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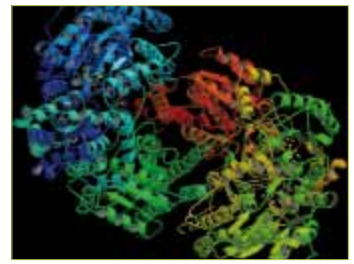
Chair:
Prof. Renato Rota

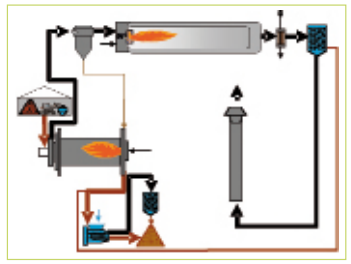
DOCTORAL PROGRAM IN INDUSTRIAL CHEMISTRY AND CHEMICAL ENGINEERING

The Doctoral Program in Industrial Chemistry and Chemical Engineering (***CII***) is designed for students aiming to get a deep expertise on chemical processes and on material processing either as the inherent *research* or in the *process design and development* activities.
The program is the ideal extension of the *Laurea Magistrale* degrees in *Chemical Engineering*, *Safety and Prevention Engineering, Materials Science*, *Material Engineering*, *Industrial Chemistry* and *Chemistry*, but it is also open to graduated in other scientific disciplines.
The general topic for the doctoral program in Industrial Chemistry and Chemical Engineering is the application of the chemical and physical knowledge to all the activities related to the synthesis, design, production and transformation of chemical substances and materials (like advanced inorganic, polymers and biomaterials). These studies involve not only the synthesis processes but also the related plants, here analyzed starting from the laboratory tests and the pilot plant experiments up to the industrial size ones, always including the exam of the related energetic, safety and environmental issues.
The final goal is to provide to the Research Doctor the tools and the skills: (1) to design and manage industrial processes at any size scale; (2) to develop new technical applications and (3) to create and to characterize new products and services.
The ***CII*** program covers three years for an overall amounts of 180 credits. The responsibility of the organization and of the contents of the doctoral program is attributed to the Professor Committee (PC). At the beginning of the Doctoral program, a tutor and a thesis advisor is assigned to each student. The tutor has a supervisor function during the whole doctoral program, whereas the thesis advisor is responsible for the thesis work.
The PC defines a specific curriculum for each student, on the basis of the tutor suggestions. The curriculum has to be designed in order to both cover deficiencies in the student scientific formation and to give a high-quality technical and scientific preparation.
Since 2001 (XVI cycle) the ***CII*** program graduates 88 students, being the 80% now working in industry and the remaining in the university or government research centers. This point demonstrate the great link existing between the performed researches and the industrial environment. In fact, more than 70% of the research topics were directly supported by industrial companies, like ENEL, LPE Epitaxial Technology, Bracco, Flamma, Mapei Solvay Solexis.

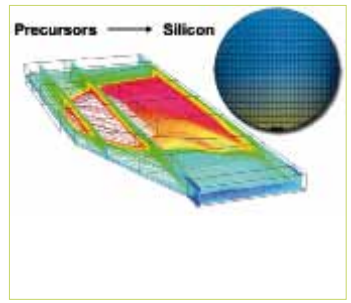
1. Structure simulation of Nitrogenase enzyme for N_2 conversion to NH_3



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



3. Contaminated soil remediation process



4. Hazardous gas dispersion simulation from an industrial accident

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

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SYNTHESIS OF BIOLOGICALLY ACTIVE MOLECULES AND METHODS TO CHARACTERIZE THEIR SYNTHETIC ORIGIN

Daniela Acetti

The present work is focused on two important aspects of the chemistry of biologically active molecules.
The first aspect deals with the stereoselective synthesis of biologically active molecules, while the second one concerns the application of stable isotope analysis to trace back their synthetic history.
In recent years, there has been an increasing interest in the synthesis of single enantiomers of chiral molecules, especially in the pharmaceutical field.
This interest has resulted from the advances in the synthesis, analysis and separation of chiral molecules, together with an increased appreciation of the potential significance of the differential biological properties of the enantiomers of chiral drugs administered as racemates.
Among the techniques used to synthesize pure enantiomers, biocatalysis is widely employed by the industries for the production of optically pure intermediates of pharmaceutical relevant drugs and chromatography on a chiral phase has become a more and more adopted technique for the preparative and production scale separation of fine chemicals.
In this work we used biocatalysed kinetic resolution, enzyme-mediated stereoselective synthesis and a chromatographic technique on a chiral phase to obtain enantiomer separation.
The enzymes employed in the reactions performed were baker's yeast whole cells or lipases. The former were employed to catalyse the enantioselective reduction of carbonyl moieties, while the latter to perform enzymatic kinetic resolution by selective acetylation of one enantiomer of a racemic mixture.
In this way, many chiral building blocks or key intermediates of pharmaceutical relevant products known in literature have been synthesised in enantiomerically pure form by new and alternative synthetic approaches based on biocatalyzed reactions using baker's yeast whole cells or lipases.
All the molecules were produced with an enantiomeric excess in the range of 95-99%.
Moreover, in the case of molecules with more than one stereogenic centres, all the possible stereoisomers were synthesised, since the enzymes employed resulted to be highly regio- and enantioselective for the chosen substrates.
In this way, we can use environmental-friendly, easy to use and safe to manage enzymes to control the stereochemistry of different stereocentres within a molecule.
As a part of an European project in which we are involved, one of the compounds synthesised, which is the precursor of an important key intermediate in the synthesis of many antifungal drugs, was also submitted, in racemic form, to the chiral chromatographic technique named Intermittent Simulated Moving Bed (I-SMB) to obtain enantiomer separation.
In particular, a careful study and calculations of process parameters allowed us to perform I-SMB experiments in which the two enantiomers were recovered with purity values in the range of 98-99%.
This work has been done in the prof. Marco Mazzotti's laboratory at ETH of Zürich, since our research groups are involved in an European project named INTENANT (INTegrated synthesis and purification of single ENANTiomers).
The primary goal of INTENANT project is to develop integrated strategies combining the available chemical and physical methods to provide single enantiomers at high optical purity. The project is based on a strong cooperative consortium of 13 workgroups situated at 11 European research centres, each one specialized in individual process technologies (synthesis, chromatography, racemization, dynamic kinetic resolution, etc.).

