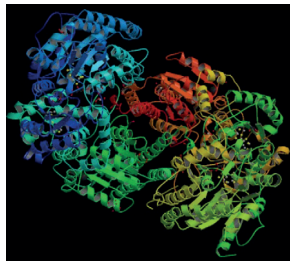
MECHANICAL ENGINEERING I PHYSICS I PRESERVATION OF THE ARCHITECTURAL HERITAGE I SPATIAL PLANNING AND URBAN DEVELOPMENT I STRUCTURAL SEISMIC AND GEOTECHNICAL ENGINEERING I TECHNOLOGY AND DESIGN FOR ENVIRONMENT AND BUILDING I TERRITORIAL DESIGN AND GOVERNMENT I URBAN PLANNING, DESIGN AND POLICY I AEROSPACE ENGINEERING I ARCHITECTURAL AND URBAN DESIGN I ARCHITECTURAL COMPOSITION I ARCHITECTURE, BUILT ENVIRONMENT AND CONSTRUCTION ENGINEERING I ARCHITECTURE, URBAN DESIGN, CONSERVATION OF HOUSING AND LANDSCAPE I BIOENGINEERING I DESIGN I ELECTRICAL ENGINEERING I ENERGY AND NUCLEAR SCIENCE AND TECHNOLOGY I ENVIRONMENTAL AND INFRASTRUCTURE ENGINEERING I INDUSTRIAL CHEMISTRY AND CHEMICAL ENGINEERING I INFORMATION TECHNOLOGY I INTERIOR ARCHITECTURE AND DESIGN I MANAGEMENT ENGINEERING I MATERIALS ENGINEERING I MATHEMATICAL MODELS AND METHODS IN ENGINEERING

PhD Yearbook | 2017

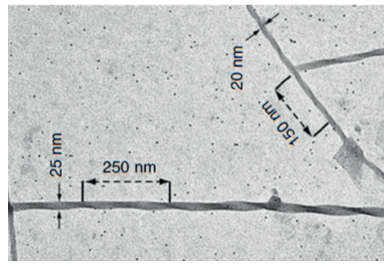
Chair:
Prof. Alessio Frassoldati

DOCTORAL PROGRAM IN INDUSTRIAL CHEMISTRY AND CHEMICAL ENGINEERING (CII)

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.



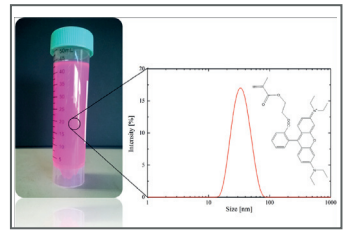
Structure simulation of Nitrogenase enzyme for N_2 conversion to NH_3



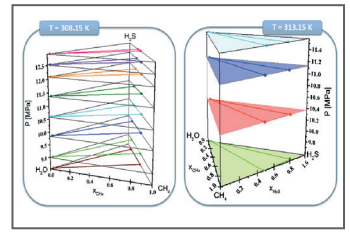
Amyloidal peptide nanohelices in solution as ordered nanomaterials (Nature Commun. 2015, 6:7574, DOI: 10.1038/ncomms8574)

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 Professors 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.

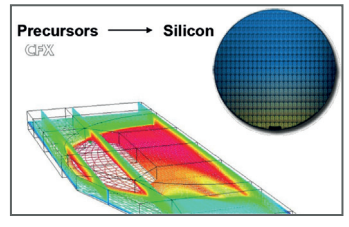


"Biocompatible polymer nanoparticles functionalized with a fluorescent dye for in vivo imaging studies"

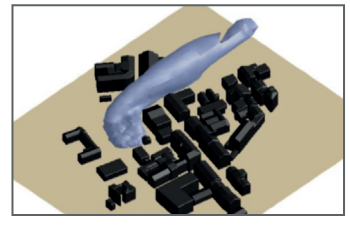


VLE and VLLE measurements for the system CH_4-H_2S-H_2O.

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 graduated more than 100 students, being ~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, numerous the research topics were directly supported by industrial companies, like ENEL, LPE Epitaxial Technology, Bracco, Flamma, Mapei, Solvay Specialty Polymers, RSE, Isagro, Tecnimont, Biochemtex, Pirelli.



Simulation of a chemical vapor deposition reaction for silicon films deposition



Hazardous gas dispersion simulation from an industrial accident

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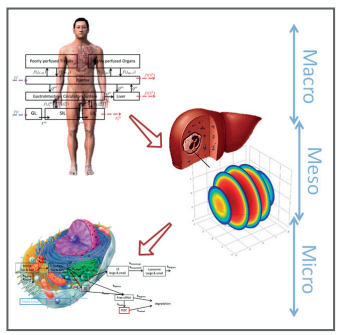
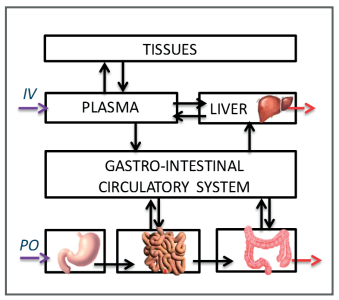
AN INTEGRATED MULTISCALE PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL TO ASSIST DRUG DEVELOPMENT AND INDIVIDUALIZED THERAPIES

Abbiati Roberto Andrea – Supervisor: Prof. Davide Manca

This research project is based on the development of mathematical models for the prediction of drugs disposition in the body, with a specific focus on cancer treatment. In particular, the model is conceived at multiple levels of detail as shown in Figure 1: the Macro-scale describes drugs concentration in the blood and in specific organs, the Meso-scale studies the time-space dependent intra-tumor concentration, and finally the Micro-scale concerns the intracellular concentration of siRNA therapeutics, which is a nucleic acid based cancer therapy. A keyword of this work is Pharmacokinetics (PK), which is a branch of pharmacology that studies how the organism interacts with the drugs administered, this is possible exploring four major phases of drugs path in the body, namely Absorption, Distribution, Metabolism, and Elimination.



1. Conceptual sketch of the PhD research structure. Full Body (macro), organs/tumor (meso), and cells (micro) are the constitutive elements of this multiscale PK model.



2. Compartmental structure of the PBPK model. Model inputs are the drug administration modalities (blue arrows, IV = IntraVenous, PO = Per Os, or Oral). Boxes are the model compartments and represent specific organs/tissues, here the black arrows link the compartments describing the drug distribution process. Finally, red dashed arrows are the elimination terms. The model can be applied with different levels of complexity

Macro-scale

At this level the entire organism body is considered for the formulation of a so called "Physiologically Based Pharmacokinetic model" (PBPK, Figure 2). This is a mathematical model, based on a set of differential equations, for the simulation of drugs concentration-time course in the body. The model is based on the assumption that the body, with its organs and tissues, can be idealized as perfectly mixed tanks (*i.e.*, CSTR) and consequently drug course can be modeled by the definition of mass balances.

Meso-scale

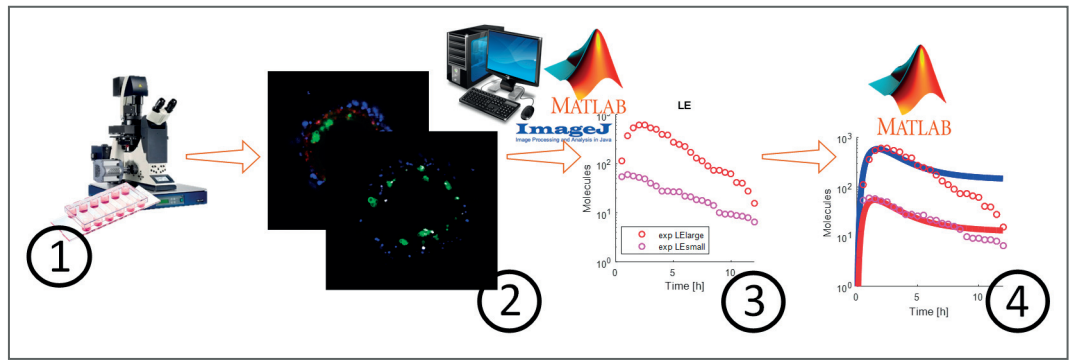
This model aims to overcome the simplifying hypothesis of perfectly mixed tanks applied at the macro-scale, by the introduction of a model based on mass transport equations and simulated with the Finite Element Methods (FEM). Specifically, since the focus of the research is cancer treatment, we studied nanoparticles (NPs) PK inside tumor masses.
The first step is the investigation of the tumor mass physical characteristics, considering its anatomical and physiological properties, and the evolution of tumor progression. The second stage is the search of data for the model parameterization, which calls for the acquisition of data such as: tumor interstitial fluid pressure, oncotic pressure, tumor cells density, and NPs diffusivity.
An innovative aspect of this work is that we considered the spatial variation of tumor properties, since it is established that there are significant differences between tumor core and periphery.

$$\frac{\partial C_i}{\partial t} = D\nabla^2 C_i - \nabla(u_i C_i) + \phi \qquad (1)$$

The mass transport is governed by the general Equation 1, the accumulation is determined by diffusion, convection, and mass source terms which respectively appear at the right side of the equation.
Finally, the model was implemented and solved in COMSOL FEM program. Model simulation produced interesting results concerning the spatial and temporal distribution of NPs in tumors.

Micro-scale

At the highest level of detail, the intercellular cell environment is concerned together with specific cancer treatments, such as the administration of siRNA therapeutics using nanoparticles (i.e. lipoplexes) as vehicles. This model completes the multiscale approach and allows modeling the drug course in the intracellular environment. This activity was particularly complex because the intracellular siRNA trafficking is still partially unknown and the experimental PK data, even if measured with sophisticated microscopy imaging techniques, have to be processed and interpreted.
This was a two-step activity, first we generated the experimental data of intracellular pharmacokinetics of siRNA molecules. Then we implemented the mathematical model for the PK simulation. This model was solved in Matlab and is based on a set of ordinary differential equations that were parametrized via a nonlinear regression with respect to the experimental data.
The integrated multiscale model is highly innovative and showed good predictive performance. This work is important because constitutes a complete framework for the simulation of drugs administration in a field (*i.e.* pharmacology), which is intrinsically experimental and is now moving toward computer simulation to assist drug development.

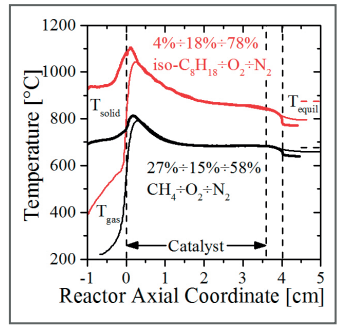


3. Summary of the intracellular trafficking study. Step 1 refers to the experimental in vitro study where tumor cells were treated with siRNA-lipoplex nanoparticles and observed via a confocal microscope. Step 2 is the analysis of the microscope images, which is possible through the study of pixel properties. The complete experimental study was conducted for over 12 h producing a total of 873 images and generated the PK course of the siRNA in various sub-compartments of the cell (Step 3). The final Step 4 is the assessment of the PK model and the parameters fitting. The integrated multiscale model is highly innovative and showed good predictive performance. This work is important because constitutes a complete framework for the simulation of drugs administration in a field (i.e. pharmacology), which is intrinsically experimental and is now moving toward computer simulation to assist drug development.

CATALYTIC PARTIAL OXIDATION OF LIQUID FUELS: EXPERIMENTAL AND MODELING ANALYSIS OF A LAB-SCALE ADIABATIC REFORMER

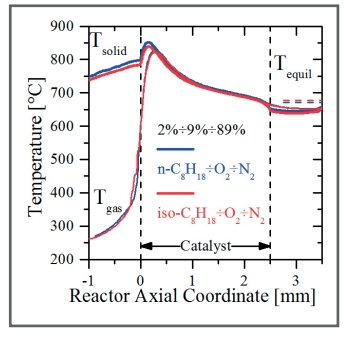
Carrera Andrea – Supervisor: Prof. Alessio Frassoldati

The need of efficient processes for energy conversion and abatement of pollutant emissions keeps high the interest towards efficient energy systems, such as fuel cells, and prompts towards the improvement of combustion and exhaust after-treatment systems. Hydrogen is attractive for its possible usage as energy carrier as well for the reduction of pollutant emissions. The superior combustion properties of hydrogen can be exploited in Internal Combustion Engines or Gas Turbines, for the generation of mechanical work, electricity or heat. Syngas, i.e. a mixture of hydrogen and carbon monoxide, when purified from particulate matter and sulfur compounds, may also be fed to Solid Oxide Fuel Cells, for the conversion into electric energy. The development of SOFC-based Auxiliary Power Units has a great interest because of the availability of electric energy when the engine is off. Synthesis gas may also regenerate Lean NO_x Traps during their rich phase.
Hydrogen may be either stored or produced on board of vehicles. Though the stationary production of hydrogen is well established, the first solution should face many challenges before becoming a commercial technology. In fact, hydrogen storage is costly, and requires specific infrastructures for its distribution. Hydrogen on-board production represents an interesting alternative, as several technologies allows the conversion of primary fuels into this energy vector. The development of a compact and light device for hydrogen production is necessary when considering mobile applications. Currently, the main commercial hydrogen production processes are steam reforming (SR), partial oxidation (PO, either non-catalytic, or catalytic), auto-thermal reforming (ATR). Steam reforming is a well consolidated technology, which consists in the reaction between hydrocarbons and water, in the presence of a catalyst. Though steam reforming is widely used in the industry, it is an endothermic and energy-demanding process, which requires external heat supply, therefore it is not suited for small-scale applications. In the Partial Oxidation process, oxygen reacts with hydrocarbons to produce carbon dioxide, water, carbon monoxide and hydrogen. This technology works in harsh conditions, hence it is not valid for the small-scale hydrogen production, Catalytic Partial Oxidation requires shorter contact times (t ~ ms) than the non-catalytic process (t ~ s) to achieve equilibrium. The CPO process is globally exothermic and this allows the use of simple adiabatic reactors. In the catalytic Auto-Thermal Reforming, both water and oxygen are reacted with the hydrocarbon feedstock. This process may be thermally neutral or exothermic, according to the reactant composition employed. ATR operates at lower temperatures than CPO, but the former requires slightly higher reactor volumes, as well as water storage and dosing systems.
The CPO process is globally exothermic and may be carried out in adiabatic reactors, loaded with a structured catalyst, which offer a better trade-off between pressure drops and transfer properties with respect to random packings. Rh catalysts offer several advantages, compared to transition metal and Pt catalysts, such as high activity and selectivity to syngas, low tendency to form coke and good thermal stability.
In this work, the CPO of iso-octane and n-octane has been investigated on Rh based catalysts, supported over a 400 CPSI cordierite honeycomb monolith in a lab-scale auto-thermal reformer, equipped with the spatially resolved sampling technique. A one



1. Comparison among experimental temperature profiles in the CPO of methane and iso-octane; methane CPO: CH_4=27.3%, C/O=0.9, F=10Nl/min, T_{IN}=25°C; iso-octane CPO: iso-C_8H_{18}=4%, C/O=0.9, F=10Nl/min, T_{IN}=85°C.

dimensional, single-channel, heterogeneous, adiabatic reactor model have been used to verify the reaction mechanism and to better understand the interplay between chemical kinetics and transport phenomena.
Both iso-octane and n-octane exhibit an indirect-consecutive reaction scheme, with oxidation of the fuel to CO_2 and H_2O and reforming of the excess fuel with H_2O with production of syngas, which results in the presence of an Oxy-Reforming zone next to the catalyst inlet and a Reforming zone downstream, and leads to the onset of a hot spot of temperature.
The impact of mass transfer on the CPO of octane isomers is important, and affects significantly the thermal management of the reactor. In fact, due to the decrease of molecular diffusivity with increasing size of the hydrocarbon molecule, and thus to the decrease of steam reforming efficiency, the hot spot temperature increases when passing from methane to octanes, at constant carbon and oxygen flow rates, as detailed in Figure 1.
Temperature profiles along the reactor axial coordinate are similar between the two octane isomers, as reported in Figure 2. High temperatures in the gas phase (T>700°C) activate gas phase cracking reactions, with the production of olefins and light alkanes, which can condensate, forming soot or coke, or can further react on the catalyst surface, producing syngas. While the heterogeneous reactivity of the two isomers, n-octane and iso-octane is similar, the two octanes undergo different gas phase decomposition pathways, which lead to different distributions of olefins and light alkanes: iso-octane is more selective towards iso-butylene and propylene, while n-octane mainly produces ethylene.
Temperature Programmed Oxidation revealed that different forms of coke are deposited onto the catalytic monolith. Coke deposition mainly occurs in the reforming zone and is more pronounced in the case of n-octane. Deposition of carbon species is thermodynamically favored by N_2 dilution, which was adopted in the experiments to prevent catalyst overheating. However, reactant dilution can be practically implemented in combination with Internal Combustion Engines using the Exhaust Gas Recirculation. Thermodynamic calculations show that, thanks to the H_2O content of the diluting gas, this is effective in the reduction of the operating temperature of the reactor, while keeping the process in a thermodynamically safe zone with respect to coke deposition. Still, coke deposition is an important issue, especially when using alumina as support. The introduction of a more basic support with higher surface area than α-alumina, such as $MgAl_2O_4$ spin el, contributes to enhance the rate of steam reforming, with the twofold benefit of lowering the hot spot temperature and hindering the deposition of carbon species on the catalyst; both aspects contribute to preserve the catalyst stability under octanes CPO conditions. TPO analysis confirms that the alumina support, more acidic, is subjected to higher coke deposition than magnesium aluminate. The co-feed of aromatics and naphthenic hydrocarbons and sulphur poisoning should be addressed in more detail in the future.



