Technical University of Denmark

Annual Report 2010

DTU, Department of Chemistry

Contents

A new synthesis path for a well established institute

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Maintaining our position as a leading chemistry department while engaging even further in cooperation with industry and other stakeholders will be our prime focus.

Having just come onboard as Head of Department at DTU Chemistry, I am very impressed with our core line of work at the institute. Educating chemical engineers with a deep understanding of chemistry at a very advanced level can only be achieved if the research is at the highest international level. This is the situation at DTU Chemistry.

Our prime focus, the next couple of years will be maintaining our position as a leading education and research entity, while engaging stronger in cooperation with industry and other stakeholders.

The Faculty members of the department create the core of the scientific work. Their ideas form the basis for the further development of the department, and they attract the funding that is needed to test these ideas. In 2010 the funding by new grants has been overwhelming, which means that several of the activities you read about in this report will expand over the coming years.

In order to support the positive development, initiatives will be launched with the goal of achieving excellent scientific results, offer outstanding education, and interact with the surrounding society. Our goal is to become even more visible in the landscape of Chemistry.

New initiatives implemented in 2010

We have applied a new structure based on three sections; Inorganic Chemistry, Organic Chemistry and Physical Chemistry. The key idea is to make our organization more transparent and more approachable to students, industry and other stakeholders. This report will briefly introduce the three sections and show examples of their current focuses.

In November 2010 the first PhD Symposium was held. The symposium includes a full day program where all PhD students from the department present their work. The event serves at least three purposes: networking among the PhD students, strengthening the collaboration between Faculty members, and presenting our research to external collaborators and sponsors. The day was well attended and very positively evaluated by the participants. We look forward to hosting the event again in 2011 – November 11th - and for many years to come.

Finally, we will aim to use other channels for outreach, including both mass media and designated media. These efforts will be supported by a new position as Deputy Head of Department. I am happy to introduce Charlotte Mondrup who has taken on the position, coming from a corporate background.

A new building underway

I am happy to note that the top management and Board of Directors of DTU have approved a new DTU Chemistry building to be erected at DTU's Campus. This will bring our laboratory facilities to the cutting edge of advanced education and research, and will also enhance our possibilities to engage in new collaborative projects, involving state of the art research equipment. We are indeed looking forward to the opening of the new building planned for the summer of 2013.

New position as deputy head

As of December 1st 2010 a new position as Deputy Head of Department at DTU Chemistry was created. The position will support the Head of Department in general. B. Sc. Charlotte Mondrup has taken on the position coming from a corporate career including CEO positions. Her primary focus has been management, including process optimization, organization and performance.

Charlotte Mondrup
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Phd students met our stakeholders

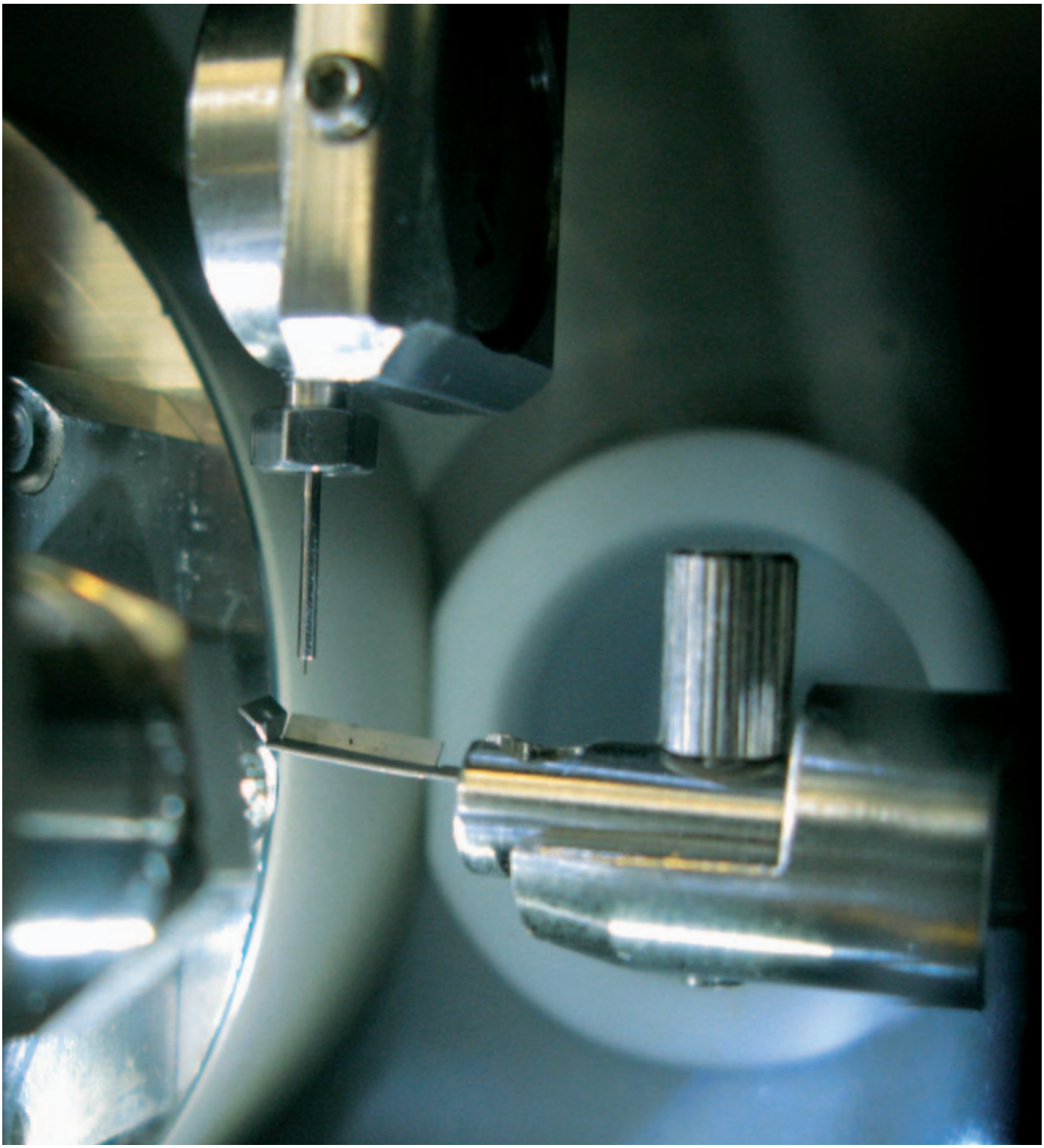
For two days, 4th and 5th of November 2010, all PhD students at DTU Chemistry were invited to the institute's first PhD Symposium, held at Schæffergården conference centre.

The first day was open to the institute's external stakeholders, mainly within industry. Here, all PhD students gave an introduction to their current work. The day was well attended with participation from Haldor Topsøe A/S, Novozymes, LEO Pharma, Chr. Hansen A/S, Danish Power Systems, Amminex.

The second day was designated subjects of special interest to the PhD students – one theme was dealing with stressful work situations.

THE INORGANIC CHEMISTRY SECTION OF DTU CHEMISTRY

The Inorganic Chemistry section of DTU Chemistry consists of the Centre for Catalysis and Sustainable Chemistry (CSC) and the research groups on Energy and Material Science, Metalloprotein Chemistry and Nano-Chemistry. The different research groups interact strongly, thus securing an efficient use of the section's advanced research equipment. Faculty from all research groups contribute to education under the section. The section contributes to the cooperation of DTU Chemistry with industry (see list of companies at page 34). The section is coordinated by Professor Rasmus Fehrmann. A full staff list is found at page 46.



The research at DTU within energy, material science, metalloprotein chemistry and nano-chemistry has been joined in the Inorganic Chemistry section.

Polymer Based Fuel Cells go High Temperature

Every dwelling can have its own micro heat and power plant fuelled by natural gas or biogas. This is one of the perspectives in a new type of Polymer Electrolyte Membrane (PEM) fuel cells able to tolerate up till 200 degrees C.

A combination of high energy efficiency and low pollution has caused many to see fuel cells as one of the energy technologies of the future. A joint research and development program by three Danish companies and DTU Chemistry has brought that future closer.

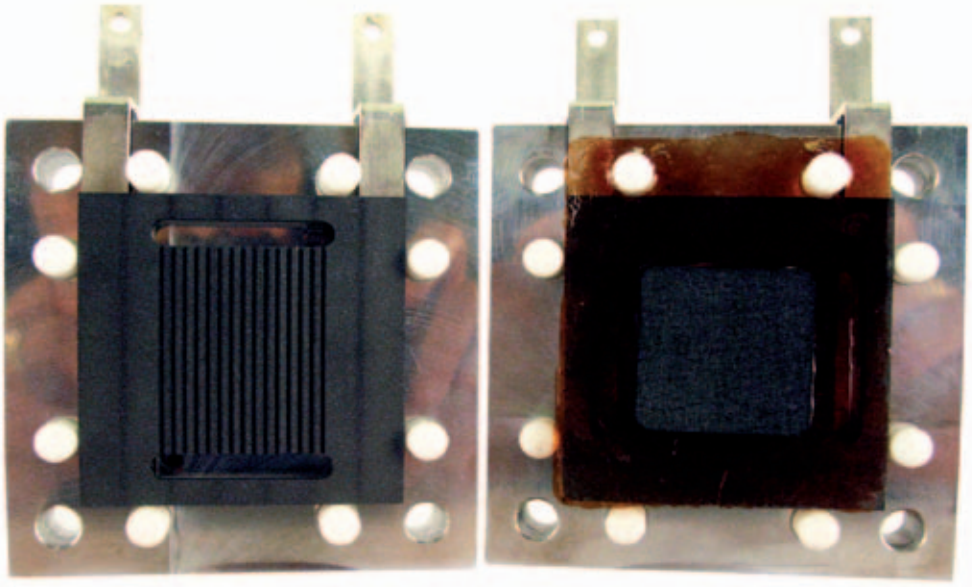
Polymer Electrolyte Membrane (PEM) fuel cells have already been commercially available for a number of years but have issues around their durability which make them feasible only for some niche applications. The new HT-PEM (High Temperature PEM) cells are able to operate at temperatures ranging from 150 till 200 degrees C, which makes them interesting for applications relevant on a much broader scale. Ultimately, it will be possible to have individual dwelling houses equipped with its own micro heat and power plant fuelled by natural gas or biogas.

"The first commercial products should be ready in about six month's time. We have already received the first expressions of interest from our customers," says Steen Yde Andersen, CTO of IRD A/S. The Danish company, headquartered in Svendborg, is a leading supplier of fuel cells.

Till date the largest market for fuel cells has been Uninterupted Power Supply (UPS), meaning stand-alone units capable of maintaining power supply in case of a general black-out or local breakdown in normal power supply. I.e. many hospitals and banks have UPS generators. Traditionally these have been fuelled by diesel, but a PEM fuel cell using pure hydrogen is able to react faster and without noise, smell or undesired emissions. Pure hydrogen is an expensive fuel, but as an UPS unit is only expected to work for a short period of time until normal power supply is restored fuel price is not critical.

Phosphoric acid replaces water

A fuel cell produces electricity from a chemical reaction involving both oxygen – normally taken from air – and either pure hydrogen or a fuel containing hydrogen like natural gas or bio-



At low temperatures undesired substances are formed, primarily carbon monoxide which tends to gradually hamper the efficiency of the membranes. At higher temperatures the problem is significantly smaller.

Polymer Fuel Cells

gas. Fuel cells have no sulphur or particle emissions and they have a higher energy efficiency compared with traditional sources of energy meaning a lower contribution to climate change.

The carrier substance of a PEM cell is water. This limits its working temperature to below 100 degrees C, as otherwise all water would vaporize. In fact, the temperature needs to be well below that in order to limit the need for adding water to the system. However, at low temperatures some undesired substances are formed, primarily carbon monoxide which tends to gradually hamper the efficiency of the membranes. Again, this is not a major problem for an UPS unit which is only supposed to work for some hours maximum. But for a vehicle's engine or a micro heat and power unit in a dwelling house this is unacceptable.

Therefore a new type of polymer cells capable of working at temperatures up till 200 degrees C is good news. The HT-PEM cells are developed in cooperation between Danish Power Systems and Professor Niels J. Bjerrum's group at DTU Chemistry, and they are stacked and integrated into commercial units by IRD and by Serenergy (headquarter in Holstebro).

In experiments at DTU Chemistry the new HT-PEM (High Temperature Polymer Electrolyte Membrane) fuel cells have shown good performance at temperatures well above 100 degrees C.

> "The first commercial products should be ready in about six month's time. We have already received the first expressions of interest from our customers.
> Steen Yde Andersen, Chief Technical Officer, IRD A/S

Firstly, instead of water the new fuel cells have phosphoric acid (H_3PO_4) as carrier medium. Phosphoric acid is stable at temperatures well above 200 degrees C. Secondly the cells are manufactured in a different polymer, polybenzimidazol (PBI). As opposed to many other polymers, PBI sustains temperatures up till 200 degrees C without deformation or loss of internal strength. The resulting phosphoric acid doped PBI membrane achieves a high level of conductivity.

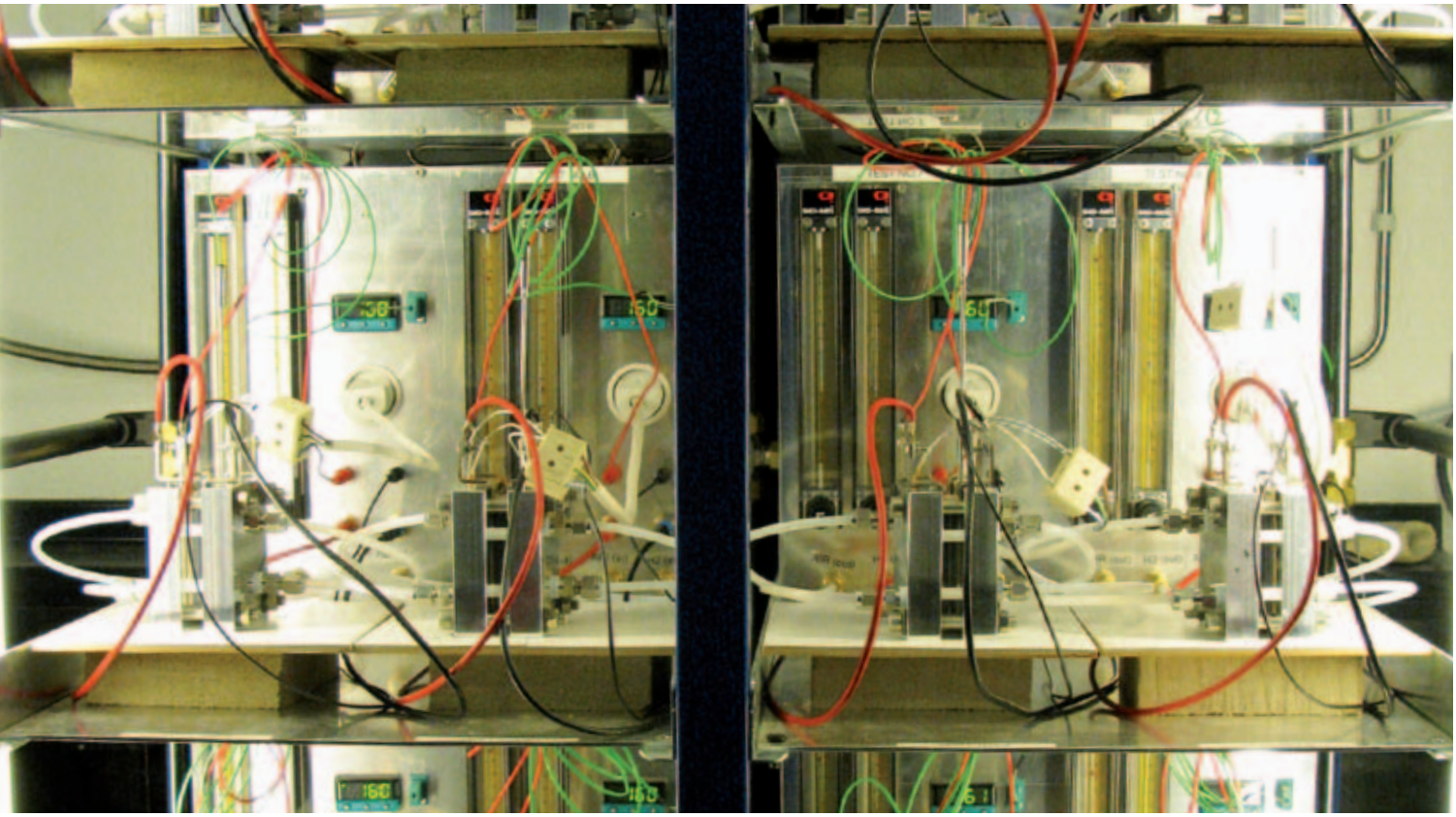
Can be fuelled by natural gas

Steen Yde Andersen stresses that IRD does not intend to produce HT-PEM cells exclusively:

"We don't see just one type of fuel cells becoming the winner. We believe that different cells are likely to be best suited for different purposes. Still, this new cell type really has outstanding qualities. First of all it can be fuelled by natural gas instead of pure hydrogen. Natural gas is much cheaper and many districts already have a distribution system for natural gas in place."

