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Sede dell'incontro

Aula A del Dipartimento di
Chimica e Tecnologie del Farmaco,
Sapienza Università di Roma
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- Comitato organizzatore -

Alessia CIOGLI (alessia.ciogli@uniroma1.it)

Catia CORVIA (catia.corvia@uniroma1.it)

Giuseppe PIERRI (giuseppe.pierri@uniroma1.it)

Rocchina SABIA (rocchina.sabia@uniroma1.it)

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- **I partecipanti possono ritirare il badge identificativo, il materiale congressuale e l'attestato di partecipazione presso il Registration Desk.**
- **I coffee break e i pranzi saranno serviti, come da orari riportati in programma, nel foyer dell'edificio di Chimica Farmaceutica.**
- **La Cena Sociale si svolgerà mercoledì 9 settembre alle ore 21:00 presso Eataly Roma, piazzale XII Ottobre, 1492.**
- **La durata di ogni presentazione comprende 5 minuti aggiuntivi per eventuali domande e discussioni.**

- PROGRAMMA SCIENTIFICO -

Martedì 8 Settembre 2015

10:30 - 11:30	**Registrazione, Aula A Dipartimento di Chimica e Tecnologie del Farmaco**
11:30 - 11:45	**Benvenuto** Bruno Botta (Direttore del Dipartimento di Chimica e Tecnologie del Farmaco) Claudio Villani, Roberto Purrello, Lorenzo Di Bari
11:45 - 13:00	**SESSIONE 1** Moderatore: Claudio Villani
11:45 - 12:35	**L.01** **Manifestations of vibrational excitons and of local modes in mid-IR VCD spectra.** *Sergio Abbate, Giovanna Longhi, Giuseppe Mazzeo* **Circularly Polarized Luminescence (CPL) spectra of isolated molecules and molecular aggregates.** *Giovanna Longhi, Ettore Castiglioni, Giuseppe Mazzeo, Sergio Abbate* **VCD spectra of possible organic catalysts.** *Giuseppe Mazzeo, Giovanna Longhi, Sergio Abbate*
12:35 - 13:00	**L.02** **Enantioselective supramolecular devices in the gas phase.** *Caterina Fraschetti*
13:00 - 15:00	***Pranzo e Sessione Poster***
15:00 - 16:35	**SESSIONE 2** Moderatore: Roberto Purrello
15:00 - 15:35	**L.03** **Conformational Behavior and Properties of Bioactive Peptides Derived from Food Proteins.** *Emma Fenude*
15:35 - 16:00	**L.04** **α-Nitro Ketones in Nitro-Mannich Reactions on Trifluoromethyl Imines.** *Stefania Fioravanti, Alessia Pelagalli, Lucio Pellacani*
16:00 - 16:35	**L.05** **Bifunctional Noncovalent Organocatalysis as a Tool for the Asymmetric Synthesis of Heterocycles.** *Alessandra Lattanzi, Sara Meninno*
16:35 - 17:00	***Coffee Break***
17:00 - 18:00	**SESSIONE 3** Moderatore: Lorenzo Di Bari
17:00 - 17:25	**L.06** **Kinetic Selection of Chirality in Porphyrin J-Aggregates.** *Maria Angela Castriciano, Roberto Zagami, Mario Samperi, Andrea Romeo, Luigi Monsù Scolaro*
17:25 - 18:00	**L.07** **Computation of ECD and CPL vibronic spectra: adiabatic and nonadiabatic approaches.** *Fabrizio Santoro*

Mercoledì 9 Settembre 2015

9:15 - 10:50	**SESSIONE 4** Moderatore: Ettore Castiglioni
9:15 - 9:50	**L.08** **Nonlinear Optical Chiral Spectroscopies: a computational chemist viewpoint.** *Antonio Rizzo*
9:50 - 10:15	**L.09** **Normal-phase HPLC enantioseparation of aldols on polysaccharide-based chiral stationary phases bearing chlorinated substituents.** *Sonia Pedotti, Angela Patti*
10:15 - 10:50	**L.10** **Flow Chemistry: Catalytic Reactors and Microreactors for Stereoselective Transformations.** *Alessandra Puglisi, Riccardo Porta, Maurizio Benaglia*
10:50 - 11:15	***Coffee Break***
11:15 - 13:00	**SESSIONE 5** Moderatore: Sergio Abbate
11:15 - 11:50	**L.11** **Chirality Sensing and Chirality Induction by Flexible Biphenyl.** *Stefano Superchi, Patrizia Scafato*
11:50 - 12:15	**L.12** **Non Conventional Approaches to Chiral Ionic Liquids.** *Simona Rizzo, Francesco Sannicolò, Voichita Mihali,Tiziana Benincori, Marco Pierini, Roberto Cirilli, Patrizia Mussini, Serena Arnaboldi, Armando Gennaro, Abdirisak A. Isse, Sergio Abbate, Giovanna Longhi, Giuseppe Mazzeo*
12:15 – 12:50	**L.13** **Synchrotron Radiation Circular Dichroism Conformational Study of Peptaibols.** *Marta De Zotti, Edoardo Longo, Fernando Formaggio, Giuliano Siligardi*
12:50 - 15:00	***Pranzo***
15:00 - 17:00	**SESSIONE 6** Moderatore: Stefano Superchi
15:00 - 15:35	**L.14** **Short Foldamers as Efficient Hydrogelators.** *Nicola Zanna, Lorenzo Milli, Claudia Tomasini* **Oxazolidin-2-ones based Foldamers for the Preparation of Supramolecular Materials and for Biomedical Applications.** *Claudia Tomasini, Lorenzo Milli, Nicola Zanna*
15:35 - 16:10	**L.15** **Chirality in MultiMetal-MultiLigand Supramolecular Architectures.** *Elena Badetti, Carlo Bravin, Francesca A. Scaramuzzo, Giulia Licini, Cristiano Zonta*
16:10 - 16:35	**L.16** **3D vs. 2D aggregation of porphyrin-based chiral structures of mesoscopic size.** *Mariano Venanzi, Donato Monti, Raffaella Lettieri, Antonio Palleschi, Pavel Drazar*
16:35 - 17:00	**L.17** **Atomistic description of the transfer of chirality from molecules to supramolecular architectures.** *Marco D'Abramo, Francesca Ceccacci, Chiara Giuliani, Giovanna Mancini*

Giovedì 10 Settembre 2015

9:15 – 11:30	**SESSIONE 7** Moderatore: Ilaria D'Acquarica
9:15 - 9:50	**L.18** **Intense chiral optical phenomena in racemic polymers by co-crystallization with chiral guest molecules.** *Paola Rizzo, Gaetano Guerra*
9:50 - 10:35	**L.19** **Development, characterization and applications of new sub-2micron totally porous WhelkO-1 brush-type and macrocyclic chiral stationary phases.** *Omar H. Ismail, Alessia Ciogli, Giuseppe Pierri, Rocchina Sabia, Marco Pierini, Claudio Villani, Francesco Gasparrini* **Recognition mechanisms and structural lability of chiral molecules endowed with synthetic, analytical or pharmaceutical interest: experimental and theoretical investigations.** *Alessia Ciogli, Roberto Cirilli, Ilaria D'Acquarica, Francesco Gasparrini, Sergio Menta, Marco Pierini, Claudio Villani*
10:35 - 11:00	**L.20** **Chirality induction in porphyrin supramolecular systems: amplification, memory and switches.** *Alessandro D'Urso, Maria Elena Fragalà, Roberto Purrello*
11:00 - 11:30	***Coffee Break***
11:30 - 12:45	**SESSIONE 8** Moderatore: Marco Pierini
11:30 - 11:55	**L.21** **Bis(diamido)-bridged basket resorcin[4]arenes: highly preorganized receptors for pyrimidine nucleosides.** *Federica Aiello, Federica Balzano, Francesca Ghirga, Deborah Quaglio, Ilaria D'Acquarica, Bruno Botta, Gloria Uccello-Barretta*
11:55 - 12:40	**L.22** **CD@Pisa: a 2015 update.** *Gennaro Pescitelli, Lorenzo Di Bari*
12:40 - 13:00	***Chiusura dei lavori***

- POSTER –

P.01	**STUDY OF STRUCTURAL, CONFORMATIONAL AND DYNAMIC PROPERTIES OF EXORPHIN FRAGMENTS** *Emma Fenude*
P.02	**MONITORING PROTEIN AGGREGATION DURING CIRCULAR DICHROISM THERMAL UNFOLDING USING SIMULTANEOUS MULTI-PROBE (SMP) ACQUISITION** *Ettore Castiglioni, Paolo Albertini*
P.03	**SOME PRACTICAL SUGGESTIONS AFTER 5 YEARS OF EXPERIENCE RUNNING CIRCULARLY POLARIZED LUMINESCENCE (CPL) SPECTRA** *Giovanna Longhi, Ettore Castiglioni, Giuseppe Mazzeo, Sergio Abbate*
P.04	**KINETIC ENANTIOSELECTIVITY OF A RESORCIN[4]ARENE TOWARDS ALANINE PEPTIDES** *Laura Guarcini, Andrea Calcaterra, Caterina Fraschetti, Antonello Filippi, Maria Elisa Crestoni, Maria Montagna, Luca Santi, Bruno Botta, Maurizio Speranza*
P.05	**SYNTHESIS AND NMR INVESTIGATION OF N-PEPTIDORESORC[4]ARENES AS α-CHYMOTRYPSIN INHIBITORS** *Andrea Calcaterra, Simone Berardozzi, Valentina Iovine, Ilaria D'Acquarica, Bruno Botta, Federica Aiello, Federica Balzano, Gloria Uccello-Barretta*
P.06	**BIOTRANSORMATION AND PREFERENTIAL CRYSTALLIZATION: TWO PRACTICAL APPROACHES FOR THE RESOLUTION OF MILNACIPRAN** *Claudia Sanfilippo, Angela Patti*
P.07	**CHEMICAL REACTIONS EMBEDDED IN LIPOSOMES: FIRST MOVES TOWARD A NOVEL APPROACH IN ORGANOCATALYSIS** *Carola Tortora, Martina Miceli, M. Antonietta Loreto, A. Gambacorta, Tecla Gasperi, Pasquale Stano*
P.08	**CD SPECTRA OF TRP-CONTAINING PEPTIDES IN THE NEAR-UV: A USEFUL TOOL TO ASSESS PEPTIDE CONFORMATIONAL STABILITY** *Fernando Formaggio, Marta De Zotti, Gianfranco Bocchinfuso, Antonio Palleschi, Daniela Arosio, Umberto Piarulli, Simone Zanella, Luca Pignataro, Laura Belvisi, Cesare Gennari, Lorenzo Stella*
P.09	**ABSOLUTE CONFIGURATIONS OF INULOXINS B AND C, PLANT PHYTOTOXINS WITH POTENTIAL APPLICATION AS BIOHERBICIDES BY COMPUTATIONAL ANALYSIS OF CHIROPTICAL PROPERTIESAUTORI** *Marco Evidente, Ernesto Santoro, Ana G. Petrovic, Alessio Cimmino, Antonio Evidente, Nina Berova, Stefano Superchi*
P.10	**A PEPTIDE TOPOLOGICAL TEMPLATE FOR THE DISPERSION OF [60]FULLERENE IN WATERAUTORI** *M. Mba, S. Bartocci, D. Mazzier, A. Moretto*

P.11	**ACHIRAL DYE/SURFACTANT HETEROAGGREGATES FOR CHIRAL SENSING OF PHOSPHOCOLINESAUTORI** *Francesca Ceccacci, Anita Scipioni, Barbara Altieri, Luisa Giansanti, Giovanna Mancini*
P.12	**SYNTHESIS OF KUWANOL E METHYL ETHER VIA DIELS-ALDER REACTION** *Valentina Iovine, Andrea Calcaterra, Franco Ferrari, Ilaria D'Acquarica, Bruno Botta*
P.13	**3-(PHENYL-4-OXY)-5-PHENYL-4,5-DIHYDRO-(1H) PYRAZOLE: A FASCINATING MOLECULAR FRAMEWORK TO STUDY THE ENANTIOSEPARATION ABILITY OF THE AMYLOSE TRIS(3,5-DIMETHYLPHENYLCARBAMATE) CHIRAL STATIONARY PHASE** *Simone Carradori, Sergio Menta, Marco Pierini, Daniela Secci, Rossella Fioravanti, Roberto Cirilli*
P.14	**NEAR-UHPLC QUININE-LIKE CHIRAL STATIONARY PHASE BASED ON 2.5-MICRON SILICA PARTICLES IMPLEMENTING THE NORMAL PHASE APPLICATIONS.** *Michela De Martino, Giorgio Bencivenni, Andrea Mazzanti, Rocchina Sabia, Francesco Gasparrini, Alessia Ciogli***.**
P.15	**CHIRAL RECOGNITION IN GAS PHASE. AN IR-R2PI STUDY ON THE EFFECT OF FLUORINE SUBSTITUTION.** *S. Piccirillo, A. Ciavardini, F. Rondino, A. Paladini, M. Speranza, S. Fornarini, M. Satta, D. Catone*.
P.16	**CHIRALITY SENSING WITH METAL-LIGAND SUPRAMOLECULAR ARCHITECTURES** *Elena Badetti, Klaus Wurst, Giulia Licini, Cristiano Zonta*
P.17	**CHIRAL VANADIUM COMPLEX AS BUILDING BLOCK FOR A CATALYTIC MACHINE** *Alessandro Bonetto, Elena Badetti, Giulia Licini, Cristiano Zonta*

Giornata di studio

in occasione dei 70 anni del prof. Francesco Gasparrini

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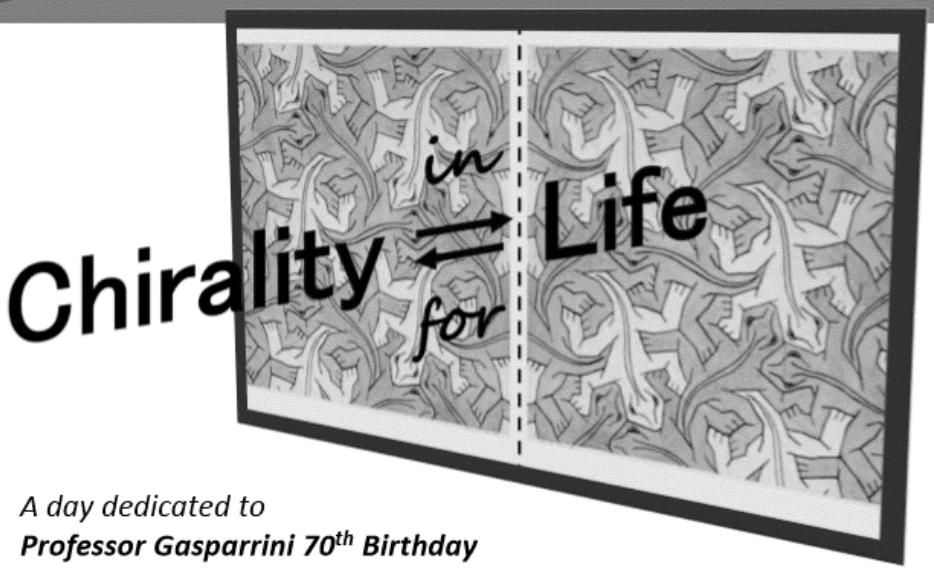

A day dedicated to
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Opening:
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September 11, 2015
DEPARTMENT OF CHEMISTRY AND TECHNOLOGY OF DRUGS
Aula A, 10-17 h

- BOOK OF ABSTRACT -

COMUNICAZIONI ORALI

Manifestations of vibrational excitons and of local modes in mid-IR VCD spectra

Sergio Abbate,[1] *Giovanna Longhi*[1], *Giuseppe Mazzeo*[1]

[1]*Dipartimento di Medicina Molecolare e Traslazionale, Università di Brescia, Viale Europa 11, 25123 - Brescia*
sergio.abbate@unibs.it

Recently the "coupled oscillator" concept was re-examined in the context of Vibrational Circular Dichroism spectroscopy and in particular in the C=O stretching region, between 1650 and 1750 cm^{-1}. Direct correlation with the *P* and *M* helicity of two coupled dissymmetrically disposed C=O bonds [1,2] to the observed (+,-) or (-,+) VCD couplet, in increasing order of wavenumbers, respectively, was established. For these vibrational modes the name of vibrational excitons has been proposed. The usefulness and immediate application of the observed (+,-) or (-,+) vibrational excitons for proposing configurational and conformational assignments is self-evident, even with possible limitations and *provisos*. However not only do vibrational excitons provide immediate structural information, but also localized modes do: a recent example in VCD has shown that the C≡O stretching mode can easily monitor the chirality at the metal in a Ru-organometallic complex [3], through the sign of the observed VCD band.