2. Comparison among experimental temperature profiles in the CPO of iso-octane and n-octane; x-C_8H_{18}=2%, C/O=0.9, F=10Nl/min, T_{IN}=85°C.

EVALUATION AND DEVELOPMENT OF BIOMASS CONVERSION PROCESSES FOR THE CHEMICAL AND BIOCHEMICAL VALORIZATION OF LIGNIN

Carrozza Chiara Francesca – Supervisor: Prof. Attilio Citterio

Abstract

Through the integration of green chemistry into biorefineries and the use of low environmental impact technologies, future sustainable production chains of biofuels and high value chemicals from biomass could quickly forecast. Despite the fact that a massive amount of lignin is obtained from the biorefineries, the use of lignin in real industrial processes is far to be obtained. Hence, approaches to develop lignin conversion into high-value co-products are progressively investigated in the attempt to improve the economics of the biorefineries.

In this sense, the PhD project deals with the valorization of biorefinery lignin as by-product from second-generation bioethanol production involving either a biochemical or chemical treatments. The starting materials were obtained from different stages of the cellulosic ethanol plants powered by Proesa™ technology and operated in Crescentino (Italy).

More specifically, the research activity was divided in four main Chapters:

Chapter 1: Introduction

In order to face the challenges of becoming independent of crude oil and switching to a more sustainable and carbon neutral society, biomass has emerged as most prospective raw material in the next future. The basic knowledge about plant origin materials, with specific attention to lignin component will be introduced in this chapter. In this sense, a deep understanding of biomass as renewable feedstock will be provided. Then, the sustainable use of lignin, as the other major constituent in biomass and its potential as starting material for the production of chemicals due to its aromatic structure, will be investigated. Several approaches either focus on the direct utilization of lignin with suitable modification to find application in low value products including dispersant, binders, emulsifiers and resins, or target the depolymerization of lignin macromolecule into high value aromatic fine chemicals will be presented. Finally, a general overview of Crescentino plant and its technology will be reported in order to understand where the raw materials used among all experiments come from.

Chapter 2: Lignin isolation and characterization

Starting from protocol procedures, optimization of extraction and purification treatments combining mechanical treatment (ball milling) and an intensive washing step will be performed. All the materials were fully characterized by means of different spectroscopic techniques and their properties compared with the raw material. It was found that soxhlet extraction as washing procedure will lead to a material containing 96% of lignin. Meanwhile, in collaboration with the University of Pavia, the effect of the growth of two fungal species, *Trichoderma asperellum* EVT4 and *Pleurotus ostreatus*, which respectively are able to degrade polysaccharides or lignin aiming the biodegradation of the material, was tested. It was found that *Trichoderma asperellum* EVT4 is able to purify the material lowering the content of sugar (reducing sugars or glucose) in a strong way but leaves a complicated tri-dimensional structure. Comparison between chemical and biochemical purification have been done and it can be assumed that both procedure can purify lignin rich residue with a good degree of lignin purity but with different structural properties.

Finally, in collaboration with Lawrence Berkeley National Laboratory, a complete biorefinery process (pretreatment, hydrolysis and fermentation) in lab scale using ionic liquid as solvent to degrade and solubilized two different feedstocks, switchgrass and poplar, was performed. Compared with the traditional pretreatments, IL pretreatment is a relatively new approach and has several parameters that need more investigation. The main drawbacks in ILs pretreatment consist in the extensive washing procedure of the pretreated biomass to remove residual amounts of ILs that may inhibit downstream saccharification and fermentation. To overcome this issue, recently a new wash-free approach was developed. It is based on a one-pot system where IL pretreatment, saccharification and fermentation followed by direct extraction of sugar and recovery of lignin will take place simultaneously. The one-pot process performed gaves us good result in term of ethanol yield since the whole hydrolysed glucose was converted. Hence, it was demonstrated that IL pretreatment improves the "delignification" process and significantly increases the enzymatic hydrolysis efficiency. Physical and chemical alterations in lignin structure were investigated with the aim to understand its reactivity during the whole IL treatment.

Chapter 3 and Chapter 4: Catalytic oxidation of lignin and lignin depolymerization by hydrogenolysis.

Since lignin is the richest source of renewable aromatic compounds on earth, its conversion into well-defined aromatic chemicals was deeply investigated by either oxidative and reductive approaches in mild conditions of temperature and pressure.

As it is known in literature, the recalcitrance of lignin and its ability to recondensate represent a challenge that inhibit an efficient depolymerization.

In the first case, two different catalytic conditions were tested on the purified material by using $CuSO_4$ or Co(salen) as catalysts. With copper sulphate the three main aldehydes (vanillin, siringaldehyde and p-hydroxy aldehyde) were produced at pressure equal to 3 bar with an overall conversion of about 5% (coherent with literature results). Instead by using Co complex, p-benzoquinones were formed (mainly methoxy benzoquinone and dimethoxy benzoquinone) with a total yield of 7.2% at 3.5 bar. On the other hand, the purified materials were depolymerized by catalytic hydrogenolysis in alcoholic media with a combination of palladium on carbon and/or nickel(II) acetate as catalyst. To increase the efficiency of the reaction, in-situ preparation of the nickel-based catalyst was carried out by adsorption of metal salt on the material. In 1,2-propanendiol as solvent at 210 °C, up to 80% of the material was solubilized with an overall yield of reduced monolignol derivatives of about 18%. Depolymerized lignin fragments (both the liquid residue and the solid residue recovered after precipitation with water) were detected by MALDI-ToF analysis with a molecular weight between 400-1400 Da.

To this end, catalytic depolymerization reaction through hydrogenolysis was performed on the one-pot ionic liquid residues. Different conditions of temperature and pressure were tested: at 200 °C the alcoholic solvent (1,2-propanendiol) acts as source of hydrogen, while at 90 °C and 140 °C the reaction was performed adding 20 bar of H2. Solid residues, from either switchgrass or poplar, reach a maximum value of about 35% but the distribution of product is opposite: about 60% of S unit in switchgrass residue and about 60% of G unit in poplar residue.

TOWARDS ENGINEERING OF SOLID-STATE SUPRAMOLECULAR ROTORS VIA HALOGEN BONDING

Catalano Luca – Supervisor: Prof. Pierangelo Metrangolo

My PhD research activity had a twofold objective:

a) Studying halogen-bonding interactions (XB) at a fundamental level by focusing on new tools for the identification and characterization of this non-covalent interaction;
b) Engineering crystalline supramolecular rotors based on halogen bonding and studying the effect of the strength of XB on the dynamics of these systems.

Far-IR spectroscopy is seldom employed to prove the occurrence of halogen bonding. This is essentially due to low frequencies (< 400 cm-1) and weak intensities of the vibrations involving halogens. However thanks to new standard instrumentations the detection limit of vibrational spectroscopy is moving to lower frequencies allowing the exploration of the Far-IR region. To proof this concept, we built a prototypical series of supramolecular adducts based on halogen bonding and then we characterized them with X-ray diffraction, DSC and IR spectroscopy. We coupled the experimental IR analysis with calculations in order to correctly assign the different vibrations to the peaks of the IR spectra. The adducts were formed between strong halogen bond donors (iodopentafluorobenzene and bromopentafluorobenzene) and strong Lewis bases (pyridyl moieties and TMEDA).
All new species were obtained via cocrystallization from standard solvents and their crystal structures were either confirmed (if already known) or solved through XRD analysis. One species was liquid at room temperature, thus, to obtain its crystal structure, we successfully employed the *in situ* cryo-crystallization technique. Far-IR analysis showed red-shifting and intensity increase of the main vibrations involving the halogen atoms. These effects are diagnostic of the occurrence and the relative strength of the XB.

Solid-state nuclear magnetic resonance (SSNMR) spectroscopy is a versatile characterization technique that can provide a plethora of information complementary to single crystal X-ray diffraction analysis. In order to apply this powerful technique to the study of XB, we designed an experimental and computational investigation of the relationship between the geometry of XB and the SSNMR chemical shifts of the non-quadrupolar nuclei either directly involved in the interaction (^{15}N) or covalently bonded to the halogen atom (^{13}C).
To reach this goal we prepared two series of X-bonded cocrystals based upon two different dipyridyl modules, and several halobenzenes and diiodoalkanes, as XB-donors. All cocrystals were fully characterized *via* IR spectroscopy, thermal analysis, single crystal and powder XRD. We then investigated our systems via SSNMR. For the first time, the change in the ^{15}N SSNMR chemical shifts upon XB formation is shown to experimentally correlate with the normalized distance parameter of the XB. The same overall trend is confirmed by density functional theory (DFT) calculations of the chemical shifts. ^{13}C NQS experiments show a positive, linear correlation between the chemical shifts and the C-I elongation, which is an indirect probe of the strength of the XB. These correlations can be of general utility to estimate the geometry of the XB.

Amphydynamic crystals are materials built to possess rapidly moving components in the solid state. Nowadays there is a growing interest in this class of compounds for the development of new functional materials and molecular machines.
The aim of our research is to take advantage of crystal engineering principles to assemble stators and rotators into cocrystals shown highly efficient molecular dynamics. This strategy has few advantages such as its intrinsic flexibility and hence the trivial access to a vast number of different supramolecular rotors. Firstly, we were able to synthesized crystalline supramolecular rotors self-assembled by XB of diazabicylo[2.2.2]octane (dabco), a well known C_3-symmetric cylindrically shaped rotator, and a set of five fluorine-substituted iodobenzenes, acting as strong halogen bond donors, that take the role of the stators. We characterized the adducts via single crystal and powders XRD, IR spectroscopy and melting point measurements to confirm their formation. Then we used variable temperature ^{1}H T_1 spin-lattice relaxation measurements to characterize the dynamics of the rotors. All structures display ultrafast Brownian rotation around the XB with activation energies ranging from 2.4 to 4.9 kcal/mol,. In all cases the activation energies are lower than the one of pure dabco (8.3 kcal/mol). Within the cocrystals, the rotators are partially isolated from their neighbouring rotator molecules by XB donors, which work both as stators and bearings. The pre-exponential factors of the dynamics are in the range 1–9 x 10^{12} s^{-1}. These results are comparable to those found in rotors with covalent rotational axis, suggesting that XB is robust enough to work as an efficient axle of rotation. Lineshape analysis of quadrupolar echo ^{2}H NMR measurements in selected samples indicated rotational trajectories consistent with both 3-fold and 6-fold symmetric potential of the rotator.
The second step of the supramolecular rotors project was to understand how the strength of XB, working as axle of rotation, influences the dynamics of the rotors. To do so, we successfully realized two new halogen-bonded supramolecular rotors with isomorphic crystal structures at 100 K and room temperature. The only difference lies in the halogen atom involved in the XB (X = Br, I). Solvent assisted mechanochemical crystallization allowed us to prepare pure cocrystals. The increasing dynamic disorder of dabco from low to high temperature observed by single crystal X-ray diffraction and quadrupolar-echo ^{2}H NMR led us to conclude that the rotation of dabco in both cocrystals can be described by a six-fold rotation potential surface with three low energy minima and three minima of higher energy that, by this reason, at low temperatures are less populated. ^{1}H T_1 relaxometry experiments allowed us to calculate the activation parameters for the rotation of dabco in both cocrystals. We observed good correlation between the low crystal packing, C_k = 0.66 at 100 K, and the small rotational barriers of dabco, 1.15 and 0.71 kcal/mol, respectively, with the later being the lowest reported in the field of molecular rotors. The two cocrystals showed pre-exponential factors of almost the same magnitude (t_0^{-1}), 1.3 x 10^{12} s^{-2} and 1.3 x 1012 s-2 respectively.
Using isomorphous cocrystals, as demonstrated by X-ray diffraction and IR data, we were able to sort out the origin of enthalpy and entropy of activation. Accordingly, by fitting ^{1}H T_1 data to the Arrhenius, Eyring and Kubo-Tomita equations, it was found negative entropies of activation of the same magnitude ($\Delta S^{\neq}$ = -3.0 cal/mol K) supporting the similarity of the normal modes and lattice phonons. On the other hand, the enthalpy of activation for the rotation of dabco in co-crystal involving iodine ($\Delta H^{\neq}$ = 0.95 kcal/mol) was shown to be almost twice as that of the one involving bromine ($\Delta H^{\neq}$ = 0.54 kcal/mol) that correlates well with the subtle crystal structure differences, namely a more hindered environment in the dabco cavity in the iodine-based cocrystal.

In conclusion relevant results were obtained in both the research strands of my PhD career.

- We demonstrated that Far-IR spectroscopy and SSNMR are powerful diagnostic tools for the detection XB and for the characterization of its strength and geometry.
- We synthesized and fully characterized the first examples of XB-based amphidynamic cocrystals. Furthermore we were able to sort out the origin of enthalpy and entropy of activation of the rotators dynamics.
The discovery of these new crystalline multicomponent systems thus opens up new avenues in the development of new smart materials and molecular machines.

