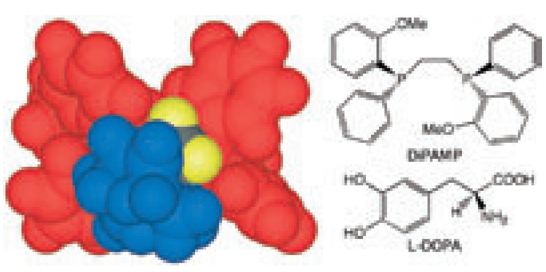
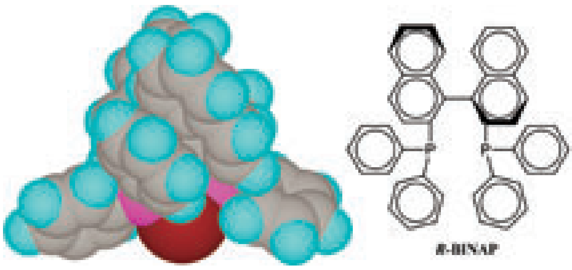
Katalytisk syntes av spegelbildsmolekyler



Till vänster: En katalysatormolekyl i färd med att göra sitt jobb. Den kirala liganden är röd, metalljonen (rodium) grå, det organiska startmaterialet blått och väteatomerna gula. Väteatomerna kommer i nästa steg att adderas till startmaterialet, en sk hydrogenering. Till höger: Streckformler för DiPAMP liganden och läkemedlet L-DOPA.

Streckformler visande den katalytiska hydrogeneringen i Monsantos L-DOPA syntes.



Till vänster: Ett fragment av en katalysator molekyl med rutenium och Noyoris BINAP ligand.
Till höger: Kemisk streckformel för BINAP

Årets kemipris är frukten av 30 års arbete av organiska och oorganiska kemister i de delområden av kemin som betecknas organisk syntes, koordinationskemi och metallorganisk kemi. Med Knowles, Noyoris och Sharpless metoder har vi fått effektivare läkemedel med färre biverkningar och dessutom framställda på ett mer miljövänligt sätt.

Det sista Mr Harrison gör i livet är att äta en stuvning av egenhändigt plockad svamp. Död genom olyckshändelse blir domarens föga förvånande utslag. En viss John Muntig råkar dock snappa upp några kemisters samtal på ett cocktailparty och tar därefter med sig ett prov av det dödande svampgiftet till ett laboratorium.

Polarimetern sätts på, ljusets släcks och provet förs in. Men se, giftet vrider inte det polariserade ljuset. Alltså består det av en blandning av det ”riktiga” muscarinet och måste därför vara syntetiskt framställt! Det naturliga muscarinet förekommer nämligen bara i den ena formen och när polariserat ljus passerar genom en sådan lösning vrids det kraftigt. Slutsatsen i Doro- thy Sayers roman ”Handlingarna i målet ” kan bara bli en: Mord!

1930-talets syntesmetoder var visserligen osofistikerade med våra mått mätt, men faktum är att den selektiva framställningen av enbart den ena spegelbilden av en molekyl fortsätter att vara ett av den organiska kemins stora problem. Ett problem som dock årets nobelpristagare i kemi, William Knowles, Ryoji Noyori och Barry Sharpless tacklat mycket framgångsrikt genom sina upptäckter inom asymmetrisk katalys. Nu går knappast några mördare fria genom att använda Knowles, Noyoris och Sharpless metoder. Däremot har vi t ex fått effektivare läkemedel med färre biverkningar och framställda på ett mer miljövänligt sätt.

Att bygga spegelbildsmolekyler

Vid tillverkning av kirala föreningar med klassisk syntetisk kemi får man lika mycket av båda spegelbilderna. Önskar man endast den ena omvandlas alltså hälften av startmaterialet till en icke önskvärd biprodukt. En ekonomisk förlust och ett potentiellt miljöproblem. Biprodukten måste sedan avskiljas, vilket är svårt eftersom båda molekylerna har samma fysikaliska egenskaper i normal laboratoriemiljö.

