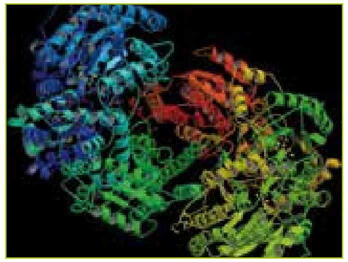
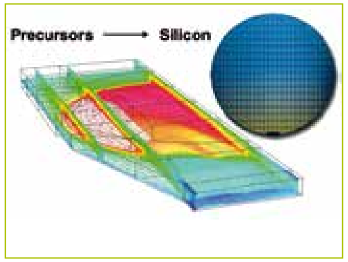
Chair:
Prof. Tiziano Faravelli

DOCTORAL PROGRAM IN INDUSTRIAL CHEMISTRY AND CHEMICAL ENGINEERING

The Doctoral Program in Industrial Chemistry and Chemical Engineering (***CII***) is designed for students aiming to get a deep expertise on chemical processes and on material processing either as the inherent *research* or in the *process design and development* activities.
The program is the ideal extension of the *Laurea Magistrale* degrees in *Chemical Engineering*, *Safety and Prevention Engineering, Materials Science*, *Material Engineering*, *Industrial Chemistry* and *Chemistry*, but it is also open to graduated in other scientific disciplines.
The general topic for the doctoral program in Industrial Chemistry and Chemical Engineering is the application of the chemical and physical knowledge to all the activities related to the synthesis, design, production and transformation of chemical substances and materials (like advanced inorganic, polymers and biomaterials). These studies involve not only the synthesis processes but also the related plants, here analyzed starting from the laboratory tests and the pilot plant experiments up to the industrial size ones, always including the careful evaluation of the related energetic, safety and environmental issues.
The final goal is to provide to the Phd student the tools and the skills: (1) to design and manage industrial processes at any size scales; (2) to develop new technical applications and (3) to create and to characterize new products and services.
The ***CII*** program covers three years for an overall amounts of 180 credits. The responsibility of the organization and of the contents of the doctoral program is attributed to the Professor Committee (PC). At the beginning of the Doctoral program, a tutor and a thesis advisor is assigned to each student. The tutor has a supervisor function during the whole doctoral program, whereas the thesis advisor is responsible for the thesis work.
The PC defines a specific curriculum for each student, on the basis of the tutor suggestions. The curriculum has to be designed in order to both cover deficiencies in the student scientific formation and to give a high-quality technical and scientific preparation.
Since 2001 (XVII cycle) the ***CII*** program graduates more than 100 students, being the 80% now working in industry and the remaining in the university or government research centers. These data demonstrate the great link existing between the performed researches and the industry. In fact, more than 70% of the research topics were directly supported by industrial companies, like ENEL, LPE Epitaxial Technology, Bracco, Flamma, Mapei, Solvay Specialty Polymers.

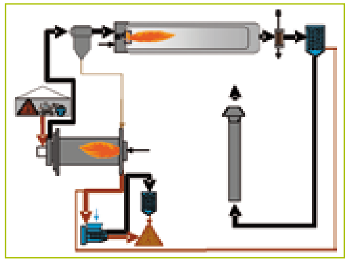


1. Structure simulation of Nitrogenase enzyme for N_2 conversion to NH_3.

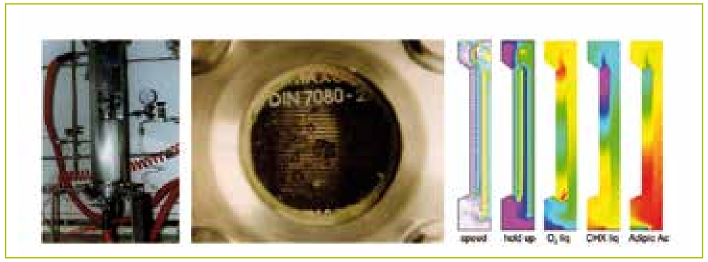


2. Simulation of a chemical vapor deposition reaction for silicon films deposition.

3. Hazardous gas dispersion simulation from an industrial accident.



4. Contaminated soil remediation process.



5. Lab-scale air-lift gas-liquid reactor and simulation of flow field, gas hold up and concentrations of main reactants (cyclohexane oxidation to adipic aci.

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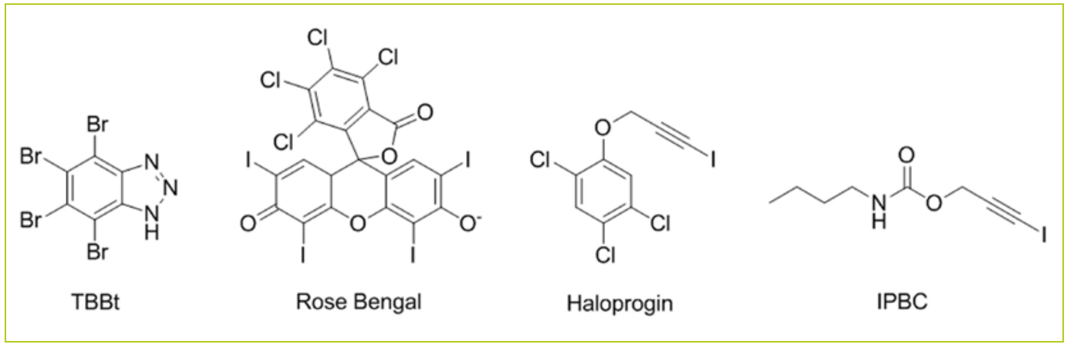
NEW PHARMACEUTICAL COCRYSTALS ASSEMBLED VIA HALOGEN BONDING

Michele Baldrighi - Supervisor: **Pierangelo Metrangolo**



Halogen Bonding (XB) and Pharmaceutical Cocrystals arise from the scientific literature of the last years as two of the most innovative research field in solid state chemistry. The former has proven to be a robust noncovalent interaction, while the latter is the demonstration of the successfully application of Crystal Engineering to the noncovalent modification of APIs physicochemical and biopharmaceutical properties. Although both research fields have been deeply investigated in the years, it was never thought, until now, of using XB in order to synthesize Pharmaceutical Cocrystals by exploiting the presence of XB donors in the APIs. These investigations will allow to add an innovative tool for the improvement of technological and biopharmaceutical properties of this molecules. In these studies four halogenated APIs (**TBBt**, **Rose Bengal**, **Haloprogin** and **IPBC**) have been selected for the presence in their molecular scaffold of XB donor motifs. Cocrystallization experiments involving these APIs were planned using as cocrystal formers (CCFs) model molecules which electronrich moieties were well-recognized Halogen Bonding acceptors. Hot-stage microscopy, DSC, FT-IR and XRPD were used to provide initial information regarding the obtainment of new solid products. In the case of 1-iodoalkynes it was also possible to gather indications about the occurrence of XB in the product by analyzing the position of the FT-IR triple bond stretching band. Crystal structures of products were determined in order to provide evidence of the XB formation and to identify its role in the product. For a particularly interesting case, since it was not possible to obtain single crystals of the product, SSNMR studies were performed in order to prove the occurrence of XB. The contribution of XB was found to be fundamental in every product obtained. The most emblematic case was that of **Haloprogin**, where the use of the classical Hydrogen Bonding (HB) based strategy for the Pharmaceutical Cocrystals synthesis was precluded by the absence of HB donors or reliable acceptors. The presence of the 1-iodoalkyne XB donor was found on the contrary to provide the obtainment different polymorphic forms of this API, and to allow the synthesis of Pharmaceutical Cocystals with both neutral (**BYP**) and ionic (**TBAI**, **TBACl**) CCFs.

Differently from the previous case, in **TBBt** the XB donor was weaker and, moreover, a very strong HB donor was also present. Crystals obtained in this case study were a **Methanol** solvate, a salt with **TMEDA** and a cocrystal with **BYP**. Even if the difference in strength of the two donors was too high to allow the XB donor to provide the interaction with the CCFs, Halogen Bonding was found to play a key role in stabilizing the crystals structure by allowing intermolecular connections between different **TBBt** molecules.

Rose Bengal was found to provide a Halogen Bonded cocrystal with **DABCO-Cl**, in which the occurrence of an acid-base reaction deprotonated all the HB donors in the API, giving a total freedom to the XB donors to interact with the acceptors of both the CCF and the API itself. This crystal structure highlights also the independence of XB from pH, which on the contrary is able to inactivate HB donors.

In **IPBC** cocrystals XB was found to be always responsible for the interaction with the acceptor moiety of the CCFs, while HB was always involved in the formation of the NH···O supramolecular synthon among **IPBC** molecules. Thanks to the orthogonality of the two interaction it was possible to synthesize cocrystals with both the acceptors of neutral (**BYP**, **BYPETH**, **HMBI**) and ionic (TBAI, **$CaCl_2$**) CCFs.

Relevant properties of cocrystals obtained in the **IPBC** case study, the most interesting both for the high number of biopharmaceutical and technological criticalities of this compound (low water solubility, low melting point, poor powder flow properties), and for its high economical importance and widespread use, were also evaluated. The comparison of melting points evidenced that, in almost every case, cocrystals have a higher melting point than **IPBC**, and therefore they are more suitable to be used in technological processes where the solid products are subject to heat. The equilibrium water solubility of cocrystals was also evaluated. Unfortunately data showed that cocrystals were in general showing similar water solubility with respect to that of the pure API. Interestingly **IPBC:$CaCl_2$** was found have a greater water solubility than pure **IPBC**.

Being **IPBC:CaCl2** a very interesting compound, the flow property of the powders were analyzed, in order to see if the cohesiveness problem of **IPBC** can be overcame.

The cocrystal showed a non-cohesive behaviour, with an estimated angle of repose of ≈17°, indicative of a free-flowing powder. **IPBC:CaCl2** cocrystal is therefore a promising substitute for **IPBC** in several industrial applications, since it is characterized by a higher water solubility, a higher melting point and excellent powders flow properties with respect to the original compound.

Resuming, results demonstrate that Halogen Bonding successfully found a role in the synthesis of Pharmaceutical Cocrystals, opening a new world of possibilities to modify the physicochemical and biopharmaceutical properties of an API by means of this previously neglected (in this field) noncovalent interaction. There is still lot of room for the application of Halogen Bonding in the field of Pharmaceutical Cocrystals. The ones here analyzed were only a little portion of the molecules for which the use of this strategy can be applied. A strong contribution will be surely given from Medicinal Chemistry and the Pharmaceutical Industry, whose interest in Halogen Bonding is rapidly rising. The discovery of this application of XB will provide great benefits to new drugs which, thanks to the recent introduction of the rational use of XB donors in dugs R&D processes, will be tailor-made substrates for the use of this interaction in the synthesis of Pharmaceutical Cocrystals.

Legend: **BYP**= 4,4’-bipyridyl; **BYPETH**= 1,2-bis(4-pyridyl) ethane; **DABCO-Cl**= 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium; HMBI= N,N’-hexamethylenebis-isonicotinamide; **IPBC**= 3-iodo-2-propynyl-N-butylcarbamate; **TBACl**=: tetrabutylammonium chloride; **TBAI**= tetrabutylammonium iodide; **TBBt**= 4,5,6,7-tetrabromo-*1H*-benzotriazole; **TMEDA**= N,N,N’,N’-tetramethylethylenedimine.

MOLECULAR MODELING OF TRANSPORT PHENOMENA IN HYDROGELS

Tommaso Casalini - Supervisors: **Carlo Cavallotti, Giuseppe Perale**

This PhD thesis is focused on the molecular modeling of hydrogels, *i.e.* hydrophilic amorphous polymeric matrices, able to retain up to 99% of water in weight terms, nowadays widely used for drug delivery applications, in tissue engineering and regenerative medicine fields. In particular, this work is aimed at understanding and describing the mechanisms which govern transport phenomena that take place in the bulk phase of these materials. The here presented investigation is performed using molecular models, which contain an atomistic detail: this is fundamental in order to achieve an exhaustive overview and a full understanding of solute diffusion in such systems.

Many macroscale mathematical models have been developed in order to compute a solute diffusion coefficient, each based on different theories (free volume, obstruction effects, and so on) aimed at properly describing hydrogel environment. However, the assumptions behind every approach constitute a limit for these models, thus reducing the field where they can be employed. A molecular modeling approach introduces the necessity of an atomistic model of the polymeric matrix, but removes all the assumptions that limit the application of a specific model, hence leading to a wider-ranging approach. Moreover, being molecular diffusion the main mechanism governing the drug release rate both in *in vitro* and *in vivo* environments, it is immediate to discern that such approach can become a complementary and synergic tool for experimental activity. The atomistic detail offered by molecular modeling can help researchers to understand the peculiarities of various materials formulations, thus leading to a smart material design according to various exigencies and also allowing a better and more efficient experimental design.

This thesis work considered the diffusion of sodium fluorescein in hydrogels made of Carbomer 974P (an high molecular weight cross-linked polyacrylic acid) and agarose (a polysaccharide), cross-linked with glycerol and propylene glycol through esterification, performed by means of microwave assisted synthesis approach. Sodium fluorescein was chosen since it possesses a steric hindrance and a molecular weight (376.28 $g\ mol^{-1}$) similar to commonly used drugs. The formulation and the synthesis of agarose – Carbomer hydrogels have been conceived and developed by our research group specifically for tissue engineering purpose. This material was widely characterized in terms of chemical/physical properties and mechanical and release behavior. Moreover, agarose – Carbomer hydrogels have been fruitfully tested in *in vivo* conditions proving to be suitable and promising drug delivery devices for spinal cord injury treatments.