A STRUCTURAL APPROACH TOWARDS CELL ADHESION MODULATION AND PROTEIN ENGINEERING

Dalle Vedove Andrea – Supervisor: Dr. Emilio Parisini

Protein X-ray crystallography is a very powerful tool that provides, at the molecular level, the high quality and high resolution structural information that is necessary for structure-function correlation analysis, protein engineering, structure based drug design and molecular dynamics (MD) simulations.
In this thesis, this technique has been extensively used for the investigation of the structure, properties and possible application of the extracellular portion of some selected cell-adhesion proteins of the type I classical cadherin family and of a deglycating enzyme from the large Fructosyl Amino Oxidase family, called Amadoriase I.
Cadherins are calcium-dependent trans-membrane proteins that comprise three clearly discernible regions: intracellular, trans-membrane and extracellular. The extracellular portion is formed by a variable number of so-called extracellular cadherin (EC) repeat domains, each formed by approximately 110 amino acidic residues and rigidified by the presence of $Ca^{2}+$ ions between them.
They are of critical importance for cell-cell adhesion, a fundamental process that results in cellular organization and tissue differentiation, thus allowing the formation of tissues and organs and ultimately the development of complex multicellular organisms. Other than their adhesive function, cadherins also perform a cell-cell signaling function. It is well known that variations in cadherin natural expression level and changes in their ability to form either homophilic dimers or bind to selected protein substrates correlate with the onset and the progression of diseases such as cancer, asthma and chronic inflammation states.
Although the cadherin main functions (adhesion and signaling) have been quite extensively investigated over the last two decades, the mechanism by which such tasks are performed still needs to be fully elucidated. Over time, a combination of biophysical techniques (mainly X-ray diffraction, NMR and SAXS) have provided a clear, albeit still incomplete, picture of the adhesion mechanism, leaving the complete trajectory that leads, very dynamically, from the monomer to the dimeric adhesive state and back still partially elusive. The implications of such lack of complete structural characterization are important: to date, no clear molecular bases for cadherin homo-selectivity and for their energy activation profiles have been unambiguously identified.
In this thesis work, I have studied selected cadherin family members at the molecular level by single crystal X-ray crystallography. Overall, my goal was to contribute to the characterization of their adhesion mechanism. Furthermore, in the context of this thesis, I combined this structural analysis with biophysical, computational and functional studies aimed at the development or the identification of molecules that are capable of modulating cadherin homophilic adhesion. Finally, starting from the structural information, I have engineered a cadherin family member with the goal of producing functionalized biomaterials. In fact, due to the important role of the protein in tissue sorting and formation, such cadherin-functionalized hybrid materials may be employed as scaffolds in tissue engineering and tissue regeneration or be used for the development of cell-sorting or sensing lab-on-chip platforms.
The second project that I focused on in my thesis is the X-ray crystal structure of the deglycating enzyme Amadoriase I. A member of the Fructosyl Amino Oxidase family, this enzyme is capable of hydrolyzing the bond between the amine and the sugar moiety of a glycated amino acid.
From a biomedical point of view, the study of this enzyme is very important since protein glycation reactions occur spontaneously in the body over time due to the sugar present in blood. As a result of this spontaneous glycation reaction (usually referred to as the Maillard reaction) proteins are progressively glycated and, especially those with long half-life, tend to become heavily crosslinked over time. These non specific modifications negatively affect the function of the proteins and may eventually lead to the development of diseases such as Alzheimer's disease, arteriosclerosis, nephropathy and retinopathy, with a higher incidence in elderly people and in people with abnormally high blood sugar levels.
Moreover, deglycating enzymes are also utilized for the measurement of the concentration of the glycated form of hemoglobin (HbA1c) in the blood. In fact, due to the relatively long life-time of hemoglobin (90-120 days) and therefore its tendency to be glycated over time, this is a very good indicator of the concentration of blood glucose over a period of 2-3 months. Unfortunately, however, due to the fact that the available enzymes only work on glycated amino acids, this process is not immediate since HbA1c must be proteolytically cleaved before the enzymatic detection of selected glycated amino acids can actually take place.
During my thesis, I contributed to the structural characterization of of the apo form and the substrate-bound form of Amadoriase I from *Aspergillus fumigatus*.
Moreover, I have been actively involved in the first attempts to engineer this enzyme in order to enhance its natural substrate recognition capabilities. All these studies have been conducted using a combination of molecular biology, protein chemistry, X-ray crystallography and molecular dynamics techniques. The ultimate goal with this project is to engineer the Amadoriase I enzyme in order to enlarge its catalytic cavity and allow its catalytic activity on large substrates such as polypeptides or even whole glycated proteins. This would, for instance, potentially improve the current procedures employed for the measurement of HbA1c in diabetic patients, possibly leading to new, efficient and low cost diagnostic tools for diabetes monitoring. Other potential applications of such molecular technology include the use of such chimeric enzyme to slow or even reverse collagen rigidification in aging tissues as well as in the food industry, to limit protein glycation in aliments that need thermal treatment (e.g. UHT milk).

REACTIVITY ASSESMENT OF BIOL-OILS IN HYDRODEOXYGENATION REACTIONS USING MODEL COMPOUNDS

De Vecchi Sebastiano – Supervisor: Prof. Massimo Morbidelli

In the last decade the growing dread of fossil fuel depletion as well as the increasing change in climate due to anthropogenic emissions have provided a compelling motivation for exploring alternative source of fuel, chemicals and energy.
First generation bio fuels (i.e Bioethanol and Biodiesel) developed in the last 30 years from food grade feedstock and edible crops have pointed out the potentiality of biomass conversion into chemicals and fuels; however, these technologies have a major disadvantage in the competition with land usage for food production. In order to prevent this problem and avoid unjustified land usage researchers and industries have focused their attention on second generation biofuels, which are based on the conversion of biomass obtained from agricultural waste.
The variable chemical composition of lignocellulosic biomass and the possibility of converting this feedstock in different high value products has prompted an important analogy with the refinery infrastructure, and from this comparison the concept of "Bio-refinery", an integrated facility that could produce power, fuels and chemicals, has been introduced.
Nowadays the carbohydrate fractions (i.e. hemicellulose and cellulose) are converted respectively by fermentation and chemo catalysis in fuels (i.e. bio-ethanol) and chemicals (i.e. diols), while a unique and competitive conversion pathway for lignin has not yet achieved a commercial level, even if some lignin conversion processes have been tested on pilot scale. The progressive diffusion of second generation bioethanol plant will make available in the next future massive amount of lignin and therefore the study of its conversion in high value chemicals is key step that will enhance the biorefinery sustainability.
Moreover in the Kraft Pulp Industry new technologies to separate and extracts lignin from black liquor have been developed, and some industrial plant are already existing. This will put on the market additional volumes of lignin for possible bio-based chemical production.
Currently lignins are cracked into liquid products by different processes. The liquid product obtained from these technologies are generally named "bio oils" and is a complex mixtures of different chemical compounds such as phenols, ethers and carboxylic acids. Due to their high oxygen content (15 - 40%wt), this mixture presents some detrimental properties like high viscosity, thermal instability and immiscibility with the most common liquid fuel; therefore, overcoming these deleterious properties by implementing an efficient deoxygenation process is an essential processing goal.
Catalytic hydrodeoxygenation offers a suitable way to convert oxygen rich bio oils into hydrocarbons: an optimal tuning of the operating conditions (i.e. hydrogen pressure and temperature) allows the modulation of the deoxygenation degree from a simple stabilization (elimination of reactive functions such as carbonyl and olefin) to a complete conversion toward aromatic or aliphatic hydrocarbons. Most of the works published in recent years have demonstrated that HDO of bio oil is feasible, although it requires a significant effort in overcoming operating problems such as reactor plugging, catalyst deactivation and yields optimization.
The complex composition and the variability of bio oils enhance the difficulty of understanding the main variables involved in HDO reactions and increases the effort of developing an efficient analytical background. A solution which allows to overcome this problems by simplifying both the reactivity of the system and products analysis is the study of a model compounds. The model compounds of choice are mono- or di-aromatic molecules which keep the linkage and the functional groups contained in bio-oils (i.e ether linkage, hydroxyl groups); the most important model used to mimic the reactivity of real mixtures are phenol, guaiacol, siringol and dimeric models such as dibenzyl etherl/biphenol.
A stable and active catalyst is necessary for the conversion of bio-oils through HDO reaction; several works have been focused on conventional hydro-treating catalysts based on nickel or cobalt promoted by molybdenum, typically used in hydro-desulfuration (HDS) of crude oil.
A critical review of the state of art has pointed out how pre-sulfide catalyst such as $CoMo/Al_2O_3$ or $NiMo/Al_2O_3$ are very active in HDO reactions, nevertheless in order to maintain constant their activity H_2S has to be fed, leading to sulfur contamination in the products. The limitations of sulfide catalysts have prompted the use of more stable catalysts based on metal oxides such as cobalt and nickel.
Initially, the performance of four commercial catalysts have been evaluated in the batch HDO of GUA, an aromatic molecule which carries the typical functional groups found in several bio-oil type. The catalysts were selected considering the state of the art and criteria such as cost and availability. The best performances were obtained using nickel based catalysts, as the cobalt ones have shown a lower activity towards deoxygenation reactions
The aromatic ring saturation is a side reaction that always occurs during HDO, causing a lack of selectivity towards aromatic compounds such as benzene, toluene and xylene. This work has pointed out how an optimal tuning of hydrogen pressure could limit this reaction and reduce waste of hydrogen.
Temperature and residence time were also evaluated through a series of reactions carried out at 25 bar. The optimal processing temperature was found to be 300°C; at low temperature hydrogenation reaction are thermodynamically favored, and a higher selectivity toward naphtenics has been registered. Conversely, at high temperature the increase of both the aromatic components and the hydro-deoxygenation degree does not economically justify the choice of the highest temperature as an industrial plant operating parameters.
In all the configurations tested, GUA reached a full conversion in one hour of reaction, while at lower residence times the main products has always been oxygenated compound such as cyclohexanol and phenol, this investigation has pointed out the predominance of hydro-deoxygenation reaction at long contact time
The study of other monomeric and dimeric compounds has also carried out. Monomeric molecules such as cresol, anisole, and eugenol have shown results consistent with the results found for GUA. Conversely, dimeric model compounds exhibit a very complex reactivity, directly correlated with the presence of aromatic carbon-oxygen or carbon – carbon bonds.
The final part of this work has been focused on the development of a continuous process carried out at low pressure, aimed at converting GUA in methylated phenol thought trans-methylation reactions. In this case cobalt/alumina catalyst at different temperatures and residence times has been used, and the experimental data have been collected to fit a good agreement with a first order kinetic model.

NITROGEN-CONTAINING ORGANIC COMPOUNDS: FROM AGRICULTURE TO MEDICINAL CHEMISTRY

Fiorati Andrea – Supervisor: Prof. Stefano Servi

Nitrogen containing compounds

Nitrogen is one of the most common chemical element present on our planet. It is involved in almost all biological processes and it is part of many important chemicals with industrial relevance like drugs and fertilizers. Since the invention of the Haber-Bosch process for the conversion of gaseous nitrogen into ammonia, the industrial production of nitrogen containing compounds and fertilizers has grown significantly fuelling the increase in food production over the past century. However, in order to meet the needs of future population growth rate novel form of nitrogen containing fertilizers are needed. Moreover, nitrogen is present as amino group in most bioactive natural and non-natural compounds.

Urea

Urea is a colorless, odorless solid, with a high nitrogen content (46 %), highly soluble in water. It possesses a low toxicity, and it is involved in numerous biological processes. More than 75 % of manufactured urea is consumed as nitrogen containing fertilizer. It has been estimated that the world's urea producing capacity will reach 226.1 million tons (Mt) in 2016 from 44 Mt in 2011.

Amines

Organic amines are widespread compounds of extreme interest. These amines, in particular the isomerically pure ones, have applications ranging from intermediates for the synthesis of pharmaceutical active ingredients, to resolving agents for separation of enantiomers, or ligands for asymmetric synthesis. The synthesis of amines and chiral amines is subject of intensive studies. Despite the historical and actual interest in chiral amines their synthesis remains challenging. The stereoselective production of amines can be accomplished both by chemical and biocatalytic synthesis. The classic chemical approaches often require harsh conditions and expensive catalyst. Due to the possibility of performing the same reactions in mild condition with a high stereoselectivity, biocatalysis is gaining consideration as valuable alternative to the standard chemical synthesis. The term "biocatalysis" denotes the use of enzymes as catalyst to perform chemical transformations. This field merge together biology, chemistry, enzymology and biotechnology.
This PhD thesis is focused on two main topics:

- The production of isomerically pure amines using a biocatalytic approach.
- The development of a novel approach for obtain slow release urea containing fertilizer.

Isomerically pure amines by a biocatalytic approach

Transaminases are enzymes able to catalyse the enantioselective reductive amination of carbonyl moieties. While the R/S selectivity of this class of enzymes has been extensively studied there are only few references in the literature about the investigation on the *cis*/*trans* selectivity when carrying out the reductive amination on substituted cyclohexanones. These references reported only the investigation on 2- or 3-substituted cyclohexanones, while 4-substituted and 4,4-disubstituted cyclohexanones results totally unexplored. The amines obtained in the reductive amination are structurally related to important pharmaceutical compounds. Thirteen different ω-transaminases (ωTAs) were investigated as catalyst for the stereoselective synthesis of 4,4′-substituted-cyclohexylamines, both in aqueous media and in organic solvents. Substrates ketones were synthetized starting from the common commercial precursor 1,4-cyclohexanedione monoethylene acetal and all the corresponding amines as references were obtained by reductive amination.
The activity of ωTAs on 4-4′-disubstituted cyclohexanones was explored giving interesting results. Tested in their aqueous environment the stereoselectivity of these enzymes result, generally, high (d.e. 90-99.9%), in particular for substrate with bulky substituent in position 4. Surprisingly, all the *R*-selective ωTAs tested results inactive on these substrates. Some of the tested enzymes showed a different stereospecificity in function of the dimension of the substituent in position 4, suggesting that the substituent in position 4 has a great influence on the positioning of the planar quinonoid intermediate in the active site. However, while the solubilities of some proposed ketones allow to perform the biotransformations in water, other substrates have such a low water solubility to result completely unaffected. In addition, the recovery of the produced amines is not trivial as the extractive procedures result inefficient. To overcome these problems, a new, efficient approach for the reductive amination with ω-transaminases in organic solvents was set up. This approach involves the use of surfactants producing a catalytic microemulsion that encapsulates the enzymes. Different parameters (*e.g.* temperature, solvents and surfactant nature) were finely tuned in order to optimize the process. Once this approach was set up, it was applied for the conversions of all the cyclic ketones proposed to the corresponding amines using six different enzymes. The amines were obtained with high yield and high stereospecifity.
In conclusion in this work 13 different ω-transaminases were employed, both in aqueous media and in organic solvents, for screening the activity of this class of enzymes on 4,4′-substituted-cyclohexanones producing isomerically enriched amines, structurally related to pharmaceutical compounds.