In this note we will also report on other examples of vibrational excitons in the mid-IR region VCD spectra, which we recently found for CC-stretching modes of aromatic moieties. In presence of these groups, VCD contains information apparent in usual ECD spectra, however often providing at the same time, nice signatures of the presence of other chiral elements. To this instance we will review the manifestation of localized modes, with relevance for either C*H stretching or bending modes, from our own work or from the literature [4].

References

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[3] M. Fusé et al. Chem. Commun. 51, 9385-9387 (2015)
[4] G. Mazzeo et al. Eur. J. Org. Chem. 7353-7363 (2014)

Circularly Polarized Luminescence (CPL) spectra of isolated molecules and molecular aggregates

Giovanna Longhi,[1] *Ettore Castiglioni*[1,2], *Giuseppe Mazzeo*[1], *Sergio Abbate*[1]

[1]*Dipartimento di Medicina Molecolare e Traslazionale, Università di Brescia, Viale Europa 11, 25123 Brescia, Italy;*
[2]*Jasco Europe, Via Confalonieri 1, Cremella (LC), Italy.*
giovanna.longhi@unibs.it

The availability of a home-built apparatus in our lab for measuring circularly polarized luminescence (CPL), with the possibility of using different excitation and detection geometries, different sources and a couple of photomultiplier tubes as detectors, has permitted to us to investigate several systems, on some of which even some kind of computational analysis was possible.
We studied several molecules, with increasing complexity, for which characterization of the first excited state was possible through DFT calculations or at least with reasonable analysis: the systems comprised camphor [1], hexahelicene [2].
Characterization of a compound via CPL spectra can be an important prerequisite if aiming to develop systems with photo-electronics applications: good results have been obtained, among the others, for thiophene-based conjugated molecules [3] and Europium-organic complexes [4].
Finally, we experimentally studied supramolecular systems as tricarbamide based columnar systems [5] or insulin fibrils winding in two opposite modes, detected by interaction with thioflavine.

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[3] F. Sannicolò et al. Chem. Eur. J. 20, 15298-15302 (2014)
[4] F. Zinna et al. Chem Commun 51, 11903-11906 (2015)
[5] B. Nieto Ortega et al. Chem Commun. 11, 2633–2641 (2015)

VCD spectra of possible organic catalysts

Giuseppe Mazzeo,[1] *Giovanna Longhi*[1], *Sergio Abbate*[1]

[1]*Dipartimento di Medicina Molecolare e Traslazionale, Università di Brescia, Viale Europa 11, 25123 Brescia, Italy*
giuseppe.mazzeo@unibs.it

Organic catalysts (OC) are a class of organic molecules, which may promote reactions through guiding orientation of reacting molecules; they are opportunely designed by putting together various moieties endowed with searched properties, like excluded-volume parts, or hydrogen bond entertaining parts, often containing Nitrogen atoms. As such their interaction with other molecules is stereospecific. For this reason their absolute and relative configuration, as well as their conformations, are actively studied since they are supposed to be relevant for understanding their own catalytic activity. All chiroptical methods are thought to be relevant to this scope [1]. Vibrational circular dichroism (VCD) is expected to be useful in two instances: when one of the moieties of the OC does not contain any chromophore possibly providing a UV-CD response or is kind of inaccessible or remote, such that their interactions with other parts of the molecule may be difficult to monitor by NMR-NOE.
We were provided with two classes of molecules, the first one with an inherently chiral bis-thiophene and carbon chiral bis-oxazoline moiety and another one with chiral sulfoxide [2] of known AC with an unknown AC chiral carbon centre. Both types possess two stereogenic sources and VCD has allowed to describe the contribution and signature from either one.

References

[1] Palumbo C. et al. *Organic Letters*, **2011**, *13*, 6248-6251.
[2] Lingmin W. et al. *J. Org. Chem*., **2014**, *79*, 7677-7681.

Acknowledgements

This work was carried out in collaboration with Professor Renzo Ruzziconi, who provided chiral sulfoxides derivatives, and Professor Tiziana Benincori and Dr. Sara Gabrieli, who provided chiral bisthiophene based compounds.

Enantioselective supramolecular devices in the gas phase

Caterina Fraschetti

Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, Piazzale A. Moro 5 – Roma
caterina.fraschetti@uniroma1.it

Resorcin[4]arenes represents a class of widely studied macrocycles with remarkable complexing properties towards inorganic and organic compounds. In 2007 Zhang et al. indicated them as the third best host molecules, right after cyclodextrin and crown ethers. Their success in the host-guest chemistry is principally due to the tunability of their synthesis. In principle the lower rim's chains of resorcin[4]arenes can be functionalized with a large number of chemical groups, which strictly influences the conformational space available to the structure. Furthermore the conformation of the macrocycle defines its coordinating capabilities as well as its selectivity. Such a versatility can include the possibility to employ even a supramolecular chirality which can be obtained in two ways: 1) the presence of stereogenic centres in the lateral chains; 2) the hindered spatial arrangement of achiral subunits forming a chiral macrocyclic scaffold. In the last decade the application of resorcin[4]arenes in different analytical and biochemical fields has been continuously growing: i) chromatography, as stationary phase as well as component of liquid phases;[1,2] ii) NMR, as solvating agent;[3] iii) pharmacology, as biocompatible drug carrier.[4] These applications are usually carried out in liquid media, where the host-guest interactions result from the superimposition of the intrinsic effect of the non-covalent supramolecular interactions and the solvation effect.Here we present a comprehensive gas phase study of the molecular recognition of several chiral resorcin[4]arenes towards different enantiopure compounds (*i.e.* amino acids and their derivatives, nucleosides, alkaloids).[5-9] The isolated state allows us to exclude the solvation effects and to purely investigate the intimate nature of the host-guest interactions. The gaseous adducts have been studied by means of different mass spectrometry approaches which provided us multifaceted information on the structure (IRMPD), thermodynamics (ESI-CID), and reactivity (ESI-FT-ICR) of resorcin[4]arenes based adducts, in order to shed light on the effect which supramolecular chirality exerts on chemico-physical properties of these host-guest complexes. Information of this kind provide the organic chemists a positive feedback to stimulate or even inspire the synthesis of new macrocycles applicable to different chemical fields.

References

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Conformational Behavior and Properties of Bioactive Peptides Derived from Food Proteins

Emma Fenude

ICB- Dipartimento di Scienze Chimiche Tecnologia dei Materiali-CNR, Trav. La Crucca 3 Sassari
emma.fenude@cnr.it

Many biologically active peptides are generated by proteolytic processing of various higher molecular weight multifunctional precursor peptides and proteins. The enzymes of different structures and specificity are involved in the synthesis, posttranslational modifications and release of peptide products, including hormones, neurotransmitters, and opioids. During the last two decades a variety of "atypical" exogenous opioid peptides derived from enzymatic digest of various food proteins sources has been demonstrated. Most of the food-derived opioids are peptides fragments of milk proteins (caseins, alpha-lactalbumin, beta-lactoglobulin, and lactotransferrin), plant proteins (wheat gluten) or constituents of meats (hemoglobin and bovine serum albumin). These peptides identified in exogenous sources were named exorphins. Most of the information available so far has been collected about exorphins isolated from alpha- or beta-casein, casomorphins (CM-7, Tyr-Pro-Phe-Pro-Gly-Pro-Ile). Five opioid peptides were derived from the wheat gluten: Gly- Tyr-Tyr-Pro-Thr, Gly- Tyr-Tyr-Pro, Tyr-Gly- Gly-Trp-Leu, Tyr-Gly- Gly-Trp, Tyr-Pro-Ile-Ser-Leu, which were named gluten exorphins A5, A4, B5, B4, and C respectively. A series of "nonclassical" endogenous peptides (hemorphins) have been identified in the course of the study of proteolytic fragments of bovine blood hemoglobin. The primary structure determined by Edman degradation (Leu-Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg-Phe) corresponded to the fragment (31-40) of bovine hemoglobin beta-chain (LVV-hemorphin-7). In this work we have observed tetra- and penta-peptides fragments of N-terminal protected exorphins. These products have been synthesized, purified and then analyzed by NMR spectroscopy in order to obtain structural and conformational informations to use in molecular simulation experiments. A comparison of experimental spectroscopic data with structural information from empirical models allow us to understand behaviour of these peptides in solution.

References

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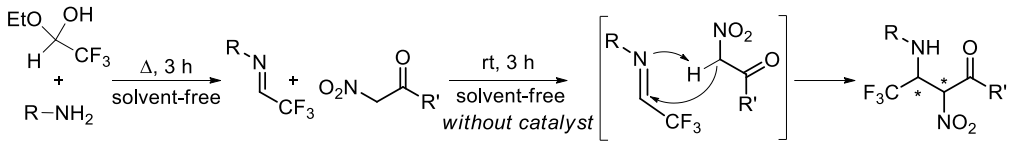
α-Nitro Ketones in Nitro-Mannich Reactions on Trifluoromethyl Imines

Stefania Fioravanti, Alessia Pelagalli, Lucio Pellacani

Dipartimento di Chimica, Università degli Studi di Roma "La Sapienza"
alessia.pelagalli@uniroma1.it

Trifluoromethyl ketones are compounds of considerable interest due to their importance as synthetic intermediates of other trifluoromethyl-containing targets (1) as well as for biological activity (2).
Of even greater importance and interest is the synthesis of nitrogenated trifluoromethyl carbonyl compounds and here we report our first results on the α-nitro ketone (3) additions to trifluoromethyl *N*-protected aldimines (4) by nitro-Mannich reactions (5).



The nitro-Mannich additions were performed under solvent-free conditions and without added catalyst and can be considered a good example of green chemistry. In fact, the reactions took place at room temperature, with very low environmental impact, no work-up was needed and they proceeded with total atom economy.
Starting from optically pure primary amines, even the stereochemical reaction outcome was successfully studied.

References

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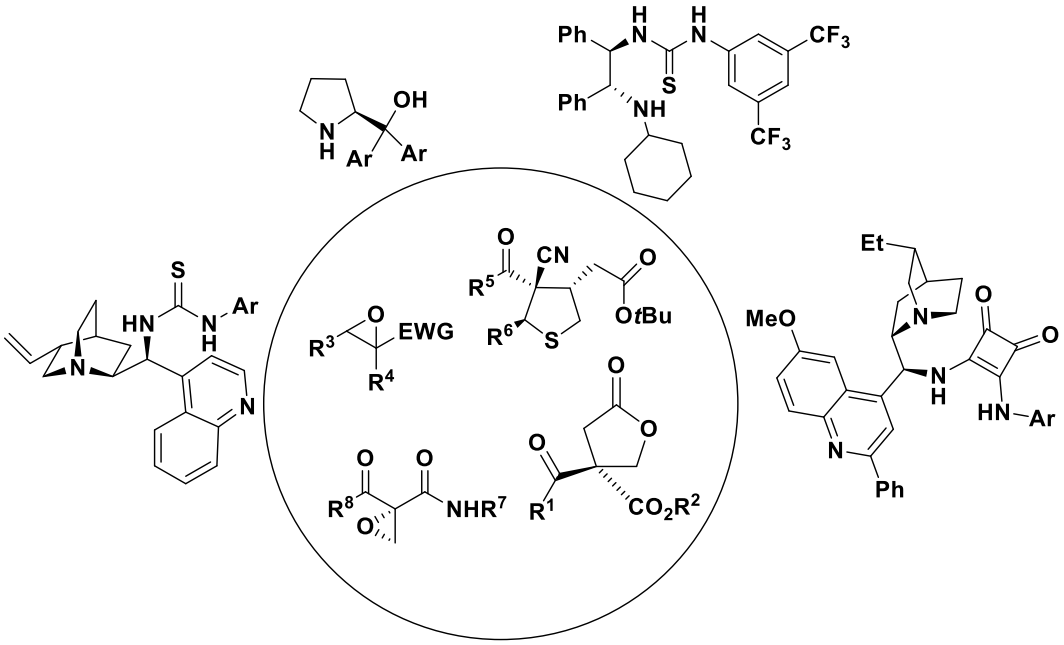
Bifunctional Noncovalent Organocatalysis as a Tool for the Asymmetric Synthesis of Heterocycles

Alessandra Lattanzi, Sara Meninno

[1]*Dipartimento di Chimica e Biologia, Università di Salerno, Via Giovanni Paolo II– Fisciano, Salerno;*
lattanzi@unisa.it

Ring forming reactions are fundamental processes useful for the synthesis of molecular scaffolds found in a plethora of products having different biological activities. The development of stereoselective cascade reactions to access heterocyclic compounds received a huge interest in recent years, mostly in the realm of organocatalysis.[1] Inherent advantages over multistep classical synthesis rely on environmentally friendliness of reaction conditions, cost and time-savings, high atom economy. Bi- and multifunctional organocatalysts have been increasingly used to address this goal by means of noncovalent activation of the reagents. This communication will focus on our efforts to access small and medium heterocyclic compounds, bearing quaternary stereocenters, exploiting noncovalent asymmetric organocatalytic tandem reactions.[2]



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Kinetic Selection of Chirality in Porphyrin J-Aggregates

Maria Angela Castriciano,[1] Roberto Zagami,[1] Mario Samperi,[2] Andrea Romeo,[1,2] Luigi Monsù' Scolaro[1,2]

[1]Istituto per lo Studio dei Materiali Nanostrutturati, c/o Dipartimento di Scienze Chimiche V.le F. Stagno D'Alcontres n.31, 98166 Messina, Italy.
[2]Dipartimento di Scienze Chimiche, University of Messina, V.le F. Stagno D'Alcontres n.31 98166 Messina, Italy.
lmonsu@unime.it

Reports of optical activity for assemblies of achiral entities in the absence of templates were greeted at first with skepticism. However, now that these findings have been confirmed, considerable attention has been focused on this phenomenon. The possibility that what is being observed in these systems is a spontaneous mirror-symmetry breaking has led to speculation about the relationship of these processes to those responsible for the ubiquitous homochirality in our universe. Achiral chromophores, especially porphyrins, have been of some considerable importance for such symmetry-breaking studies due to their rich spectral properties and their ability (under appropriate conditions) to self-assemble into chiral supramolecular structures. In particular, *meso*-tetrakis4-sulfonatophenyl (TPPS) and aryl-substituted porphyrins have been widely used as starting materials. TPPS J-aggregates, obtained in aqueous solution in the absence of any added chiral templating agent, show an unpredictable chirality, resulting in controversial proposals for their basis. Recently, we demonstrated the fundamental role of kinetic parameters in the expression and transmission of chirality in this supramolecular system.[1] Whatever the source of the chiral bias promoting such symmetry breaking, the rate of the aggregation process leading to the formation of J-aggregates strongly affects the size of these nanoassemblies and the chiral induction.