Before natural gas can be used in a fuel cell it needs to be reformed into a hydrogen and carbon dioxide mixture. This mixture will contain impurities, primarily carbon monoxide. As carbon monoxide tends to "poison" today's PEM cells the gas needs to be thoroughly rinsed first. This process requires energy which in turn leads to a lower energy efficiency of the whole fuel cell system. But the HT-PEM, working at much higher temperature, is significantly more tolerant of carbon monoxide and other impurities. A simple rinsing, hardly consuming any energy, will do.

"As the HT-PEM concept is quite new, all we have by now is prototypes. Still, commercial products are not far away. While the new membranes are quite different from traditional PEM membranes, our part of the job is pretty much the same. We stack the cells in



a graphite composite structure with flow channels. This structure is almost the same for PEM and for HT-PEM. In fact, the design is even a bit simpler for HT-PEM," Steen Yde Andersen explains.

Ideal for fork trucks

The first customers are likely to be producers of UPS and similar stand-alone units.

"Looking a bit further down the road another major group of applications will be for units providing single dwelling houses with their own heat and power. For instance this would be very relevant indeed here in Denmark where large districts have natural gas supply," the CTO continues.

"In principle cars would be another really relevant area, but realistically it won't be us that going to be a supplier. The automotive industry is dominated by large producers who prefer to keep their key technologies in-house. Still, we could come in for special vehicles like fork trucks – where also work environment considerations would favour fuel cells."

While the HT-PEM cells are significantly more durable compared with PEM it will still take further improvements, especially for some applications.

"Presently the HT-PEM cells have been proven able to last for 5,000 hours of production. For a micro heat and power unit in a dwelling residence it may be necessary to achieve duration of something like 40,000 hours," Steen Yde Andersen estimates.

The research resulting in the new fuel cell type was initiated at DTU Chemistry more than a decade ago. The process has not been without difficulties, admits Professor Niels J. Bjerrum:

"At one point our polymer was suddenly cut off. Our PBI supplier decided to venture into producing fuel cells themselves – which made us a competitor. Fortunately we happened to have a fair stock of PBI, so we knew we could keep going for a while."

Delicate stoichiometry

Ironically, the stop in supplies actually turned out to be an advantage. The group was forced into developing its own PBI synthesis. Through Danish Power Systems – a DTU Chemistry spin-out company – a license required for the use of PBI for fuel cell purposes was bought.

Presently the start-up company, renting its facilities at DTU, produces about one kilogramme of PBI weekly. This is sufficient to cover present demand.

Production is far from straight forward as PBI is produced from two raw materials as opposed to most commonly used polymers where you start out with just one raw material from which large molecules – polymers – are formed.

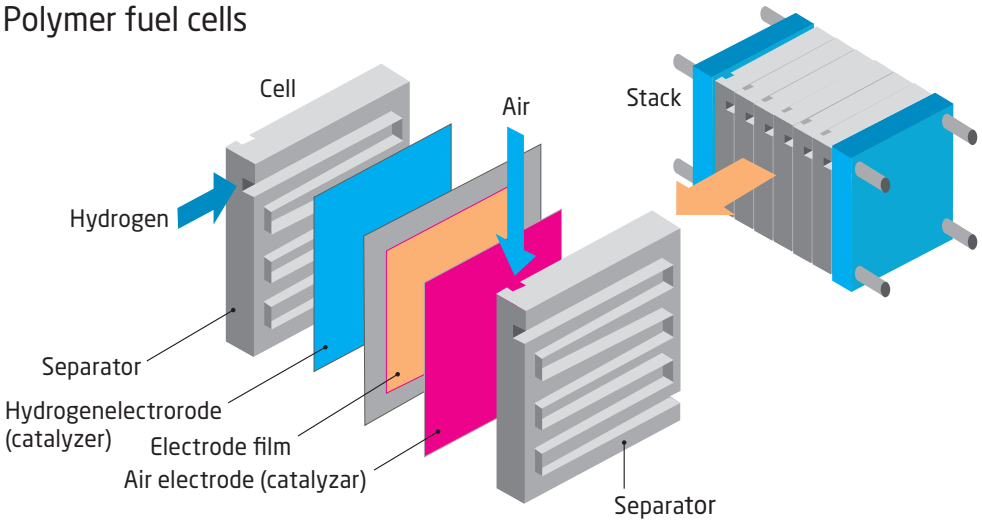
"You need to control your stoichiometry very delicately if you want to succeed," says Niels J. Bjerrum, while emphasizing that it is possible to up-scale production quickly once demand is there:

"Neither lack of PBI nor lack of phosphoric acid could become barriers for HT-PEM fuel cell expansion."

Nor will lack of production capacity in later stages, assures CTO Steen Yde Andersen of IRD:

"We have established a production facility in Albuquerque, New Mexico. Should fuel cells penetrate a large volume market like i.e. micro heat and power units for individual dwelling houses we'll be ready to expand production capacity quickly."

Polymer fuel cells



Fuel Cell Technologies

In a fuel cell a chemical reaction creates a voltage difference between two poles – much like in any ordinary battery. However, while the battery runs dry and is disposed of, the fuel cell keeps going – in principle indefinitely – as fresh fuel is supplied. The fuel will always contain hydrogen. Some fuel cells require pure hydrogen while others can cope with cheaper hydrogen containing fuels like natural gas or biogas. Another raw material needed is oxygen which in all present designs is just taken from surrounding air. Hydrogen and oxygen react, forming water which is disposed of – or steam which is just allowed to vaporize.

One characteristic is a minimal loss of energy as fuel is transformed into power. This corresponds to a high level of energy efficiency. Also fuel cells are free from sulphur and particle emissions.

The core of any fuel cell is a so called electrolyte which allows for electrically charged particles to pass. Different kinds of electrolytes are used. The name of a fuel cell type is defined by its sort of electrolyte.

Fuel cells are divided into two main categories which are so fundamentally different that they should actually be considered two completely separate technologies. Solid cells have oxide ions (O_2^-) as carriers of electric charge, while membrane (or "soft") cells have protons (H^+) as carriers. An example of solid cells is the SOFC (Solid Oxide Fuel Cell).

PEM (Polymer Electrolyte Membrane) and the new HT-PEM (High Temperature PEM) are examples of membrane cells.

A fuel cell produces electricity from a chemical reaction involving both oxygen – normally taken from air – and either pure hydrogen or a fuel containing hydrogen like natural gas or biogas. The core of any fuel cell is a so called electrolyte which allows for electrically charged particles to pass. Different kinds of electrolytes are used. The name of a fuel cell type is defined by its sort of electrolyte.

Cloning, Expression, Purification and Characterization of Tryptophan Hydroxylase Variants

PhD Defence

PhD Jane Boesen
Main supervisor: Associate Professor Hans Erik Mølager Christensen

The neurotransmitter and hormone serotonin (5-hydroxytryptamine) is involved in many physiological functions, such as appetite and sleep rhythm, as well as a wide range of psychiatric disorders such as depression and obsessive-compulsive disorder (OCD). The enzyme tryptophan hydroxylase (TPH) catalyzes the first and rate-limiting step in the biosynthesis of serotonin. Characterization of TPH and elucidation of the enzymes regulation and catalytic mechanism is therefore vital to our understanding of the serotonin balance.

The thesis concerns variant of both human TPH isoform 1 (*h*TPH1) and human TPH isoform 2 (*h*TPH2). The main goal was to purify full-length *h*TPH1. This was done using detergent. After incubation of the *h*TPH1 sample with 0.1 per cent of n-dodecyl-β-D-maltopyranoside (DDM) the protein binds to the anion exchange column and elute over a large area in the anion exchange, indicating that the protein still exists in different oligomer forms. Variant of both *h*TPH1 and *h*TPH2 containing the regulatory domain or parts of it were constructed and tested for expression in *E. coli* as well as solubility. It was observed that changes in the amino acid sequence of the

Understanding Catalytic Activity Trends for NO Decomposition and CO Oxidation using Density Functional Theory and Microkinetic Modeling

PhD Defence

PhD Hanne Falsig
Main supervisor: Professor Rasmus Fehrmann

Catalysis facilitates production of many chemicals and materials that we use every day. It provides a range of products from fuels and fertilizers to plastics and pharmaceuticals. Catalysts are also utilized for cleaning of exhaust from cars, power plants and industrial production.

The thesis focuses on catalytic limitation of NO_x formation from combustion of fossil and renewable fuels through heterogeneous catalysis, where the catalyst is in the solid state and the reactants and products in the gas phase.

A catalytic reaction takes place at the active site of the catalyst, which is therefore of special interest. Density functional theory (DFT) calculations have reached good accuracy and efficiency for obtaining adsorption and transition state energies for catalytic reactions in heterogeneous catalysis. In combination with microkinetic modelling it is possible to study trends in catalytic activity from one metal to the next; and from one local structure to the next. We can thus obtain an atomic level understanding of the optimal catalyst composition and structure.

In the thesis DFT calculations combined with microkinetic modelling is used to describe trends in catalytic activity of transition metals for the direct NO decomposition reaction and the CO oxidation reaction. Both adsorption energies and transition state energies are obtained. Linear scaling between adsorption energies of reaction intermediates and between transition state energies and adsorption energies makes it possible to describe catalytic activities with few descriptors; one for the NO decomposition and two for the CO oxidation.

For NO decomposition on stepped transition metal surfaces the following activity trend was obtained: Pd > Pt > Rh > Ru > Ag > Au.

For CO oxidation reaction on transition metal nanoparticles, kinks, steps and closed packed surfaces was investigated. The catalytic activity of gold was found to increase strongly, when the metal coordination number of Au decreases. This provides part of the explanation for the unusually high catalytic activity of Au.

It was concluded that the observed structural effect in CO oxidation on different catalyst structures is electronic in nature. It is therefore possible that pronounced nano-effects in catalysis is not restricted to Au. For reactions with less reactive molecules, it would be expected that the best nanoparticle catalyst would not be Au, but metals to the right in the Periodic table. This opens up for the possibility of enhancing the catalytic activity for all sorts of reactions by using nanoparticle catalysts.

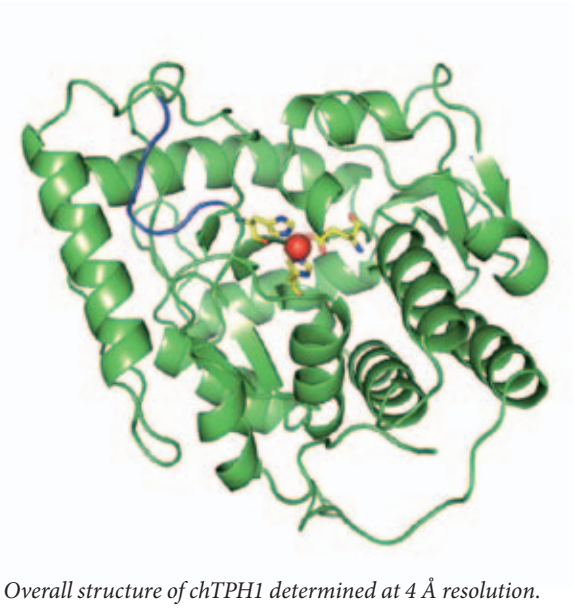
PhD Hanne Falsig

regulatory domain by point mutations or truncations in the N-terminal had a huge impact on the solubility of the protein and caused the protein to be insoluble.

The regulatory domain of the human TPH1 (r*h*TPH1) and two fusion proteins of r*h*TPH1 fused to the green fluorescent protein (GFP) in the C-terminal and the glutathione S-transferase (GST) in the N-terminal, respectively, were expressed in a soluble form. Purification trials of the variants containing the regulatory domain showed that a high salt concentration was necessary to stabilize the variant. The GST-*rh*TPH1 variant could be purified using affinity chromatography followed by gel filtration with high purity and a yield of 40 mg/l culture. The purified GST-*rh*TPH1 exists as a dimmer in solution due to dimerization of GST. The GST could be cleaved successfully from the fusion protein using Factor Xa and r*h*TPH1 was successfully purified from GST after cleavage.

Characterization was performed on the three *h*TPH variants: The catalytic domain of both *h*TPH1 (c*h*TPH1) and *h*TPH2 (c*h*TPH2) as well as the catalytic and tetramerization domain of *h*TPH2 (ct*h*TPH2).

Crystallization of c*h*TPH1 was achieved both without substrate and with bound substrate (tryptophan and pterin) but resulted in very small crystals. A data set of the variant without bound substrate was collected to 4 Å and the structure was solved by molecular replacement. The structure was refined to an R_{free} of 33.5 per cent and the overall structure is compared to the overall structure of the catalytic domain of *h*TPH2 co-crystallized with BH2. A structural change in the residues 125 to 130 is observed. This is the first structure of c*h*TPH1 without any substrates or inhibitors.



Overall structure of chTPH1 determined at 4 Å resolution. His272, His273 and Glu317 are shown with sticks and the iron as a brick red sphere. The amino acid from 125 to 130 is highlighted in blue and the electron density map for this region is shown in figure 10.4. The figure was made using pymol.

Alternative deNO$_x$ Catalysts and Technologies

Nitrogen oxides, NO_x, are unwanted by-products formed during combustion, i.e. in engines and power plants. If emitted to the atmosphere, they are involved in the formation of acid rain and photochemical smog. This thesis revolves around removal of NO_x.

A vanadia-titania-based catalyst is commercially available for selective catalytic reduction (SCR) of NO_x. It exhibits high activity and selectivity towards N_2. However, it is very sensitive to deactivation by alkali-species, which are typically present in high amounts in the flue gas when biomass is combusted. By co-firing with large amounts of CO_2-neutral straw or wood (to meet stringent CO_2 emission legislation), the lifetime of the traditional SCR catalyst is thus significantly reduced due to the presence of deactivating species originating from the fuel.

To develop at catalyst less susceptible to the poisons present in the flue gas, a number of catalysts have been synthesised and tested in the project, all based on commercially available supports. A highly acidic support consisting of sulphated zirconia was chosen. A number of different active species distributed on the support were investigated, such as iron, copper and vanadium oxides. However, based on the catalysts performance in the SCR reaction and their resistances towards potassium, the most promising candidate of the formulations studied was the vanadia-loaded catalyst, i.e. V_2O_5-SO_4^{2-}-ZrO_2.

The catalyst candidate was mixed with the naturally binding clay (sepiolite) to upscale it to the monolithic level, suitable for installation in gas stream with high flows, e.g. a flue gas duct of a power plant. A series of catalyst pellets with increasing levels of sepiolite were produced to evaluate the optimum mixing ratio. Based on these results, a monolith containing V_2O_5-SO_4^{2-}-ZrO_2 in 25 wt per cent sepiolite was produced, and evaluated with respect to the influence of space velocity, reaction temperature, and NH_3/NO feed ratio on the NO reduction efficiency.