A novel approach to slow release urea containing fertilizer

Urea is applied in soil to feed plants with the nitrogen content and it is the most widely used fertilizer. The high water solubility of urea (55% w/w at 25°C) has a great impact in all the degradation processes, such as leaching and chemical transformations, which lead to the formation of ammonium ions, nitrites, nitrates and other nitrogenated gas. Only a small part of all these nitrogen-containing compounds can be adsorbed by plants as nutrients. As consequence the major part of urea added to the soil as plant nutrient are wasted with a great environmental impact. Controlled-release urea (CRU) fertilizers should behave like less soluble organic materials releasing urea in a controlled manner over time. A novel urea containing fertilizer able to control the urea solubility can be of great interest from environmental and industrial point of view. In the pharmaceutical field it is already well known that the solubility of active compounds can be increased or decreased by co-crystallizing them with some coformers. The idea of this project is to decrease the urea solubility by co-crystallizing it with some low solubility coformers in order to obtain a controlled urea release preparation which is able to reduce the leaching in soil, and the (bio)chemical urea degradation. Urea was already successfully employed as a coformer for the preparation of a high number of co-crystals. Starting from these already known co-crystals, leaching experiments were carried out in order to validate the hypothesis that co-crystals can be employed as controlled release urea form. Leaching experiments clearly demonstrates that the bioavailability of urea in soil is strictly dependent from its solubility, and co-crystal technology may be successfully applied for produce novel slow-release urea forms. Thus six different novel compounds able to act both as co-crystal coformers and as slow release fertilizer were designed, synthetized, fully characterized and studied as co-crystal coformer. In this work, it was demonstrated that, co-crystallization could be efficiently applied for controlling the urea leaching in soil and two novel urea co-crystal were observed for the first time.

NOVEL COBALT-BASED CATALYSTS FOR THE INTENSIFICATION OF THE FISCHER-TROPSCH SYNTHESIS

Fratalocchi Laura – Supervisor: Prof. Luca Lietti

The development of the optimal cobalt based FT catalyst, with improved activity and selectivity to desired products, has been the goal of this PhD thesis work. This goal has been pursued by a combination of experimental activities at different scales, starting from the preparation of the catalysts, to their characterization and eventually the assessment of their catalytic performances in the FTS.

In the first part of this thesis work the development of a novel preparation procedure for an eggshell-type Co/γ-Al_2O_3 catalyst is reported. The main characteristics of the obtained material are a diameter smaller than 1 *mm* which is the most common value in the scientific literature, and a diffusive length ensuring the absence of mass transfer limitations. Interestingly, the prepared eggshell catalyst shows great catalytic performances if compared with those of a powdered catalyst (obtained by grinding and sieving the eggshell catalyst) working in a kinetically controlled regime. This result has been explained by considering the onset of weak mass transport limitations in the case of the eggshell catalyst, which boost both the CO conversion kinetics and the catalyst hydrogenating ability. These results show that engineered eggshell catalysts with an optimal thickness of the active shell represent an optimal solution for applications purpose. In fact, it is possible to achieve high C_{15+} yields per mass of cobalt in the reactor, while limiting the ΔP in compact packed-bed reactors for the FTS.

The second part of this thesis work focuses in developing a highly active Co/γ-Al_2O_3 catalyst as uniformly impregnated with a pellet size of 300 mm in diameter. In compact FT reactors, such diameter represents a compromise to keep under control mass transfer and pressure drop issues. In this regard, two strategies have been adopted in this thesis work to increase the number of cobalt metal surface sites available for the FTS. The decrease of the cobalt metal particle size through the improvement of the preparation methods commonly applied at the industrial scale (in view of the necessity not to complicate the catalyst synthesis) and the enhancement of the catalyst reducibility with the addition of a small amount of noble metals (in view of the catalyst cost).

Concerning the first approach, a highly active Co-based catalyst has been synthetized by diluting the Co-nitrates impregnating solution with an organic compound (i.e. diethylen glycol, DEG). It has been found that thanks to the occurrence of combustion phenomena between Co nitrates, which act as oxidizers, and DEG, which act as fuel, the decomposition from Co nitrates to Co oxides species during calcination becomes exothermic and fast. This generates highly dispersed Co oxides particles, which, however, are difficult to reduce by a standard reduction treatment in H_2 at 400°C. Despite the lower reducibility, when compared with a catalyst with the same formulation but prepared without using DEG, the catalyst prepared with DEG shows very interesting catalytic performances, thanks to the fact that the small Co^0 particles are intrinsically very active. In line with the decrease of the Co^0 crystallite size, the catalyst prepared with DEG shows slightly higher hydrogenating activity. Nevertheless, the increase of the CO conversion overcompensates the decrease of the C_{5+} selectivity, thus resulting in a raised C_{5+} yield.

Concerning the second approach, the possibility to increase the number of active Co^0 centers through the addition of small amount of platinum in the catalyst formulation has been investigated. In particular, the effect of 0.1wt.% of Pt has been studied on the properties and catalytic performances of a catalyst prepared with (small crystallites) and without (big crystallites) DEG, in the Co-impregnating solution. The Pt-promoted catalysts have been prepared by varying the impregnation order of Pt and Co: (i) Pt after Co (sequential deposition order, SDO) and (ii) Pt before Co (reverse sequential deposition order, RSDO). Regardless of the initial Co_3O_4 crystallites size, all the Pt-promoted catalysts show a strong enhancement of the catalyst reducibility and Co^0 dispersion with respect to the corresponding unpromoted catalysts. This indicates the ability of Pt in favoring the reduction of cobalt oxides species, even if present in small quantity. Moreover, it has been found that the catalytic activity trend reflects that of the Co^0 dispersion with the catalysts prepared without DEG, thus justifying why the RSDO catalyst is more active than SDO, which in turn is more active than the unpromoted sample. Furthermore, the selectivity to the main FTS products is almost unvaried with respect to the unpromoted sample, thanks to the small amount of Pt used. On the contrary, the promising results obtained with the Pt-promoted catalysts prepared with DEG in terms of catalyst characterization (good reducibility and increase of the number of Co^0 sites) do not reflect the catalyst activity, which results (in the bad case) almost halved with respect to the unpromoted catalyst. This result has been explained with the fact that the intrinsic activity of the Co0 sites (turnover frequency, TOF) of the Pt-promoted catalysts is significantly decreased. This has been attributed to the fact that these catalysts have a Co^0 particle size distribution shifted to lower values than that of the unpromoted sample, thus entering in the TOF-size range where the FTS has been reported to be structure sensitive.

In the final part of this thesis work, the effect of water on the catalytic performances of Co-based catalyst is investigated. This is of interest in view of the fact that commercial FTS practices require that Co-based catalysts withstand long-term use at high CO conversion, and hence at high water concentration levels. The obtained data indicate that water addition leads to a remarkable catalyst deactivation already at low water concentration. This phenomenon is a rather slow process, whose rate depends on the feed concentration of water and whose extent depends on the duration of water co-feeding. The presence of water in the feed also affects the process selectivity, and both reversible and irreversible effects have been observed. In particular, the exposure of the catalyst to water results in an irreversible increase of the olefin to paraffin ratio (mostly due to the increased olefin selectivity), of the 1-olefins in the alkenes pool (due to the decreased double bond shift activity) and of the CO_2 selectivity (due to increased WGS activity). These effects have been explained considering that the active sites evolve during the water co-feeding in those cobalt oxides species which are formed as a result of the oxidation of a fraction of the metallic cobalt sites initially present on the catalyst. Reversible effects, which mostly consist in the increased chain growth probability and CO_2 selectivity and in the decreased CH_4 and alcohol selectivities, have been explained by assuming that the water inhibits the hydrogenation reactions and acts as reactant in the WGS reaction.

DESIGN OF LIPOSOMAL AND POLYMERIC NANOCARRIERS CAPABLE OF CROSSING BIOLOGICAL BARRIERS

Huang Xiaoyi – Supervisor: Prof. Francesco Cellesi

This PhD thesis work focused on the design of new liposomal and polymeric nanocarriers capable of crossing specific biological barriers. Depending on the application, the physicochemical characteristics of the nanocarriers were tuned in order to maximize barrier penetration and drug delivery at the specific site.

Firstly, new targeted therapies directed to treat glomerular diseases in kidneys were developed, based on the use of new protein drug-loaded, engineered liposomes. These lipid-based nanocarriers were designed to target the glomerular endothelium and release the drug in close proximity to the glomerular filtration barrier.

Once released, the draug should present a hydrodynamic diameter small enough to penetrate the glomerular barrier by diffusion and reach podocytes, i.e. glomerular cells which are known to play a central role in kidney diseases.

In order to identify the key parameters which may influence drug encapsulation and release, different lipid formulations and payloads were investigated.

Four thermosensitive liposomal formulations were selected: DPPC/DSPE-PEG2000 95/5 (mol/mol) (TSL1), DPPC/DSPC/DSPE-PEG2000 80/15/5 (mol/mol) (TSL2), DPPC/DSPC/Chol/DSPE-PEG2000 50/25/15/3 (mol/mol) (TTSL) and DPPC/P-lyso-PC/DSPE-PEG2000 90/10/4 (mol/mol) (LTSL). Water soluble molecules, including a low molecular weight molecule (Carboxyfluorescein (CF)), a hydrophilic linear polymer (dextran), a custom-made PEGylated star polymer and a protein (albumin) were used as model drug molecules for encapsulation and release. Results showed that all liposomal formulations displayed higher loading efficiency for carboxyfluorescein (CF) mainly due to its low molecular weight. The presence of hydrophobic domains in albumin enhanced the interaction between this protein and the hydrophobic lipid bilayer to some extent, thus leading to higher encapsulation efficiency compared to that of dextran and PEGylated star polymer. LTSL not only showed the highest encapsulation efficiency for albumin compared to other liposomal formulations, but it was also able to release CF and albumin in the mild-hyperthermia temperature range (40-42 oC). The release of albumin was much more limited than that of CF due to slower diffusion and potential interaction with the lipid bilayer through hydrophobic domains. LTSL was further selected for encapsulation and release of therapeutic proteins, such as lysozyme and the brain-derived neurotrophic factor (BDNF), which has been recognized as a potential therapeutic agent for kidney diseases. *In vitro* release tests confirmed that LTSL was capable of retaining lysozyme and BDNF at the physiological temperature while releasing them under mild hyperthermia conditions. Moreover, BDNF maintained structural stability and bioactivity towards damaged podocytes during the encapsulation process, as confirmed by SDS-PAGE analysis and immunofluorescent tests. The BDNF-loaded LTSL showed good therapeutic effects towards podocytes in standard 2D cell cultures (**Fig. 1**) as well as in a 3D podocyte–endothelial co-culture system, which was designed to mimic the glomerular filtration barrier *in vitro*. Therefore, BDNF-loaded LTSL nanotherapeutic may present a powerful new strategy for effective treatment of kidney glomerular diseases.

In order to enhance the targeting properties of liposomes towards glomerular endothelial cells, specific peptides, such as cRGD, Ac-IELLQARC-NH2 (IEL), Ac-HITSLLSC-NH_2 (HIT) and Ac-CLPVASCK-NH_2 (CLP), were selected as ligands and conjugated to liposomes. Cellular uptake experiments showed that cRGD-conjugated liposomes exhibited extremely high uptake by

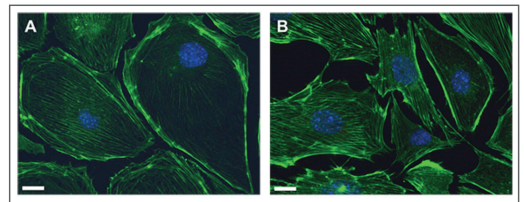


Fig. 1. Immunofluorescence studies of podocytes. The cytoskeleton of podocytes was stained by phalloidin (green) and the nuclei were stained by DAPI (blue). Scale bar: 20 μm. Damaged podocytes (A). Repaired podocytes after incubated with BDNF-loaded LTSL (B).

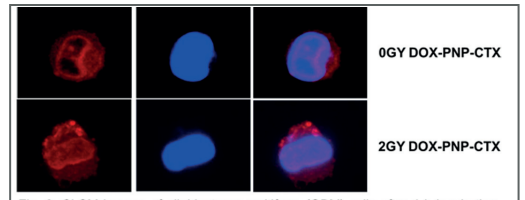


Fig. 3. CLSM images of glioblastoma multiform (GBM) cells after 4 h incubation with CTX conjugated DOX-loaded PNP (DOX-PNP-CTX) either treated with 2 GY radiation dosage or not. For each panel, images from left to right show DOX fluorescence in cells (red), cell nuclei stained by DAPI (blue), and overlays of two images.

mouse microvascular endothelial cells (EOMA) and glomerular endothelial cells isolated from rat glomeruli. cRGD conjugated liposome uptake was likely due to the overexpression of αvβ3 integrin receptors on the cell surface.

IEL conjugated liposomes also showed substantial interaction with EOMA due to the expression of E-selectin (a receptor for IEL) on the tumour vascular endothelial cells. HIT and CLP showed enhanced selectivity towards rat glomerular endothelial cells (**Fig. 2**). *In vivo* biodistribution of liposomes in mice revealed that the conjugation of cRGD to liposomes enhanced accumulation of these nanocarriers in the liver, spleen and kidney. Therefore, the specificity of peptidic ligands towards kidney should be enhanced to improve the targeting delivery to the glomeruli; HIT and CLP could be potential candidates in achieving this goal.

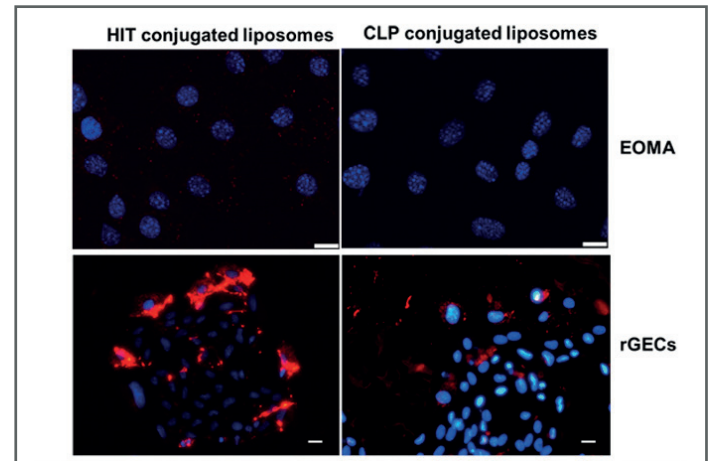


Fig. 2. Fluorescent images of mouse microvascular endothelial cells (EOMA) (top panel) and rat glomerular endothelial cells (rGECs) (down panel) after being incubated with HIT conjugated liposomes (0.5 mg/mL) (left panel) and CLP conjugated liposomes (0.5 mg/mL) (right panel) for 24 h. Peptides conjugated liposomes were labeled by rhodamine (red) and the nuclei were stained by DAPI (blue). Scale bar: 20 μm.

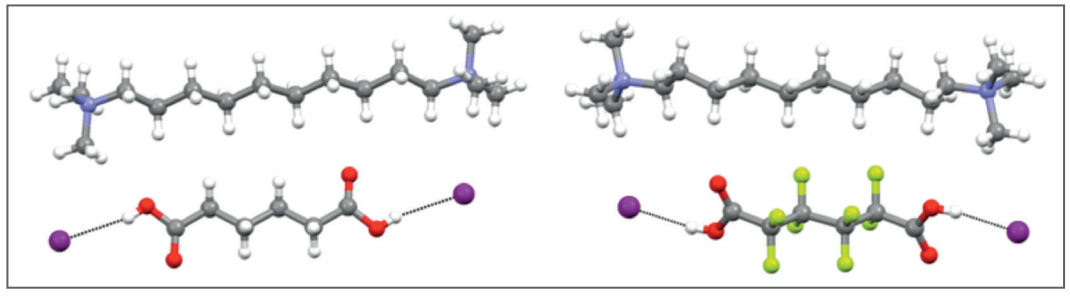
Secondly, a glioblastoma multiform-targeted therapeutic approach based on the use of PLGA-PEG polymeric nanoparticles (PNPs) loaded with the anti-tumor drug doxorubicin (DOX), was developed. DOX was efficiently loaded into PNPs by nanoprecipitation, and DOX loaded PNPs were further functionalized with chlorotoxin (CTX), which is known to selectively bind to glioma cells with high affinity. The engineered targeted PNPs offer the potential for delivering therapies directly to invasive brain cancer cells, thus improving the desired therapeutic effects while minimising unwanted toxicity. Preliminary *in vitro* cellular uptake and cytotoxicity studies suggested that further modification of the polymer structure may be necessary to control the release rate of DOX and improve cell targeting. Moreover, a combination strategy based on radiation therapy and CTX modified PNPs may have a great potential in enhancing blood brain barrier penetration, and strengthening the anti-tumor efficacy of chemotherapeutics towards glioblastoma multiform diseases (**Fig. 3**).

