of nano-structured catalysts have been synthesized and characterized.

Gold (Au) nanoparticles are particularly interesting. While bulk gold is chemically inert, supported gold nanoparticles can promote several reactions under mild conditions.

A novel method for the two-step synthesis of amides from alcohols and amines using Au/TiO2 and base as catalysts is presented. In the first step, a methyl ester is obtained by gold-catalyzed aerobic oxidation of the alcohol in methanol. In the second step, amine is added and the methyl ester undergoes base-catalyzed aminolysis to give the desired amide. As the same base promotes both reactions, the synthesis can be performed in a one-pot procedure. The reaction protocol was applied to a number of different alcohols and amines, demonstrating the versatility of the method.

A Hammett study indicated that the gold-catalyzed oxidation of benzyl alcohol occurs with build-up of positive charge in the benzylic position, which corresponds well with a H-abstraction step. The results were in good agreement with the generally accepted perception that the gold catalyzed esterification of alcohols with methanol occurs through an aldehyde intermediate. The rate of amide formation was seen to be very sensitive to substituent effects, and negative charge was formed during the reaction.



A green method to synthesis imines by aerobic oxidative coupling of amines and alcohols under mild reaction conditions with Ag/Al2O3 as catalyst was shown.

Further, imines were synthesized directly by oxidative coupling of alcohols and amines using different supported silver catalysts. The reactions were performed at relatively mild conditions (100 °C and atmospheric pressure) and afforded the desired imines with high selectivity (up to 99%). The highest catalytic activity was obtained with 5 wt% Ag/Al2O3 in toluene with air as oxidant.

Pyridine was oxidized to pyridine N-oxide using TS-1 and H2O2 as oxidant. Mesoporous TS-1 prepared by carbon templating was significantly more active than conventional TS-1. UV-Vis spectroscopy indicated that desilication causes a surface densification of less active extra-framework Ti species, while carbon-templating is a more gentle and effective method to introduce mesopores.

Finally, a simple and effective method to encapsulate gold nanoparticles into silicalite-1 is presented. The crystals were modified by recrystallization, which creates intra-particle voids and mesopores that facilitated the formation of gold nanoparticles by simple impregnation. Remarkable stability, catalytic activity, and selectivity for gas-phase oxidation of bioethanol to acetaldehyde were demonstrated. This may become a favorable and green alternative to the conventional ethylene route.

While previous attempts to encapsulate metal nanoparticles in zeolites have relied on expensive additives and complex procedures, the presented approach is simple, effective and scalable. The method could thus become a helpful tool in the further development of nanostructured catalysts.

Jerrik J. Mielby, PhD

"Selective Oxidations using Nanostructured Heterogeneous Catalysts"

Based on the high impact of the research, Jerrik J. Mielby was selected to represent Denmark at the 63rd Lindau Nobel Laureate Meeting for Chemistry in Germany in 2013. He also won DTU's Young Researcher Award in 2014 for his research during his PhD.

CONTACT

Supervisor:
Søren Kegnæs
skkl@kemi.dtu.dk
Anders Riisager
ar@kemi.dtu.dk

Funded by:
The project was funded by the Danish National Research Foundation and by DTU.

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Characterization of Blood Coagulation Protein Complexes

Characterization of protein complexes involved in the blood coagulation cascade can lead to improved treatment for haemophilic patients.

Jesper Jonasson Madsen, PhD

"Structural and Functional Characterization of Protein Complexes in the Blood Coagulation Cascade"

Up until a certain point, the blood is capable of repairing traumatic injury and stop bleedings. The network of inter-connected biochemical coagulation reactions which occurs upon vessel injury is called haemostasis. Insufficient ability of the blood to coagulate is called haemophilia. The thesis focuses on characterization of protein complexes involved in the blood coagulation cascade.

More specifically, molecular dynamics simulations have been performed to elaborate in atomistic detail intricate structural and functional relationships of constituting components of the two principal factor X-activating protein complexes in the cascade. Such insights can lead to development of improved treatment for haemophilic patients. The results are also of relevance for anti-coagulant treatments for patients with the reverse problem, namely too strong coagulation – thrombosis.

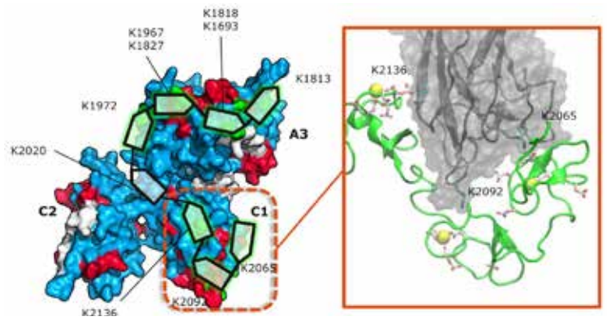
Roughly 400,000 males around the world suffer from haemophilia. Symptoms include prolonged bleedings, joint bleedings, muscle and sub-cutaneous bleedings, internal bleedings, and inter-cranial bleedings. The disease can be treated, with NovoSeven® being one of the leading products for treatment of patients with inhibitory antibodies against FVIII or FIX.

The number "seven" in the name of the product refers to the coagulation factor VII (FVII), or more precisely FVIIa. Dosing of a recombinant form of this coagulation factor can provide haemostasis in patients with severe haemophilia A or B, offering a safe treatment without significant side-effects.

In the project, the complex between FVIIa and Tissue Factor (TF) was studied. It was shown that TF could preserve the productive conformation of the activation domain in FVIIa. This decisive result suggests for the first time an allosteric mechanism involving the E2 strand-following segment acting as a gating-residue for the active site cleft. While it is long established that FVIIa binds TF in an extended conformation, it has not previously been shown how this extension is related to the flexibility of the said linker.

The membrane-bound states of the co-factors FVIII and FIX are important for their function. The resulting conformations of the membrane-anchoring domains from FVIII were studied. Surprisingly, FVIII C1 and FVIII C2 did not converge to similar distribution of membrane-bound states. Lastly, an illustrative canonical binding mode between the LRP receptor and FVIII as ligand was constructed.

Overall, the studies presented have added structural insight at the atomistic scale and a dynamical perspective on FVII activation and FVIII trafficking.



Canonical (triplet) binding mode.

CONTACT

Supervisor:
Günther H. Peters
ghp@kemi.dtu.dk
Ole H. Olsen

Funded by:
The project was funded by Novo Nordisk A/S.

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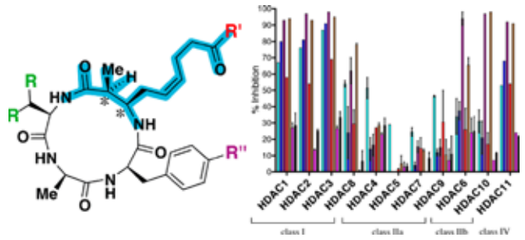
Anti-cancer Drugs Based on Epigenetic Modulation (II)

The thesis presents synthesis pathways for a number of histone deacetylases (HDAC) inhibitors of which several are synthesized for the first time.



Jesper Villadsen, PhD

"Total Synthesis and Biochemical Evaluation of Azumamides A-E and Analogs"

Histone deacetylases (HDACs) are a family of enzymes, which serve as epigenetic modulators. Epigenetics is defined as the processes that regulate gene expression in cells without changing the DNA sequence. The function of HDACs is related to DNA transcription and regulation of various biochemical pathways. It is established that HDACs are relevant targets for anti-cancer drugs, and several HDAC inhibitors are already either approved medicines or undergoing clinical trials. The thesis presents synthesis pathways for a number of HDAC inhibitors of which several are synthesized for the first time.
Macrocyclic peptides and depsipeptides constitute an interesting class of HDAC inhibitors. These compounds are found in nature, and they are highly potent and moderately selective HDAC inhibitors. The focus of the preent thesis was a sub-class of these substances, namely cyclic tetrapeptides known as azumamides.