Traceability is the ability to describe and follow the history of a certain product, from its origins, through its development, to its subsequent employment. There is great need for reliable analytical techniques to assess the origin and the synthetic history of drugs, in order to fight counterfeit medicines and to achieve patent and brand protection. SNIF-NMR (Site specific Natural Fractionation NMR), for example, is a useful analytical techniques to assess the traceability of organic compounds. It determines stable isotope ratio at natural abundance level measuring the enrichment or depletion usually of deuterium or ^{13}C of each hydrogen and carbon atom of the molecule, thus giving site-specific information. This is very important because sometimes, only a few D/H isotope ratios are diagnostic, corresponding to the molecular positions effectively affected by the synthetic path.
In this work SNIF-NMR technique was applied to samples of the anti-inflammatory drugs Ibuprofen and Naproxen, with different origin. We compared the results obtained with those of reference compounds synthesized according to the known patent literature: the D/H isotope ratios values of specific positions within the molecule allowed us to understand in which way each sample was synthesized. The ability of SNIF-NMR technique to discriminate samples on the basis of the synthetic sequence followed for their preparation is fundamental in order to identify patent infringement and counterfeit drugs.

DYNAMIC KINETIC RESOLUTION OF UNNATURAL N-PROTECTED AMINOACID THIOESTERS

Dario Arosio

Unnatural amino acids are important tools for modern drug discovery research.
Due to their structural diversity and functional versatility, they are widely used as chiral building blocks and molecular scaffolds in constructing combinatorial libraries. In this field, biocatalysis represents the most important tool in the industrial production of amino acids as single enantiomers.
The resolution of racemic compounds continues to be a valuable method for obtaining chiral compounds in high optical purity, using both enzymatic and non-enzymatic catalysts. A disadvantage of standard kinetic resolution procedures is that a maximum 50% yield of the desired product is obtained based on racemic starting material. To overcome this limitation, recovered starting material may in some cases be racemised and resubmitted to the resolution procedure.
As a potentially more efficient procedure, resolution processes have been coupled with continuous in situ racemisation of the starting material.
This allows a quantitative conversion of the racemic starting material into one stereoisomer of the product in a single deracemisation process. This process is known as dynamic kinetic resolution (DKR).
Requisites for a successful DKR are: an enzyme selective for one form of the racemic mixture, a racemising system (chemical or enzymatic) acting on the substrate but not on the product, and a rate of racemisation higher than the enzymatic reaction rate.
These conditions require the design of suitable substrates.
Recently the use of a thioester of a carboxylic acid having a chiral center at the α-carbon in an enzymatic DKR procedure was reported. In fact, in contrast to an oxoester, the α-protons of the thioester are sufficiently acidic to allow continuous racemisation of the substrate by base-catalyzed deprotonation (trioctylamine, TOA) at the α-carbon.
The aim of this research has been to develop a novel method of enzymatic DKR (mediated by subtilisin) to obtain unnatural α-amino acids as single enantiomers. For that purpose a library of both aryl and aliphatic N-Boc-aminoacid-thioesters was synthetized and detailed studies on the racemisation step have been carried out.
In these racemisation studies the Bronsted catalysis equation was used to correlate the experimental kinetic data of racemisation with the acidity of the α-proton; this equation gives the relationship between acid strength and catalytic activity in general acid catalysis: $lnk = \alpha ln(Ka) + \beta$. This relationship implies that the Gibbs free energy is proportional to the activation energy for the catalytic step.
The relation is linear when the catalyst operates through the same reaction mechanism.
In this work the acidity of the α-proton in amino acids thioesters was correlated with the measured kinetic constant.
Computational calculations were also performed to predict the thermodynamic parameters, in particular the ΔH value.
It has then been shown that the presence of the sulfur atom is essential in providing a useful racemisation rate which also strongly depends on the nature of the R group on the skeleton of the amino acid molecule.
The synthesised library of α-aryl- and non- α-aryl-substituted amino acid thioesters was racemised with different bases.
For the first group TOA has been used successfully; for the second one a stronger base as DBU has been necessary, because the acidity of the α-H was lower and the racemisation was more difficult. In fact *pKa* values of thioesters of amino acid derivatives increase markedly from α-aryl-substituted compounds to aliphatic ones.
Kinetics of racemisation have been performed with two methodologies: ^{1}H-NMR experiments and polarimetric analysis. In the first one, the racemisation conditions were studied by observing the exchange rate of the α-proton of the thioesters with deuterium in d_6-DMSO, in the second one the actual racemisation rate was measured by a polarimetric method.
Then two methods for DKR of racemic N-Boc-aminoacid-thioesters were reported.
Starting from a racemic mixture, the thioester in the L-form was hydrolyzed in the presence of subtilisin (in solution or as Cross Linked Enzyme Aggregates, CLEA) to the corresponding aminoacid.
The D-enantiomer was indeed continuously racemised in the presence of an organic base (DBU or TOA). The combined reactions lead to the complete deracemisation of the racemate giving the L-amino acid in excellent yield and high enantiomeric excess.
Finally, the recyclability of subtilisin CLEA has been studied in order to get the maximum exploitation of the enzyme and then a cost reduction in view of a possible industrial application.

