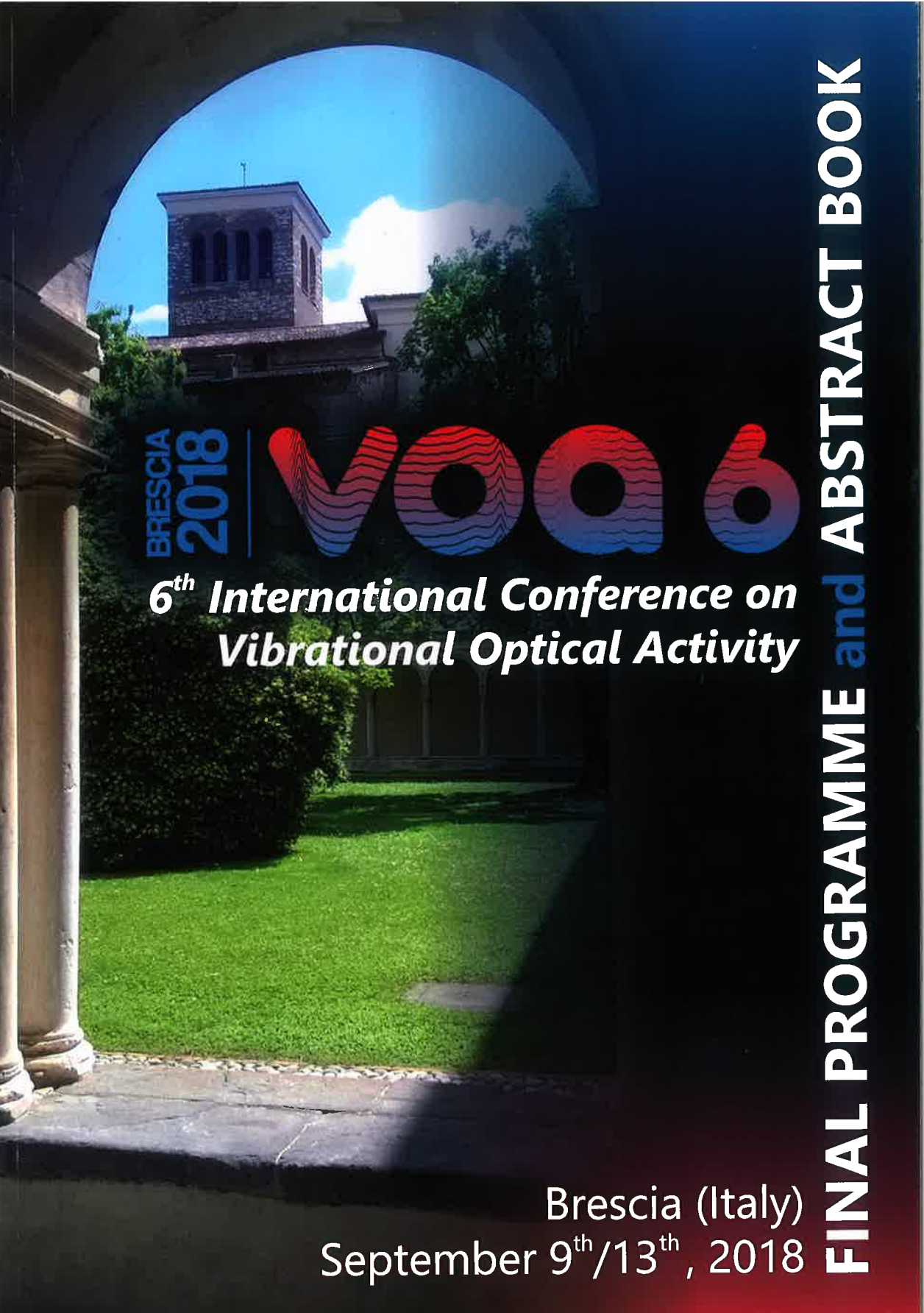
BRESCIA 2018
VOA 6
6th International Conference on
Vibrational Optical Activity
Brescia (Italy)
September 9th/13th, 2018
FINAL PROGRAMME and ABSTRACT BOOK

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Welcome to Brescia!

On behalf of the local organizing committee, we welcome you at the sixth installment of the VOA conference series. As in the previous version of the series, the main focus of this meeting is to present the cutting edge in vibrational optical activity (VOA), highlighting the newest research developments in the field, both experimentally and theoretically. In addition to the newest progress in vibrational circular dichroism (VCD) and Raman optical activity (ROA), and in continuity with the previous edition, this year's program will also host some latest developments of neighboring fields, CPL (circularly polarized luminescence), MCD (magnetic circular dichroism) and superchiral field spectroscopy. Most importantly, the conference will contain two sessions on Astrochemistry, dealing with the investigation and (possible) spectroscopic detection of chiral molecules in the Universe. The meeting offers a total of 55 lectures, divided out on 24 invited talks and 31 oral contributions. One of the invited talks will be the opening lecture, rewarding the best journal paper in the field of VOA in the last two years, in honor of the late Philip J. Stephens. We are happy to announce that some of the invited talks and oral contributions will be presented by young scientists, at the beginning of their scientific life. In addition to the oral program 23 (and counting) poster presentations will conclude the scientific offerings of VOA-6. We hope that the all the conferees will enjoy the program, and, most importantly, will take the opportunity to exchange ideas and projects, and establish new collaborations.

To make the participants appreciate the history and atmosphere of Brescia, which has been an old Celtic, Roman and Lombard city, a guided tour of the City Museum of Santa Giulia will be offered to all participants. Santa Giulia is an old convent hosting ruins from the first century A.D.; in this convent Irmgaard, the repudiated wife of Charle Magne, spent her last days as a nun, and nowadays it hosts masterpieces from Middle Ages to Renaissance.

Finally we are pleased and grateful from the contributions of our sponsors, whose support has been vital for keeping the registration fees at the same level of the previous edition, and for allowing the programme being offered.

Sergio Abbate and Vincenzo Barone
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VENUE

MAIN HALL of the SCHOOL OF ECONOMICS
of the UNIVERSITY OF BRESCIA
Via S. Faustino, 74/B – 25122 Brescia (I)

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Brescia (I) - sergio.abbate@unibs.it

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ORGANIZING SECRETARIAT

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SUNDAY September 9th

03.30 pm **Secretariat Desk Opening & Participants' Registration**

05.00 pm **Opening Ceremony and Welcome Address**
Sergio Abbate (Italy)
Vincenzo Barone (Italy)
Maurizio Tira (Italy)
Silvano Sozzani (Italy)

STEPHENS AWARD PRESENTATION & AWARD ADDRESS

05.15 pm **IS 1**
Effective fully polarizable QM/MM approach to model vibrational circular dichroism spectra of systems in aqueous solution
Chiara Cappelli (Italy)

06.00 pm **Welcome Cocktail**

MONDAY September 10th

08.30 am **Secretariat Desk Opening**

I SESSION "PAST, PRESENT and FUTURE of VOA"

09.00 am **IS 2**

45 years of vibrational optical activity

Prasad L. Polavarapu (USA)

09.45 am **IS 3**

Variability of VOA Theory and Experiment

Petr Bouř (Czech Republic)

10.30 am *coffee break*

II SESSION "VCD&ROA EXPERIMENTAL"

11.00 am **IS 4**

VCD studies on matrix-isolated molecule

Corina Pollok (Germany)

11.30 am **O IDN 25**

A Spectroscopic Ruler for Measuring Active Site Distortions based on Raman Optical Activity of a Hydrogen Out-of-Plane Vibration

Masashi Unno (Japan)

11.50 am **O IDN 56**

Biofluid Ananlysis – A challenge to chiroptical spectroscopy

Lucie Harbatová (Czech Republic)

12.10 pm **O IDN 74**

Molecular structure analysis of pantolactone using chiroptical spectroscopies

Jun Koshoubu (Japan)

12.30 pm **O IDN 58**

Resonance-Induced Enhancement of Solvent Vibrational Raman Optical Activity

Jiří Kessler (Czech Republic)

12.50 pm *lunch*

III SESSION "VCD&ROA Theory and Ab-Initio Calculation"

01.50 pm **IS 5**

Accurate vibrational spectra of chiral medium-sized molecules: simulations beyond the harmonic approximation

Julien Bloino (Italy)

02.20 pm **O IDN 66**

Complementarity in Chiroptical Spectroscopy: divide and conquer molecular flexibility

Valentin Paul Nicu (Romania)

02.40 pm **O IDN 38**

Exploring the combination and overtone vibrations by Raman optical activity

Pavel Michal (Czech Republic)

03.00 pm **O IDN 48**

A Partial Spectrum Approach in Infrared Absorption and Vibrational Circular Dichroism

T.Q. Teodoro (The Netherlands)

03.20 pm **O IDN 51**

An efficient technique to calculate vibrational circular dichroism spectrum

Chandan Kumar (The Netherlands)

03.40 pm **O IDN 75**

Problems with interpretation of chiroptical spectra by using quantum chemical calculations

Joanna Rode (Poland)

04.00 pm *coffee break*

IV SESSION "VCD&ROA: MD simulations (QM/MM and some address to Aggregation, Band-shape, etc.)"

04.30 pm **IS 6**

Calculation of Vibrational Circular Dichroism: Correlations in Space and Time

Sascha Jähnigen (Germany)

05.00 pm **O IDN 10**

Probing molecular chirality, learning about solvation

Christian Merten (Germany)

05.20 pm **O IDN 60**

VOA of Aqueous Solutions: Hydrogen Bonding vs. Conformational Flexibility

Tommaso Giovannini (Italy)

05.40 pm **O IDN 29**

Exploring resonance ROA of bioactive chromophores: ligand binding to a highly ruffled haem moiety

Roberta Sgammato (Belgium)

06.00 pm **O IDN 39**

Astaxanthin aggregates studied by molecular dynamics and electronic circular dichroism spectroscopy

Grzegorz Zajac (Poland)

06.20 pm **O IDN 45**

Explicit solvation of carboxylic acids for vcd studies: limiting the computational efforts without loosing accuracy

Karoline Bünnemann (Germany)

06.40 pm **O IDN 72**

Explicitly solvating small molecules with a Monte Carlo approach

Matteo Tommasini (Italy)

TUESDAY September 11th

08.30 am **Secretariat Desk Opening**

V SESSION "ROA/VCD Experimental Old&New"

09.00 am **IS 7**

Time-domain measurement of the complex chiro-optical susceptibility by an ultra-stable common-path interferometer

Dario Polli (Italy)

09.30 am **IS 8**

Resonance Raman Optical Activity of xanthophylls' supramolecular assemblies: homomolecular and mixed systems

Małgorzata Barańska (Poland)

10.00 am **O IDN 47**

Spectrometer for measurement of Raman optical activity in the extended spectral range

Josef Kapitán (Czech Republic)

10.20 am **O IDN 64**

Resonance Raman optical activity of human serum transferrin

Jonathan Bogaerts (Belgium)

10.40 am **O IDN 15**

Histidine complexes with metals studied by multiple spectroscopic methods

Jana Hudecová (Czech Republic)

11.00 am *coffee break*

VI SESSION "ROA and non-linear spectroscopies"

11.30 am **IS 9**

High sensitive chiral Discrimination by heterodyne-detected VSFG Spectroscopy

Taka-aki Ishibashi (Japan)

12.00 pm **O IDN 17**

Enhancing circular dichroism at the nanoscale

Paolo Biagioni (Italy)

12.20 pm **O IDN 59**

Is it Possible to Enhance Vibrational Circular Dichroism Signals with Tailor-Made Gold Nano-Antennas?