Direkt syntes av den ena spegelformen (enantiomeren) är därför att föredra. Det vanligaste sättet är att som reagens eller startmaterial använda en annan enantiomert ren förening, ofta extraherad från någon naturlig källa. Nackdelen är att man då behöver enantiomert rent startmaterial i samma mängd som den önskade produkten.

En fiffigare metod är att få startmaterial och reagens att kombineras med hjälp av en kiral katalysator. Katalysatorn både ökar reaktionshastigheten och styr kiraliten så att endast en av de två möjliga spegelformerna av produkten bildas, och detta utan att själv förbrukas under reaktionens gång. En enda katalysatormolekyl kan alltså katalysera bildandet av flera miljoner produktmolekyler, vilket kraftigt reducerar behovet av kiralt startmaterial.

Övergångsmetallernas roll

Gemensamma nämnare i pristagarnas arbete är kiralitet och övergångsmetalljoner. Själva katalysatorn består av en kiral organisk molekyl, kallad ligand, bunden till en metalljon. Medan kiraliten hos produkten styrs av den kirala liganden görs själva katalysen av metalljonen. Man kan säga att årets pris är frukten av 30 års arbete av organiska och oorganiska kemister i de delområden av kemin som betecknas organisk syntes, koordinationskemi och metallorganisk kemi.

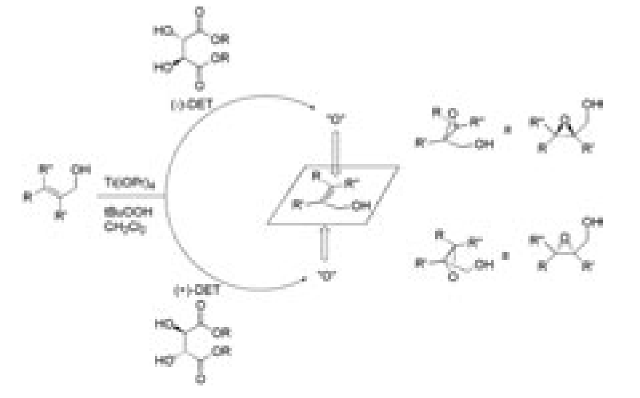
Pristagarna

William S. Knowles är den äldste av pristagarna, 84 år. Han tog sin doktorsexamen vid Columbia University 1942 och arbetade sedan vid Monsanto Company i St. Louis fram till sin pensionering 1986. Inspirerad av G. Wilkinsons (nobelpris 1973) framställning av den första lösliga hydrogeneringskatalysatorn Rh (trifenylfosin)3Cl utvecklade Knowles 1968 en metod för asymmetrisk katalytisk hydrogenering. Med hjälp av en kiral rodiumkatalysator tog han 1977 fram en industriell process för framställning av L-DOPA, ett läkemedel som används vid behandling av Parkinsons sjukdom. *(Se bilder föregående sida.)*

Ryoji Noyori är 63 år och född i Kobe, Japan. Han har sin doktorsexamen från Kyotos universitet 1967 och arbetade sedan på Harvard. Han återvände sedermera till Japan och utnämndes 1972 till professor vid Nagoya University där han verkar än idag. Noyori vidareutvecklade Knowles teknik genom att framställa nya kirala fosforbaserade ligander för användning i olika typer av katalytisk asymmetrisk syntes med övergångsmetaller. Framför allt en av liganderna, kallad BINAP, har använts flitigt av organiska kemister världen över och utnyttjats industriellt för framställning av läkemedel och finkemikalier. *(Se bild längst ner föregående sida)*

Barry Sharpless föddes i Philadelphia och är 60 år. Han doktorerade vid Stanford University och jobbade sedan i olika omgångar vid MIT, Harvard och Stanford. Sedan 1990 är han professor på The Scripps Research Institute i San Diego. Medan de två föregående forskarna, som delar på ett halvt pris, främst utvecklat hydrogenerings-katalysatorer har Barry Sharpless jobbat med oxidationsreaktioner. 1980 presenterade han den första katalytisk asymmetriska oxidationsreaktionen. Ett stort genombrott som dessutom gav en för synteskemisten ovanligt användarvänlig process, idag kallad Sharpless asymmetriska epoxidering. *(Se bild nedan)*

Därefter har hans arbete resulterat i flera viktiga reagens, vilka fått ett enormt genomslag t ex inom den akademiska utbildningen och grundforskningen. Vid Chalmers används t ex Sharpless reagens i grundutbildningen i kemi.

