

Catalysts, mediators in chemistry



>>> Philippe KALCK, professor at the Toulouse National Polytechnic Institute. Director of the Catalyse et Chimie Fine team at the CNRS Coordination Chemistry Laboratory, associated with UPS.

Chemistry in Toulouse is renowned for its expertise in catalysis, a process that allows for faster chemical reaction rates.

Producing reaction products using less energy than through direct heating of reactants, that is the promise offered by catalysis according to its classical definition. More interestingly today, small amounts of catalysts are introduced into the reaction medium, not only to facilitate a reaction, but also to favour a given pathway. Homogeneous catalysis involves transition-metal complexes in which a metal atom is surrounded by ancillary ligands and the reactants. Usually, noble metals, like rhodium, ruthenium, palladium, iridium or platinum, are involved in what is called coordination catalysis. In the homogeneous process, coordination chemistry is a powerful tool for understanding the subtle interactions that occur between the metal centre and the reactants at each step. It thus allows researchers to introduce appropriate modifications in the catalytic system, so that the selectivity required by modern chemistry can be reached.

Expertise at Toulouse

More than a century ago, Paul Sabatier discovered heterogeneous catalysis and provided the first rational explanations. His work, which was awarded the Nobel Prize in 1912, made Toulouse famous in this field, although our university is now also renowned for homogeneous catalysis as well as enzyme catalysis carried out by our colleagues at INSA. Within Paul Sabatier University, and in association with the Institut National Polytechnique, the Toulouse Molecular Chemistry Federation has developed a very active policy for cooperative research in various areas, among them catalysis.

Several teams are directly involved in catalysis and in collaborations with industry to design novel outstanding systems. These teams include the CNRS Coordination Chemistry Laboratory and the Fundamental and Applied Heterochemistry Laboratory. More than

70 researchers are involved in this field and contribute to Toulouse's outstanding reputation in homogeneous catalysis.

Sustainable development

The following six articles illustrate several methodologies that Toulouse has recently developed. They represent our research in this field and also show that highly efficient reactions can be designed. They allow a sophisticated level of selectivity so that only the desired product – be it for pharmaceutical, material or chemical intermediates – is obtained at the lowest energy cost with no loss of starting material. Thus, chemistry can be used for sustainable development – an important issue today.

The word catalysis has largely exceeded the concept originally outlined by Paul Sabatier because it has also entered our everyday language. For example, a diplomatic person may sometimes be called a “catalyst”. According to the classic definition he should remain unchanged after his interventions but no doubt he may also improve and even be acknowledged for his talent.

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Note: All photos in the catalysis section are courtesy of Cyril Fréssillon



>>> The mass spectrometer at the scientific and technical platform

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>>> The magnetic resonance instrument at the scientific and technical platform

The Chemistry Federation

The Toulouse Molecular Chemistry Federation is organized thus:

- > Coordination Chemistry
(LCC, CNRS lab associated with UPS, director **Bruno Chaudret**).
- > Molecular Chemistry and Nanoscience at the Centre for Material Elaboration and Structural Studies
(CEMES, CNRS lab associated with UPS, team leader: **André Gourdon**)
- > Synthesis and Physical Chemistry of Molecules with Biological Interest
(SPCMIB, joint UPS/CNRS lab, director: **Michel Baltas**).
- > Fundamental and Applied Heterochemistry
(HFA, joint UPS/CNRS lab, director: **Antoine Baceiredo**)
- > Molecular Interactions and Chemical and Photochemical Reactivity
(IMRCP, joint UPS/CNRS lab, director: **Monique Mauzac**).
- > Pharmacology of Natural Substances and Redox Pharmacophores
(Joint UPS/IRD lab, director: **Françoise Nepveu**).

The federation consists of a scientific and technical platform that regroups 20 joint departments that work together for the scientific community as whole. It regroups 300 permanent staff and 200 temporary staff (PhD students, post-doctorats, short-term contracts and interns).

The director is **Philippe Kalck** and deputy director is **Antoine Baceiredo**.