The scientific issue behind this work lies in a counter-intuitive behavior observed during experimental activity, *i.e.* fluorescein self-diffusion enhancement with respect to water solutions, found through HRMAS (high resolution magic angle spinning) NMR (nuclear magnetic resonance) DOSY (diffusion ordered spectroscopy) technique. This self-diffusion coefficient increase has, moreover, a dependence on both hydrogel mesh size and solute concentration.

The methods offered by computational chemistry, and in particular by molecular dynamics simulations, allow computing a theoretical self-diffusion coefficient (through the well-established Einstein equation), which implicitly contains all the effects due to the peculiarity of the environment and the interactions with the other species present in the system, such as water, ions, and other solute molecules. The obtained values can be directly compared with experimental data, while the detail offered by the simulations can suggest some insights about this particular behavior.

The first part of the thesis was aimed at verifying if the chosen computational approach (that is, the adopted force field along with charge derivation protocol) is suitable to describe fluorescein diffusion; this is assessed analyzing fluorescein behavior in water solutions, thus in systems that can be easily described and that are not dramatically different from hydrogel environment, because of their very high water content. In particular, fluorescein behavior is investigated by computing a self-diffusion coefficient and a dimerization free energy, quantities that can be directly compared with experimental data obtained by our research group or available in literature.

The core of this thesis is constituted by the development of a representative molecular model of agarose – Carbomer hydrogel and the study of sodium fluorescein transport phenomena inside the bulk phase of these materials. Molecular trajectories obtained through molecular dynamics simulations do not only allow computing a theoretical self-diffusion coefficient, but also highlighting the main mechanism behind the “curious” self-diffusion enhancement.

Five different models were built, corresponding to five different mesh size values: 7, 9, 12, 14 and 19 nm. These structures were employed in order to investigate the mesh size dependence of fluorescein diffusion in the bulk phase of agarose – Carbomer hydrogels, by means of molecular dynamics simulations, at low solute concentration. Indeed, this situation is more representative of real applications, where low drug concentration are employed.

Computations were able to reproduce the experimental trend of fluorescein diffusion mesh size dependence. The most intuitive reason of diffusion enhancement can be related to the presence of carboxylic moieties in the Carbomer backbone, which lead to repulsive electrostatic interactions with negatively charged fluorescein molecules. The analysis of molecular trajectories, instead, evidenced the formation of fluorescein/matrix complexes. Focusing on Carbomer, the formation of an electrical double layer can be observed: indeed, all ionized carboxylic moieties form a complex with a Na+ or K+ ion, creating a positively charged surface where fluorescein is adsorbed. For what regards agarose, the assessment of hydrogen bonds between fluorescein oxygen atoms and agarose polar hydrogen atoms occurs. Thus, the negative charges which imply the repulsive force are due to fluorescein molecules themselves.

This evidence also contributed to achieve a better understanding of experimental data. Indeed, diffusion coefficient measurement through NMR DOSY is based on the NMR signal attenuation during a pulsed field gradient experiment; the echo attenuation gives information about the molecular motion along the gradient axis that has occurred between two magnetic field gradient pulses. Consequently, the adsorbed molecules do not give a contribution to echo decay, being “fixed” on the matrix, and thus the recorded signal attenuation involves only diffusing molecules.

The experimental diffusion coefficient is then not referred to all the solute molecules present in the system, but only to the fraction that can effectively diffuse through the matrix. This means that, in order to reproduce the experimental data, theoretical diffusion coefficient must be computed averaging only over moving molecules, excluding the adsorbed ones.

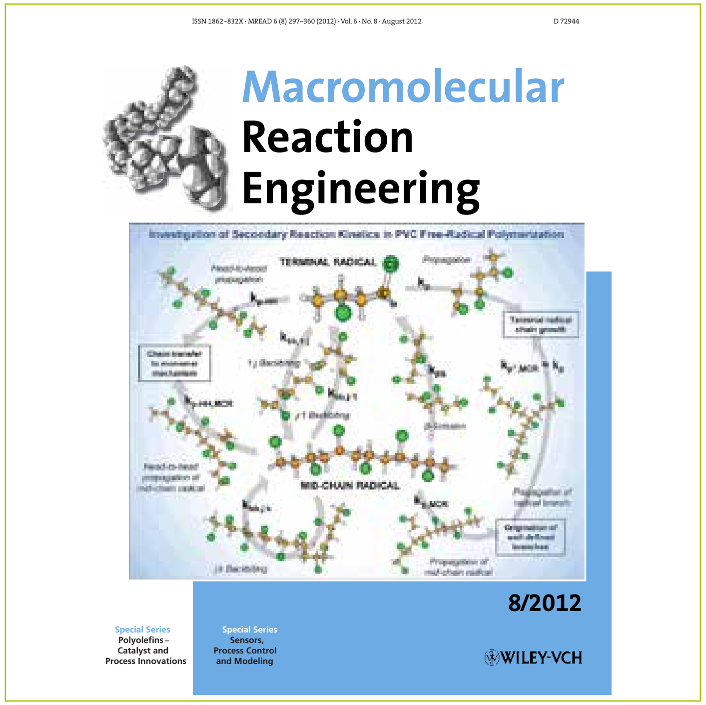
This analysis also highlighted the concept of super-diffusion regimen, which occurs when Brownian motion is perturbed by an external force; in this case, by the electrostatic repulsion. Einstein equation, strictly valid only for Brownian motion regimen, states that a linear relation between the mean square displacement (MSD) and time subsists; indeed, when Brownian regimen effectively takes place, the slope of log(MSD) vs. log(t) is equal or very close to one. Instead, super-diffusion regimen is characterized by a slope of logarithmic plot higher than one. This is a very important and highly relevant result, because, up to the author’s best knowledge, such a behavior in a solid matrix has never been observed and reported in the literature.

QUANTUM CHEMISTRY INVESTIGATION OF FREE RADICAL POLYMERIZATION KINETICS: POWER AND LIMITS OF THE TOOL

Danilo Cuccato - Supervisor: **Davide Moscatelli**

Free radical polymerization (FRP) is a common and versatile way to synthesize macromolecular materials. However, a proper regulation of chain length distribution and morphology of the resulting polymer is often not easily achievable. With regard to the latter aspect, the presence of side-reactions makes FRP a complex network of kinetic steps, which involve a large number of species characterized by different physical-chemical behavior. Moreover, they originate a huge variety of chemical pathways beside the conventional scheme of radical polymerization. The kinetics of such secondary reactions may have a strong impact on the final polymer features, from chain microstructure to the macroscopic properties, depending on their relevance in the selected polymerization conditions.

The most important secondary steps are those involving the formation of mid-chain radicals (MCRs), which exhibit quite different reactivity in comparison with conventional chain-end radicals. Backbiting reactions are the primary source of MCRs, which can undergo monomolecular β-scission or propagate, thus producing branches. In the case of copolymer systems, chain composition is an additional source of complexity of the whole kinetic mechanism, while cross-propagation reactions represent another relevant class of secondary steps. A common feature of all secondary reactions is the difficulty in determining the corresponding kinetics, due to the very small concentration and high reactivity of the active species involved as well as the large number of reactions that are in competition.


ISSN 1862-832X · MREAD 6 (8) 297–360 (2012) · Vol. 6 · No. 8 · August 2012 D 72944

Macromolecular
Reaction
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Investigation of Secondary Reaction Kinetics in PVC Free-Radical Polymerization

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1. Scheme of relevant secondary reactions active in the free radical polymerization of vinyl chloride investigated through quantum chemistry (picture from the front cover of Issue 8 of Macromolecular Reaction Engineering, 2012)

Nowadays, the development of pulsed-laser polymerization based techniques of analysis has led to a large investigation of reaction kinetics, mostly focused on acrylates. However, the experimental advances are still not sufficient to provide a detailed characterization of the kinetics of some interesting secondary steps. On the other hand, computational chemistry based on quantum mechanics allows the investigation of less-accessible reaction pathways through the use of cost-effective methods.

On the basis of these issues, the PhD research summarized hereinafter has been focused on the quantum chemistry investigation of secondary reaction kinetics in FRP. Specifically, the first aim of the work was an attempt to improve the latest theoretical studies on the topic through an enhancement of the computational procedure. Afterwards, the investigation has been extended to more complex and challenging systems, in order to test the predictive capability of the tool to examine quite inaccessible reactions. Finally, the limits of applicability of the method have been studied, taking into account borderline systems. A consolidated quantum chemistry approach based on the Density Functional Theory (DFT) has been adopted for the purpose, therefore kinetic and energy parameters could be estimated combining reasonable accuracy and computational effort. Rate coefficients have been determined through the conventional Transition State Theory, taking into account the quantum tunneling effect for hydrogen transfer reactions.

The quantum chemistry investigation of FRP kinetics has been focused primarily on homopolymer systems. Specifically, rate coefficients of reactions active in the polymerization of vinyl chloride have been determined using an improved DFT method, starting from a well-known reaction scheme and extending the kinetic study to a wide range of secondary reactions. Moreover, an efficacious modeling of the FRP process on the basis of a detailed reaction scheme including MCRs has been carried out. A particular attention has been focused on backbiting kinetics, where the relevance of the quantum tunneling effect on hydrogen transpositions has been highlighted for well-known FRP systems. Investigations have been moved to acrylates, and secondary reactions active in butyl acrylate polymerization have been studied with respect to a set of interesting side-steps. Specifically, the relevance of consecutive internal hydrogen shifts has been determined, and a novel mechanism for the origination of short branches through backbiting involving short-branch radicals has been proposed.

Afterwards, the attention has been turned toward the kinetic study of secondary reactions in acrylate copolymers. In particular, a terpolymer system composed by methyl acrylate, methyl methacrylate, and styrene monomer units has been adopted in order to examine the effect of copolymer composition on the kinetics of backbiting, propagation, and β-scission steps. The physical-chemical behavior of different radical species with respect to the investigated reactions has been determined, providing the estimation of a large number of kinetic parameters. Reactions of atom transfer from poly(butyl acrylate) active chains to various chain transfer agents (CTAs) have been also investigated, with the aim of shedding light on their features when radicals of different nature and size are involved.

The results have led to a deeper understanding of the mechanism of MCR patching by the action of CTAs in the context of branching in acrylates.

With the aim of exploring the limits of application of this computational approach, the capability of the method in predicting solvent effects as well as the kinetics of copolymer systems characterized by functional monomers has been tested. The quantum chemistry tool improved with the implementation of an implicit solvent model has proven to be useful in determining the qualitative behavior of copolymerization involving functional acrylic monomers in presence of polar solvents. Finally, the geometry optimization of reactants and transition states has been addressed, with the aim of elucidating the impact of side-group torsion conformers in the estimation of propagation rate coefficients.

In conclusion, quantum chemistry has proven to be suitable to the kinetic study of secondary reactions, especially when the attention is focused on the most challenging and inaccessible steps. Moreover, this approach represents a valid support to the experimental investigation, as well as a useful tool for the comprehension of complex polymerization mechanisms.