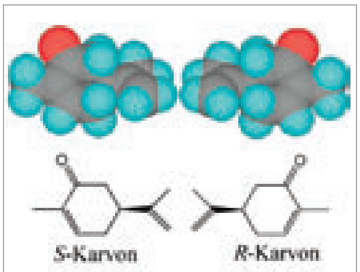


Sharpless asymmetriska epoxidering. Bilden visar hur syret kan komma antingen ovanifrån eller underifrån och på det sättet ge upphov till de två olika spegelbilderna.

TEXT OCH BILDER

LARS ÖHRSTRÖM, JERKER MÅRTENSSON, GUNNAR WESTMAN, NINA KANN

Kemiforskare vid Chalmers och Göteborgs universitet



Dilldoftande S-karvon till vänster och mintdoftande R-karvon till höger.

Faktaruta

Det finns miljontals kemiska föreningar alla med sina specifika egenskaper. Dessa bestäms av molekylens kemiska struktur, d v s det tredimensionella arrangemanget av atomer. Vissa föreningar har egenskapen att inte vara identiska med sin spegelbild, precis som höger och vänsterhänder. Detta kallas kiralitet och molekylerna kallas för kirala föreningar. Händer, fötter, handskar och skor är exempel på saker som är kirala.

En förening kan identifieras med hjälp av t ex sin smältpunkt och kokpunkt, och dessa egenskaper är lika för båda spegelbilderna (enantiomererna). De vrider dock planpolariserat ljus åt olika håll. I kontakt med andra kirala föreningar blir däremot kiraliteten viktig. Försök till exempel att sätta en högersko på vänster fot!

Eftersom vi är uppbyggda av kirala molekyler, t ex aminosyror och socker, utgör vi en kiral omgivning, där två föreningar som är varandras spegelbilder kommer att ha olika egenskaper. Ett exempel är karvon där den ena enantiomeren får oss att tänka på kräftfest, då den ger dill och kummin dess karakteristiska dofter. Den andra leder tankarna till tandborstning och tuggummi, eftersom den är en huvudkomponent i myntaolja. *(Se bild ovan)*

Does Erasing Academic Borders Mean Improving Quality ?

Experiences from the integration of smaller courses in different disciplines into a $1^{1}/2$ semester chemistry course

Lars Öhrström, School of Chemical and Biological Engineering, Chalmers Tekniska Högskola

The problem

Bringing together 5-6 courses from different disciplines means finding which subjects overlap and defining which material that will benefit from being taught in the context of one or more of the other disciplines. It creates problems and opportunities in assessment and may open up for new teaching methods. Course literature may be a problem as will the assessment of the outcome of the new course. In this communication I will describe the results of our work on the new integrated chemistry course (14 credits, Aug.-March coordinated with 15 credits of mathematics) for the chemical engineering, chemical engineering with physics and biotechnology programs and the implications for the "quality".

What do we mean with quality?

A simple view of the "quality" of a course is the amount of the learning achieved by the students after the course. However, there are good reasons for using a broader perspective.

For example, it may be argued that the capabilities of a graduate with a few years of working experience is only affected to a small degree by the approaches to teaching at his or her undergraduate institution. On the other hand, significant differences may be seen in the students subjective experience from the undergraduate years, and (more important in economic terms) the number of dropouts from a program.