When a catalyst is too “lazy”, adding another one can help

Making acetic acid, a basic chemical compound, is an energy-intensive process, but thanks to a remarkable collaboration between academy and industry, this is not true anymore.

How do we assure the annual world production of 9M t/y of acetic acid needed to manufacture artificial fibres or for use as a solvent? An industrial process that satisfies the criteria of easy accessibility to raw materials at a cheap price, and that presents a high selectivity, was discovered and developed in the early 1970s by the American Monsanto company. It is based on rhodium homogeneous catalysis in the presence of an iodide promoter and uses two cheap (300 €/t) building blocks, carbon monoxide and methanol, to produce acetic acid. The reaction selectivity is very high since it reaches 99.5% with respect to methanol, but the selectivity regarding CO is only 90% since part of the CO reacts with water present in the medium to give hydrogen and carbon dioxide through the water-gas-shift reaction. However, to prevent catalyst deactivation, a water content of 14% in the medium must be maintained during catalysis. But, using such large quantities of water introduces a costly distillation step to remove water from the acid, since the latter needs to be sold as anhydrous.

Pilot micro-unit

Very early on, researchers from Monsanto noticed that iridium gave similar results to rhodium. However, if the water content was reduced to 5%, the kinetics of the reaction were very slow.

Thanks to a detailed spectroscopic study of the catalytic cycle, based on high-pressure NMR experiments in the presence of labelled compounds (^{13}CO , $^{13}\text{CH}_3\text{I}$), and to infrared observations under pressure, we were able to obtain a realistic view of the rate determining step of the reaction, and realised that adding a second metal, platinum, could help "unlock" the system. This discovery was patented in 1998 as part of a collaboration with Acetex, a company that owns a large capacity plant near Lacq, close to Pau. This patent has now been extended to many countries. A technological research team worked on this subject from 1999-2002, and we built a pilot micro-unit to study the pre-development phase of the [Ir-Pt] catalytic system. For long-term runs, the kinetics of the reaction is 20% higher than that obtained with rhodium, the selectivity with respect to methanol and acetic acid reaches 99% and the water content can be as low as 5%. Globally, the high rate and the easier removal of water from acetic acid by distillation allows us to save 30% in energy costs!

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>>> Pilot micro-unit of methanol carbonylation to acetic acid.



>>> Philippe SERP, professor at INP, Philippe Kalck, professor at INP and Carole Le Berre, research engineer at INP, members of the catalyse et chimie fine team at the CNRS Coordination Chemistry Laboratory, associated with UPS.

Asymmetric Catalysts

Without being aware of it, snails are chiral...



>>> Martine URRUTIGOÏTY, assistant professor at INP, Eric MANOURY, CNRS scientist and Maryse GOUYGOU, assistant professor at UPS, at the LCC (CNRS laboratory, associated with the UPS)

You would think that there would be equal numbers of right-handed helicoidal snail shells as left-handed ones but in fact, this is not the case: only one snail in 1000 has a left-handed shell. Both kinds of helices are symmetrical but not superimposable and are therefore chiral, like most bioactive molecules found in nature.

Chiral molecules often possess an asymmetrical carbon, leading to two spatial configurations, called right and left-handed. These two molecules, almost identical but chiral, are called enantiomers.

Very often, only one of the two enantiomers has pharmacological activity while the other enantiomer is toxic or, at best, inactive. This is because the spatial geometry of the four substituents around the asymmetrical carbon leads to only one configuration being recognized by the active site of a target biological macromolecule.

Chiral molecules are synthesized to make drugs, but also for food additives, agrochemicals or fragrances. In the drug industry, for instance, 80% of molecules now in clinical or preclinical development, are chiral. A major challenge for organic synthesis is to develop efficient processes to produce chiral molecules with good yields and selectivities. Furthermore, these processes have to be economically viable and environment-friendly. In this context, the concept of "atom economy" is crucial, and asymmetric or enantioselective catalysis is a major challenge for "green chemistry". Asymmetric catalysis allows a small amount of catalyst bearing a chiral auxiliary to produce a large amount of product as a single enantiomer (only the right-handed shells for the example of snails) starting from non-chiral materials.

