

Chemistry Research, a crossroads of knowledge

2011 has been declared the International Year of Chemistry by the United Nations and was an excellent opportunity to demonstrate the latest research in the subject at the University Paul Sabatier in Toulouse. Paul Sabatier, after whom the University was named, received the Nobel Prize for Chemistry in 1912.



>>> Sylviane SABO-ETIENNE, CNRS senior scientist at the Laboratoire de chimie de coordination (LCC, CNRS and UPS) and Antoine BACEIREDO, CNRS senior scientist, head of the ICT and member of the Laboratoire d'Hétérochimie Fondamentale et Appliquée (LHFA, UPS/CNRS)

Chemistry plays a vital role in our lives and in almost all industrial and economic sectors and continuing advances in chemistry have led to significant changes in society over the last century. In keeping with the motto "Chemistry - our life, our future", the discipline helps provide appropriate responses to major issues affecting today's society, including: health, nutrition, energy, sustainable development and climate change. For these reasons, chemical research must be inventive, and based on fundamental research at the highest level. The reputation and influence of Toulouse chemists has been rewarded by many national and international awards and three elections to the French Academy of Sciences.

There are 300 permanent staff working in the area of molecular chemistry at Toulouse. The department is linked to the Institute of Chemistry of Toulouse (ICT-<http://ict.ups-tlse.fr>), which includes five chemistry laboratories (LCC LHFA, IMRCP, SPCMIB, PharmaDev) and two physical chemistry teams (CEMES and LPCNO). The ICT shares heavyweight equipment, available to the scientific community of Toulouse and a team of 20 engineers and technicians contribute to the powerful research platform, which provides an efficient support to research teams. The ICT platform is also developing new methodologies to meet the ever demanding needs of researchers.

The scientific teams of the ICT cover virtually all areas of chemistry, ranging from very basic studies to more applied aspects, and research at the interface of physics and biology.

To better understand this research activity, which aims to be at the highest international level, we can highlight four major recent advances:

New concepts, hetero- and organometallic-chemistry.

This research area aims to develop highly reactive molecules, based on original concepts, opening new perspectives in many areas, including synthesis and catalysis.

Supra- and macromolecular chemistry.

This area aims to develop new giant well-defined molecules, self-organization of molecules and polymers that have unique physical and biological properties with important future applications. Interface between chemistry and physics.

This area aims to build new objects (molecules, molecular materials, nanoparticles) and develop their physical properties.

Chemistry for health.

This area aims to synthesize new biologically active molecules and study how they act.

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ICT: Institut de Chimie de Toulouse / Institute of Chemistry of Toulouse

LHFA: Laboratoire d'Hétérochimie Fondamentale et Appliquée/Laboratory for fundamental and applied heterochemistry

IMRCP: Laboratoire des Interactions Moléculaires et Réactivité Chimique et Photochimique/ Laboratory of Molecular Interactions and chemical and photochemical reactivity

LSPCMIB: Laboratoire de Synthèse et PhysicoChimie des Molécules d'Intérêt Biologique /Laboratory of Synthesis and Physical Chemistry of Molecules of Biological Interest

PHARMA-DEV: Pharmacochimie et pharmacologie pour le développement/Medicinal Chemistry and Pharmacology Development

CEMES: Centre d'Elaboration de Matériaux et d'Etudes Structurales/ Center for Material Elaboration and Structural Studies

LCC: Laboratoire de Chimie de Coordination/ Coordination Chemistry laboratory

LPCNO: Laboratoire de Physique et Chimie des Nano-objets/ Laboratory of Physics and Chemistry of Nano-Objects



>>> The team in charge of the ICT platform

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The Interface with Physics



>>> Azzedine BOUSSEKSOU, CNRS senior scientist at the Laboratoire de chimie de coordination (LCC, joint CNRS/UPS lab)

For several years, research at the interface between chemistry and physics has advanced dramatically: molecular magnets, conduction and molecular bistability are new areas, to name but a few. The materials developed in the Toulouse laboratories have already led to more than fifty patents, showing that chemistry in Toulouse can lead to a wide range of applications for society.