With the aim to resolve some of the confounding issues still open in literature related to the TPPS J-aggregate optical activity, here we report on detailed kinetic investigation on self-assembly processes induced by different inorganic achiral acid in the absence of an added chiral template and in presence of various chiral acids opportunely selected to have variability in terms of structure and strength. The results obtained have allowed to gain important information in the field of supramolecular architectures, highlighting the importance of the role of experimental parameters such as concentration and/or mixing order of the reagents. We anticipate that, depending on the overall rate of the process, a distinctive kinetic difference, together with a difference variance in the extent of the chiral transfer, is evident for the various acids and strictly connected with medium properties.

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Computation of ECD and CPL vibronic spectra: adiabatic and nonadiabatic approaches

Fabrizio Santoro[1]

[1] *Consiglio Nazionale delle Ricerche-CNR, Istituto di Chimica dei Composti Organometallici, Area della Ricerca del CNR, Via Moruzzi 1, I-56124-Pisa.*
fabrizio.santoro@iccom.cnr.it

In recent years we developed time-independent (TI) and time-dependent (TD) approaches to simulate the lineshapes of electronic spectra of large molecules, computing the associated vibronic structures[1]. Here we illustrate their application to chiroptical spectroscopies and in particular to electronic circular dichroism (ECD) and circularly polarized luminescence (CPL). We show how these computations can help to determine the dominant conformers of large chiral pyridocyclophanes [2], to explain the difference in the lineshapes of absorption and ECD and in emission and CPL of a series of substituted helicenes [3], and to understand the origin of the change of sign in the ECD spectra of chirally substituted benzenes [4].
Furthermore we present some recent applications of a nonadiabatic quantum dynamical approach we recently proposed to compute the ECD vibronic shapes of exciton coupled dimers and multimers [5].

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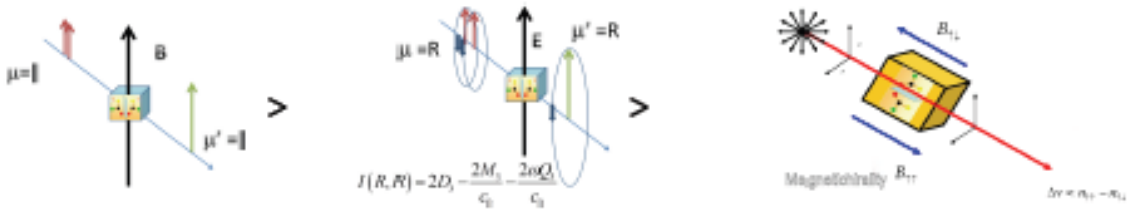
Nonlinear Optical Chiral Spectroscopies: a computational chemist viewpoint

Antonio Rizzo

Consiglio Nazionale delle Ricerche – CNR, Istituto per i Processi Chimico Fisici (IPCF-CNR), UOS di Pisa, Area della Ricerca, I-56126, Pisa, Italy

The latest developments in the theoretical and computational studies of nonlinear optical properties and spectroscopies involving the concept of chirality will be reviewed. Focus will be on both electric and magnetic field induced second harmonic generation (EFISHG[1] & MFISHG[2]), and the related circular intensity differences (CIDs) in chiral samples. The phenomenon, never having been explored experimentally to date, is related to special nonlinear mixed electric and magnetic frequency dependent responses, conveniently computed nowadays employing modern analytic response theory tools. We will present, on the other hand, also other nonlinear chiroptical spectroscopic properties, all proven to be amenable to *ab initio* simulation resorting to the tools of modern analytical response theory: magnetochiral dichroism and birefringence,[3] and circularly polarized phosphorescence. [4]



Examples of MFISHG, EFISHG and Magnetochiral Dichroism

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Normal-phase HPLC enantioseparation of aldols on polysaccharide-based chiral stationary phases bearing chlorinated substituents

Sonia Pedotti and Angela Patti

CNR-Istituto di Chimica Biomolecolare, Via Gaifami 18, 95126 Catania
sonia.pedotti@cnr.it

Aldol condensation of two carbonyl compounds is one of the most important methods for the construction of carbon-carbon bonds and the increase of molecular complexity through the introduction of one or two stereogenic centres starting from relatively simple and achiral compounds. The products of such reaction, the aldols, are important synthons in the preparation of polyhydroxylated compounds and aldol structural units are found in many important molecules, whether naturally occurring or synthetic [1-3]. Two families of aldols, obtained from the condensation of aromatic aldehydes with cyclohexanone or acetone (ten examples in each group), were analysed in normal phase elution mode on three polysaccharide-based chiral stationary phases of the Lux serie, namely Lux Cellulose-2, Lux Cellulose-4 and LuxAmylose-2, which share the common feature of chlorinated substituents in the chiral selectors. Following simple optimization steps, the enantioseparation of all aldols derived from cyclohexanone was achieved and the highest values of separation factor α ($1.38 < \alpha < 1.99$) and resolution (R_s, $4.5 < R_s < 11.90$) were observed on Lux-Cellulose 2, with the only exception of the 4-nitro-substituted derivative that was better resolved on Lux-Cellulose-4. On the contrary, Lux-Amylose 2 was the best choice for aldols derived from acetone and only specific analytes in this group could be resolved on the cellulose-based CPSs and the enantiodiscrimination ability markedly increase using EtOH as alcohol modifier in the mobile phase.

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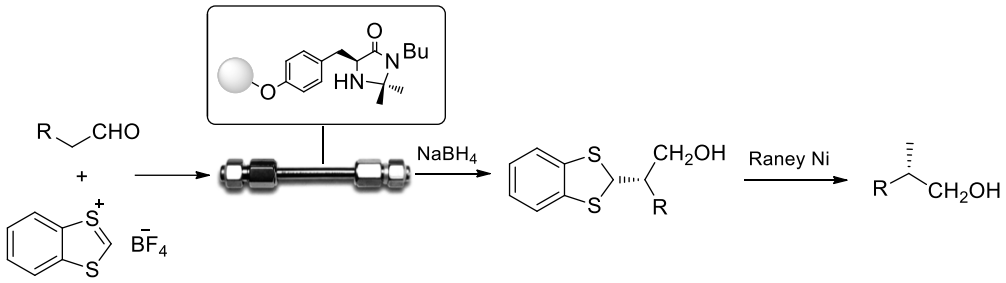
Flow Chemistry: Catalytic Reactors and Microreactors for Stereoselective Transformations

Alessandra Puglisi, Riccardo Porta, Maurizio Benaglia

Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi, 19 – 20133 Milano
alessandra.puglisi@unimi.it

Flow chemistry has recently gained a renewed interest by researchers thanks to an improved productivity, a more efficient heat transfer and a general safer handling procedure with respect to the batch mode. It is possible to perform stereoselective organocatalyzed reactions under continuous flow conditions by either flowing the homogeneous catalyst together with the reagents in the microreactors or, more conveniently, by immobilizing the catalyst into the reactor. In particular, the use of immobilized metal-free catalysts offers the unique possibility to develop sustainable processes in flow mode, since the separation step of the catalyst from the product is avoided.[1] As a consequence of the group's work on immobilized catalysts we are extending our activities into technological and engineering aspects. We focus on developing novel catalytic packed-bed and monolithic reactors, exploiting the unique features of such devices in stereoselective transformations. The development of efficient catalytic enantioselective α-alkylations of carbonyl compounds has been for a long time a challenging task. The first example of stereoselective continuous-flow α-alkylation of various aldehydes with 1,3-benzodithiolylium tetrafluoroborate was performed in flow reactors at room temperature affording the products with great productivity (higher than those obtained with homogenous catalyst) and excellent enantioselectivity (up to 95% ee). [2] The treatment of the alkylated products with Raney Nickel allows to obtain enantiomerically enriched α-methyl derivatives, key intermediates for the production of APIs and natural products.



During the talk, many examples of stereoselective reactions promoted by organocatalysts performed both in catalytic reactors[3] and in microreactors[4] under continuous flow conditions will be discussed.

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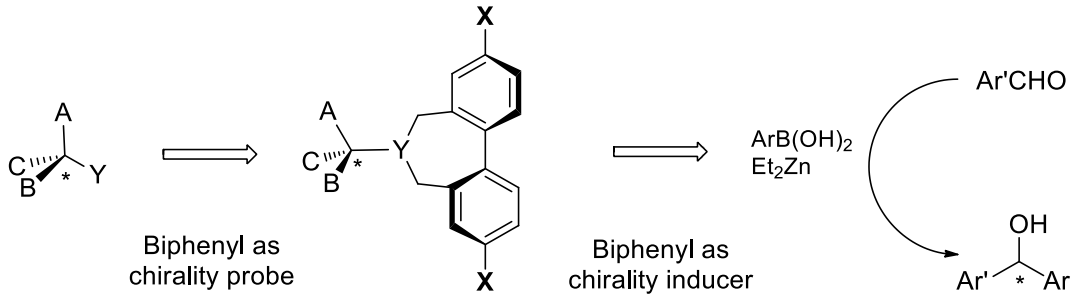
Chirality Sensing and Chirality Induction by Flexible Biphenyl

Stefano Superchi, Patrizia Scafato

Dipartimento di Scienze, Università della Basilicata, Viale Ateneo Lucano 10, – Potenza
stefano.superchi@unibas.it

The assignment of the absolute configuration of chiral molecules and the synthesis of enantiomerically enriched compounds are two strictly related important issues of modern organic chemistry. In the former, molecular chirality is "detected" by suitable spectroscopic techniques, while in the second molecular chirality is "induced" by a suitable chiral environment. We will show herein how flexible biphenyls can be used for both chirality sensing, designing probes for detection of absolute configuration of chiral molecules by chiroptical spectroscopies, and for chirality induction, providing the scaffold to design efficient chiral catalysts for asymmetric synthesis.
When a non-atropisomerically stable biphenyl moiety is covalently liked to a chiral molecule a central to axial chirality transfer occurs and the biphenyl system assumes a preferred *M* or *P* twist depending on the absolute configuration of the derivatized molecule. Such chirality transfer allows absolute configuration assignment because the sign of the biphenyl torsion can be easily detected by the sign of the biphenyl A band at 250 nm in the electronic circular dichroism (ECD) spectrum. Therefore, once established the mechanism of chirality transfer from the stereogenic center(s) to the biphenyl twist, just looking at the sign of such a band in the ECD spectrum of the biphenyl derivate it is possible to arrive at determining the absolute configuration of the molecule under investigation. Such approach proved to be practical and reliable for the absolute configuration determination of aliphatic 1,2-, 1,3-, 1,4-diols,[1] 2-substituted carboxylic acids,[2] and primary amines. Moreover, the same approach has been extended, using 4,4'-disubstituted biphenyl probes, to the more accessible optical rotatory power measurements, envisaging the possibility to reliably determine the absolute configuration by a simple $[\alpha]_D$ measurement. The same central to axial chirality transfer mechanism makes these flexible biphenyls also suitable *tropos* moieties[3] for designing efficient ligands for asymmetric catalysis. In fact, the presence of such moiety can allow to expand the chiral environment of the ligand. Accordingly, the synthesis of novel biphenyl based chiral ligands and their employment in the asymmetric aryl boronic addition to aldehydes will be also reported.[4]



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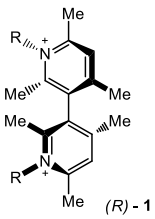
Non Conventional Approaches to Chiral Ionic Liquids

Simona Rizzo,[1] Francesco Sannicolò,[2] Voichita Mihali,[2] Tiziana Benincori,[3] Marco Pierini,[4] Roberto Cirilli,[5] Patrizia Mussini,[2] Serena Arnaboldi,[2] Armando Gennaro,[6] Abdirisak A. Isse,[6] Sergio Abbate,[7] Giovanna Longhi,[7] Giuseppe Mazzeo[7]

[1]Istituto di Scienze e Tecnologie Molecolari, CNR, Via C. Golgi, 19 – Milano;
[2]Dipartimento di Chimica, Università di Milano, Via C. Golgi, 19 – Milano;
[3]Dipartimento di Scienza e Alta Tecnologia, Università dell'Insubria, via Valleggio, 11 - Como;
[4]Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, Piazzale A. Moro 5 – Roma;
[5]Dipartimento del Farmaco, Istituto Superiore di Sanità, Viale Regina Elena, 299 – Roma;
[6]Dipartimento Scienze Chimiche, Università di Padova, Via Marzolo, 1 – Padova;
[7] Dipartimento di Medicina Molecolare e Traslazionale, Università degli Studi di Brescia, viale Europa, 11 – Brescia.
simona.rizzo@istm.cnr.it

Ionic liquids have been recently recognized as highly versatile solvents and reagents thanks to their largely tunable features for various chemical tasks and their eco-friendly properties. Chiral ionic liquids (CILs), in particular, have attracted special attention since they can be successfully employed as mediators in asymmetric synthesis, as chiral phases for gas chromatography and as chiral shift reagents in NMR spectroscopy. The current design of CILs involves attachment of chiral substituents, generally provided by the chiral pool and characterized by one or more stereocenters, either on cationic or anionic moieties. In this work we illustrate different approaches to CILs where chirality is due to the presence of a stereogenic axis coincident with the functional units responsible for the IL properties of the material. This concept of "inherent chirality" has been recently applied for preparing electroactive oligo-heterocycles with unprecedented enantiorecognition ability[1] and some atropisomeric 1,1'-bibenzimidazoles exhibiting peculiar chromatographic and electrochemical properties.[2] The CILs we are presenting here are based on 3,3'-bipiridinium and 3,3'-bithianaphthene scaffolds. Synthesis, resolution of the racemates, DFT calculations and enantio-recognition experimental proofs are discussed.