This type of process is more productive and consumes less reagent, often making it superior to other techniques.

Asymmetric catalysis has been relevant for industry since 1975 to prepare (L)-dopa (an amino acid used for treating Parkinson's disease) via a hydrogenation reaction developed by Nobel Prize winner William S. Knowles of Monsanto Company.

Another important example is (-)-menthol, which possesses 3 asymmetric carbons, which means 8 stereoisomers. Only one of these stereoisomers has the refreshing taste and special flavour of mint. Half the world's production (1500t/year) of this chemical is obtained by an asymmetric isomerization reaction designed by the Nobel Prize winner Ryoji Noyori and developed by the Japanese company Takasago. It is up to 99% pure.

Through a collaboration with Holis Technologies, a start-up company at Toulouse, we are interested in the asymmetric hydrogenation of enamines and imines to synthesize chiral amines, which are important chemical intermediates in the drugs industry.

We are also studying asymmetric carbonylation reactions catalyzed by transition metals because they are excellent for obtaining enantiomerically pure intermediates to synthesize drugs or agrochemicals. Carbonylation reactions allow us to introduce one additional carbon using the cheap (300 euros per ton) and easily obtained synton CO. We have chosen to functionalize monoterpenes which are natural products obtained from plants. However, existing catalysts do not produce expected reaction rates and selectivities. In the field of asymmetric catalysis, the role of the chiral auxiliary (1) is important because it is rather like an orchestra conductor, giving instructions ("to the right or to the left") during chemical transformations. This is why we are involved in the design and synthesis of new chiral auxiliaries for specific catalytic transformations like other teams at LCC.

(1) Chiral auxiliary: chiral molecule used in asymmetric synthesis to control the construction of a new chiral unit.

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>>> The two snails are mirror images of each other.

“Sigma” complexes: New tools for catalysis

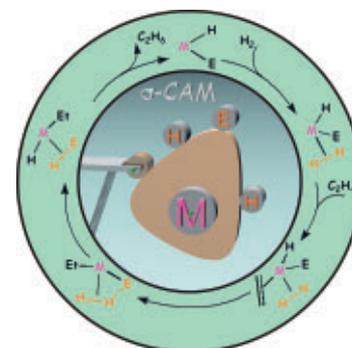
Step-by-step catalysis with low energy cost, this is the promise of “sigma complexes”

A reaction catalyzed by a complex with a metal M yields new products via a series of simple chemical reactions. These catalysts are often organometallic complexes made of a central metal stabilized by different organic or inorganic building blocks, called ligands. Our research team is interested in a particular type of organometallic complex, the ruthenium “sigma” complex and its applications in homogeneous catalysis that respect “green chemistry”.

Coordination without disconnection

Three families of “sigma” complexes are now known. They result from the coordination of either a dihydrogen molecule H_2 , a silane ($HSiR_3$), or a borane (HBR_2) with a metallic centre. The key to this type of coordination is that it occurs without H-H, H-Si, or H-B bond breaking. The hydrogenation reaction, which allows the synthesis of many products that we use on a daily basis, is without a doubt one of the most important industrialized chemical process. During catalysis, the organometallic precursor undergoes a series of transformations, one of which is “oxidative addition”. This key step consists of breaking the H-H bond of the dihydrogen in order to form two M-H bonds. It is at this specific stage of the process that the “sigma” complexes play a crucial role.

Because the intermediates are stable, it is possible to go from one species to another (the dihydride complex) by very gradually tuning the stability of the bonding modes during the reaction. When we face more complex functionalizations, such as in the case of silanes and boranes, it is possible to go through the same type of catalytic process via the formation of a series of “sigma” complexes that lower the energy cost. This is the “sigma-CAM”



>>> The “sigma-CAM” mechanism for catalysis.

mechanism that is being developed in our group. Of course, optimizing such catalytic systems requires a better understanding of the mechanistic pathways involved.