An alternative strategy for NO_x removal, namely by NO absorption in ionic liquids, was also investigated. Based on a preliminary study, two imidazolium-based solvent candidates, [BMIM]OAc and [BMIM]OTf, were selected due to high sorption capacities. Both solvents revealed solubilities about twofold higher than those previously reported for e.g. CO_2-capture in ionic liquids. Especially [BMIM]OAc demonstrated extraordinary absorption capabilities, being able to retain around four NO molecules per molecule liquid fluid. [BMIM]OTf exhibited promising behaviour due to its reversible absorption/desorption properties. This in principle allows recycling of the ionic liquid as well as harvesting the NO. The accumulated NO could hereby be used in e.g. the synthesis of nitric acid allowing production of value-added chemicals from waste flue gas effluent. Although additional understanding of the mechanisms of the presented system is required, the perspective of a selective NO stripping technology is a very interesting alternative to catalytic removal of NO from industrial flue gas.

PhD Johannes Due-Hansen

PhD Johannes Due-Hansen
Main supervisor: Professor Rasmus Fehrmann

PhD Defence

A Breakthrough in Catalysis

Lactic acid can be produced directly from sugar by use of an inorganic catalyst. This finding opens a range of applications in green chemistry; i.e. production of bio-polymers with lower costs and less environmental impact compared with current methods.

In a joint effort, DTU Chemistry and researchers at Haldor Topsoe A/S have developed a zeolite catalyst for production of lactic acid methyl ester directly from various sugars. Lactic acid has several applications, one of them being as a raw material for production of bio-polymers. Many hope that bio-polymers may replace crude oil as the primary component in production of plastic

"As crude oil is becoming a scarce resource it is a sound approach to look for areas where it can be substituted by renewable resources. Also, when a product produced from lactic acid polymer is disposed of, it will decompose to lactic acid which is fully degradable and ecologically safe," says researcher Esben Taarning, Haldor Topsoe A/S.

"Finally, bio-polymers are more climate friendly as production releases less carbon dioxide compared with production of crude oil based polymers."

Raw materials for bio-polymers are currently produced by use of fermentation. Here a high volume of by-products cannot be avoided. The main by-product is calcium sulphate. The production of one tonne of lactic acid by fermentation will also produce one tonne of calcium sulphate.

The catalyzed process – a world first - does not involve the co-formation of large amounts of by-products.

"This fact, together with the environmentally benign profile, makes our process an attractive alternative to fermentation for production of raw materials for bio-polymers," says Esben Taarning.

Friendly to health, environment and climate

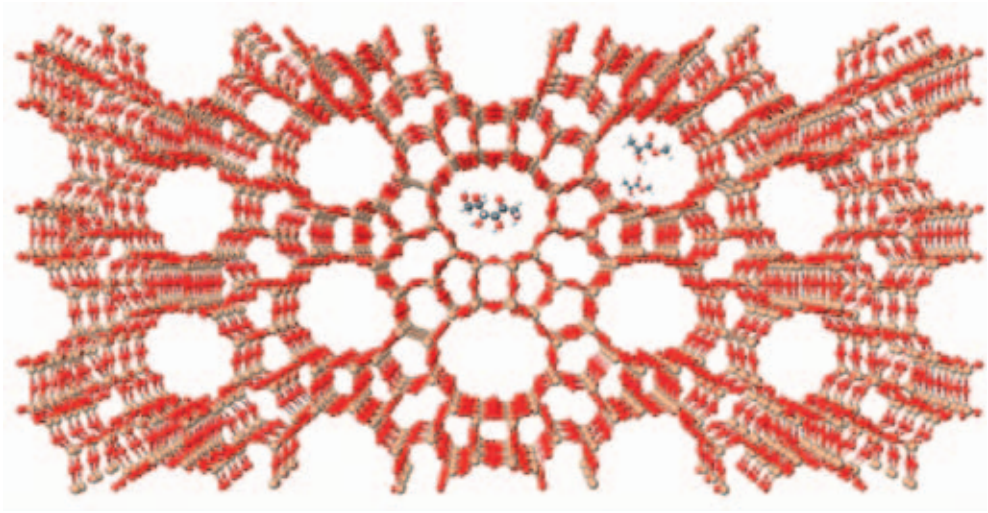
A commercial market for bio-polymers already exists. A number of companies and public organisations prefer bio-polymers over polymers produced from crude oil either due to environmental, health safety, climate or green image considerations.

"Despite various efforts to prevent it, we know that some proportion of products like bottles for soda water tend to end up in nature. Therefore it would of course be attractive if the bottles could just decompose to a harmless substance like lactic acid. The same would be true for a range of polymer products ranging from food packaging to clothes," Esben Taarning comments.

Another type of products, which today are based on crude oil are solvents – the so called Volatile Organic Compounds (VOC's). As these have been shown to cause various health problems mainly in the work environment, substitution by lactic acid based solvents would be highly attractive.

Current bio-polymers are produced from food resources like corn, but in the near future second generation raw materials like straw and other agricultural waste products are hoped to take over.

Green Chemistry



The zeolite catalyst is able to convert a range of sugars into lactic acid methyl ester. The pore size is extremely fine; the tiniest pores just allow individual sugar molecules to enter.

Photo: Bigstock

Lactic acid has several applications, one of them being as a raw material for production of bio-polymers. Many hope that bio-polymers may replace crude oil as the primary component in production of plastic.

Sustains heat and high pressure

The zeolite catalyst is able to convert a range of sugars into lactic acid methyl ester; i.e. sucrose, glucose or fructose. Atoms of titanium, tin and zirconium scattered over the catalyst surface speed up reactions. But not just the chemical composition is important; another key feature is the topology – the physical structure of the catalyst. The pore size is extremely fine; the tiniest pores just allow individual sugar molecules to enter.

Another advantage of the catalyzed process over fermentation is its ability to sustain high temperatures and pressure. This is believed to allow for a more stable production which in turn enables a higher cost-effectiveness.

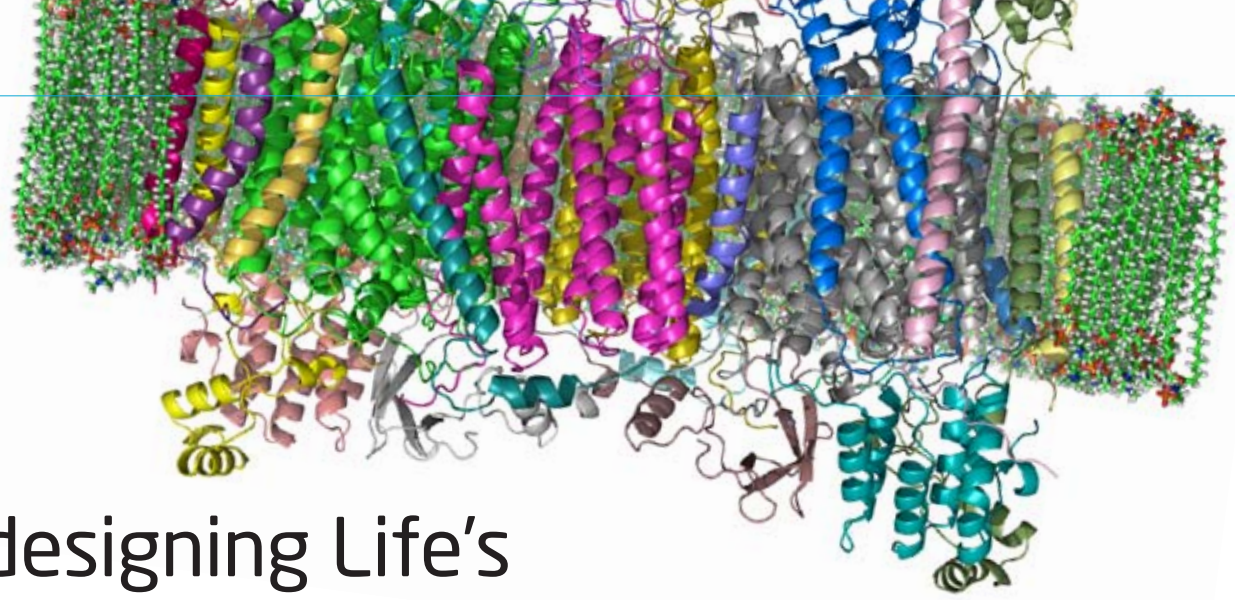
In the trials a process temperature of 160 degrees C was used. Sugar dissolved in methanol was used as the raw material.

> "The catalyzed process does not involve the co-formation of large amounts of by-products. This fact, together with the environmentally benign profile, makes our process an attractive alternative to fermentation for production of raw materials for bio-polymers.
> - Research chemist Esben Taarning, Haldor Topsoe A/S

Before the new catalyst can have its wider commercial breakthrough, the process' yield will have to be improved. As fermentation is a mature process, it has been optimized several times and has reached high yields – up till 90 percent. The catalyzed process is currently able to convert 70 per cent of the carbon hydrates used into lactic acid.

"This is quite a gap in yield. We will need to improve our catalyst further," Esben Taarning admits.

The team's results were published in Science, April 30th 2010: Holm, Martin Spangsberg; Shunmugavel, Saravanamurugan; Taarning, Esben "Conversion of Sugars to Lactic Acid Derivatives Using Heterogeneous Zeotype Catalysts"



Redesigning Life's Metallic Components

Industry researchers looking for novel enzymes and other proteins to ease our daily life in new ways are still able to find inspiration in i.e. fungus and microbes living in remote, exotic locations. But in not so many years this kind of discovery inspired by nature will be rare. Thus, in the future inspiration may need to be found in the laboratory instead. One path could be novel design of the so called metalloproteins.

During the last decades companies in the "white biotech industry" have joined forces with academic researchers in efforts to find fungus and microbes in ever more remote and exotic environments like volcanoes, geysers and deep jungles. The scope of this quest has been to broaden our "libraries" of micro-organisms and to extract enzymes and other naturally produced substances that are tailor made to tolerate certain conditions. For example an enzyme found in proximity to a geyser would be more likely to cope with the conditions in a hot steam industrial process than a random enzyme.

This development has brought a range of discoveries from washing powder able to do its job at low temperatures - saving energy and helping in climate conservation – to improvements in the quality of dairy products, bread and wine.

Metallo-proteins

The study of metalloproteins began some 25 to 30 years ago. It is still a relatively young discipline.

"The value of this kind of discovery is huge, but we are slowly running out of parts of nature where we haven't looked already. I would say that in 20 years time breakthroughs inspired by new findings in nature will be scarce. But by then alternative methods to find inspiration are likely to be at hand," says Associate Professor Hans E. M. Christensen, DTU Chemistry.

Catalysts of our body

The research group is focused at metalloproteins. Roughly one third of all proteins contain one or more metal atoms – they are metalloproteins – and they have been found to play a part in a number of key life processes. One example is hemoglobin – this protein is in charge of moving oxygen around in our body. It is exactly hemoglobin which gives blood its red colour. The hemoglobin molecule contains four iron (Fe) atoms. Other examples of metals frequently found in proteins are copper (Cu) and zinc (Zn). Intake of these and some other metals through food is crucial to our life functions.

A large group of metalloproteins are enzymes. Enzymes are the biological analogues of catalysts; they speed up chemical processes in the body. An example is the enzyme carbonic anhydrase which is able to speed up hydrolyses of carbon dioxide to hydrogen carbonate by a factor of 10,000,000. The metal in carbonic anhydrase is zinc (Zn). While carbon dioxide is able to penetrate the cell's membrane, hydrogen carbonate will need a carrier. By transforming carbon dioxide to hydrogen carbonate the

molecule is kept inside the cell instead of being released.

The close surrounding to a metal atom in a metalloprotein is known as the metal centre. As proteins are large molecules containing 100,000-1,000,000 or even more atoms the metal centre takes up just a tiny fraction of the protein but it is often here we find the key to the function of the particular protein.

Still a young discipline

"Industry has actually begun to take interest in modifying proteins as an alternative or parallel approach to discovering new proteins in nature. Our angle is that maybe you don't need to mutate the entire protein. Could it be that a change focused at just the metal centre would do the job?" asks Hans E. M. Christensen, while stressing that his group is not looking into drastic changes to the metal centre as a means of designing novel proteins:

"In nature you hardly ever find organisms with a drastically different metal centre as that would generally imply a malfunction of a magnitude that the organism would not survive. However, we do study the metal centre to learn about these key functions. Our idea is that either very subtle changes in the centre or changes in the surroundings of the metal centre could make the molecule better suitable for a given task."

The study of metalloproteins began some 25 to 30 years ago. It is still a relatively young discipline.

"We have much basic work to do before we get to the point where we may suggest new candidates for specific applications. Experiments and simulations need to go hand in hand. First we may design a new metalloprotein, then we need to synthesize it and validate if it has the properties we anticipated. Most likely we were not entirely accurate and will be required to adjust our models before we can progress further."

> "I would say that in 20 years time breakthroughs inspired by new findings in nature will be scarce. But by then alternative methods to find inspiration are likely to be at hand.
> - Hans E. M. Christensen, Associate Professor, DTU Chemistry

Grown in bacteria

Before one can even consider suggesting a modified version of a given metalloprotein, however, one needs to study the original substance. These kinds of studies require both a substantial amount of the metalloprotein – typically in the range of milligrams to grams – and a high purity.

The study of a given metalloprotein will always begin from the gene which encodes for production of this specific protein. The gene, normally a human gene, is inserted into the DNA of a microbe. Often *E.coli* is the organism of choice as it is thoroughly described and easy to manipulate. The organism will then be able to produce the protein in question. Proteins produced in this manner are called recombinant proteins. The organism may even be stimulated through various techniques to increase the yield.

Next step is to destroy the organism's cellular membrane releasing the protein to the surrounding solution. The protein of interest will then be identified and captured from the "soup" which will also contain a large number of other proteins produced by the organism. This separation is done by chromatography. Different methods exist, but basically chromatography always involves both a fluid and a solid phase. The various proteins in the mixture will differ from each other in various ways. Some types of chromatography use variations in the size of proteins to identify the ones of interest, while others exploit differences in electrical charge.

An open academic environment

In other words the study of metalloproteins involves a range of scientific disciplines – including biology, biotechnology, nanotechnology, protein chemistry, inorganic chemistry, structural chemistry and biophysics. Coming from different academic backgrounds the group's members need to have a high level of insight in the fields of their colleagues.

"When we attend scientific conferences hardly ever is one of us the very best in a given field. You'd always have somebody from another group with a high degree of expertise at just that. But still we take great pride in our ability to work in a range of fields. We have a strong sense of being able to reach outstanding results by combining a number of disciplines," says Hans E. M. Christensen, adding:

"On a personal note I would also say that this is something that goes well with Danish mentality. We enjoy cooperation and are not protective of our special interests. This is especially true with our young staff members."

The research within metalloproteins at DTU Chemistry is largely funded by a grant from The Danish Council of Independent Research / Technology and Production Sciences.

Expression and Purification of the Metal-Containing Monooxygenases Tryptophan Hydroxylase and Dopamine β-hydroxylase

PhD Pernille Efferbach Karlsen
Main supervisor:
Associate Professor
Hans Erik Mølager Christensen

PhD Defence

Abnormal levels of neurotransmitters are linked to a number of neurological diseases, including depression, anxiety disorders, obsessive-compulsive disorder (OSD), schizophrenia, Parkinson's disease and attention deficit-hyperactive disorder (ADHD). Since all these diseases are the cause of huge economical and personal costs it is very important to gain more knowledge of possible targets for medicine against them.

Two such possible targets are the enzymes tryptophan hydroxylase (TPH) and dopamine β-hydroxylase (DβH). Both are metal-containing monooxygenases that function in the brain where they are involved in the biosynthesis of neurotransmitters.

TPH catalyse the rate-limiting step in the biosynthesis of serotonin, namely the conversion of tryptophan to 5-OH-tryptophan, whereas DβH catalyse the conversion of dopamine into norepinephrine in the catecholamine neurotransmitter synthesis and thereby control the levels of both these neurotransmitters. With these functions both TPH and DβH are involved in a range of neurological disorders related to abnormal levels of the neurotransmitters serotonin, dopamine and norepinephrine.