Keywords: Thermosensitive liposomes; Polymeric nanocarriers; Biological barrier; Kidney diseases; Glomerular filtration barrier; Glioblastoma multiform; Blood brain barrier; Targeted delivery

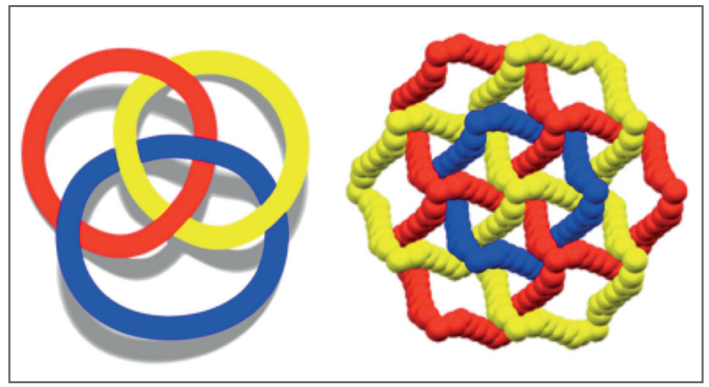
HYDROGEN AND HALOGEN BONDING TOWARDS MOLECULAR RECOGNITION AND SEPARATION

Kumar Vijith – Supervisor: Prof. Giuseppe Resnati

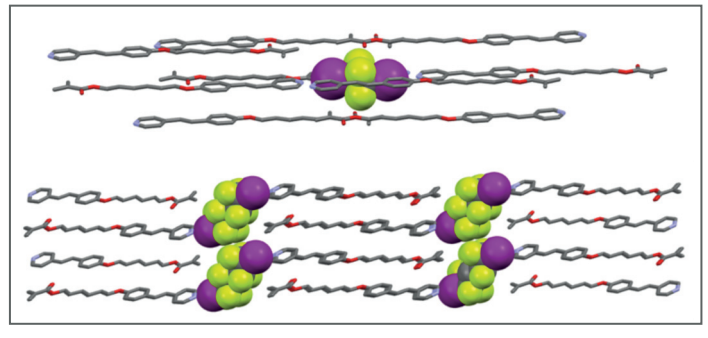
Molecular self-assembly has been well-acknowledged as one of the efficient bottom-up approaches to synthesize various materials with controllable architectures and useful properties. It has clearly been proven that the formation of the well-ordered structures of self-assembled architectures can be driven by a single interaction or by the synergistic action of multiple interactions. In this thesis metal coordination, hydrogen bond (HB) and halogen bond (XB) have been used for the design and synthesis of self-assembled systems tailored to topological studies, separation processes and obtainment of supramolecular functional materials.
The first part of the thesis describes how metal coordination enables twenty four bis-pyridyl ligands (L), functionalized with an iodotetrafluorobenzene moieties, and twelve Pd(II) ions (M) to undergo, in solutions, a quantitative self-assembly process and to form discrete nanocages of general formula $M_{12}L_{24}$. Artificial self-assembled cages can often encapsulate guest molecules and promote unusual reactivity; the XB donor groups decorating the inside face of the obtained nanosized capsule will be used to control the nature of the guest molecule(s) encapsulated in the cage and to direct the reactivity of these molecule(s).
In the second part of the thesis, HB is employed in selective recognition and effective separation of industrially important dicarboxylic acids from either their mixtures through solid or solution phase processes. The size-matching of the interacting partners plays a major role in allowing for selective self-assembly and ensuing separation process. Specifically, we have demonstrated that bis-(trimethylammonium) alkane diiodides, a well-known class of porous organic salts, can reversibly encapsulate dicarboxylic acids through intermolecular hydrogen bonding between the host I— anions and the guest carboxylic OH group. The process is highly effective for separating in pure form of dicarboxylic acid chain that forms an I—···HOOC–(CH_2/CF_2)n–COOH···I— superanion matches in length to the chosen dication. The size-matching controlled formation of cocrystals allows for the selective solubility variation of dicarboxylic acids and provides a new direction for selective recognition and separation.
The strategy is reminiscent of the effective exchange of α,ω-diiodoperfluoroalkanes via the formation of halogen bonded I—···I$(CF_2)_n$I···I— adducts where cation/supramolecular anion size matching plays a key role.
In the third part of the thesis XB is used to form a great variety of supramolecular architectures. Specifically, naked halide anions have been used to form several halogen bonded networks with different and fascinating topologies. A library of supramolecular anionic networks showing Borromean interpenetration has been prepared by self-assembly of crypt-222, several metal or ammonium halides, and five bis-homologous a,w-diiodoperfluoroalkanes. Halogen bonding has driven the formation of these anionic networks. Borromean entanglement has been obtained starting from all the four used cations, all the three used anions, but only two of the five used diiodoperfluoroalkanes. As the change of the diiodoperfluoroalkane, the cation, or the anion has a different relative effect on the metrics and bondings of the self-assembled systems, it can be generalized that bonding, namely energetic, features play here a less influential role than metric features in determining the topology of the prepared tetra-component cocrystals. This conclusion may hold true for other multi-component systems and may function as a general heuristic principle when pursuing the preparation of multi-component systems having the same topology but different composition.
In addition to this, the role of I···I- XB is used to assess the proton localization in the product that hydrogen iodide forms with crypt-111, a proton sponge with unique and useful protonation kinetics.
Finally the synthesis and characterization of new trimeric complexes obtained upon XB driven self-assembly of 1,4-diiodotetrafluorobenzene or a,w-diiodoperfluoroalkanes, acting as XB-donors, with an alkoxystilbazole derivative functionalized with a methacrylate terminal group , acting as XB-acceptor has examined in detail. Despite the fact that the starting materials are not mesomorphic in nature, the obtained halogen-bonded complexes exhibit monotropic LC behaviour with smectic A phases possibly resulting from segregation between fluorocarbon and hydrocarbon chains. The obtained supramolecular mesogens possess reactive groups suitable for incorporation into liquid crystalline elastomeric actuators.



1. Crystal structure of supramolecular size matching complexes: Top: decamethonium iodide adipic acid complex; Bottom: decamethonium iodide octafluoro adipic acid complex; Colour codes: grey, carbon; blue, nitrogen; white, hydrogen; red, oxygen; green, fluorine; magenta, iodine



2. Left: Schematic view of discrete Borromean ring. Right: Partial view (Mercury 3.8, space-filling) of the three honeycomb nets present in the cocrystal crypt-222 potassium iodide diiodoperfluorooctane. Red, yellow, and blue colours differentiate the three translationally related nets showing Borromean entanglement. Supercations K^+⊃1 are omitted for clarity



3. Crystal packing of complexes alkoxystilbazole diiodotetrafluorobenzene (top) and alkoxystilbazole diiodooctafluorobutane (bottom) showing a clear segregation between hydrocarbon and perfluorocarbon modules in complex. Hydrogen atoms have been omitted for the sake of clarity. Color codes: grey, carbon; blue, nitrogen; magenta, iodine; red, oxygen; yellow, fluorine.

PHYSICO-CHEMICAL STUDY AND MODELLING OF PARTIAL DISCHARGE PHENOMENON IN POLYMERIC DIELECTRIC MATERIALS

León Garzón Andrés Ricardo – Supervisor: Prof. Giovanni Dotelli

Polymeric dielectrics are employed extensively in the power transmission industry, mostly because of their low cost and excellent dielectric properties; however, these materials tend to degrade and eventually fail and are often considered a vulnerability when assessing the reliability of several devices and equipment. Several phenomena can be attributed to the degradation of these materials when subject to an electric eld but, in particular, the occurrence of partial discharges (PDs) is considered one of the main sources of irreversible insulator degradation. A partial discharge occurs by the electric breakdown of a gaseous free volume embedded or in close contact with the solid dielectric thanks to its lower ionization threshold. The ionization and excitation of the gaseous components generate several species that are responsible for the degradation that takes place in the interface between the gas and the solid phase. We have studied experimentally the effects of surface discharges over polyethyelene (PE), polypropylene (PP), polymethyl methacrylate (PMMA) and polytetrauorethylene (PTFE) samples under nitrogen and air atmospheres. The morphological modications were characterized employing Scanning Electron Microscopy (SEM) while the chemical nature of the degradation was assessed qualitatively employing Fourier transform infrared spectroscopy (FTIR) and X-ray photoelectron spectroscopy (XPS). The discharges under both types of atmospheres introduce structural and chemical alterations over the surface of the polymer. From a chemical perspective, our results are consistent with the modication of polymer surfaces by plasma and dielectric barrier discharges and it is expected that polymeric materials under partial discharges suffer a similar degradation as an internal PD discharge shares a similar plasma chemistry mechanism with surface, corona and other gaseous discharge types. Currently, the modelling of the partial discharge phenomenon is carried out assuming a purely electric circuit equivalent, while the evolution of the degradation of the solid dielectric is assessed employing experimental data tting. These two approaches do not take account the actual physics and chemistry behind this phenomenon. We have, therefore, studied the mechanisms of the inception and evolution of the partial discharge phenomenon from physico-chemical principles. First, the availability of the rst electrons that trigger the free volume breakdown was studied from ab initio methods in solid-state physics. A comprehensive model of the evolution of the discharge in the free volume was developed employing a full-edged chemical reaction set which, in the literature, is usually lumped in only a couple of generic species. The chemical phenomena involved in the degradation by partial discharges was studied, rst, through a thermodynamic modelling of the depolymerization process and the consecutive equilibrium conversion of volatilization products into both mixture gaseous of components and a combination composed of gaseous and solid compounds. Finally, a primary reaction mechanism of the degradative oxidation process, based on a low temperature hydrocarbon combustion chemistry, was studied employing rst principles calculations to obtain the correspondent chemical kinetics parameters. Within the scope of progressively integrating the previous elements, the purpose of this work is to progress towards the modelling of the partial discharge phenomenon from a fully physicochemical perspective.

RECOVERY OF SUGARS FROM LIGNOCELLULOSIC HYDROLYSATES BY CONTINUOUS ION EXCLUSION CHROMATOGRAPHY FOR THE PRODUCTION OF GREEN CHEMICALS

Lodi Gabriele – Supervisor: Prof. Laura Annamaria Pellegrini

Today, the depletion of fossil resources, the increasing greenhouse gas emissions and the resulting climate change, joined with a growing world population, make imperative to find processes able to produce fuels and chemicals from alternative, renewable resources. Lignocellulosic biomasses, e.g. forestry wastes, wheat straw, corn stover and sugarcane bagasse, can be used to obtain monomeric sugars, which are valuable raw materials and can be subsequently converted into fuels or chemicals through chemical or biochemical processes.

Biochemical conversion of biomasses involves pretreatment and hydrolysis processes for deconstructing the recalcitrant lignocellulosic matrix and for hydrolyzing the polysaccharides (namely, cellulose and hemicellulose) to monosaccharides like glucose, xylose, arabinose, galactose and mannose. These monosaccharides are then fermented or catalytically converted into the desired products. Biochemical processes are often referred to as "sugar-platform" conversions: the production of monomeric sugars from lignocellulosic biomass is thus the key to a sustainable, renewable chemical industry.

However, pretreatments of lignocelluloses release not only the desired pentose and hexose sugars, but also various compounds that can inhibit the fermentation microorganism or poison the conversion catalyst. This can deeply reduce the product yield and process productivity, severely limiting the usefulness of the derived sugars. In order to enhance the efficiency of sugars conversion, it is necessary to remove these inhibitors from the hydrolysate before the fermentation.

The recovery of sugars from hydrolysates and the removal of by-products can be successfully accomplished using chromatography. The separation is based on a chromatographic technique known as Ion Exclusion. In this technique, strong electrolytes are separated from nonelectrolytes and weak electrolytes using a strong ion-exchange resin as a stationary phase. The strong electrolytes are excluded from the resin due to electrostatic repulsion with the fixed groups, while the nonelectrolytes and weak electrolytes are partitioned between the mobile phase and the stagnant liquid inside the particles. No actual ion exchange takes place during the separation and hence no chemical regeneration of the resin is required.

The Italian company Biochemtex developed the GREG™ process, in which monosaccharides are converted into ethylene and propylene glycols. The process is based on traditional catalysts and a straightforward purification of the sugars is thus essential in order to increase the catalyst lifetime. The process involves an innovative pretreatment, where the hydrolysate is neutralized to pH 6 before the chromatographic separation making all the electrolytes in solution completely dissociated and therefore excluded from the resin pores. The electrolytes elute unseparated as a first group in the chromatogram followed by the sugars, allowing a baseline binary separation that is performed in continuous in an I-SMB process.

In this work, the recovery of lignocellulosic sugars obtained with this innovative pretreatment has been studied.

Experimental investigations on model systems, aimed to understand the mechanisms involved in the separation, have been carried out at different scales. The column dynamics has been analyzed using equilibrium and pulse elution data measured in batch columns. A systematic investigation of the adsorption behavior of the main components found in the hydrolysate has been performed and the effects of the main electrolytes on resin shrinking and sugars adsorption have been studied. Afterwards, a quantitative description of the experimental observations was provided.

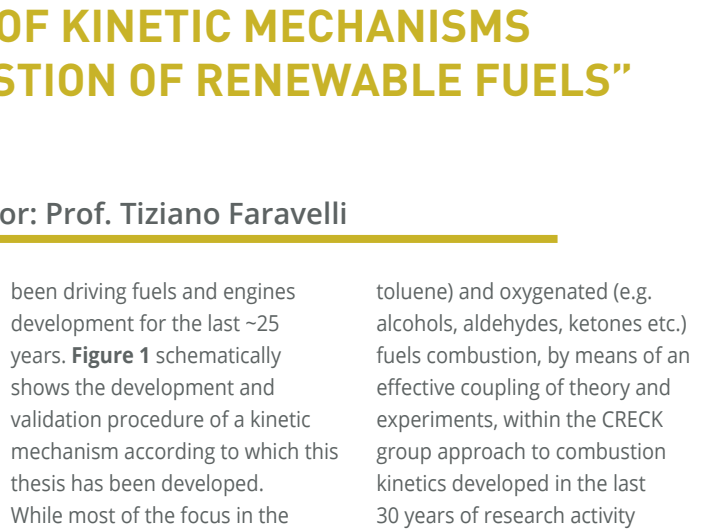
On this basis, a dynamic column model for IEC has been developed and used to simulate pulse tests of real hydrolysates. The exclusion of ions from the resin pores has been explained in terms of Donnan Theory, which describes the partition of charged species between two phases separated by a semipermeable membrane. The equilibrium relationships for this model have been derived and implemented in the material balances. These were written taking into account changes in interparticle and intraparticle porosity due to resin shrinking.