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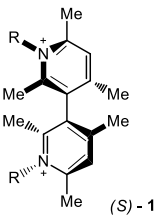

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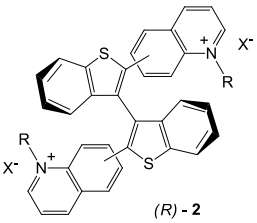

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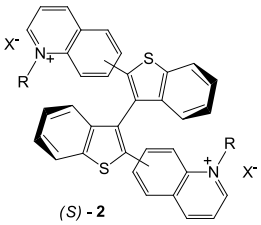

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Synchrotron Radiation Circular Dichroism Conformational Study of Peptaibols

Marta De Zotti,[1] *Edoardo Longo*,[2] *Fernando Formaggio*,[1] *Giuliano Siligardi*[2]

[1]*Dipartimento di Scienze Chimiche, Università degli Studi di Padova, Via Marzolo, 1 – Padova;*
[2]*Diamond Light Source Ltd. Harwell Innovation Campus, Chilton, Didcot, Oxfordshire, UK.*
marta.dezotti@unipd.it

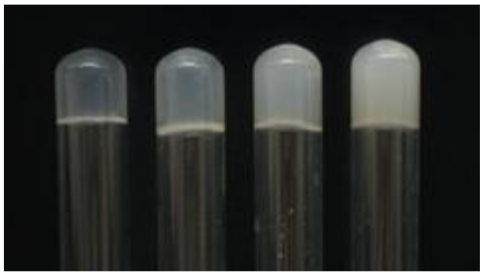
Peptaibols are a group of natural antimicrobial peptides (AMPs). Their name comes from two, peculiar features of their sequences, namely a high amount of noncoded α-amino acids, *e.g.* α-aminoisobutyric acid (Aib), and a C-terminal 1,2-aminoalcohol moiety. They are attractive for the development of peptide-based antibiotics, because of their significant resistance to the action of hydrolytic enzymes and the very stable helical structure (even if the sequence is less than 10-residue long). The widespread presence of Aib, a sterically-demanding residue and a known helix inducer, explains, at least in part, these properties. Peptaibols exert their biological activity by perturbing bacterial membranes through mechanisms promoted by their helical structure. Recently, we focused our attention on the structural role of the C-terminal 1,2-aminoalcohol. By exploiting the unique instrumentations present at the B23 beamline of the UK's synchrotron Diamond Light Source, we acquired synchrotron radiation circular dichroism (SRCD) spectra of a number of trichogin analogs in organic solvents at cryogenic temperatures. In this presentation, we will illustrate the results of our SRCD analysis. Surprisingly, we found that by replacing the C-terminal 1,2-aminoalcohol leucinol with Leucine methyl ester, the stability of the peptide helix at low temperatures was dramatically affected. Moreover, the presence of a clear isodichroic point suggests the possibility of a thermally-driven conformational switch between the well-characterized, mixed 3_{10}-/α-helical structure adopted by trichogin at room temperature and another, yet unidentified, three-dimensional structure at very low temperatures.

Short Foldamers as Efficient Hydrogelators

Nicola Zanna,[1] *Lorenzo Milli*[1], *Claudia Tomasini*[1]

[1]*Dipartimento di Chimica Ciamician, Università degli Studi di Bologna, Via Selmi, 2 – Bologna*
nicola.zanna3@unibo.it

Hydrogels are solid like materials composed mainly by water, as they are formed by a water phase immobilized by a scaffold that results in a gel. Their applications range from the preparation of new materials, drug delivery, biomineralization, growth of cultured cells, mimicking the extracellular matrix, etc.[1] Low molecular weight gelators (LMWGs) are small molecules able to gelate water and/or organic solvents by the formation of reversible supramolecular architectures governed by interactions such as π–π stacking, non-covalent interactions, hydrophobic and hydrogen bond, that favor the formation of layers that in turn get organized into fibers able to trap liquids.
Recently, the gelation behavior of Fmoc-protected dipeptides has been studied and reported.[2] Now we want to show here the gelation properties of some Fmoc-protected foldamers, that is a privileged scaffold for the preparation of supramolecular materials.[3]



Rheology studies have been carried out on all the prepared gels. Most samples furnish better results than the gels prepared with Fmoc-Phe-Phe-OH, thanks to the introduction of D-Oxd and D-pGlu unit.

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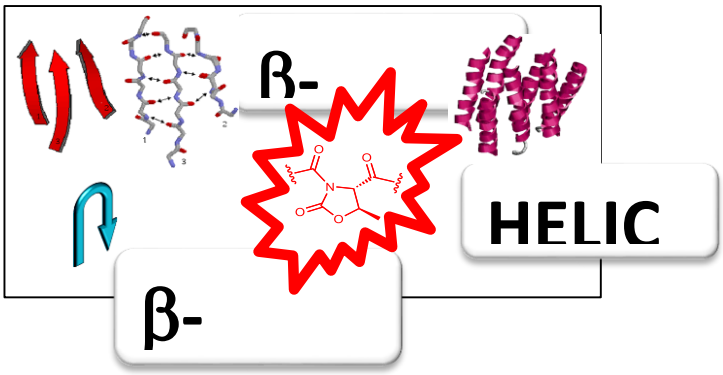
Oxazolidin-2-ones based Foldamers for the Preparation of Supramolecular Materials and for Biomedical Applications

Claudia Tomasini,[1] *Lorenzo Milli*,[1] *Nicola Zanna*[1]

[1]*Dipartimento di Chimica Ciamician, Università degli Studi di Bologna, Via Selmi, 2 – Bologna*
claudia.tomasini@unibo.it

Foldamers are artificial molecules able to get organized in well-defined secondary structures, such as helixes, β-sheets and turns. These compounds may be composed of any kind of subunits, but most of them contain unusual amino acids and/or aromatic units.[1]
We have recently studied the synthesis, the conformational analysis and the application as supramolecular materials of foldamers containing the 4-carboxy oxazolidin-2-one unit or related molecules, where an imido-type function is obtained by coupling the nitrogen of the heterocycle with the carboxylic acid moiety of the next unit.[2] As a consequence of this locally constrained disposition effect, these imide-type oligomers are forced to fold in ordered conformations, such as PPII helixes, β-band ribbon spirals, β-sheets and turns.[3]



In the solid state, some of these compounds form supramolecular materials, such as fibers, layers and gels, that may be used for several applications. For instance we have recently described the preparation, the analysis and the biological evaluation of gold nanoparticles linked to pseudopeptide foldamers containing one to eight L-Ala-D-Oxd (Ala = alanine; Oxd = 4-carboxy-5-methyl-oxazolidin-2-one) residues.[4] Short foldamers are also able to behave as efficient organogelators or hydrogelators.

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Chirality in MultiMetal-MultiLigand Supramolecular Architectures

Elena Badetti[1] *Carlo Bravin,*[1] *Francesca A. Scaramuzzo,*[1] *Giulia Licini*[1], *Cristiano Zonta*[1]

[1]*Dipartimento di Scienze Chimiche, Università di Padova, Via Marzolo, 1 – Padova*
cristiano.zonta@unipd.it

In recent years we have been involved in the use of *tris*(2-pyridylmethyl)amine **TPy** metal complexes as molecular scaffolds for the development of new supramolecular architectures (Figure 1).[1] In this communication, we report about the formation of a these self-assembled molecular systems and the study of their recognition properties with a special attention at their capability to act as stereo-optical probes. [2]

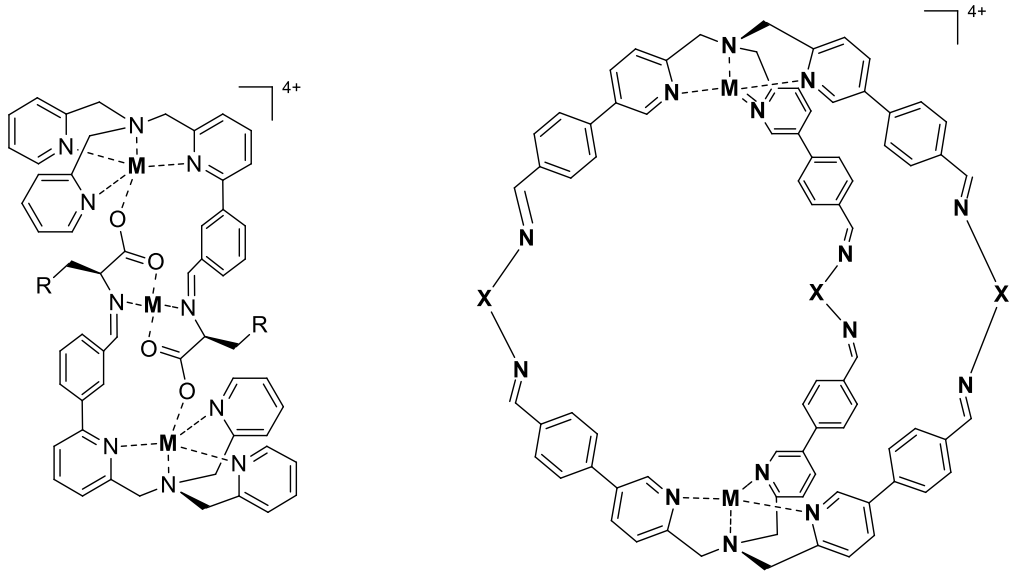

Figure 1

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3D vs. 2D aggregation of porphyrin-based chiral structures of mesoscopic size

Mariano Venanzi,[1] *Donato Monti*,[1] *Raffaella Lettieri*,[1] *Antonio Palleschi*,[1] *Pavel Drazar*[2]

[1]*Dipartimento di Scienze e Tecnologie Chimiche, Università degli Studi di Roma 'Tor Vergata', Via Ricerca Scientifica, 1, Roma, Italy;* [2]*Department of Natural Compounds Chemistry, Institute of Chemical Technology, Technicka 5, Prague, Czech Republic.*
venanzi@uniroma2.it

An issue of fundamental interest in the study of supramolecular aggregates is the chirality generated by the self-assembly of asymmetric building blocks. A chiral supramolecular system can derive from chiral or achiral elements: in the first case, the stereogenic information of the single building block can be transmitted to the aggregated structure; in the second case, the chirality is achieved by assuming a specific and macroscopically asymmetric spatial arrangement. Chiral supramolecular structures made of achiral porphyrins can be obtained through different strategies: by driven self-assembly of symmetric porphyrins, by the interaction of achiral porphyrins with chiral matrices (template aggregation), or by the coordination of chiral ligands.
Porphyrin-based supramolecular assemblies can be obtained not only in solution (3D aggregation), but even on a solid substrate. In this regard, Langmuir–Blodgett (LB) or the closely related Langmuir-Schaefer (LS) techniques allow for homogeneous deposition over large areas and formation of multilayer structures of variable layer composition and thickness (2D aggregation). Nanostructured molecular films have already been obtained by LB methods, showing potential applications in sensing, heterogeneous catalysis, optics or electronics.
These techniques are particularly useful for studying the behavior of amphiphilic molecules at the air–water interface, and valuable information on the aggregation mechanism can be obtained by comparing the chemical and structural characteristics of porphyrin aggregates in solution with those featured by molecular films deposited on a solid substrate.
In this contribution we describe the formation of chiral mesoscopic structures of several porphyrin derivatives, functionalized by one, two or four steroid groups at the *meso*-positions. The aggregation properties of these derivatives in aqueous solutions will be compared with those of porphyrin-based LB films, focusing on the chiral properties of the generated mesoscopic structures. Molecular mechanics calculations provided the possibility to analyze the role of the steroid groups in the control of the aggregation process, discriminating between hydrogen bond contribution, steric hindrance effects and the interaction of complementary amphiphilic surfaces (Fig. 1).

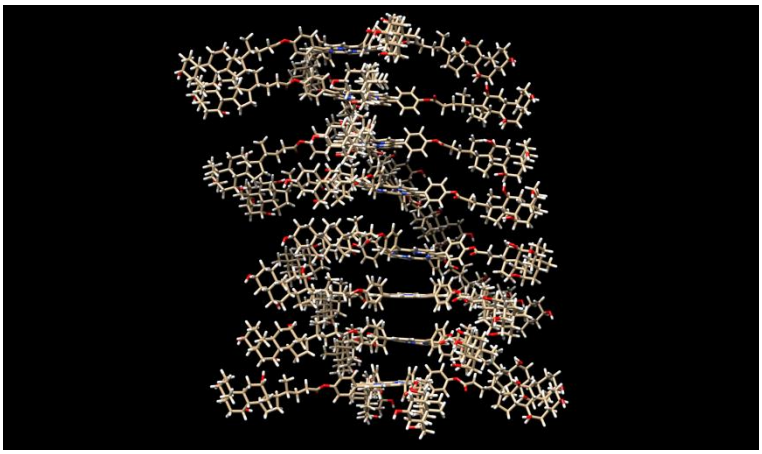

Fig. 1. Ball and stick representation of an octamer formed by tetrasteroidporphyrin building blocks.

Atomistic description of the transfer of chirality from molecules to supramolecular architectures

Marco D'Abramo,[1] *Francesca Ceccacci*[2], *Chiara Giuliani*,[3] *Giovanna Mancini*[4]

[1]*Dipartimento di Chimica, Sapienza Università di Roma, Piazzale A. Moro 5, 00185-Roma;*
[2]*CNR-IMC-Sezione Meccanismi di Reazione c/o Dipartimento di Chimica, Sapienza Università di Roma;*
[3]*CNR-ISMN, Istituto per lo Studio dei Materiali Nanostrutturati, Area della Ricerca di Roma, Via Salaria Km 29,300 – Monterotondo;*
[4]*CNR-IMC, Istituto di Metodologie Chimiche, Area della Ricerca di Roma, Via Salaria Km 29,300 - Monterotondo.*
marco.dabramo@uniroma1.it

Heteroaggregates composed of dyes and enantiopure cationic surfactants, below the *cmc* of the latter, are useful systems to investigate the transfer of chirality from molecules to supramolecular architectures. Here we report on the investigation, based on absorption and CD spectroscopy, of heteroaggregates composed of enantiopure cationic surfactants derived from benzylamine (SC) and the dye Evans Blue (EB). The combination of the experimental results with theoretical calculation allowed identifying the origin of the observed CD spectra, and thus the nature of the chiral phenomenon.