The convergence of chemistry and physics has spawned a multitude of functional molecular assemblies including single molecule commutation. Researchers at CEMES have demonstrated for the first time a reversible conformational change between two stable states of a copper complex adsorbed onto a Cu(111)/NaCl surface, induced by a tunnel bias. The molecular bistability in these systems stems from the rearrangement of the coordination sphere surrounding the metallic ion induced by the storage of a single charge. This system can be considered as a new single molecule electro-mechanic actuator.

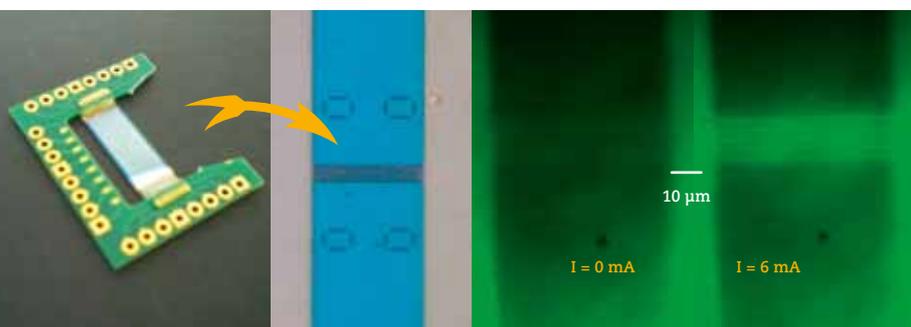
Materials with variable porosity

A second research area concerns the related fields of molecular magnetism and coordination chemistry. Porous, supramolecular magnets are being constructed at the LCC. The characteristic properties (critical temperature, coercive field) of these three dimensional architectures can be significantly modified by adsorption of guest molecules in the network. This approach to assembling molecular building blocks has also been applied to the synthesis of supramolecular or fluorescent materials with variable degrees of porosity.

The specificity of organometallic chemistry allows for a high level of synthetic control over the morphology of nanoparticles (Nps). As a consequence, preparations of such Nps in powder or colloidal suspension may be integrated into devices for a variety of applications. Thanks to the development of impeccably controlled syntheses, it is now possible to modulate the physical properties of Nps, for example by modifying their surface chemistry. This rewarding collaboration between chemistry and physics enabled the use of these Nps in various domains, including varistance, gas sensing, integrated induction, microelectronics and magnetic information storage. There is also great potential for these materials in biological applications such as MRI and biosensing.

Fully Molecular Devices

Electric transport of conducting and molecular wires is an emerging area of research, and one in which the laboratories of Toulouse are very active. The ultimate goal is to produce "all molecular" devices. Thus, following the discovery of molecular supraconductivity a few years ago at the LCC, researchers are today interested in the development of thin films or Nps based on molecular conductors/supraconductors. Recently this aim has culminated in a spectacular result: the observation of a superconductive transition in thin films, previously only observed in single crystals. Furthermore, the Nps of these conductors are currently employed in the development of composite materials with applications in the electromagnetic protection of satellites. Finally, a novel approach for thermal imaging by micro- and nano-thermometry based on spin crossover molecular materials has been recently developed and patented. The concept is grounded in the design of hybrid materials that combine optical bistability and fluorescence. This approach has led to the creation of micro- and nanometric hot spot cartographic devices with high spatial resolution, opening important avenues for exploitation in microelectronics and biology.



>>> Electronic device including nickel microwires covered by fluorescent doped spin crossover Nps before (low spin state) and after (high spin state) the application of a bias of 6mA. Clearly, the fluorescence intensity of the fluorophore is modulated by the spin state of the material.