Applications in biology

Our research team has obtained exciting results for two types of catalysis: first, hydrogenation and isotopic exchanges (hydrogen/deuterium) can be used to label molecules for biological applications or for analyzing the surface of porous materials. Secondly, the hydrofunctionalization of silicon or boron-containing products can be used to form vinylsilanes or vinylboranes. Vinylsilanes are very important building blocks for applications in organic chemistry and in the domain of silicones, while the vinylboranes are involved in the elaboration of more complex organic building blocks, such as polymers, therapeutic molecules, or sugar receptors. One of the main problems with this type of chemistry is that the sigma complexes are sensitive to oxygen. It is therefore essential to work under an inert atmosphere (argon), which requires specific equipment like a glove box. Reactions under high gas pressure are performed in reactors and the organometallic complexes are characterized by techniques such as NMR (Nuclear Magnetic Resonance), X-ray crystallography or neutron diffraction and gas chromatography.

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>>> A glove box for handling “sigma” complexes.

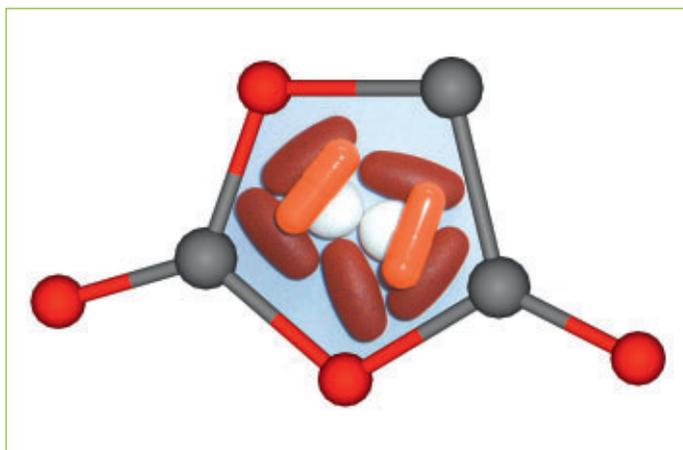
“Green” Catalysis for Life Sciences

Organocatalytic polymerization is environmentally friendly and opens up various perspectives for life sciences.



>>> Didier BOURISSOU, CNRS senior scientist, and Blanca MARTIN-VACA, Assistant Professor at UPS, both researchers in the Biofunctional Ligands and Biodegradable Polymers team at the Fundamental and Applied Heterochemistry Laboratory (LHFA, joint UPS/CNRS laboratory)

Polymer applications are varied, from commodity to specialty materials. Polymers are macromolecules resulting from the covalent linking of “repetitive units” called monomers and polymerization is the process of progressively reacting the monomer molecules together. The structure of the resulting polymers must be precisely controlled to obtain the desired properties. In this context, polymerization must involve highly efficient and selective transformations to avoid harsh reaction conditions, long reaction times and thus the formation of complex mixtures of macromolecules.



>>> Schematic of an “activated” monomer as used for the preparation, via organic or enzymatic catalysis, of biodegradable polymers to be used in drug delivery systems.

Resorbable sutures

Among the various types of polymers, our group has been particularly interested in biodegradable materials over the last decade, and especially in linear polyesters. Thanks to their ability to be assimilated by the human body, these biomaterials are crucial in surgery (resorbable stitches, for example) and pharmacology (drug delivery systems with controlled and prolonged release profiles). In this field, the organocatalytic systems are especially important for avoiding potentially toxic metal residues within the materials. In collaboration with several industrial firms (including Ipsen Pharma, Isochem and Arkema), we have demonstrated that polyesters can be efficiently prepared using very simple organocatalytic systems.

Furthermore, by replacing the standard monomers by activated equivalents, the efficiency of the catalytic polymerisation can be significantly improved. For example, the polymer derived from lactid acid, PLA, usually prepared with a tin catalyst at temperatures as high as 140°C, can be obtained within a few hours at room temperature by polymerizing an “activated” monomer in the presence of a weak organic base as a catalyst. In addition, organocatalytic polymerization can allow functional groups to be introduced along the entire polymer chain, thus allowing the physico-chemical properties of the polymer to be modulated.