TPH is a three-domain, iron-containing enzyme which belongs to the aromatic amino acid hydroxylase (AAAH) family. TPH is known as a very difficult protein to work with especially due to instability. In the project it was tried to express the isoform TPH2 in an eukaryote expression system, namely *Drosophila melanogaster* S2 cells. Stable transfected S2 cell lines with human TPH2 with and without the secretion signal BiP were constructed. No expression of TPH2 was detected from the S2/BiP-TPH2 cell line whereas TPH2 was found in the insoluble fraction when expressed from the S2/THP2 cell line.

DβH contains two copper ions in the active site and belongs to the family of ascorbate dependent type II Cu monooxygenases. Very little knowledge exists on DβH. In the project it was tried to use a D. melanogaster S2 system. Stable transfected cell lines for human DβH with and without the BiP secretion signal were constructed. From the S2/BiP- DβH cell line DβH was successfully expressed and secreted in spinner cultures. An improved purification procedure for glycosylated DβH was developed and up to 1.4 mg/l culture glycosylated tetramic DβH and 1.0 mg/l glycosylated dimeric DβH were obtained. Tetrameric DβH was deglycosolated and separated from the deglycosylation enzyme in another purification step. 0.2 mg/l culture deglycosylated DβH was obtained after this step and it was used for screening of crystallization conditions.

Synthesis, Purification and Characterization of Ferredoxins with Re-Designed Active Sites

PhD Jytte Kristensen
Main supervisor:
Associate Professor
Hans Erik Mølager Christensen

Roughly one third of all proteins contain one or more metal atoms – they are metalloproteins. These proteins have been found to play a part in a number of key life processes and they are also of major interest as catalysts i.e. in biochemical and pharmaceutical contexts.

The thesis studies two artificial metalloproteins, the design of which is based on iron-sulfur proteins. For both new metalloproteins *Pyrococcus furiosus* ferredoxin is the starting point. This metalloprotein can contain either a Fe_3S_4 cluster or a Fe_4S_4 cluster.

In the first new protein cobalt is inserted in the *P. furiosus* ferredoxin Fe_3S_4 iron-sulfur cluster, thereby creating a hetero-metallic cobalt-iron-sulfur cluster – $CoFe_3S_4$.

The second protein is designed by substituting the iron-sulfur cluster with a synthetic molybdenum-sulfur Mo_4S_4 cluster. Both new proteins are interesting for design of new catalytic systems.

The *P. furiosus* ferredoxin with the $CoFe_3S_4$ cluster was synthesized and purified in the oxidized $CoFe_3S_4^{2+}$ state. The chromatographic, mass spectrometric and EPR spectroscopic results indicated that the $CoFe_3S_4^{2+}$ ferredoxin was purified to high purity and that the protein was stable under these conditions. These results are in disagreement with previous reports of readily oxidative degradation of the $CoFe_3S_4^{2+}$ ferredoxin to Fe_3S_4+ ferredoxin. Experiments with chemical reduction and oxidation suggested a redox active protein and this was confirmed by cyclic voltammetry. One well-defined pair of redox peaks appeared and the pair was assigned to the $CoFe_3S_4^{2+/+}$ redox couple and had a formal potential of -177 mV versus SHE.

The molybdenum-sulfur analogue was synthesized by addition of pre-prepared $(Mo_4S_4(H_2O)_{12})Cl_5$ to the apo-ferredoxin which was stabilized

Insulin Adsorption and Surface Behaviour on Monocrystalline Au(111), Au(100) and Au(110) Surfaces studied with STM, AFM and Electrochemistry

PhD
Anna Christina Welinder
Main supervisor: Professor Jens Ulstrup

PhD Defence

Insulin is a protein, which is important in a number of biological processes and also of pharmaceutical importance. The thesis presents a comprehensive study of the adsorption and surface dynamics of insulin on three monocrystalline gold surfaces, Au(111), Au(100) and Au(110). These differ only in the crystallographic ordering of the surface atoms, yet promote intriguing differences in the behaviour of biomolecules from diverse categories, emphasising the subtle nature of biomolecular surface confinement.

Native insulin exists in two primary forms, monomer/dimers in metal-free solutions and hexamers coordinated with Zn(II) ions. Adsorption patterns and surface behaviour of both forms were investigated with *in situ* STM and AFM as the primary methods for visualisation, and cyclic and square wave voltammetry for characterisation of the insulin adsorption modes. AFM image analysis was supplemented with image simulations based on the 3D protein structure.

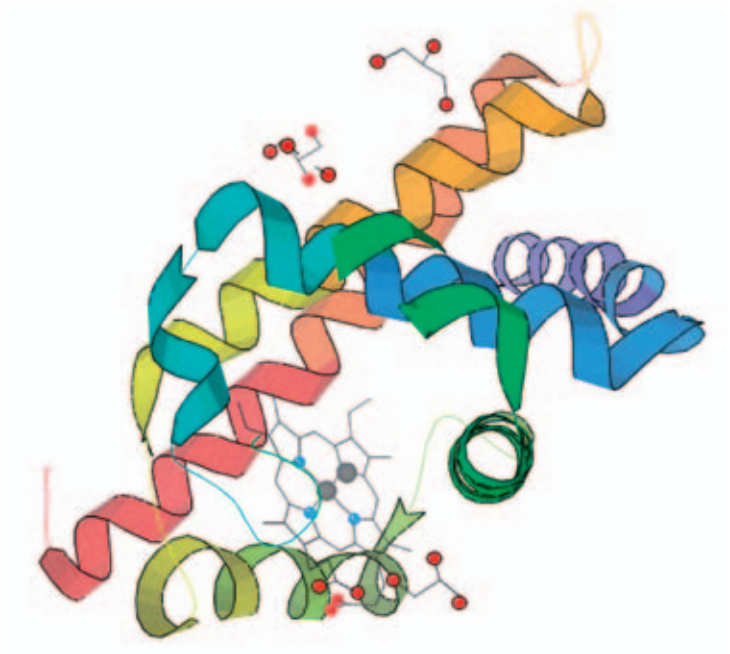
In situ STM images of monomeric/dimeric insulin show a striking contrast between the adsorption patterns on Au(111) dominated by individual molecular-scale structures vs. individual but clustered, semi-dense adsorption layers on Au(100). Domains of ordered structures within high-density insulin adlayers on Au(100) indicate extensive unfolding of the protein peptide in accordance with the premise for adsorption of disulfide-rich molecules on gold surfaces. Reductive desorption monitored by square wave voltammetry reveals notably different insulin binding modes and adsorption strength on the three different Au(111), Au(100) and Au(110) surfaces. *In situ* AFM of hexameric Zn(II) insulin on Au(111) reveals an unusual, dendrite-like adsorption pattern believed to consist of both intact hexamers and monomer/dimers originating from disassembled hexamers.

Electrochemical characterisation of metal-substituted insulin hexamer forms was a second objective of the thesis. Co(II) insulin is a commonly used spectroscopic probe for the Zn(II) site in proteins but despite a theoretical premise for redox activity of Co(II) insulin, only capacitive voltammetric signals were observed. However, square wave voltammetry of blue Cu(II) insulin under ambient conditions showed a reversible redox signal at 0.04 V vs. SCE. This signal is ascribed to direct electron transfer between the electrode and the copper centres in the insulin hexamer. Blue Cu(II) insulin mimics the unique spectroscopic features of other blue copper proteins, and the value of the redox potential for blue Cu(II) insulin is the same range as has been reported for azurin and other blue copper proteins.

Neither insulin imaging to single-molecule resolution by STM nor successful characterisation of the electrochemical properties of blue Cu(II) insulin under in vitro conditions have been reported before. These achievements offer new opportunities for the understanding of insulin surface structure and dynamics and for modelling the blue copper protein centres.

PhD Defence

by sulfonation. Purification revealed two closely related species. EPR monitored redox titration results confirmed incorporation of the intact Mo4S4 cluster and suggested stabilization of the cluster in three oxidation states; the 4+, 5+ and 6+ states. The formal potentials of the transitions between the three oxidation states were determined to -195 mV and -295 mV versus SHE for the first species and -205 mV and -380 mV for the second species. The obtained spectra after oxidative titration suggested oxidative breakdown of the Mo_4S_4 cluster.



Roughly one third of all proteins contain one or more metal atoms – they are metalloproteins – and they have been found to play a part in a number of key life processes

THE ORGANIC CHEMISTRY SECTION OF DTU CHEMISTRY

The Organic Chemistry section at DTU Chemistry focuses on catalysis and chemistry at the interface to biology. Research will typically have a dual approach of looking both at fundamental science, while also contemplating biological and pharmaceutical applications including bioscreening, drug discovery and drug delivery systems. Faculty from all research groups contribute to education under the section. The section contributes to the cooperation of DTU Chemistry with industry (see list of companies at page 34). The section is coordinated by Professor Robert Madsen. A full staff list is found at page 47.

Photo: Mikkel Adsbøl

Applying organic chemistry as a tool to learn more about fundamental biology is a key focus of the Organic Chemistry section at DTU Chemistry.

Looking at the Holy Grail of Life

While organic chemistry in itself is of course no novelty at DTU Chemistry, using it to unravel biological mechanisms relevant to a number of health issues is. The field is labelled "Chemical Biology".

Chemical Biology is a field that has been strategically lifted at DTU Chemistry over the last years. It should not be confused with organic chemistry, explains Associate Professor Mads Hartvig Clausen:

"We have had organic chemistry here "always". The novelty is that we are using it as a tool to learn more about fundamental biology. Ultimately we hope to use this knowledge for suggesting new drug candidates."

This development is largely triggered by technology, according to Associate Professor Thomas Eiland Nielsen:

"Screening libraries of thousands of chemically related organic compounds to single out a few that have the best properties for a given purpose was earlier a task which only large pharmaceutical corporations could afford to undertake. Over recent years the technology needed has come down to a price level affordable to public researchers."

"While the pharmaceutical industry would typically use this kind of screening in drug discovery we are rather looking at fundamental biological questions. If you will, we are looking at the holy grail of life."

> "If we can find a way to make a biological system tilt, we may learn a lot from the way it responds to the disturbance.
> - Associate Professor Thomas Eiland Nielsen, DTU Chemistry

Make a system tilt

In this quest one does not always desire a compound which can fix a given disorder.

"One of the ways to learn about how fundamental mechanisms work is to disturb them. If we can find a way to make a biological system tilt, which can be achieved with small molecules, we may learn a lot from the way it responds to the disturbance," Thomas Eiland Nielsen notes.

Another trend in chemical biology is drug discovery inspired by nature.

"Say that a compound found in nature in very small quantities i.e. in a rare organism seems to be a promising drug candidate. We would then let ourselves inspire by that compound but try to design a similar compound which can be synthesized on a large scale," explains Associate Professor Christian Adam Olsen.

"The advantage would be dual. Firstly, by producing the compound synthetically we can get the quantities needed. Secondly, we may be able to design a compound which is better suited for a drug than the natural compound which inspired us. You could also choose to call this approach biological chemistry or pharmaceutical chemistry. The bottom line is that our projects are more closely related to biology than what has been the tradition within organic chemistry."

Breakthroughs at border lines

Chemical biology does by no means replace traditional organic chemistry, Thomas Eiland Nielsen stresses:

"There will always be a need for fundamental research on the classical lines of starting out with a chemical hypothesis; i.e. "Can I produce substance B from substance A?" or "Will a given catalyst improve a given process?". However, we should also recognize that typically the major breakthroughs tend to occur in fields bordering other research areas. In chemical biology we have many linkages to completely different fields like physics, topology design and genetics just to mention some."

Mads Hartvig Clausen, Thomas Eiland Nielsen and Christian Adam Olsen all head research groups within different aspects of Chemical Biology at DTU Chemistry.

Novel Anti-Cancer Drug Candidates Inspired by Mould

Synthetic analogues of griseofulvin, a compound naturally produced by the fungus Penicillium, appear to be anti-cancer drug candidates that do not affect normal human cells. Hopes of anti-cancer treatment with significantly less side effects compared to present chemotherapy are high.

Chemical Biology

Cancer chemotherapy is typically a harsh experience, since the drugs involved are not able to selectively kill cancer cells but will also, to a varying degree, kill normal cells. A joint effort by researchers at DTU, the German Cancer Research Center (DKFZ) and the University of Heidelberg has produced drug candidates that promise effective anti-cancer treatment without affecting normal cells. So far, no other side effects have been seen in preliminary trials.

The drug candidates are analogues of griseofulvin and they are synthesized at DTU Chemistry.

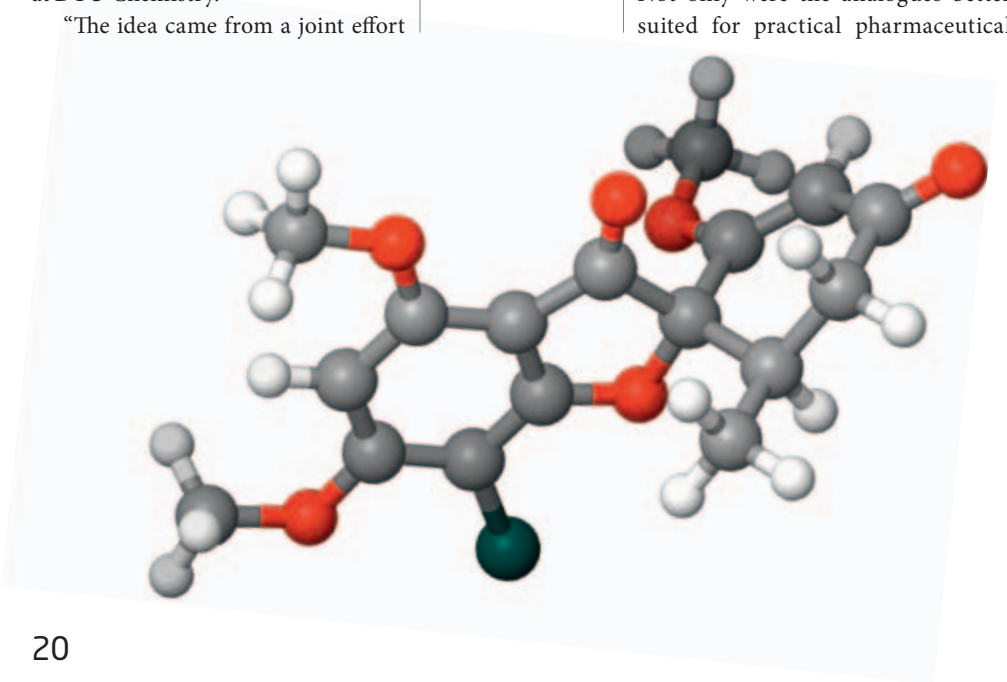
"The idea came from a joint effort by Dr. Alwin Krämer of DKFZ and Associate Professor Thomas Ostenfeld Larsen of DTU Systems Biology. They had identified grisefulvin as a potentially effective drug in cancer treatment. We then became involved due to our experience with synthetic and medicinal chemistry and our group has since synthesized about 130 grisefulvin analogues," explains Associate Professor Mads Hartvig Clausen, DTU Chemistry.

Interferes with key cell mechanism

Not only were the analogues better suited for practical pharmaceutical use compared to the type of grisefulvin naturally produced by the fungus Penicillium; some of them also proved significantly more anti-cancer efficient. For the best analogues efficiency was improved by a factor 50.

The natural product griseofulvin was first isolated by Oxford et al. in 1939 and later shown to possess antifungal properties. This antifungal agent is still in clinical use today and was, until very recently, the only orally administered drug approved by the FDA for treatment of tinea capitis (ringworm of the scalp). In the last few years, griseofulvin has received renewed attention due to reports of antiproliferative effects in cancer cells as well as suppression of hepatitis C replication.