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Chemistry and Health



>>> Michel BALTAS, CNRS senior scientist, head of the Laboratory of Synthesis and Physical Chemistry of Molecules of Biological Interest (LSPCMIB, joint UPS/ CNRS lab)

The development of new molecules of biological interest is one of the main scientific strengths of the Institute of Chemistry research programs at Toulouse. Both natural and synthetic molecules are being developed for applications in medicine, diagnostic imaging and bioanalysis. This research is based on strong and diverse skills, ranging from synthetic organic chemistry to mechanistic studies, basic methods of bioinformation technology and bioimaging and analysis.

Natural products and synthetic molecules

The PNASM LSPCMIB team has designed original molecules inspired by natural cinnamoyl derivatives of phytochemical origin. The designed molecules were found to be active in the field of cardiovascular diseases and tuberculosis. The proper functionalization of the molecules was carried out through reactions that are compatible with automation as well. The features introduced in these structures give these molecules complementary *in vivo* properties (cytoprotection, carbonyl scavenger function), which place them among the most active of all known compounds against the formation of thrombotic plaques. The team also showed that other original chemical series can also be synthesized (via reactions compatible with automation) from cinnamic acid showing strong anti-tuberculosis activity, particularly against resistant strains.

The “Metals in Biology and Medicinal Chemistry” team of the LCC has developed new inhibitors of *Mycobacterium tuberculosis* InhA, based on the core of the active metabolite of isoniazid, a major anti-TB drug (CNRS-UPS patent pending). The team also prepared promising compounds able to bind to quadruplex DNA, recently discovered as a target for cancer treatment, and binuclear complexes based on platinum and copper that are capable of producing non-repairable damage on DNA. These molecules are also excellent tools for understanding the mechanisms of cell survival. The work of the “Natural Substances” team at PHARMA-DEV conducted in Guyana on the traditional treatment of malaria has led to the isolation of a molecule that is active at all stages of the cycle of the malaria parasite (*Plasmodium*), something that has rarely been observed. The “Redstress” team at PHARMA DEV has discovered the indolones-N-oxide (radical scavengers) family of compounds that are active *in vitro* and *in vivo* against the parasite that causes malaria.