ASYMMETRIC SYNTHESIS BY ENZYME AND SOFT LEWIS ACID CATALYSIS

Assem Mahmoud El Sayed Barakat

The use of chiral catalysts which convert prochiral substrates into enantiomerically pure (or enriched) compounds. Catalysis can be performed either by biocatalysts or chemocatalysts. Biocatalysis has many attractive features in the context of green chemistry: mild reaction conditions (physiological pH and temperature), an environmentally compatible catalyst (an enzyme) and solvent (often water) combined with high activities and chemo-, regio- and stereoselectivities in multifunctional molecules. Furthermore, the use of enzymes generally circumvents the need for functional group activation and avoids protection and deprotection steps required in traditional organic syntheses. This affords processes which are shorter, generate less waste and are, therefore, both environmentally and economically more attractive than conventional routes. Chemists have discovered lipases to be one of the most versatile classes of biocatalysts in organic synthesis for a few simple reasons: they can be employed under mild reactions in common organic solvents, under atmospheric pressure, and at room temperature. They are generally safe for the environment, and can be recycled with out loss of activity. Lipases can accommodate a wide variety of synthetic substrates, while still showing chemo-, regio, and/or stereoselectivity.
Biocatalysis was applied for the synthesis of enantiopure compounds by enzymes.
We have performed two examples by enzymes.
The first example describes the straightforward synthesis of both enantiomers of *cis*- and *trans* 3-acetoxy-6-hydroxy-α-ionone. The compounds are prepared by resolution of the diastereoisomerically pure racemic 3,6-dihydroxy-α-ionone isomers. The later process is based on two steps. The enantio- and regioselective lipase-mediated acetylation of diols to afford the corresponding 3-acetoxy-derivatives, and the fractional crystallization of the latter compounds increasing their optical purity. These building blocks were used for the synthesis of both enantiomeric forms of the natural norterpenoids dehydrovomifoliol and 8,9-dehydrotheaspirone. 8,9-Dehydrotheaspirone is a natural flavour.
The second example performed by biocatalysis describes the regioselective synthesis of the methyl ionones isomers. The enantiomers of the γ isomers are prepared by enzyme-mediated resolution of the corresponding 4-hydroxy derivatives followed by reductive elimination of the hydroxy group. Since all the obtained isomers are components of the artificial violet odorants sold under the trade name of Iralia®, their odour properties have been evaluated by professional perfumers.
Despite the impressive progress achieved in asymmetric catalysis during the last decade, an increasing number of new catalysts, ligands, and applications are reported every year to satisfy the need to embrace a wider range of reactions and to improve the efficiency of existing processes. Because of their availability, unique stereochemical aspects, and a wide variety of coordination modes and possibilities for the fine-tuning of steric and electronic properties, ferrocene-based ligands constitute one of the most versatile ligand architectures in the current scenario of asymmetric catalysis. Over the last few years ferrocene catalysts have been successfully applied in an amazing variety of enantioselective processes. In modern synthetic chemistry, soft Lewis acids such as Pd(II), Pt(II) or Au(I) have become more and more important. The soft Lewis acid can thus be regarded as a chemoselective (owing to its low oxophilicity) and possibly chiral proton substitute.

The Pd(II) catalyzed *aza*-Claisen rearrangement of allylic trichloro- and trifluoroacetimidates enables the transformation of achiral allylic imidates, readily prepared from allylic alcohols in a single high yielding step, to chiral enantioenriched allylic amides**.** Since the trihaloacetamide protecting groups can be readily removed, the overall transformation leads to allylic amines, the valuable building blocks for the synthesis of important compound classes such as unnatural amino acids. To this end, pentaphenylferrocenyl oxazoline palladacycles catalyst **(PPFOP-Cl)** have been created, affording the most active enantioselective catalyst for the *aza*-Claisen rearrangement of trihaloacetimidates.

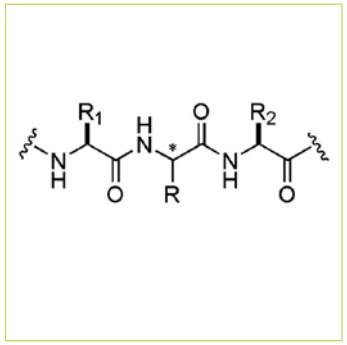
SYNTHESIS OF PEPTIDOMIMETICS OF BIOCHEMICAL INTEREST: FLUORINATED PEPTIDES AND DIASTEREOMERS OF TUBULYSIN U

Serena Bigotti

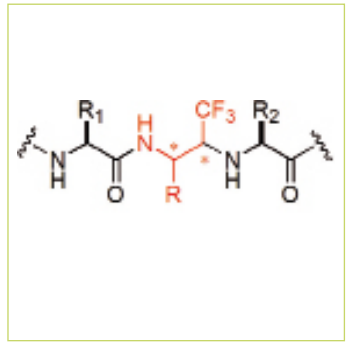
Peptidomimetics find application as drugs, in protein engineering and so on. In fact, the "druggability" of peptides could be achieved by the synthesis of suitable peptidomimetics able to retain the activity of the parent peptides, while at the same time much more stable and selective.

Fluorinated Peptides:

The replacement of peptide bonds with appropriate functionalities is a classic approach in medicinal chemistry. The trifluoroethylamine (Tfm) function is a new peptide bond surrogate which generate a metabolically stable, non-basic amine that maintains the excellent hydrogen bond of an amide.
Ψ[CH(CF_3)NH]Gly peptides have been synthesized by stereoselective addition of α-amino acid esters to *trans*-3,3,3-trifluoro-1-nitropropene. The diastereoselection of the reaction resulted to be dependent on different factors such as the solvent, the side chain of the α-amino acid esters, the base and the temperature. To fine tune such parameters in order to obtain better diastereoselectivities, we carried out a series of experiments using L-Val benzyl and *tert*-butyl ester hidrochlorides as model nucleophiles. The best result