The selectivity in cancer treatment of both griseofulvin itself and the synthesized analogues are linked to a key



Model of griseofulvin - a compound naturally produced by the fungus Penicillium. Carbon atoms are represented by the grey balls, hydrogen atoms by the white, oxygen by the red, and finally chlorine atoms by the green. Chemically induced changes in the ring at the right hand side may result in highly active analogues. Illustration: Mads Hartvig Clausen.

Photo: Bigstoch

mechanism involved in multiplication of cancer cells. In contrast to normal cells, most tumor cells contain multiple centrosomes, associated with formation of multipolar mitotic spindles and chromosome segregation defects. Many tumor cells regain mitotic stability after clonal selection by the coalescence of multiple centrosomes into two functional spindle poles.

"To overcome the limitations of current cancer treatments, we have developed a cell-based screening strategy to identify small molecules that inhibit centrosomal clustering and thus force tumor cells to undergo multipolar mitoses, and, subsequently, apoptosis," says Mads Hartvig Clausen.

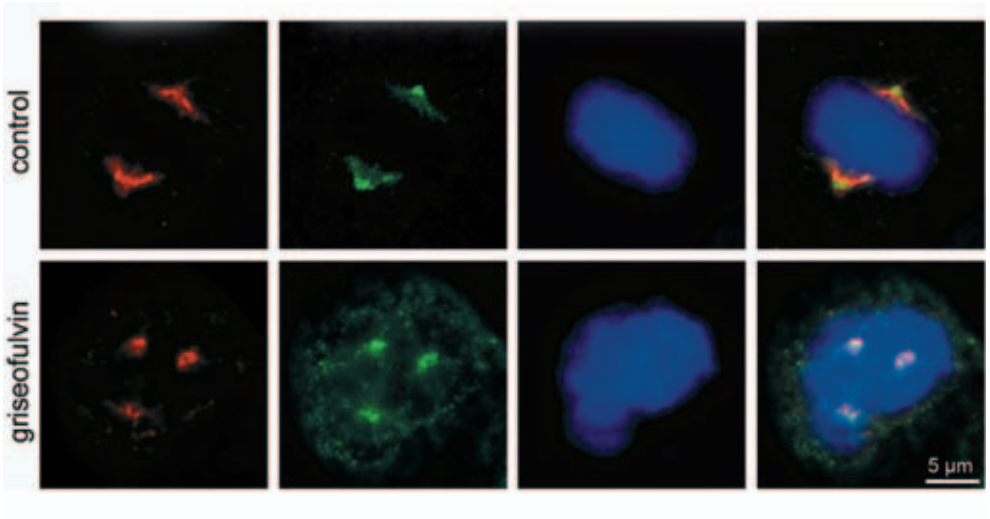
> "We have developed a cell-based screening strategy to identify small molecules that inhibit centrosomal clustering and thus force tumor cells to undergo multipolar mitoses, and, subsequently, apoptosis.
> - Mads Hartvig Clausen, Associate Professor, DTU Chemistry

Close to clinical trials

Apoptosis is a key mechanism in all cells – a mechanism which programmes the cell to collapse and die in case of malfunction. As cells in healthy tissue do not contain multiple centrosomes they are not affected by the compounds used. As a result tumor cells are targeted selectively.

"The cellular mechanisms controlling centrosomal clustering is highly complex, with a number of different proteins involved in the process", explains Mads Hartvig Clausen. "Currently, we are making different probes based on our analogues that we use to investigate centrosomal clustering using a chemical biology approach."

The griseofulvin analogues produced in the joint research project have now been patented. Preliminary experiments in mice at Harvard Medical School have confirmed the anti-cancer effect while not producing notable side-effects. Further, more extensive animal testing is currently taking place. If these tests confirm the drug candidates to be both efficient and safe, the first tests in human patients – phase I trials – will be the next step.



In contrast to normal cells, most tumor cells contain multiple centrosomes, associated with formation of multipolar mitotic spindles. Griseofulvin treatment may inhibit centrosomal clustering, which again will lead to apoptosis – collapse – of the tumor cell.

A Novel Approach to Antibiotics

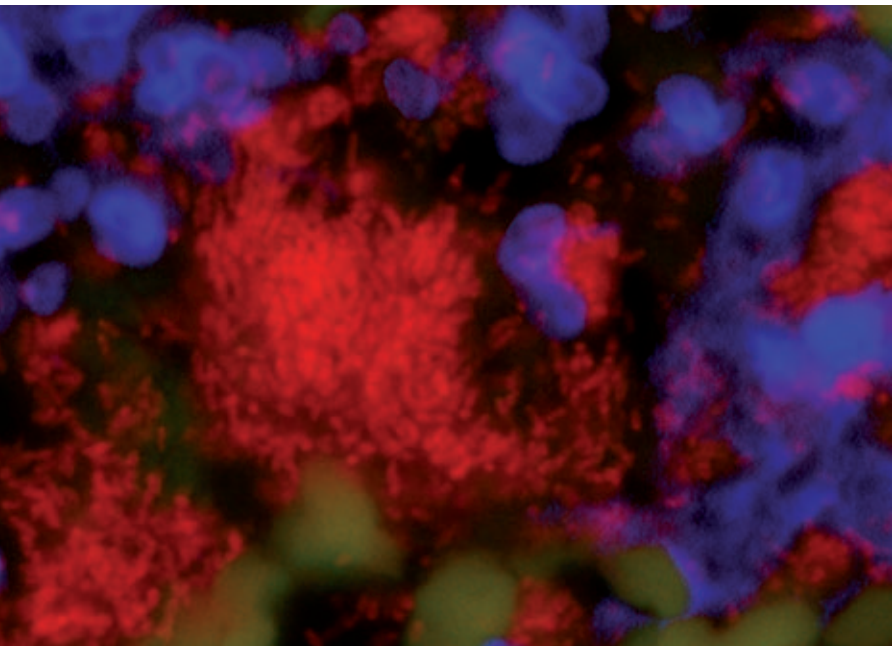
Rather than look at harmful bacteria as planktonic organisms, researchers focus at their collective behaviour, particularly in biofilms, in order to overcome increasing challenges related to antibiotic resistance.

Chemical Biology

While the merits of penicillin and other traditional types of antibiotics can hardly be overrated, the time has come to develop novel approaches for combating harmful bacteria.

"No doubt has traditional antibiotics saved millions of lives since their large-scale introduction back in the 1940'ies. But the drawback is an increase in resistant bacteria," says Thomas Eiland Nielsen, Associate Professor at DTU Chemistry and co-leader of the Centre for Antimicrobial Research (CAR). The centre is headed by Professor Michael Givskov, University of Copenhagen. Beside the two universities, the Danish Technological Institute, the University of Zürich and pharmaceutical company LEO Pharma are part of the centre.

When resistant families of bacteria first began to appear the immediate response was to increase doses. This approach, however, is unfortunately rather short sighted and will lead to increasing resistance to the drug. The next step, which is currently applied by health care authorities world wide, is to switch to a different, more potent kind of antibiotics or combinations hereof, in cases where an organism is resistant to the initial drug.



Drug discovery inspired by nature is a key focus of chemical biology. Researchers may use biologically active compounds found in nature as starting points for designing similar compounds which can be synthesized in an industrial process.

Understanding bacteria communities

For now the traditional strategy works but one day we may simply run out of new kinds of antibiotics. This is where the philosophy of CAR kicks in.

"To date, the study of single, free-living bacterial cells has dogmatically provided the basis for understanding the biology of infectious diseases. However, it has become clear that bacteria are far more advanced as they organize themselves in communities denoted biofilms," says Thomas Eiland Nielsen.

If one desires to see what a biofilm looks like, all it takes will be to dismantle the pluming under your kitchen sink. Unless the tube would happen to be brand new it will have a biofilm on its inner side. The slimy film consists of a mixture of bacteria, particles that have been lost or dropped into the sink – and substances produced by the bacteria serving as a kind of glue. These types of films are not only formed in pluming installations, but may also form on i.e. medical devices and implants – and even on the surfaces of organs and in other places inside the human body.

"In this state, the bacteria can tolerate even the highest deliverable doses of antibiotics and resist the action of the immune system as well as controlling the infectious process by internal signalling and cell-to-cell communication," Thomas Eiland Nielsen explains.

Restoring the immune system

In other words, rather than to try to kill harmful bacteria directly, a more subtle approach of interfering with their internal signalling or similar processes may be more effective. The idea is to prevent the bacterial organization which, in turn, would make otherwise resistant communities vulnerable to even low doses of antibiotics and thus reinstate proper action of the immune system.

Of particular interest are the so called small molecules. As opposed to DNA, proteins and other key biological molecules that may consist of many thousands atoms, small molecules typically contain less than hundred atoms. Their role in biological processes will typically be to regulate cellular processes and the

> The study of single bacterial cells has dogmatically provided the basis for understanding the biology of infectious diseases. However, it has become clear that bacteria are far more advanced as they organize themselves in biofilms.
> - Thomas Eiland Nielsen, Associate Professor, DTU Chemistry

flow of information between cells.

While the role of other partners in CAR is closer to clinical applications, the primary task of Thomas Eiland Nielsen's group at DTU Chemistry is to design and synthesize small molecules. They could be potential drug candidates or they could be tools for obtaining fundamental insight into the biological mechanisms involved in the organization of bacteria.

"We would typically create a library of 20 to 100 chemically related substances for our partners to screen in assays. Some of the most potent substances will be taken further into animal testing," says Thomas Eiland Nielsen.

Highly relevant to medical implants

The research is relevant to a wide variety of infectious diseases. One area, where CAR's research has progressed rapidly is antibiotics for medical implants.

Implants that have been covered with biofilms under controlled conditions have been implanted in mice. The animals will then be fed with the small molecules that CAR researchers hope will be able to disturb biofilm activity.

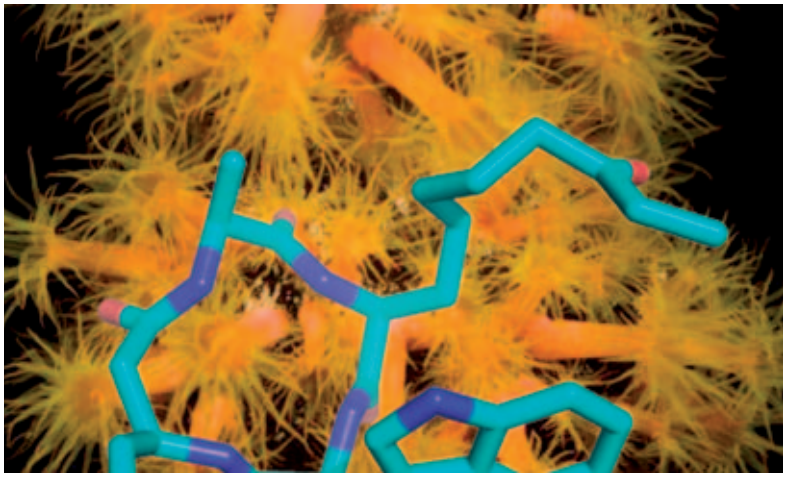
"This is in interactive process. These practical trials provide us with feedback, which often leads us to adjust our initial models. This new insight will help us to create improved versions of the small molecules we address."

CAR was formed in 2009 and its budget is guaranteed for five years.

"This should be enough time to take us close to the first applications," says Thomas Eiland Nielsen.

Cyclic peptides are small and have a physical structure that makes it possible for them to penetrate the membrane of a cell. Some marine organisms produce cyclic peptides but in extremely small quantities. Thus it is imperative to find metabolites that can be efficiently synthesized before cyclic peptides can be used for pharmaceutical applications.

Chemical Biology



Cyclic Peptides as Pharmaceutical Tools

Tricking cancer cells into self-destruction (apoptosis) is one of several promising perspectives in a group of substances found in certain fungus and marine species.

The future will see anti-cancer drugs able to target cancer cells much more selectively compared to today's chemotherapy – and inspired by compounds found in nature. One group of promising compounds are so called cyclic peptides found in certain fungus and marine organisms.

Cyclic peptides are small and have a physical structure that makes it possible for them to penetrate the membrane of a cell. This is a key feature making cyclic peptides highly interesting for pharmaceutical use. Once inside the cell, the peptides may – if designed right – interfere with processes specific for cancer cells while leaving normal cells undisturbed.

"Unfortunately cyclic peptides are produced in extremely tiny amounts in nature. Thus it is not an option to do thorough investigations aimed at pharmaceutical applications on naturally produced peptides. We let ourselves be inspired by nature but are looking for metabolites that can be efficiently synthesized," explains Christian Adam Olsen, Associate Professor, DTU Chemistry.

Next generation cancer drugs

While traditional chemotherapy act as poison to cancer cells – unfortunately also killing healthy cells to some extent – cyclic peptides would not kill cancers cell directly but rather block certain enzymes playing a key role in the cell's genes. Living cells constantly read (transcribe) pieces of DNA in their genes, which in turn serves as the blueprint for enzyme and protein synthesis. HDAC enzymes indirectly affect the transcription process. Thus, enzyme interferences may influence which genes are copied in the specific case. If a drug succeeds in blocking the right enzymes, the cancer cell will be tricked into apoptosis – a mechanism for self-destruction that all cells may potentially activate.

The first pharmaceutical drug built on this specific mechanism was approved by the US Food and Drug Administration (FDA) in 2006. A second drug has since been approved.

Christian Adam Olsen hopes for his group to play a part in next generation of these drugs:

"A total of 11 enzymes have presently been identified as related to this mechanism in cancer cells. The earliest approved drug blocks all 11, while the second blocks about half. We hope that we can provoke cancer cells to apoptosis by blocking only one or two enzymes. As a rule of thumb: the more specific

your drug would be, the lower a risk of undesired side effects you can expect."

Due diligence on side effects

Just because cyclic peptides are found in nature it is by no means a given thing that they will have less side effects compared with chemotherapy, Christian Adam Olsen emphasizes:

"Contrary to chemotherapy a mechanism involving blocking of enzymes is affecting the cells genetically. This makes it very difficult to predict if side effects will occur, and if so, what they are likely to be. Thus it would only be due diligence to already now take an interest in alternative drugs that are more specific compared with the two earliest drugs in the field."

Christian Adam Olsen's position is sponsored by a grant from The Danish Council for Independent Research / Natural Sciences. He joined DTU Chemistry in summer 2010 after three years with Professor Reza Ghadiri's group at The Scripps Research Institute, California. Reza Ghadiri is also known as the inventor of different type of cyclic peptide scaffold that interact with biological membranes and selectively kills a variety of bacteria.

"It was always my intention to return to Denmark at some point. Fortunately it was possible to do so through a position at DTU Chemistry. My present project builds on my US experiences but takes a somewhat different direction. There is no need to duplicate the efforts of Scripps – especially since the field has so many undiscovered aspects to explore."

Grant secures five years of research

Shortly after commencing his work at DTU Chemistry, Christian Adam Olsen received a 10 million DKK grant from The Lundbeck Foundation making it possible to build a research group.

> "We let ourselves be inspired by nature but are looking for metabolites that can be efficiently synthesized.
> - Christian Adam Olsen, Associate Professor, DTU Chemistry

"We are still somewhere in the zone between fundamental and applied research. However, as the grant has a five year horizon – which is a long span for a research grant – we do have a clear expectation of getting to the point of producing substances which will actually be interesting from a pharmaceutical viewpoint," Christian Adam Olsen comments.

Once a substance seems to be promising the first step will be to do an assay test. An assay is a system in the laboratory that mirrors the actual task which the substance is intended to solve. Thanks to advances in this kind of technology the requested amounts of the substance of interest are tiny.

"Something like 30 or 40 milligrams will suffice for years of testing. We can easily produce these quantities in our labs," the Associate Professor assures.

The size of the grant allows for the group to establish its own facilities for screening of compounds in preliminary assays.

"We expect to do the initial assay screenings in our own lab. From previous employment in Denmark I have experienced how this can actually be a bottle neck if you need to get others to do you screenings. At Scripps we were able to do our own screenings. I am grateful to have the same opportunity here."

Passing the dispatch to industry

Once a substance makes it through assay testing next step will be animal testing. This will increase the demand in terms of quantity. Still Christian Adam Olsen is confident the group's lab facilities will be up to the task.