By means of an extended and physically correct sampling as provided by all-atoms molecular dynamics simulations in solutions, we estimated the relative populations of the different conformers of the dye, which were employed to calculate the corresponding CD spectrum, using the rotational strength of the isolated molecule. The proper modelling of the conformational behaviour of EB/SC aggregates allowed for a good estimate of their CD signal and, thus, the experimental CD data for different mixture ratios and surfactant type could be reproduced. In our case, the effect of the excitonic coupling resulted negligible because the dye molecules in the heteroaggregates did not show a preferential chiral mutual orientation. In summary, our data strongly support the idea that in the investigated systems the CD spectra of the EB dye origin from a restraining of its conformational space due to the interaction with the chiral surfactant molecules.

Intense chiral optical phenomena in racemic polymers by co-crystallization with chiral guest molecules

Paola Rizzo,[1] *Gaetano Guerra* [1]

[1]*Dipartimento di Chimica e Biologia, INSTM Research Unit, Università degli Studi di Salerno via Giovanni Paolo II, 132, 84084 Fisciano (SA), Italy*
prizzo@unisa.it, gguerra@unisa.it

This contribution will be mainly confined to the chiral-optical behavior in the solid state of racemic synthetic polymers, which are able to form co-crystalline phases with low-molecular-mass guest molecules and whose chirality is induced by non-racemic (also temporary) guest molecules.

The observation of chiral-optical response induced in racemic polymers in the solid state, by non-covalent interactions with optically active low-molecular-mass molecules is relatively recent .[1] It is associated with the formation of polymer co-crystalline phases, [2] where the guest molecules are non-racemic. Because regular helical stretches in crystalline phases are generally much longer than in polymer solutions, it is not surprising that the corresponding chiral amplification phenomena are generally much more intense.

The macromolecular amplification of chirality in polymer co-crystalline phases can be produced by molecular and supramolecular mechanisms.

According to a molecular mechanism, a non-chiral guest induces the formation of non-racemic crystals with non-racemic unit cell where polymer chains exhibit only one-sense of helicity. This kind of behaviour has been clearly shown for poly(2,6-dimethyl-1,4-phenylene)oxide (PPO).[3] A supramolecular mechanism occurs when the non-chiral guest induces the formation of non-racemic helical crystallites, whose unit cell includes both right- and left-handed polymer helices. This supramolecular mechanism has been presently observed only for syndiotactic polystyrene (s-PS).[2] As for sPS the intense chiral optical response of the polymer films remains essentially unaltered after complete chiral guest removal leading to the nanoporous δ phase. An intense chiral-optical response of s-PS films after substitution of the optically active guest with achiral chromophores [4] or with enantiomeric guest molecules will be also presented. [5] Additional evidences on the nature of the chiral optical response for s-PS films will be also reported [6].

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Development, characterization and applications of new sub-2micron totally porous WhelkO-1 brush-type and macrocyclic chiral stationary phases

Omar H. Ismail,[1] *Alessia Ciogli*[1], *Giuseppe Pierri*[1], *Rocchina Sabia*[1], *Marco Pierini*[1], *Claudio Villani*[1], *Francesco Gasparrini*[1].

[1]*Dipartimento di Chimica, Sapienza Università di Roma, Piazzale A. Moro 5 – Roma.*
omar.ismail@uniroma1.it

Over the last ten years, the technological progress has led to the development of stationary phases on ever smaller silica particles and instuments (UHPLC/UHPSFC) with a reduced extra-column volume able to reach very high pressure. These innovations allow to obtain higher efficiencies, resolutions and permit to reduce the analysis time and the eluent consumption. For these reasons also chiral stationary phases (CSPs) are moving to sub-2µm particles diameter. This talk concerns the development of two different sub-2µm CSPs based on the WhelkO-1 [1] and on the teicoplanin macrocyclic selectors [2]. The first selector has been covalently bonded on fully porous 1.8 µm Kromasil and the second one on totally porous and monodispersed 1.9 µm Titan silica particles (TEICO-Titan). Both CSPs were packed in columns with an internal diameter of 4.6 mm and different lengths, from 10 cm down to 1 cm, the latter geometry permitting very short analysis time. The different columns containing the two CSPs were analyzed under several elution conditions to obtain a complete thermodynamic and kinetic characterization. The UHPLC columns packed with the brush-type WhelkO-1-CSP were evaluated using normal phase and supercritical fluid eluents. Kinetic performances were estimated using *trans*-stilbene oxide as a probe, and resulted in efficiencies up to 250'000 plates/m at the optimal flow-rate of 2.0 mL/min under normal phase elution conditions. To evaluate the thermodynamic performances a large library screening [3] was performed using carbon dioxide based eluents under sub-critical fluid conditions: in one working day, 81 out of 129 randomly collected racemates were resolved under identical eluting conditions using a 9 min methanol in CO_2 gradient with 0.1% TFA or 0.1% NH_3 added for acidic and basic compounds, respectively.
The TEICO-Titan 1.9 µm CSP showed a broad field of application in different environments (reversed phase, polar organic mode, sub-critical fluid and normal phase). The thermodynamic performances of the new TEICO-Titan 1.9 µm have been evaluated with several N-protected amino acids, aryloxy acids, pharmaceutical compounds, sulfoxides and phosphine oxides. This CSP frequently showed high enantio-selectivity values: these resulted in large resolutions on the 10 cm long column (Rs up to 10.7 with Fmoc-D,L-Ala) and allowed the use of 2 cm and even 1 cm long columns in many cases, providing a considerable reduction of the analysis time maintaining a baseline enantiomeric separation.

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Recognition mechanisms and structural lability of chiral molecules endowed with synthetic, analytical or pharmaceutical interest: experimental and theoretical investigations.

Alessia Ciogli,[1] Roberto Cirilli,[2] Ilaria D'Acquarica,[1] Francesco Gasparrini,[1] Sergio Menta,[1] Marco Pierini,[1] Claudio Villani.[1]

[1]Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, Piazzale A. Moro 5 – Roma;
[2]Dipartimento del Farmaco, Istituto Superiore di Sanità, Viale R. Elena 299 – Roma.
sergio.menta@uniroma1.it

As it is known, chirality plays a fundamental role in medicinal chemistry due to the importance covered by the stereochemistry in governing the ligand-receptor recognition processes, which, in turn, results in specific biological answers. At the same time, the phenomenon of molecular recognition is also at the base of the development of effective analytical methods in the field of separation science (especially when involving chiral selectors as powerful separation tools), as well as in that of the organic synthesis based on stereoselective catalysis. The understanding of the mechanisms that govern the considered supramolecular processes, as well as the in-depth knowledge of the potential stereochemical lability of the involved species, is a fundamental prerequisite in the aim to rationalize the factors modulating the molecular discriminations and improve the performances of the processes through the possible design of new targeted, frequently chiral, selectors/receptors. In such a context, this communication will be focused on the overview of findings coming from studies that our research group performed with the intent: *i*) to clarify the mechanism of chiral selector-selectand recognition involved in processes taking place in both gas phase and solution; *ii*) to gain a clear picture about the structural lability of chiral species of significant synthetic, analytical or pharmaceutical interest. The gas phase studies were monitored by various Mass Spectrometry approaches (by collision induced dissociation method, CID, and/or by kinetics of exchange reactions),[1a] while the chiral recognitions in solution by chromatographic methods, resorting to well-known chiral selectors of brush-type, proteic[1b] and polymeric nature,[2] supported on silica matrices. In all cases, the elucidation of the main factors governing the molecular discrimination have been achieved by theoretical approaches based on consolidated docking procedures. Information about the stereo-lability of chiral species were instead pursued by kinetic determinations obtained resorting to classical batch-wise approaches, dynamic-Cromatography and stopped-flow techniques.[3-6] These will be conveniently distinguished within two typologies: stereo-isomerizations of true first order (typically, atropo-isomerizations) and stereo- or constitutional-isomerizations of second order, studied in conditions of pseudo-first order (acid and/or base catalyzed processes, as in the cases involving tautomeric equilibria). Also these investigations have been integrated with dedicated molecular modeling studies, which allowed their clear rationalization. In several cases, effects induced by different solvents on the position achieved by the involved equilibrium or on the activation barriers governing the considered isomerizations have been analyzed through Linear Solvation Energy Relationships (LSER) extended on a suitable wide number of experimental data.[5,6]

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Chirality induction in porphyrin supramolecular systems: amplification, memory and switches.

Alessandro D'Urso, Maria Elena Fragalà, Roberto Purrello

Dipartimento di Scienze Chimiche, Viale Andrea Doria, 6 - 95125 Catania
adurso@unict.it

Porphyrins are quite versatile molecules successfully used in many fields: from nanotechnology to biomedicine. These hetero-aromatic macrocycles present remarkable electronic properties which bring to attractive spectroscopic features. The non-covalent interactions of water-soluble achiral porphyrins with chiral templates have been exploited to detect and/or amplify the matrix handedness.[1] As templates we used biopolymers such aminoacid[2] or DNA sequences,[3] even if more challenging is the induction of chirality with single molecules as Ruthenium phenantroline.[4]
Interestingly, for some of such systems the chiral memory phenomenon has been observed. The main features of these complexes include the following: (i) their formation is driven by the electrostatic interactions between the tetra-cationic and tetra-anionic porphyrins; (ii) they are kinetically inert (their memory lasts for many years) and thermodynamically stable (they resist up to 80 °C); and most importantly, (iii) they are very efficient templates for their own self-propagation: addition of the achiral porphyrin monomer to a 10^{-13} M solution of the supramolecular systems leads to an enantiospecific growth yield close to 100%.

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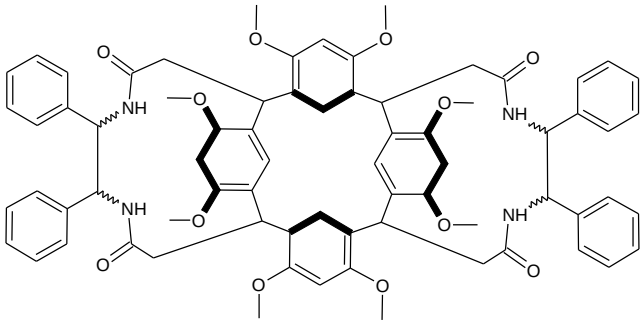
Bis(diamido)-bridged basket resorcin[4]arenes: highly preorganized receptors for pyrimidine nucleosides

Federica Aiello,[1] Federica Balzano,[1] Francesca Ghirga,[2,3] Deborah Quaglio,[2] Ilaria D'Acquarica,[2] Bruno Botta,[2] Gloria Uccello-Barretta [1]

[1] Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via G. Moruzzi 3, 56124 Pisa
[2] Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, Piazzale A. Moro 5 – Roma;
[3] Center of Life Nano Science, Istituto Italiano di Tecnologia, viale Regina Elena 295, 00185 Roma.
federica.aiello87@gmail.com

Chiral bis(diamido)-bridged basket resorcin[4]arene **1** (Figure 1) is a highly preorganized receptor for pyrimidine nucleosides (Figure 1) which originates a complex network of hydrophilic and hydrophobic interactions. Two different interaction sites were identified in the diastereoisomeric complexes [(*all-S*)-**1•2**] and [(*all-R*)-**1•2**] by exploiting the potentialities of nuclear magnetic resonance (NMR) spectroscopy in the field of chiral discrimination mechanisms investigations. Heteroassociation constants were obtained from diffusion data and titration methods. Proton selective relaxation rate measurements allowed us to identify the interaction sites.



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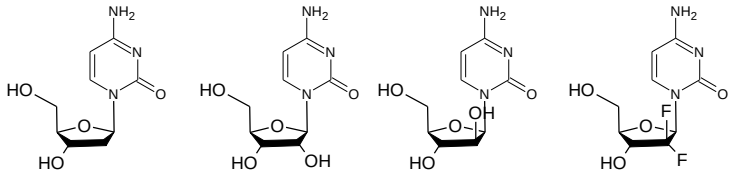

2 3 4 5

Figure 1- Chiral bis(diamido)-bridged basket resorcin[4]arene **1** and nucleoside guests **2-5**.

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CD@Pisa: a 2015 update

Gennaro Pescitelli, Lorenzo Di Bari

Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Moruzzi 13, 56124 Pisa
gennaro.pescitelli@unipi.it lorenzo.dibari@unipi.it

The lecture will present the most recent results by our group at the University of Pisa in the field of stereochemistry and chiroptical investigations, with special emphasis to the work done in collaboration with other research groups in Italy. In particular, we will discuss:
1) the assignment of absolute configurations of natural products and synthetic compounds;[1]
2) the study of aggregate phases of conjugated organic polymers[2] and organogelators;[3]
3) a new perspective on the phenomenon of exciton coupling and on the exciton chirality method, based on a quantitative quantum-mechanics tool which is capable of handling chromophores undergoing electric and magnetic-dipole allowed transitions;[4]
4) the development, the study and the application in optoelectronic devices of chiral luminophores based on lanthanide compounds which emit circularly polarized light from triplet states;[5]
5) a rational approach to supramolecular chirality and to its consequences in optical and electronic properties of materials.[3a,6]

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POSTER

Study of Structural, Conformational and Dynamic Properties of Exorphin Fragments

Emma Fenude

[1]*Dipartimento ICB- Dipartimento di Scienze Chimiche Tecnologia dei Materiali-CNR, Trav. La Crucca 3 Sassari*
emma.fenude@cnr.it

Biologically active peptides fragments derived from food proteins are inactive within the sequence of the precursor proteins but can be released by enzymatic proteolysis; they should be taken into account as potential modulators of various regulatory processes in the body. Opioid peptides are opioid receptors ligands with agonistic or antagonistic activities; they have been divided into two groups, so called 'typical' and 'atypical'. Opioid receptor are most abundant in the central nervous system, but have also been localized in many peripheral tissue of the mammalian organism, they are classified in μ, δ, κ and ε type which again can be divided into subtypes, i.e. μ_1, μ_2 receptors etc.. Opioid receptors and opioid peptides are distributed over the mammalian organism, indicating important functional significance. In fact, a variety of function has been proposed for these "opioidergic systems". For peptide neurotransmitter, transfer of their biological messages to the target cell via specific receptors requires at least two consecutive events: (1) binding of the neurotransmitter to its receptor and (2) transduction of the information from the complex into the cell. Since the structural, conformational, and dynamic properties opioid peptide and its receptor play a key role in both steps, their recognition and control are essential prerequisites to understanding the molecular basis in these systems. We have pursued this goal by examination of the conformational and dynamic properties of synthetic analogues carefully selected for their particular primary structure. Conformational change in a receptor upon binding a ligand (usually termed induced fit) could be the result of polar or hydrophobic interactions of the receptor with the ligand. We are interested to quantify the relative contributions of each of these interactions to the stability of the preferred structure that the peptide-ligand assume. In this work it has been observed tetra- and penta-peptides fragments of N-terminal protected α-lactorphin (Tyr-Gly-Leu-Phe), β-lactorfin (Tyr-Leu-Leu-Phe), gluten exorphins A4 (Gly-Tyr-Tyr-Pro), gluten exorphins C (Tyr-Pro-Ile-Ser-Leu), LVV-hemorphin-2 (Leu-Val-Val-Tyr-Pro). They have structures quite different from the endogenous and exogenous opioid peptides but are well known to be opioid receptor ligands.
These products have been synthesized, purified, and then analyzed by NMR spectroscopy, employing both mono- and bi- dimensional homo- and hetero- nuclear correlation 1H-1H, 1H-13C techniques through which it is possible to obtain structural and conformational informations. The result obtained are compared and discussed.