CATALYTIC PARTIAL OXIDATION OF LIGHT HYDROCARBONS: EXPERIMENTAL AND MODELING STUDY IN AUTOTHERMAL LAB-SCALE REFORMER

Dario Livio - Supervisor: **Alessandra Beretta**

The production of synthesis gas (or syngas), i.e. mixtures of hydrogen and carbon monoxide at different ratios is a key step in the chemical and refining industry. Along with the traditional large scale utilization, such as the synthesis of methanol and ammonia, syngas has gained increasing attention in the recent years for the distributed and small scale production of H_2-rich mixtures. Potential applications are in the field of highly efficient and environmentally friendly energy conversion systems, including the improvement of the environmental impact of gas turbines via H_2-assisted combustion, the fueling of hydrogen-driven vehicles and the on-board generation of H_2-rich streams as fuel for Auxiliary Power Units (APU) based on Solid Oxide Fuel Cells (SOFC) as well as reducing agents for aftertreatment systems.
Additionally, small to medium size plants for syngas production would allow for the extensive exploitation of remote reserves of natural gas via the on-site synthesis of transportable and valuable liquid chemicals.
All these applications require compact devices with high throughput. Thus, process intensification is a necessary operation that cannot be achieved by simple scale-down of traditional multitubular steam reformers, typically designed for large scale applications.
In order to accomplish this goal, the Catalytic Partial Oxidation (CPO) of hydrocarbon fuels at short contact time represents a valid solution. The process consists of the reaction between a hydrocarbon, such as methane, and oxygen into hydrogen and carbon monoxide. The presence of a noble metal-based catalyst allows for very high selectivity to syngas (> 90%) at contact times of 10^{-2} or 10^{-3} s with small reactor volumes. Given the exothermicity of the process, steady state autothermal operation is feasible once the reaction ignited. Simplicity and compactness of the reactor reduce its heat capacity and improve the dynamic response to load changes. Therefore, all these features make the catalytic partial oxidation an ideal candidate for the decentralized and small-scale production of H_2 and syngas. Under relevant operating conditions, the CPO process takes place as a complex coupling of heat and mass transfer with surface kinetics and possibly gas-phase kinetics. These features call for both advanced experimental tools and detailed modeling for the correct interpretation of the reactor performance.
The present Ph.D. work was focused on an experimental and theoretical analysis of the steady state performance of autothermal reformers for the catalytic partial oxidation of light hydrocarbons with Rh-coated honeycomb monoliths. A specific goal was to identify key parameters that influence the thermal behavior of autothermal CPO reactors. Along with this, another target was to elaborate and demonstrate strategies for the optimal design of the reactor.
The experimental investigation was carried out over a wide range of operating conditions in terms of nature of the fuel (CH_4, C_3H_8 and ethanol), total flow rate (5 – 21 Nl min^{-1}), inlet temperature (25 – 350°C) and composition of the feed stream (fuel/air mixtures with a carbon-to-oxygen ratio of 0.65 – 0.9). Both advanced experimental tools and detailed reactor modeling were applied to gain a deep understanding of the process. A capillary sampling technique was employed to look directly inside the reactor by the measurement of axial profiles of temperature and gas composition while keeping the reactor under adiabatic conditions. Notably, a pyrometer with fiber optics was used to measure with high resolution the surface temperature profile, which is a crucial aspect of the reactor since very high hot spot temperatures and gradients as high as 200°C/mm were commonly experienced. Special care was given to the effect of the geometry of the optical fiber tip with respect to the measurement of temperature profiles in honeycomb channels.
The experimental results were quantitatively analyzed by means of a monodimensional mathematical model of the adiabatic reactor. The model consists of mass, enthalpy and momentum balances for the gas and the solid phase and incorporates state-of-the-art heat and mass transfer correlations as well as heterogeneous and homogeneous detailed kinetic schemes for CH_4 CPO. Furthermore, a molecular heterogeneous scheme for the catalytic partial oxidation of propane over Rh/α-Al_2O_3 was developed based on an independent kinetic study performed in an isothermal annular reactor. Such a reactor configuration makes possible to operate under controlled working conditions and far from the thermodynamic equilibrium. The prevailing kinetic dependences were determined by fitting of the experimental data and a previously developed scheme of CH_4 CPO was extended by adding lumped expressions for C_3H_8 total oxidation, C_3H_8 steam reforming and CO methanation. Rate equations and kinetic parameters are in line with other studies reported in the literature. Also, a preliminary microkinetic analysis of C_3H_8 CPO was carried out to identify the rate determining step of the process. The molecular kinetic scheme represents a valid tool for design purposes and was successfully applied and validated on the basis of experiments performed with the autothermal reformer.
The adiabatic tests of CH_4 CPO showed that the thermal behavior of the reformer is a major challenge for the commercialization of the process. Even under relatively mild conditions (i.e. use of air instead of O_2, atmospheric pressure and in absence of any external heat input), hot spot temperatures well above 900°C establish in the inlet zone of the reactor. Minimization of the surface temperature peak is a vital target to prevent rapid deactivation of the catalyst and achieve durable operation of the reactor. The catalyst overheating becomes even more critical when hydrocarbons higher than CH_4 are employed because of a strong impact of mass transfer limitations on the fuel consumption. As a consequence, the optimization strategies of the thermal behavior are dependent on the fuel. In CH_4 CPO, it was experimentally demonstrated that channel opening and catalyst load are effective design parameters, whereas they do not work in C_3H_8 CPO. However, on the basis of numerical simulations, other solutions, such as a decrease of the reactor aspect ratio or the adoption of moderately dissipative reactor layout, were proposed.
Along with the thermal issue, it was shown that the CPO of C_3H_8 follows a synergistic hetero-homogeneous mechanism. Because of the vey high temperature reached in the inlet zone of the reactor, the heterogeneous oxidative chemistry activates gas-phase pyrolitic reactions with formation of intermediate hydrocarbon species, which are rapidly consumed by surface reactions in the second part of the catalyst. The occurrence of such a complex reaction network could be exclusively pointed out by the application of spatially resolved measurements of temperature and composition.
The final part of the research project was carried out during a stay at the Karlsruhe Institute of Technology, Germany. Here, the research on the CPO of light hydrocarbons was extended to the investigation of ethanol as model species for bio-fuels. It was shown that the product distribution is very sensitive to the composition of the reacting mixture (carbon-to-oxygen ratio); this has to be finely tuned in order to maximize the H_2 yield and minimize undesired gas-phase products. Finally, it was found that radial heat dissipations play an important role in determining the syngas selectivity and by-products formation and need to be accounted for in the design of autothermal CPO reformers.

KINETIC MODEL OF COAL COMBUSTION

Tiziano Maffei - Supervisor: **Tiziano Faravelli**

The continuous growth of the worldwide energetic requirements is one of the main topics of interest. Fossil fuels, as petroleum, coal and natural gas, are expected to continue supplying much of the energy used worldwide. Among these, coal is the energy source that shows the most important growth. There are many reasons for which the coal is becoming a very desirable energy source, as its wide global distribution, the lower price than oil and the availability of the worldwide reserve.

Coal is employed especially in power generation and more than 35% of the worldwide power generation is obtained throughout the coal combustion.

Unfortunately, coal is a source of environmental concern not only because of its strong greenhouse impact but also because of the emission of nitrogen and sulfur oxides and the formation of aerosol particles.

For these reasons "clean coal" technologies are of intense technological interest nowadays.

The most interesting technology is the oxy-coal combustion, where the air is substituted with an O_2/CO_2 mixture. On the one hand, it is possible to reduce the pollutant emission such as NO_x and soot or to separate easily the CO_2 from the flue gas but on the other hand, numerous gas properties such as density, heat capacity, diffusivity and gas emissivity change with important consequences on the coal reactivity.

Coal combustion is a multi-phase and multi-scale complex process which involves several species (gas, tar and char), different kinetics mechanisms (devolatilization, heterogeneous reactions, secondary gas phase reactions) as well as transport phenomena at both the particle and the reactor scale, as shown in Figure 1.

Several features of the coal combustion process have been analyzed in this work, with particular attention to the kinetic mechanism of pyrolysis and oxidations. A predictive multi-step kinetic model of coal combustion has been developed and it is constituted from two modular sub-models, one of pyrolysis and one of heterogeneous reactions.

The pyrolysis model takes into account many chemical kinetic steps as the release of hydrocarbon compounds and the formation of SO_x and NO_x precursors during the coal devolatilization. These pyrolysis kinetic models characterize the coal matrix on the basis only of the coal elemental composition through specific reference compounds. Any coal is simply considered as a linear combination of the few reference coals and the same linear combination is applied to devolatilization process and released products. A multistep devolatilization mechanism is assumed for each reference coals, with different product distributions and different kinetic parameters. The model has been compared with several set of experimental data obtained in different operating conditions (heating rate, temperature, time, coal rank). The overall agreement with experimental data is satisfactory, showing the capability of the model to catch the effect of the coal rank and the operating conditions.

Char oxidation and gasification reactions are the rate determining steps of the coal combustion, an improved knowledge of the mechanisms involved in such processes can lead to an increase in the efficiency of the combustion plants. Generally the char fraction varies between 30 and 70% by weight (depending on the nature of the coal and operating conditions), with a heating value in the range 6-8 Mcal/kg. The kinetic model of coal pyrolysis has been employed in the analysis of the char elemental composition showing a good estimation of the experimental data, moistly under high heating rate conditions.

A careful analysis of the elemental composition of the char residue has allowed the development of a kinetic mechanism of char heterogeneous reactions. The char heterogeneous mechanism is based on three different charry components with different composition and reactivity.

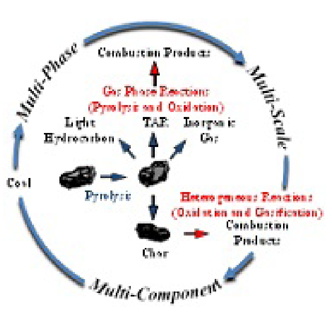
This model considers not only the oxidation and gasification reaction but also the annealing reactions. The model reproduces well the main features of the char oxidation and gasification reactions, both in terms of reactivity and in terms of selectivity to CO/CO_2.

The complete mechanism of pyrolysis and oxidations has been applied in the study of single coal particle combustion in different environments (O_2/N_2 and O_2/CO_2). In high temperature conditions the heat and mass resistance can become the rate determining step of the solid combustion. An opportune mathematical model has been developed to analyze the effect of the transport phenomena within the particle. Experimental measurements of coal particle life times and surface temperatures of a high-volatile bituminous coal and a lignite coal were performed in a drop tube furnace, under quiescent gas conditions. The model predictions show an overall good agreement with experiment data both in terms of particle life time and surface temperature. Moreover, the comparison with the experimental data shows the capability of the model to predict the effect of the background gas. The effect of the coal rank is also quite well predicted.

The CFD instruments offers the possibility to approach complex combustion system and to improve the efficiencies and to control the pollutant emissions. The direct coupling of detailed chemistry and CFD simulations is still prohibitive, moistly in the multi-phase reactive system.

For this reason, two simplified kinetic models, one for the coal pyrolysis and one for the secondary gas phase reactions of volatile matter have been developed. These models, despite their simplicity, retain the predictive capabilities of the original detailed models as shown from the comparison both with experimental data and with the respective detailed model.

Finally, these models have been employed in a CFD study of an oxy-coal pulverized furnace through the use of commercial fluid-dynamics codes. The models are able to catch the main behavior of the experimental data, even if in corresponding the first section of the furnace the model underestimates the initial reactivity. It is important to underline that these experimental data show a partial unsubstantiality, as in the case of the experimental data of CO_2 and of temperature or as in the case of experimental data of velocity.



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As highlighted in this activity, an important feature of the coal combustion is the correct coupling between solid and gas phase. Several simplifications have been introduced in this work and therefore, in a few cases, the agreement with the experimental data was not fully satisfactory. The development of a model based on an accurate description of the transport phenomena in both phases could overcome these approximations and consequently give better performances

SHORT-CUT METHODOLOGIES FOR ASSESSING EARTHQUAKE AND FLOOD RELATED NATECH RISK

Enrico Marzo - Supervisor: **Valentina Busini**

NaTech (Natural and Technological) refers to industrial accidents triggered by natural events such as earthquakes, flooding, lightning and so on. During my PhD, short-cut methodologies for the qualitative assessment of earthquake-related and flood-related NaTech risk have been developed as a screening tool in order to identify which situations require much more expensive Quantitative Risk Analysis (QRA). Methodologies, through suitable Key Performance Indicators (for hazard, KHI and for vulnerabilities, KVI), identifies the NaTech risk level (KRI) associated with a given situation (i.e., a process plant located in a given territory), using the Analytical Hierarchy Process as a multi-criteria decision tool for the evaluation of such KPIs. The developed methodologies has been validated by comparing their computational results with QRA results that involved NaTech events previously presented in literature.

Methodologies for assessing earthquake and flood-related NaTech Hazard: calculation of the Key Hazard Indicator (KHI)

Hierarchies obtained thanks to the AHP are structured with the goal at the top (the KHI), with different branches (structured at different levels) that represent a breakdown into sub-goals. Considering that the AHP is used to compare incommensurable elements, the rule used to define which elements could stay on the same level of the hierarchy is that they should respond to the same question. At the bottom of the hierarchy there are the alternatives that characterize the given plant with respect to the NaTech hazard.

When considering earthquake or flood-related NaTech accidents, the consequences are broadly related to three main phenomena: fires, explosions, and toxic dispersions. As a consequence, three different hierarchies have been developed for both types of NaTech accidents leading to three distinct KHIs: KHI_F, KHI_T, and KHI_E, for fires, toxic dispersion, and explosion, respectively. Through simple mathematical manipulations, from the normalized values assigned to the alternatives, it is possible to compute the three KHIs values on a 0-1 scale. In order to determine the hazard level of a given plant characterized by three values of KHI_F, KHI_T, and KHI_E, these values must be condensed into a global KHI (KHI_{G_EQ} or KHI_{G_FL}, respectively for earthquake and flood-related NaTech events), which should represent the overall hazard level in the KHIs space. Because the origin of the 3D KHIs space represents the optimal condition (i.e., the lower the KHI value, the lower the related hazard level), a point into the KHIs space, identified by the three values, KHI_F, KHI_T, and KHI_E, represents a hazard level related to its distance from the origin. Therefore, $KHI_{G\_EQ/FL}$ can be evaluated through a norm providing the distance from the origin, which in a 3D space can be simply obtained as the square root of the sum of the three squared KHIs.

This range can be grouped into a low ($<10^{-2}$), medium (10^{-2} - 10^{-1}), or high ($>10^{-1}$) sensitivity bracket in regards to the NaTech events of the analyzed process.

Methodology for assessing the vulnerability of a territory around an industrial plant: calculation of the Key Vulnerability Indicator (KVI)

A simple methodology able to assess the vulnerability of a territory considering the characteristics of the population (density and distribution) and the presence of vulnerable centers (hospitals, schools, fire stations and so on) has been developed in order to integrate the methodologies previously developed for earthquakes and flood-related NaTech accidents leading to a measurement of the risk and not only of the hazard (Risk = Hazard x Vulnerability). The effects of an industrial accident involve the territory surrounding the plant with decreasing dangerousness with the distance, except for the possible occurrence of a domino effect.

In Quantitative Risk Analysis, the area surrounding the plant is divided, depending on the severity, in generally circular areas of risk centered in the event's point of origin.

The solution adopted for the developed screening method is the result of further conservative simplification: it was chosen to consider as critical for events such as fire/explosion an area of radius of 1 km from the border of the plant while, for events such dispersion of toxic substances, an area of radius of 7 km. This is a conservative choice by virtue of the fact that areas involved in the dispersion of toxic substances may be, due to the intrinsic nature of the phenomenon, much greater just because toxic substances are dangerous for human health and safety till a much lower level of concentration (order of ppm) in air while the limit of flammability or explosiveness are higher (order of 10^4 ppm).