A synthetic route was developed, which allowed total synthesis of azumamides A–E. This is the first reported total syntheses of azumamides B–D.
The key step in this route was a diastereoselective Mannich reaction, which enabled preparation of two site-specifically edited epimeric azumamide analogs, where the stereochemistry in the unique β-amino acid was inverted. The two epimeric homologs were tested together with azumamide A–E against the entire panel of recombinant HDAC isoforms, providing the first full profiling of the azumamides. It was shown that the β-amino scaffold is highly sensitive to stereochemical modifications.

The profiling of the natural products showed that the azumamides are poor inhibitors of certain HDACs (class IIa) and potent inhibitors of others (HDAC1-3, 10, and 11 – with IC50 values between 14–67 nM). Furthermore, carboxylic acid containing compounds (azumamide C and E) were more potent than their carboxyamide counterparts (azumamide A and B).

Isoform selectivity was observed in class I and class IIb. In class I, azumamides C and E were 60–350 times more potent towards HDAC1-3 over HDAC8, and in class IIb they were ›200-fold more potent against HDAC10 over HDAC6. Finally, azumamide C was approximately twice as potent as azumamide E, which indicates that having a tyrosine residue in the macrolactam ring increases the activity compared with the phenylalanine homolog.
The synthetic route was elaborated to produce structurally edited azumamide analogs.
A series of β2-desmethylated compounds were synthesized in parallel to a series of β2-dimethylated analogs, and a tryptophan-containing series was also prepared.

In conclusion, the project has contributed to understanding of the structure-activity relationship for the azumamides. It was illustrated that these compounds are particularly sensitive to modifications in the β-amino acid residue. The developed diastereoselective Mannich reaction has been shown to be a powerful tool for synthesizing β-amino acid scaffolds, and this reaction will aid in future production of azumamide analogs.

CONTACT

Supervisor:
Christian A. Olsen, now Professor at University of Copenhagen
cao@sund.ku.dk

Funded by:
The project was funded by the Lundbeck Foundation. The project was related to the PhD study of Alex R. Maolanon.

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Synthesis of Peptide-mimicking Compounds

Based on natural protein folding principles, a number of bio-mimetic compounds with drug application relevance have been synthesized.

Jonas Striegler Laursen, PhD

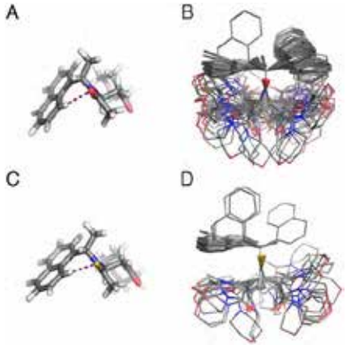
"Design, Synthesis, and Characterization of Bio-mimetic Oligomers"

Peptides and proteins are highly active and selective biological molecules. Just as these properties are vital to all functions in the body, they are also highly sought after in pharmaceutical agents. For more than a century it has been known that it is possible to design and synthesize artificial compounds based on the same folding principles, which apply to natural proteins. For many years, though, such molecules were thought to have only scientific interest. It was considered that production costs would be too high, and the level of degradation of these compounds too high in the body for them to be realistic drug candidates. This view is changing in the pharmaceutical industry with the arrival of the first so-called recombinant protein therapies. It is realized that the unnatural origin of certain bio-mimetic substances can actually be an advantage in drug applications, since they may exhibit improved stability towards enzymatic degradation.

Jonas S. Laursen's thesis presents design, synthesis, and characterization of a number of such biomimetic compounds with biomedical relevance.

Proteins are large molecules built from amino acids, which are connected by amide bond linkages, or peptide bonds. By varying the positioning of the total 20 amino acids available, the proteins constitute highly diverse class of molecules. Further, the proteins realize their diversity by folding the backbone into a well-defined three-dimensional structure, which is encoded by the sequence of amino acids. Artificial compounds with a similar ability to fold have been coined "foldamers".

This project focuses on the folding propensities of β-peptoids, a combination of two peptidomimetic foldamers, the β-peptides and peptoids. While β-peptoids have already found use in biologically active compounds, their folding propensity has been sparsely studied.
In the project the effect of structural variations, including side chain substitution, introduction of thioamides, and trifluoroacetylation, on the cis-trans amide bond rotamer equilibria in monomer model systems was studied. The latter systems revealed an increase in the preference for cis-amides as compared to their parent compounds and thus provide novel strategies for affecting the folding of peptoid constructs. Evidence was found for the presence of thioamide-aromatic interactions through C_{sp2}-H···S_{amide} hydrogen bonding.



Calculated structures of compounds 6e (A and B) and 12e (C and D). All structures within 21 kJ × mol−1 of the global minimum were superimposed.

A β-peptoid oligomer was designed from residues prone to fit a helical arrangement found by density functional theory (DFT) calculations. X-ray crystal structures for two hexameric compounds respectively with a free N-terminal amine and with an N-terminal acetyl group were solved in collaboration with Associate Professor Pernille Harris at DTU Chemistry. These are the first examples of high-resolution structures of linear β-peptoid oligomers, and clearly show that these compounds form unique helical arrangements.

In conclusion, the project underlines that the β-peptoids should be considered a valid addition to the already existing ensemble of foldamer designs.

CONTACT

Supervisor:
Christian A. Olsen, now Professor at University of Copenhagen
cao@sund.ku.dk

Funded by:
The project was funded by DTU Chemistry.

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Synthesis of Key Plant Cell Wall Components

Methods for synthesizing branched- and linear oligogalactosides have been developed by preparation of three small libraries of oligosaccharides.

Mathias Christian Frank Andersen, PhD

"Synthesis and Application of Plant Cell Wall Oligogalactans"

The cell walls represent almost half of the biomass found in plants. Understanding the plant cell walls is thus of enormous importance both in regard to economy and sustainability. Examples are the use of plants for transport fuels, functional foods, and raw materials to generate chemical building blocks for industrial purposes. In this thesis, novel methods for the synthesis of a number of key plant cell wall components are presented. The idea is that such structurally well-defined substances can serve as models for the study of the more complex components found in plants. This may aid investigations on i.e. cell wall biosynthesis and protein-carbohydrate interactions.

The cell wall is composed by a network of polysaccharides (approximately 90 %) and protein components (app. 10 %). The primary cell wall is divided into two categories. Type I walls consist of a cellulosic microfibrils cross-linked by hemicelluloses and enmeshed in a non-covalently cross-linked pectin network. Type II walls are organized in essentially the same way but with the matrix mainly composed by glucurono-arabinoxylans (GAXs) and β–D-(1→3; 1→4)-glucans (mixed-linkage glucans, MLGs).

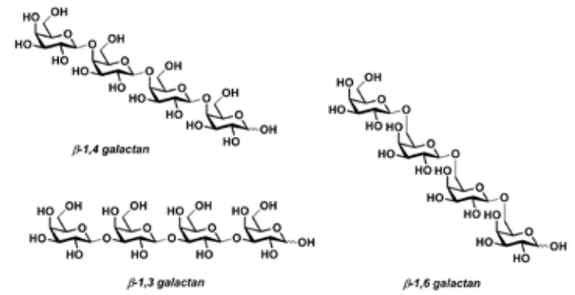
The thesis presents the chemical synthesis of fragments of galactans and arabinogalactans that are prominent side chains of the pectic polysaccharide rhamnogalacturonan I (RG-I) and the main component of arabinogalactan protein (AGP).