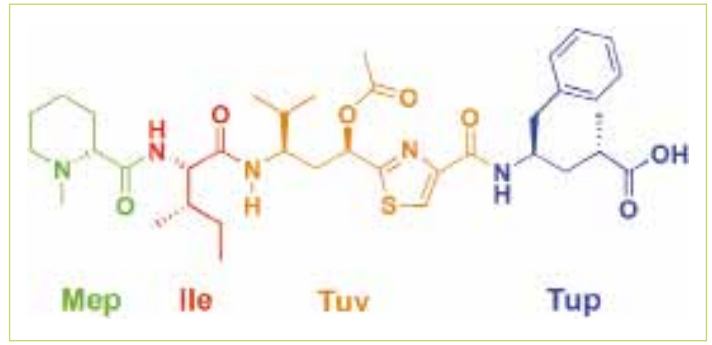


1. Parent peptide



2. Ψ[CH(CF3)NH] peptide

was obtained with bulky R group, in presence of a catalytic amount of DIPEA as base (1.1 equiv), toluene as solvent, at room temperature for 30 minutes. The stereochemistry of diastereomers obtained from the model reaction was assessed by X-Ray diffraction, whereas the configuration of the other adducts were confidentially assigned on the basis of their spectroscopic features in comparison with those of the model adduct.
This work has been expanded to novel peptidomimetics featuring Ψ[CH(R_F)NH] having different degree of fluorination, using the same strategy. Replacement of a single F atom to R_F by a hydrogen or methyl group brought about a dramatic drop of stereo control, whereas Br, Cl, and CF_3, albeit bulkier than F, provided fairly worse results in termes stereocontrol.
In order to improve our knowledge on the influence of the Tfm surrogate on the conformation of peptides, we decided to synthesized Tfm Gellman's tetrapeptides analogues changing the configuration of Proline moiety and Tfm group. By means NMR studies in nonpolar solvent, we demonstrated that these tetrapeptides were found to exist in turn-like secondary structures stabilized by an intramolecular hydrogen bond involving the aminic proton of the Tfm surrogate. We demonstred that the main properties featured by the trifluoroethylamino group are: 1)very low NH basicity, 2) a CH(CF_3)NHCH backbone angle close to 120°, 3) a C-CF_3 bond isopolar with the C=O, and 4) structural analogy with the tetrahedral proteolytic transition state. Furthermore, the Tfm unit has an sp^3 tetrahedral configuration,



3. Structure of Tubulysin U

that can contribute to the optimization of the spatial orientations of the interactions, and has high metabolic stability. Moreover the NH moiety is a good hydrogen-bond donor, due to the presence of the α-CF_3 group. All these properties confirm that the Tfm function is a promising peptide bond replacement.

Diastereomers of Tubulysin U:

The tubulysins, first isolated by the Höfle/Reichenbach group from myxobacterial cultures, are exceptionally potent cell-growth inhibitors that act by inhibiting tubulin polymerization and thereby induce apoptosis. The tubulysins have IC_{50} values between 0.01-10 nM in multidrug-resistant cell lines.

The compounds share a linear tetrapeptide core. Tubulysin U consisting of N-methylpipecolic acid (Mep) at the N-terminus, isoleucine (Ile, the only proteinogenic amino acid) at the second position, an unusual thiazole-containig amino acid featuring two stereogenic centers, dubbed tubuvaline (Tuv) at the third position, and a γ-amino acids at the C-terminus, namely tubuphenylalanine (Tup). The OH group of Tuv fragment is functionalized with an acetyl moiety. Structure-activity relationship (SAR) studies using synthetic analogues of tubulysin U could identify the essential structural features underlyng its cytotoxicity. With this in mind, the distereomers of tubulysin U were synthesized using a versatile synthetic strategy. All analogues were analyzed in HT-29 cell line. The activities of analogues whose possess a Tup-modification showed a drop in cytotoxicity relative to the natural product, expecially when the configuration of the methyl group is changed. While reversing the configuaration of Tuv stereocenters, the diastereomers exhibited activity against cell lines, albeit less than that of Tub U.
Worse results were obteined when the configuration of acetyl group is opposite to the natural tubulysin.
All the diastereomers are less active than the tubulysin U as we aspected. Comparison of the data obtained reveals that the methyl group in Tup is foundamental for the activity of Tubulysin, while the structural complexity of tubuvaline fragment can be reduced without a dramatic drop in the biological activity.