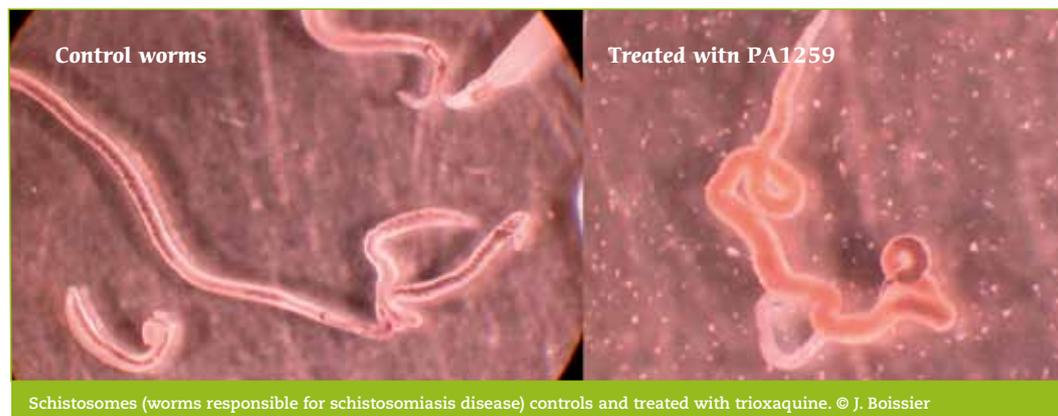
Mechanistic Studies

The PEP team of the IMRCP Laboratory is conducting research into the mechanisms of photosensitivity of biological targets through new sensitizers and photoactivatable probes for better therapeutic strategies. The team found that dihydropterines very efficiently trap singlet oxygen by being oxidized to pterins, compounds involved in important biological functions (immune responses) and diseases (depigmentation of the skin and sensitivity to UV radiation). In addition, the team identified the mechanisms by which complex polypyridyl ruthenium(II) compounds alter their reactivity with DNA in the presence of some proteins involved in cellular regulation. The “Chemical Biology” team at LCC has recently shown significant differences in binding copper(II) on human beta-amyloid peptide (directly linked to Alzheimer’s disease) and in mice, where the disease does not exist. Teams from LSPCMIB, as well as LCC PHARMA-DEV, have several research programs studying the mechanisms of action of natural and synthetic biologically active compounds, particularly those with antitumor, antiatherogenic, antituberculosis and antimalarial activity. Finally, the “Metals in Biology and Medicinal Chemistry” team of the LCC has discovered new trioxaquinones that are active against schistosomes parasitic worms. The action of these chemicals on the parasite hemozoin was confirmed by microscopy (photographs).

Diagnostic imaging, bio analysis

The “SOMAB” team in LSPCMIB (chemical, biological and medical imaging), has developed new molecules capable of complexing transition metals (Tc, Re), lanthanide ions (Gd, Eu, Tb, Yb), or related ions (In, Y). These metal complexes exhibit high stability in biological media, making them particularly interesting for applications in optical imaging, MRI or radionuclear imaging. In addition, the team has developed original

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organic architectures where two different metals (Tc/Re, Gd/Re ...) can be complexed in a single structure, thereby leading to bimodal organometallic probes. These systems are useful for two distinct imaging modes (for example, Tc-99m/scintigraphy and Re/optical imaging) and can combine the advantages of each of the two techniques in terms of sensitivity and resolution for in vitro and in vivo use. Using micro- and nano-technology techniques, the Redstress PHARMA-DEV team has developed an integrated microfluidic device (lab on a chip) to work on very small sample volumes and integrate complex processes leading to portable systems for bioanalysis (sorting, counting cell subpopulations as markers of early disease). Finally, the "Nanostructures and Organometallic Chemistry" team at LCC and the "Sensors and Biosensors" team at LGC (Laboratory of Chemical Engineering) have designed new interfaces modified with electroactive nanoparticles as biomarkers of oxidative stress, with better properties in terms of sensitivity and selectivity.

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New Concepts, Main-Group and Organometallic Chemistry

The Toulouse site is extremely active in Main-Group and Organometallic Chemistry. The groups working in these two areas have a unique expertise in the design of highly reactive molecules and the establishment of new concepts, both leading to a wide variety of applications in synthesis, catalysis, materials, life sciences...

The various topics developed at the ICT and more particularly in the two laboratories, LHFA and LCC, are spread over four areas:

- 1) New concepts: highly reactive molecules (carbenes, ylides, low-valence main-group elements...) and new bonding modes (non classical metal/ligand interactions).
- 2) Activation of small molecules with some key targets: hydrogen, methane, carbon dioxide.
- 3) Catalysis: challenging reactions of industrial relevance such as hydroamination, methanol carbonylation, C-C bond formation via C-H activation, selective silylation and borylation, enantioselective catalysis, non conventional media (water, ionic liquids) and mild conditions.
- 4) Mechanistic investigation: to gain a better knowledge of any elementary step of a catalytic cycle, to characterize key intermediates, to determine kinetics and thermodynamics, to control and optimize selectivity and activity.

This research can only be performed thanks to the excellent ICT technical platform. Moreover a strong synergy between experimentalists and theoreticians is helping to rationalize the results and predict some new key targets.

Ylides and Main group elements: Stabilization of species bearing formal charges, and applications in synthesis

Phosponium sila-ylides: the heavier congeners of Wittig reagents have been recently synthesized for the first time. They are highly reactive species exhibiting behavior similar to transition metal complexes, opening new perspectives in catalysis.