"It should be possible through efficient chemistry to produce enough. Only as we begin to approach an actual pharmaceutical drug we will need to pass on the dispatch to industry – but that would be the case anyhow."

Which specific pharmaceutical companies the group might cooperate with is still too early to say. Firstly, it is not yet known which types of cancer will be most relevant to treat with next generation cyclic peptides. Secondly, it might actually be that other diseases than cancer could be even more relevant; i.e. recent results from international research suggest a positive effect on Cystic Fibrosis and on Huntington's disease by blocking the same group of enzymes.

"We will need to have a clearer picture of the nature of possible therapeutic options before we go into industry cooperation considerations," says Christian Adam Olsen, while underlining the potential for just that:

"Both drugs approved by the FDA for enzyme blocking therapy originate from academic research."

Centre for Antimicrobial Research

Research in the Center for Antimicrobial Research (CAR) represents a multidisciplinary initiative in antimicrobial drug development which brings together key expertises in chemistry and biology, to address fundamental problems of antimicrobial discovery and resistance. In-dept knowledge of antimicrobial drug development of industrial partners is combined with state-of-the-art university biofilm research, modern diversity-oriented synthesis and medicinal chemistry, and nano-engineered materials for medical devices. CAR will design a linked multi-drug (LMDR) that simultaneously blocks a number of well-known bacterial function such as inter- and intracellular communication systems, surface adhesive properties and emerging metabolic targets. These properties will be integrated into one composite drug molecule that when administered will assist the host defence system in elimination and secures full eradication of today's antibiotic resistant infective bacteria. The centre is a cooperation between University of Copenhagen, DTU Chemistry and Universität Zürich.

Design, Synthesis and Biological Activity of Novel Reversible Peptidyl FVIIa Inhibitors / Rh-Catalyzed Enantioselective Synthesis of Diaryl Amines

Hemophilia – inability of the body to control blood coagulation – is a severe disorder. Among symptoms are prolonged bleedings and deep internal bleedings. Around 400,000 males worldwide suffer from hemophilia. As the disease is linked to the X-chromosome, typically only males exhibit symptoms.

About 90 per cent of patients have the hemophilia A form, characterised by deficiency of the blood coagulation factor FVII (or "Factor Seven"). They may be treated through replacement therapy, but about 20 per cent of patients form antibodies as FVII is administered.

The drug NovoSeven, introduced by Novo Nordisk A/S in 1996, is used for treatment of patients with inhibitors (antibodies). In the drug's name "Seven" refers to Factor VII. NovoSeven is recombinant activated Factor VII (rFVIIa). The drug is administered intravenously by reconstituting lyophilized rFVIIa in a solvent prior to injection.

PhD
Morten Storgaard
Main supervisor:
Professor David Tanner

PhD Defence

For various reasons it would be desirable, if instead the drug could be administered in an aqueous liquid formulation, i.e. the reconstituted solution is only stable for use within 24 hours at room temperature. The thesis investigates possible methods for development of an aqueous liquid formulation of rFVIIa.

Addition of an appropriate inhibitor is a useful formulation-aid for stabilization of rFVIIa. The inhibitor should be reversible and sufficiently potent to require only minor concentrations present in the final product. On the other hand, a highly potent inhibitor is not desirable, because that would completely inhibit rFVIIa an prevent it to initiate blood coagulation clinically. Moreover, the inhibitor should be non-toxic, exhibit favourable solubility in aqueous media and be selective against FVIIa without inhibiting other coagulation factors.

NovoNordisk has claimed several peptides and small molecules in the patent literature as stabilization agents for FVIIa.

The thesis consists of two projects.

In the first project a range of novel reversible peptidyl FVIIa inhibitors were designed and synthesized. Also, their biological activity was investigated. Peptidyl benzyl ketones were chosen as a new class of potential inhibitors.

The second project deals with the rhodium-catalyzed enantioselective synthesis of diaryl amines, which is an important class of compounds. For example it is found in the third generation anti-histaminic agent levocetirizine. Development of efficient synthetic routines is therefore of considerable interest. Relevant diaryl amines were synthesized in good yield and enantioselectivity at gram-scale.

Liposomal Drug Delivery of Anticancer Agents

Many potent anticancer drugs suffer from inefficient drug delivery to tumors leading to severe side effects on healthy organs. Hence there is a need for drug delivery systems which selectively can deliver chemotherapeutic agents to cancerous tissue thus minimizing side effects and increasing the therapeutic window of the administrated drug affording better antitumor efficiency and patient compliance.

The thesis describes work towards a new generation of liposomal drug delivery systems with potential in cancer treatment.

Phospholipids are among the most abundant biomolecules in nature and the major component in biological membranes. In the beginning of the 1960'ies Bangham and co-workers observed that upon dispersion of phospholipids in water a spontaneous aggregation into spherical vesicles occur due to formation of phospholipid layers. Bilayers are formed because of the amphiphilic character of phospholipids, the hydrophobic tails come together and form an inner layer shielded from water while the polar headgroups hydrated by water provide a thin shell as the outer layers.

PhD Palle Jacob Pedersen
Main supervisor:
Associate Professor Mads Hartvig Clausen

PhD Defence

Over recent decades various efforts have been undertaken to use lipids for drug delivery. For a long time the application of liposomes was hampered by fast clearance from the blood stream, but since the enhanced permeability and retention (EPR) effect was discovered by Maeda and co-workers, new momentum has come. The EPR effect results in long circulating liposomes accumulating in tumors, partly because the junctions between endothelium cells in tumor tissue is much larger compared with healthy tissue and partly due to lack of an effective lymphatic drainage system.

In the first part of the thesis a system designed to take advantage of both the elevated level of secretory phospolipase A_2 ($sPLA_2$) IIA in many tumors and of the EPR effect is described. The liposomes consists of $sPLA_2$ IIA sensitive phospholipids having anticancer drugs covalently attached to the *sn*-2 position of the glycerol backbone in phospholipids, hence drug leakage is avoided from the carrier system.

In the second part of the thesis studies towards a library of small natural-product-like molecules are described. The collection of molecules was synthesized via a diversity oriented synthesis (DOS) based strategy. Upon coupling of unsaturated building blocks ring closing metathesis cascades were used to "reprogram" the molecular scaffold and highly diverse structures were obtained. In total 20 novel compounds with a broad structural diversity were prepared.

Palladium-catalyzed Cross-couplings with Alkenes / Computer-based Discovery of Potential Histidine Biosynthesis Inhibitors

PhD
Signe Teuber Henriksen
Main supervisor:
Professor David Tanner

PhD Defence

Two organometallic reaction types have been investigated: The Heck reaction and the palladium-catalyzed ene-yne coupling. In regard to the Heck reaction, regio- and stereoselectivity have been investigated, while chemoselectivity has been addressed for the ene-yne coupling. The theoretical studies are all supported by experiments performed by collaborating groups.

A study of the β-hydride regioselectivity of the Heck acrylation of acrolein acetals and of allyl ethers provides an explanation of the divergent behaviour of the reaction path in the presence of excess acetate or chloride, respectively. Under some circumstances the regioselectivity arises from direct competition between the two β-hydride elimination transition states, while under the other there is a high energy barrier for interconversion of the transition states that negates the Curtin-Hammett conditions.

From investigation on the influence of P,N-ligands on the stereoselectivity of the Heck reaction it was demonstrated that the selectivity arises from the insertion step. The steric interactions in the insertion transition state fully account for the enantioselectivity introduced by ligands.

The catalytic cycle for the palladium catalyzed ene-yne coupling was investigated by density functional theory (DFT) methods.

Computer-based Discovery of Potential Histidine Biosy nthesis Inhibitors

The bacteria *S. aureus* is a rising cause of serious infections mainly in hospital environments, and some branches show resistance to common antibiotics. The goal of the thesis was to discover potential leads for development of antibiotics to treat *S. aureus* infections that would act by inhibiting the natural histidine biosynthesis. By HTVS a million compounds were tested against three enzymes associated with histidine biosynthesis. This resulted in 49 hits, which were subsequently rescored by MD and MM-PBSA/GBSA methods, yielding 18 potential inhibitors. Biological assays showed 10 compounds to be active against a *S. aureus* patient strain, 13 against *S. aureus* Mu50, and seven against *S. aureus* USA300.

The success of the employed drug discovery scheme suggests that when time is an issue, it is possible to omit enzyme assays and connect computational results directly to cell viability assays. However, in order to eliminate false positives, the docking hits should be further evaluated i.e. by MD simulations and MM-PBSA/GBSA calculations.

Tools for Chemical Biology: New Macrocyclic Compounds from Diversity-Oriented Synthesis / Toward Materials from Silver(I) Acetylides

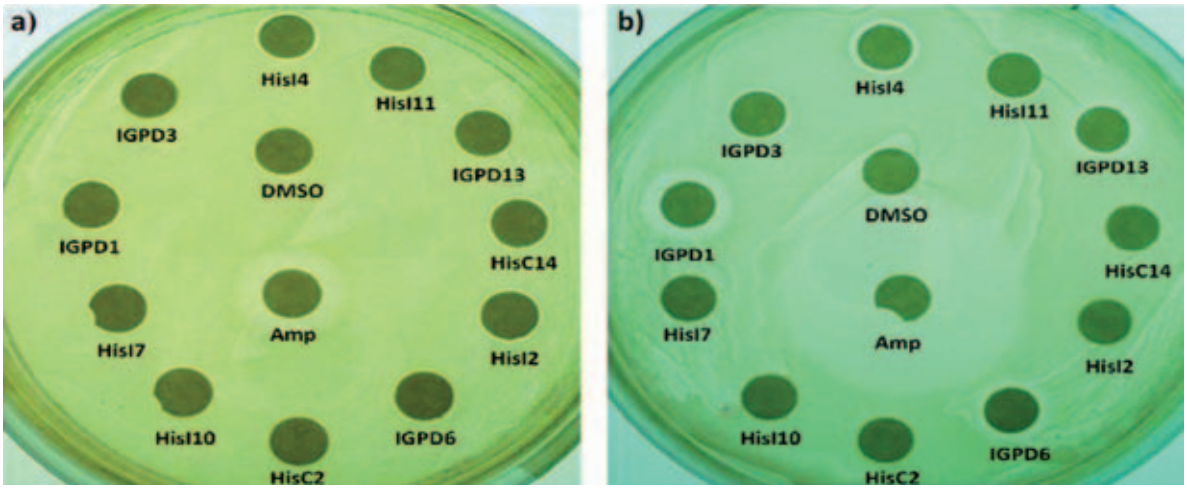
PhD Charlotte Marie Madsen
Main supervisor:
Associate Professor Mads Hartvig Clausen

Macrocyclic substances derived from natural sources are already used for medicine – more than a hundred macrocyclic drugs have been commercially introduced. Synthetic macrocyclic compounds could open new opportunities within drug discovery.

Macrocyclic compounds are attractive for drug discovery as they often display diverse and interesting biological activity, including for example antibiotic, antifungal, anticancer and immunosuppressive activity as seen for erythromycin, amphotericin B, epithilone B and rapamycin respectively.

The reason for the biological activity can be found in several structural advantages. Macrocyclic compounds are conformationally pre-organized, enabling them to bind selectively to targets with minimal entropic loss. Also, they have a certain flexibility, which, in combination with their functionally independent sub-regions, enables them to bind non-covalently to each other or to mediate the assembly of other macromolecules by non-covalent interactions. Furthermore, they have the ability to bury away polar functionalities, leading to improved membrane permeability as compared to their linear analogues. Proteolytic and metabolic stability is also improved as a consequence of the reduced accessible conformational space.

Current macrocyclic drugs are almost exclusively derived from natural sources and are either identical to or closely related to naturally occurring macrocycles. The main reason why this compound class has been little explored in drug discovery is the complex structures of naturally occurring macrocycles and the synthetic effort thus required. However, it is possible to prepare significantly less complex synthetic macrocycles. In recent year diversity-oriented synthesis (DOS) has been employed within chemical



Bacterial disc inhibition assays. The inhibitory effect of small molecules against a) an E. coli patient strain an b) a S. aureus patient strain is shown with ampicillin (Amp) as positive control and negative solvent control (DMSO). Each disk contained 10 ul of 10 mg/ml of the indicated small molecule inhibitor (dissolved in DMSO), exept the ampicillin (Amp) positive control that was dissolved to 1 mg/ml. The plates were incubated at 370 for 14 hours befor they were read.

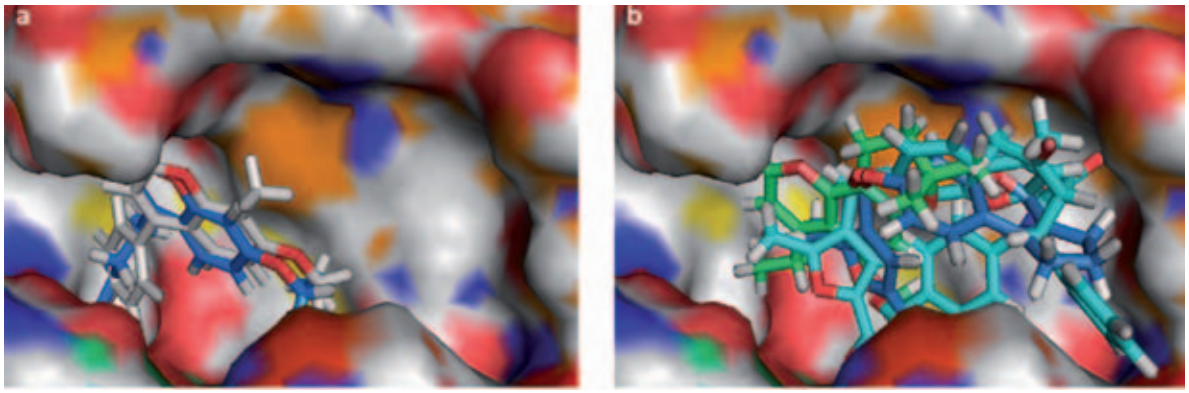


Photo: Thorkild Amdi Christensen

a) Docking poses of HisI2 and HisI4 in the HisI active side, with a phenyl and a butyl group, respectively, pointing into a hydrophobic pocket (on the left). b) Docking poses of HisI1, HisI8, HisI9, and HisI11 in the active site of HisI.

biology. DOS is planned by using forward-synthetic analysis, going from simple and similar to complex and diverse, leading to branched and divergent synthetic pathways. This can lead to highly complex and diverse products in just a few synthetic steps starting from simple and similar building blocks.

Toward Materials from Silver(I) Acetylides

The formation and subsequent coupling of a monosilver(I) acetylide of 2,3-diethynyltriptycene is presented. The silver(I) acetylide is formed in high yield from both 2,3-diethynyltriptycene and 2,3-di(trimethylsilylethynyl) triptycene by use of the same reagent. Coupling of the silver(I) acetylide with 1-iodoadamantane is demonstrated. Furthermore, attempts at the synthesis of 1,3-difluoro-5,7-diiodoadamantane from 1,3,5,7-tetraiodoadamantane are presented. Overall, the results provide a good starting point for the synthesis of new triptycene and adamantine-containing molecules that can interact with carbon nanotubes.

PhD Defence

Photo: Mikkel Adsbøl

THE PHYSICAL CHEMISTRY SECTION OF DTU CHEMISTRY

The Physical Chemistry section of DTU Chemistry is built around the Physical and Biophysical Chemistry Group, complemented by X-ray and Protein Crystallography, Analytical Chemistry and Raman Spectroscopy. The Physical Chemistry Section is also involved in the Center for Molecular Movies (CMM), the Center for Biomembrane Physics (MEMPHYS) and the Danish Centre for the use of Synchrotron X-ray and Neutron facilities (DANSCATT). Faculty from all research groups contribute to education under the section. The section contributes to the cooperation of DTU Chemistry with industry (see list of companies at page 34). The section is coordinated by Associate Professor Kenny Ståhl. A full staff list is found at page 49.