Due to the expeditious nature of the methodology, the choice of using the medium density of population at municipal level is a reasonable choice if no other and more detailed data about the population around the plant are available. The elements to be considered as vulnerable are identified by the Italian Ministerial Decree of 9 May 2001 according to the following parameters: difficulty of evacuation of weak and needy subjects (sick, children, elderly); difficulty to evacuate subjects in buildings higher than 5 floors or large aggregations of people in public places; higher vulnerability of outdoor activities with respect to the indoor ones and lower vulnerability of the activities characterized by a short time of permanence of people, which result in less exposure to risk, compared to activities that require longer time of permanence.

The used short-cut procedure is easy to apply, require a small amount of resources and information and summarize, through a suitable Key Vulnerability Index (KVI), the level of vulnerability associated to a given territory around a process plant, existing or not (e.g., a plant in the design phase).

Estimating the value of such KVI requires a simultaneous comparisons among different parameters, ranging from the characteristics of population (density and distribution) to presence of vulnerable centers (hospitals, schools, fire stations and so on). Thus, a multi-criteria decision method was necessary to account for the different and incommensurable effects of various parameters and the Analytical Hierarchy Process, AHP, has been chosen.

Hierarchies obtained thanks to the AHP are structured with the goal on top (the KVI), with different branches. At the bottom of the hierarchy there are the alternatives, which characterize the given territory around the considered plant. Through simple mathematical manipulations, from the normalized values assigned to the alternatives, it is possible to compute the KVI value on a 0-1 scale. This range can be grouped into a low ($<10^{-2}$), medium (10^{-2} - 10^{-1}) or high ($>10^{-1}$) sensitivity bracket in regards to the NaTech events of the analyzed territory.

Aggregation of the indexes: calculation of the Key Risk Indicator (KRI)

Reminding that a measure of the Risk is the result of the product between Hazard and Vulnerability, we can obtain the first piece of information, i.e. the danger of the expected accidental event that could insists on the considered area, by the KHI while the second piece of information, i.e. the presence of the population and of vulnerable centers, by the KVI. Crossing in a table the values of KHI (rows) with values of KVI (columns) we can obtain the relative Index of Risk (KRI). Highly rated plants require further NaTech risk analysis, while lowly rated plants do not; however, the NaTech risk related to medium rated plants is neither negligible nor unacceptable. This is a sort of ALARP region, where the decision on how much further the NaTech risk assessment must be conducted, is determined by the analyst on a case-by-case basis.

FISCHER-TROPSCH SYNTHESIS OVER AL_2O_3-SUPPORTED COBALT CATALYSTS

Marina Mascellaro - Supervisor: **Enrico Tronconi**

The low temperature Fischer-Tropsch synthesis (LTFT, or simply FTS) is a CO hydrogenation process applied to produce synthetic long chain hydrocarbons and oxygenates that can be marketed as high added value fuels (gasoil, kerosene) or chemicals (base oils, normal paraffins, naphta). The process, that can be used to exploit and to monetize either natural gas (GTL, gas to liquid), coal (CTL, coal to liquid) or biomasses (BTL, biomass to liquid), is presently applied at the industrial scale by Sasol at Sasolburg (GTL), Secunda (CTL) and Ras Laffan (GTL) and by Shell at Bintulu and Ras Laffan (GTL). Promoted cobalt and iron-based catalysts are adopted in these plants. Cobalt is selected to liquefy the H_2-rich syngas obtained from natural gas, while iron is the choice in the case of H_2-deficient syngas obtained from coal gasification. Under typical process conditions, the reacting mixture is biphasic, with reactants and light products in the vapor phase and heavy products (the waxes) in the liquid phase. Accordingly, when packed-bed reactors are used (e.g. Shell), the reactor behaves as a trickle-bed, whereas the hydrodynamics are those of a bubble column when tank (slurry) reactors are adopted (e.g. Sasol).

In the present PhD work different aspects of FTS (VLE, kinetics and diffusive limitations) have been studied. A short resume is presented here.

In order to correctly design any industrial reactor for the LTFT and to identify the best operating conditions, it is extremely important to be able to correctly compute the yield of liquid products within the reactor. During my PhD thesis a comprehensive model has been developed, which is able to compute the amount and the composition of liquid products formed in the low-temperature FTS over a representative cobalt-based catalyst, working in a packed-bed reactor operated at process conditions representative of industrial operation. To achieve this goal, a complete set of steady-state FTS runs has been carried out in a lab-scale packed-bed reactor loaded with a 20 wt.% Co/Al_2O_3 catalyst, investigating the effects of the main process conditions (T, H_2/CO inlet ratio, content of inert gas in the feed, syngas space velocity) on the reactants conversion and on the C_1-C_{50} product selectivity. Then, a conventional CO conversion kinetic model and a conventional product distribution model have been separately developed and have been jointly adopted to estimate the product yields in the reactor as a function of the process conditions. The latter have been finally used as input for a non-ideal isothermal and isobaric vapor-liquid equilibrium calculation. It has been found that at the typical process conditions more than 95 mol.% of the C_1-C_{30} hydrocarbons are in the vapor phase, while the C_{30+} fraction, that in general represents no more than 1 mol.% of the products, is almost entirely liquid. At representative process conditions, the most abundant product in the liquid phase formed in the reactor is the heptacosane, whose liquid fraction represents more than 78% of the total amount of C_{26} formed in the reactor. This information assumes a key-importance when designing an industrial reactor for the LTFT and when defining the best operating conditions. In fact, the presence of a liquid phase within the reactor may strongly affect the performances of the LTFT, in particular in terms of mass and heat transport phenomena.

The second part of this PhD work concerns the development of a kinetic model able to describe the distribution of FTS products, not only in terms of hydrocarbon products, but also of oxygenates, including carbon dioxide. Given that the Co-based FTS does not produce many oxygenated species, it has been decided to group the alcohols with more than five carbon atoms into a single pseudo component. In order to achieve this results, an old kinetic model previously developed has been modified to predict oxygenated species, too. For the range of industrially relevant conditions, the developed model accurately predicts the observed reactants conversions, as well as the hydrocarbon products distribution up to a carbon atom number of 50, distinguishing between n-paraffins and a-olefins. In particular the model is able to describe the linear hydrocarbon product distribution typical of the polymerization reactions like the FTS. Furthermore, the same model is now able to properly describe the distribution of oxygenated products and the CO_2 selectivity.

The analysis of the effects of intraparticle mass transfer plays a fundamental role in identifying the most appropriate size of the catalytic particles to be used in a fixed bed reactor for the low temperature FTS. In the presence of mass transfer limitations, alterations of the net rate of reactants conversion can occur, accompanied by a change in the product distribution, from hydrocarbons of high molecular weight to lighter ones, which is generally undesirable. The present work addresses indeed the effect of internal diffusive limitations on the reactivity of Co/Al_2O_3 catalysts for the FTS, operating at around of the conditions of industrial interest. To study such effects tests have been conducted on two catalytic systems having the same composition but different particle size, and operating at different temperatures. In particular, catalyst particles having a diameter of about 100 and 800 mm have been tested. The first was obtained by mechanical grinding and sieving of the second one, so as to ensure exactly the same chemical composition and the same morphology. Both catalyst systems were tested at different temperatures, in order to estimate the activation energy of the FTS reaction as a function of the catalyst particle size. The effects observed over the 100 mm investigated particles show, upon increasing the reaction temperature: the increase of the CO conversion, the decreasing trend of the selectivity to heavy products, and the corresponding growth of the light species, the reduction of the olefin content in the products and the growth of the CO_2 selectivity, which remains however a minor reaction product. Similar trends have been observed in the case of the 800 mm catalyst but in this case the temperature effect on the process selectivity are visibly amplified. This suggests a different apparent activation energy of the process according to the adopted particle size of the catalyst. This is confirmed by the corresponding Arrhenius plots used to estimate the activation energy of the FTS. The first of the two values (108 kJ/mol) is in line with literature values for the FTS, which confirms that the powder system (100 mm) works in of the chemical regime. The second one (71 kJ/mol), instead, is fully compatible with a diffusive limitation regime, where the observed activation energy is equal to the average value between the intrinsic activation energy of the chemical reaction and that of the physical process. In order to prevent the onset of mass transfer limitations, it is also possible to choose a catalytic system of egg-shell type, constituted by particles (usually using Al_2O_3 or SiO_2 supports) in which the catalytically active phase is arranged on a thin layer which constitutes the outer part of the granule. Adoption of these catalyst systems enables a compromise between pressure drop and diffusive limitations. The particles have a diameter sufficiently high to contain the pressure drop but also thin catalytic layers, of a characteristic size that minimizes the diffusive limitations phenomena. The use of egg-shell catalysts, however, could lead to an insufficient density of catalytically active phase within the reactor. The method developed in this PhD work represents a combination of two literature methods and allows to prepare eggshell catalysts of 0.8 or 0.6 mm diameter of the support and 50 mm of active phase thickness. This home-made catalyst is active in FTS.

NEW FRONTIERS IN HALOGEN BONDING: FROM POLYHALIDES TO SUPRAMOLECULAR GELS

Lorenzo Meazza - Supervisor: **Giancarlo Terraneo**

Introduction

Supramolecular chemistry is a field of chemistry which focuses on the development of complex chemical architectures and devices starting from components interacting by noncovalent intermolecular forces. These forces drive the molecular recognition processes allowing the formation of highly complex systems.

Many useful applications in as many different areas have been achieved using supramolecular systems obtained by taking advantage of non-covalent interactions like hydrogen bonding, electrostatic forces, van der Waals and p-p interactions.

In the last years another non-covalent interaction has been studied and applied in these systems becoming more and more relevant: the halogen bonding (XB).

Halogen bonding is a non-covalent interaction involving halogen atoms as acceptors of electron density (as an example, basic nitrogen ligands are typical halogen bond acceptors).

Applications of halogen bonding can be found in many different areas: anion sensing, scavenging systems, polymers, soft and electronic materials, catalytic, recycling and resolution processes, nanoparticle organizations.

The first objective of the following studies is to investigate the rule of halogen bonding and size matching in bis(trimethylammonium)alkane dihalide salts which, despite being nonporous in nature, function as very effective dynamically porous materials, in order to obtain new polyhalide species.

In the meanwhile, the increasing interest in supramolecular gels induced us in trying to apply halogen bonding in this field to try to obtain the first halogen bonding supramolecular gel ever reported.

New polyhalide species

Hexamethonium tribromide, diiodochloride, and dibromochloride were synthesized by exposing crystals of dihydrate hexamethonium bromide and chloride to vapors of Br_2 and I_2 (figure 1). The trihalides were isolated in pure form if the stoichiometry in the gas-solid reactions was conveniently chosen. The gas-solid reactions occur homogeneously and are reversible if suitable temperature and pressure are used.

The mixed trihalides I_2Cl^- and Br_2Cl^- are hard to obtain as crystalline solids and their quality and purity was good enough to allow for structural and Raman characterization. The method we applied is general and can be extended to the predictable preparation of other uncommon trihalides species.

Moreover, using thermal treatment in the solid-state we have synthesized two new organic salts containing mixed $I_2Br_2^{2-}$ and $I_2Cl_2^{2-}$ dianions.

The products are obtained as uniform materials by controlled deiodination reactions upon heating nonporous trihalides. The process is reversible, suggesting that the materials discussed can be used in gas adsorption processes. The good crystallinity and purity of the products allowed its structural characterization by ab initio XRPD analysis, proving the potential of XRPD as a powerful tool to study uncommon solid-state reactions resulting in microcrystalline solids.

These results confirm that the bis(trimethylammonium)alkane dihalide salts, despite being nonporous in nature, function as very effective dynamically porous materials trapping dihalogen molecules from the gas phase and stabilizing polyhalides and mixed polyhalides.

The reported solids can find applications in interesting industrial processes. Such polyhalides are important species in dyes regeneration in dye sensitized solar cells (DSSCs) wherein the redox couple I^-/I_3^- is used as electrolyte.

Halogen bonding supramolecular gels

Tunable gel phase materials are an emerging topic of interest in potential applications in many various fields. Within this context low molecular weight supramolecular gelators (LMWG), with their reversible and dynamic intermolecular interactions, are achieving increasing prominence. Works on switchable gels include systems involving photo- and pH and redox based switching, ultrasound induced gelation and switchable catalysis.

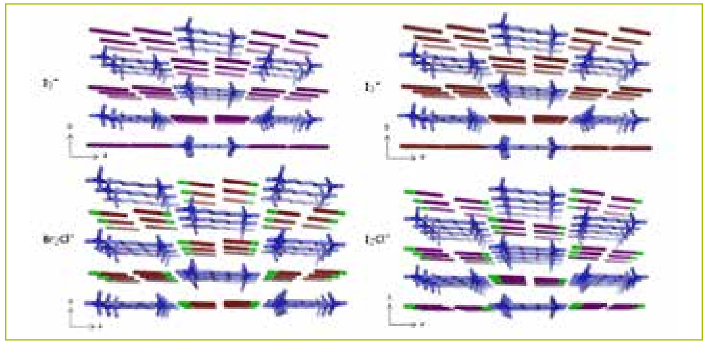
As a starting point for this work we focused our attention on the usage of metallogels in which the metal coordination results in metal binding to the pyridyl group of pyridyl-urea compounds, which suppresses the alternative, gel-inhibiting, urea-pyridyl hydrogen bonding interaction, freeing the urea groups to form fibrils (urea tape hydrogen bonding motif) and hence gels (figure 2a).