A novel, mild procedure for hydrolysis of n-pentenyl glycosides was developed, making it possible to obtain the corresponding PTFAI donors in high yields. These proved to be exceptional donors for glycosylation of pentenyl glycoside acceptors and gave access to fully protected pentenyl disaccharide donors.

A 3,6-O-benzyl protected donor made it possible to prepare a small library of oligogalactans including linear tetra-, penta-, hexa-, and heptasaccharides and six (1→6)-branched hepta- or octasaccharides. The assembly of the oligosaccharides went smoothly with good to excellent yields and high selectivity for the desired β–linked products. This constitutes the first reported synthesis of branched β–(1→4)-linked galactans.

Proof of concept for the utility of the synthetic cell wall fragments was obtained by researchers at Lawrence Berkeley National Laboratory, California, at DTU Systems Biology in Lyngby, and at University of Copenhagen, while further studies are currently undertaken by the German Cancer Research Center in Heidelberg.

In conclusion, methods for synthesizing branched- and linear oligogalactosides have been developed and exemplified by preparation of three small libraries of oligosaccharides. The value of synthetically prepared, well-defined oligosaccharides for plant research has been shown.



Lipid I biosynthesis and the target Tunicamycin analogue.

CONTACT

Supervisor:
Mads Hartvig Clausen
mhc@kemi.dtu.dk

Funded by:
The project was funded by DTU and the Danish Council for Strategic Research.

Towards Nano-scale Electrochemical Sensors

Prussian Blue nanoparticles were synthesized and proven highly efficient in interfacial electrochemical electron transfer and as enzyme mimetic nanoscale electrocatalysts.

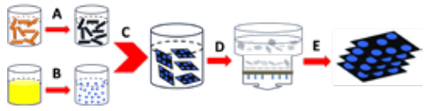
Nan Zhu,
PhD

"Nano-scale Electro-catalysts for Chemical and Biological Sensors"

Nano-size sensors are attractive for several reasons. They can be highly sensitive, and analyte quantities in principle right down to a single molecule can be detected. Secondly, the space requirements are very small, contributing to lab-on-a-chip technology. The amount of material required for sensor construction is finally small. Focus of the present thesis is how catalytic properties of different types of nanostructures can be utilized in nanoscale chemical and biological sensing. The thesis also contributes to understanding of the fundamental catalytic processes. Surface catalytic reactions are very sensitive to the atomic-level structure of the interface. A core feature of nanostructures in relation to sensing is further their ability to catalyze electrochemical reactions. Different dimensions and types of nanomaterials can enhance electrocatalytic activity, and thus offer to be highly suitable for nanoscale sensing.

Prussian Blue (PB) – $Fe_4[Fe(CN)_6]_3$ – has been widely used for centuries as a dye. In 1978, Neff showed PB to be electro-active, and in 1984 Itaya discovered that PB can catalyze electrochemical reduction of hydrogen peroxide (H_2O_2) and O_2. Detection of H_2O_2 is important in many contexts. It is a waste product from nuclear power stations and industry, and monitoring H_2O_2 in ground water or rain is often relevant. Further, H_2O_2 is used to disinfect beverage and food packaging, water pools, and in several other applications. Later it has been suggested to use PB mixed with enzymes as a biosensor probe to detect glucose, galactose lactate, cholesterol, choline, and other biological substances.

PB nanoparticles with excellent redox electroactivity have been synthesized in the Ph.D.-project. They proved highly efficient both directly in interfacial electrochemical electron transfer and as enzyme-like nanoscale or even molecular scale electrocatalysts. The particles were immobilized on a single-crystal, atomically planar Au (111) electrode surface modified with functionalized alkanethiol linkers and shown to display highly efficient electrocatalysis towards reduction of H_2O_2, and a quantitative relationship between the electron transfer kinetics and electrocatalytic activity.



Schematic illustration of the experimental preparation procedures. A) Wet-chemical conversion of graphene oxide (GO) to reduced GO via hydrazine reduction, B) synthesis of PNBPs starting from the mixture of $FeCl_3$ and $K_4[Fe(CN)_6]$, C) preparation of PBNPs–RGO hybrid nanosheets, and D,E) processes of preparing PBNPs–RGO hybrid paper including filtration, drying and annealing. Not drawn to scale.

Graphene is a single-atom thick plane of layered graphite. So-called graphene paper was first introduced by Ruoff and co-workers in 2007. Graphene paper doped with PB nanoparticles was prepared and studied in the present Ph.D.-project. The product was shown to have increased electrical conductivity compared with the components, making it a nano-hybrid electrocatalyst of high functional variability. It was shown useful as electrochemical sensor material for detection of H_2O_2 or organic peroxides. Noting the high stability, low cost and efficient electrocatalysis, the PB-doped graphene paper has potential to be produced in large scale, not only for sensing but also for other applications such as electrocatalytic energy conversion.

A new method for fast fabrication of large-area graphene nanosheets doped with "quantum dots" (2-3 nm CdSe nanoparticles) was finally developed. This type of mixed nanomaterial showed new fine-structure for enhancement of photo-induced electron or energy transfer, and could potentially be used in applications such as photo-voltaic material in solar cells.

CONTACT

Supervisor:
Jens Ulstrup
ju@kemi.dtu.dk
Qijin Chi
cq@kemi.dtu.dk

Funded by:
The project was funded by DTU Chemistry, DTU, and NanoScience Center, University of Copenhagen.

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Ionic Liquid Catalysts for Biomass Conversion

Two ionic liquid catalyst systems were used to catalyze dehydration of glucose into HMF, which is an important building block in biorefineries.

Phillip Malcho,
PhD

"Catalytic Deoxygenation of Renewable Chemicals – Structure-Performance Studies"

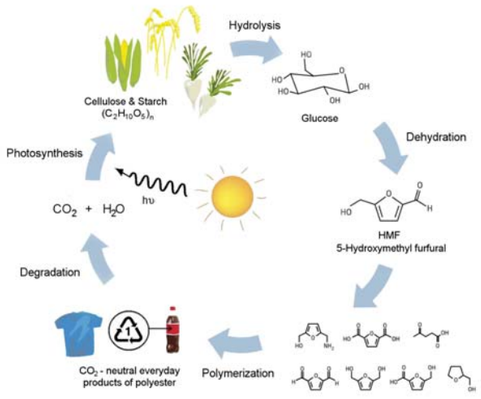
Generation of chemicals from biomass is subject to increased interest. The use of biomass feedstock instead of fossil raw materials is desirable both due to the fact that biomass is a renewable source, and climate considerations. Biomass is CO_2 neutral in the sense that the CO_2 released would have been taken up by plants during their growth. One approach is to build a platform of chemicals that are less used today, but potentially easily obtained from biomass, and which could replace other chemicals that are produced from fossil raw materials. The thesis focusses on catalytic processes that enable production of such platform chemicals.

HMF (5-Hydroxymethylfurfural) can be made from sugars and further processed into a range of chemicals, which can be used for production of polymers or into DFF (2,5-diformylfuran), which is the starting material for various medical and cosmetic products. In the project glucose (which can be obtained from biomass) was converted into HMF.

More specifically, two ionic liquid catalyst systems with either Cr(II) chloride or Cr(III) chloride, were used to catalyze dehydration of glucose into HMF. The system was investigated via several spectroscopic techniques to observe the catalytically active sites. It was shown that during the catalytic reaction, a species of the form $[CrCl_4(OR)_2]$- was formed from $[CrCl_6]^{3-}$ in the solution. These are the predominant chromium containing species in the solution.