With most of these organic systems, the catalytic process involves several weak interactions, and results in the simultaneous activation of both the monomer and growing chain. Such a mode of action is similar to that of enzymes. With activated monomers, the organocatalyst can be replaced by a lipase, so that the biodegradable polymers are produced thanks to a biocatalyst.

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Nanometric catalysts

The main advantages of nanometre-scale catalysts are their small size and a multi-site surface that is ready to interact with the reaction medium. However, we need to perfectly control how these catalysts are produced...



Nanoparticles form the base for nanoscience and nanotechnology and have gone from strength to strength in the last two decades. Nanoparticles, and in particular metallic nanoparticles (metallic aggregates 1-10 nm in size), are also important for making catalysts and the goal is to obtain highly active and selective transition metal nanocatalysts. These new catalysts have a high surface/volume ratio, which means they have a significant number of active sites. For instance, nanoparticles 1.5 nm across possess around 80% of active atoms. Furthermore, nanoparticles display different properties to those observed both for molecular complexes of Angstrom size and for bulk materials. Nanoparticles therefore lie at the border between homogeneous and heterogeneous "classic" catalysts.

To guarantee reproducibility, we need to be able to synthesize nanoparticles whose composition and size can be perfectly controlled. However nanoparticles are not thermodynamically stable and can evolve into bulk metals by agglomeration or molecular complexes by atom loss. Protective agents, like polymers, ligands, surfactants or dendrimers, are therefore crucial for making sure the nanoparticles remain stable.

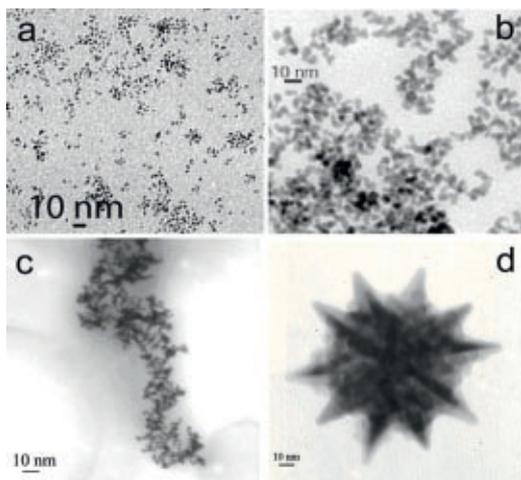
catalytic reactions represents one of our main research areas. Our aim is to design nanoparticles of controlled size, shape and composition that show original catalytic properties, mainly in terms of selectivity.

The catalytic efficiency of these nanocatalysts is evaluated in a number of reactions (including hydrogenation, carbon-carbon coupling and hydroformylation). Their activity and selectivity are compared to those obtained using analogous homogeneous catalytic systems. Thanks to the collaboration between our two laboratories (LCC and LHFA), we have already obtained interesting and promising results. For example, we have demonstrated that ligands commonly used in coordination chemistry, like oxazolines, aminoalcohols and phosphines, are also capable of stabilizing nanoclusters. Specifically, excellent kinetic resolution has been achieved for the allylic alkylation catalyzed by palladium nanoparticles when compared to the corresponding molecular system. An extension of our research concerns preparing nanocatalysts in non-contaminating solvents (ionic liquids and water, for instance) for applications in sustainable chemistry. In particular, ionic liquids can also stabilize nanoparticles, which avoids the use of expensive ligands and volatile organic solvents in some cases. Moreover, immobilizing metallic catalysts in ionic liquids allows for easier recycling than for common solvents.