CATALYTIC SYSTEMS FOR THE ABATEMENT OF CH_4 EMISSIONS FROM COMPRESSED NATURAL GAS ENGINES

Paola Castellazzi

Catalytic combustion of methane represents a promising way to reduce emissions of CH_4, a strong green house gas, from lean burn compressed natural gas vehicles (NGVs) engines.
In the reaction conditions specific of the exhausts, Pd-based catalysts are the most active towards CH_4 combustion. Nevertheless Pd superiority is accepted, many aspects remain still debated: the effect of Pd dispersion on catalytic activity, the exact nature of the active sites, the role of the support and of its interaction with Pd.
A major drawback for Pd practical application in the catalytic muffler of the NGVs is related to deactivation problems during operation under the reaction atmosphere, containing poisons as H_2O and SO_2.
The addition of promoters such as Pt to Pd-supported catalysts may improve stability under reaction conditions.
In this context, alternated lean combustion/CH_4-reducing pulses at constant temperature allow an effective strategy for regeneration of activity lost for both H_2O and S-poisoning.
In this thesis work, the effect of the alternated cycles treatment at 350°C on catalytic performances of Pd/Al_2O_3 and $Pd-Pt/Al_2O_3$ catalysts was investigated.
The effect of Pd dispersion was considered over three samples having different Pd loading: 1, 2 and 4 wt% Pd/Al_2O_3, the first one more dispersed (48%) than the latter two ones, which are equally dispersed (21 and 19%, respectively). For each catalytic systems,
the alternated cycles result in a marked increase of the activity and in the achievement of stable performances, significantly higher than that of the as-prepared samples (*fresh* samples).
Focusing on the stable catalytic performances, each sample slowly deactivates, during the time exposure to the lean conditions, because of the H_2O poisoning; nevertheless, the activity lost is fully recovered after performing a CH_4-pulse and restoring the lean conditions.
The less dispersed catalysts exhibit superior combustion activity compared to that of the more dispersed one; at the same time, in situ Raman and CH_4-TPR tests, performed over the three catalysts after stabilization under the alternated cycles (*conditioned* samples), show that for each sample the total amount of palladium is in the form of PdO, during the lean reaction conditions, and that PdO reduces at high temperatures for the 1% Pd catalyst respect to the 2 and 4% Pd ones which, on the other hand show similar reducibility. This indicate a direct relationship between PdO reducibility and combustion activity, which is in line with a Mars van Krevelen mechanism controlled by the PdO reduction step for CH_4 combustion.
Another important indication about the effect of dispersion comes from the study of Pd oxidation process during the lean conditions restored after each CH_4-reducing pulse, during which PdO is completely reduced to metallic Pd. The study evidences that during the lean conditions, immediately after the CH_4-pulse, each catalyst exhibit firstly a marked increase of CH_4 conversion with time, up to a maximum value, then the deactivation trend briefly described above. At the same time also the extent of Pd oxidation increases with time, suggesting that activity is strictly related to the extent of Pd oxidation and that PdO is necessary for combustion activity; our data on the 2% Pd sample also evidence that activity decreases if the Pd oxidation extent exceeds a level of 85-90%, indicating that PdO/Pd mixture is likely the most active phase, according to a direct role of metallic Pd in CH_4 activation. The reactivation/re-oxidation dynamic is slower for the more dispersed sample than for the less dispersed one.
As a whole, the study pointed out that the use of too high dispersion Pd catalysts is not advantageous for practical application since they are less active and reducible and they slowly reactivates under lean conditions, after a reducing pulse, respect to the less dispersed systems.
For the same Pd/Al_2O_3 catalysts the reason behind the marked activation observed during the alternated cycles was investigated. Modifications of Pd dispersion during the treatment can be invoked to explain the observed activation only in the case of the 1% Pd sample, which becomes less dispersed at the end of the alternated cycles, while for the other two samples dispersion remains constant. The study of PdO reducibility over the fresh and conditioned samples, evidences that after the alternated cycles process PdO reducibility increases, thus explaining the increase of combustion activity in line with the Mars van Krevelen mechanism.
The reason for the increased reducibility was investigated by means of FT-IR performed over fresh and conditioned 2% Pd sample, after reduction in H_2 at 500°C. The FT-IR spectrum of CO chemisorption over the fresh sample evidences the presence of partially oxidized $Pd^{\delta+}$ species, strongly interacting with the support, which strongly reduce in intensity in the case of the conditioned sample; this suggests that the alternated cycles treatment results in the weakening of Pd-support interactions which likely stabilize palladium in its oxidized phase, thus being detrimental for catalytic activity.
Finally, the effect of Pt addition to Pd supported on Al_2O_3 catalysts was investigated over catalysts with a constant Pd loading and different Pt/Pd atomic ratio. It was found that Pt addition hinders Pd oxidation and promotes PdO reduction.
At the same time, the comparison of activity level under lean combustion conditions of the fresh samples indicates a progressive promoting effect of Pt on activity, suggesting, at a first approach, a direct correlation activity/reducibility as in the case of the monometallic Pd sample. However, a closer inspection, evidences that, while Pt effect on activity is gradual with Pt amount, its effect on reducibility is abrupt, i.e. reducibility markedly increases in the case of the bimetallic samples respect to the Pd-only one but the differences between each Pt-Pd catalysts are slight.
The lack of correlation between activity and reducibility may be due to the fact that while Pt strongly promotes CH_4 activation in absence of O_2 (and thus PdO reducibility) it may be less effective under oxidizing conditions.
An alternative explanation for the promoting effect of Pt may be the weakening of Pd-support interactions, in presence of Pt, as suggested by the lower dispersion values and by the lower thermal stability of PdO of the bimetallic samples. The alternated cycles treatment results in a marked activation only in the case of the Pd-monometallic and in the bimetallic with low Pt content samples, while the high Pt amount sample catalysts results completely deactivated and the sample with intermediate Pt amount exhibits a final activity equal to the initial level. The deactivation of the high Pt-containing sample is due to the complete suppression of the re-oxidation of Pd° reduced during the first CH_4-pulse, evidencing the importance of PdO for combustion activity, which represents the active phase also in the presence of Pt. On the other hand, the conditioned samples with low and medium Pt contents contain 85 and 35% of total palladium as PdO but their activity is respectively superior and equal to the activity of the same fresh sample, containing the entire amount of palladium as PdO, thus indicating the increase of PdO intrinsic activity after the alternated cycles process. This increase is not related to an increase of PdO reducibility, since the comparison of CH_4-TPR profiles of fresh and conditioned samples indicates a lower reducibility of the latter ones, confirming the lack of reducibility/activity correlation in presence of Pt. A possible reason for the activity increase might be the presence of a fraction of Pd in the metallic form, able to dissociate CH_4 also in oxidizing conditions, which is stabilized by Pt also during the oxidizing lean combustion conditions.

KINETIC MODELING AND THERMODYNAMIC ANALYSIS OF THE FISCHER-TROPSCH WAX HYDROCRACKING PROCESS

Simone Gamba

Fischer-Tropsch (FT) based technologies can be considered a valid means to obtain cleaner fuels from both fossil and renewable sources. Recent works have proven that FT-derived diesel has excellent combustion properties and it is characterized by reduced emissions. FT fuel production from fossil sources (coal or natural gas) has already reached the commercial scale while the production from renewable sources (from biomass gasification) has no commercial application yet. In any case, several studies have been conducted in order to investigate the feasibility of an integrated biomass gasification and Fischer-Tropsch system and second-generation biofuels via FT-processes seem to be promising as renewable fuels.
Regardless of the syngas source, FT wax must be subjected to a hydrocracking process over a bifunctional catalyst in order to obtain an acceptable yield in middle distillate cut (i.e., kerosene and gas oil) as well as fuels with both good cold flow properties and high cetane number. These two goals are reached in a hydrocracking process by means of isomerization and cracking reactions, the former being equilibrium reactions and the latter being irreversible reactions. Branched paraffins assure the improvement in the cold flow properties while the catalytic cracking of the heaviest hydrocarbons in the wax fraction (i.e., hydrocarbons with more than 22 carbon atoms) leads to an increase of the middle distillate cut.
In this thesis, kinetic and thermodynamic aspects of the hydrocracking of a cobalt catalyzed FT wax are studied in order to develop a mathematical model of the bench scale process that is able to take into account the influence of the main operating conditions on produced fuels.
As for the Thermodynamics of the process, the work of our group has led to:

1. the development of a computational method for obtaining "lumped equilibrium constants" for isomerization reactions. In order to compute the "lumped equilibrium constants" for heavy paraffins it has been necessary to overcome the lack of experimental data for branched paraffins with more than 10 carbon atoms and thus a procedure has been worked out to determine equilibrium constants extrapolating the thermodynamic data of low carbon number paraffins. The coherence of the estimated constants has been verified by comparison with the little data available in literature on lumped equilibrium constants;
2. the introduction of the Vapor-Liquid-Equilibrium calculation in the kinetic model in order to better take into account the effect of the H_2/wax inlet mass ratio on the product composition experimentally observed. This allows to correctly predict a wax conversion that increases with increasing the H_2/wax inlet mass ratio due to a thermodynamic effect (the enrichment of the more reactive liquid phase in the heaviest hydrocarbons because of the "stripping effect" of the hydrogen);
3. the development of normal boiling-point-based correlations for the prediction of heavy paraffin critical constants (which are experimentally unavailable or subject to large errors due to the instability of these compounds at their critical temperatures) and Mathias-Copeman alpha function parameters that allow a good pure component vapor pressure calculation when a cubic equation of state, such as the SRK EoS, is employed.

Regarding Kinetics the introduction in a lumped model of a "breakage probability function" for the C-C bonds, elaborated from experimental evidence reported in literature, is shown. This modification, along with the results of the thermodynamic study, has allowed to obtain a model with an improved response to the variation of the operating conditions and better product distributions.

A molecular pathway-level kinetic model, developed using an automated kinetic model builder software in a collaboration between our group and Prof. Klein's group at Rutgers University, has also been worked out. A relumped procedure that potentially allows the model to be easily applied to a complex feedstock is proposed as well. This procedure is based on a reaction classification that takes into account information from a deeper mechanistic level: at the mechanistic level both isomerization and cracking reactions lead to a change in the configuration of the carbenium ion involved.
The tuning procedure for the molecular pathway model requires experimental data with a higher level of detail than that of the experimental data used to develop lumped models (i.e., at least the distinction between monobranched and multibranched alkanes could be required to obtain meaningful kinetic parameter values).
This kind of data has been made available very recently and its analysis is presented in this thesis. In particular, for the hydrocarbons in the middle distillate cut, the effect of the operating conditions (temperature, pressure, weight hourly space velocity and H_2/wax inlet mass ratio) on the extent of the isomerization reactions is shown along with an analysis of the mono-branched and multi-branched isomer distribution at different levels of wax conversion.
This analysis represents the starting point for future works on tuning of a more detailed model.

USE OF CARBODIIMIDES IN NEW ONE-POT SEQUENTIAL PROCESSES FOR THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

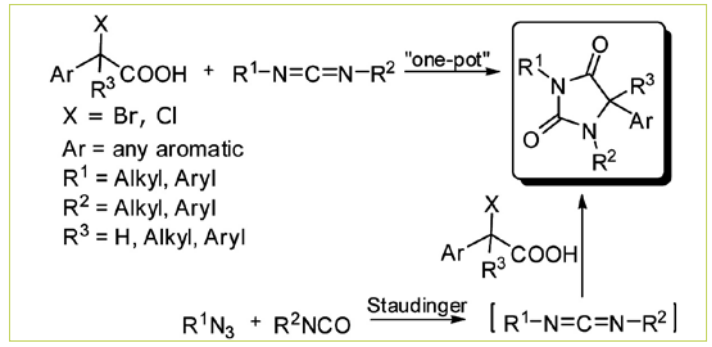
Francesca Olimpieri

Small substituted heterocyclic compounds play an important role in the development of biologically active substances. In fact, a large number of synthetic organic molecules, showing high medicinal potential, contain heterocyclic rings. Furthermore, the most potent ligand systems in metal-mediated catalysis are often based on heterocyclic cores. However, the range of easily accessible and suitably functionalised heterocyclic building blocks is surprisingly limited and the construction of even a small array of heterocyclic compounds is far from trivial. For this reason, there is a lot of interest in developing new strategies for the straightforward synthesis of such compounds, whose preparation is usually achieved using harsh reaction conditions, such as strong basic/acidic conditions, high temperatures and long reaction times. Meanwhile, pharmaceutical industries require increasingly improved performances in the syntheses of target molecules, especially in terms of waste reduction. A powerful approach toward this goal is the combination of two or more distinct reactions into a single transformation, thereby producing a sequential reaction process involving two or more reactants, namely a domino process. In effect, compared to the usual stepwise-fashion procedures, domino reactions show both economical and environmental assets and are especially suitable for diversity-oriented synthesis applications.

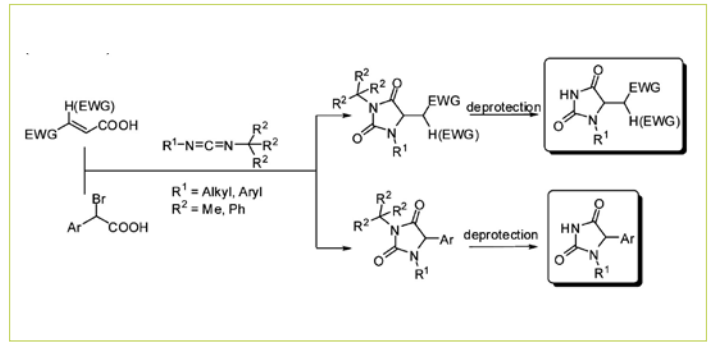
Carbodiimides are very popular reagents in synthetic organic chemistry, easy to prepare and often used in order to activate carboxylic acids toward nucleophilic substitutions. In the past years, our research group exploited the reactivity of carbodiimides with suitable carboxylic acids for the synthesis of small heterocycles of great biological interest, such as hydantoins and barbiturates. In particular, it has been demonstrated that carbodiimides and activated α,β-unsaturated carboxylic acids smoothly react, affording a vast array of 1,3,5-trisubstitued hydantoins by means of a novel domino condensation/aza-Michael addition/O→N acyl migration process. Furthermore, it has been proved that condensation between carbodiimides and malonic acid monoesters leads to the formation of N-acyl urea derivatives which, by *in situ* addition of a suitable base and an electrophile, undergo cyclization, affording fully substituted barbiturates in a one-pot, three-component sequential fashion. This PhD project takes place in such ongoing research program, focusing on the development of novel mild and efficient procedures for the synthesis of small heterocycles of potential biological interest, such as hydantoins and dihydrouracils, through reactions of carbodiimides with suitable activated carboxylic acids. First, we demonstrated that reactions of carbodiimides with α-halo arylacetic acids produce fully substituted 5-aryl hydantoins, under very mild conditions, in high yields and, in most cases, with complete regioselectivity. The subsequent development of such procedure consisted of *in situ* generation of carbodiimides from the corresponding azides and isocyanates, through the Staudinger reaction, followed by treatment with a suitable α-halo-arylacetic acid, resulting in a novel and efficient three-component, one-pot sequential process for the preparation of libraries of fully substituted 5-arylhydantoins (Scheme 1).