The Physical Chemistry section at DTU Chemistry joins the Physical and Biophysical Chemistry Group, X-ray and Protein Crystallography, Analytical Chemistry and Raman Spectroscopy.

Bringing Synchrotron Flavour to a Lab near You

As structure-based drug design is growing in importance, so is the demand for high-resolution X-ray structure characterization. An alternative to growing single crystals – which is often tricky – is the use of powder probes. Traditionally this would require sending your probe to a synchrotron facility, but results at DTU Chemistry demonstrate that in-house X-ray powder diffraction (XRPD) – using equipment already available in most chemistry laboratories – may be applied instead.

Both to pharmaceutical industry and academia, methods for characterizing the structure of proteins are in high demand. X-ray diffraction on single crystals is a highly reliable method, but a bottleneck here is the need to find the right conditions for growing suitable single crystals. The process is time consuming and in some cases may even prove impossible. Thus, it would be attractive if the process of crystal growing could be complemented by just looking at the protein in a powder. Research at DTU Chemistry has opened new doors in the field.

"High-resolution synchrotron X-ray powder diffraction (XRPD) is a well proven method for structure solution and refinements of small protein structures from powder samples, but since synchrotron time is a scarce resource, many researchers have been discouraged from using the method," explains Kenny Ståhl, DTU Chemistry.

Not surprisingly, when an article on "In-house characterization of protein powder" was published by the Journal of Applied Crystallography in spring 2010, it attracted wide interest. Authors were Ph.D. student Christian G. Hartmann, Associate Professor Kenny Ståhl, Associate Professor Pernille Harris (all DTU Chemistry) and Associate Professor Ole Faurskov Nielsen, University of Copenhagen.

Triggered by Novo Nordisk

In the underlying study, X-ray powder diffraction patterns of lysozome and insulin were recorded on a standard in-house powder diffractometer. The experimental powder diffraction patterns were compared with patterns calculated from Protein Data Bank coordinate data with good agreement.

The efforts at DTU Chemistry were triggered by a request from Novo Nordisk A/S, the world's leading supplier of insulin and other products for diabetes treatment. The company's idea was that instead of producing insulin with random structured molecules, by designing a desired mixture of different structures (or polymorphs) one would be able to control the clinical effect. In other words, as different insulin polymorphs would be dissolved at different rates over time, you would achieve a more controlled release. This has a dual advantage of the patient being able to reduce the number of his injections, and a better prevention of side-effects, primarily less risk of so called insulin chock events. However, verifying that the desired mixture of polymorphs is actually achieved was imperative to the idea.

> "The ability to screen early precipitates for crystals and possible polymorphs would save large amounts of time and effort.
> - Kenny Ståhl, Associate Professor, DTU Chemistry

"I have to admit being sceptical at the outset," Kenny Ståhl recalls.

"The feeling at the time was that only synchrotron measurements were able to give this kind of information accurately. But we decided to give it a try – and it worked."

Straightforward corrections

One challenge to overcome was the fact that protein crystals contain up till 70 per cent solvent – if dried out,

they will break. This greatly adds to the complexity of the task. In fact, as the team tried to predict the outcome through advanced calculations they were seldom correct. However, by use of Principal Component Analysis (PCA) it proved possible to verify the actual composition of the powder on the basis of a few hours of measurements.

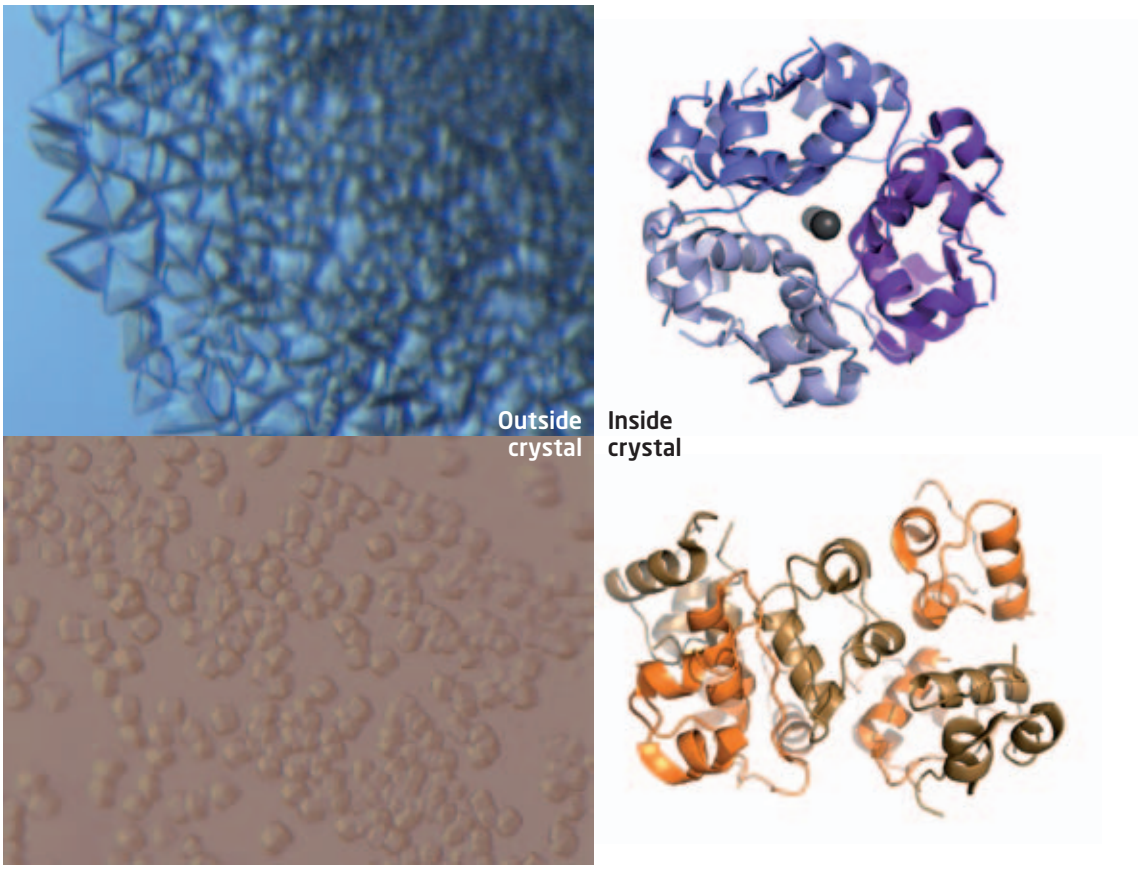
Still, it should be noted that good agreement with Protein Data Bank data was not achieved directly. By including various corrections for background, unit-cell parameters, disordered bulk solvent and geometric factors the desired results were obtained. In particular the solvent correction was found crucial for a good agreement.

"However, these corrections are fairly straightforward to make," Kenny Ståhl notes.

"Another vital part of this success was improvements made in the signal/noise ratio; in other words reducing the "noise" from background sources. This increased the value of the signal we were looking to investigate," Kenny Ståhl explains.

"After the publication of our article we have been pleased to learn that quite a number of our colleagues at other universities and in industry are curious and are wondering whether to adopt the method. The ability to screen early precipitates for crystals and possible polymorphs would save large amounts of time and effort. Furthermore, as structure-based drug design is a growing field and drug candidates are often proteins themselves, there is a growing need for quick characterization of polymorphs and substrate-protein complexes."

X-ray and Protein Crystallography



Crystals of hexameric insulin (blue) and dimeric insulin (brown). The symmetries of the complexes are reflected in the apparent shapes of the crystal.

Center for Antimicrobial Research

Research in the Center for Antimicrobial Research (CAR) represents a multidisciplinary initiative in antimicrobial drug development which brings together key expertises in chemistry and biology, to address fundamental problems of antimicrobial discovery and resistance. In-dept knowledge of antimicrobial drug development of industrial partners is combined with state-of-the-art university biofilm research, modern diversity-oriented synthesis and medicinal chemistry, and nano-engineered materials for medical devices. CAR will design a linked multi-drug that simultaneously blocks a number of well-known bacterial function such as inter- and intracellular communication systems, surface adhesive properties and emerging metabolic targets. These properties will be integrated into one composite drug or probe molecule that when administered will assist the host defence system in elimination and secure full eradication of today's antibiotic-resistant infective bacteria. The center is a co-operation between KU Health, DTU Chemistry, University of Zürich, Technological Institute and LEO Pharma.

"We are the Spider in the Web"

Besides collaborating with practically all other groups at DTU Chemistry, the X-ray and Protein Crystallography group provides both advanced and routine services to industry

Using X-ray diffraction it is possible to determine and explore the three-dimensional atomic structure of chemical compounds, materials and proteins. The atomic arrangement is the basis for understanding the properties, whether it is materials properties or reaction mechanisms in enzymes. This combined knowledge is the key to improve and manipulate structures and the design of new pharmaceuticals.

At DTU Chemistry the full range from small molecules to protein structures is covered. The work is highly interdisciplinary and includes basic chemistry, physics and biology as well as computer programming and biotechnology. The institute has state-of-the-art X-ray diffractometers for powders and single-crystals and access to powerful X-ray synchrotron sources around the world.

While in-house X-ray powder diffraction on proteins is a new "product on the shelf" for DTU Chemistry, X-ray diffraction on single crystals is still the dominant method for characterizing protein structures as well as organic and in-organic structures. The latter is a service provided to industry by the institute on a routine basis.

"Most pharmaceutical companies are able to grow single crystals and analyze them by methods such as Nuclear Magnetic Resonance (NMR) but at the end of the day they often desire X-ray diffraction as this gives unambiguously clear results, when the structure is revealed," says Kenny Ståhl.

Imperative when applying for patents

A well known example of the risk of not knowing ones crystal structure is thalidomide. The drug - a mild sleeping medicine, introduced in 1960 – totally unexpectedly was seen to cause birth defects in the form of phocomeli and abrachi – meanings limps deformed or missing; it was shown that the defects were caused by the mother taking thalidomide during the initial phase of pregnancy. It was later realized that the substance exists in two versions, mirroring each other. While one is the mild sleeping medicine, the other causes severe effects in the foetus.

"The case strongly underlines the need for knowing which polymorphs are present in a given product. In fact, when you apply for a patent, it is practically imperative to know the crystal structure of your compound and be able to document it," Kenny Ståhl states.

Another service to industry is routine characterization of drugs that have been stored for certain periods of time under controlled conditions in order to establish whether the drugs have been moderated over time.

X-ray and Protein Crystallography

At the service of industry

The service to industry within X-ray diffraction is a regular source of income to the group and DTU Chemistry.

"It allows us to maintain the equipment and associated data bases plus IT structure without straining the institute's research budget," Kenny Ståhl explains.

The X-ray and Protein Crystallography group is a part of the institute's new Physical Chemistry section, headed by Kenny Ståhl, but is a bit untypical:

"We have ongoing cooperation with practically all research groups in all sections of the institute, as X-ray diffraction has so many applications. You may say we are sitting as the spider in the middle of the web," Kenny Ståhl smiles.

Let's go to the Movies

Filming chemical reactions at the atomic level is an old dream, which is approaching realization through the creation of the Linac Coherent Light Source in California. Competition for time on the new facility is fierce. DTU Chemistry researchers are on board.

Any reaction scheme in chemical textbooks will traditionally give you reactant(s) on the left hand side and end product(s) to the right, while sub-reactions in-between are left to the readers imagination. This is not just in order to save the reader's time. Often even simple reactions involve a set of sub-reactions so complex that they are not fully understood and it would, if at all possible, take vast amounts of modelling and computer calculations to describe them. But with the Linac Coherent Light Source, operated by University of California, just opened in 2010, for the first time will researchers be able to "film" chemical reactions using X-rays.

Together with groups at University of Copenhagen (KU) and Risoe DTU, the femtosecond spectroscopy group at DTU Chemistry constitutes the Centre for Molecular Movies. A centre which opened about five years ago based on funding from the Danish National Research Foundation.

"The fact that Science Magazine had the new facility on its top-ten of scientific achievements in 2009 speaks for itself. Obviously, competition for time on the facility is fierce and we are in the race to be among the chosen few," Associate Professor, Niels Engholm Henriksen, DTU Chemistry, states.

> "The fact that Science Magazine had the new facility on its top-ten of scientific achievements in 2009 speaks for itself.
> - Niels Engholm Henriksen, Associate Professor, DTU Chemistry

Almost like a football game

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, while not really idle, 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; in the world of chemistry, the transformation of a molecule takes just a few hundred femtoseconds (one femtosecond is 10^{-15} second).

The Linac Coherent Light Source generates X-ray pulses so short that processes at this incredibly small time scale may be seen. The same will be true for a similar European facility, the XFEL, to be inaugurated in Hamburg in 2014. The Centre for Molecular Movies will also aim for time at the European centre.

"This is a completely new and very exiting tool. One field where it could be applied is for medicine as both pharmaceutical industry and academia involved in drug discovery would benefit from obtaining "molecular movies", "says another member of the group at DTU Chemistry, Associate Professor Klaus B. Møller.

A new generation of x-ray sources named x-ray free electron lasers will make it possible to "film" chemical reactions in the near future.

Femtosecond Sprectroscopy

A wealth of experimental data to come

It is still too early to say precisely in which field the technology will prove to be most groundbreaking:

"I would compare it with the discovery of static X-ray diffraction. When first discovered, it was seen as a new tool, but the precise implications were not clear. Today, we know that X-ray diffraction has gained enormous importance within many scientific disciplines. If we could have just a fraction of that kind of success we would be more than happy," says Klaus B. Møller.

Measurements at the Linac Coherent Light Source in California and the future European XFEL facility in Hamburg will create an enormous amount of experimental data.

"A molecular movie showing the time-dependent atomic positions can, however, only be created after an extensive theoretical analysis of the data," Niels Engholm Henriksen stresses.

"Thus, theory and experiments are strongly interdependent in this field."

Theory and Modelling of Ultrafast X-ray Imaging of Dynamical Non-equilibrium Systems

PhD Ulf Lorenz
Main supervisor:
Associate Professor
Niels Engholm Henriksen

PhD Defence

For almost a century x-ray diffraction has been used to establish the positions of individual atoms in a given sample. The incoming x-ray is scattered by the atoms in the sample, and at a detector plate the scattered waves from each atom interfere and produce a diffraction pattern that is highly sensitive to the relative positions of the atoms.

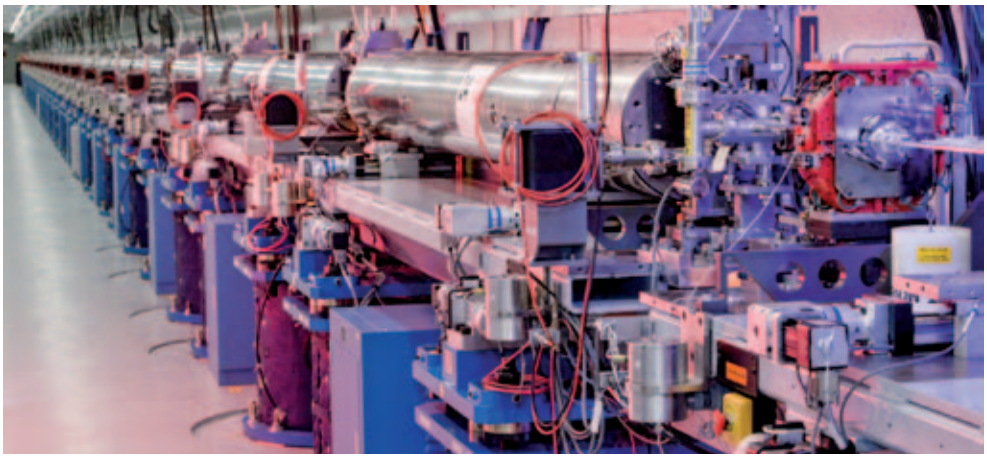
A new generation of x-ray sources named x-ray free electron lasers have just become operational or will in the near future. These are the Linear Coherent Light Source (LCLS) and the Spring-8 Compact Sase Source (SCSS), both in the US, and the European XFEL. These facilities will provide pulses with picosecond duration and a photon flux, which is orders of magnitude above that of current synchrotron facilities. These new features make it feasible to combine the traditional advantage of x-ray diffraction – which is the direct determination of the nuclear geometry – with time-resolved studies of ultrafast processes.