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Perfect size, shape and composition

We are interested in preparing nanocatalysts in solution from organometallic precursors, which are usually decomposed under an atmosphere of hydrogen and mild temperatures and pressures in the presence of a ligand. In addition to its stabilising role, the ligand can also "tune" the nanocatalyst surface state and therefore its chemical properties and reactivity. The potential poison effect of the ligand must be taken into account too to avoid catalyst deactivation and to obtain the desired reactivity. Adding well-adapted ligands to the nanocatalyst surface (via anchoring centres and flexible structures) bearing appropriate functional groups compatible with the target



>>> a) Ruthenium nanoparticles stabilized by an oxazoline ligand active in hydrogen transfer reactions
b) palladium nanoparticles stabilized by a diphosphite ligand active in allylic alkylation reactions and
c) palladium nanoparticles stabilized in an ionic liquid active in C-C cross-coupling reactions.

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Catalysis without metals: what a challenge!

Organocatalysis offers many advantages. Excluding metallic contaminants is environmentally friendly and makes the systems biocompatible. However, we need to overcome the lack of efficiency compared to organometallic catalysts... The answer: carbene catalysts!

Organocatalysis is one of the most promising approaches to green chemistry. However, the catalytic activity of these catalysts is often inferior to that of organometallic complexes. But, carbenes are the exception.

Carbenes, which comprise a divalent carbon atom with a pair of electrons (singlet carbene), are extremely reactive and, for a long time, were considered to be only short-lived reactive intermediates. However, in 1987, our research group succeeded in synthesizing the first stable carbene. Since then, the chemistry of stable carbenes has developed tremendously.

Bathroom sealants and breast implants

We are now able to synthesize variable stable carbenes with different properties and tune them to explore their unique reactivity as organocatalysts, particularly in the polymerization of silicones. Carbenes have remarkable physical properties (including high thermal stability) and are biocompatible too. Applications range from bathroom sealants and breast implant material to coatings for rockets such as Ariane V.

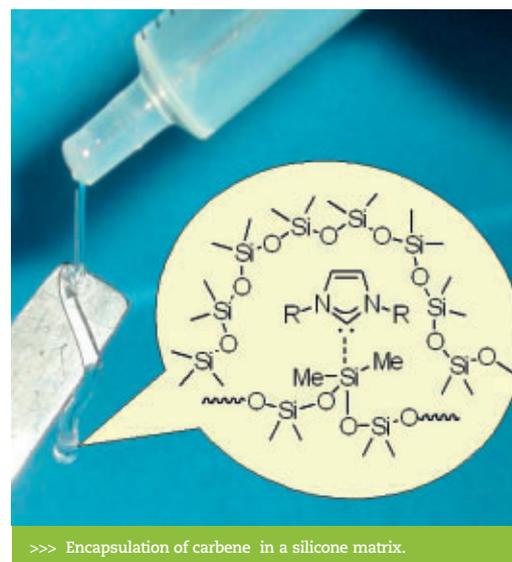
In collaboration with international industry (Rhodia, Bluestar and MAP), we have demonstrated that the N-heterocyclic carbenes (NHCs) are very efficient catalysts for silicone synthesis. Indeed, they are active catalysts for the ring-opening polymerization (ROP) of cyclic monomers such as D4 (the carbene acts as nucleophile), and the polycondensation of dihydroxyoligosiloxane with the elimination of water (the carbene behaves as an organic base).

High purity

In contrast to classical synthetic methods using ionic strong bases and high temperatures, our polymerization system is neutral and efficient at relatively low temperatures. The catalytic system can be deactivated simply by heating the resulting polymers, which avoids the complicated neutralization-filtration step. Moreover the silicone polymers obtained are remarkably clean.

In addition, silicone derivatives are an efficient protective medium for moisture-sensitive N-heterocyclic carbenes. The weak carbene-silicon interaction stabilizes these highly reactive species and allows us to handle them in air without any special precautions. The NHCs in silicone also behave as free reactive carbene in organic solvents, which can be thought of as a new type of encapsulation of carbene in silicone matrices that does not affect the high reactivity of these materials. The discovery that carbenes are compatible with water could also expand the scope of carbene organocatalysts for new catalytic reactions.

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