Jan Helbing (Switzerland)

12.40 pm **O IDN 4**

Emergence of Raman optical activity spectroscopy as a sensitive tool for lanthanide circularly polarized luminescence

Tao Wu (Czech Republic)

01.00 pm *lunch*

VII SESSION "APPLICATIONS of VOA - materials"

02.00 pm **IS 10**

Harnessing electronic and taming structural degrees of freedom in vibrational circular dichroism

Wybren Jan Buma (The Netherlands)

02.30 pm **IS 11**

Intense VCD response of achiral guest Molecules of co-crystalline polymer Films

Gaetano Guerra (Italy)

03.00 pm **O IDN 18**

Sequential induction of chirality in poly(phenylacetylene)s

Francisco Javier Ramírez Aguilar (Spain)

03.20 pm **POSTER SESSION**

04.20 pm *coffee break*

VIII SESSION "APPLICATIONS of VOA – natural products and drugs"

04.50 pm **IS 12**

Stereochemistry of Natural Cepharanthine Using Chiroptical Spectroscopies

Hua-Jie Zhu (China)

05.20 pm **IS 13**

Vibrational Circular Dichroism in the Pharmaceutical Industry

Leo A. Joyce (USA)

05.50 pm **IS 14**

Model-averaging of ab initio spectra in vibrational Spectroscopy

Guglielmo Monaco (Italy)

06.20 pm **O IDN 27**

Absolute configuration assignment of caffeic acid ester derivatives by VCD: the pitfalls of deuteration

João M. Batista Jr. (Brazil)

06.40 pm **O IDN 46**

Molecular specificity in resonance ROA – B12 vitamin case

Agnieszka Kaczor (Poland)

WEDNESDAY September 12th

08.30 am **Secretariat Desk Opening**

IX SESSION "APPLICATIONS of VOA – proteins, sugars, Lipids and Nucleic Acids; fibrils" part A

09.00 am **IS 15**

Pushing our understanding of the Raman Optical Activity Spectra of Proteins

Carl Mensch (Belgium)

09.30 am **IS 16**

Biomolecules and model membranes by vibrational circular dichroism

Marie Urbanova (Czech Republic)

10.00 am **POSTER SESSION**

11.00 am *coffee break*

CHIROPTICAL SPECTROSCOPIES AND ASTROCHEMISTRY "IN FRONT OF THE MIRROR: THE SEARCH OF CHIRAL MOLECULES IN THE UNIVERSE" part A

11.30 am **Opening Remarks**

Vincenzo Barone

11.35 am **IS 17**

title tbd

Roberto Battiston (Italian Space Agency, Italy)

12.15 pm **IS 18**

Mirror molecules and chemistry in the Universe - new challenges and methods

Melanie Schnell (Germany)

12.45 pm **IS 19**

From chiral ACOMS to the origin of life: a quantum chemical and spectroscopic journey

Cristina Puzzarini (Italy)

01.15 pm *lunch*

SOCIAL PROGRAMME

02.30 pm **Guided visit to Santa Giulia Museum**

07.30 pm **Social Dinner**

(Private-Bus Transfer headed to VEDETTA RESTAURANT in Brescia)

THURSDAY September 13th

08.30 am **Secretariat Desk Opening**

X SESSION "General Aspects of Chirality and VOA"

09.00 am **IS 20**
Calculating natural optical Activity of helicene Derivatives
Monika Srebro-Hooper (Poland)

09.30 am **O IDN 41**
Visual exploration of the vibrational chiroptical properties
Marco Fusé (Italy)

09.50 am **O IDN 44**
DrawMol and DrawSpectrum: new programs to visualize and interpret (optically active) vibrational spectra
Vincent Liegeois (Belgium)

10.10 am **O IDN 33**
Combinated Vibrational Circular Dichroism and Circularly Polarized Luminescence Studies of Protein Folding
Monika Krupová (Czech Republic)

10.30 am *coffee break*

XI SESSION "APPLICATIONS of VOA – proteins, sugars, Lipids and Nucleic Acids; fibrils" part B

11.00 am **O IDN 12**
IR, vcd and ecd spectra, dft simulations, plus MD and T-jump dynamics for three-strand b-sheet peptides. Turn and aromatic effects and isotopically edited spectra and dynamics
Tim Keiderling (USA)

11.20 am **O IDN 42**
Isotopically engendered chirality from enzymatic naphthoyl-ring reduction studied by vibrational circular dichroism
Steffen Lüdeke (Germany)

11.40 am **O IDN 7**
Supramolecular chirality and enhanced vcd of dna quadruplexes
Valery Andrushchenko (Czech Republic)

12.00 pm **O IDN 13**
Enhanced VOA as a probe towards intermolecular interactions
Evelien Van de Vondel (Belgium)

12.20 pm *lunch*

CHIROPTICAL SPECTROSCOPIES AND ASTROCHEMISTRY "IN FRONT OF THE MIRROR: THE SEARCH OF CHIRAL MOLECULES IN THE UNIVERSE"
part B

01.20 pm **IS 21**
title tbd
Filippo Maria Zerbi (Italian Institute of Astrophysics, Italy)

02.00 pm **IS 22**
CH and OH Stretch Vibrations as Probes of Local Environment
Edwin L. Sibert (USA)

02.30 pm **IS 23**
Looking for prebiotic species and chiral molecules in young solar analogs
Linda Podio (Italy)

03.00 pm **IS 24**
Vibrational density matrix renormalization group
Alberto Baiardi (Switzerland)

03.30 pm **Closing Remarks**
Sergio Abbate

STEPHENS AWARD

The Philip J. Stephens Award was established in 2014 by the International Steering Committee of Vibrational Optical Activity (VOA) at the VOA-4 meeting in Baoding, China. The award was presented for the first time at the VOA-5 conference in Antwerp, Belgium in 2016 and honors Philip J. Stephens (West Bromwich, UK, 10/9, 1940 – Los Angeles, CA, 7/31, 2012) as one of the leading founders of the VOA field with particular influence on vibrational circular dichroism (VCD) measurement and theory.

In order to distinguish this award from those in more established fields, and to place greater emphasis on encouraging the creative development of VOA as a field, the award is presented at each VOA conference to the authors of the paper judged to be most deserving published in the two calendar years prior to the conference.

The designated author of the paper presents the Philip J. Stephens Award Address at the VOA conference. All authors of the award will receive a framed certificate commemorating the award. The International Steering Committee considers all papers published on VCD and ROA in the two years prior to each VOA conference, without any nomination process, and votes for an award selection. In VOA-5 the paper was: "A novel Raman optical activity instrument operating in the deep ultraviolet spectral region" by Josef Kapitán; Laurence D. Barron; Lutz Hecht, Journal of Raman Spectroscopy (2015), 46(4), 392-399, presented by Josef Kapitán, Palacký University Olomouc, Czech Republic.

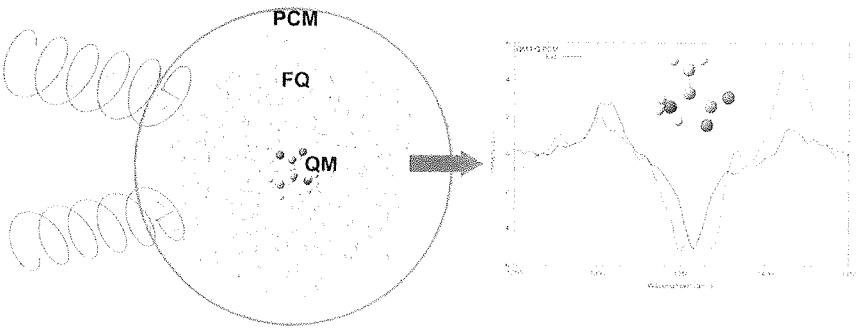
The winning paper for VOA-6 is: "Effective Fully Polarizable QM/MM Approach To Model Vibrational Circular Dichroism Spectra of Systems in Aqueous Solution" by Tommaso Giovannini; Marta Olszowka; Chiara Cappelli, Journal of Chemical Theory and Computation (2016), 12(11), 5483-5492. The paper (and further developments) will be presented by Chiara Cappelli, Scuola Normale Superiore, Pisa, Italy.

IS 1

Effective Fully Polarizable QM/MM Approach to Model Vibrational Circular Dichroism Spectra of Systems in Aqueous Solsution

Tommaso Giovannini, Marta Olszowka, Chiara Cappelli
Scuola Normale Superiore – Piazza dei Cavalieri 7, I-56126 Pisa, Italy
chiara.cappelli@sns.it

We propose a methodology, based on the combination of classical Molecular Dynamics (MD) simulations with a fully polarizable Quantum Mechanical (QM)/ Molecular Mechanics (MM)/Polarizable Continuum Model (PCM) Hamiltonian, to calculate Vibrational Circular Dichroism (VCD) spectra of chiral systems in aqueous solution. Polarization eff ects are included in the MM force field by exploiting an approach based on Fluctuating Charges (FQ). By performing the MD, the description of the solvating environment is enriched by taking into account the dynamical aspects of the solute– solvent interactions. On the other hand, the QM/FQ/PCM calculation of the VCD spectrum ensures an accurate description of the electronic density of the solute and a proper account for the specific interactions in solution. The application of our approach to (R)-methyloxirane and (L)-alanine in aqueous solution gives calculated spectra in remarkable agreement with their experimental counterparts and a substantial improvement with respect to the same spectra calculated with the PCM.



Reference
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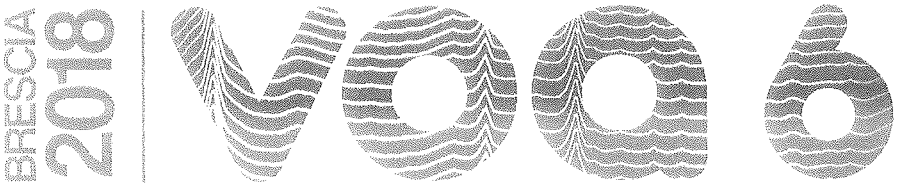
INVITED SPEAKERS



IS 2

45 years of Vibrational optical activity

Prasad L Polavarapu[1]
Vanderbilt University[1], Department of Chemistry, 37235, Nashville, TN, USA
E.mail: Prasad.L.Polavarapu@vanderbilt.edu

Raman optical activity (ROA) was measured for the first time in 1973 (1), 45 years ago, and vibrational circular dichroism (VCD) was first measured in 1974 (2). These two research areas constitute vibrational optical activity (VOA). I was fortunate to have been personally involved (3-6) in the developments in VOA spectroscopy since 1977. This journey has been full of excitement and pride. From the modest beginnings, when the full potential of VOA was speculative, to the current day where many novel and practical applications are being established, the development of VOA as a useful tool is a success story that practitioners can be proud of. There are growing pains during this process, as there would be in any new research area. Balanced interpretations and tempered excitement can advance VOA spectroscopy to new heights. In this presentation, I will review the developments in VOA spectroscopy, identify the remarkable successes and potential limitations, and highlight some new developments that we have undertaken.

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IS 3

VARIABILITY OF VOA THEORY AND EXPERIMENT

Petr Bouř

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Vibrational optical activity (VOA) can be used to study a range of molecular kinds and sizes. Specific procedures are required to interpret spectra of particular systems. For the flexible and polar Ala-Ala dipeptide, for example, a large number of solvent-solute clusters had to be generated to decompose the experimental Raman opticla activity (ROA) spectrum into calculated ones ($S_{EXP} = \sum c_i S_{i,CAL}$). We looked at this decomposition in detail, investigated mathematical uniqueness and the error of the conformer populations ci (1, Fig. 1).

For larger molecules, we use the transfer from vibrational properties calculated for smaller fragments (2). This led to good results for rigid proteins (3,4, Fig. 2), while measurement and interpretation of protein fibril aggregates, for example, are associated with a number of problems (5,6).

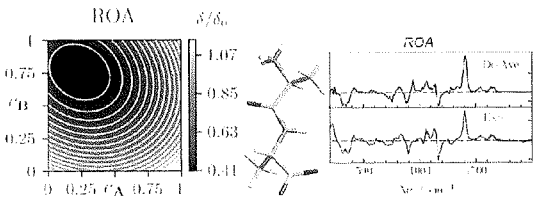

Fig 1. The relative spectra error (δ/δ_0) indicates that the decomoposition is unique, will well defined solution.

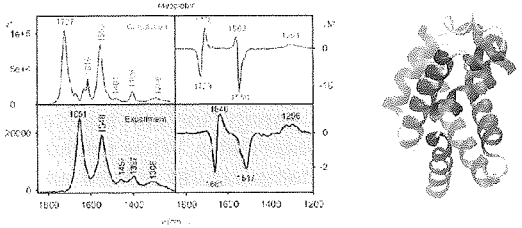

Fig 2. Simulated (top) IR and vibrational circular dichroism (VCD) spectra of myoglobin reasonably well agree with experiment (bottom).

In the past, we also experimented with a combination of VOA and magnetic field. This lead to a discovery of magnetic ROA of paramagnetic (7) and diamagnetic (8) gasses. The phenomenon could be at least at a semi-qualitative level described by the Zeeman splitting of rotational energy levels and the angular momentum theory. Theoretical simulations may also provide a new impulse to molecular magnetic vibrational circular dichroism (9); density functional computations of second derivatives of the atomic axial tensor seem to provide a good basis for understanding the experiment (unpublished).