Therefore we can demonstrate that halogen bonding is sufficiently strong to competitively interfere with inhibitory urea-pyridyl hydrogen bonding in order to favor fiber formation and hence gelation in a similar way to metal coordination giving the first example of application of halogen bonding in order to control and "switch on" gelation (figure 2b).

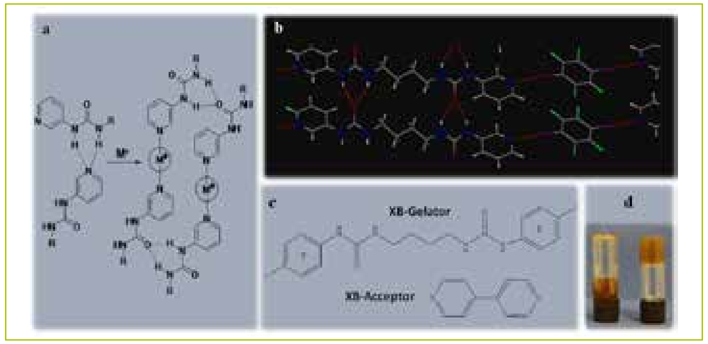
Once demonstrated that halogen bonding induced gelation is a general phenomenon we designed a halogen bonding donor gelator combining bis(urea) and perfluoroaryliodide components in the same molecule (figure 2c) and we "turned on" gelation simply by adding 4,4'-bipyridine, a strong halogen bonding acceptor (figure 2c,d).

In conclusion we demonstrated that Halogen bonding is a versatile, general gel-forming interaction that may be incorporated into either the gelator structure or introduced through a gel-forming partner compound.

The addition of halogen bonding to the toolbox of controllable supramolecular gel formation substantially expands the possibilities for manipulating these smart soft materials and eliminates complications arising from metal coordination to solvent, anions and other components of the gel.



1. Crystal structures of trihalide and mixed trihalide salts viewed along the c-axis. The new obtained trihalides Br_3^- I_2Cl^- and Br_2Cl^- are isostructural with the already reported I_3^-.The alternation of cationic and anionic columns is shown. Hydrogen atoms are omitted for clarity



2. a Metal coordination frees the urea moieties to produce parallel gel-forming α-tape motifs. b X-ray crystal structure of the halogen bonded gel showing the gel-forming urea-tape interaction and the halogen bonding cross-links involving the pyridyl groups (using 1,4-diiodotetrafluorobenzene as halogen bonding-donor molecule). c Chemical structure of the new halogen bonding donor gelator (XB-Gelator) and the acceptor 4,4'-bipyridine. d A 1% solution of the XB-Gelator (left) and the same solution with the addition of 4,4'-bipyridine which drives the gel formation (right)

SIMULATION OF THE GAS PURIFICATION PROCESS WITH AQUEOUS SOLUTIONS OF AMINES

Stefania Moiolo - Supervisor: **Laura Annamaria Pellegrini**

Gas treatments have been representing for more than fifty years an important industrial application and nowadays are becoming increasingly important to control the composition of gas streams. Natural gas, syngas, exhaust gases from power plants and refinery gases are all sources of CO_2 and/or H_2S, two components whose presence is strictly limited by the commercial specifications of the final product and/or by environmental regulations.

Acid gas removal by amine scrubbing is widely used in industry: due to this widespread utilization there are many plants that use "open art" processes with traditional amines, such as monoethanolamine (MEA), methyldiethanolamine (MDEA) and piperazine (PZ).

Amine scrubbing presents several advantages, in particular in the mass transfer phenomenon, which is promoted by chemical reactions in the liquid phase. The presence of the amine dramatically influences the solubility of the acid gas in water.

An accurate description of the phenomenon, in terms of thermodynamics, kinetics and mass transfer, is fundamental for a reliable representation of the absorption process.

The aim of the work is the analysis and modeling of the absorption process with amine solutions to remove acid gases from natural gas, refinery gas and flue gas. Modeling of removal with aqueous solutions of methyldiethanolamine (MDEA) has been analyzed in detail, considering also the influence of aromatics and mercaptans, because it is widely used in presence of these compounds, both as selective and non selective solvent, and to process different types of gas streams. In addition, MEA and PZ have been studied with the aim of modeling the process of removal of CO_2 from flue gases, for which they are industrially used.

A comparison of the results obtained with different commercial simulators has shown significant differences and little agreement with experimental data. A reliable tool for simulation is required, mainly from engineering companies with the aim of reducing uncertainties in plant design and to be sure to fulfill the stringent contractual guarantees.

An accurate description of the phenomenon, in terms of thermodynamics, kinetics and mass transfer, has been performed in order to best describe the absorption process with MDEA, MEA and PZ solutions.

ASPEN Plus® has been chosen as the basis for the analysis and the improvements on thermodynamics and on diffusion with reaction, because of its "rate-based stage" approach and of the possibility of linking external Fortran user's subroutines.

VLE is influenced by reactions that occur in liquid phase. Moreover, because of the presence of ions in the liquid phase, the system is strongly non-ideal. One of the most accurate model available has been proposed by Chen and coworkers and is a development of the NRTL theory for electrolytic systems containing ionic species. It is supported by theoretical bases and allows the description of the system with the local composition of the aqueous solution. In this way, the activity coefficients are considered as the sum of different contributions due to long-range and short-range interactions. Adaptive parameters can be used to describe interactions between molecular and ionic species and are obtained by regression of VLE experimental data. Both vapor and liquid phases are considered as non-ideal, so a good agreement between the representation and the physical phenomenon can be obtained.

Thermodynamics has then been improved by the determination of ad hoc interaction parameters and, when missing or not close to experimental data, of Henry's constants and/or chemical equilibrium constants. In particular, for the MDEA system, Electrolyte-NRTL parameters have been determined not only for CO_2 and H_2S, but also for aromatic and sulfur compounds, whose presence has not yet widely studied in literature, but should be considered for a complete description of the process, since MDEA solvent is often used when these compounds are in the gaseous stream to be purified.

A proper description of mass transfer with reaction is fundamental in designing acid gas removal units, because absorption of carbon dioxide is kinetic controlled, for all the considered amine systems, even when fast reactions occur. ASPEN Plus® is provided with a rate-based model, that takes into account the mass transfer limitations occurring in the absorption phenomenon. The "rate-based stage" approach analyses the mass and heat transfer phenomena that occur in a real tray or section of packing. The method considers each real tray individually, and is based on separate mass and heat balances for each phase, which are solved simultaneously with mass and energy rate equations on the tray. It is considered the most reliable method for amine scrubbing modeling, because developed on theoretical bases. In ASPEN Plus® the film theory is used, which predicts a linear dependence of the mass transfer coefficient on the diffusivity of carbon dioxide, while for amine scrubbing systems a square root dependence on diffusivity is observed.

1. Acid gas removal by amine scrubbing is widely used to control the composition of gaseous streams leaving process plants

The prediction of the correct dependence has been obtained in the proposed model by-combining the Eddy Diffusivity with the Interfacial Pseudo First Order model. ASPEN Plus® has been used as the framework for simulation by linking an external Fortran user subroutine.

The process simulator uses generalized correlations for physical properties, in order to describe different mixtures by simply changing values of parameters. This generalization affects the accuracy in describing the behavior of the amine system and high deviations from experimental data are observed. Density and viscosity of the amine solution and their dependence on temperature and on amine concentration have been widely studied in literature, also by analyzing the influence exerted by the presence of other compounds, as carbon dioxide, on the considered amine solutions. Diffusivity of CO_2 is fundamental in the description of the absorption phenomenon, in particular with a "rate-based stage" approach, because it influences the mass transfer coefficient. A deep analysis of literature models has shown that sometimes available correlations are not in good agreement with experimental data. For these cases, in order to obtain a correct description, regressions have been performed.

The developed model has been applied to different amine scrubbing systems, for which experimental data are available, showing an improvement in the prediction of the chemical absorption process.

ENANTIOSELECTIVE SYNTHESIS OF CHIRAL PHARMACEUTICAL INTERMEDIATES MEDIATED BY ENE-REDUCTASES

Fabio Parmeggiani - Supervisor: **Francesco G. Gatti**

The generation of up to two stereogenic centres by reduction of a suitably substituted prochiral C=C double bond is a very valuable strategy in the synthesis of optically active molecules. With respect to the more common metal-catalysed hydrogenation, biocatalysis can provide a cheaper, greener and complementary alternative, highly enantioselective on a wide range of substrates under mild conditions.

The bioreduction of "activated" C=C bonds, ***i.e.*** those conjugated to an electron-withdrawing group (EWG), is a widespread activity in nature and its potential applicability to preparative organic synthesis has been early recognized.

Historically, the first approach has been the exploitation of resting cells of various microorganisms, among which **baker's yeast** (*Saccharomyces cerevisiae*, BY) unquestionably occupies the predominant place. The vast majority of the enzymes (including those present in BY) responsible for C=C bioreduction are called **ene-reductases**, known to act on suitably substituted double bonds, such as those of α,β-unsaturated carbonyl compounds, nitroolefins and maleimides. Most of the ene-reductases that have been identified in the last decades belong to the well-known and thoroughly characterised family of **Old Yellow Enzymes** (OYEs), nicotinamide-dependent flavoproteins which mediate the addition of a hydride and a proton to the C=C bond, with an ***anti*** mechanism.

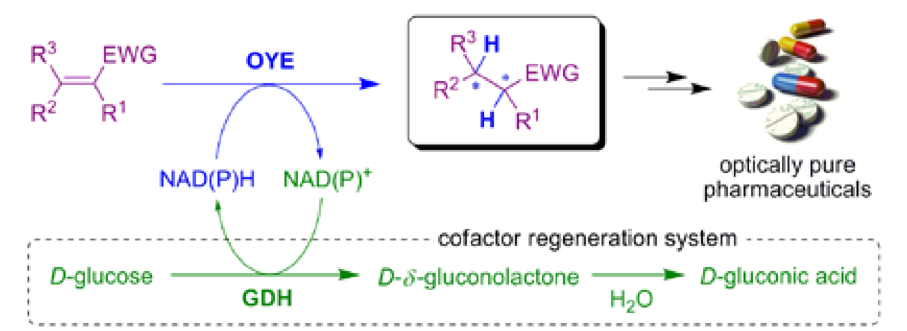
Despite the simplicity and cheapness of the setup, the BY mediated reduction suffers from several disadvantages which hinder its industrial scale application: low tolerated substrate concentrations, that lead to an intrinsically too low productivity, difficult work-up, occurrence of side reactions, need for a complex chromatographic steps. One of the adopted strategies to address these issues is the use of isolated ene-reductases, which often allow to obtain complete conversions without the formation of side-products.

In spite of the fact that OYE-like ene-reductases have been known since a very long time, their full synthetic potential began to be appreciated and exploited only in the last decade, with the availability of overexpressed and purified enzymes.

The main goal of this project was the **development of new applications of isolated OYEs to the stereoselective synthesis of chiral pharmaceutical intermediates**. In order to add such bioreductions to the toolbox available for asymmetric synthesis and to implement them in industrial manufacturing processes, two main targets need to be pursued: **to increase the productivity of the system** in terms of mass of product per unit of volume and time, and **to investigate new classes of substrates**, gaining insight into the stereoelectronic factors that control the reaction and guiding the selection of new promising synthetic applications.

The first part of the project was aimed at the cloning and overexpression of three ene-reductases (OYE1-3) in host cells of ***Escherichia coli***, implementing an easy and efficient purification system by affinity chromatography. In order to regenerate the expensive NAD(P)H cofactor, also a glucose dehydrogenase (GDH) was overexpressed and purified, allowing to set up a readily scalable biocatalytic system (Figure 1).

Employing as a case-study the reduction of an α,β-unsaturated aldehyde, precursor of several antidiabetic pharmaceuticals such as tesaglitazar, the reaction was optimized (also employing the substrate-feeding-product-removal strategy) to obtain a quantitative conversion, an excellent optical purity and a more than 100-fold improvement in productivity with respect to the BY mediated process.



1. Biocatalytic system for C=C bioreduction.

Disappointingly, in related cases, such as α-alkylcinnamaldehydes or the precursors of the active ingredients robalzotan and rotigotine, high optical purities could not be obtained with the same system, because the saturated aldehydes were found to racemize easily. The coupling of an alcohol dehydrogenase (ADH) in cascade with the ene-reductase allowed to transform the saturated aldehyde in the saturated alcohol, preserving the optical purity provided by the OYEs. The productivity improvement achieved with respect to BY mediated processes was up to 470-fold.

It was also found that the stereochemical outcome of the reaction can be controlled by selecting a suitable regioisomer of the substrate, leading to the same final product with the opposite configuration. On the other hand, in a few cases an opposite stereochemical result was observed with two OYEs on the same substrate. Both these strategies are precious stereocontrol methods.

The biocatalytic system was then tested on several libraries of "unconventional" substrates, determining yield, stereochemical outcome and enantiomeric excess, in order to evaluate the practical applicability of each reaction to the synthesis of optically active intermediates. Particular attention was given to poorly activated substrates, such as unsaturated esters, because the reduced products are much less prone to racemization.

The presence of an additional electronegative group in α position was found to be crucial for the efficient reduction of unsaturated monoesters.