Another point is that apart from the specific learning quality of a course, especially in the first year, we have to consider the implications of this learning on the program as a whole. A course "A1" should then be judged, maybe primarily, on its merits preparing the student for courses "B1, C1, D1…" and not only for the needs of course "A2". This may seem self-evident, but does in fact put a heavy responsibility on the teachers in the first academic year. Indeed, we demand them to have in depth knowledge of the whole program in all its varieties. For example, a mathematics teacher in the first year of the chemical engineering program would be required to know that Fourier transforms appear in the fourth year course "Applied Organic Molecular Spectroscopy".

Background

First year general chemistry courses spanning over several chemistry disciplines are the rule in the USA, although less common in Scandinavia, so at a first glance it may seem that we are reinventing the wheel. However, these courses usually take great care to avoid any mathematics and as a consequence this results in "chemistry light"; almost no moent can be treated with any depth.

Furthermore, these courses are by tradition taught by inorganic or physical chemists and subjects like organic chemistry and biochemistry are treated lightly. Alternatively, the subject matter is divided into small courses organised by different departments and thus lack coherence and clear goals.

The chemical educators dilemma

Most scientists (I believe) take pride in the presentation of their subjects in a logical order, letting one brick follow another until the tower has reached a sufficient height. This seldom represent the historical development of the subject, or the way its applications have evolved but it is aesthetically pleasing and may be a great help for students.

However, for the chemical educator this is a major dilemma. Exaggerating a little (but just a little!) you may say that in order to understand chemistry you need three years of university mathematics and physics. To step around this we have in general taken great care to avoid any mathematics in the first years chemistry courses, and as a consequence, treated no subject in sufficient depth. Many of these subjects then have to be brought up again in subsequent years when the appropriate mathematics courses have been completed.

This means more work for teachers in many cases, and may result in good students earning double credits for some things while weaker students may be more confused than helped (different notation, sign conventions and emphasis are common differences between courses).

The challenge

There may be a way out of this dilemma, but one that represent a great challenge to both mathematics and chemistry teachers. We can turn things the other way around, point the students to the problem and they may perhaps appreciate the solution. Teach chemistry from first principles while taking advantage of the mathematics taught in parallel. Thus one finds that for almost every mathematical concept introduced there is a chemical problem to be solved! The challenge involved here is making both mathematics and chemistry teachers aware of the possibilities.

A second point is that such an approach means aligning the mathematics and chemistry courses and this will be much easier if there is *one* mathematics course to align with *one* chemistry course. Thus, once the mathematics course started to change, there was a simple and practical reason for starting to look at an integrated chemistry course extending through most of the first year of the study programs at the School of Chemical and Biological Engineering.

Is there anything wrong with the classical approach?

However, before going into details, we have to ask if the classical approach, with smaller and subsequent courses in introductory chemistry, inorganic chemistry, physical chemistry, analytical chemistry, organic chemistry and biochemistry is not producing good enough students? (The order may vary somewhat, nowadays organic and biochemistry can often be found in the first year of study.)

The increased interdiciplinarity of both research and the professional rôle of the chemical engineer is one reason. Other reasons are the fragmentation of knowledge and the marked tendency to study only for the exam when courses are small (Learning by heart is still a strategy that may work for small courses.) and the increased competition for prospective students we see. New courses have to be more motivating and selling while not compromising on content. We believe this is easier done in a large course than in smaller ones. Moreover, no matter how well intentioned and ambitious the teachers in each of the small courses are, there is neither time nor incentive to get a real grip on what is going on in the other courses and the coherence of the curriculum will be wanting.

Let me now describe some issues I believe have some interest beyond the chemistry and chemical engineering comunity.

Course literature

A major issue for a course like this is the literature. Could we find one book for the entire course or, rephrasing the question, was it so important to have only one book that compromises could be made on the course content? Should we then have in-house produced material to cover the gaps? Should we have an extensive collection of exercises (other than those in the book(s))?

The following decisions were made:

- No compromise on course contents but the three books chosen will be used also in subsequent courses
- No in-house produced compendia etc.