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2. Yamamoto, S.; Li, X.; Ruud, K.; Bouř, P. *J. Chem. Theory Comput.* **2012**, *8*, 977-985.
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IS 4

VCD studies on matrix-isolated molecules

Corina H. Pollok, Dr. Christian Merten[1]
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Vibrational Circular Dichroism (VCD) has found its position as spectroscopic tool for the study of stereochemistry, conformational preferences and interactions of chiral molecules. Recently, VCD spectroscopy has been combined with the matrix isolation (MI-VCD) technique, a sample preparation method which has already proven to be a powerful tool for the characterization of stable molecules as well as reactive intermediates when combined with infrared spectroscopy (MI-IR). MI-VCD enables interesting new applications, for instance the possibility to investigate interactions, which are not observable in solution measurements. This was exemplified by a study on the complex of methyl lactate and ammonia, in which induced vibrational optical acitivity from the chiral methyl lactate to the achiral ammonia was observed.[1] The narrow-bandwidth achieved by MI-VCD furthermore supported the development of theoretical methods to correct for anharmonic effects in IR and VCD spectra.[2]

The solid environment of the cold matrices are known to occasionally cause frequency shifts. These so-called matrix effects may arise from minor perturbations of molecular structures due to non-homogeneous encapsulation sites.[3] The first matrix effects not strongly influencing the MI-IR but having a tremendous effect in the MI-VCD spectra were reported in our recent study on α-phenylethyl amine (PEA). Its potential energy surface features five different conformers connected by very low conformational transition states. While solution-phase measurements show spectra over all populated conformers, the low-temperatures utilized under matrix-isolation conditions enforces conformational cooling to the global minimum structure. Based on the MI-IR spectra, it could be confirmed that all conformational energy barriers are passed at the deposition temperature of 20 K - only the global minimum conformation of PEA is populated. However, differences in the calculated and experimental VCD spectra indicate deviations from the minimum structure by perturbation of the phenyl ring as well as the amine orientation. The degree of perturbation was found to also depend on the choice of the host gas, which shows the subtle influence of the environment in the conformational distortion of PEA.[4]

In order to explore new applications for the investigation of photochemical reactions of chiral molecules we investigated the chiral camphorquinone imine, which served as example for a photochemical switch with two different living states. In this contribution we show that both E- and Z-camphorquinone imines can be photochemically generated at cryogenic temperatures in argon matrix, and more importantly, that the stereochemistry of both switching states can be reliably characterized.[5]

During our MI-VCD research we encountered interesting challenges on both experimental and theoretical sides. Some examples will be shown and insights to our theoretical and experimental approaches to solve the remaining puzzles of MI-VCD spectroscopy will be given.

References

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IS 5

ACCURATE VIBRATIONAL SPECTRA OF CHIRAL MEDIUM-SIZED MOLECULES: SIMULATIONS BEYOND THE HARMONIC APPROXIMATION

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Vibrational spectroscopy is a powerful investigative tool for the study and determination of the structural and dynamical properties of molecular systems. Improvements in experimental techniques lead to finer band-shapes, which in turn can provide more details on those properties. However, it represents new challenges to interpretation, as simpler theoretical models become insufficient to support an extensive study. Nowadays, computational spectroscopy is routinely used for this task, providing reference data to help the identification and assignment of observed bands, or guide the discovery of new findings. However, the reliability and accuracy of theoretical calculations, in particular for sensitive spectroscopies like vibrational circular dichroism (VCD) and Raman optical activity (ROA), depend strongly on the accuracy of the underlying theory. Thanks to progresses in algorithms and hardware performance, models beyond the harmonic level of approximation are now applicable to medium-large molecular systems of several dozens of atoms. In particular, second-order vibrational perturbation theory (VPT2) is an appealing method, since it offers a significant improvement in accuracy and reliability over harmonic, including frequency-scaled, results for a reasonable raise of the computational cost(1,2).

In this contribution, we will present the general aspects of VPT2 applied to the calculation of transition energies and intensities of chiroptical spectra, and show how fully anharmonic spectra can lead to a better understanding of their structure(2,3). The reliability of the results not only derives from a proper choice of the electronic structure calculation method but also from a careful assessment of limitations and shortcomings of the theory employed for the vibrational part. With the aim of providing robust methods to build automatic procedures and facilitate such calculations, we will also address the well-known problem of resonances in VPT2, their impact on band positions and intensities, and the strategies available to overcome them.

While the data produced during simulations can provide in-depth insights on the origin of each band, they can be difficult to analyze to their fullest. Suitable graphical representations can overcome this issue by giving a more qualitative, overall picture of the computational results and thus assist the interpretation of the spectra. Besides, they can help set up reliable reduced-dimensionality schemes to be applied to larger systems where a full anharmonic treatment would be too expensive or strategies for hybrid schemes, for instance to treat large amplitude motions with ad hoc models. Some of the possibilities offered by such support programs will be illustrated.

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IS 6

Calculation of Vibrational Circular Dichroism: Correlations in Space and Time

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Vibrational circular dichroism (VCD) has enriched the toolbox of analysing and classifying chiral supramolecular organisation due to its outstanding sensitivity towards absolute and relative configurations. Yet, the theoretical description of VCD in large-scale supramolecular setups poses challenges as the size of molecular models is limited depending on the computational costs of ab initio calculations. Moreover, the success of a VCD calculation depends on proper coverage of thermal fluctuations as conformers strongly determine the spectrum. There are powerful empirical models that are attractive due to their lower costs. Nevertheless, a crucial point often lies in the modulation and polarisation of charges, which requires an accurate description of the electronic structure.

The calculation of complicated VCD spectra can be addressed by means of Nuclear Velocity Perturbation Theory (NVPT) that is convoluted with a phase space obtained from ab Initio Molecular Dynamics (AIMD).[1,2,3] Important progress has been made in the field of AIMD-based vibrational spectroscopy, where IR and VCD spectra are obtained as Fourier transformed time-correlation function and spatial dissection.[2,4] AIMD calculations allow for an improved sampling of the statistical ensemble, naturally including entropic effects and coupled oscillations. Hence, thermal fluctuations, anharmonicities, and peak shapes will enter the spectra. Moreover, conveniences, such as fully-periodic supercells and enhanced sampling methods may be profitably exploited. Upon the modelling of supramolecular aggregates, one can identify building blocks of non-local chirality and gets to understand how supramolecular VCD is actually built up.[4] Some of the possibilities offered by such support programs will be illustrated.

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IS 7

Time-domain Measurement of the Complex Chiro-Optical Susceptibility by an Ultra-stable Common-path Interferometer

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We present an innovative device for measuring circular dichroism (CD) and circular birefringence (CB) spectra over a broad wavelength range from the IR (to access vibrational fingerprints) to the UV spectral region (e.g. to study protein structures), combining time-domain detection with self-heterodyne amplification. Fig. 1(a) shows the experimental setup. The light from a broadband incoherent source is first polarized at a small angle γ with respect to the vertical direction. An ultra-stable birefringent common-path interferometer (CPI) then creates two phase-locked replicas of the input light with orthogonal polarization. Depending on the insertion of one birefringent wedge, the CPI imposes a relative delay τ between the major (vertical, V) and minor (horizontal, H) components of the electric field (see relative arrows in Fig. 1(a)). The V component excites the chiral sample, which in turn emits a synchronous chiral free-induction-decay (FID) signal with H polarization. A second polarizer oriented along the H direction finally selects the FID signal and the delayed H component (acting as a time-delayed phase-coherent local oscillator, LO in Fig. 1(a)). These two H fields interfere at the detector as a function of the wedge position, providing the interferograms in Fig. 1(b) for the two enantiomers of Nickel Tartrate. A Fourier transformation allows the extraction of the CD (solid lines) and the CB (dotted lines) signals, shown in Fig. 1(c). The CD signal perfectly matches the one acquired with a commercial spectropolarimeter (circles and squares). With respect to commercial spectropolarimeters, our device is considerably faster, more compact, simpler and cost effective, as it does not require any monochromator, photo-elastic modulator or lock-in amplifier. Moreover, it does not only provide CD but also CB chiral spectra, which provide valuable extra information for extracting important structural properties of molecules.

Our time-domain approach has great potential for time-resolved optical activity measurements to study ultrafast stereochemical processes. The device accepts broadband ultrashort pulses, whereas standard spectropolarimeters in the UV-visible only allow for monochromatic beams. In addition, time-domain detection enables modulation of an actinic pump pulse at high repetition rates, up to the MHz range. Demodulation of the signal as a function of pump-probe delay T and CPI delay τ should allow rejecting any spurious background from linear birefringence and linear dichroism and extracting the pump-induced differential chiral interferogram, from which the transient optical activity spectra can be obtained by FT, with much higher sensitivity than the linear measurements reported here.

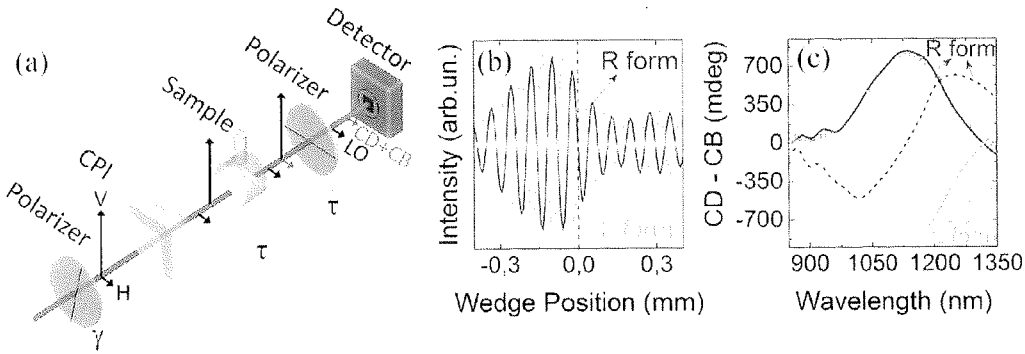

Fig. 1: (a) Experimental setup. (b) Measured interferograms of the enantiomers of Nickel Tartrate and (c) CD and CB spectra (solid and dotted lines, respectively).

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IS 8

Resonance Raman Optical Activity of xanthophylls' supramolecular assemblies: homomolecular and mixed systems

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Xanthophylls aggregation occurs in biologically important systems such as photosynthetic apparatus and lipid bilayers. Under the influence of hydrophobic effects and intermolecular forces, xanthophylls molecules form supramolecular chiral structures, which type depends on the local environment. In our recently published work, it was shown that aggregation of xanthophylls can lead to the resonance Raman Optical Activity (RROA) effect and may play a significant role in chiroptical studies. We reported a new mechanism, where the chirality enhancement is achieved through resonance due to supramolecular aggregation and coupling of the incident laser light with an electronic transition of a supramolecular assembly. This effect brings a strong enhancement of chiroptical signal and was named by us, Aggregation-Induced Resonance Raman Optical Activity (AIRROA). Up to now, we applied the AIRROA phenomenon to several xanthophylls (astaxanthin[1], zeaxanthin[2], and lutein[3]).

We have made several trials to optimize the resonance conditions for other supramolecular chiral systems. Our main objective is formation of the supramolecular mixed systems showing an induced chirality and intense RROA signal. Interesting examples are chiral superstructures built from structurally similar species: chiral and achiral ones. This kind of chirality amplification is called "sergeant and soldiers" effect. When a small amount of chiral compound (the "sergeant") is added to achiral ones (the "soldiers"), a strong ECD signal is obtained similar to that observed for the "sergeant" alone[4]. If the ECD absorption band coincides with the ROA excitation wavelength, registration of the RROA spectrum is possible. Using mixture of two naturally occurring xanthophylls, astaxanthin (chiral) and β-carotene (achiral) (Fig. 1), we have obtained supramolecular assembly that exhibits strong chirality and resonance ROA effect. Moreover, achiral βcarotene molecules are forced by a chiral addition (astaxanthin) to form chiral arrangement. Our model is reflected in Nature, as the carotenoid crystals extracted from carrot roots exhibit extremely similar chiroptical spectra as the astaxanthin-β-carotene aggregates. Implications of this fact and, in general, aggregation-induced signal enhancement are still discussed.

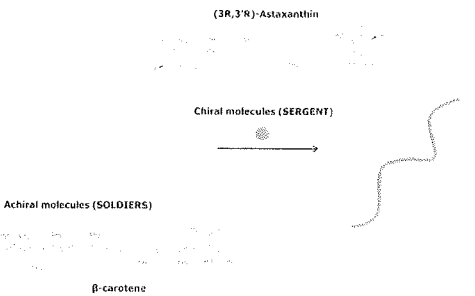

Figure.1 The schematic illustration of chirality amplification called 'sergeant and soldiers' effect.