Submitting several α-chloro and α-bromoacrylates to OYE mediated bioreduction gave access to many useful active pharmaceuticals and intermediates such as antibiotics, antidiabetics and *D*-phenylalanines.

Studying the reduction of doubly activated compounds such as diesters and cyanoesters allowed to obtain several target molecules (***e.g.*** γ^2-amino acids) and to understand more deeply the stereochemical course of the reaction.

Finally, a rationalization of the results obtained in this work and in previous literature allowed to propose an empirical model to predict the best binding arrangements of the substrate into the catalytic site.

The introduction of biocatalysed transformations such as OYE reductions in multi-step chemical processes provides evident advantages and is becoming a well-established practice. In summary, this work contributed to the analysis and understanding of the reaction, sorting out the best substrates that give access to chiral intermediates in high yield and optical purity, and to design more practical processes (***e.g.***, boosting the productivity of whole cell bioreductions of up to two orders of magnitude), broadening the range of application of these versatile biocatalysts in preparative organic synthesis.

DEVELOPMENT OF METHODOLOGIES FOR THE ACCURATE ESTIMATION OF REACTION RATE COEFFICIENTS

Daniela Polino - Supervisor: **Carlo Cavallotti**

Gas phase reactions play a major role in many reacting systems. Among them combustion processes, atmospheric chemistry and polymerization technologies are just a few examples. From a chemical engineering point of view, it can be of fundamental importance to know the consumption or production rate of key species in the reacting system under study. This information can be used to design new chemical reactors, engines or burners in order to obtain the best performances at the minimum cost. In addition, they can help reduce the production of dangerous or undesired byproducts.
In this scenario, the ability to determine accurately the rate coefficients of elementary key reactions has become progressively more important. A very powerful tool that has assisted the scientists in the past decades in calculating the rate coefficient of gas phase elementary reactions is transition state theory (TST). Nevertheless, the theoretical estimation of a rate coefficient is not univocally and straightforwardly resolved for all kind of gas phase reactions. In particular, its accuracy depends on two fundamental factors: the accuracy of the electronic structure calculations and the level of the kinetic theory that depends on the assumptions made.
The level of accuracy of the electronic structures calculation is decisive in determining the precision of the final rate coefficient. The level of improvement of such *ab initio* methods, both in the methodology and computer technology, has been dramatic over the last years and this allowed to compute energies and structural properties with increasing speed and accuracy. Even so, it is important to choose the appropriate method for each reaction investigated between the several available. On the other hand, from the point of view of the kinetic theory, classical TST provides reasonably accurate rate coefficients, but, unfortunately, we can find a number of additional complications for which it proves to be not sufficient. Thus, during the years much work has been dedicated to its improvement and generalization that led to the formulation of several new methods and theories which hold in common all or a part of the assumptions that lay under the transition state theory.
In this framework, the goal of the present work has been to address the major limitations of transition state theory and to develop and implement ad hoc methodologies in order to overcome these issues. Specifically, we concentrated on the solutions of the following topics: spin forbidden reactions, hindered rotors, multi-well and multi channel potential energy surfaces, tunneling corrections and a microcanonical description of bimolecular reactions. The methods adopted for each one of these issues were validated against literature data and tested on chemical reactions of scientific interest, which will be here briefly described.

The dissociation kinetics of germane

It was found that the main germane decomposition channel leads to the formation of germylene, which rapidly decomposes to atomic Ge and H_2. The dissociation of GeH_2 to Ge and H_2 is a formally spin forbidden reaction thus intersystem crossing probability was explicitly included in the microcanonical simulations through Landau–Zener theory. Kinetic constants of the main decomposition channels were determined as a function of pressure and temperature between 0.0013 and 10 bar and 1100 and 1700 K and a quantitative agreement with experimental data for GeH_4 decomposition was obtained.

Investigation of the reaction pathways active within toluene pyrolysis secondary chemistry.

First, the reactivity and decomposition kinetics on the C_7H_6 potential energy surface was investigated. This analysis revealed that two main decomposition channels are possible with equal probability after visiting a potential energy surface (PES) comprised of 10 wells and 11 transition states. The first is active on the singlet PES leading to the formation of the fulvenallenyl radical and atomic hydrogen. The second instead requires intersystem crossing to the triplet PES and leads to acetylene and cyclopentadienylidene. After this investigation, due to inconsistencies between our theoretical results and new experimental evidences, we were directed to re-explore benzyl decomposition mechanism. This research allowed us to individuate a new pathway active during benzyl decomposition, which yields benzyne and a methyl radical. These findings allowed us to build a new kinetic scheme able to reproduce fairly well the experimental data reported by different authors on toluene and benzyl decomposition.

Analysis of the reactions active during cyclopentadiene pyrolysis

The recombination of two cyclopentadienyl radicals and the addition of a cyclopentadienyl radical to a cyclopentadiene molecule have been investigated. New routes to the production of naphthalene in the first case and indene in the second have been proposed. The rate coefficients calculated were included in the overall POLIMI_1202 kinetic model and allowed to reproduce properly the experimental concentration profiles of key species, such as naphthalene, indene and styrene. This study permitted us to appraise the ability of our treatment to describe correctly microcanonical bimolecular reactions.

Quantum tunneling within hydrogen transfer reactions

In this study, we implemented the SCT theory of Truhlar and coworkers to calculate tunneling corrections. The ability of this method to describe properly tunneling effects was tested studying the CH_4 + H benchmark reaction. A sensitivity analysis was also performed on the main parameters that enter as input data and the results were compared with the rate coefficient suggested in the literature. Our analysis revealed the critical role that the accuracy of the activation energy and the minimum energy path play on the prediction of the rate coefficient. Overall, the methodology implemented provided rate coefficients in good agreement with the reference values and with the predictions obtained with other more sophisticated theoretical approaches.

Addition of singlet methylene to unsaturated hydrocarbons

Finally, a study on a specific class of reactions was performed in collaboration with Dr. Stephen J. Klippenstein, which confirmed the reliability of the multifaceted VRC-TST approach. The present theoretical approach in fact has proven to be an effective strategy for the estimation of the high-pressure rate coefficients for the addition of singlet methylene to unsaturated hydrocarbons. Specifically, the CASPT2 method was demonstrated to yield a valid procedure for the direct evaluation of the interaction energies within variable reaction coordinate transition state theory. Moreover, the introduction of the one-dimensional correction potential yielded predicted rate coefficients that are in good agreement with the available experimental data.

As evidenced by the investigations performed during the course of this PhD thesis, the methods studied and implemented permitted us to improve our understanding of a number of reactions of scientific interest. However, the methodology presented can be still subject to development. Overall, we can say that great progress has been achieved in our ability to model the kinetics of gas phase reactions, but we anticipate that continued improvements will follow this research project.

EXPERIMENTAL AND MODELING STUDY OF THE NH$_3$-SCR ACTIVITY ON SCR-CATALYZED WALL-FLOW DIESEL PARTICULATE FILTERS

Silvia Redaelli - Supervisor: **Isabella Nova**

Vehicle exhaust gases have gained nowadays a considerable role in the emission of pollutants. To control and reduce them, a specific legislation exists: in Europe, Euro V regulations were introduced in 2009 and an even stricter legislation, Euro VI will be enforced in 2014. The emission limits are different for vehicles with Otto and Diesel engines. The latter ones, in particular, are responsible for the emission of large amounts of particulate matter (PM) and nitrogen oxides (NOx), which are both among the most dangerous pollutants for the environment and for human health. So, in order to satisfy the upcoming regulations, it is necessary to develop more efficient technologies which result in reduced formation of pollutants (primary techniques), but also in improved abatement of the pollutants emitted in the flue gases (secondary techniques).

For lean burn Diesel engines, primary techniques such as fuel composition, air/fuel ratio, recirculation of gases, cannot possibly reduce both NOx and PM emissions at the same time. So, in the last few years secondary techniques have become necessary on Diesel engines equipped vehicles in order to control both NOx and soot emissions. Among different secondary techniques NH$_3$- or urea-SCR is one of the most promising technologies for the abatement of NOx, whereas particulate filters are now currently used for PM removal. For instance, one solution is to use a Diesel Particulate Filter (DPF) to abate PM, followed by an NH$_3$ Selective Catalytic Reduction (NH$_3$-SCR) converter to reduce NOx. One major issue for the after treatment devices, however, is represented by volume constraints, most of all for passenger cars. Furthermore, compact after treatment systems permit a reduction of vehicle weight and, as a consequence, a lower fuel consumption and CO$_2$ production. In this respect, combined DPF + NH$_3$-SCR devices are now being considered, consisting of a wall-flow filter with a SCR catalyst deposited within the porous walls (SDPF). This single device permits the simultaneous abatement of both PM mechanically filtered and NOx catalytically removed with the SCR catalyst. Very few people in the literature considered so far combined DPF+SCR systems, then research in this area was and is still necessary.

My PhD project was developed in this context in collaboration with the company Corning Incorporated, USA. My PhD thesis project was devoted to the experimental and modeling study of the NH$_3$-SCR reactions over Fe- and Cu-zeolites catalyzed wall-flow Diesel Particulate Filters (DPFs) provided by Corning Inc., not considering the presence and the interaction with soot.

Since Fe- and Cu- promoted zeolite catalysts in form of powder are the precursor materials deposited on the filters, it is meaningful to analyze the intrinsic behavior of the SCR powder catalyst itself before investigating the SCR activity over the coated filters.

A systematic experimental investigation of the main reacting systems was carried out on the powder catalysts. Then the kinetic parameters describing the SCR activity were estimated fitting the experimental runs for both the powdered catalyst.

The coating of the Diesel Particulate Filters with the powder catalyst is provided by Corning Inc. USA for big bricks of substrates that have real full-scale sizes, for which a nominal catalytic load is then defined.

The filters tested at the lab-scale are usually cut from this bigger bricks. Due to possible non-uniform catalyst distribution, it is important to understand if the nominal load value could be considered truly representative also for the lab-scale samples.

This was the motivation that pushed us to look for a method in order to verify that. We introduced the concept of Specific Adsorption Capacity of a catalyst, which represents an intrinsic feature directly related to the amount of catalytic active phase and independent of the catalyst configuration, i.e. powder or structured. For this reason dedicated NH$_3$- and NO$_2$-adsorption runs were performed on catalysts in the form respectively of powder and of structured filter. Comparing the adsorption capacities of the two configurations it was possible to evaluate the actual active phase present on the filter. The results obtained by both NH$_3$- and NO$_2$-adsorption runs agreed. This was a good result since NH$_3$ and NO$_2$ adsorb on different sites, respectively acid zeolite sites and metal sites So, this method gives a double check on the estimated catalyst loads.

To understand if an effect exists on the deNOx activity of the filters due to the possible uneven distribution of the active phase mentioned above, three wall-flow lab-scale samples were coated with Fe-zeolite precursor powder catalyst in different ways. One filter was coated homogeneously along its whole length, another one was coated only on the inlet section and the last one only in the outlet section. From the comparison between the three modalities of coating distribution it could be concluded that the homogeneous coated sample always shows higher conversions than the inlet and outlet coated samples. So effectively a not-homogeneous distribution of the active phase along the filter could cause decrease of its deNOx activity.

The next step was to investigate if and how a specific fluid dynamic configuration of the SDPF affected the deNOx performances. So the purpose was the comparison between the wall-flow systems and the traditional and well established flow-through monolithic converters in terms of SCR performances by means of experimental runs and CFD simulations at the same conditions. Both the approaches showed that despite the different fluid dynamic features of the two systems, the deNOx performances are very similar, indicating that the fluid dynamic configuration does not significantly affect the DeNOx performances at the relevant tested conditions.

The comparison between lab- and full-scale was another important topic that needed to be addressed. The issue was if a lab-scale catalyzaed filter sample could be really representative of a full-scale one in terms of deNOx performances, in view of a possible scale-up process. The goal was then to compare the deNOx performances of filters on the two operating scales.

Experimental runs were carried out over the same catalyst deposited onto filters of different sizes. The results showed that a medium-scale filter provides a better deNOx performance than a lab-scale filter. This could be due to mass transfer resistances caused by diffusional limitations in the peripheral walls of the lab-scale filter, which are characterized by a double thickness in comparison with the internal porous walls.

In the lab-scale sample the ratio between the peripheral walls and the internal walls is higher than in the medium-scale sample, as it tends to zero with growing sample size. Thus, the impact of diffusional limitations is more significant in the lab-scale filter adversely affecting the overall deNOx efficiency. CFD simulations confirmed and supported the collected experimental evidence as well as the related physical interpretation.

The last section of my PhD thesis regards the kinetic modeling work carried out developing subroutines for a Fortran code named CHARM (Corning Heat Up And Regeneration Model), provided by Corning Inc.. My contribution for CHARM was the implementation of two different kinetic schemes dedicated to the deNOx functionality : an LNT (Lean NOx trap) kinetic model taken from the literature and an NH$_3$-SCR kinetic scheme studied and developed at PoliMI. Since both the implementations gave positive outcome, the CHARM model, including our SCR and LNT kinetic schemes, is now used industrially by Corning Inc. in order to develop combined wall-flow DPF+deNOx systems.