- The collection of exercises kept to a minimum and only such that lacked counterparts in the books.

The arguments were that a "real book" is a very useful working tool for the future engineer. If it looks nice and has been used it will stay on the shelf for many years to come (unless sold for food out of necessity). An in-house produced compendium will soon be both forgotten *and* thrown away. However, since all selected books are in English a brief collection of exercises in Swedish is an essential help to develop the Swedish chemical vocabulary.

New or old teaching methods?

Ideas about new teaching methods are abundant. AL, PBL, LBD and IT are but some of the acronyms that promise to deliver the students from ignorance. Although all of the above are to some extent integrated in this course, we believe that one persistent problem in today's higher education in Sweden is the lack of contact between teachers and students. There is simply no time; the stressed teachers always have to run to the next assignment after each class. Especially the first year students need to be seen and acknowledged.

This is a structural and economical problem that is out of reach for us, but with available resources we want to do the following:

- Reduce the number of large (160 students) lectures to about half (once a week)
- Two lessons a week, including lecture material, demonstrations, problem solving and students own activities (ALE).
- Let the same teachers follow the students from September to March. This will allow confidence and relation building between teacher and students in a way that is impossible in a brief 7-week course.

I think (the final evaluation will tell us) this has lead to more unscheduled contacts, a benefit for the students, but further trashing the researches time into unworkable pieces. We are not quite sure how to tackle this potential problem.

Moreover, we will make some additional gains from the large scale of the course:

- Each lesson will be pre-prepared by one teacher so that some material and ideas can be used also by the others, thus saving time and effort.
- Courses for the different programs are no longer separated in time and literature, meaning that we now have an efficient backup system that did not exist before with the one teacher/one course concept. (Teachers can now stay at home if they have 40° fever. Someone else can easily take his or her lessons.)

Some comments on the specific learning situations in the course:

Lessons

Lessons (tutorials) are the backbone of the course. Here the more difficult and abstract material is presented, problem solving discussed, and an occasional experiment shown. We also allow time for students own problem solving, and encourage them to work in groups or pairs. One teacher follows a group (30-40 students) from end of August to March. Since this is a very though assignment, every group has a replacement teacher. He or she cover for weeks when the teacher have other important assignments (thesis defences, conferences, travel) and will have to be active even during the other parts of the course, for example by lecturing.

Lectures

Cover less abstract material, give more of an overview and are, on the whole, more entertaining, without loosing their relevance for the assessment. Some are directly aimed at showing the applied side of chemistry, in the kitchen, factory or in the environment. Since many teachers (5 + 5 replacements) are available they can chose to lecture about things they find passionate. The number of "performances" by each teacher will also be low (total of 27 lectures) which means one can try for 1-2 really good lectures instead of 12 mediocre ones.

Occasionally, people from outside the teacher group are invited to lecture. In those cases we try to keep close control of the lecture content and "tutor" these lecturers to the right level. One of the teachers in the group is responsible and present each outside lecturer.

"Counting cottages"

Teachers are be available for consulting at each weeks scheduled problem solving session. For these occasions we recommend special integrated exercises from the books and some more complex and "real world" problems from our compiled exercise collection.

Practical laboratory work

Here we first need to note a major difference between chemistry and other subjects. From the very start the practical laboratory work is aimed not only at demonstrating principles and facilitate learning by doing, but to actually teach the students professional skills. It is also important for the environmental awareness that they do practical work and are faced with, for example, waste problems.

However, as this author understands it, we are under direct orders from Chalmers administration to cut down on laboratory work, and in this new course the laboratory time has been reduced to roughly the half. We will nevertheless try to make the most of what there is.