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IS 9

HIGH SENSITIVE CHIRAL DISCRIMINATION BY HETERODYNE-DETECTED VSFG SPECTROSCOPY

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Chiral vibrational sum frequency generataion (VSFG) is a new, sensitive chiroptical technique. In the sum frequency generation (SFG) process, two laser beams with different frequencies (ω_{vis}, ω_{IR}) shine a sample to generate sum frequency light at $\omega_{vis}+\omega_{IR}$. SFG signal intensity is greatly enhanced when the IR laser frequency, ω_{IR}, is in resonance with a vibrational frequency of sample molecules. The resonance enhancement enables us to conduci vibrational spectroscopy with the SFG process. This is VSFG spectroscopy. The SFG process is electric dipole forbidden in centrosymmetric media. By virtue of the selection rule, SFG is usually used to selectively observe an interface between two centrosymmetric bulk media since the symmetry is broken at the interface. The chirality of a sample also breaks the symmetry and therefore can be probed by SFG process. We have developed the first heterodyne-detected (HD) multiplex chiral VSFG spectrometer.[1] Thanks to the heterodyne detection, we can detect the phase of the VSFG signal electric field that carries the information on which chirality the sample has.

The advantage of chiral VSFG over conventional chiral vibrational spectroscopies, such as VCD and ROA, is its high sensitivity. One reason is that chiral VSFG is an electric dipole allowed process unlike the conventional chiral spectroscopies. The other reason is that chiral VSFG is background free. When measuring VCD or ROA spectra, one has to calculate the difference between signals with left and right circularly polarized light. In this case, a large achiral signal can easily overwhelm a tiny chiral signal. In centrasi, chiral VSFG signals can be obtained directly in some chiral-specific polarization combinations. This feature is very helpful to detect chiral signals with high sensitivity. Chiral VSFG is applicable to both bulk and interface, and it can be practically surface specific when conducted in the reflection mode under electronic nonresonant conditions. So far, we have applied chiral VSFG to chiral liquids, chiral solutions, proteins at interface, chiral monolayers, and chiral polymers.

The sensitivity of chiral VSFG can be improved further by electronic resonance. To examine such enhancement, we measured HD chiral VSFG signal from acetone solutions of R- and S-binaphthol with 353-nm ultraviolet probe; in this case the wavelength of VSFG signals was in resonant with the electronic absorption band of binaphthol located at around 335 nm.[3] We have confirmed that the chiral VSFG signal from a solution of 20-mM concentration was detectable. It should be emphasized that the effective depth of the probed volume was only about 20 nm because the measurement was conducted in the reflection mode. The equivalent molecular area density (0.24 nm^{-2}) suggests that the observation of chiral VSFG from monolayers is quite feasible. We have actually succeeded in measuring HD chiral VSFG spectra of binaphthyl derivative monolayers on water.[4]

HD chiral VSFG spectroscopy has also been applied to proteins at air-aqueous solution interfaces.[5] Even in the electronic non-resonant condition, HD chiral VSFG spectra at the interfaces were successfully obtained for the following proteins: bovine serum albumin, pepsin, concanavalin A, and α-chymotrypsin. The observed phases of vibrational bands indicated the spectra were not from bulk solution, but from protein layers much thinner than the effective thickness (~30 nm) of the VSFG observation. NH stretching and amide-I bands of the examined proteins in the chiral VSFG spectra were different in their frequencies and intensities, while those in the achiral VSFG spectra were rather similar. This observation suggests that chiral VSFG spectra are more informative than achiral ones in terms of protein structures at air-aqueous solution interfaces.

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IS 10

Harnessing electronic and taming structural degrees of freedom in Vibrational Circular Dichroism

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Vibrational Circular Dichroism has proven to be a powerful means to unravel the stereochemistry of chiral molecules in solution. Presently, furthering its applications is facing a number of key challenges involving signal intensities and conformational flexibility. In recent years we have shown that coupling the electronic degrees of freedom to vibrational ones is an effective and highly attractive means to boost signal intensities. However, harnessing these electronic degrees of freedom has so far been employed for systems in which the relevant electronic part is rather localized.[1] How delocalization influences amplification of VCD signal intensities is one of the topics that will be discussed in this context.

VCD is also a technique that so far has predominantly been applied to rigid molecular systems with preferably limited conformational heterogeneity. In real life, molecules are dynamic and experience varying interactions with neighboring solvent molecules. As a result, the molecule probes effectively a much larger structural phase space than one normally would take into account. We will show which far-reaching consequences this flexibility may have and present methods[2] that allow one to analyze and incorporate their effects in theoretically predicted spectra.[3,4] A final issue that will be addressed concerns conformational heterogeneity which standardly is dealt with by Boltzmann-weighting. We will discuss our recent efforts to come up with alternative methods.

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IS 11

INTENSE VCD RESPONSE OF ACHIRAL GUEST MOLECULES OF CO-CRYSTALLINE POLYMER FILMS

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Intense Circular Dichroism (CD) and Vibrational Circular Dichroism (VCD) phenomena for racemic macromolecules interacting with non-racemic guests are well known for polymers in solution. More recently, analogous phenomena have also been observed in the solid state (1-5) and are associated with formation of polymer co-crystalline phases (1), i.e. crystalline phases constituted by a helical polymer host and non-racemic low-molecular-mass guest molecules.

This induction (and amplification) of chirality in racemic polymers by co-crystallization with non-racemic guests generally occurs by molecular mechanisms, where a non-racemic guest induces the formation of co-crystals with a non-racemic unit cell, with polymer chains with one-sense of helicity. An alternative *supramolecular mechanism*, involving formation of non-racemic helical crystallites that does not require the presence of a non-racemic unit cell (with polymer chains exhibiting only one-sense of helicity), has been observed only for syndiotactic polystyrene (s-PS) (1-5). In this case, the chiral optical response of s-PS remains essentially unaltered up to the polymer melting, not only after the non-racemic guest removal but also after thermal crystal-to-crystal transitions (1), which involve the change in the molecular conformation from chiral helical to achiral trans-planar. The supramolecular nature of the chiral response of s-PS is also confirmed by the intense CD and VCD response of achiral chromophores, when they replace the non-racemic guest in the crystalline cavities of s-PS co-crystalline phases (2)(Figure 1).

It is also rather surprising that not only CD but also VCD of non-racemic molecules, being guests of co-crystalline phases of s-PS films, do not depend on their R or S molecular chirality but essentially only on the polymer host supramolecular chirality (4).

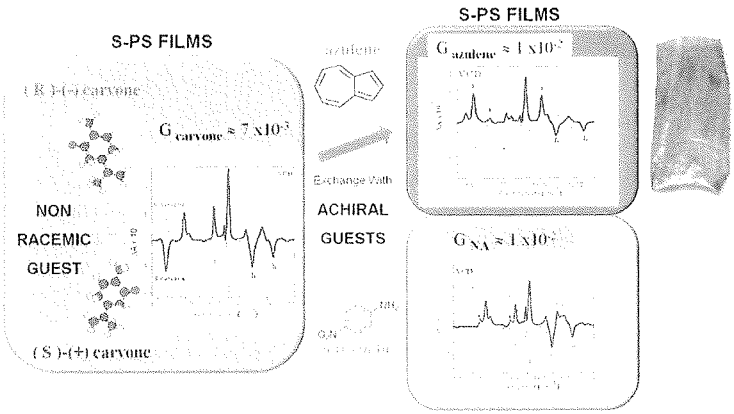

Figure 1. VCD response of the polymer host after co-crystallization with R or S carvone and of achiral guest molecules (azulene and 4-nitroaniline) after replacement of carvone guest molecules.

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IS 12

Stereochemistry of Natural Cepharanthine Using Chiroptical Spectroscopies

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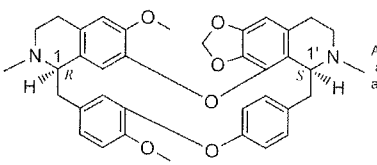
The cepharanthine (**1**) has a strongly bioactive bisbenzylisoquinoline alkaloid exhibiting 12 specific bioactivities without any reported negative side-effects (Fig. 1), also has been used for the treatment of patients with radiation-induced leukopenia, exudative otitis media, alopecia areata, and venomous snakebites in Japan for more than 40 years.[1-2] Its stereochemistry has been reassigned from (1*R*,1'S) to (1*R*,1'R)based on the calculations of chiral optical rotation, electronic circular dichroism and vibrational circular dichroism have been studied using various method for the structural stereochemistryand comparison with experimental results.[3-7]



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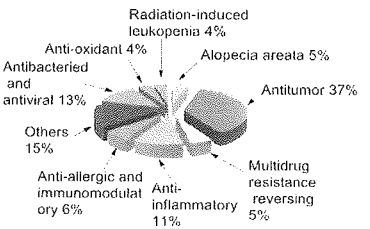

Fig. 1 Left: The species, Stephania, in China.
*Middle: Structure of cepharanthine (**1**).*
*Right: Distribution of various bioactivities of **1**.*

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Vibrational Circular Dichroism in the Pharmaceutical Industry

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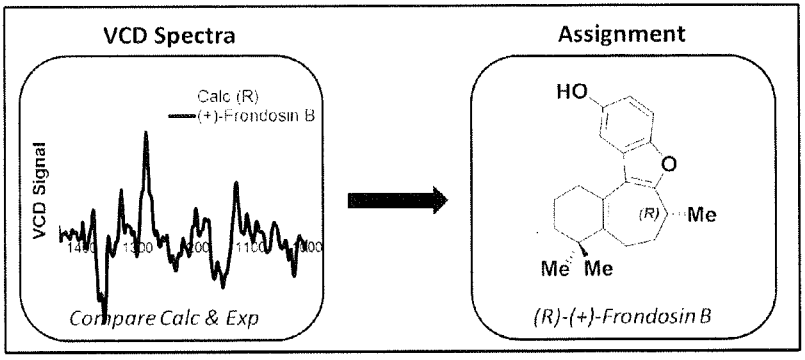
With the tremendous advances in asymmetric synthesis over the last few decades creating numerous novel and innovative synthetic methodologies, the determination of the absolute configuration of chiral compounds is a fundamentally important task in the pharmaceutical industry. Historically, these assignments have routinely been made using single crystal x-ray diffraction. However, the amount of time and material that can be required to get suitable crystals and make an assignment can limit the scope of the analysis. With the simultaneous need to analyze many starting materials, intermediates, metabolites, and active pharmaceutical ingredients (APIs) for numerous projects, there was a need to expand beyond the scope of x-ray crystallography. The use of vibrational circular dichroism (VCD), combining computational and experimental chemistry workflows, has proven itself to be a robust technique that is optimal to ensure that assignments are made efficiently and correctly. This presentation will cover the application of VCD within the context of synthetic organic chemistry in the pharmaceutical industry. We will cover the methodology that has been developed at Merck to systematically sample conformers and calculate spectra that can be matched to those experimentally obtained. We will then move to some real case studies, highlighting samples where the absolute configuration assignment led to a better understanding of the stereochemical course of reactions. Next, we will highlight challenging cases where additional work was required in order to correctly assign the absolute configuration. Taken together, these examples will definitively show how the synergy between analytical and organic chemistry can lead to a deep understanding of asymmetric synthesis.



Comparison of calculated and experimental VCD spectra for natural product (+)-Frondosin B And assignment of absolute configuration

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IS 14

MODEL-AVERAGING OF AB INITIO SPECTRA IN VIBRATIONAL SPECTROSCOPY

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The study of vibrational spectra, both in absorption and circular dichroism (VA and VCD), is nowadays routinely enriched by computational investigations, even for condensed phases.[1] However quantitative agreement, i.e. one that could be checked by a standard goodness-of-fit indicator (GOFI) as the MSE, is generally off mark. In many cases, expert corrections of the calculations and expert procedures of data rejection are used in combination with visual inspection to achieve a confident assignment of the absolute configurations (AC) via VCD spectroscopy, especially in the case of flexible molecules with more than a single chiral center.

In addition to the use of alternative GOFIs, such as the cosine similarity[2] and the mean absolute error, which can be of significant help, we have recently proposed to cope with the variability of the ab initio results as with statistical errors. The statistical perspective allows obtaining model-averaged (MA) ab initio spectra, which come together with their uncertainties, and should thus allow a more confident assignment, as compared with the plain ab initio spectra normally used (Figure 1).[3]

The error associated to the plain ab initio calculations stems from the assumption of Normal distributions for some relevant computed parameters, i.e. the relative energies of the conformers, the moduli of dipolar and rotator strengths, the absorption frequencies and the angles ξ_k between the k-th electric and the k-th magnetic dipole moment.