Then, we developed an efficient two-step procedure for the synthesis of 1,5-disubstituted hydantoins. Such procedure exploited the highly regioselective process involving activated α,β-unsaturated carboxylic acids or α-halo aryl acetic acids, respectively, and N-*tert*-butyl- or N-trityl-substituted carbodiimides, leading to the formation of hydantoins, bearing on the iminic nitrogen the tertiary alkylic substituent, which is selectively removed afterwards (Scheme 2). Finally, we developed a straightforward two-step reaction sequence involving carbodiimides in the presence of β-aryl/alkyl-β-hydroxy-α,α-difluoro carboxylic acids, to afford a vast array of fully substituted *gem*-difluoro dihydrouracils. In the first step, condensation between the two reactants led in most cases to the formation of a mixture of the desired dihydrouracils and *N*-acylurea co-products. However, the latter could be easily recovered and efficiently converted into the target compounds (Scheme 3).

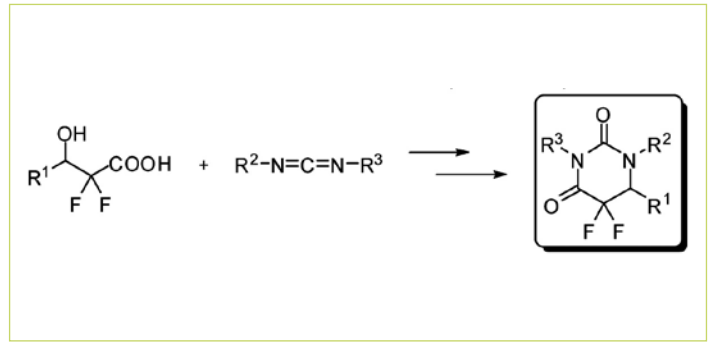
The methodologies developed during this PhD project, completely overcome the drawbacks of previous ones, such as harsh reaction conditions and use of toxic reagents. The operational simplicity, good chemical yields and easy access to the starting materials, combined with a favourable atom economy and a small number of steps, make these new synthetic strategies highly attractive and promising for the preparation of new heterocyclic compounds with potential synthetic and biological applications. Furthermore, such methodologies appear particularly suitable for solid-phase/diversity-oriented synthesis applications.



Scheme 1. One-pot sequential synthesis of 5-aryl hydantoins



Scheme 2. Two-step synthesis of 1,5-disubstituted hydantoins



Scheme 3. One-pot synthesis of gem-difluoro dihydrouracils

RISK ASSESSMENT OF HAZARDOUS GAS DISPERSION IN URBAN AREAS WITH COMPUTATIONAL FLUID DYNAMIC (CFD) TOOLS

Marco Pontiggia

In this thesis work a new methodology for CFD simulations of hazardous gas dispersion in complex geometries has been established, including a new turbulence model for atmospheric stability, a procedure for geometry importation and cleaning, mesh generation criteria, and new post-processing tools for absorbed dose evaluation.
A new model for pool-evaporation source-term representation in CFD has been also proposed. A comparison between CFD and integral model approaches has been carried out pointing out the range of applicability of integral models.
Results have been validated with well established experimental benchmarks as well as a relevant case study (Viareggio accident).
CFD is quite CPU demanding compared to integral models; therefore well established criteria are needed to define the range of applicability of integral models (cheaper but not suited for complex geometries) and CFD tools (heavier but capable of full geometries simulation).
The first part of the work has been devoted to atmospheric turbulence representation in CFD simulations; standard k-ε RANS model has been modified through user-defined source term in the ε equation to guarantee the consistency between turbulence model and Monin-Obukhov similarity theory in stable and neutral stratification. A procedure for terrain roughness description has also been carried out as well as a methodology for inlet profiles tuning through 2D periodic simulations, obtaining a significant reduction in term of CPU costs. Results have been validated using Prairie Grass and Falcon test series.
Once having a turbulence model suited for atmospheric flows representation, it has been possible to make a comparison between CFD and integral models for several experimental tests (Prairie Grass, Coyote, Thorney Island), with a growing level of geometrical complexity.
Results pointed out that in open field, where integral models are tuned, there is a substantial agreement between both approaches and experimental data. Large obstacles (compared to the cloud dimensions), instead, make integral models too inaccurate for industrial purposes, while CFD remains capable of good predictions.
A parametric analysis has been consequently carried out and a general methodology has been developed for the best approach selection.
Geometrically complex environment, like urban areas or industrial sites, are well beyond the threshold calculated with the developed method; therefore CFD tools are strictly required. A geometry importation, cleaning and meshing procedure (which is often the rate-limiting step when complex geometries are involved) has been developed and applied to the simulation of a realistic accident involving hazardous material transportation in the Lecco municipality. The building shapes and positions have been directly imported from a topographical database with a resolution up to 20 cm.
Since the consequences of toxic gas releases depend upon both inhaled concentration for acute intoxication and absorbed dose for long-period exposure, besides concentration profiles tracking, a specific sub-routine for the dose evaluation has been developed, allowing for a PROBIT analysis of the toxic release effects. The release has been simulated using 2F and 5D stratifications (which are the most widely used for consequences analysis) and the results have been compared with integral model predictions: it has been found that integral models can not accurately predict turbulence generated by building wakes, leading to a substantial overprediction of the maximum distances reached by high concentrated clouds; on the other hand, stagnation zones, where very long life-time of the cloud raises the absorbed dose even for relatively small concentration, are also undertaken, leading to severe underestimation of the PROBIT value.
Since accidental scenarios often include pool formation (for instance LNG spill) a model for pool evaporation has been also developed. Very low evaporation rates can be represented through a diffusive flux with a specified wall-concentration, but for strongly evaporating flux an equivalent velocity has to be used based upon the single bubble rising velocity and diameter. Model predictions have been validated using two different CFD codes against Falcon test series.
Finally the developed methodology has been applied to a case-study: the recently occurred Viareggio accident. 14 tankcars of LPG derailed while passing through the rail station of Viareggio. One of the derailed tankcars was punctured and released all its content. Since no-immediate ignition took place the gas spread in a large area (about 500 meters range) before resulting in a severe fire. The release has been simulated and cloud shape has been obtained at the estimated ignition time. The region included in the flammability limits has been compared with the damage-report map leading to a good agreement between simulation results and observed data.
A new methodology for risk assessment of accidental releases of hazardous gases has been developed, including a modified k-ε model, consistent with Monin-Obukhov theory for both neutral and stable stratifications, which are the most relevant ones in risk assessment;
a source term for the e equation has been obtained and the improvements in the predictions have been tested against experimental data; 2D periodic simulations have been used for profiles tuning; this approach provides full developed profiles, making adjusting zones in 3D simulations not longer needed. Therefore computational domains and CPU costs are reduced; a general method has been developed to choose the better approach between CFD and integral models in relation with single obstacle influence on gas dispersion;
a methodology for direct import of geometry from topographical databases has been developed and applied to two different urban areas (Lecco and Viareggio municipality); a new procedure has been developed for absorbed dose evaluation and PROBIT analysis in toxic gas releases; a model for pool evaporation representation has been developed and implemented in the CFD code.
A case study has been simulated, pointing out the good agreement between CFD predictions and observed data.