A model for the I-SMB process was developed coupling the single-column dynamic model to the appropriate material balances at the nodes. The model was then used to predict experimental data of continuous separations, obtained with the I-SMB unit of the GREG™ pilot plant. The results were in good agreement with the experimental data, correctly representing the main features of this separation. The simulation tool can be used for the design and optimization of the operating conditions of the I-SMB separation process.

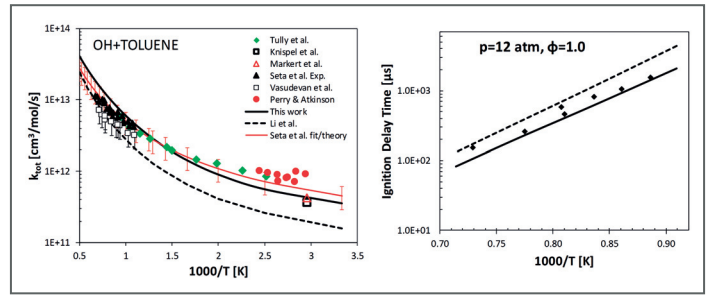
"DEVELOPMENT OF KINETIC MECHANISMS FOR THE COMBUSTION OF RENEWABLE FUELS"

Pelucchi Matteo – Supervisor: Prof. Tiziano Faravelli

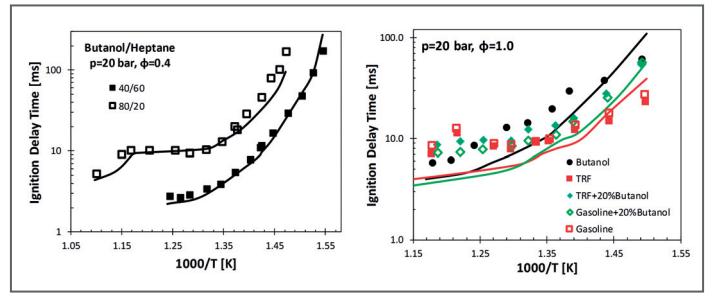
Pursuing a sustainable energy scenario for transportation requires the blending of fuels from renewable sources (alcohols, methylesters etc.) into hydrocarbon fuels from fossil sources (gasoline, diesels, jet fuels etc.). In fact, while effective alternatives to combustion exist for electricity production (nuclear, hydroelectricity, solar, wind etc.), the high energy density required for road, sea and air transport endorses biofuels as the only viable and realistic option. Moreover, from an environmental perspective, undeniable and dramatic climate change phenomena impose to act with long term sustainable solutions for reducing greenhouse gases, NO_x and soot emissions.
If on one side the production of biofuels from biomasses satisfies the requirement of a net *zero-*CO_2 balance, new fuels and new engines technology have been investigated to improve fuel economy and reduce pollutant emissions. The correct characterization of a fuel or fuel mixture reactivity and the evaluation of its compatibility with existing engine infrastructures in terms of pollution and efficiency is, for a major part, a chemical kinetics problem.
Combustion kinetic modelling, which is the topic of *this thesis*, has been driving fuels and engines development for the last ~25 years. **Figure 1** schematically shows the development and validation procedure of a kinetic mechanism according to which this thesis has been developed.
While most of the focus in the first decade has been devoted to the understanding of alkanes chemistry, the need of better representing commercial fuels by means of surrogate mixtures, extended the interest to aromatics and lastly to oxygenated fuels from renewable sources. *This thesis* extended the knowledge of the chemistry involved in alkanes (e.g. n-heptane), aromatics (e.g. toluene) and oxygenated (e.g. alcohols, aldehydes, ketones etc.) fuels combustion, by means of an effective coupling of theory and experiments, within the CRECK group approach to combustion kinetics developed in the last 30 years of research activity at Politecnico di Milano. The left panel of Figure 3 shows a comparison between experimental measurements of the reaction OH+toluene and results from theoretical calculation presented in this thesis. Also the impact of the updated rate constants on ignition delay times is reported in the right panel.
The model obtained coupling



1. Development and validation procedure of the chemical kinetic mechanisms for pyrolysis and combustion of hydrocarbon fuels



2. Left panel: comparison of the total rate constant of OH+toluene with other theoretical studies and with experimental measurements from the literature. Right panel: Impact of the update rate constant on toluene/ air ignition delay time predictions (solid line). Dashed line: POLIMI mechanism with different rate constants for OH+toluene



3. left panel: Ignition delay times for n-butanol/heptane blends at p=20 bar and φ=0.4. Right panel: Ignition delays for TRF on blending with 20% n-butanol, stoichiometric TRF and n-butanol mixtures at p = 20 bar in Rapid Compression Machine. Symbols: experimental data, lines: POLIMI mechanism

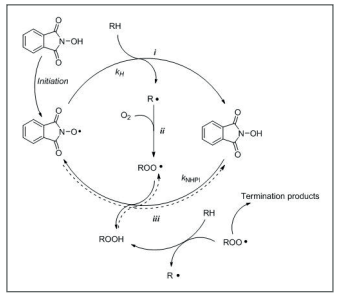
the different revised portions, accurately reproduces recent experimental measurements of surrogate mixtures representative of real gasoline fuels. Ignition delay time measurements are compared with model predictions in **Figure 3** for mixtures of butanol/heptane (left panel) and n-heptane/iso-octane/toluene/butanol (right panel).
Beside the definition of key model parameters and standard kinetic mechanisms validation procedures, other important challenges of modern kinetic modelling have been a topic of research. The necessity of automatically assessing the validity of increasing complexity kinetic mechanisms has been tackled, providing an innovative and effective method, of application also to mechanism reduction and optimization, and to experimental design.
Inputs for future refinement of the presented models have been provided throughout the discussion, highlighting for example the need of a hierarchical revision starting from the core C_0-C_4 portion of the POLIMI mechanism or a better assessment of other key channels, whose parameters still carry high degrees of uncertainty. Perspectives concerning the possibility and potentials of effectively and extensively exploiting theoretical kinetics, and the necessity of fully automatized the iterative process of kinetic mechanisms development are also discussed, providing directions for future research efforts.

AEROBIC OXIDATION CATALYZED BY N-HYDROXY COMPOUNDS: NEW FRONTIERS IN INDUSTRIAL AND BIOLOGICAL APPLICATIONS

Petroselli Manuel – Supervisor: Prof. Carlo Punta

In recent years, intensive research efforts have pursued the development of new reliable oxidative transformations capable of combining high chemical efficiency with minimization of both waste production and energy consumption. In this context, N-hydroxy compounds, the most representative of which is NHPI, are effective organocatalysts for the oxidation of organic substrates by using dioxygen as the final oxidant. The oxidations catalyzed by NHPI and N-hydroxy compounds more in general, is affected by some limitations. The solubility of this kind of organocatalysts is often too low in apolar mediums, leading them to be unusable at mild conditions and often high temperature (>100 °C) is required in order to operate under homogeneous catalysis. In this context, I focused on the sythesis of new N-hydroxy compounds in order to improve the properties of this kind of organo-catalysts for industrial and biological applications. The corrsponding N-oxyl radicals, derived from the abstraction of the hydrogen by N-hydroxy group (*initiation*, Figure 1), are the active species in the catalytic cycle. N-oxyl radical is able to abstract hydrogen from hydrocarbons in order to form carbon centered radical, re-generating its protonated form (step *i*, Figure 1). The carbon centered radicals, under aerobic condition, reacts with oxygen and forms peroxyl radicals (step *ii*, **Figure 1**). The latter are converted to the corresponding hydroperoxides by the N-hydroxy derivatives (step *iii*, Figure 1), which behave also as good hydrogen donors, leading to the formation of new N-oxyl radicals.

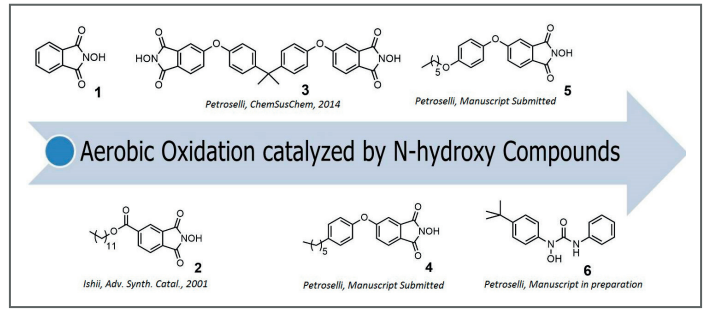
In this contest, the OH bond dissociation energy (BDE) of the N-hydroxy group plays a crucial role in order guarantee the high selectivity of the process. At mean time, the solubility, the thermal and chemical stability of the catalyst is crucial for the efficiency of the protocol. For this reasons preliminary computational screening was performed in order to provide information about OH BDE,



1. The catalytic cycle of NHPI in the aerobic oxidation of organic substrates

transition state (TS) in the hydrogen abstraction and the correlated activation energy (Ea). These theoretical studies allowed to synthesize two different new families of organocatalysts bearing N-hydroxy group and their catalytic efficiency was tested in industrial and biological applications.

Alkyl aromatics are oxidized easly to intermediate oxidation product (hydroperoxide) under mild condition (45°C and 1 oxigen or air atmosphere). NHPI requires often a co-solvent (i.e. acetonitrile (ACN)) to maintain the polar catalyst in apolar solutions. Catalyst **4** and **5** do not require any co-solvent at room temeprature, due to their high lipophilic character. Moreover, the structural modifications on the catalysts do not modify the catalytic activity, on the contrary of alternative solutions previously reported in literature as catalyst **2**. The high solubility in lipophilic mediums of **4** and **5** allowed to conduct catalytic oxidations under solvent-free conditions for the firtst time. Alkyl aromatic were converted to the corresponding hydroperoxides in higher yields in comparison with the classical oxidation using co-solvent, with a considerable increase of the productivity of the process. Moreover, by operating in the absence of polar solvents,



2. Time line of the new N-hydroxy catalysts

it was possible to observe for the first time the aggregation of the catalyst in apolar mediums, due to the intermolecular hydrogen bonding (HB) between N-hydroxy and carbonyl moieties present in the structure of the catalyst (see **Figure 2**).

This aggregation causes the decrease of the catalytic activity, due to the involvement of the N-OH group in the intramolecular HB rather than in the hydrogen atom transfer (HAT) process. Several studies were done in order to understand the role of the co-solvent and how exploit the new revealed properties. In this direction, catalyst **6** was synthesized. Catalyst **6** in solution is in equilibrium between conformers, due to the possible intramolecular HBs between N-hydroxy group and carbonyl or urea groups. These conformers have different catalytic properties, due to the different structure, leading catalyst 6 to be the first dynamic N-hydroxy organocatalyst modulated by the temperature. The high catalytic efficiency of N-hydroxy derivatives in promoting oxidative processes and the really milder operative conditions, suggested a possible alternative use as pro-oxidants for biological applications, namely the promotion of oxidative stress in cancer cells. Methyl linoleate with its bis-allylic position was choisen like model molecule for its analogy with the phospholipids of the cellular membrane. Good results were obtained in terms of yield and selectivity of the peroxidation process. The preliminary good results on suggested to move to the oxidation of liposomes, in order to mimic the cellular membrane. The oxidation of liposomes were performed in phosphate buffer solution (PBS) at pH 7.4, biological temperature (37 °C), using air as oxidant and without the use of any radical initiator in order to simulate the real biological condition. These experiments were followed using special probes, purposely synthesized, active to UV light or fluorescence. Using these protocols, formation of hydroperoxydes was confirmed and N-hydroxy catalyst could be proposed as pro-oxidant for the oxidative therapy against tumor cells. The high numbers of advantages and the improvments using these new organo-catalysts were demostrated and confirmed in industrial and biological applications in term of solubility, efficiency and innovation.

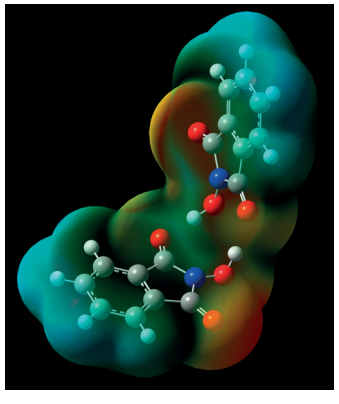


Figure 3. Theoretical structure and relative electrostatic potential surface (ESP) for the most stable dimer of NHPI (1), calculated in gas phase at 298 K at B3LYP/6-311+G(d,p) level of theory

HALOGEN BONDING AS A NEW SUPRAMOLECULAR TOOL TO CONTROL PROTEIN AND PEPTIDE SELF-ASSEMBLY

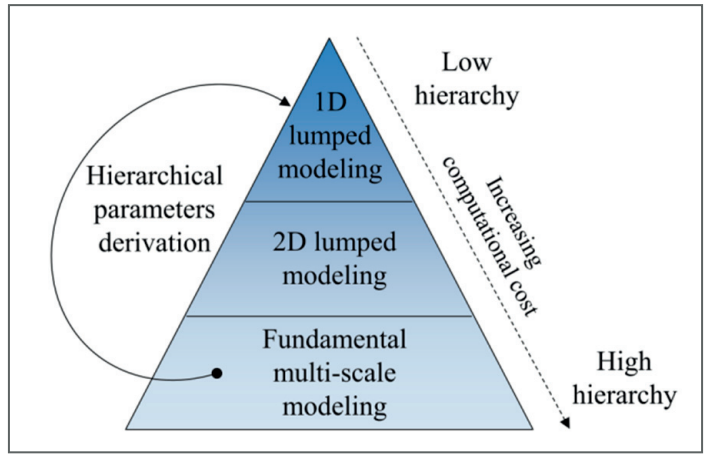
Pizzi Andrea – Supervisor: Prof. Pierangelo Metrangolo