Another group of interesting platform chemicals is aldehydes. For the first time in the reported literature, ionic liquids were shown to be viable solvents for the homogeneous decarbonylation of aldehydes. $[Rh(dppp)_2]Cl$ (dppp = 1,3-bis(diphenylphosphino)propane) was used as catalyst. Decarbonylation of both aromatic and aliphatic aldehydes proved possible to an excellent extent. A series of ionic liquids were tested. The best system was comprised of $[Rh(dppp)_2]Cl$ in [BMIm]Cl (1,3-butylmethylimidazolium chloride). It was shown that the ionic liquid stabilized the catalytic system to a degree where the reuse of the catalyst was possible for three cycles while maintaining good catalytic activity (99-85 %). The catalytic reaction yielded a biphasic system, and therefore the separation of the product from the reaction mixture was done with ease, showing the benefits of this system compared to traditional organic solvents.

Finally, $[Rh(dppp)_2]Cl$ impregnated on a silica support was used for heterogeneous decarbonylation of aldehydes in a continuous flow setup. The catalyst showed yields up to 95 % at elevated temperature and both aromatic and aliphatic aldehydes could be decarbonylated. This setup could be a novel way to run industrial decarbonylation.



The use of biomass in the industry, a representative illustration showing the promise of the valorization of biomass.

CONTACT

Supervisor:
Anders Riisager
ar@kemi.dtu.dk

Funded by:
The project was funded by The Danish Council for Independent Research, Sapere Aude.

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Catalytic Tools for Carbon-Carbon Bond Applications

A classic reaction for creating carbon-carbon bonds was revisited in order to minimize its demand for magnesium through modern, catalytic pathways.

Stig Holden Christensen, PhD

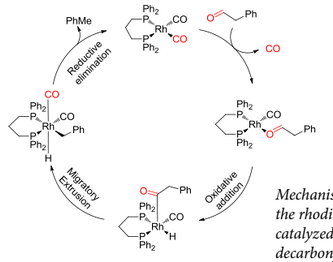
"Organometallic Methods for Forming and Cleaving Carbon-Carbon Bonds"

Carbon-carbon bonds are fundamental in organic chemistry. Forming and cleaving of carbon-carbon bonds is involved in numerous reactions. The Grignard addition reaction, discovered by Victor Grignard in 1900, is a commonly employed method for creating carbon-carbon bonds. In this reaction however, a stoichiometric amount of magnesium is required. This is not unfeasible in itself, since magnesium is an abundant element, and not too costly. Still, it would be desirable if modern, catalytic pathways could minimize this relatively large demand for magnesium. In the project, the Grignard reaction was revisited for this purpose. The results are hoped to also be relevant for other types of catalyzed reactions. In some of these, stoichiometric amounts of catalyst would be unacceptable due to the high cost of the catalyst material.

The Grignard reaction is an example of organometallic chemistry, which is an overlapping field of inorganic and organic chemistry, since it involves bonds between a metal and carbon. The reaction uses organometallic substances known as Grignard reagents. A Grignard reagent is a magnesium halide bound to a carbon compound. It has to be prepared prior to the addition step. The addition must be performed under strictly anhydrous conditions in ethereal solvents (usually diethyl ether or tetrahydrofuran). Grignard reagents react with a great variety of carbonyl compounds, including aldehydes, ketones, formaldehyde, esters, and amides.

Revisiting the Grignard reaction, this benzyl addition reaction was found to be a reversible transformation. The retro benzyl addition was shown by the addition of benzylmagnesium chloride to di-t-butyl ketone followed by exchange of both the benzyl and the ketone moiety with another substrate.

Ring-opening of cyclic ethers with concomitant C-C bond formation was studied with a number of Grignard agents. The transformation was performed in a sealed vial by heating to about 160 °C in an aluminum block or at 180 °C in a microwave oven. Good yields of the product alcohols were obtained with allyl- and benzylmagnesium halides when the ether was tetrahydrofuran or 3,3-dimethyloxetane.



Mechanism for the rhodium catalyzed decarbonylation.

Carbohydrates with protecting groups on all alcohol groups except the primary alcohol were prepared and subjected to the iridium catalyzed dehydrogenative decarbonylation reaction where primary alcohols are converted into the corresponding one carbon shorter products.

The syngas evolved from the iridium catalyzed dehydrogenative decarbonylation reaction was consumed in a palladium catalyzed reductive carbonylation reaction in a two-chamber system setup. Of the simple primary alcohols investigated, 2-(2-naphthyl)ethanol, hexane-1,6-diol and dodecane-1,12-diol were found to be the most promising syngas sources. A substrate scope for the reductive carbonylation of aryl bromides is currently under development with hexane-1,6-diol as syngas source.

The synthesis of the anticancer antibiotic tetrahydroisoquinoline alkaloid jorumycin progressed via a route consisting of a crucial aryne annulation step where an isoquinoline scaffold was prepared. A more promising, alternative route was also identified.

CONTACT

Supervisor:
Robert Madsen
rm@kemi.dtu.dk

Funded by:
The project was funded by The Torkil Holm Foundation and DTU.

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Bacterial Enzymes as Bleach Alternatives

A number of novel laccase-like multi-copper oxidases (LMCOs) from bacterial origin were identified, expressed and biochemically characterized.

Søren Brander, PhD

"Characterization of Novel Thermostable Bacterial Laccase-like Multi-copper Oxidases"

Laccase-like Multi-copper Oxidases (LMCOs) catalyze reduction of molecular oxygen into water. LMCOs may be used in paper pulp bleaching and laundry detergents and dishwashing powders, in lignin degradation for production of biofuel, and as green catalysts in industrial synthesis. The thesis focuses on bacterial LMCOs due to their desirable high stability. Also, bacterial enzymes are attractive due to the relative easy cloning of bacteria to form recombinant protein expression systems.

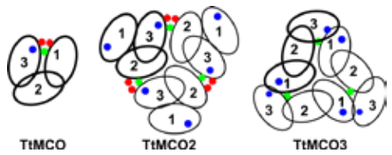
LMCOs encompass four connected copper atoms that function as a small battery, and only when the enzyme is fully charged – with four electrons – does reaction with oxygen proceed. In popular terms this makes LMCOs clean machines that drive a chemical reaction powered only by oxygen and with only water as a byproduct. This feature is highly relevant to industrial applications where oxygen is cheap and clean reactions a bonus.

In the project, a number of novel LMCOs from bacterial origin were identified and expressed and biochemically characterized.

One of these was the laccase from *Bacillus clausii* KSM-16, an organism known to produce a potent alkalophilic and thermostable protease. The protein was found highly salt-, alkali- and thermostable with substrate specificity similar to that of the well-characterized Bacillus subtilis CotA. The preferred pH for stability and catalytic activity was shifted about 1 unit to the more alkaline compared to Bacillus subtilis CotA. This suggests that pH adaptation of LMCOs can be deduced from the habitat of the natural host. Also, the amino acids causing increase alkali- and salt tolerance in this protein may be useful in design of new tolerant laccases.

Thermobaculum terrenum is a thermophilic bacterium cultured from a hot dirt patch in the Yellowstone National Park. Its genome codes for a LMCO, which was expressed and characterized. It was shown to be the second most thermostable LMCO characterized. A specific role for this LMCO in maturation of antibiotics is proposed. This is the first characterization of a protein from T. terrenum and the first laccase from the evolutionary distinct plylum chloroflexi. The laccase is very different from anything else characterized and this - together with its very high stability - makes it very promising as a template in future protein engineering.

Measurement of activity of LMCOs is often hampered by heat-induced increase in enzyme activity. It was observed that this activation is followed by a change of the Electron Paramagnetic Spectroscopy (EPR) signals. This feature was used to characterize the mechanism behind the process, which was found to be controlled by temperature and NaCl, while the similar transformation in B. *subtilis* CotA also needed a reducing agent, ascorbate, in order to take place. The discovered mechanism can most likely be expanded to also encompass other LMCOs that have previously been shown to undergo heat-activation.