DEVELOPMENT OF NEW RADICAL PROCESSES AND NEW CATALYSTS APPLIED TO BASIC AND FINE CHEMISTRY

Raffaele Spaccini

The main goal of this work is to develop new processes that lead to high added value products or to improve existing processes, through the knowledge and the study of particular radical reactions with the support of new catalytic systems. The work focus on four topics with that common goal: radical cross-coupling reactions, radical domino reactions, catalytic oxidation of alkylbenzenes and catalytic epoxidation in continuous flow.
Radical reactions have long attracted research effort for the ongoing demand for more efficient, mild and general synthetic methodology of a large range of molecules. There is big literature coverage about addition of carbon centered radicals to imines and related compounds for the synthesis of amides, chiral amines and other compounds with possible applications like useful synthetic intermediates in organic synthesis of complex natural products targets. In the field of the radical cross-coupling reactions and radical domino reactions I developed new simply methodologies to the synthesis of polyfunctionalized molecules in simple one-pot way. The development of new radical processes involving one-pot more bond-forming transformations are particularly fascinating toward the goal of decreasing the waste and minimizing handling, while increasing molecular complexity from simple starting materials. This intriguing approach has been widely applied in the field of nucleophilic free-radical addition to imines mediated by transition metal derivatives, allowing to develop more attractive synthetic routes as compared with the classical ionic ones, which often require multi-step procedures, expensive reagents, long reaction times and highly controlled operating conditions. Taking advance of particular behavior of some radicals in presence of Titanium salts I worked for the development of processes that, through the persistent radical effect or domino reaction, permit to obtain interesting derivatives with simply procedures, good yields and high selectivity.
With the goal to develop interesting processes also for basic chemistry I worked on aerobic oxidation of hydrocarbons with the use of N-hydroxyphthalimide like catalyst. Oxidation of organic compound is always an important reaction because these kinds of reaction are used in large-scale production of several crucial substrates of industrial and biological interest. The reaction condition, the catalyst and the initiator needed for that oxidation reaction are the three main factors that affect the eco-compatibility of the processes (for the problems of waste disposal and recycle of the catalyst that are both economic and ecologic problems). The researchers are always more oriented on the development of metal-free oxidation achieved with organic catalysts that can be easily recovered, like N-hydroxyphthalimide. It was indeed found that N-hydroxyimides catalyze the aerobic oxidation of hydrocarbons and attempts were made to also use this type of catalysis for synthesis of the hydroperoxide of ethylbenzene and other alkylbenzenes of industrial interest. From those interesting results my work concerned the development of the oxidation of alkylbenzenes with N-hydroxyphthalimide catalist in mild conditions for possible industrial applications.
Intrigued also from recent improvements obtained with the use of flow-chemistry in organic reactions, I used a novel milli-flow reactor system on a reaction of epoxidation that works very well in batch process.
During the last decade there has been a steadily growing interest within the chemical community for flow chemistry approaches to synthetic targets due to inherent benefits such as automated and telescoped reaction sequences, quick reaction optimizations and in-line work-ups and purification. The epoxidation of alkenes in continuous flow is the application of a novel approach with a different reactor system that could contribute to a substantial improvement of the efficiency of an epoxidation process already developed. It is interesting to develop flow-reaction systems for the several benefits that it's possible to achieve (high control on the pressure and temperature of the system, fast mixing system, possibility to arrange multi-step reactions in a continuous sequence, possibility to scale-up with ease).
The continuous flow reactor I used was already tested with some reaction leading interesting improvement due to the particular system of matter and heat exchange.
The radical reaction tested showed good result in term of reactivity and selectivity for the desired products. We also proposed mechanisms to explain the behavior of the radicals in different reaction conditions.
To understand mechanisms of those reactions is important for further development in that field. The catalytic oxidation of alkylbenzenes with N-hydroxyphthalimide catalyst has proven to be a significant improvement with respect to the known art: it is possible indeed to work at lower temperature, with higher selectivity in the formation of the hydroperoxide and with the possibility of a facilitated recovery and recycling of the catalyst, which remain unaltered.
Finally the use of a milli-flow reactor for the epoxidation reaction permitted to obtain the desired product with high conversions and high yields in a shorter reaction time.