In this contribution we will present the basics of the model-averaging method and we will present results obtained for VCD spectra already reported in literature, but recorded from new samples, using as statistical variables the origin-independent dissymmetry factors g_k,[4] in place of the origin-dependent magnetic dipole transition moments m_k and angles ξ_k.

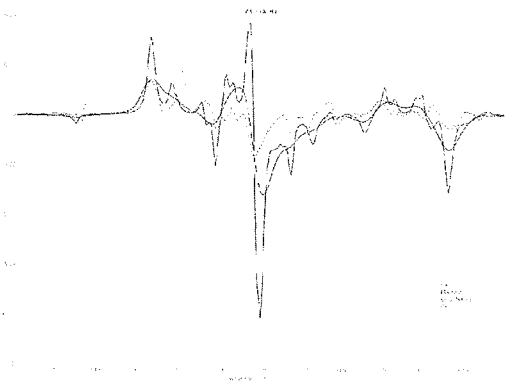

Figure 1. A comparison of an experimental VCD spectrum (dotted line) with a plain ab initio (continuous line) and a model-averaged ab initio calculation (dashed line) coming with error estimates (shaded area).

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IS 15

PUSHING OUR UNDERSTANDING OF THE RAMAN OPTICAL ACTIVITY SPECTRA OF PROTEINS

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Raman optical activity (ROA) has been proven to be a unique probe of the structure of biomolecules in many experimental studies. The spectral assignments however relied on the comparison with available structural information from, for example, crystal structures and other spectroscopies. Due to the rise in computational power and the implementation of the necessary algorithms to compute ROA spectra in different available computational software packages, the use of quantum chemical calculations has dominated the recent literature on ROA. Using such computations, it is now possible to verify earlier tentative spectral assignments and to probe how much structural details we can extract from ROA spectra.

In our group, a database was developed to study the relation between the secondary structure of proteins with the corresponding ROA patterns in a systematic fashion.(1) It was shown that for different peptides with varying solution structures, the experimental spectra could be elucidated very well with this database approach. Since the database was constructed by calculating the Raman and ROA spectra of regular peptide models with fixed backbone torsion angles, it was surprising that for a flexible peptide the ROA patterns also matched very well. Therefore, in our recent work we further explored the effect of conformational disorder and dynamics on the spectral patterns. Furthermore, we explored the effect of explicit solvent molecules on the computed patterns and how specific side-chains affect the ROA patterns. These latter topics cover questions that were not addressed by the database and hence push our detailed understanding of experimental ROA spectra. Specifically to further understand the ROA spectra of flexible proteins such as intrinsically disordered proteins this could be of high relevance.(2)

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IS 16

BIOMOLECULES AND MODEL MEMBRANES BY VIBRATIONAL CIRCULAR DICHROISM

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Many biochemical interactions are mediated by a membrane scaffolding. Here we focus on two such systems: the interaction of peptides with the model membranes and the interaction of bile pigments with the model membranes at different conditions. Membranes were modelled by liposomes and micelles of various composition. Vibrational circular dichroism (VCD) was demonstrated to be an appropriate method having some advantages in comparison with the electronic circular dichroism routinely used for the model membrane characterization: VCD enabled to follow structural changes of the both liposomes and interacting biomolecules (1), an example is shown on Fig. 1. A mull samples with Nujol and Fluorolube was used (2) for the VCD measurements in the IR spectral regions where the measurements in solution are impossible (Fig. 2). The VCD method was used to describe high concentration of bilirubin, which may occur in the membrane systems *in vivo*. Using supporting spectral method (ECD, fluorescence) it was shown that the enantioselective interaction of bilirubin with the cell membranes provide molecular basis for the neurotoxic effect of bilirubin.

For pure serum albumin with no ligands the effect of model membranes on the bilirubin binding to serum albumin, which is important part of the bilirubin transportation in the body, was found to be negligible. Here it is demonstrated that in the presence of natural ligands (fatty acids) in the bilirubin-serum albuminmembrane system, bilirubin bind to the membrane even at the concentrations where the binding to primary binding site of serum albumin is preferred.

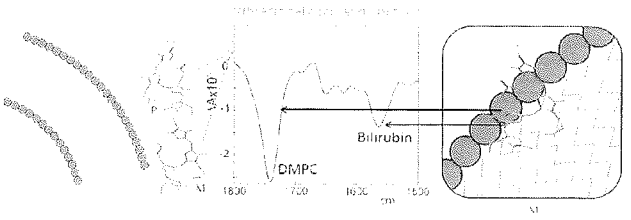

Fig.1 Bilirubin and the DMPC membrane

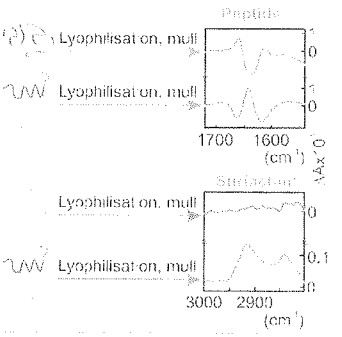

Fig. 2 Poly-L-arginine hydrochloride and sodium dodecyl sulfate using the mull in the two spectral

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IS 18

Mirror molecules and chemistry in the Universe – new challenges and methods

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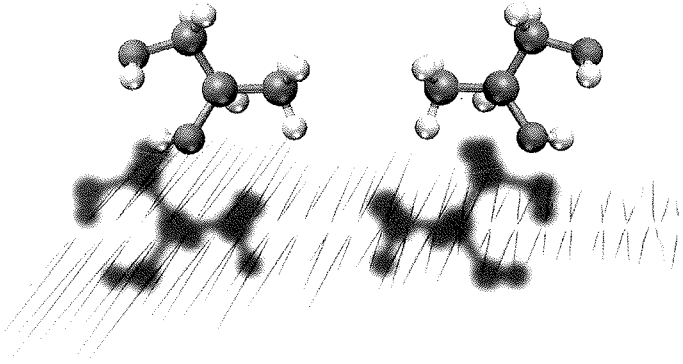
Most molecules of biochemical relevance are chiral. In nature and as products of chemical syntheses, chiral molecules often exist in mixtures with other chiral species. The analysis of these complex mixtures to identify the molecular components, to determine which enantiomers are present, and to measure the enantiomeric excesses (ee) remains a challenging task for analytical chemistry.

In collaboration with Dave Patterson (UC Santa Barbara) and John Doyle (Harvard University), we experimentally demonstrated a new method of differentiating enantiomeric pairs of chiral molecules in the gas phase. It is based on broadband rotational spectroscopy and is a three-wave mixing process that involves a closed cycle of three rotational transitions. The phase of the acquired signal bares the signature of the enantiomer, as it depends upon the product of the transition dipole moments, and the signal amplitude is proportional to the ee. A unique advantage of our technique is that it can also be applied to mixtures of chiral molecules, even when the molecules are very similar. It also bears the potential for enantiomer separation, as was recently shown. In my lecture, I will introduce the technique and give an update on the recent developments, also with respect to controlling and finally manipulating chirality.

In another research branch, we are interested in chemical processes in the Universe. These often occur under extreme conditions, which can be very different from those on earth. Modern methods of high-resolution molecular spectroscopy as well as novel, ultrafast light sources (such as the free-electron laser FLASH in Hamburg) allow us to identify new molecule classes in space as well as to study chemical reactions. The expected results might also have the potential to contribute to a better understanding of the origin of life.



IS 19

FROM CHIRAL ACOMS TO THE ORIGIN OF THE LIFE: A QUANTUM-CHEMICAL AND SPECTROSCOPIC JOURNEY

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RTo disclose the "secrets" of the origin of life on Earth (and elsewhere?), the first step is to understand how and where small prebiotic species could form and then, most importantly, how the chemical complexity could evolve toward chirality. Indeed, biological molecules are chiral and only the right-handed version is found in living organisms, with "handedness" serving an essential function in living beings. However, the prebiotic molecules are non-chiral and pre-biological molecules can be both left- and right-handed. At some stage in the origin of life, an informational polymer should have arisen by purely chemical means and, according to the 'RNA world' hypothesis, this polymer was RNA. So how did right-handed RNA emerge from a mix of molecules?

While this contribution does not aim at solving such a puzzle, it focuses on the investigation of the chemical evolution in the interstellar medium (ISM) as well as in planetary atmospheres as a very first step toward its comprehension. In particular, it focuses on the role played by molecular spectroscopy and quantum- chemical computations in disclosing how small prebiotic molecules (also denoted as ACOMs – astronomical complex molecules) are formed in different astronomical environments, like interstellar clouds (ISCs) and Titan's atmosphere, and in understanding how these species can further evolve in complexity toward building blocks of biomolecules, with particular focus on chiral molecules.

Indeed, spectroscopic signatures provide the unequivocal proof of the presence of chemical species in a given astronomical environment [1], which is the starting point for the development of any astrochemical model and for laying the foundation of astrobiology. The present situation is that only one chiral molecule has been detected in the ISM so far [2] and even glycine, the simplest amino acid, has not been identified yet [3]. On the other hand, meteorites (and specifically the carbonaceous chondrites), their content in terms of extraterrestrial amino acids and the corresponding enantiomeric excess shown carry a record of the organic chemical evolution of the early solar system [4].

To summarize, in this contribution it will be presented the role that a joint effort of molecular spectroscopy and quantum-chemistry can play in this context and the strategies to be pursued in order to understand what the current inventory of identified molecules the ISM can tell us, to discover new chiral ACOMs in space, and to understand how the chiral building-blocks of life can originate from small achiral prebiotic molecules.

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IS 20

CALCULATING NATURAL OPTICAL ACTIVITY OF HELICENE DERIVATIVES

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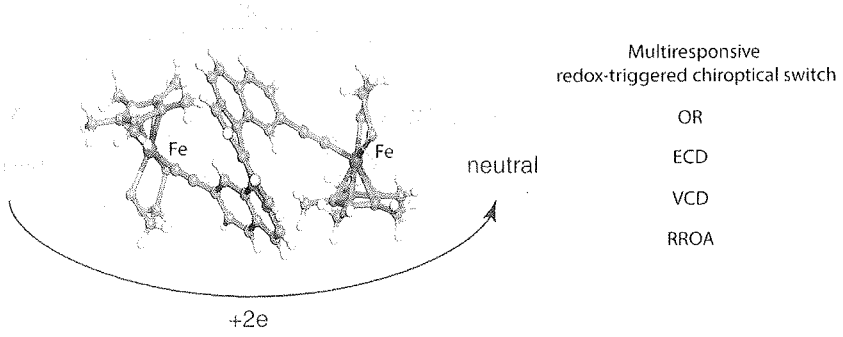
Due to intrinsic spatial chirality combined with π-conjugated electronic structure, helicenes and their derivatives demonstrate unique, large-magnitude chiroptical properties. Those features along with rapidly growing, rich chemistry, make them very promising candidates for multifunctional optoelectronic materials used, for example, as molecular chiroptical switches or phosphorescent dopants in organic light emitting diodes (1). Molecular engineering of such helical systems requires the discovery of efficient synthetic routes and the development of simples strategies to enhance and tune their (chir)optical properties. In this respect, the importance of first-principles calculations cannot be understated, since quantum-chemical analysis can provide direct information on how experimentally measured properties depend on atomicscale structure and bonding (2). Accordingly, theory does not only enable a meaningful interpretation of experimental data, but may also lead to deeper understanding of the factors responsible for the observed experimental trends. This is the first step in enabling the possibility of designing and proposing new systems with the desired properties.

Recently, a variety of helicene-based systems has been successfully studied in our laboratories via extensive combined experimental and theoretical research, including, for example, redox- (see figure below) and chemically-triggered chiroptical switches, and chiral phosphors with circularly polarized luminescence activity (3). Selected results will be presented in this contribution, covering optical rotation (OR), electronic and vibrational circular dichroism (ECD, VCD) spectra, circularly polarized luminescence (CPL), and Raman optical activity (ROA), and focusing on our understanding, from quantum-chemical (time-dependent DFT) calculations, of the factors that determine unique optical properties of helicene derivatives.