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Monitoring Protein Aggregation During Circular Dichroism Thermal Unfolding Using Simultaneous Multi-Probe (SMP) Acquisition

Ettore Castiglioni[1,2], *Paolo Albertini*[1]

[1] *JASCO Europe srl, via L. Cadorna 1, 23894 Cremella, Italy*
[2] *Dipartimento di Medicina Molecolare e Traslazionale, Università di Brescia, viale Europa 11, 25123 Brescia, Italy*
ettore.castiglioni@jasco-europe.com

About ten years ago[1,2] the Olga Gursky group at University of Boston proposed a method to monitor in real time protein aggregation during thermal folding/unfolding CD experiments by recording simultaneously:

- turbidity at 0°
- light scattering at 90°

Turbidity was monitored measuring the dynode voltage applied to the photomultiplier tube, while scattering was detected by a second photomultiplier, as available from commercial total fluorescence accessories.

Soon we verified these approaches with a solution of latex microspheres, using a JASCO J-815 with FDP-425 Peltier accessory[3], later on we also reported some data, using catalase as reference sample, at CD2009 conference in Brescia[4].

We decided to reinvestigate the same effects using a more modern CD spectrometer which allows to detect simultaneously at 0° turbidity as absorbance and, at 90°, not only the scattering total intensity, but also the contribution of chiral scattering (Circularly Intensity Differential Scattering) , in FDCD mode.

Instead that single wavelength temperature ramp experiments, spectral scans were performed to collect more information.

Catalase is a suitable sample for the job, being easy to aggregate even at low temperatures.

CD data were further analyzed using Kuhn's dissymmetry factor[5,6].

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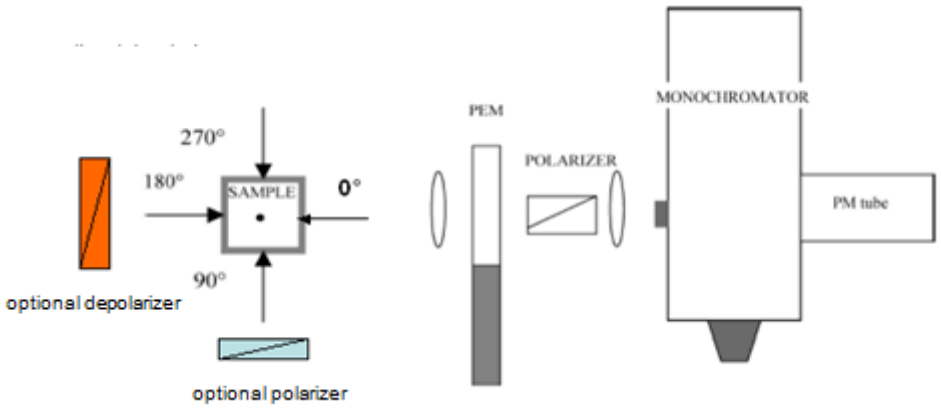
Some Practical Suggestions after 5 Years of Experience Running Circularly Polarized Luminescence (CPL) Spectra

Giovanna Longhi[1,2], Ettore Castiglioni[1,3] , Giuseppe Mazzeo[1] and Sergio Abbate[1,2]

[1] Dipartimento di Medicina Molecolare e Traslazionale, Università di Brescia, viale Europa 11, 25123 Brescia, Italy
[2] CNISM, Consorzio Interuniversitario Scienze Fisiche della Materia Via della Vasca Navale 84, 00146 Roma (Italy)
[3] JASCO Europe srl, via L. Cadorna 1, 23894 Cremella, Italy
ettore.castiglioni@jasco-europe.com

While Circularly Polarized Luminescence technique is far from new, in the last few years the number of publications reporting CPL results have been dramatically increasing. A good deal of recent papers are related to with lanthanide complexes, often showing strong, easy to detect, CPL signals. Other chiral, fluorescent, molecules are typically far more difficult to analyze, but since CPL is the only technique monitoring the chirality of the excited state, the interest toward CPL has been growing, even because quantum chemical calculations are now possible.
We assembled our apparatus about five years ago and we had been refining it in these years[1]. A wide variety of amples have been analyzed; we will report here our measurement approaches, taking into account the various built-in difficulties and the potential artifacts always behind the corner, in the hope to provide useful suggestions for the newcomers.



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Kinetic enantioselectivity of a resorcin[4]arene towards alanine peptides

Guarcini Laura, Andrea Calcaterra, Caterina Fraschetti, Antonello Filippi, Maria Elisa Crestoni, Maria Montagna, Luca Santi, Bruno Botta, Maurizio Speranza

Dipartimento di Chimica e Tecnologia del Farmaco, Sapienza Università di Roma, Piazzale A. Moro 5 – Roma.
laura.guarcini@uniroma1.it

The presence of D-amino acids and peptides with known biological activity in microorganisms and animals, is nowadays well documented[1] as well as their formation by ageing, diseases, or enzymatic post-translational modification. Chiral discrimination of amino acids and short peptides and the measure of their enantiomeric excess in biological matrices are generally based on reliable and sensitive analytical procedures, like liquid/gas chromatography,[2] capillary electrophoresis,[3] as well as NMR,[4] and stereoselective enzymatic digestion.[5] These methods often require the utilization of chiral auxiliaries, either in the form of stationary phases, mobile phases, or derivatizing agents. It follows that the selection of the most appropriate approach can be influenced not only by the nature of the chiral analyte but also by the accessibility of massive amounts of the necessary chiral auxiliary.[6] In practice, such procedures are complicated and matter- and time-consuming. Such drawbacks can be minimized, if not eliminated, by resorting to mass spectrometry (MS) which, after the development of soft ionization techniques, such as electrospray (ESI), revealed particularly suitable for high-throughput screening of biological samples.

This poster shows the chiral discrimination of some representative alanine-containing di- and tri-peptides (A) by a chiral bis(diamido)-bridged basket resorcin[4]arene (1) investigated in the gas phase by ESI-FT-ICR mass spectrometry. The rate constants for the displacement of A from the proton-bound diastereomeric complexes $[1{\bullet}H{\bullet}A]^+$, induced by the attack of the 2-aminobutane enantiomers (B), were found to depend on several factors, including the configuration of the receptor 1 and of the amine B as well as the number and the sequence of the amino acidic residues in the peptide A.

$$[1{\bullet}H{\bullet}A]^+ + B \rightarrow [1{\bullet}H{\bullet}B]^+ + A$$

Molecular dynamics simulations and DFT calculations point to the receptor 1 asymmetric frame as well as to the basicity of the amino acid residues at the C- and N-termini as determining the net charge and the orientation of the peptide moiety in the complex. These factors bear on the preliminary proton transfer from A to 1 involved in the displacement mechanism and, thus, on the overall reaction kinetic. Because of the pronounced enantioselectivity of the displacement reaction between B and the diastereomeric $[1^L{\bullet}H{\bullet}A]^+$ (A=AA, AL, and AP) complexes, the present kinetic methodology is amenable to determine the composition of complex enantiomeric mixtures of alanine-containing peptides.

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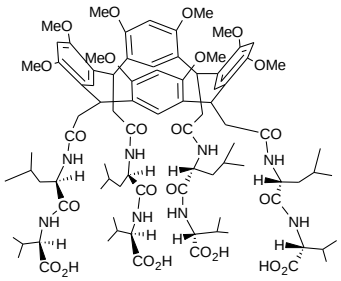
Synthesis and NMR investigation of *N*-peptidoresorc[4]arenes as α-chymotrypsin inhibitors

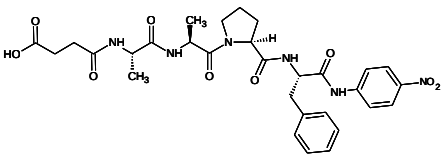
Andrea Calcaterra[1], *Simone Berardozzi*[1,2], *Valentina Iovine*[1], *Ilaria D'Acquarica*[1], *Bruno Botta*[1] *Federica Aiello*[3], *Federica Balzano*[3], *Gloria Uccello-Barretta*[3].

[1] *Dipartimento di Chimica e Tecnologie del Farmaco, "Sapienza" Università di Roma, P.le Aldo Moro 5, 00185 Roma, Italy.*
[2] *Center for Life NanoScience@Sapienza, Istituto Italiano di Tecnologia, Viale Regina Elena 295, 00185 Rome, Italy.*
[3] *Dipartimento di Chimica e Chimica Industriale, Università degli Studi di Pisa, Via Risorgimento 35, 56126 Pisa, Italy.*
andrea.calcaterra@uniroma1.it, simone.berardozzi@uniroma1.it

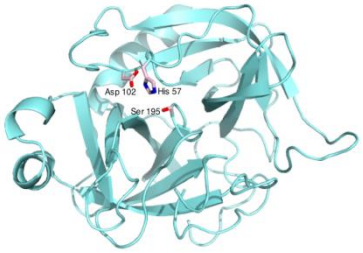
α-Chymotrypsin (ChT) is a proteolytic enzyme, which belongs to the serine proteases family. High levels of this enzyme are connected with the development of several important diseases like gastric carcinoma, chronic hypertrophic gastritis and ulcerative colitis. Inhibition of α-chymotrypsin can prevent all these diseases[1]. Recently we found that some *N*-peptidoresorc[4]arenes are good inhibitors of the hydrolytic activity of bovine α-chymotrypsin towards the model substrate N-Succinyl-Ala-Ala-Pro-Phe-pNA by UV-vis spectroscopy[2]. In this study with the aim of analyzing more in dept the nature of this interaction, we synthesized *N*-peptidoresorc[4]arene **1** and studied the molecular recognition phenomena in **1**/ChT and **1**/N-Succinyl-Ala-Ala-Pro-Phe-pNA mixtures in D_2O and DMSO-d_6 by NMR spectroscopy. 1D and 2D NMR experiments, such as NOESY, ROESY, DOSY, and the study of the dihedral angles, obtained on the basis of Karplus equation from vicinal coupling constants, allowed us to define the conformation assumed by macrocycle **1** and by the model substrate *N*-Succinyl-Ala-Ala-Pro-Phe-pNA in solution. Then we measured the selective relaxation rates of some protons nuclei of **1**. We could extrapolate the normalized affinity indices ($[A^N]$) for these protons which highlights the ^1H nuclei mainly involved in the interaction between **1** and α-chymotrypsin that is at the base of the inhibition. Despite what we can imagine, most of the interaction affects protons belonging to the resorcarene core rather than to the peptide mojety of **1**, indicating that the macrocyclic core mainly stabilize the [**1**•ChT] complex, causing the loss of proteolytic ChT activity[3].



Structure of *N*-peptidoresorc[4]arene **1**



Structure of *N*-Succinyl-Ala-Ala-Pro-Phe-pNA



Bovine α-chymotrypsin

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Biotransormation and preferential crystallization: two practical approaches for the resolution of milnacipran

Claudia Sanfilippo, Angela Patti

Istituto di Chimica Biomolecolare, CNR, Via P. Gaifami, 18 – Catania
claudia.sanfilippo@cnr.it

Enzymatic catalysis is a valuable approach used in organic synthesis to achieve chemical transformations in mild reaction conditions and with a high degree of selectivity. The use of enzymes, especially lipase, in organic solvent is an advantageous way to obtain single stereoisomers of a drug and biotransformations are today accepted as a powerful methodology for the industrial preparation of chiral pharmaceuticals.

Enantiomerically pure molecules containing amino functions are important synthons for the preparation of drugs. Primary and secondary amines, where the amino group is directly located on a stereogenic carbon, have been obtained in good yields and optical purity by lipases-catalyzed kinetic resolution of the racemates through a transamination reaction in the presence of carboxylic esters as acyl donors.[1] However, aminomethyl compounds are challenging substrates for their high reactivity and distance from the chiral center.

Milnacipran, Z-(±)-2-(aminomethyl)-N,N-diethyl-1-phenyilcyiclopropane, is an active antidepressant drug belonging to the class of inhibitors of the reuptake of serotonin and has recently attracted interest for its painkiller effects in the treatment of fibromyalgia.[2] Milnacipran is currently marketed in many countries, but not yet in Italy, in racemic form, however, recent pharmacokinetic studies on single enantiomers showed greater activity for (1S, 2R)-levomilnacipran.

The aim of this study is the development of a simpler and more economical strategy alternative to the reported an enantioselective synthesis. The kinetic resolution of racemic milnacipran in the presence of lipase was then investigated and optimized by means of a careful choice of the reaction conditions (lipase source and form, temperature, solvent and acyl donor nature). The amide product and the unreacted substrate were obtained in satisfactory chemical yields and enantiomeric purities.[3]

During this study we identified one of the amides obtained from the enzyme-catalyzed resolution as a conglomerate, whose nature was confirmed by the physical properties (melting points, solubility and X-ray diffraction). The properties of this specific amide of milnacipran were then exploited for its spontaneous resolution by conglomerate crystallization through a sequence of crystallization steps. Starting from a substrate with quite low enantiomeric excess, crystals of both enantiomers were obtained in enantiopure form.

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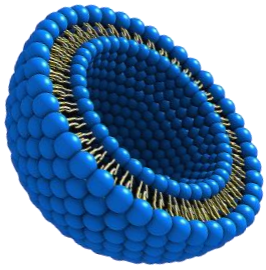
Chemical Reactions embedded in Liposomes: First moves toward a novel approach in Organocatalysis.