Low valent compounds: extremely active pi-systems

Compounds featuring cumulated P=C and Ge=C double bonds : a phospho-germa-allene. The presence of the main-group elements induces peculiar reactivity. Instead of the common 1,2-addition reactions, a 1,3-dipole behavior has been seen for acetylenic



>>> Pressure NMR tube (NMR = Nuclear Magnetic Resonance) for in situ monitoring of the catalyzed hydrogenation of benzonitrile.

derivatives. Upon [3+2] cycloaddition, a cyclic phospho-germa-carbene is obtained. This derivative, which appears as a heavier analog of the carbenes isolated so far, has original properties.

Truly odd metal / ligand interactions: coordination of Lewis acids

While transition metals normally tend to surround themselves with electron-donating ligands, Lewis acids, archetypal electron-deficient moieties, have been shown to also behave as ligands to form coordination complexes. This umpolung (polarity reversing) behavior involves unprecedented interactions between the metals and the main-group elements (boron, gallium, silicon...) and leads to original geometric and electronic properties.

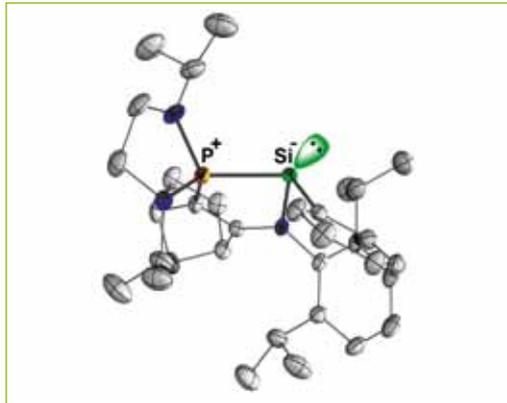
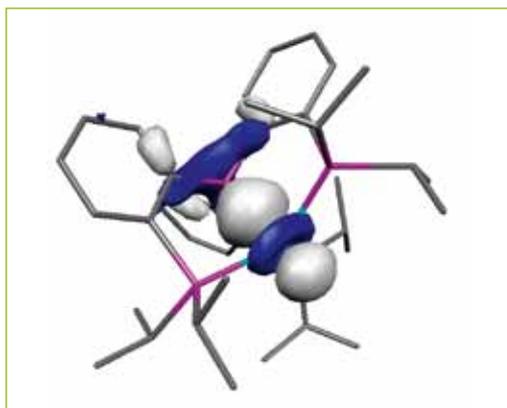
Hydrogen in catalysis and energy

Paul Sabatier, the father of the catalyzed hydrogenation process, received the Nobel Prize of Chemistry in 1912 and gave his name to the Faculty of Science, now belonging to the University of Toulouse. Almost 100 years later, hydrogen is still attracting a lot of interest in two main fields: catalysis and energy.

Two recent achievements at LCC illustrate this domain: Nylon synthesis is one of the most important industrial

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processes. As a key step, it involves hydrogenation of a nitrile function. Mechanistic investigation on a model substrate, benzonitrile, allowed us to develop a process that operates under mild conditions (room temperature and low pressure of H_2). The catalyst precursor is a sigma ruthenium complex which is able to coordinate dihydrogen in a reversible manner. The second example deals with the use of hydrogen as an energy carrier. Can we consider hydrogen as “the fuel of the future”? Again, sigma ruthenium complexes play a key role: ammonia borane (H_3NBH_3), an attractive molecule to produce H_2 , can be dehydrogenated, and for the first time, aminoborane (H_2NBH_2), a very elusive compound, has been trapped and clearly identified as a key elementary step in the dehydrogenation process.



>>> Bottom: X-ray diffraction structure of a phosphonium sila-ylide.
Top: Molecular orbital involved in the coordination of a Lewis Acid to a transition metal.