Outline of the 3 domain MCOs from T. terrenum. Uniparc codes for the protein sequences are written in paranthesis. TtMCO (D1CEU4) is a three domain LMCO. TtMCO2 (D1CHB6) is a two domain typeB MCO with an extraneous cupredoxin domain fused to the n-terminal. C) TtMCO3 (D1CH29) is a nitrite reductase with an extraneous cupredoxin domain fused to the c-terminal.

CONTACT

Supervisor:
Kasper Planeta Kepp
kpj@kemi.dtu.dk
Jørn Dalgaard Mikkelsen

Funded by:
The project was funded by the Danish Council for Independent Research (FTP).

Scan the QR-code and get the thesis as a pdf.

Structural Studies of Small Molecules using NMR Spectroscopy

NMR spectroscopy is an important analytical technique that, among other things, is used for exploring the three-dimensional world of molecules.

Louise Kjærulff, PhD

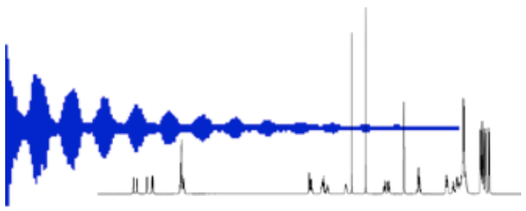
"NMR Structural Studies of Oligosaccharides and other Natural Products"

Many natural products, whether proteins, carbohydrates, or secondary metabolites, require specific configurations to be recognized in the body. If a protein, peptide or oligosaccharide is folded incorrectly, the biological function disappears. Similarly, a small change in the stereochemistry of a bioactive molecule can lead to a change in the biological activity from therapeutic to toxic. It is thus very important to know the absolute structure of new molecules, either created as drug candidates or for other scientific purposes. Absolute structure means knowing the configuration of all stereo-centers in the molecule. Nuclear Magnetic Resonance (NMR) is a well-established method to aid in such studies. The thesis work is centered around the use of NMR spectroscopy in three main projects ranging from the design of new NMR experiments, over discovery of bacterial and fungal natural products, to NMR structural studies of human milk oligosaccharides.

The NMR structural studies of human milk oligosaccharides (HMO) was key in a larger project with the goal of producing HMOs by synthetic and enzymatic approaches. Oligosaccharides in human milk play a role in the development and protection of newborns and are commercially interesting as potential additives in infant formula. They have rather well-defined structures consisting of a backbone with disaccharides lactose, *N*-acetyllactosamine and/or lacto-*N*-biose whereupon the monosaccharides fucose and/or sialic acid are attached. NMR spectroscopy was used, among other techniques to identify the chemically and enzymatically produced HMO molecules, and to screen a range of enzymes for their trans-fycosylation abilities.

In a separate part of the project, a range of new natural products were discovered, isolated and described. These included the solonamides and the ngercheumicins; two families of cyclic depsipeptides isolated from a marine bacterium with the ability to prevent virulence in the pathogenic *S. aureus*. *A. fijiensis*, a relatively unknown fungal species, was also investigated to explore its chemistry in the search for new biological active compounds. This resulted in the discovery of one novel metabolite.

Finding the three-dimensional structure of molecules involves obtaining knowledge of several structural parameters, such as angular and distance information between the nuclei in the molecule. In the project, a new NMR experiment was developed for measurement of *J* coupling constants that so far have been difficult to obtain. The new NMR experiment was applied to several known smaller molecules and has yielded new structural information that allows for the computation of more reliable three-dimensional structures. The experiment has also been tested on new molecules and given excellent results both in studies of oligosaccharides and other natural products. With both the experiment and the subsequent processing running smoothly, the hope is that a range of NMR users, both experienced and less experienced, will make use of this experiment for easier structural analysis of complex molecules.



CONTACT

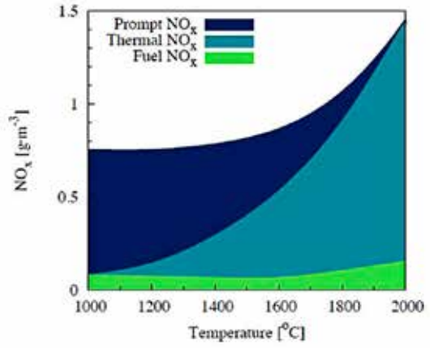
Supervisor:
Charlotte H. Gotfredsen
chg@kemi.dtu.dk

Funded by:
The project was funded by the Danish Council for Strategic Research (DSF).

Removal of NOx after Biomass Combustion

Practically all combustion processes have nitrogen oxides, NOx, as by-products. These are unwanted as they are known causes of a number of health effects.

While in coal- and gas-fired power plants, technology for NOx removal is mature, this is not the case for biomass fired power plants. This use of biomass has increased strongly over the latest decade and is expected to increase even further in the near future. The thesis investigates several selective catalytic reduction (SCR) solutions of relevance to NOx reduction after biomass combustion. These solutions are also relevant in relation to flue gases from waste incineration.



Leonhard Schill, PhD

"Alternative Catalysts and Technologies for NOx Removal from Biomass- and Waste-fired Plants"

At coal- and gas-fired power plants NOx is usually removed by SCR using a vanadia-tungstatinania (VWT) catalyst and ammonia (NH_3) as reductant. However, flue gas from both biomass fired power generation and from waste incineration contains large amounts of potassium, which deactivates the VWT catalyst rapidly. This is known as alkali poisoning.

Commonly, the catalyst is placed at the so-called tail-end position, just before the stack. The advantage here is that the flue gas is very clean, so the catalyst has a long life-time. However, tail-end placement usually requires costly reheating of the flue gas. Thus, there is a need for a different type of catalyst, which is either able to sustain the potassium levels, or can function at the lower tail-end temperatures without need for flue gas heating.

For the first approach, a catalytic process with hydrocarbons as reductants was developed, but proved unable to sustain potassium better than the traditional VWT catalyst based process.

For the second approach, a number of catalysts were tested, and especially one of these proved able to function at significantly lower temperatures than the best commercial VWT catalysts. As a patent application has been filed on this catalyst, only limited information can be disclosed.

The catalyst under patenting is a binary, supported transition metal catalyst. At 10 % water concentration the catalyst performs at the same level at 150 °C as does the commercial VWT at 220 °C. However, data from biomass combustion practice show that water content may actually come as high as 20 % at which strong inhibition occurs at 150 °C, which indicates that it will be needed to operate the catalyst at 180° C. If used at low temperature and high water concentrations, the catalyst needs to be made more hydrophobic by e.g. coating with polymers. Also, the catalyst can probably only be used in SO_2 free applications.

Furthermore, the catalyst might have potential for removal of volatile organic compounds (VOC) due to its high chemi-sorbed surface oxygen.

CONTACT

Supervisors:
Rasmus Fehrmann
rf@kemi.dtu.dk

Anker Degn Jensen
aj@kt.dtu.dk

Funded by:
Energinet.dk through the PSO (Public Service Obligation) framework

Scan the QR-code and get the thesis as a pdf.