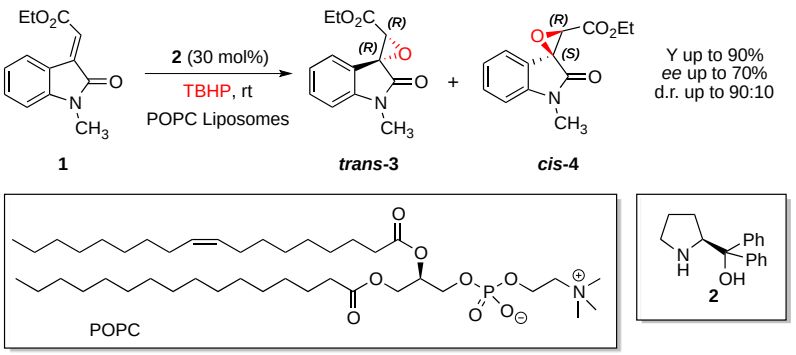
Carola Tortora,[1,2] Martina Miceli,[1,2] M. Antonietta Loreto,[2] A. Gambacorta,[1] Tecla Gasperi,[1] and Pasquale Stano[1]

[1]Dipartimento di Scienze, Università degli Studi Roma Tre, Via della Vasca Navale 79 – Roma;
[2]Dipartimento di Chimica, Sapienza Università di Roma, Piazzale A. Moro 5 – Roma.
carola.tortora@icloud.com, martina.miceli@uniroma1.it

The spontaneous formation of highly ordered structures is a fascinating aspect in supramolecular chemistry that can be exploited for creating micro-environments of unique features. Within this context, the formation of liposomes, derived from lipid self-assembly in water, lets the emergence of two distinct micro-compartments, i.e. the aqueous core surrounded by the lipid membrane. The latter provides a distinctive microenvironment to carry out organic reactions due to its highly ordered – yet fluid – structure and a vectorial chemical diversity (the deepest membrane core, the intermediate zone, the outmost polar surface). Guest molecules will preferentially occupy well-defined zones in the membrane. Taking into account such a scenario, we envisioned that the lipid membrane can be exploited as a peculiar reaction medium for carrying out organocatalytic reactions. Specifically, we are interested in investigating how liposomes can mediate, promote, and guide chemical reactivity as well as stereoselectivity in a peculiar and unprecedented way. [1]
Previous efforts from our laboratories provided a novel nucleophilic approach to the organocatalytic epoxidation of α,β-unsaturated carboxylic acid derivatives, which mainly relies on the noncovalent action mode of (*S*)-α,α-diphenylprolinol as catalyst. [2]
Pursuing this research, herein we report our preliminary results carrying out the nucleophilic epoxidation of α-ylideneoxindoles in the liposome membrane. The reaction has been reconstituted, for the first time, in synthetic phosphatidylcholine (POPC) liposomes suspended in pure water, and it is characterized by high yields (up to 90%) and quite good stereochemical outcomes (d.r. up to 90:10, enantiomeric excess up to 70% for the *trans* isomer).



LIPOSOME



Results are discussed from the standpoint of organocatalysis (relevant for the effects of the lipid medium on regio- and stereoselectivity), green chemistry (the elimination of organic solvents), and systems chemistry (self-organizing systems).

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CD spectra of Trp-containing peptides in the near-UV: A useful tool to assess peptide conformational stability

Fernando Formaggio,[1] Marta De Zotti,[1] Gianfranco Bocchinfuso,[2] Antonio Palleschi,[2] Daniela Arosio,[3] Umberto Piarulli,[4] Simone Zanella,[5] Luca Pignataro,[5] Laura Belvisi,[5] Cesare Gennari,[5] Lorenzo Stella[2]

[1]ICB CNR, Padova Unit, Department of Chemistry, University of Padova, 35131 Padova, Italy; [2]Department of Chemical Sciences and Technologies, University of Rome 'Tor Vergata', 00133 Rome, Italy; [3]ISTM CNR, 20133 Milan, Italy; [4]Department of Science and High Technology, 22100 Como, Italy; [5]Department of Chemistry, University of Milan, 20133 Milan, Italy.

fernando.formaggio@unipd.it

Angiogenesis is a key target in cancer therapy. With the aim at regulating this process, we recently designed, synthesized and investigated an array of peptides based on the IDNEWRKTQ sequence of the vascular endothelial growth factor (VEGF)-C. The new peptides were optimized to increase both helix stability and binding affinity towards the VEGF receptors. In particular, we exploited the known helix-inducing capabilities of C^{α}-tetrasubstituted α-amino acids to stabilize the secondary structure of our peptides. In addition, we inserted Trp residues at appropriate positions to enhance the binding affinity.

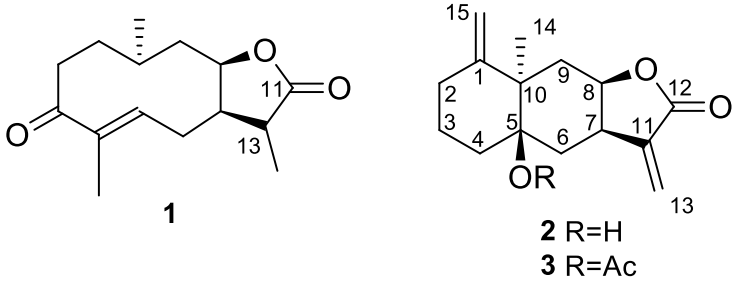
The conformational preferences of our peptides were investigated by CD and 2D-NMR in aqueous solution. Data analysis confirmed the onset of helical structures. Interestingly, we observed that the absorption bands in the near-UV of the indole (Trp) chromophore constitute a reliable probe to assess the conformational stability of our helical peptides. In this presentation we will correlate this CD feature to the information extracted from the NMR analysis.

Absolute configurations of inuloxins B and C, plant phytotoxins with potential application as bioherbicides by computational analysis of chiroptical properties

Marco Evidente[1,4], Ernesto Santoro,[2] Ana G. Petrovic,[3] Alessio Cimmino,[1] Antonio Evidente,[1] Nina Berova,[4] and Stefano Superchi[2]

[1]*Dipartimento di Scienze Chimiche, Università di Napoli Federico II, Via Cintia 4, – Napoli;*
[2]*Dipartimento di Scienze, Università della Basilicata, Viale Ateneo Lucano 10, – Potenza;*
[3]*Department of Life Sciences, New York Institute of Technology,1855 Broadway, New York, USA;*
[4]*Department of Chemistry, Columbia University, 3000 Broadway, New York, USA.*
stefano.superchi@unibas.it

From the aerial part of *Inula viscosa*, a perennial weed native to the Mediterranean basin, four new bi- and tri-cyclic sesquiterpenoids, named inuloxins A-D, as well as the well known α-costic acid were isolated. When assayed against broomrapes (*Orobanche crenate* and *O. ramosa*) and dodder (*Cuscuta campestris*), inuloxins A, C (**2**), and D were the most active on both parasites and caused up to 100% inhibition of the seed germination. Inuloxin B (**1**) was less active on *Cuscuta* and completely inactive against *Orobanche*.[1] Moreover, inuloxins A, C, and D demonstrated strong activity against *Leishmania donovani*, the protozoan parasite causing visceral leishmaniosis, with inuloxin A being the most active one.[2] The structures of all these compounds were determined by NMR spectroscopy, as well as their relative configuration.[1] However, for a complete structural characterization of such chiral natural compounds the assignment of their absolute stereochemistry was mandatory. Therefore we undertook an investigation aimed at establishing the absolute configuration of inuloxins in a reliable and nonempirical manner by quantum mechanical computational prediction of Optical Rotatory Dispersion (ORD) and Electronic Circular Dichroism (ECD) spectra. In a first investigation we recently established the absolute configuration of inuloxin A,[3] while now our interest was focused on the inuloxins B and C with the aim to establish their absolute configuration by computational analysis of ECD and ORD data. Notably, acetylation of compound **2** provided the more conformationally constrained ester **3**, displaying a single populated conformer and more intense chiroptical properties. The disclosure of a fundamental stereochemical information like the absolute configuration allows to investigate in a more rational way the biological properties of these naturally occurring terpenes, as well as to shed light on their biosynthetic relationship.



1

2 R=H
3 R=Ac

Figure. Structure and assigned absolute configuration of inuloxin B (**1**), inuloxin C (**2**), and inuloxin C acetyl ester (**3**).

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A Peptide Topological Template for the Dispersion of [60]Fullerene in Water

M. Mba [1], *S. Bartocci* [1], *D. Mazzier* [1], *A. Moretto* [1]

[1]*Dipartimento di Scienze Chimiche, Università degli Studi di Padova, Via F. Marzolo, 1 – Padova;*
miriam.mba@unipd.it

Solubilization of [60]fullerene in water is a major challenge for biological and medical applications. Covalent functionalization with suitable hydrophilic substituents leads to water-soluble fullerene derivatives, but disruption of the π-system may modify its properties and consequently the biological activity. For this reason, non-covalent approaches have been attempted. Non-covalent complexation of fullerene with a water-soluble host is a successful approach. Hosts that are biocompatible and easily synthesize are of interest for biomedical applications. In this communication, we describe the use of peptide-based solubilizing systems that allow to solubilize up to 1.3 mg/mL of fullerene in water. Formation of stable supramolecular composites was possible by means of mechanochemical methods. The presence of [60]fullerene in water was verified through UV-Vis, CD and NMR spectroscopies while its concentration was determined by thermogravimetric analysis.

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Achiral dye/surfactant heteroaggregates for chiral sensing of phosphocolines

Francesca Ceccacci,[1] *Anita Scipioni*,[2] *Barbara Altieri*,[3] *Luisa Giansanti*,[3] *Giovanna Mancini*.[4]

[1]*CNR, Istituto di Metodologie Chimiche – Sezione Meccanismi di Reazione, c/o Dipartimento di Chimica Sapienza Università di Roma, P.le Aldo Moro 5, 00185 Rome, Italy;* [2]*Dipartimento di Chimica, Sapienza Università di Roma, Piazzale A. Moro 5, 00185 Roma;* [3]*Dipartimento di Chimica, Università dell'Aquila, Via Vetoio, 67100 Coppito, Italy;* [4]*CNR-IMC Istituto di Metodologie Chimiche, Area della Ricerca di Roma 1, Via Salaria Km 29, 300 00015 Monterotondo.*

francesca.ceccacci@uniroma1.it

Previous investigations on the transfer of chirality from molecules to complex systems highlighted that beside interactions such as hydrogen bond, coulombic and π-π interactions, also hydrophobic interactions are involved in the propagation process.[1-3] Given the crucial role of hydrophobic interactions in the transcription of chirality, the present work was aimed at exploring the effect of chiral lipids on achiral heteroaggregates composed of an anionic dye and an achiral cationic surfactant, below the *cmc* of the latter. In particular, the investigation, based on absorption and circular dichroism spectroscopy, was carried out on assemblies formed in water upon interaction of heteroaggregates, composed of Congo Red (or Evans Blue) and CTAB, with four enantiopure phopshocholines characterized by different hydrophobic tails (DMPC, DPPC, DOPC and POPC). Results show that the nature of the lipid as well as the concentration ratios influences sensitively the absorption and chiroptical properties of the supramolecular structure. Intriguingly, the transfer of chirality from the lipid to the assembly may be triggered or not, depending on the nature of the lipid hydrophobic chain. These findings confirm the fundamental role of hydrophobic interactions in the transcription of chirality from molecules to complex architectures.

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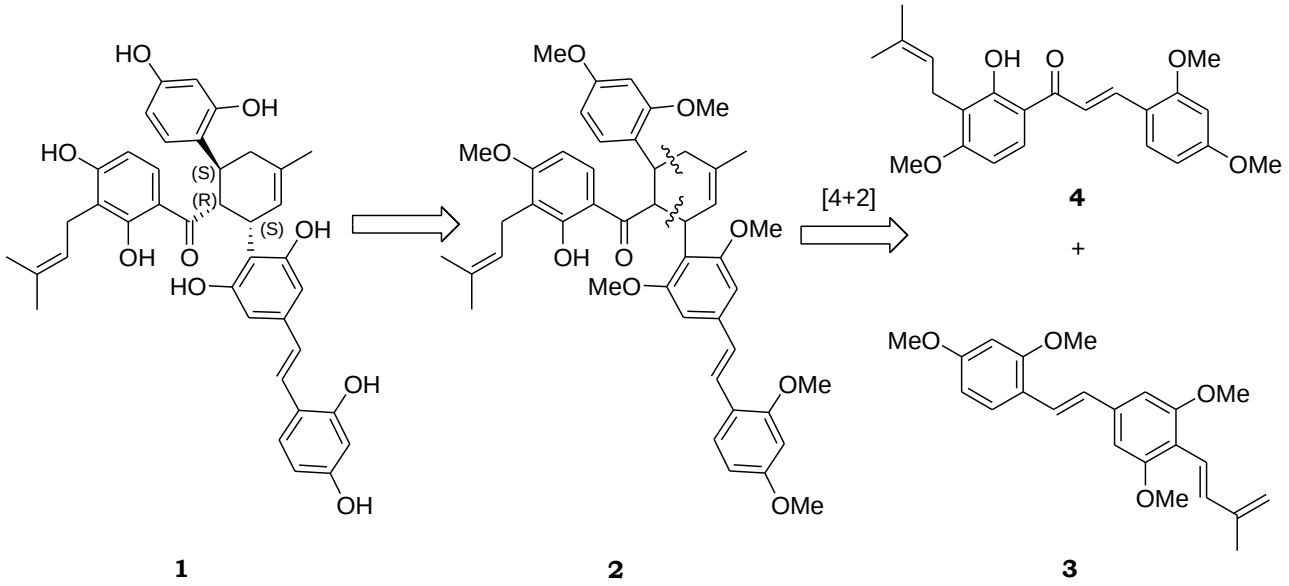
Synthesis of kuwanol E methyl ether *via* Diels-Alder reaction

Valentina Iovine, Andrea Calcaterra, Franco Ferrari, Ilaria D'Acquarica, Bruno Botta

Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma
e-mail: valentina.iovine@uniroma1.it

Kuwanol E (**1**) is a natural compound belonging to the mulberry Diels-Alder adducts isolated from *Morus alba*, *Morus nigra* and *Sorocea ilicifolia*. Recent studies reported **1** as the most potent natural inhibitor of protein tyrosine phosphatase B (PtpB), a virulence factor secreted into the host cell by *Mycobacterium tuberculosis*[1].
Herein we describe several strategies to synthesize kuwanol E methyl ether (**2**) *via* Diels-Alder reaction[2], a biomimetic intermolecular [4+2]-cycloaddition between diene **3** derived from stilbene and dienophile **4** featuring a chalcone skeleton. Intermolecular Diels-Alder reaction is an extremely useful tool for the formation of 6-membered systems with good control over regio- and stereochemical properties.



The required Diels-Alder partners **3** and **4** have been obtained by five and three synthetic steps, respectively. Afterwards, cycloaddition between **3** and **4**, which proved to fail in boiling *o*-xilene, was effectively promoted by Lewis acid catalysis, and clearly improved by AgOTf/Bu_4NBH_4, affording the desired compound **2**.