VALORIZATION OF GLYCEROL FROM BIODIESEL WASTE TO HIGH VALUE CHEMICALS

Suresh Udhavrao Shisodia - Supervisor: **Attilio Citterio**

The present thesis will focus on the use and potentiality of glycerol (even crude) and ethyl lactate as C-3 chemical platforms obtained from biomass, to generate new green products, polymers, and bioactive compounds, under as much as possible green conditions. In the 21st century major issues are the generation of energy, sustainable chemicals & materials for industry, by less consumption of energy & reduce pollution by using biomass instead of fossil fuels. Glycerol has emerged as relevant renewable resource, spurred by the growing of the biodiesel production. It has more than 3000 different actual industrial uses but still surplus of glycerol needs to be valorized. Ethyl lactate emerged as important chemical commodity as environmentally benign solvent and reagent, which is obtained by esterification of lactic acid with ethanol, lactic acid is obtained from both bacteria and animal cells in an anaerobic respiration method.

In this thesis work ethyl lactate was investigated mainly as green solvent for oxidations with hydrogen peroxide of organic compounds, identifying the eco-friendly peracids-like nature of this system. On the contrary, glycerol studies were addressed to control the chemo- and regio-selectivity of O and N nucleophilic substitutions to C-O bonds through activation of carbonate substituents, or electrophilic substitution to O-H bonds. In particular, the aim was to investigate the factors affecting the unexplored area of regio-selective poly-condensation of glycerol derivatives by using cascade and solvent free reactions by green methods, to produce stereo-ordered oligomers, polyglycerol ethers or urethanes and other functional products. In this area a further target was to synthesize simple derivatives by incorporate ferrocenyl or indolyl units to test the antifungal activity of the resulting products and identify the role of homo- & hetero- geneous catalysis in electrophilic substitution or alkylation reaction by stabilized cations (i.e. ferrocenylmethyl and hydroxyalkyl). The specific topics investigated can be summarized as follows (based on the thesis chapters):

Chapter-1. Synthesis, purification, reactivity of diglycerol dicarbonate (DGDC) and conversion to stereoselective oligomers and polymers. In this context the following aspects were studied and explored: a) Green synthesis of DGDC from impure diglycerol using carbonatation reaction by thermal or by microwave irradiation; b) Purification of ***d,l***- and ***meso***-DGDC by crystallization; c) Hydrolysis of pure ***d,l***- and ***meso***- DGDC to stereoordered α-diglycerols; d) Selective nucleophilic substitution reactions at terminal C-O bond of pure ***d,l***- and ***meso***- DGDC by N and O centred nucleophiles, e) Selective synthesis of stereo-ordered monomer and polymers from pure ***d,l***- and ***meso***- DGDC diastereoisomers. In all cases progress of reactions were controlled by using TLC, HPLC, GC-mass or capillary electrophoresis and the purified products were obtained by silica gel column chromatography and crystallization, and then characterized via ^{1}H-/^{13}C-NMR, IR, and LCMS. X-ray crystallographic study and SEM analysis were made where ever necessary. For the characterization of polymers, DSC & TGA analysis were applied. The same analytical techniques were applied also in the following explored areas.

Chapter-2. Cascade synthesis of α-glycerolcarbamates. Polyhydroxyurethanes are compounds of great interest having a wide range of applications in pharmacology, agriculture, and chemical industry, their conventional synthesis is based on the use of toxic reagents like isocyanates, phosgene, nitro derivatives, etc. It is important to substitute these reagents with green reagents like CO_2 or organic carbonates, but the drastic conditions generally used with these reagents prevented any selective transformations on poly-substituted derivatives.

In order to solve the problem we have developed a new efficient synthetic route for the preparation of difunctional and polyfunctional molecules from C-3 inherent natural polyol monomer glycerol and green alkyl carbonate. α-glycerolcarbamates were selectively synthesized by single-step three components system (glycerol, dialkyl carbonates, and aliphatic amines or polyamines). Factors affecting the selectivity at terminal to internal carbamate isomers were investigated and the key role of the intermediate ***in-situ*** formed linear carbonate ester of glycerol for selective substitution at the terminal position was ascertained.

Inhibition of further substitution by the carbamate product was also observed, facilitating the selective mono-functionalization of substrate. By this approach polyurethanes can be obtained under mild conditions and good productivity by using di- or poly-amines.

Chapter-3. Easy Solvent Free Synthesis of Novel 1-Ferrocenylmethylglycerols and its derivatives as antifungal agents. For the synthesis of ferrocenylglycerol derivatives (in principle useful as bioactive compounds) a direct, green method was studied consisting in condensing ferrocenylalkanols with glycerol or its derivatives under mild conditions (20-90°C) without or in the presence of co-solvent and/or catalyst. Homogeneous Brönsted acid catalysis was mainly investigated but some work was carried out, in collaboration with the Pune University (India), with the heterogeneous Lewis acid catalyst aluminum nitride (AlN/Al). The role of CO_2 as promoter was investigated and proved effective, in condensation reactions of ferrocenylalkanols with glycerol or 1,2-diol substrates, but not in general.

The novel ferrocenylglycerol derivatives were tested in vitro for their antifungal activity towards 3 different plant fungi, ***Fusarium spp***., ***Botrytis cinerea***, ***Penicillium spp***. The experiments were performed by surface and inclusion treatment of the cultural growth mediums, and shown significant antifungal activity in surface treatment method. The novel AlN/Al catalyst was mainly investigated in the condensation of carbonyl compounds with indoles to afford the corresponding bis(indolyl)methanes, compounds known to be biologically active.

The catalyst, characterized by SEM, Raman and particle size analysis, and is recyclable (retains its activity for 10 cycles)

Chapter-4. Hydrogen peroxide/Ethyl lactate: A New Eco-Friendly Peracids-like System for the Oxidation of Organic Compounds. Oxidation of organic substrates by using H_2O_2 is a widely explored area, frequently applied on industrial scale. However H_2O_2 is relatively unreactive molecule and strong efforts have been devoted for selection and use of catalysts to accelerate or control the processes. Inorganic and metal catalysts were deeply investigated where as the use of organic catalyst was more scantly analyzed and applied (except for formation of alkyl or arylalkyl peroxides and peracids). However, for a “green oxidation” point of view the ideal system is the one which use environmentally-friendly oxidants together with recyclable catalysts in a nontoxic solvent.

Thus, the use of organic solvents able to dissolve a wide variety of substrates and to activate H_2O_2 was explored as oxidant system, focusing on natural esters of α-hydroxy carboxylic acids.

We found that ethyl lactate, an easily available, green and safe solvent, has the peculiarity to react rapidly with H_2O_2 to give an intermediate able to oxidize organic sulfides RSR’, reduced organophosphorous substrates of general structure [$PR_x(OR)_{3-x}$ with x = 0-2], to the corresponding oxygen addition products sulfoxides, phosphine oxides, phosphates, phosphinates and phosphonates, where as carbonyl compounds were converted to the ester in a Bayer-Villiger oxygen insertion reaction. The oxygenation of aryl methyl sulfides, follows an overall second-order kinetics, first order in H_2O_2 and sulfide and involve general acid catalysis.

In *p*-substituted phenyl methyl sulfides the negative r value obtained in the correlation analysis of rate constants with s constants indicate that positive charge is generated on sulfur atom and the electrophilic oxygen of “perlactic acid” is responsible for the acceleration by electron withdrawing substituents. The fast decay of the peroxidic intermediate prevents the possibility to apply the system to less reactive substrates, i.e. olefins and electron withdrawing substituted aromatics.

EXPRESSION, STRUCTURAL AND FUNCTIONAL CHARACTERIZATION OF THE PROTEIN PROLINE OXIDASE INVOLVED IN DIFFERENT HUMAN DISEASES

Elena Tallarita - Supervisor: **Loredano Pollegioni**

Proline oxidase (PO) is a mitochondrial inner-membrane enzyme that catalyzes the first step in the proline degradation pathway. It is encoded by ***PRODH,*** a gene localized at 22q11.2: at least 16 ***PRODH*** missense mutations on the ***PRODH*** gene have been identified with moderate to severe effect on PO activity. Intracellular synthesis and degradation of free proline occur through a distinct set of enzymes with unique properties and regulatory mechanism: together they constitute a "catalytic cycle" which represents an important connection with other metabolic pathways. All organisms oxidize proline to glutamate in two enzymatic steps coupled by a non-enzymatic equilibrium: in the first step, proline oxidase (PO) catalyzes the oxidation of L-proline to Δ^1-pyrroline-5-carboxilyc acid (P5C) a reaction that involves flavin adenine dinucleotide (FAD) as a cofactor. P5C is then alternatively subjected to three metabolic reactions: oxidation to glutamate, transamination to ornithine or reduction back to proline. Even if the biosynthetic pathways and biological role of proline have been well established, the role of proline oxidation in the cell remain largely unknown. The ***PRODH*** gene, maps in a genomic region (22q11) where several studies have localized genes that potentially confer increased susceptibility to schizophrenia. Schizophrenia is a common chronic and disabling brain disease of still largely unknown etiology and pathogenesis, that affects about 1% population worldwide. Schizophrenia occurs in all populations and is considered a complex disease with multiple factors contribution: the most widely accepted neurodevelopmental hypothesis of schizophrenia integrates environmental influences and causative genes. ***PRODH*** is considered a positional candidate gene for schizophrenia since delections of the 22q11 locus are found in 0.3-2% of patients with schizophrenia; moreover microdeletion of chromosome 22q11 is associated with velocardiofacial syndrome (VCFS) (or Di George syndrome) and patients with 22q11 deletion also exhibit cognitive deficits similar to those observed in schizophrenia. Interestingly, the localization of specific proline transporters within the glutamate synapses suggests that proline might serve as a modulator of glutamate transmission, hypothesis strongly supported by the observation that proline and glutamate are involved in the same metabolic pathways. Finally, association between plasma proline level and schizophrenia revealed that schizophrenia patients have significantly higher plasma proline levels than controls and that subjects with hyperprolinemia (HPI) have a 6-fold greater chance to develop schizophrenia than controls. HPI is an autosomal recessive disorder characterized by plasma proline concentration above normal, caused by absence or reduced activity of PO.

This PhD project was aimed at understanding the role of PO under physiological and/or pathological processes and particularly as a candidate risk factor for schizophrenia. Despite the intriguing role of this protein in different human diseases, a correlation between genotype and phenotype of PO is still lacking mainly because the structural and functional characterization of the human protein has not yet been performed. For this reason we decided to characterize the recombinant PO by expressing the human protein in an heterologous system and to evaluate the effects of reported mutations on its catalytic properties. The final aim was to formulate a possible mechanism of PO regulation in the framework of glutamate metabolism and pathologies.

E. coli is usually the most used organism for heterologous expression of recombinant proteins, but the expression of mammalian proteins, such as PO, results sometimes difficult in this host since ***E. coli*** does not perform most of the post-translational modifications. Moreover, human PO is localized in the mitochondrial inner membrane, so it could possess regions that negatively affect its expression in ***E. coli*** as a soluble protein. Therefore, by using an accurate bioinformatic analysis, several PO deletion variants were produced: all PO variants include a core region corresponding to the catalytic domain but they lack regions which could negatively affect the expression. Among the expressed PO variants, the PO-barrelN-His variant was expressed as a soluble protein and was subjected to a detailed biochemical characterization.

A second aspect of the project focused on the expression of the wild-type and L441P inactive PO variant in a mammalian cell system. The U87 human glioblastoma cell line was selected since, despite representing the worst malignant form of astrocytic brain tumors, it is used as ***in vitro*** model of astroglia which is the responsible of the release and reuptake of signaling molecules, among which the key neurotransmitter glutamate. U87 clones stably expressing wild-type and L441P inactive variant PO were successfully produced, as confirmed by Western blot analysis. PO has been reported to be a mitochondrial protein thus, to verify the subcellular localization, PO variants were also overexpressed as chimeric proteins with EYFP fluorescent protein. Confocal images show that the fluorescent signal corresponding to PO-EYFP displays a peculiar "spaghetti like" pattern typical of mitochondria. Furthermore, PO-EYFP variants signal distribution largely overlapped with mitochondrial immunostain. Subsequently, the investigation of the functional differences between U87 cells transfected with the wild-type or the mutant PO was started. The cell growth rate was assayed over a period of 7 days: the growth curves (cell density/well vs time) display the typical pattern of exponential growth. No significant difference was evident between cells stably expressing the variant or the wild-type PO, while both grew slower than untransfected U87 cells. This result could indicate that expression of PO negatively affected the growth rate of transfected U87 cells, while the PO activity did not. The next step was the investigation of the cellular content of proline, since variation in the concentration of the amino acid is indicative of the cellular PO activity. Proline is reported to be directly involved in glutamatergic transmission and even though the biochemical mechanism by which this happens is still unknown, two hypotheses have been formulated: proline may accumulate in the synaptic terminals inhibiting glutamate release or act on a cell surface transporter inhibiting the release through a complex signaling cascade. For these reasons we measured the proline/glutamate and glutamine levels in cellular and extracellular space of U87 cells by HPLC analysis. At the same time we started the investigation of the expression level of the glutamate transporters GLT-1 and EAAT-1 by Western blot analysis to verify if expression of active or inactive PO variants could affect glutamatergic functionality.

In conclusion, the purification of a soluble, active human PO variant (encompassing the whole catalytic domain of the enzyme), as obtained in the first part of the project, represents the fundamental step to investigate structure-function relationships in proline oxidase in analogy to the biochemical studies performed on the prokaryotic homologues of the protein. Further studies will be necessary for the identification of the effect of the reported polymorphisms of the enzyme on its structure and activity and to understand how they could affect the proline/P5C redox cycle. These studies represent a required step for the identification of compounds acting as positive or negative effectors of this enzyme and that, modulating its properties at the molecular level, could be potentially used as drugs.