Master Theses 2014

Veronica Oliver Alvarez de Lara
Spectroscopic and dynamic analysis of plasmas generated by LIBS of Aluminum alloys

Serena Monaco
Elucidation of transglycosylation by NMR spectroscopy

Marie Hvidberg Velk
In-situ EPR spectroscopy of SCR catalysts

Niclas Hoeck
Characterization and Stabilization of Human Tryptophan Hydroxylase 2 by Rational Protein Engineering

Kasper Damgaard Tidemand
Characterization and Stabilization of Human Tryptophan Hydroxylase 2 by Rational Protein Engineering

Dimitrios Tsolakis
Oil Characterization by Combining Physical Distillation and Simulated Distillation

Karolina Kleani
Oil Characterization by Combining Physical Distillation and Simulated Distillation

Christian Kjeldsen
Towards the total synthesis of (+)-Sieboldine A

Ronja Maja Malinowski
An enantioselective approach to (+) Sieboldine A

András Purak
Molecular characterization of BAMLET and BAGLET anti-cancer lipoproteins

Jesper Brandt Rasmussen
Quality Assurance and Determination of Ionized Calcium in Blood

Anna Marie Thiel Pedersen
Characterisation of membrane-diffusion properties by analysis of ionic species and molecular species

David Hamrah
Calculation of Minimum Miscibility Pressure Using Fast Slimtube Simulation

Mette Hvas Falkesgaard
Crystal form transofrmations in insulin; monitored by in situ protein X-ray powder diffraction

Rikke Bloch
Determination of hormone disruptives in solutions for forward osmosis

Johan Jeziorski Jensen
Structural studies of fluorinated surfactants in technical blends and food packaging material

Bahar Secilmis
Formulation of amorphous system for poorly soluble drugs using polymer matrices

Tina Sørensen
Synthetic Studies of alpha-1,4 Linked Galacturonic Acid Related to Sugar Beet Pectin

Sanne Mygind
Design, Synthesis and Biological Evaluation of New Antibiotics against Staphylococcus aureus

Sarah Elizabeth Jones
Crystallization of full-length tryptophan hydroxylase isoform 1

Maria Northved Elf-Lind
Molecular modeling of human serum albumin - liraglutide system based on molecular dynamics simulations and small-angle X-ray scattering data

Theis Kirkhoff Guldbech
Crystallinity and fiber properties of cellulose in biocomposites

Kira Løw Larsen
Substrates for Assay of Phospholipase C

Jorge Peiro
The Influence of Fluorine in Medicinal Chemistry

Martin Ellegaard Pedersen
Characterization of metalloenzymes

Simon Suhr Borkenfelt
Evaluation of wetability as a predictive parameter for pharmaceutical performance of compounds

Rasmus Bødker Lassen
A flow cell attached to an X-ray powder diffractometer allow for following in situ crystallization. The method must be optimzied so it can be used for both proteins and smaller organic molecules.

Peter Langelund Thomassen
Absorption and oxidation of NOx in ionic liquids

Amir Saad Boulos Morcous
Study of PVT Properties of Hydrocarbon Mixtures at High Pressures

Camilla Anna Søholt
Metalloprotein Chemistry

Abdulmecit Araz
Experimental Study of Combined Low Salinity and Surfactant Flooding Effect on Oil Recovery

If you want more information on a specific project, please contact Teaching Administrator Signe Møller Jørgensen, smjo@kemi.dtu.dk

Acknowledgement

DTU Chemistry highly appreciates the active involvement of our Advisory Board:

Kim Andersen
Lundbeck A/S

Thomas Högberg
Leo Pharma A/S

Tue Johannessen
Amminex A/S

Ole Kirk
Novozymes A/S

Jesper Nerlov
Haldor Topsoe A/S

DTU Chemistry has a wide cooperation with industry.

Among the Department's industry partners are:

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Amminex
Arla
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Bayer
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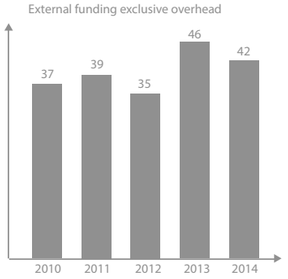
SprinkIr
Vattenfall
Veloxis
Wacker Chemie
Welltec

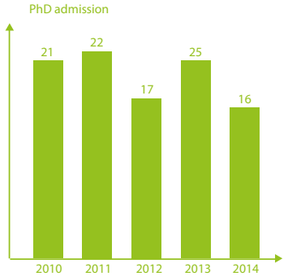
A leading Research Department

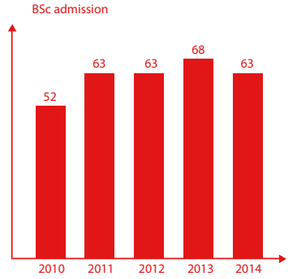
DTU Chemistry focuses on scientific excellence through people, projects, and results in order to keep strengthening our position as a leading research department. During 2014, the Department has continued to attract the necessary resources, ensure recruitment of the best candidates, and strengthen the external cooperation.

DTU Chemistry is still successful in attracting scientific talent. We had a very high number of applicants for the BSc in Chemistry and Technology exceeding the number of applicants, we can actually accommodate.

The funding and PhD admission reflects the reduction in Faculty staff in 2012 and 2014. However, once again the Department had a high success rate in applications for external funding in 2014 and many of our PhD projects are financed from sources outside DTU as public funds, private companies, and private foundations take growing interest in our Department.





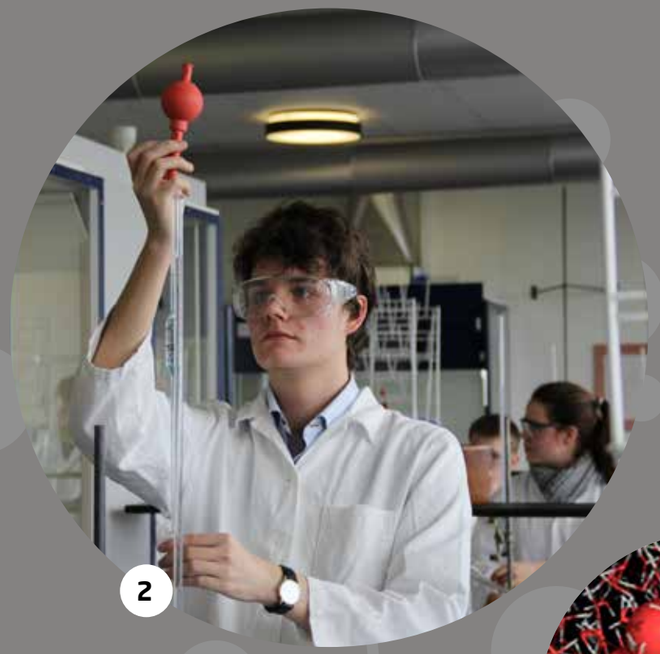


Publications 2014

DTU Chemistry has a high performance in the world of chemical science. This is reflected in all the publications produced every year. In this Annual Report you can find six features based on scientific results published in high impact journals during 2014. The Department has a strong track record in scientific publications with an increase of 20 % in ISI publications in 2014. For a complete list of DTU Chemistry's publications in 2014, please scan the code or see: kemi.dtu.dk/Omos/Publikationer

Highlights 2014


1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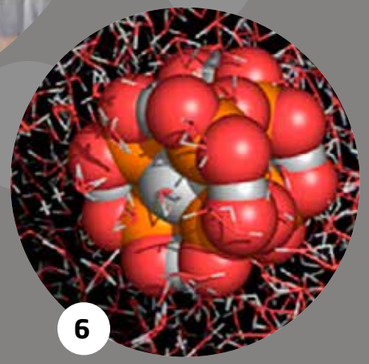
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7

DTU Chemistry wishes to show you more of the Department's many excellent results and achievements. We have selected some diverse highlights from 2014. You can read more about these highlights and many more at our website kemi.dtu.dk/english/Nyheder. You can also follow our activities at facebook/DTUKemi.

1. New laboratories are rising and the new DTU Chemistry building will be equipped with ultramodern laboratories for research and teaching in chemistry. It will be ready for use in the fall 2015 and will take us a giant step up when it comes to state-of-the art equipment and standards for work environment conditions. The new building will link the two existing buildings making the Department more coherent physically, logistically and intellectually.