Methane functionalization

Methane is the main component of natural gas. A real breakthrough would be to functionalize this abundant molecule instead of burning it or just producing H_2 . The C-H bonds of alkanes, and particularly of methane, are strong and difficult to activate. In the frame of an ERA chemistry program, the first catalyzed functionalization of methane into esters was performed under very mild conditions. The catalyst is a silver complex decorated with a highly fluorinated ligand, which makes it very reactive and soluble in supercritical CO_2 , a crucial solvent for this reaction. It is a remarkable reaction whose mechanistic as well as selectivity properties are currently being investigated at LCC.

Hydroamination and atom-economy

The intermolecular hydroamination of non-activated olefins is another great scientific and economical challenge tackled by the chemists at Toulouse. It is an atom economical transformation (no by-product, no waste) to obtain amines, important industrial intermediates for the production of a vast array of consumer products. An efficient catalysis of this process by platinum complexes has been discovered and the detailed investigation of the catalytic mechanism will help us improve it.

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Supramolecular systems



>>> Monique MAUZAC, CNRS senior scientist, head of the Laboratoire des Interactions Moléculaires et Réactivité Chimique et Photochimique (IMRCP, UPS/CNRS). Montserrat GÓMEZ, professor at UPS, SYMAC team member at the Laboratoire Hétérochimie Fondamentale et Appliquée (LHFA, UPS/CNRS)

Making larger structures via low or high energy interactions, leads to a wide diversity of chemical systems or nanomaterials with various applications. Toulouse researchers are involved in several projects concerning chemistry at the nano- and micro-meter scales, that is, in the conception and study of chemical objects that are larger than a single molecule. As such, it has been recognized as a European research training site.

Carbon nanotubes and metallic nanoparticles

The molecular approach developed at LCC allows us to modulate the size and shape of metallic nanoparticles (MNP). These nanometric materials have applications in different fields, in particular catalysis. LCC and LHFA have made efficient nanocatalysts for hydrogenation (Pt) and C-C coupling (Pd) reactions. Indeed, the preparation of composite nanomaterials comprising metallic oxide nanoparticles in a silica matrix (by LCC), has led to the development of catalytic filters for gas sensors.

The complementary skills of these two labs have led to new catalytic systems assembling metallic nanoparticles and multiwall carbon nanotubes (MWCNT) exhibiting original catalytic properties. The pre-development for the production of these MWCNT has been developed at the LCC, in collaboration with Arkema and LGC. Tuning the surface chemistry of MWCNTs allows us to selectively introduce MNP into the inner cavities of MWCNTs or fix MNP on the MWCNT surface, leading to different catalytic behaviors. Selective and efficient catalysts have also been obtained by supporting catalytic ionic liquid phases on functionalized MWCNT. With regard to other areas, the SPCMIB lab in collaboration with CIRIMAT has developed the functionalization of double-wall carbon nanotubes (DWCNT) for biomedical applications (imagery, vectorization, implants for tissue engineering).

Supramolecular chemistry, ionic liquids

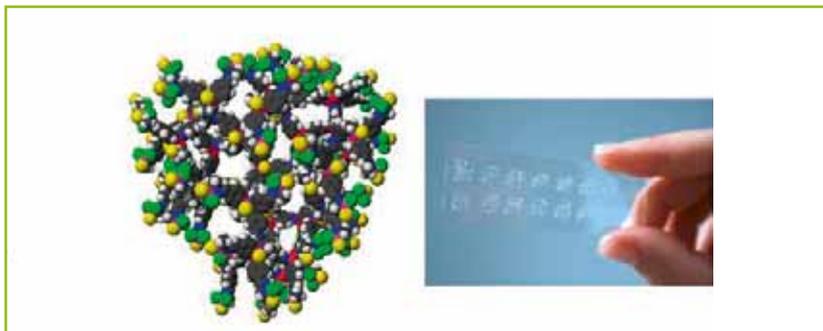
Supramolecular self-assemblies in which molecules interact with each other via low energy interactions are largely studied in the IMRCP laboratory, for example to develop "green" bioactive formulations. A key step in the development of a drug from an active ingredient is in fact the choice of the best formulation. A new concept was established by implementing so-called bioactive formulations, based on supramolecular self-organization in which the active ingredient is an amphiphile that reduces the number of ingredients in the final product. At the same time, specific therapeutic activity is achieved, thanks to the nature of the supramolecular self-assemblies formed, such