Redox-active chiroptical switch based on iron-ethynyl-carbo[6]helicene (3a)

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IS 22

CH and OH Stretch Vibrations as Probes of Local Environment

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The CH and OH stretch vibrational frequencies are sufficiently distinct from other vibrational frequencies, that their presence in an IR spectrum is a good indicator of the presence of these functional groups. In this talk, we extend these ideas. It turns out that both the OH and CH stretches exhibit a surprising sensitivity to molecular structure. If the IR spectra are high enough resolution, then we can take advantage of this sensitivity, and use the spectra to provide information regarding molecular structure and local environment. I will describe the interplay between theoretical and experimental groups that has enabled the development of models with which we are able to determine what the experimental spectra tell us about molecular structure and local environments. Central to the theoretical development is the availability of high resolution, low temperature, and conformer specific spectra. To illustrate these ideas, I will show how IR spectra help answer the following three questions. Where does the Na^+ ion go when attached to cyclohexane molecule? If we 'mix' seven water molecules with a benzene molecule, how do the water molecules arrange themselves in order to minimize the total energy of the system? How long does the tail of an alkylbenzene molecule C_6H_5-$(CH_2)_n$-CH_3 have to be, before the chain bends back on itself?

IS 23

Looking for prebiotic species and chiral molecules in young solar analogs

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To study chemical complexity in young solar-like stars is crucial to understand the origin of life. Thanks to the advent of (sub-)millimeter interferometers, such as NOEMA and ALMA, it is now possible for the first time to investigate the chemistry of protostellar disks around young Suns, where planets are believed to form, and to compare their molecular content with that of Solar System bodies, which are the relics of our pristine Solar Nebula. In this context we will present the work that is being developed thanks to the NOEMA-SOLIS and ALMA-FAUST large programs on astrochemistry, involving astrophysicists and chemists from Europe, Japan, and USA. We will show the detections of complex organics, and the state-of-art of the searches for the simplest amino acids and molecules of prebiotic interests, around young stars. Finally, we will discuss the detections of chiral molecules in the Solar System and the perspective to detect such molecules in Sun-like star forming regions.

IS 24

Vibrational Density Matrix Renormalization Group

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One of the main goals of astrochemistry is the identification of molecular species present in the interstellar medium and the study of their reactivity. This characterization usually relies on molecular spectroscopy, mostly involving radiation in the microwave and infrared regions. However, the complexity of the experimental spectra is very high due to the simultaneous presence of contributions arising from several molecular systems, possibly in different conformational states. For this reason, a full characterization of experimental results heavily relies on quantum-chemical simulations (1).

The simulation of vibrational spectra requires two steps. Electronic properties, such as potential energy surfaces, are obtained from the solution of the electronic Schrödinger equation. Those quantities then define the nuclear Schrödinger equation, whose solution determines the vibrational properties of the molecule. Several theories to solve the electronic Schrödinger equation have been extended to vibrational problems. Similarly to its electronic structure analogue, vibrational self-consistent field (VSCF) fails to describe strongly-correlated systems, i.e. molecules characterized by large-amplitude modes, along which the potential energy surface displays several minima.

An accurate description of such systems requires post-SCF approaches, such as vibrational configuration interaction (VCI). In VCI, vibrational states are computed from the exact diagonalization of the vibrational Hamiltonian in a given basis set. The range of applicability of VCI is, however, limited by its exponential scaling with the size of the target systems, a problem also known as the curse of dimensionality. A possible solution to this limitation is offered by the density matrix renormalization group (DMRG) algorithm (2). However, the application of DMRG to vibrational problems has been hardly explored (3). In the present contribution, we demonstrate how DMRG can be exploited to optimize vibrational wave functions expressed as matrix product states (MPSs) by encoding the vibrational Hamiltonian as a matrix product operator (MPO). The resulting algorithm will be referred to as vibrational DMRG (vDMRG). The major features of vDMRG will be presented by highlighting the most relevant differences with respect to its electronic analogue.

First, the extension of a general, MPS/MPO-based DMRG algorithm devised for electronic structure calculations to bosonic Hamiltonians, such as the ones encountered in vibrational simulations, will be presented (4). A straightforward formulation of vDMRG optimizes the energy of the ground state, i.e. the zero-point vibrational energy. In vibrational calculations, in contrast to the electronic case, ground state energies are of little interest compared to excitation energies. To lift this limitation, in this contribution several energy-specific variants of vDMRG based on shift-and-invert techniques will be presented (5). The coupling of the resulting algorithm with root-homing will also be discussed, to further increase the reliability of vDMRG in targeting excited states in regions with a high density of states.

VDMRG enables one to compute anharmonic vibrational transition energies. However, to obtain fullyanharmonic vibrational spectra, band intensities are required as well. The latter are related to transition properties, such as the transition dipole moment for infrared spectroscopy. In this contribution, a strategy for evaluating transition properties between two wavefunctions expressed as MPSs based on a stochastic sampling of the configuration interaction space will be presented (6).

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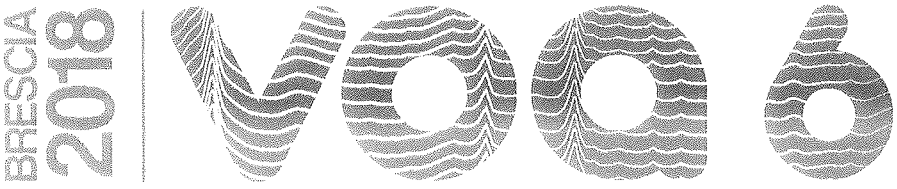
ORAL PRESENTATIONS



O IDN 4

EMERGENCE of RAMAN OPTICAL ACTIVITY SPECTROSCOPY AS A SENSITIVE TOOL FOR LANTHANIDE CIRCULARLY POLARIZED LUMINESCENCE

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Luminescent lanthanide complexes are widely used as biomolecular probes, owning to their uniqure electronic structure and sensitivity to their vicinity. For chiral species, circularly polarized luminescence (CPL) reveals even more information, and proved to be very useful in biophysics and analytical chemistry.[1,2] Recently, we have demonstrated that europium(III) CPL can be detected by the Raman optical activity (ROA) spectrometer, too.[3] Magnetic CPL can also be measured, combining the ROA instrument with a magnet.[4] Weak bands sometimes invisible in unpolarized measurement could be detected this way. Most of observed transitions were assigned to f-transitions of lanthanide(III) ions, with the support of the ligand-field theory. The ROA-CPL methodology offers a versatility useful for biospectroscopy; we explored CPL of simple Eu(III), Sm(III), and Er(III) salts induced in sialic acid solution (Figure 1),[5] and of the $[Eu(DPA)_3]^{3-}$ complex induced in various histidine-containing peptides (Figure 2).[6] Currently, imaging applications are explored.

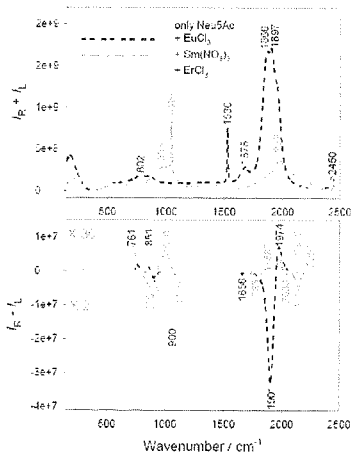

Fig. 1 ROA/CPL spectra of lanthanides with Neu5Ac.

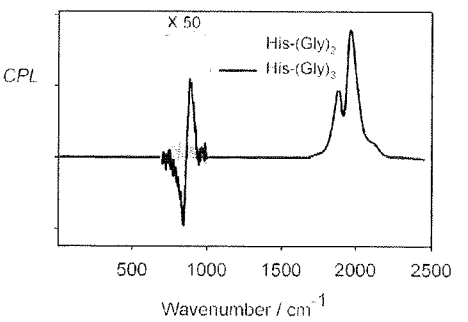

Fig.2 CPL spectra of $[Eu(DPA)_3]^{3-}$ with peptides

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O IDN 7

SUPRAMOLECULAR CHIRALITY AND ENHANCED VCD OF DNA QUADRUPLEXES

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Under specific conditions guanosine monophosphate (GMP) and guanine-rich oligonucleotides can form unique tetrameric structures with four coplanar guanine bases, known as G-quadruplex motif[1] (Figure 1a). They self-assemble into four-stranded helical structures, stabilized by monovalent cations (e.g., Na^+ or K^+) inside the channel (Figure 1b). At lower concentrations G-quadruplexes represent an isotropic solution. However, above certain concentration these structures can self-associate and form liquid crystalline phases (Figure 1c). The optical behaviour of these supramolecular systems is astounding. They exhibit abnormally high optical rotation, which can be most conveniently measured in the infrared region by vibrational circular dichroism (VCD) spectroscopy.

Another unusual four-stranded structure can be formed by DNA containing stretches of cytidine residues. These can self-assemble into parallel-stranded duplexes at acidic pH stabilized by hemiprotonated CH^+...C base pairs. The duplexes further intercalate with each other and form a four-stranded supramolecular complex called *i*-DNA[2] (Figure 2).

G-quadruplexes and *i*-DNA participate in various processes *in* vivo and are considered in medicinal applications. Controlled self-assembly of these structures on the nanometer scale was also exploited in different areas of nanotechnology and supramolecular chemistry, e.g. for nanowires, artificial ion channels, biosensors, pH-dependent nano-switches, etc.[1]

In the present work we used VCD spectroscopy in a combination with molecular dynamics (MD), transition dipole coupling (TDC) and quantum chemistry calculations to study isotropic and liquid crystalline phases formed by guanine octanucleotides $d(G)_8$ and *i*-DNA structure formed by cytosine dodecamers $d(C)_{12}$.

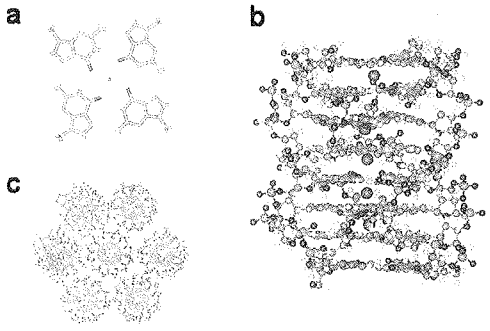

Figure 1. Guanine quadruplex: a) single guanine quartet; b) $d(G)_8$ quadruplex after 20 ns of MD simulation; c) hexagonal liquid crystalline phase of $d(G)_8$ quadruplexes after 5 ns of MD simulation

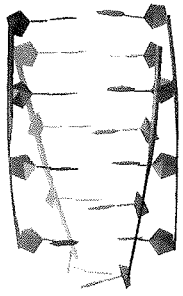

Figure 2. Schematic structure of i-DNA composed of four single-stranded $d(C)_4$ molecules at acidic pH[2]

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Acknowledgements
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O IDN 10

Probing molecular chirality, learning about solvation

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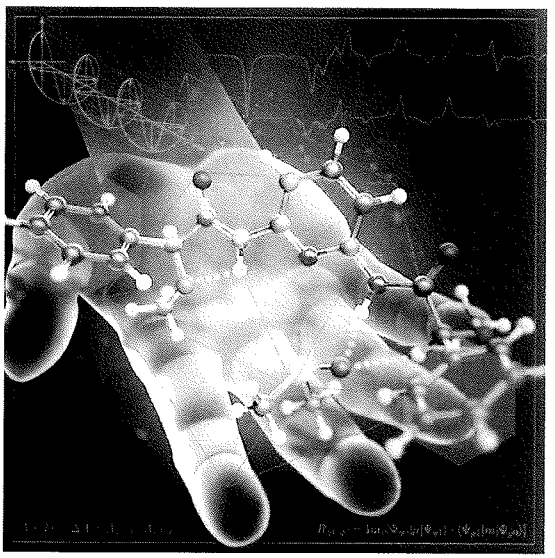
Vibrational Circular Dichroism (VCD) spectroscopy measures the small difference in the absorption of left- and right circular polarized infrared light by a chiral sample. It allows the unambiguous assignment of absolute configurations by comparison of experimental VCD spectra with computationally predicted spectra. Besides its unique sensitivity to chirality and absolute configurations, VCD spectroscopy is highly sensitive to even very subtle differences in structures, such as conformational changes induced by solute-solvent interactions.[1] In our work, we take advantage of this conformational sensitivity and use VCD spectroscopy to probe intermolecular interactions of interest in catalysis[2,3] and recognition processes as well as in inert rare gas matrices.[4,5]

In this contribution, I will give a brief introduction to the spectroscopic technique by showcasing a typical application of VCD spectroscopy for the determination of absolute configurations.[6] Afterwards, I will discuss some of our recent studies, in which we used the VCD spectroscopic signatures of chiral solutes to understand solvation effects. While in some cases the analysis of the VCD spectra gave insights into preferred solute-solvent structures,[7] the explicit consideration of solvation was found to be tremendously important in the assignment of absolute configurations.[8]