This opens a new field named time-resolved x-ray diffraction (TRXD). The aim of this thesis is to study theoretical aspects within TRXD.

The thesis describes basic theory for x-ray diffraction and move on to derivation of general formulas for TRXD. In traditional time-independent x-ray diffraction theory, it is usually assumed that the scattering is always "elastic". It is demonstrated that this assumption is in general wrong and not required; dropping it simplifies derivation of the time-dependent signal considerably.

Finally, some new issues that arise in a time-dependent context are studied. A first new phenomenon is molecular alignment. The strength of the interaction between a molecule and a polarized laser field depends on the relative orientation of the molecule with respect to the polarization vector. Consequently, the laser-molecule interaction produces aligned ensembles of molecules, and probing these ensembles with TRXD produces anisotropic diffraction patterns. How to systematically decompose and interpret these is studied.

Another new effect, which is briefly studied, is delocalized wave packets after photo-excitation. Typically, in a ground-state molecule, the constituent atoms are strongly bound, and the nuclear wave function is strongly localized around a specific bound-state geometry. When we excite such a molecule, we frequently observe wave-packet dispersion; the initially well-defined bond lengths give rise to a continuous distribution of bond lengths.



Looking east down the LCLS undulator array. Thirty-three LCLS undulator magnets will create intense X-ray laser light from a pulse of electrons traveling near the speed of light.
Photo: lcls.slac.stanford.edu/ImageGallery

Centre for Molecular Movies

The Centre for Molecular Movies was inaugurated in 2005, at the Niels Bohr Institute, University of Copenhagen. The Centre is made possible through a five year grant from the Danish National Research Foundation. The aim is to obtain real time "pictures" of how atoms are moving while processes are taking place in molecules and solid materials, using ultrashort pulses of laser light and X-rays. The goal is to understand and in turn influence, at the atomic level, the structural transformations associated with such processes.

The Centre combines expertise from DTU Chemistry, Risø DTU and University of Copenhagen in structural investigation of matter by synchrotron X-ray based techniques, femtosecond laser spectroscopy, theoretical insight in femtosecond processes, and the ability to tailor materials, and design sample systems for optimal experimental conditions.

cmm.nbi.ku.dk

DTU CHEMISTRY INDUSTRIAL COLLABORATION

The DTU Chemistry deals with all aspects of chemistry – meaning the study of the composition, structure and properties of matter, and with the reactions by which matter may be converted into new forms.
DTU Chemistry has wide cooperation with industry:
Lundbeck A/S, NovoNordisk A/S, Leo Pharma A/S, Arla, QuantiBact A/S, CP Kelco A/S, Vattenfall A/S, Danish Power System ApS, Amminex A/S, Daka a.m.b.a., Danisco, Dong Energy A/S, Dinex, Eastman Chemical Company, Grundfos A/S, Haldor Topsøe A/S, Wacker Chemie, LAB S.A., Novozymes A/S , OK a.m.b.a., Teknologisk Institut.

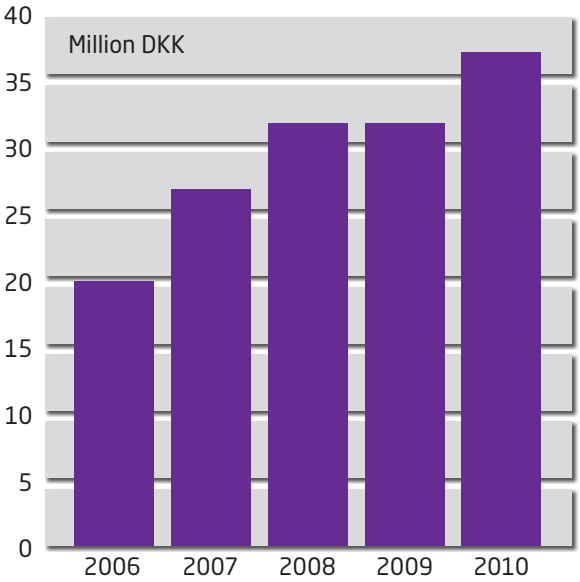
Glassblower Patrick Scholer supplies both DTU Chemistry and external partners within industry and academia with glass flasks and tubes designed especially for given purposes.

Maintaining a High Level of Activity

DTU Chemistry's position as a leading research institute was solidly maintained in 2010

During 2010 our external funding has increased to 37.4 million DKK (exclusive overhead) and the startup of new PhD projects was 21. Both figures represent an upward trend. Also within education a high level of activity was maintained, a total of 27 students completed their bachelor degree (B.Sc.) and 16 students completed their Master degree (M.Sc.) at DTU Chemistry.

External funding exclusive overhead



PhD admission

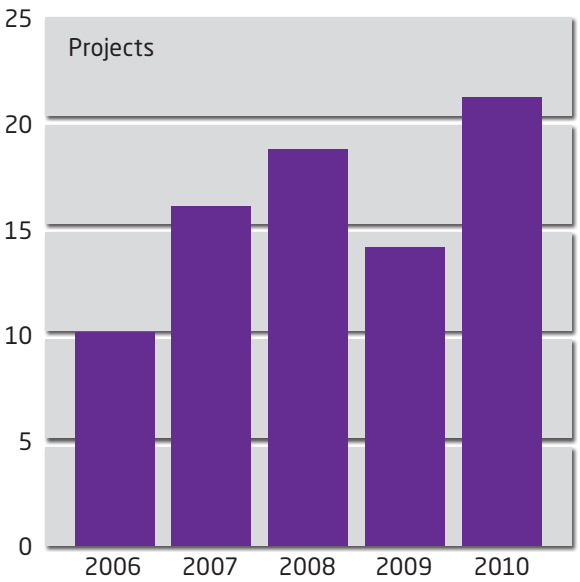


Photo: Thorkild Amdi Christensen

PhD Thesis 2010

Johannes Due-Hansen
"Alternative deNO$_x$ Catalysts and Technologies"
See summary page 11

Hanne Falsig
"Understanding Catalytic Activity Trends for NO Decomposition and CO Oxidation using Density Functional Theory and Microkinetic Modeling"
See summary page 10

Jytte Kristensen
"Synthesis, Purification and Characterization of Ferredoxins with Re-Designed Active Sites"
See summary page 16

Pernille Efferbach Karlsen
"Expression and Purification of the Metal-Containing Monooxygenases Tryptophan Hydroxylase and Dopamine β-hydroxylase"
See summary page 16

Anna Christina Welinder
"Insulin Adsorption and Surface Behaviour on Monocrystalline Au(111), Au(100) and Au(110) Surfaces studied with STM, AFM and Electrochemistry"
See summary page 17

Jane Boesen
"Cloning, Expression, Purification and Characterization of Tryptophan Hydroxylase Variants"
See summary page 10

Palle Jacob Pedersen
"Liposomal Drug Delivery of Anticancer Agents"
See summary page 25

Morten Storgaard
"Design, Synthesis and Biological Activity of Novel Reversible Peptidyl FVIIa Inhibitors / Rh-Catalyzed Enantioselective Synthesis of Diaryl Amines"
See summary page 25

Signe Teuber Henriksen
"Palladium-catalyzed Cross-couplings with Alkenes / Computer-based Discovery of Potential Histidine Biosynthesis Inhibitors"
See summary page 26

Charlotte Marie Madsen
"Tools for Chemical Biology: New Macrocyclic Compounds from Diversity-Oriented Synthesis / Toward Materials from Silver(I) Acetylides"
See summary page 26

Ulf Lorenz
"Theory and Modelling of Ultrafast X-ray Imaging of Dynamical Non-equilibrium Systems"
See summary page 33

DTU Chemistry staff and external participants – the photo was taken during a break in the institute's first PhD Symposium, November 2010, held at Schæffergården conference centre.

Master Thesis 2010

Maria Mikolajczak
"Determination of Anions by Ion Chromatography and Capillary Electrophoresis"

Christian Berg Oehlenschlæger
"Biochemical and Structural Characterization of Enzymes Involved in the dUMP Synthesis in B. Halodurans"

Anton Vassiliev
"Direct HT-PEM Fuel Cell"

Jesper Jonasson Madsen
"Enzymatic Hydrolysis of Cellulose Fibers: A Computational Study"

Pernille Mansgaard Simonsen
"Solid-Phase Synthesis of Anti-Cancer Peptides"

Claus Gunnar Bang
"Solid-Phase Synthesis of HDAC Inhibitors"

Christian Mårup Osmundsen
"Syntheses of Zeolitic Lewis Acids using Post-treatment"

Þórey Anna Grétarsdóttir
"Ionic Liquids in the Selective Gas Absorption of Nitrogen Monoxide - Application and Characterization"

Nadia Muhammad Akram Mirza
"Metalloenzymes Related to Neuropsychiatric Disorders"

Casper Junker Engelin
"Stereoselective Synthesis of Aminotetralins"

Mathias Christian Franch Andersen
"Synthesis of Oligosaccharides for Microarray Galectin Screening"

Andreas Jonas Kunov-Kruse
"Synthesis and Spectroscopic Characterization of Sulfated Metaloxide SCR Catalysts"

Kasper Torp Madsen
"Towards a Fluorinated Cyclooctyne for Click Chemistry"

Jacob Frederik Kure
"Towards Stereoselective Synthesis of a Monodentate, C3-symmetric Triarylphosphine"

Kim Lasse Christensen
"Development of an Industrial-scale Synthesis of a Novel Drug Development Candidate"

Antonio Luis Tomas Garcia
"Development and Testing of New Materials for High Temperature Polymeric Electrolyte Membrane Water Electrolysis"

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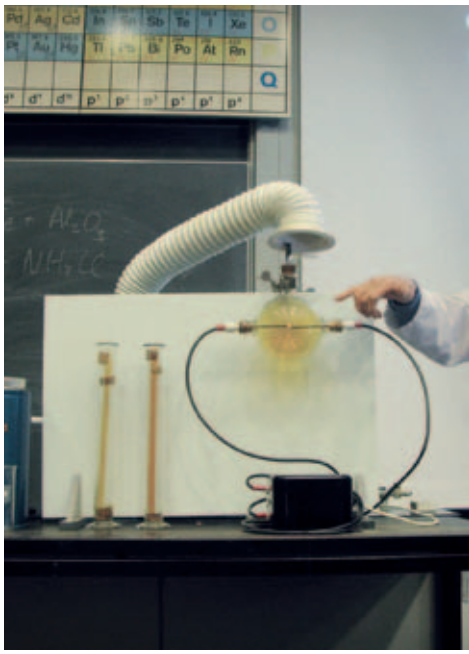

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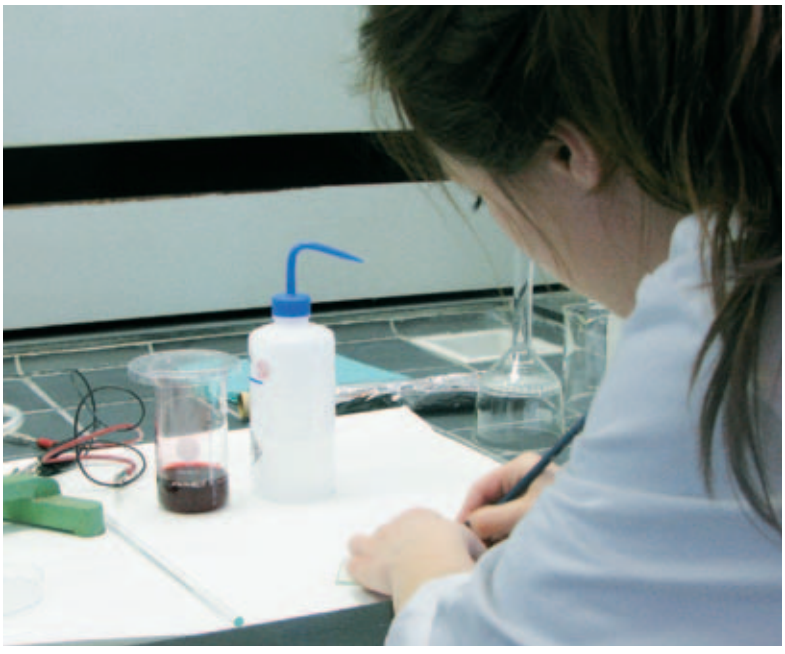

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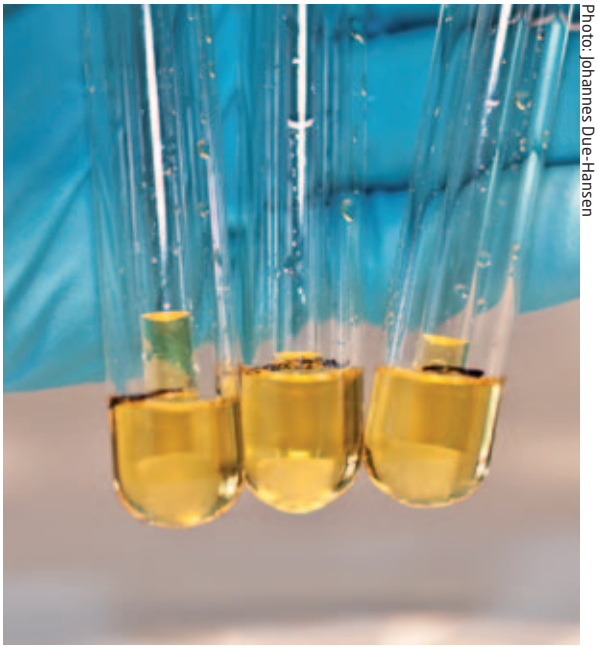
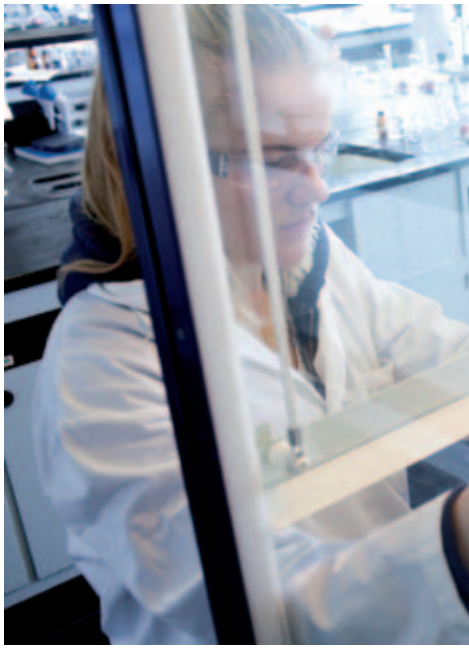


Photo: Johannes Due-Hansen



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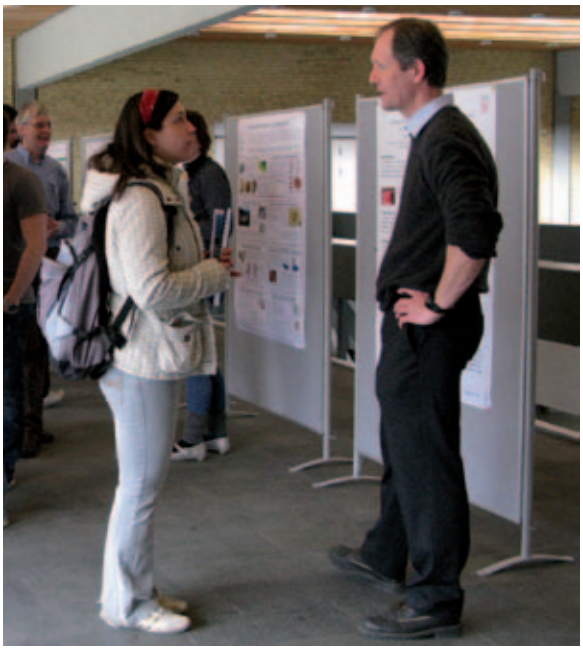

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