2. Three Olympic medals was the outcome for the Danish participants at the Chemistry Olympics 2014 held in Hanoi, Vietnam: one of silver, two of bronze. As always, DTU Chemistry hosted one of the Danish qualifying rounds for the international event, welcoming 15 talented high school students. The 2015 Chemistry Olympics are to be held in Baku, Azerbaijan.

3. Open Doors at DTU has become a tremendous success for DTU Chemistry as chemistry has become very attractive in the eyes of future generations of chemical engineers. Chemistry and Technology at DTU has become a known brand associated with high quality education and very good job opportunities. This awareness in the market attracts the talented young people we need. Once again the Bachelor of Science in Chemistry saw many more applicants that we could accommodate, and we were fortunate to be able to pick the best from a pool of talented young people.

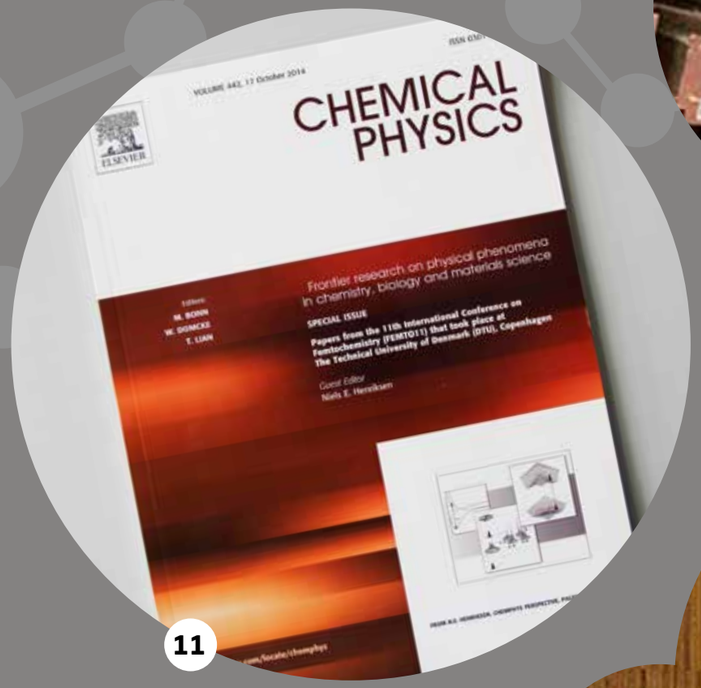
4. Centre for Oil and Gas - DTU is a new research centre to generate new solutions and train tomorrow's oil experts. The new centre will develop technology and knowledge with a view to boosting extraction of North Sea oil. At the same time, the new facility will pave the way for the next generation of petroleum engineers. Head of Department at DTU Chemistry, Professor Erling H. Stenby, is also the centers' Scientific Director of Enhanced Oil & Gas Recovery.

5. Web-based training for high schools is possible with "Around the World with Chemistry", a new educational tool kit developed by DTU Chemistry. The kit targets both high school teachers and their students with a mix of inspirational videos and additional training manuals and articles that can be freely downloaded at kemi.dtu.dk/Gymnasietilbud/Verdenrundtmedkemi

6. Molecuar Movies can pave the way for better use of solar energy. Associate Professor Klaus B. Møller, DTU Chemistry and Professor Martin Meedom, DTU Physics, have received a grant of DKK 6.5 million from the Danish Council of Independent Research | Natural Sciences (FNU). The 4-year project aims at refining the descriptions of the processes that occur when a material is hit by light and thus changes its state of energy.

7. Center for Hyperpolarization – through our extensive research in Nuclear Magnetic Resonance (NMR), DTU Chemistry will play a key role in a new "Center for Hyperpolarization in Magnetic Resonance" to be set up at DTU. The Danish National Research Foundation has granted DKK 55 million for the new center under its so called Center of Excellence program. For further information contact Professor Jens Duus, jduus@kemi.dtu.dk or Associate Professor Susanne Mossin, slmo@kemi.dtu.dk

Highlights 2014



8. The Children's University was established at DTU for the second time in 2014. A team from DTU Chemistry, headed by PhD student Jonas Andersen, contributed with a "Crystal lab". The event attracted no less than 520 kids, of which 40 made their own crystals and studied them in microscopes, just as they could model salt, sugar and other crystals.

9. DTU's Young Researcher Award was received by Jerrik Mielby, DTU Chemistry, for his PhD thesis on *Selective Oxidations using Nanostructured Heterogeneous Catalysts*. His merits also include being co-author of two articles in the prestigious Angewandte Chemie. He is currently Postdoc at DTU Chemistry.

10. Catalysis for green energy applications is the subject of a new project headed by Associate Professor Jingdong Zhang, DTU Chemistry. The project focusses on graphene biocatalysts for enzymatic biofuel cells and has been granted DKK 6.5 million by the YDUN-program (Younger women Devoted to a University carreer) of the Danish Council for Independent Research.

11. Femtochemistry editor – following the organizing of the 11th International Conference on Femtochemistry – FEMTO 11 – held at DTU, Associate Professor Niels E. Henriksen from DTU Chemistry was Guest Editor of the special issue of Chemical Physics with papers from the conference.

12. Enzyme research using graphics cards is the unusual approach in a joint DTU – University of Copenhagen project with possible cancer treatment applications. The researchers let a computer with four graphics cards generate ideas on how key enzymes are constructed. The project is supported by the Lundbeck Foundation. Associate Professor Peter Fristrup coordinates the DTU Chemistry participation.

13. Spectroscopy for better beer is the number one product from a new start-up company spun out from DTU Chemistry. During his PhD project at the Department, Andreas Kunov-Kruse developed an original addition to infrared spectroscopy. His invention has spurred the company Specshell. Commercial considerations have led the young company to target the brewery market first.

The DTU Chemistry Support Unit

The aim of the DTU Chemistry support units is to keep adding value to the supply chain by offering the right support and complementary skills to the Department's researchers in educational and scientific matters.

The central administrative and technical staff functions at the Department:

1. Machine Center
2. IT Support
3. Communication & Graphic Design
4. Laboratory Technicians
5. Administrative Support, Project and Innovation Support
6. Reception and Service Center

MANAGEMENT

Head Of Department
Erling H. Stenby
ehst@kemi.dtu.dk

Deputy Head Of Department
Charlotte Mondrup
cmon@kemi.dtu.dk

INORGANIC CHEMISTRY

Section Coordinator
Rasmus Fehrmann, Professor
rf@kemi.dtu.dk

Faculty

Jens H. von Barner
Associate Professor
jvb@kemi.dtu.dk

Hans Erik Mølager Christensen
Associate Professor
hemc@kemi.dtu.dk

Søren Kegnæs
Associate Professor
skkl@kemi.dtu.dk

Susanne L. Mossin
Associate Professor
slmo@kemi.dtu.dk

Anders Riisager
Associate Professor
ar@kemi.dtu.dk

Jens Ulstrup
Professor
ju@kemi.dtu.dk

Jingdong Zhang
Associate Professor
jz@kemi.dtu.dk

Qijin Chi
Associate Professor
cq@kemi.dtu.dk

Scientific staff

Siva Sankar Reddy Putluru, Postdoc
Saravanamurugan Shunmugavel, Senior Researcher
Eduardo José Garcia Suárez, Postdoc
Ramendra Dey, Postdoc
Martin Nielsen, Senior Researcher
Christian Engelbrekt, Postdoc
Leonhard Schill, Research Assistant
Jerrik Jørgen Mielby, Postdoc