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O IDN 12

IR, VCD AND ECD SPECTRA, DFT SIMULATIONS, PLUS MD AND T-JUMP DYNAMICS FOR THREE-STRAND β-SHEET PEPTIDES. TURN AND AROMATIC EFFECTS AND ISOTOPICALLY EDITED SPECTRA AND DYNAMICS

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Peptide β-sheets have many forms (parallel vs. anti-parallel, degree of twist, varying register) and are subject to aggregation making the experimental molecular state difficult to model theoretically. Simple hairpin models (strand-turn-strand) can have monomer structures with cross-strand anti-parallel H-bonding characteristic of sheets, but each strand is solvated on one edge. The limited stability of hairpins in isolation can be partially overcome by stabilizing the turn with selected sequences (e.g. ^{D}Pro-Gly or Aib-Gly) or by incorporating hydrophobic cross-strand interactions between aromatic residues. Three-stranded b-sheet models, composed of coupled anti-parallel hairpins, have a central strand H-bonded to two others which leads to the possibility of complex folding mechanisms, depending on the relative importance of cross-strand interactions and turn stabilities. We have designed and prepared a series of related three-strand hairpins based on turn stabilization. These 23-residue peptides have two turns composed of either ^{D}Pro-Gly or Aib-Gly sequences and include or delete cross-strand aromatic coupling of a Trp and Tyr residue to impact the hairpin from two selected strands. ECD, fluorescence, IR and VCD thermal equilibrium spectroscopic studies are supported by determination of NMR-based structures and by theoretical modeling of both DFT vibrational spectra and MD dynamics. The latter are probed by IR-detected temperature-jump kinetics. All our designed compounds have β-sheet structure, but have differing stabilities and extents depending on the positions of aromatic residues. ECD gives evidence of cross-strand coupling of the aromatics, and the NMR structures show them to be partially stacked. Full DFT computations for an Ala-based structure with constrained ϕ,ψ angles obtained from the NMR structures yield IR and VCD simulations consistent with experimental data. The structures have sharply twisted three-strand sheets with better formed hairpins between the first two strands. Aromatic stabilization was effective for Trp-Tyr on strands 1-2, but more disorder resulted when on strands 2-3 and better formed sheets were obtained for peptide models without aroamtic interactions [1]. MD studies show bistable fluctuation in the ^{D}Pro-Gly turns from Type 1' to 2' with the 2-3 cross link being less stable. Aib-Gly turns sampled more conformational forms, presumably due to less torsional barrier. These differential behaviors were evident in selected IR-detected T-jump relaxation kinetics. Isotopic labeling allows site selected IR and VCD studies, as well as T-jump dynmics, and with Aib-Gly turns there is less interference from unlabeled ^{D}Pro-Gly amide absorbance bands [2]. Thermal equilibrium as well as T-jump relaxation studies are consistent with higher relative stabilities for cross-strand interaction between strands 1-2.

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O IDN 13

Enhanced VOA as a probe towards intermolecular interactions

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The phenomenon of enhanced vibrational circular dichroism (VCD) has been well documented since its discovery in 2002, but remains poorly understood. To our best knowledge, theoretical predictions, as reported recently (1), do not seem to fit the experimental results completely. In order to help understand this phenomenon, it was opted to perform an experimental comparative case study on the peptide KLVFF and its halogenated derivatives. It has been reported that different fibril architectures of these peptides could be obtained in a controlled manner, depending on the number, position and nature of the halogen atoms introduced into either on or both phenylalanine benzene rings of the amyloid β peptide-derived core-sequence KLVFF. (2) The study of these peptides with vibrational optical activity (VOA) suggests that the shape of the enhanced VCD signal does not seem to be linked to the morphological properties of the fibrils, but is linked to the directional properties of the intermolecular binding properties of the peptides. Moreover, enhanced Raman optical activity (ROA) out of resonance has been observed for the first time. We therefore believe that this set of experimental data will help develop the understanding of the enhanced phenomenon in VOA.

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O IDN 15

HISTIDINE COMPLEXES WITH METALS STUDIED BY MULTIPLE SPECTROSCOPIC METHODS

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Histidine may exist in four different charged forms, depending on pH.[1] It plays an important role in metallo-enzymatic reactions and peptide folding. The imidazole ring also facilitates metal binding to proteins.[2] By a combination of more experimental and computational approaches we studied properties of histidine and its complexes with zinc and nickel (*Figure*). Prefered conformations of free histidine in aqueous solutions were determined on the basis of Raman and ROA spectra. Many clusters with water molecules obtained from molecular dynamics simulations were averaged for a realistic theoretical model. Conformer probabilities obtained from the weighted histogram analysis method (WHAM) were compared to those obtained from a decomposition of the spectra.[3]

Estimating the effect of pH or metal binding on the conformation appeared more difficult. A 2:1 His:Zn^{2+} binding ratio was revealed by a factor analysis of Raman and ECD titration experiments on zinc-histidine complexes. Currently, simulated Raman and ROA spectra are compared with experiment to further explore the binding.

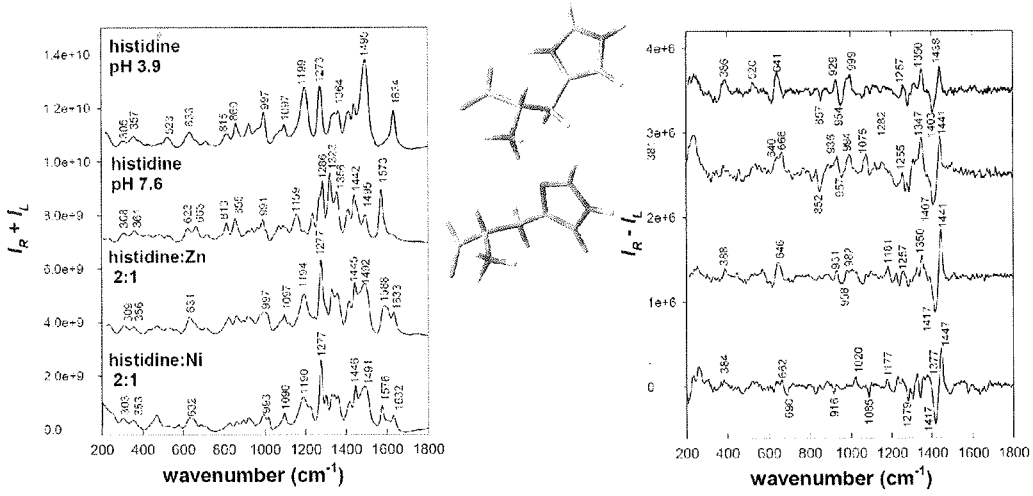

Figure: Experimental Raman and ROA spectra of histidine (pH 3.9 and 7.6), and its complexes with zinc and nickel. Geometries of a protonated and zwitterionic form of histidine.

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O IDN 17

ENHANCING CIRCULAR DICHROISM AT THE NANOSCALE

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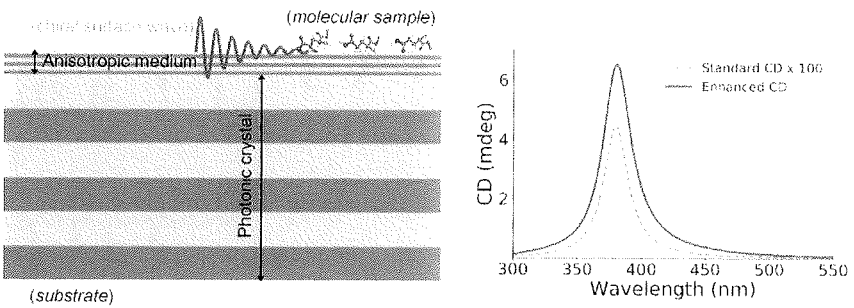
Circular dichroism (CD) spectroscopy is one of the most relevant tools for the discrimination of enantiomers and for the determination of their configuration and conformation. However, CD signals are extremely weak, making the analysis of small amounts of chiral analytes very challenging. Recently, novel 'superchiral' approaches have been proposed to enhance the CD signal by tailoring the properties of the electromagnetic field through the control of the associated optical chirality (1). In this framework, plasmonic chiral sensing holds exciting perspectives (2,3) but several challenges have also been discussed (4-6).

In this talk we first introduce a universal limitation to plasmonic superchirality, demonstrating that in the quasi-static limit the average optical chirality in the surrounding of a plasmonic nanostructure is analytically bound and the upper limit poses significant challenges in the visible spectral range (6). These findings also justify the recent proposals to move to dielectric materials for superchiral spectroscopies (5).

Along this line, we then introduce the novel concept of 'superchiral surface waves' originating from the coherent superposition of the TE and TM surface modes in a one-dimensional photonic crystal with an anisotropic metamaterial surface defect (7,8). The resulting platform provides superchiral fields over arbitrarily large areas and wide spectral ranges (down to the UV), with CD signal enhancements of more than 2 orders of magnitude. Moreover, the original spectral fingerprint associated with a specific CD resonance is reconstructed with high fidelity. These findings pave the way towards on-chip surface-enhanced chiral sensing, spectroscopy, and all-optical manipulation.



Left: a sketch of the photonic crystal supporting superchiral surface waves; right: the results of numerical simulations demonstrating a CD enhancement of two orders of magnitude with superchiral surface waves (7,8)

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O IDN 18

SEQUENTIAL INDUCTION OF CHIRALITY IN POLY(PHENYLACETYLENE)S

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Several hierarchical levels of chirality have been detected in functionalized poly(phenylacetylene)s (PPA).[1] In this work we have studied the chirality induction throughout these levels in PPA functionalized with phenylglycine methyl ester groups, Fig. 1.[2] These pendant groups force the PPA chain to lose its planar *all-transoid* shape to form helical structures. The chiral seed of the pendants, [(*R*)- or (*S*)-], dictates the preferent handedness of the helices, both the internal polyacetylene helical covalent backbone and the external helix formed by the side pendants which forms a complementary helix or counter-helix. In this work, we afford a full assessment of the interconnection between stereocenter and helix sources of chirality and the action of these polymers as chiral templates of other supra-molecular structures with inherited chiral properties. We then used VCD spectroscoy to demonstrate the chiral induction from the stereogenic centers to the backbone helix and from this to the pendant helix, which are largely promoted by two mechanisms: steric effects and hydrogen bonding. In addition, the VCD spectra supported that the helical setup of the pendants induces the solvent DMSO molecules to adopt a solvation helix around the polymer, thus proving how an achiral solvent becomes chirally organized owing to the template effect of the covalent polymer helices. A similar effect was observed in DMSO solutions of the monomeric units. Interestingly, this resulted in opposite helical sense to the one observed in the polymer with identical enantiomeric form.

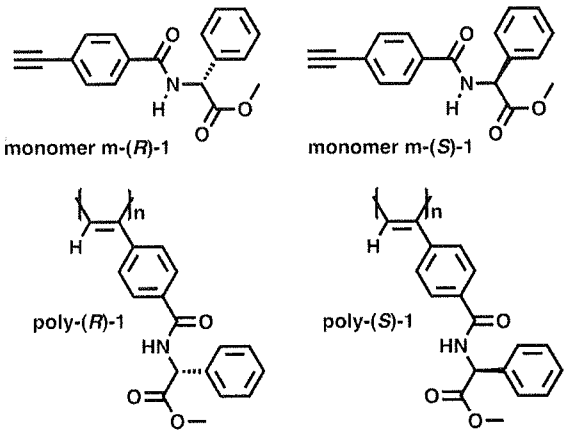

Figure 1. Chemical structures of poly-(R)-1 and poly-(S)-1 and their constituent monomers.

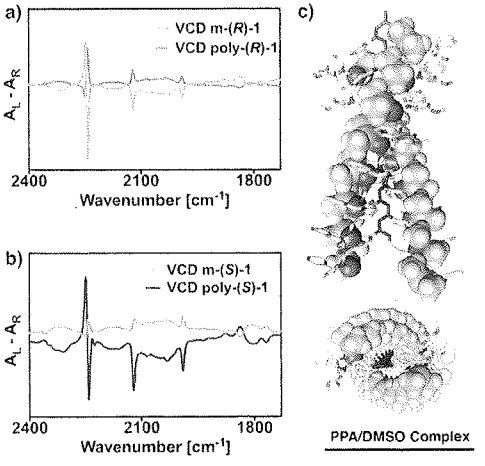

Figure 2. a) VCD spectra of m-(R)-1 and poly-(R)-1 (b) VCD spectra of m-(S)-1 and poly-(S)-1 recorded as solutions in DMSO-d6. b) 3D model (c) of the helical arrangement of the DMSO molecules around a phenylglycine-PPA polymer.