Although the abundance of halogens in the environment is not remotely comparable to that of other elements, a remarkable number (more than 5000) of naturally occurring halogenated compounds has been discovered to date. Halogenation is a minimal structural modification; however, it can induce deep changes in the molecular properties because of the different chemical features characterizing halogen atoms. Among these features, their tendency to act as electrophilic species is by far the most studied. The strong, specific and directional non-covalent interaction resulting from this electrophilic behavior is halogen bonding (XB). Although halogens are among the most electronegative elements, they can act as electrophilic species because of their anisotropic distribution of the electron density around their nucleus. When halogen atoms form covalent bonds, the new chemical environment affects the halogen electron density, which is no more equally distributed in all directions. The electrostatic potential of the halogen atom becomes anisotropic, showing distinct regions around the nucleus with different chemical behavior. The external region located along the extension of the covalent bond results in lower electron density. Differently, the region perpendicular to the covalent bond shows increased electron density. The resulting shape of the halogen atom is an ellipsoid having the shorter radius (named polar flattening) along the covalent bond direction. According to this electrostatic configuration, nucleophiles form linear interactions (160°-180°) respect to the C−X bond, while electrophiles give rise to lateral contacts (90°-120°) against the bond axis. The strength of halogen bond can be tuned upon changing the nature of the halogen atom and its covalently bound residues. Increasing halogen atom polarizability (decreasing electronegativity) and raising electron-withdrawing propensity of its covalently bound moiety result in a stronger XB. Consequently, halogen bond strength increases following the trend I > Br > Cl >> F. In general, strong – hence short – interactions are more directional than long ones, thus even XB directionality follows the same trend depending on halogen atom polarizability, with iodine that is the more prone to be involved in halogen bonding. Because of its peculiar properties of strength and directionality, halogen bonding has become one of the most exploited interactions in supramolecular chemistry and crystal engineering. However, extensive studies focusing on XB relevance in biomolecular systems started quite recently. Since it is known that halogen atoms can improve biochemical properties like membrane permeability and half-life, their introduction in potential drug candidates is a common procedure of pharmaceutical optimization. Although the importance of halogens in biomolecular systems is longer established, a molecular interpretation correlating the interaction pattern of halogen atoms with the chemical properties of biomolecules is unusual. A recent survey on the Protein Data Bank (PDB) nicely rationalizes XB in biological systems, showing the more frequently occurring halogen bond acceptors. Considering the 567 halogen bonds resulting from this survey, 430 involve halogen atoms and protein residues. All of the twenty amino acids form C−X•••Y halogen bonds, with leucine as favorite residue. XBs involving amino acid main chains are the majority (64.6%) respect to the ones formed with side chains (35.4%). Considering C−X•••π halogen bonds involving aromatic amino acids, nearly half (46.4%) are C−Cl•••Tyr contacts while 22.3% are C−Cl•••Phe interactions. This thesis highlights the role of XB in the self-assembly of biomolecules containing halogenated phenylalanine (Phe) residues. The first part of the thesis describes halogenation as a tool to improve the self-assembly properties of a phenylalanine-based organic gelator: N-Fmoc-Phe. The hydrogel rigidity of mono halogenated derivatives of N-Fmoc-Phe (Fmoc-4-X-Phe, where X = F, Cl, Br, I) has been related for the first time with halogen atom polarizability, i.e. the propensity to act as halogen bond donor. In particular, iodinated and brominated derivatives (containing the most polarizable substituents) were found to form the strongest gels. This trend is opposite to the one reported in previous studies, where hydrogel strength increases with halogen electronegativity. Kinetic studies confirm that iodinated and brominated compounds have the highest fibrillation propensity, indicating a greater efficiency to assemble into high ordered and compact materials. Gel strength and self-assembly efficiency are due to the contribution of halogen bonding in driving the aggregation process, as demonstrated by the crystal structures of Fmoc-4-I-Phe and Fmoc-4-Br-Phe, showing halogen bond between the halogen atom and the electron density of Fmoc aromatic moiety. The second part of the thesis shows the impact of halogenation on the self-assembly behavior of a more complex system. The peptide KLVFF, core sequence of the amyloid beta (Aβ) protein, was modified at the para position of the phenylalanine residues to obtain seven different halogenated derivatives. It was found that some of the halogenated peptides showed an increased rate of fibrillation compared to the wild-type sequence. In general, iodinated derivatives self-assembled into more stable nanostructures, as confirmed by rheological experiments showing the mechanical properties of the peptide hydrogels directly connected with halogen substituent polarizability. Similar results were obtained with another amyloidogenic sequence (DFNKF) although there was a lack of structural evidence about the role of halogen atoms in the self-assembly of this segment. In this thesis, the crystal structure of some of the halogenated KLVFF peptides is the first, direct demonstration that halogen interaction pattern nicely correlates with the aggregation properties of the peptides. The crystal structure of the di iodinated peptide KLVF(I)F(I), showing the peculiar cross-β spine further stabilized by halogen bonding between iodine and peptide carbonyl oxygens, is consistent with the strong self-assembly efficiency of iodinated derivatives. Brominated and chlorinated derivatives, forming less compact aggregates, do not show the contribution of halogen bonding in their respective crystal structures. In addition to the dependence on halogen atom polarizability, the self-assembly of the halogenated KLVFF peptides resulted to be strongly affected by the number and position of halogen atoms in the amino acidic sequence. A single point mutation like halogenation was able to induce a deep change in the self-assembly of the peptide. Indeed, TEM images of each halogenated derivative showed an impressive variety of nanostructures. These results enriches the structural landscape for peptide self-assembly, giving access to a new supramolecular tool to control the morphology of peptide-based materials. Considering the biological context, these results may also shed light on the impact of halogenation in vivo, where oxidative stress mechanisms lead spontaneously to halogenated biomolecules. Finally, halogens were used as “heavy atoms” to aid the phase determination in X-ray diffraction experiments. The KLVFF peptide was modified by placing iodine and bromine substituents on the para position of the terminal phenylalanine ring. KLVFF(I) and KLVFF(Br) were successfully crystallized and their structure was determined with excellent resolution, by using a conventional X-ray source. Since these crystal structures do not show the halogen substituents involved in any kind of specific interaction, they can be considered a reliable model of the wild-type sequence, which structure has never been solved. These crystal structures confirm the overall features of the amyloid cross-β spine, showing in detail the key non-covalent interactions driving the self-assembly of the peptide. For this reason, the crystal structures of these KLVFF derivatives may contribute to enlighten the amyloidogenic behavior of this deeply studied core sequence.

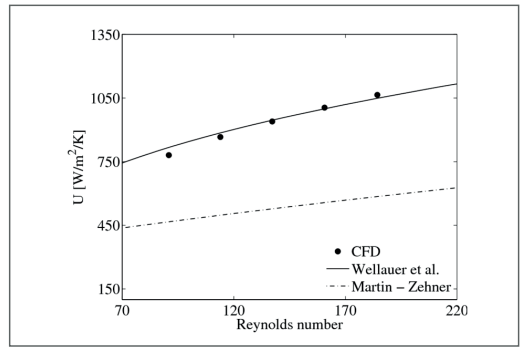
DEVELOPMENT OF HIERARCHICAL METHODOLOGY FOR THE ANALYSIS OF NOVEL CATALYTIC REACTORS: AN APPLICATION TO MICRO PACKED BED REACTORS

Rebughini Stefano – Supervisor: Prof. Matteo Maestri

The first-principles reactor engineering is becoming a very promising tool for the analysis of catalytic reactors. It relies on a fundamental description of all the phenomena occurring in the reactor, where each scale is represented by means of its own governing equations. In heterogeneous catalysis, this approach allows for the accurate description of the interplay between chemistry and transport processes, which is of primary importance in the understanding of the macroscopic observed functionality of the catalyst.
Despite its attractive potential, the first-principles reactor engineering is still hampered by numerical issues and computational costs, even for simple reactor geometries. Therefore, it requires the development of specific tools and methodologies to enable its application to advanced reactor design.
The main aims of this Ph.D. are to develop a numerical framework for multi-scale simulations of catalytic reactors and to propose a hierarchical methodology for the design and the analysis of unconventional and novel reactor configurations. In fact, despite its attractive potential, the first principles multi-scale modeling of complex reactor geometries is still impractical. Indeed, it is mainly limited by numerical issues/limitations related to high number of variables and the high computational cost. Therefore, the first aim of this Ph.D. is the development a framework, which can be used for the first principles multi-scale modeling of catalytic reactors. In particular, a new numerical multi-scale framework able to represent catalytic reactor with different geometries has been developed. This new framework enables the concomitant description of transport phenomena in the gas phase and in the catalyst. It has been applied to analyze the effect of the channel cross-section in the catalytic partial oxidation of methane in a honeycomb reactor. In particular, this framework allows a detail description of the transport phenomena between the gas and the catalyst, which has been used to investigate the effect of the geometry on the reactor performance. This analysis shows that the channel shape strongly affects the reactor behavior in terms of temperature and composition profile. In fact, due to the different diffusion length of the two different cross-sections, a different amount of reactants reach the catalytic wall, affecting the reactor performance.
One of the main limitations of this framework is the high computational cost. Thus a numerical method to reduce the computational effort when the surface chemistry is described by means of microkinetic models has been developed. This methodology enables the use of complex homogeneous kinetic schemes coupled with micro-kinetic heterogeneous schemes, which are applied to investigate the adequacy of lumped parameters in describing the heterogeneous and homogeneous chemistries interaction in the catalytic partial oxidation of hydrocarbons fuel in monolith reactors. This analysis shows that when the effect of the homogeneous chemistry is weak the lumped parameters implemented in the 1D model are adequate to describe the reactor behavior. On the contrary, when the effect of the homogeneous chemistry is enhanced by increasing the pressure, the lumped parameters are not accurate enough to correctly describe the interaction between the surface and the gas chemistries.
The previous analyses clearly show the deeper understanding of the reactor behavior which can be obtained by using this multi-scale numerical framework. However, the high computational cost of multi-scale simulations limits their application for routinely reaction design of complex reactor geometries (e.g. packed bed, foams), which is still based on classical chemical reaction engineering models. This type of modeling adopts lumped parameters, usually experimentally derived, to represent the main phenomena occurring inside the reactor. Therefore, the second goal of this Ph.D. is to develop a methodology to enable the application of the multi-scale framework to the routinely reactor design. In this regard, the hierarchical approach has been selected as an interesting approach to meet this goal. In fact, it can be adopted to enable a first principles multi-scale design of the novel reactors with an affordable computational cost. In essence, as shown in Figure 1, it consists in using the first principles multi-scale model to analyze a selected and limited number of operating conditions for the novel reactor geometry. Then, the results of these simulations are used to derive lumped parameters. Consequently, the implementation of these parameters in simplified models enables a fundamental description of the phenomena in the reactors with a reasonable computational cost. The potentialities of this methodology are presented by analysis the behavior of micro packed bed reactors in high exothermic processes.
This study allows the selection of the most adequate literature correlations for describing the transport phenomena in micro packed bed reactors. Then, this correlation is implemented in a steady-state, pseudo-continuous 2D heterogeneous reactor model to analyze the selective oxidation of o-xylene to phthalic anhydride in this novel reactor configuration. This study shows that the micro packed bed reactor is characterized by higher heat transfer properties than a packed bed reactor. In fact, the micro packed bed reactor has a quasi-isothermal behavior.
On one side, this work shows that micro packed bed reactors are a valid alternative to the classical multi tubular packed bed reactor for selectivity oxidation. On the other side, it clearly shows the potentiality of the hierarchical analysis and how it can be employed for the efficient and fundamental analysis and design of novel reactor technologies.



1. Schematic description of the hierarchical modeling applied to novel reactor configurations.
The hierarchical modeling is applied to investigate the capabilities of micro packed bed reactors in dealing with high exothermic processes. In particular, the hierarchical approach can be also used to determine the overall heat transfer coefficient between the micro-packing and the wall of the single channel of the honeycomb matrix. Figure 2 illustrates the comparison between the overall heat transfer coefficient estimated with CFD simulations and the literature correlations.



2. Overall heat transfer coefficient as a function of the Reynolds number

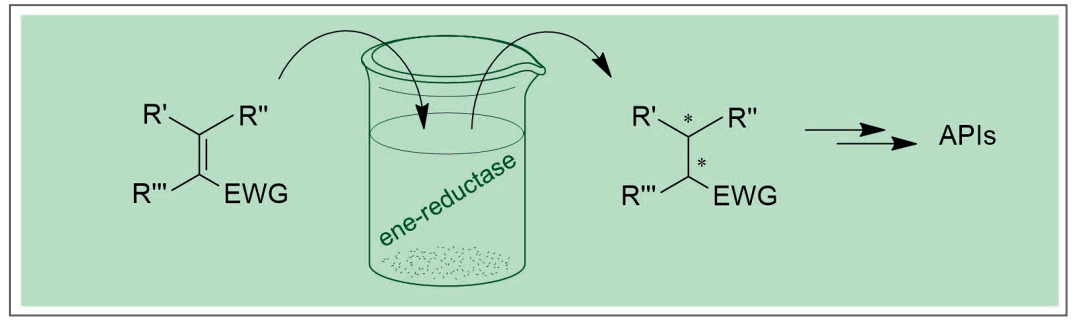
"ENANTIOSELECTIVE SYNTHESIS OF CHIRAL PHARMACEUTICAL INTERMEDIATES BY WHOLE CELL MICROORGANISMS AND ENGINEERED ISOLATED ENZYMES"

Santangelo Sara – Supervisor: Prof. Maria Elisabetta Brenna

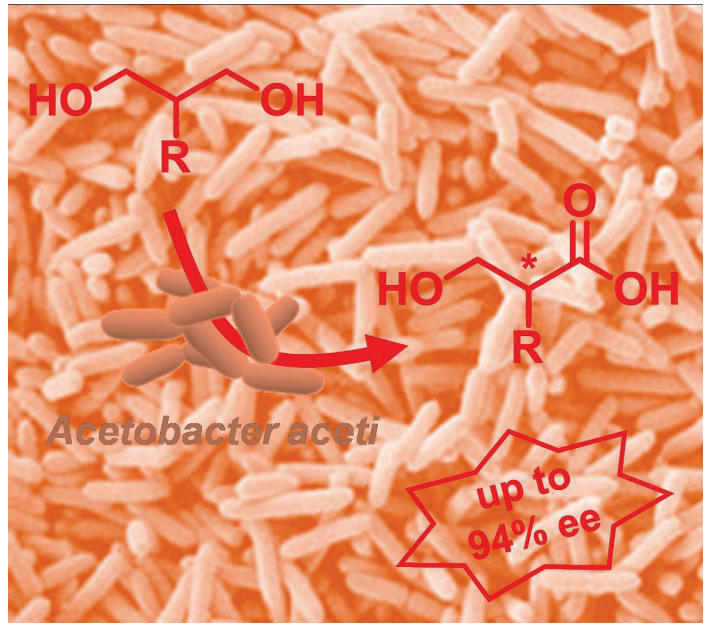
The role of biocatalyzed reactions is becoming more and more influential in the toolbox of available reactions for the synthesis of enantiopure compounds, also on industrial scale.
In the scenario of the possible options to design the synthetic pathway of chiral molecules, enzymatic biotransformations started to be evaluated more frequently, also considering the distinctive features of this methodology. Enzyme catalyzed reactions are highly chemo, regio and stereo-selective and therefore of great interest for fine chemical synthesis, both for economic and environmental reasons.
Enzymes catalysed reactions can be performed in different conditions: the natural expressing microorganism can be considered as source of enzyme and it can be used directly as biocatalyst.
To improve overexpression and to reduce side reactions, a more convenient host can be identified. The enzymes can work in a more known and controlled overexpression system, leading to better results. Using engineered procedures, the possibility to purify the enzymes becomes available.
In this way, they can be used for biotransformations also as purified enzymes. All these options have been considered and investigated.
The work during these past three years has explored the effectiveness of combining chemical and biochemical procedures for the synthesis of chiral building blocks in high enantiomeric purity. Specifically, this has involved three different topics:

- Stereoselective reduction of C=C and C=O double bonds;
- Desymmetrisation of achiral compounds by biocatalysed oxidative biotransformation
- Combination of multiple enzymes in cascade reactions