as micelles. Several products have been developed, especially from active amphiphilic molecules derived from rhamnose. One of them, easily obtained from renewable resources (seeds from Brazil) and marketed by Pierre Fabre as Selectiose®, can successfully treat many inflammatory conditions associated with skin allergies such as eczema. A second product, Effectiose® has been recently marketed against acne. Ionic liquids are salts often made up of an organic cation and an inorganic anion, liquids at room temperature and highly organized structurally. They have multiple properties: they are non-volatile, stable at high temperatures, non-flammable, good conductors, recyclable ... and can be used in a vast number of fields. The SPCMIB, IMRCP and LHFA labs are involved in developing and utilizing these new solvents, prepared from renewable sources and sustainable technologies. The labs are interested in new strategies for synthesizing molecules exhibiting biological activity and in auto-assembling molecules or amphiphilic polymers in ionic liquids. These solvents also allow for stable metallic nanocatalysts for applications in organic synthesis (LHFA in collaboration with Solvionic).

Dendrimers, nano-engines, polymers

Dendrimers are branched, perfectly defined and highly functionalized macromolecules. They belong to the family of polymers because of their repetitive structure, but are synthesized layer by layer and not by polymerization. The presence of many terminal chemical functions that are easily accessible gives them unique properties. The LCC team is specialized in the synthesis and study of the properties of phosphorus dendrimers that have very diverse applications, from catalysis to biology/medicine. For detection and diagnosis, dendrimers bring an increased sensitivity, a perfect reproducibility and an excellent stability. The start-up Dendris™ created in 2009 at the Center Pierre Potter of the Cancéropôle of Toulouse, aims to produce "ready to use" diagnosis kits in the fields of health, agriculture and the environment. Moreover, the application of near-field microscopy techniques (CEMES) has allowed the synthesis of

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>>> from a phosphorus-based dendrimer to a Biochip @DENDRIS

molecular-devices such as rotors, motors, memories and logic gates.

In order to replace metal-based catalysts in polymerization processes, carbenes were recently developed and successfully employed as organocatalysts for the synthesis of silicones and polyurethanes.

Following the same trend, sulfonic acids were shown to catalyze the polymerization of cyclic monomers. The resulting biodegradable polymers with a controlled size could be incorporated into more complex macromolecular architectures. All these research projects are backed-up by industrial partners (Rhodia, Arkema, Bluestar Silicones, Map). The RAFT/MADIX controlled radical polymerization process (LHFA, Rhodia funding) is an alternative synthetic strategy that can yield well-defined functional copolymers with controlled architectures. It exploits xanthates as reversible chain transfer agents. Other methods (LCC) based on organometallic chemistry (reversible cleavage of a metal-carbon bond) are suited for the control of "difficult" monomers and help extend the range of available technologies.

Polymers can be considered either as bulk materials or as a matrices for making composites. Inorganic nanoparticles, with controlled geometry and size, can be incorporated in the polymeric medium or formed in situ (IMRCP, LHFA, LCPNO). The obtained materials possess properties that can be modified by light, temperature, solution acidity, magnetic fields ... Materials from a liquid crystalline polymer matrix and cobalt nanoparticles have been synthesized that respond to very low 50 mT magnetic fields at room temperature. Block copolymers (IMRCP, LHFA) were obtained in order to stabilize metal particles or for applications such as photodynamic therapy used for

cancer treatment. Copolymers bearing small DNA parts are also interesting nano-objects with recognition properties that can be used in biochemistry. Lastly, a study by the InNaBioSanté foundation (IMRCP, LAAS), aims at detecting cancerous biomarkers using an electronic device containing an imprinted polymer and a detection process.

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