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3-(Phenyl-4-oxy)-5-phenyl-4,5-dihydro-(1*H*) pyrazole: a fascinating molecular framework to study the enantioseparation ability of the amylose tris(3,5-dimethylphenylcarbamate) chiral stationary phase

S. Carradori[1], S. Menta[2], M. Pierini[2], D. Secci[2], R. Fioravanti[2], R. Cirilli[3]

[1]Department of Pharmacy, 'G. D'Annunzio' University of Chieti-Pescara, Via dei Vestini 31, 66100 Chieti, Italy
[2]Dipartimento di Chimica e Tecnologie del Farmaco, "Sapienza" Università di Roma, P.le A. Moro 5, 00185 Rome, Italy
[3]Istituto Superiore di Sanità, Dipartimento del Farmaco, Viale Regina Elena 299, 00161 Rome, Italy
rcirilli@iss.it

According to literature[1], amylose tris(3,5-dimethylphenylcarbamate) (ADMPC) may be considered as the chiral selector with the broadest spectrum of enantioselectivity among those commercially available. The use of ADMPC is considered a priority choice in enantioselective HPLC analysis, not only for its enantiodiscrimination power but also for its ability to operate enantioseparation under any type of eluent condition (NP, PO, RP, HILIC) and high loading capacity for preparative applications.
Unfortunately, due to lack of adequate crystallographic models, the nature of the selectand-selector interactions involved in the chiral recognition mechanism has not been fully clarified at the molecular level, thus making the chromatographic behavior of the ADMPC-based CSPs difficult to predict. As demonstrated in our previous works[2,3], investigations on chiral discrimination mechanism of polysaccharide-based CSPs can be facilitated by designing and analyzing chiral probes whose enantiomers show large differences in the free energy of interactions with the CSP (corresponding to $\alpha > 10$). This strategy seems promising for the *in silico* development of molecular models of polysaccharide selectors capable to mimic the experimental chromatographic results and to clarify the driving forces operating in the enantioseparation process[3].
The aim of the present communication is to show the chromatographic behavior of a series of chiral compounds incorporating the 3-(phenyl-4-oxy)-5-phenyl-4,5-dihydro-(1*H*) pyrazole scaffold (Fig. 1) on the coated-type ADMPC-based Chiralpak AD-3 CSP.

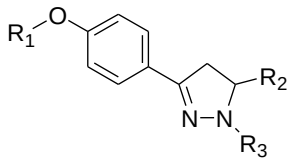

Figure 1

The functionalization of the molecular framework in the insertion points O, C5, and N1 is quite easy to achieve and offers the possibility of placing in the molecular skeleton different functional groups in key positions for chiral recognition. Pure alcohols such as methanol and ethanol as well as mixtures of n-hexane or pentane with alcoholic modifier were tested as mobile phases in the enantioseparation of chiral 2-pyrazolines. Further investigations focused on the influence of the temperature on retention and enantiodiscrimination processes.

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Near-UHPLC Quinine-like Chiral Stationary Phase based on 2.5-micron silica particles implementing the normal phase applications.

Michela De Martino[1], Giorgio Bencivenni[2], Andrea Mazzanti[2], Rocchina Sabia[1], Francesco Gasparrini[1], Alessia Ciogli[1].
michela.demartino16@gmail.com

[1]Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, P.le Aldo Moro 5, 00185 Roma, Italy
[2] Dipartimento di Chimica Industriale "Toso Montanari", Alma Mater Studiorum Università di Bologna, Viale del Risorgimento 4, 40136-Bologna-Italy

Direct liquid chromatography for enantiomer separation relies on the reversible formation of transient diastereomeric molecule associates on the surface of chiral stationary phases. The energetic differences_between the two diastereomeric complexes are the physical key for stereoselective retention. In principle, the greater the number of specific, discrete, simultaneous interactions between chiral solute molecules and a chiral recognition site on the stationary phase, then the greater the chance of effective chiral discrimination, and hence chromatographic resolution of enantiomeric solutes. Starting from this premise, brush-type Chiral Stationary Phases have to contain at least one each of three types of functional groups, near the chiral center: (i) p-acidic or p-basic aromatic groups, capable of donor-acceptor interaction; (ii) polar hydrogen bond and/or stacking sites and (iii) bulky non-polar groups, providing steric repulsion and van der Waals interaction. In this context, a new bush-type chiral stationary phase was designed by introducing a new selector, having multi-site interaction sites both typical of the Pirkle-type phases and classical of weak anion exchanger phases [1,2]. A 3,5-dinitrobenzamido group was introduced as hydrogen bonding and π-π donor/acceptor system in addition to the quinoline and quinuclidine moieties having two nitrogen with different basicity. The synthetic approach involved the preparation of DNB-epi-NH2-QN selector, starting from the 9-amino-9-deoxy-epiquinine. The next immobilization step took place through thiol-ene addition onto 3-mercaptopropyl-silica gel and gave a grafting density of 180 µmol of chiral selector per gram of silica (0.52 µmol /m^2). First, the kinetic performances of the new chiral stationary phase were evaluated by van Deemter analysis, considering that reduced particle size (Daisogel silica, pore size 120 Å, particle size 2.5 µm, specific surface area 343 m^2g^{-1}) was employed as bare silica. Secondly, the ability of chiral discrimination was studied in polar organic mode for amino acids derivatives as well for *profens*. Interesting results were obtained in normal phase elution, where the chiral selector behaves like a Pirkle type stationary phase. Acidic samples, amides, esterified DNB amino acids, benzodiazepines, binaphthol and benzoin were well resolved with very good peak symmetry and in short analysis time (mainly in less than 5 minutes).

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Chirality Sensing with Metal-Ligand Supramolecular Architectures

Elena Badetti,[1] *Klaus Wurst*,[2] *Giulia Licini*[1] *and Cristiano Zonta*[1]

[1]*Dipartimento di Scienze Chimiche, Università di Padova, Via Marzolo 1, 35131 Padova*

[2]*Institute of General, Inorganic and Theoretical Chemistry University of Innsbruck Innrain 80/82, A-6020 Innsbruck, Austria*

elena.badetti@unipd.it

Optical probes own generally a molecular fragment present in two enantiomeric forms which in presence of an analite give rise to a preferential diasteroisomer able to furnish an optical readout.[1] Recently we reported about a new molecular probe used for the reliable determination of the enantiomeric excess of free amino acids.[2] In this communication we will discuss the use of new metals and the measurement of the induced circular dichroism of the resulting multicomponent assembly. The study highlights the complex equilibria present in solution for the formation of the assembly and the specie responsible of the CD signal (Figure 1).

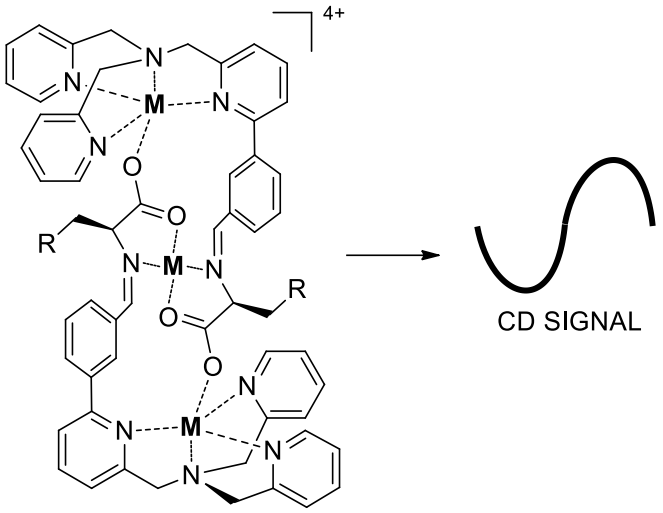

Figure 1

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Chiral Vanadium Complex as Building Block for a Catalytic Machine

Alessandro Bonetto,[1] *Elena Badetti* [1], *Giulia Licini*[1] *and Cristiano Zonta*[1]

[1]*Dipartimento di Scienze Chimiche, Università di Padova, Via Marzolo, 1 – Padova*
alessandro.bonetto1987@gmail.com

Triphenolamines are highly modular tetradentate molecules that effectively coordinate to transition metals and main group elements with podand topology.[1] They form chiral complexes with intrinsically well defined coordination geometries controlled by the ligand, in particular by the nature of the substituents in *ortho* position to the phenol, which are able to influence their reactivity and stability. Depending on the associated metals, they have been used in catalysis, and in particular, in oxygen transfer processes.[2]

In the present communication we will present the design and initial attempts of synthesis of a new molecular machine based on vanadium aminotriphenolate complexes. The proposed system will be able to control the catalytic activity of the vanadium complex in function of the amount of product produced, mimicking product inhibition processes occurring in enzymatic catalysis.

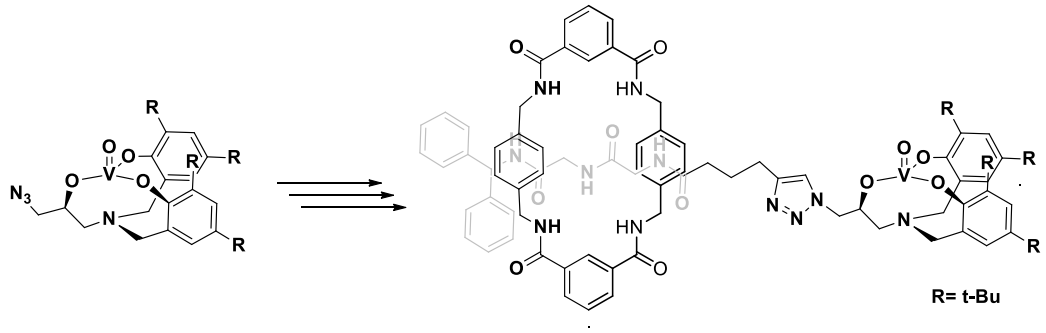

Figure 1

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- ELENCO DEI PARTECIPANTI –

Abbate S.	*Università di Brescia*	sergio.abbate@unibs.it
Aiello F.	*Università di Pisa*	federica.aiello87@gmail.com
Badetti E.	*Università di Padova*	elena.badetti@unipd.it
Benincori T.	*Università degli Studi dell'Insubria*	tiziana.benincori@uninsubria.it
Berardozzi S.	*IIT-Istituto Italiano di Tecnologia*	simone.berardozzi@uniroma1.it
Bonetto A.	*Università di Padova*	alessandro.bonetto1987@gmail.com
Calcaterra A.	*Università di Roma Sapienza*	andrea.calcaterra@uniroma1.it
Castiglioni E.	*JASCO Europe & Università di Brescia*	e-m.castiglioni@libero.it
Ceccacci F.	*CNR-IMC- sezione meccanismi di reazione*	francesca.ceccacci@uniroma1.it
Cerezo J.	*ICCOM-CNR UOS di Pisa*	j.cerezo@pi.iccom.cnr.it
Ciogli A.	*Università di Roma Sapienza*	alessia.ciogli@uniroma1.it
Cirilli R.	*Istituto Superiore di Sanità, Roma*	rcirilli@iss.it
D'Abramo M.	*Università di Roma Sapienza*	marco.dabramo@uniroma1.it
D'acquarica I.	*Università di Roma Sapienza*	ilaria.dacquarica@uniroma1.it
De Martino M.	*Chiesi Farmaceutici*	michela.demartino16@gmail.com
De Zotti M.	*Università di Padova*	marta.dezotti@unipd.it
Di Bari L.	*Università di Pisa*	lorenzo.dibari@unipi.it
D'Urso A.	*Università di Catania*	adurso@unict.it
Fenude E.	*ICB-CNR*	emma.fenude@cnr.it
Formaggio F.	*Università di Padova*	fernando.formaggio@unipd.it
Fraschetti C.	*Università di Roma Sapienza*	caterina.fraschetti@uniroma1.it

Gasparrini F.	*Università di Roma Sapienza*	francesco.gasparrini@uniroma1.it
Ghirga F.	*IIT-Istituto Italiano di Tecnologia*	francesca.ghirga@uniroma1.it
Guarcini L.	*Università di Roma Sapienza*	laura.guarcini@uniroma1.it
Guglielmi P.	*Università di Roma Sapienza*	paolo.guglielmi@uniroma1.it
Hailu Solomon G.	*Università di Roma Sapienza*	gebremedhinsolomon.hailu@uniroma1.it
Iovine V.	*Università di Roma Sapienza*	valentina.iovine@uniroma1.it
Ismail O. H.	*Università di Roma Sapienza*	omar.ismail@uniroma1.it
Lattanzi A.	*Università di Salerno*	lattanzi@unisa.it
La Regina G.	*Università di Roma Sapienza*	giuseppe.laregina@uniroma1.it
Longhi G.	*Università di Brescia*	giovanna.longhi@unibs.it
Mazzeo G.	*Università di Brescia*	giuseppe.mazzeo@unibs.it
Mba Blazquez M.	*Università di Padova*	miriam.mba@unipd.it
Menta S.	*Università di Roma Sapienza*	sergio.menta@uniroma1.it
Miceli M.	*Università di Roma Sapienza*	martina.miceli@uniroma1.it
Misiti D.	*Università di Roma Sapienza*	domenico.misiti@uniroma1.it
Monsù Scolaro L.	*Università di Messina*	lmonsu@unime.it
Patti A.	*ICB-CNR Catania*	angela.patti@cnr.it
Pedotti S.	*ICB-CNR Catania*	sonia.pedotti@cnr.it
Pelagalli A.	*Università di Roma Sapienza*	alessia.pelagalli@uniroma1.it
Pellacani L.	*Università di Roma Sapienza*	lucio.pellacani@uniroma1.it
Pescitelli G.	*Università di Pisa*	gennaro.pescitelli@unipi.it
Piccirillo S.	*Università di Roma Tor Vergata*	piccirillo@fisica.uniroma2.it
Pierini M.	*Università di Roma Sapienza*	marco.pierini@uniroma1.it
Pierri G.	*Università di Roma Sapienza*	giuseppe.pierri@uniroma1.it
Puglisi A.	*Università degli Studi di Milano*	alessandra.puglisi@unimi.it

Purrello R.	*Università di Catania*	rpurrello@gmail.com
Quaglio D.	*Università di Roma Sapienza*	deborah.quaglio@uniroma1.it
Rizzo A.	*IPCF-CNR Pisa*	rizzo@ipcf.cnr.it
Rizzo P.	*Università di Salerno*	prizzo@unisa.it
Rizzo S.	*CNR – ISTM Milano*	simona.rizzo@istm.cnr.it
Sabia R.	*Università di Roma Sapienza*	rocchina.sabia@uniroma1.it
Sanfilippo C.	*ICB-CNR Catania*	claudia.sanfilippo@icb.cnr.it
Santoro F.	*ICCOM-CNR Pisa*	fabrizio.santoro@iccom.cnr.it
Speranza M.	*Università di Roma Sapienza*	maurizio.speranza@uniroma1.it
Superchi S.	*Università della Basilicata*	stefano.superchi@unibas.it
Tomasini C.	*Università di Bologna*	claudia.tomasini@unibo.it
Tortora C.	*Università degli Studi Roma Tre*	carola.tortora@icloud.com
Venanzi M.	*Università Di Roma 'Tor Vergata'*	venanzi@uniroma2.it
Villani C.	*Università di Roma Sapienza*	claudio.villani@uniroma1.it
Zanna N.	*Università di Bologna*	nicola.zanna@unibo.it
Zonta C.	*Università di Padova*	cristiano.zonta@unipd.it

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