- The safety and security regulations test will be upgraded in status and actually have a weight in the final grading.
- Some of our laboratory work involves chemical analysis, but the analytical chemistry side of these operations have not been highlighted until now. We will use small parts of lecture time to discuss the combined results of all students to illustrate important concepts as probability distribution, precision and reproducibility, thus increasing the value of the exercise.
- Even more emphasis than before on the students own preparations before the excerises.
- With fever laboratory exercise we can now align them correctly with the rest of the course. No students will have to take a lab long before or after it has been treated in the lessons and lectures.
- This also means that each lab is given during a relatively short period of time and the PhD-students running the lab will have to work very hard for three weeks, but can then get on with his or her research. We thus avoid having their time cut up into pieces during 8-9 weeks.
- We will re-introduce bound laboratory notebooks that have to be countersigned by the laboratory supervisor after each session.

Individual and group assignments

There are be both individual and group assignments; several of these giving credit in both mathematics and chemistry.

IT

IT isl be used all along the course for distributing information, teacher presentations, student input and ouput from laboratory excercises. The students can view their "learning portfolio" status and bonus points. Web presentations will be used for some group work etc. Some reports to be submitted in electronic form. Automaticaly corrected tests taken in computer studios for appropriate moments.

Assessment

One of the initial thoughts with this course was to change the assessment, and make it more varied. With small courses there is almost no replacement for a final exam, while we in a larger course can do many things on the way. Before the final exam we thus want the student to build up a learning portfolio containing the following elements:

- Safety regulations and good laboratory practice.
- Chemical vocabulary including the elements and names of common chemicals.
- Written communication skills.
- Oral communication skills.
- Elementary handling of most mathematical relations encountered.
- Numerical solutions and mathematical model building for selected cases.
- Concepts of chemical bonding.
- Basic understanding of thermodynamics.
- Basic concepts of biochemistry, organic, inorganic and analytical chemistry.

This continuous assessment consist of:

- Written tests. Necessary for safety regulations and chemical vocabulary. The latter one is actually also a kind of safety test. Convenient in a few other cases (fast correction of exams, almost complete correlation between course goal and correct answer).
- Oral test. Chemical bonding is much better tested this way than by written exams.
- Failure of any of these means retrial in a few days until a satisfactory result has been obtained. None of these are "tentor" directly corresponding to a number of credit points and repeated three times a year (another gain from the course format).
- Individual reports (written/oral) on projects/assignments.
- Group reports (written/oral) on projects/assignments.
- Individual hand-in exercises.
- The following of good laboratory practices will be surveyed by the lab supervisors.

Each achievement is graded and if it significantly exceeds the basic level, i.e. grading "very good", the student will be given a certain number of extra bonus points. These points will later be added to his/her result on the final examination, thus making it easier to "pass" or get a good grade. There will also be a limit on the number of points that can be used to get a "pass". Over this level, extra points will just elevate your grade.

The final grade of the course will be determined solely by the final (open book) exam result, but this in turn will be greatly influenced on the number of bonus points in the students learning portfolio. The final exam is worth 3 credits.

The bonus points can be kept during the entire academic year, thus they will also be added to the exam result in the Easter period and the summer period.

We hope that this system will:

- Make the students work hard during the course. Everything they do will not only tick of an item in the compulsory assignment list but could also help them pass the final exam.
- Encourage the good students to achieve more.

Work during the implementation of the course

The teachers met regularly for lunch on Fridays. Five meetings was held by the teachers with the class representatives, and representatives from the student unions committees on Chemical Engineering, Chemical Engineering with Physics and Biotechnology.

We planned to have a pedagogical expert visiting lectures and lessons during the course, but this was not possible due to a Chalmers reorganisation of the pedagogical support group.

Maintaining the course

A very serious issue is how to maintain the enthusiasm of the teachers and keep them from being over-worked. It will be essential that the heavy teaching is restricted to three years in a row

It is desirable that we somehow can make the staff feel that to be asked to teach in this course is a proof of competence, both for permanent staff and PhD-students.

Other quality issues

As pointed out in the introduction, there is more to quality in higher education than just the learning outcome of a specific course. In addition to what has been mentioned above I would like to add:

- The teachers gain in knowledge of materials, teaching and assessment methods used by the different disciplines.
- The possiblity to indentify and help students with special problems.
- The possiblity to have longt-term project work (Sept-March).