A complete investigation of the steric and electronic effects of substituents on the course of ER-mediated reductions of alkenes has been performed, considering the substitutions on aromatic rings and on alkyl chains. The conversion yields and the enantioselectivity of the reactions were then evaluated.
At the same time, the effect of different electron withdrawing groups has been investigated: in order to perform the enzymatically catalysed reduction of the molecules, the of C=C double bond has to be efficiently activated under the electronic point of view.
The role of the nitrile (CN) and the nitro (NO_2) functions as EWG, either alone or in combination with other functional moieties have been considered. The enantioselective reduction of alpha-methylenic nitrile derivatives catalysed by ene-reductases affords the corresponding (R)-2-arylpropanenitriles with high conversion values. The reaction is investigated either in aqueous medium (with an organic cosolvent or by loading the substrate unto hydrophobic resins), and in a biphasic ionic liquid / water system). Compounds bearing either alkyl chains of increasing length at the carbon atom in position β to the nitro group or different substituents on the aromatic ring are prepared and submitted to bioreduction, in order to define the synthetic potential of this enantioselective reaction in the preparation of chiral fine chemicals. A complete screening has been performed, analysing all the factors influencing the reactions. The synthetic versatility of the nitrile and nitro functions were further investigated with the transformation of reduced compounds in the corresponding chiral amides, acids and amines.
When the wildtype enzyme wasn't able to perform the required biotransformations, also the possibility of use an enzyme library, a whole set of variants, was considered. Protein engineering procedures were employed to obtain a single mutation in a position with a critical role for the catalytic function of the protein.
The effects of this mutation on



enantioselectivity were deepen in relationship with the substrates of interest.
The study of the desymmetrisation of achiral 1,3-diols by biocatalysed oxidation has been conducted by exploring the scarcely known world of Acetic Acid Bacteria. The ability of AAB to oxidize several substrates has long been known and is still attracting attention. The oxidation of alcohols by AAB is an old and established microbial method for obtaining production of vinegar and various carboxylic acids, sometimes with remarkable chemo and enantioselectivity. The enzymatic oxidation of primary alcohol is attractive because it can be carried out under mild conditions that are also suited for labile products. Two different enzymes are involved in two different steps for the oxidation to obtain carboxylic acid in physiologic pathways and conditions: The first reaction is catalyzed by alcohol dehydrogenase (ADH) and the second by aldehyde dehydrogenase (ALDH). The procedure, carried out in aqueous medium under mild conditions of pH, temperature and pressure, contributes to enlarge the

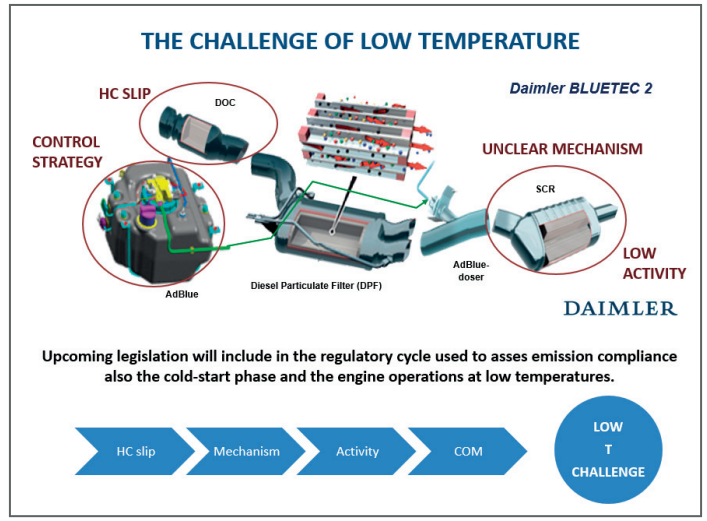


portfolio of enzymatic oxidations available to organic chemists for the development of sustainable manufacturing processes.
The optimization of enzymatic cascade procedures has involved coupling more than one enzyme into an efficient pathway for the biosynthesis of compounds of commercial interest. The most odorous stereoisomers of the chiral commercial fragrance Muguesia® are prepared by a very effective linear biocatalysed cascade reaction, in which a suitable unsaturated ketone is submitted to the sequential action of two enzymes, an ene-reductase and an alcohol dehydrogenase, which are added together to the same reaction vessel with the cofactor regeneration system.
Two stereogenic centres in 1,2 relative position are thus created under high stereochemical control by a two-step one-pot enzymatic procedure.
These procedures represent a further demonstration of the synthetic potential of enzyme-mediated reactions: the high chemo and stereoselectivity that enzymes can achieve are key requisites for the optimization processes, which are now extensively investigated for the synthesis of valuable compounds.

NH_3-SCR ABATEMENT OF NOX IN LEAN BURN ENGINES: THE CHALLENGE OF LOW TEMPERATURES

Selleri Tommaso – Supervisor: Prof. Enrico Tronconi

NH_3-SCR currently represents the leading technology for the NOx abatement from lean burn and Diesel engines. However, in the upcoming years, due to the enforcement of stricter emission regulations (Euro 6b, 6c), demanding challenges await. In particular, the low temperature and cold start performances of the deNOx systems are of major concern. In these conditions: i) the chemistry and reaction mechanism of the Standard SCR reaction is still unclear; ii) state-of-the-art metal promoted zeolite catalysts are inactive and unable to reduce NOx; iii) the catalytic devices upstream of the SCR converter (such as the Diesel Oxidation Catalyst) are not operative, leading to significant hydrocarbon (HC) slip that impacts negatively the activity of the catalyst; iv) process optimization and control models are becoming essential tools in emission abatement. The research activity of the third year has addressed all these major aspects with significant results.
Concerning the catalytic mechanism governing the low-T Standard NH_3-SCR reactivity over metal promoted zeolites we have developed and applied with success a novel chemical trapping technique that has permitted to gain important insights on the reaction intermediates and underlying mechanistic aspects. By performing experiments on Fe- or Cu-zeolite (active phases) + BaO/Al_2O_3 (NOx trap) powders in different spatial configurations (physical mixture versus double-bed, corresponding to different degrees of separation of the two component phases) we have identified nitrites precursors (such as HONO and N_2O_3) as potential key intermediates in SCR reactivity at low temperature. In particular, our data point out very clearly that a crucial redox step in the SCR mechanism involves the oxidation of the N atom in NO to a state of +3. In addition, we have shown that nitrites generated by the oxidative activation of NO on Fe-ZSM-5 and stored on BaO react readily with NH3 adsorbed on the zeolite acid sites, likely via their decomposition to NO + NO_2. Most important, such a reactivity proceeds regardless of the presence of redox metal sites on the zeolite: in fact, a comparable activity was observed on Fe-ZSM-5 and on H-ZSM-5, with no NH_3 oxidative activation required.
On the basis of these and other results, a consistent mechanistic proposal has been developed and discussed in the literature. Notice that chemical trapping studies have highlighted the possibility of trapping NOx at low T (25-120 °C) in the form of nitrites, which can be easily released and decomposed in an intermediate T window, where the catalyst activity is maximal. This suggests the possibility of using combined BaO/Al_2O_3 + M-zeolite systems as Passive NOx Adsorbers (PNA) to reduce and possibly eliminate cold start temperature emissions. Such systems are at the core of an industrial collaboration with Daimler AG that is ongoing at the moment.
Additional issues in the low-T operation of aftertreatment systems come from the positioning of the SCR catalyst closer to the engine (e.g. in the form of SDPF) and from the additional measures to increase its temperature by means of converting unburnt hydrocarbons (HCs) over the DOC. This was originally done to shorten the system heating period. Combined with the low catalytic activity right after cold start, this increases the probability of HC-slip onto the SCR with negative impact on its DeNOx performances. These effects have been studied in details by means of a dedicated experimental campaign in the previous year and a comprehensive kinetic model of the HC deactivation process according to a dual site approach has been finally developed. This includes: i) a redox site (S1), where NO and O2 are activated and HC poisoning occurs due to partial oxidation, intermediates adsorption and coke formation; ii) an acid site (S2), responsible for ammonia adsorption. The HC compound undergoes an activation step on the catalyst leading to the poisoning of redox metal sites. Effects on the ammonia storage and desorption dynamics, even if limited, were described according to a spillover mechanism.
A third problem related to the increased tightening of emissions and low T operation is the development of robust real time control-oriented models (COM) able to adjust urea injection strategies on board depending on the driving conditions and catalyst performances. To this purpose, we have started the development of a mathematically explicit SCR model, with consequent minimization of the computational effort. The model is embedded with a fully detailed kinetic scheme, able to account for many of the typical features of Standard SCR reactivity, such as NH_4NO_3 deposition and decomposition. Moreover, both internal and external mass transport phenomena, that may become important depending on the operative conditions, are accounted for, maintaining the explicit nature of the formulation. Finally, in order to correctly describe the heat up dynamics of the converter, a suitable energy balance is included. The resulting model has been used to simulate a World Harmonized Transient Cycle (WHTC) with cold start for heavy-duty Diesel engines, normally used to assess deNOx after-treatment systems performances. Results have been compared with a state-of-the-art complete chemical-physical model, already validated and developed at PoliMi in the past years.

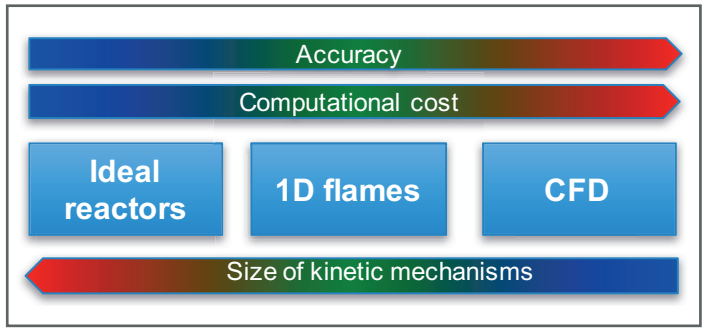


1. NH3-SCR exhaust aftertreatment system with the main low temperature challenges

IMPLEMENTATION OF DETAILED CHEMISTRY IN LARGE-SCALE COMBUSTION COMPUTATIONS

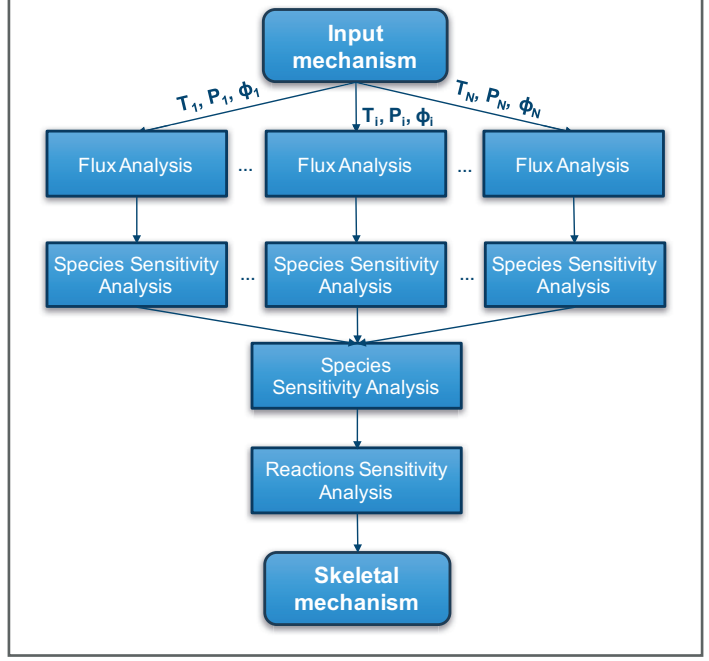
Stagni Alessandro – Supervisor: Prof. Tiziano Faravelli

Nowadays, combustion holds a central role in 21st century societies and economies, where it currently satisfies more than 80% of the global energy demand. Nevertheless, the main drawback of such a leading role, originated from the cheap availability of fossil fuels, their energy density and a consolidated production and distribution network, is its environmental unsustainability: combustion processes are among the major producers of greenhouse gases and air pollutants, with negative consequences on human health, climate and the whole ecosystem. Thus, considering the time scales of transition to more sustainable energy sources, a continued effort in combustion research towards higher efficiencies of combustion devices and lower emissions is of primary importance.
In this background, the role of numerical simulations in support of experimental research has been gaining a more and more central role: the technological improvements in computer science has enabled the use of more sophisticated numerical models with improved predictive capabilities. In these simulations, an essential feature to ensure an acceptable predictive value is constituted by the level of detail of the available kinetic models: the current computational capability allows to use detailed kinetic models for the simplest fuels (methane/hydrogen); on the other hand, this is not possible for the more complex ones, like those used for transportation purposes, for which detailed chemistry can be adopted only for 0-dimensional or, sometimes, 1-dimensional applications (**Figure 1**).



1. Competition between complexity of numerical simulations and size of kinetic mechanisms.

The purpose of this PhD thesis has been conceived from this last limitation: a generalized methodology for the automatic reduction of detailed kinetic mechanisms, with the desired degree of accuracy on user-defined target properties, has been developed. The possibility of targeting mechanism reduction is indeed essential to retain accuracy on the dynamics of formation of pollutant compounds, like soot or nitrogen oxides, whose time scales are order of magnitudes higher than ignition delay times, usually adopted as single target in the state-of-the-art reduction techniques.
Throughout the PhD activity, a multistep methodology for automatic mechanism reduction has been developed (**Figure 2**), where several techniques have been combined in a synergistic way. An upstream chemical lumping of isomers has been coupled to techniques of flux analysis and sensitivity analysis of reacting fluxes in ideal reactors. In addition, in order to include user-defined targets, a *Species-Targeted Sensitivity Analysis* has been devised and included in the reduction framework. To this aim, a metric based on curve comparison via Functional Data Analysis has been created to quantify the ability of a kinetic mechanism in reproducing the evolution of species over time. The availability of such framework allows a significant upstream simplification of the original detailed mechanisms, thus allowing to carry out large-scale, demanding combustion simulations in acceptable times. Two case studies have been analyzed throughout the Thesis to show the obtainable advantages.
The role of preferential evaporation phenomena in the ignition of multicomponent jet fuel surrogates has been first investigated through a two-phase model, describing the evaporation and ignition of fuel droplets in a homogeneous gas-phase environment. In order to quantify the effects of a time-variable composition of the evaporating mixture on ignition, a representative surrogate of jet fuels has been selected, and a simplified kinetic mechanism has been obtained through the methodology described before. A wide range of starting conditions could be explored, and a parametric analysis to droplet diameter and global equivalence ratio has been carried out. Through this study, a narrow region of operating conditions, critical for gas turbine engines, has been discovered, where the time scales of ignition and evaporation are of the same order of magnitude: here, the effect of preferential evaporation is particularly evident, and undesired effects of delayed ignition delay time have been identified; thus, the inclusion of volatility and liquid diffusion properties in the formulation of fluid-dynamic models could become necessary.
The dynamics of soot formation from the two-phase combustion of real fuels has then been considered, where the accuracy of the underlying kinetic mechanism has often proved to be a critical requirement. Starting from a discrete-sectional model describing soot kinetics, and using n-heptane as sample fuel, the Species-Targeted Sensitivity Analysis has been adopted to obtain a simplified mechanism, able to retain accuracy on the dynamics of mass fraction and particle size distribution. Its application to the combustion of isolated droplets in microgravity conditions has allowed to characterize the role of the main phenomena affecting soot formation. An inner soot layer could be observed, surrounded by the flame front, both progressively moving away from the droplet surface, and the key role of the thermophoretic effect could be identified as the key factor causing soot volume fractions of the order of the parts per million. Moreover, a strong coupling could be observed between soot layer and flame structure, because of the high volume fractions at stake.
In conclusion, the activity carried out throughout this PhD project has provided a generalized framework to exploit the precious information contained in detailed kinetic mechanisms, which cannot be directly used in the complex combustion simulations. Such a tool can act as an important keystone for the next research in combustion science, towards the final targets of improved efficiency and decreased pollution.



2. Schematic of the reduction algorithm developed in the PhD thesis. T = initial temperature. P = initial pressure. Φ = initial equivalence ratio