PRODUCTS AND MATERIALS FROM BIOLOGICAL SOURCES: ISOLATION, ANALYSIS AND CHEMICAL REACTIVITY

Laura Tinè - Supervisor: **Attilio Citterio**

The PhD project deals with physical and chemical elaboration of biological materials and their analysis. The aim was to obtain new or alternative valuable products to be used in different broad areas. More specifically, the activity was designed along three different topics: **1)** Synthesis of antimetastatic sulfated oligosaccharide mimics (Supervisor: Prof.ssa Elena Vismara); **2)** Isolation and modification of polyisoprene from alternative crops; **3)** Synthesis of chiral ionic liquid for separation applications (Supervisor: Dr. Martin Earle).

Setion 1: The aim of this research is the synthesis of a novel potential heparanase inhibitor. We have focused our attention on C-C hexasaccharide-like-mimics inhibitors because of the similarity of such compounds with the enzyme substrate.

In the present work, we have applied an electrochemical approach to synthesize the C-C oligomer: the electoreduction of per-acetyl-1-bromo-maltotriose in acetonitrile at a silver cathode that afforded three diastereoisomers according to the C-C linkage configuration. Furthermore, such compounds were deprotected, sulfated and fully characterized by NMR. The resulting purified compounds were tested for antimetastatic properties and compared with sulfated maltohexaose, an established heparanase inhibitor, and some representative glycosides. The comparison of antimetastatic activity in lung cancer shows that the C-C hexasaccarhides are more active with respect the C-O-C analogue and in particular among the obtained diastereoisomers the α,α was the most active. In conclusion were developed new sulfated C-C hexasaccarhide mimics as semisynthetic heparanase inhibitors and antimetastatic agents.

Section 2: Natural rubber (NR) is a polymer consisting of isoprene units (C_5H_8)n linked together mostly in a 1,4 cis-configuration. The main source of natural rubber is *Hevea brasiliensis*, a tree native of Brazil. To look for alternative sources of natural rubber appears nowadays to have a strategic importance, in the light of the predicted shortages in NR supply from *Hevea brasiliensis*. Among the main identified alternative plants sources there is *Partenium argentatum* (also known as *Guayule*) that is a flowering shrub used already in the early 20th century as a commercial alternative source of natural rubber. Therefore *Guayule* is the target of this work because it appears to have a great potential as an alternative source of NR. The main difference between *Hevea brasiliensis* and *Guayule* is the location of latex in plants and the content of proteins and terpenes. This strongly affect the choice of the extraction and purification method. We have focused our efforts on development of potential industrial approaches to isolate polyisoprene, especially from *Guayule* latex. Four different approaches were developed: 1) evaporation, 2) ultracentrifugation, 3) precipitation and extraction with solvent, 4) extraction with Ionic Liquid (IL). The first two methods are useful to fully characterize and then use by products isolated from their latexes to understand their influence on *Guayule* Natural Rubber (GNR) performance in items (mainly tyres). Both component of latexes derived from *Guayule*, polymeric and low molecular components, were characterized. It's results that GNR have thermal behaviour and structure very close to the Hevea's one. On the contrary, content and distribution of low molecular weight components and proteins are very different. From *Guayule* were isolated significant amount of mono- and sesqui-terpenes (i.e. cinnamate and anisate esthers of germacrene alcohol named guayulin A and B, respectively) and several steroids (i.e. argentatin). The methods 3 and 4 were developed to obtain the cleanest as possible polyisoprene from *Guayule*. The third method afforded clean GNR with the handicap to use large amounts of solvents. In the last method IL were used to extract rubber from *Guayule* latex. Some particular IL were choosen for their ability to disrupt cell walls (dissolving cellulose and lignin). So rubber extraction by means of IL can be applied both on latexes and whole plants, allowing to recover a larger amount of components from plant and at the same time minimizing the amount of waste solvents produced.

Efficient coagulation of *Guayule* latex with remarkable decrease of proteins and polysaccharides was obtained at 25°C.

Recovering of GNR from IL and recycling of IL was investigated.

Chemical modification of the obtained rubber was studied through oxidation reaction by dimethyl dioxirane (DMDO) and chain breaking by oxygen in the presence of different catalysts to obtain telechelic oligomers.

In particular epoxidation with DMDO provided new methods to obtain block copolymers of GNR and HNR that were further functionalized by opening the oxirane ring with different nucleophile reactants affording rubber analogues with halogen and amino functional groups. In conclusion GNR has suitable molecular features to replace HNR but the different distribution of other latex components provides a different spectrum of applications.

The developed four different extraction methods investigated have clarified the opportunities and limits of the purification of GNR and side products recovery, suggesting alternative processes for industrial methods to obtain rubber from Guayule latex.

The performance of extracted GNR was evaluated by stress relaxation and mechanical testing (in collaboration with Pirelli Tyre S.p.A. analytical laboratory) on starting and vulcanized rubber under standard conditions, identifying the role of by-products and purification procedure.

Section 3: I joined QUILL- Queen's University Ionic Liquid Laboratory- as a visiting student for a period of three months.

During this period I worked on the synthesis of chiral IL to be tested in Ionic Liquid-Liquid chromatography (ILLC). In this chromatography technique a compound of interest is partitioned between a molecular solvent and an ionic liquid using state of the art chromatography machinery and IL chemistry.

IL may form biphasic liquid systems with numerous solvents, including water, which makes them possible candidates in counter-current chromatography (CCC). The only limitation is in finding an IL capable of dissolving the compounds under test. The aim of the project is to synthesize chiral IL to achieve chiral separation in ILLC. This technique is based on different forms of CCC and it is accomplished at QUILL by means high performance counter-current extraction machine based on Ito design, but it has been extensively modified to handle ionic liquids.

Two different kind of chiral IL were synthesized to be tested on ILLC machine. The first was ethylmethyl imidazolium camphor-10-sulfonate, already prepared at QUILL but it was not already tested on ILLC. It was prepared in big amount starting from ethylmethylimidazolium chloride and commercially available camphor-10-sulfonic acid. It was tested on ILLC with biphasic system made up of IL /H_2O/ EtOAc in different percentage to set all parameters of the system. The main aim of these experiments is to evaluate the behavior of the system at different flow rate to establish its best value to operate the separation. Meanwhile it was arranged the synthesis of potential chiral ionic liquid starting from L-proline. The separation of the obtained distereoisomers salts was accomplished although not in the enough amount to be tested in ILLC. In conclusion the analyzed biphasic system of EMIM CS/H_2O/EtOAc is potentially suitable for chiral separation in ILLC.

PERFLUOROACYLFLUORIDES: VERSATILE INTERMEDIATES FOR THE PREPARATION OF FUNCTIONAL FLUORINATED MATERIALS

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Thanks to the development of the electrochemical fluorination process (ECF), perfluoroacylfluorides R_F-C(O)F can be easily prepared starting from their parent hydrocarbon acids. Different perfluorocarboxylic derivatives like perfluorocarboxylic acid R_f-C(O)OH and perfluorocarboxylic ester R_f-C(O)OR_h can be sequentially produced using the standard hydrolysis and esterification reactions. This work aims at exploring the important role of perfluoroacylfluorides as precursors and/or intermediates in the synthesis of functional organofluro compounds. Herein, several reactions using perfluoro acylfluorides as starting material or as precursor of starting material to produce valuable functional fluorinated compounds are reported and discussed. The perfluoroacylfluorides based products mentioned here including hexafluoropropene (HFP), hydrofluorocarbons (HFC), hydrofluoro ether (HFE), and low boiling point perfluoro acylfluorides.are prepared.

Hexafluoropropene (HFP) $CF_3CF=CF_2$ is one of the primary raw materials in organic fluoro chemical industry. As an important perfluorinated monomer and precursor, it is widely used in manufacturing of thermoplastic and elastomeric fluoropolymers. Industrialized methods for its preparation are mostly based on pyrolysis of perfluorinated or partially fluorinated carbons, which present several disadvantages due to complicated workups, high energy consumption and the presence of extremely dangerous by-products. The decarboxylation of perfluoro carboxylic acid and its derivatives to produce HFP shows its potential to avoid the above mentioned problems. In this work, the development of catalytic decaboxylation of perfluorinated carboxylic acid and its derivative (specially its ester form) in presence of highly active metal fluoride (supported-CsF) has been carried out and verified as reaction with appropriate characteristic to be applied and scaled up for production of HFP. Another valuable product- hydroflurorocarbon (HFC 227ea)- has been detected as the main byproduct along with carbon dioxide and methyl fluoride in this process.

A highly active cesium fluoride which is supported and promoted by porous NaF has been verified as effective catalyst for this pyrolysis reaction. It has also been shown are capable of preventing solicitation of the catalyst which is quite often occurred on porous less catalysts used in the olefin preparation. The higher recovery ability and the high catalytic acitivity of CsF may compensate for it's larger expense compare with other alkali methal fluorides.

The manual effort required to monitor the reaction and isolate the products were much reduced and simplified by using continuous methodology. On-line IR and GC-MS have been recognized as appropriate analytical techniques for detecting and separating products and reagents involved in this continuous reaction. One major concern about this methodology is that isomerization and hydrolysis are likely to occurred during ECF process, formed ester or other derivatives may contain undemanding impurities, extra purification procedure is needed for getting high purity HFP from this pyrolysis reaction. In addition, the high hydrous property of CsF may negate its advantage due to the formation of troublesome hydro fluoride acid.

In response to environmental issues, hydrofluoroethers (HFE) R_fOR_h has been evaluated and commercialized as substituent of perfluorinated fluids and chlorofluorocarbon compounds (CFCs). There are two types of general methodologies to produce HFE: direct fluorination of the hydrocarbon ether compound, or building the ether linkage during the reaction with a fluorinated precursor. Because the former is prone to result in isomerization and is a very exothermic reaction, the latter shows more attractive practical features for industrial applications. Concerning fluorinated precursors for building the ether linkage, α-fluoro alcohols (R_FOH) are thermally unstable and difficult to be synthesised or isolated, these difficulties make them not practical as reagents for organic synthesis, especially for the generation of α-perfluoro alkoxide(R_fO-) synthon. Instead, α-perfluoro alkoxide (R_fO-) can be prepared more easily by the reaction of perfluoro acyl fluorides R_F-C(O)F or perfluorinated ketone R_F-C(O)-R_F with fluoride ions in anhydrous polar, aprotic solvent. Due to the fact that perfluoro alkoxides have lower nucleophilicity compared with their non-fluorinated alkoxideanaloges, strong alkylating agents with high electrophilicity are needed to introduce the alkyl group to the formed α-perfluoro alkoxide(R_fO-) and produce HFE. Herein we report the use of perfluorinated carboxylic ester $R_FC(O)OR_h$ as a new family of alkylating agents which is not only able to introduce alkyl group to perfluoro alkoxide but also serves as source of fluoride ions for the formation of perfluoro alkoxide. For the first time perfluoroacyl fluoride (COF_2) is herein successfully alkylated to hydrofluoroethers HFE 143ea, in presence of metal fluoride (CsF), by using methyl perfluorobutanoate in polar aprotic solvent.

Based on experimental results got up till now, this method is not as attractive as we thought to be apply as a practical methodology for preparation of HFE, owing to the poor yield (<40%), long reaction time (≥72 h) and the high requirement for anhydrous experimental condition (many failed tests). However it does widened the scope of the limitated alkylating agents for the thermal unstable perfluoroalkoixdes. As reported, uptill now, besides fluoroformate, all the feasible alkylating agents are tranditional strong alkylating agants like alkyl suilfonates ($CF_3SO_3CH_3$, methyl mesylate, methyl tosylate, CF_3SO_3Et,$CF_3SO_3C_6H_{13}$-n) and fluorovinyl alkyl ethers. These group of alkylating agent can't offereing fluoride ions like fluoro formate does, a stoichiometric amount of metal fluoride (which is expensive) is usually needed to provide perfluoroalkoxides, and large amounts of partially reacted solid metal fluoride is left over after the reaction. If our reaction is proceeds with the pathway that in situ generated fluoro formate is alkylating perfluoroalkoixdes. It is actually an improved methodology for the known fluoro formate alkylating method. Since fluoro formate is not a commercially available coumpound, it needs to be prepared using COF_2. Our method actually combines the preparation of fluoro formats and its alkylating reaction into a "one pot" reaction, the extra procedure for prepare fluoro formate can be avoided.

We also found that this reaction only occurs in the polar aprotic solvent. In absence of the aprotic polar solvent, the same reaction precedes along two different pathways at the same time: 1) The acylating reaction of perfluorocarboxylic ester by COF_2 takes over the alkylating reaction and produces the perfluoro acylfluoride linear $R_fC(O)F$. 2) The thermal decomposition of perfluorocarboxylic ester is dominating reaction; then the generated HFP is further condensed with COF_2 and forms the branched isomer of perfluoro acyl fluoride iso-$R_fC(O)F$. The ratio between these two isomers can be modulated by adopting the appropriate the reaction conditions. Besides offering an understanding of acylation reaction, the method herein studied also provides a new way to transform perfluorinated esters to perfluoro-acyl-fluorides. Comparing acyl-fluorides to methyl-esters, the latter are less toxic, easier to handle, the one-step conversion from methyl-esters to acyl-fluorides also deserves to be studied. By controlling the experimental conditions adopted, like reagents molar ratio and temperature is possible to modulate the proportion of the two types of acylfluorides isomers.