PhD Students

Emily Catherine Nordvang
Jonas Jensen
Khokarale Santosh Govind
Helene Kolding
Philip Malcho
Dario Paolicchi
Raju Poreddy
Mayra Melián Rodriguez
Jacob Oskar Abildstrøm
Agata Gallas Hulin
Anita Godiksen
Gunnar Olsen
Arnab Halder
Minwei Zhang
Peter Langelund Thomassen
Nedjeljko Seselj
Amalie Elise Modvig
Nan Zhu

ORGANIC CHEMISTRY

Section Coordinator
David Tanner, Professor
dt@kemi.dtu.dk

Faculty

Mads Hartvig Clausen
Professor
mhc@kemi.dtu.dk

Peter Fristrup
Associate Professor
pf@kemi.dtu.dk

Charlotte Held Gotfredsen
Associate Professor
chg@kemi.dtu.dk

Robert Madsen
Professor
rm@kemi.dtu.dk

Jens Øllgaard Duus
Professor
jduus@kemi.dtu.dk

Thomas Eiland Nielsen
Professor
(Today at Novo Nordisk)

Christian Adam Olsen,
Professor
(Today at University of Copenhagen)

Scientific staff

Erhad Ascic, Postdoc
Peter Hammershøj, Postdoc
Andreas Stahl Madsen, Postdoc
Rico Petersen, Postdoc
Sebastian Thordal le Quement, Postdoc
Katrine Qvortrup, Senior Researcher
Peng Wu, Postdoc
Esben P. K. Olsen, Research Assistant
Johannes Rytter Dethlefsen, Postdoc
Vitaly Komnatnyy, Postdoc
Amanda Birgitte Sølvhøj, Postdoc
Niels Johan Christensen, Postdoc
Michael Åxman Petersen, Postdoc
Ayele Teshome Gorfo, Postdoc
Sebastian Meier, Senior Researcher
Asger Bjørn Petersen, Researcher

PhD Students

Stig Holden Christensen
Jens Engel-Andreasen
Claus Gunnar Bang
Beatrice Bonora
Mathilde Daugaard
Clotilde d'Errico
Thomas Flagstad
Casper Lykke Hansen
Mette Ishøy
Betül Kitir
Louise Kjærulff
Gyrithe Lanz
Jonas Striegler Laursen
Daniel Lupp
Alex Maolanon
Remi Jacob Thomsen Mikkelsen
Faranak Nami
Ragnhild Gaard Ohm
Lasse Bohn Olsen
Martin Jæger Pedersen
Mette Terp Petersen
Helle Marie Stephansen
Dominika Alina Niedbal
Christine Kinnaert
Henrik Schaarup-Jensen
Casper Hoeck
Carola Santilli
Kim Mortensen
Søren Tolborg
Andrea Mazziotta
Andreas Ahlburg
Lasse Bo Nielsen
Enzo Mancuso
Giuseppe Antonacci
Maximilian Felix
Jorge Peiro
Christian Kjeldsen
Ana Rita Freitas Colaco
Gauthier Scavée
Jesper Villadsen
Mathias Andersen
Camilla Arboe Jennum
Ignacio Segundo

PHYSICAL CHEMISTRY

Section Coordinator
Kenny Ståhl, Associate Professor
Kenny@kemi.dtu.dk

Faculty

Jens Enevold Thaulov Andersen
Associate Professor
jeta@kemi.dtu.dk

Rolf W. Berg,
Associate Professor
rwb@kemi.dtu.dk

Pernille Harris,
Associate Professor
ph@kemi.dtu.dk

Niels Engholm Henriksen,
Associate Professor
neh@kemi.dtu.dk

Kasper Planeta Kepp,
Associate Professor
kpj@kemi.dtu.dk

René Wugt Larsen,
Associate Professor
rewl@kemi.dtu.dk

Klaus Braagaard Møller
Associate Professor
Klaus.moller@kemi.dtu.dk

Günther H. Peters
Associate Professor
ghp@kemi.dtu.dk

Irene Shim
Associate Professor
shim@kemi.dtu.dk

Esben Thormann
Associate Professor
esth@kemi.dtu.dk

Jonas Rosager Henriksen
Assistant Professor
(Associate Professor from 1 January 2015)
jhen@kemi.dtu.dk

Wei Yan
Senior Researcher
weya@kemi.dtu.dk

Scientific staff

Christian Grundahl Frankær, Postdoc
Manish Tiwari, Postdoc
Roberto Ortiz, Postdoc
Sindrila Dutta Banik, Postdoc
Teresa Regueira Muniz, Postdoc
Sumera Tubasum, Research Assistant
Geoffrey Marchal, Postdoc

PhD Students

Jonas Andersen
Søren Brander
Asmus Ougaard Dohn
Jesper Jonasson Madsen
Pernille Sønderby
Denise Andersen
Farhad Vanzandeh
Arun Kumar Somavarapu
Diego Rolando Lemus
Kasper Damgaard Tidemand
Duncan Paterson
Saeed Zajforoushan Moghaddam
Christos Tsanas
Gokce Engudar
Gianluca Levi

TECHNICAL AND ADMINISTRATIVE STAFF

IT Manager
Bo Sørensen
bso@kemi.dtu.dk

Dan Seegert Hansen, System Administrator
Kenneth Pihl Aamand, IT Supporter
Jonas Jan Mansoor, IT Supporter

Laboratory Manager
Bodil Fliis Holten
bh@kemi.dtu.dk

Lise Lotte Berring, Managing Laboratory Technician
Brian Brylle Dideriksen, Laboratory Technician
Brian Ekman-Gregersen, Laboratory Technician
Tina Gustafsson, Laboratory Technician
Anne Hector, Laboratory Technician
Steen Bæk, Chemical Process Technician
Betina Margrethe F. Roesdahl, Chemical Process Technician
Lise-Lotte Jespersen, Managing Laboratory Technician
Martin Hasling Pedersen, Laboratory Technician
David Frej Nielsen, Laboratory Technician
Tove Rønne, Service Assistant
Susanne Thyssing Nielsen, Laboratory Washer

Chief Operating Officer
John Madsen
jm@kemi.dtu.dk

Head of Service Section
Christian Kirk Christiansen
ckchr@kemi.dtu.dk

Lars Egede Bruhn, Service Assistant
Stephan Jean Galsøe, Service Assistant
Thomas Bachau Pedersen, Service Assistant

Head of Machine Section
Jimmie Thomsen
jth@kemi.dtu.dk

Ishaq Khaliqdad, Industrial Technician
Paul Erik Wibe, Assistant Engineer

Administration
Maria Blanner Bang, AC-TAP / Chemist
Maria Bundgaard, Executive Secretary
Mette Hansen, Special Adviser, PhD Administrator
Susanne Helmark, Graphic Designer
Lillian Karen Holm, Receptionist
Bente Hviid, Administrative Assistant
Signe Møller Jørgensen, Teaching Administrator
Charlotte Malassé, Special Adviser, Communication
Jette Berg Nestén, Receptionist
Majken Kramer Overgaard, Special Adviser
Patricia Wagner, Project Administrator
Anne Frejberg, Web and Graphic Designer
Birthe Jessen, Special Adviser, Project Coordinator
Mette Lange, Special Adviser, Project Coordinator
Lotte Skafte Jespersen, Office Administrator

Trainees
Johnny Malmberg, IT-supporter
Troels Varming-Petersen, Industrial Technician
Ragnar Lava Olsen, Industrial Technician
Mads Norre, IT-supporter
Stefan Hjarsø, IT-supporter
Rasmus Storgaard, Laboratory Technician
Philip Charlie Johansen, Laboratory Technician

Other Staff
Michael Bæk, Student Assistant
Martin Lieb, Service Assistant
Astrid Schøneberg, Consultant

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