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O IDN 25

A Spectroscopic Ruler for Measuring Active Site Distortions based on Raman Optical Activity of a Hydrogen Out-of-Plane Vibration

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Many biological cofactors, including light-absorbing chromophores in photoreceptors, are modulated upon insertion into a protein binding pocket by both electrostatic and steric interactions. The electrostatic component of these effects, including hydrogen bonding and charge-charge interactions, has been studied in some detail. The steric contribution can cause structural distortions in the cofactor, and such effects have been considered to be crucial for biological function, but are less well understood. Proposed functional roles for cofactor distortions include the out-of-plane distortion of chromophores as a key factor in controlling their absorption spectra. Furthermore, photoexcitation of these proteins produces primary high-energy intermediates with structurally perturbed chromophores, which drive subsequent protein conformational changes. Such structural distortions have proven difficult to measure experimentally.

Recent progress in Raman optical activity (ROA) spectroscopy has revealed this technique as a promising avenue to derive structural details on the distortion of a chromophore within a protein environment (1-5). A protein environment can distort an achiral chromophore into a chiral conformation, and ROA spectroscopy provides an approach to derive detailed structural information of the chromophore in the protein under physiological solution condition. This method can be extended to a structural study of short-lived intermediate (5). These studies suggested that the hydrogen out-of-plane (HOOP) mode is especially sensitive to the distortion of the chromophore. We recently reported that pre-resonance conditions are ideal for measuring structurally informative ROA spectra, since chromphore signals are substantially enhanced without the disruption of the ROA effect that occurs under full resonance conditions (4). Here we aim to further develop the use of pre-resonance ROA spectroscopy in determining chromophore distortions in photoactive yellow protein (PYP).

PYP from the phototrophic bacterium *Halorhodospira halophila* is a small water-soluble photoreceptor protein and contains p-coumaric acid (*p*CA) as a chromophore. PYP has been an attractive model for studying the physical chemistry of protein active sites. Here we explore how ROA can be used to extract quantitative information on distortions of the *p*CA chromophore at the active site in PYP. We use ^{13}C8-*p*CA to assign an intense signal at 826 cm^{-1} in the ROA spectrum of PYP to a hydrogen out-of-plane vibration of the ethylenic moiety of the chromophore. Quantum chemical calculations based on density functional theory demonstrate that the sign of this ROA band reports the direction of the distortion in the dihedral angle about the ethylenic C=C bond, while its amplitude is proportional to the dihedral angle. These results document the ability of ROA to quantify structural deformations of a cofactor molecule embedded in a protein moiety.

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O IDN 27

Absolute configuration assignment of caffeic acid ester derivatives by VCD: the pitfalls of deuteration

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Recently, it was observed that infrared (IR) and vibrational circular dichroism (VCD) calculations including deuterated hydroxyl groups in phenolic and saccharide moieties improved significantly the agreement with experimental data obtained in methanol-d_4.[1] In the present study,[2] the relative and absolute configurations of three methanol-soluble caffeic acid ester derivatives, isolated from *Tithonia diversifolia*, were established by a combined use of experimental and calculated ^{13}C NMR chemical shifts, as well as electronic circular dichroism (ECD) and VCD spectroscopies. Interestingly, the attempt to reproduce the deuteration pattern arising from possible isotopic exchange in methanol-d_4 solution led to nearly mirror image calculated VCD spectra for **1** when compared to the non-deuterated molecule with the same absolute configuration (Figure 1). This latter fact can potentially lead to absolute configuration misassignments. A closer inspection of the vibrational chiroptical properties of **1** revealed that the deuteration status of the tertiary hydroxyl group at C-2 is critical for the correct reproduction of experimental VCD data in protic solvents. Therefore, in the case of stereochemical analysis of polar chiral natural product molecules, a combination of VCD and ECD is recommended.

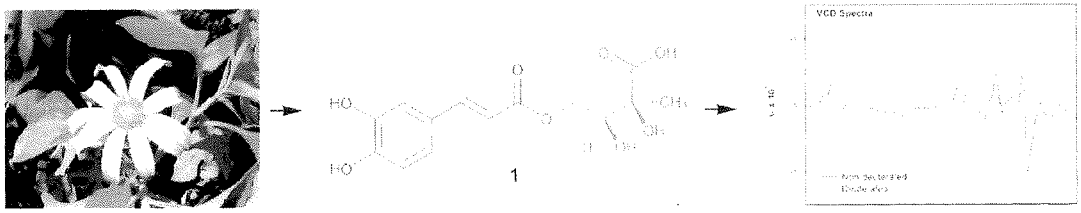

*Figure 1. Calculated VCD spectra for the caffeic acid ester derivative **1** isolated from Tithonia diversifolia*

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O IDN 29

Exploring resonance ROA of bioactive chromophores: ligand binding to a highly ruffled haem moiety.

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Classified as a globin coupled sensor ancestor, Protoglobin from *Metanosarcina acetivorans* (MaPgb) is a haem containing protein, playing a yet undisclosed role in the CO metabolism of archaea and showing surprising structural features[1]. The native conformation of the porphyrin of MaPgb, which is predicted to be unusually ruffled compared to that one of other globins1, was investigated via resonance Raman and ROA analysis, in solution. This contribution focuses on the structural characterization of the ligand-free haem moiety of MaPgb and its complexes with small molecules, using a combination of chiroptical methods.

Because of the sensitivity of Raman spectroscopy to the porphyrin distortions[2], this technique is extremely suitable for the investigation of transition between different bioactive conformations of such a chromophore[3]. The laser excitation of 532 nm, in resonance with the s_0-s_1 electronic transition of the sample[4], and the low concentration of the globin used for the measurements (around 2 mg/mL), allows a direct probe of the haem group acquiring spectra which are free from any other contribution from the protein backbone. The resonance Raman optical activity (ROA) spectra of the free MaPgb and those of the globin in complex with small haem-ligands have been investigated, in order to assess whether the pattern of the porphyrin marker bands of the treated sample could be correlated to conformational changes at the active chromophore upon ligand binding. This study was combined with visible absorption spectroscopy and electronic circular dichroism.

The titration of MaPgb with azide ion, imidazole, and nicotinamide revealed an enhancement of the Soret ellipticity and a reshaping of the Q bands. At the same time the resonance ROA spectra of the complexes reported not only a rearrangement of the marker bands pattern, but also a selective enhancement of certain vibrational modes upon treatment with ligands in a concentration depending manner.

Looking forward for theoretical models to be available, in order to better interpret the experimental data, this work is proposed as a contribution to the state of the art[5,6,7] concerning the investigation of bioactive chromophores via resonance ROA.

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O IDN 33

Combinated Vibrational Circular Dichroism and Circularly Polarized Luminescence Studies of Protein Folding

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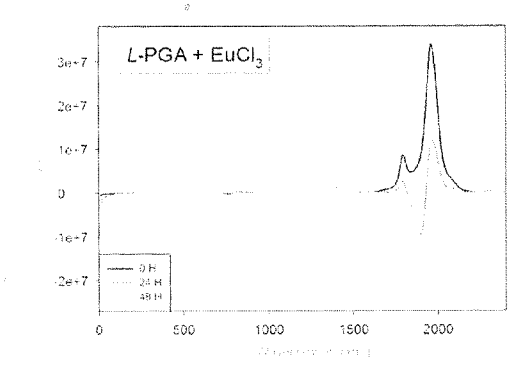
Fibrous protein aggregates, β-amyloids, are implicated in a variety of neurodegenerative disorders, such as Alzheimer, Parkinson or Huntington disease. Understanding of protein folding and misfolding is thus important for better diagnostics and treatment of these disorders. Many traditional techniques for protein structure determination, such as X-ray or NMR, are often not suitable for examination of these systems. Their limited solubility and large molecular size represent additional difficulties.

In this context, we explore usage of a Raman optical activity spectrometer to measure circularly polarized luminescence (CPL) of lanthanide luminescent probes mixed with the protein aggregates formed by polyglutamic acid (PGA) and hen egg-white lysozyme (HEWL). The CPL spectra of $EuCl_3$ and $Na_3[Eu(DPA)_3]$ seem to be very sensitive to protein structure (Fig. A). The data can be correlated to vibrational circular dichroism (VCD), in particular to the typical enhancement of VCD intensity in the Amide I region. For HEWL, VCD appeared more useful in discrimination of different polymorphic fibril forms (Fig. B).

(A)



(B)

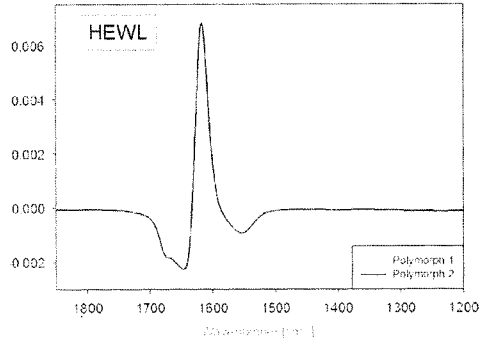


Fig. A. *CPL of EuCl3 coupled to L-PGA in different stages of fibrillation (black – non-fibrillated; dark grey – partially fibrillated; light grey – mature fibrils)*
Fig. B. *VCD spectra of two polymorphs of amyloid fibrils formed by HEWL.*

O IDN 38

Exploring the combination and overtone vibrations by Raman optical activity

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Raman scattering and Raman optical activity (ROA) provide precious information on molecular structure and conformational dynamics of chiral molecules in solution. Usually, spectra within ~200-1700 cm^{-1} are interpreted based on simulations using the harmonic approximation. As measurement of higher-wavenumber bands becomes possible, we focused on this region where anharmonic effects are much larger (1). The second-order vibrational perturbational theory (VPT2) (2) and a limited vibrational configuration interaction (LVCI) (3) were used to understand the signals of fundamental, overtone and combination modes.

Spectral intensities of the overtone and combination modes are rather weak, nevertheless their ROA could be measured for several small molecules, and the reliability verified by a comparison of the enantiomers (e.g., Figure 1). First results also suggest that the simulations are usable for the spectral interpretations, although the accuracy is lower than for the fundamental modes.

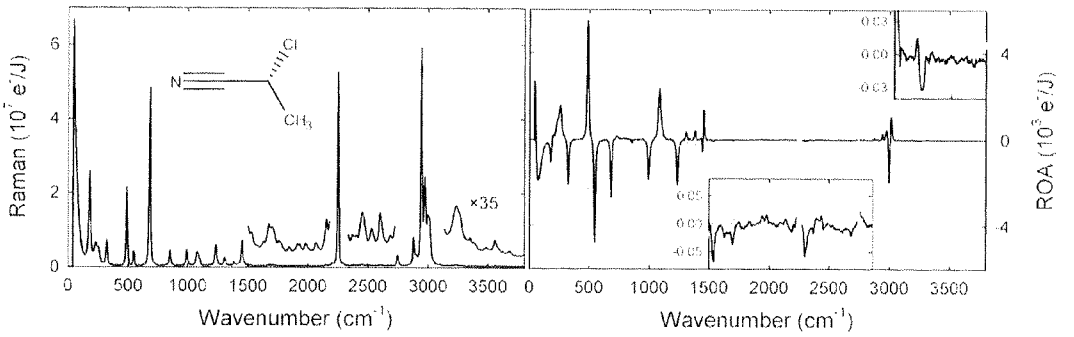

Figure 1: Experimental Raman and ROA spectra of 2-chloropropionitrile enantiomers; regions of overtone and combination modes are enlarged.

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O IDN 39

Astaxanthin aggregates studied by molecular dynamics and electronic circular dichroism spectroscopy

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Astaxanthin (3,3'-dihydroxy-ß-carotene-4,4'-dione, AXT) is a red xanthophyll pigment used as a dietary supplement and animal feed additive. Such xanthophylls possess high antioxidant activity due to the presence of long polyene chain that captures reactive radical species. In some conditions (e.g. water-organic media) carotenoids aggregate into chiral, e.g., helical supramolecular structures. Unlike monomers, they generate a strong electronic circular dichroism (ECD) intensity of the main electronic absorption band. If the band position is close to the ROA laser line (532 nm), the AIRROA effect (Aggregation-Induced Resonance ROA) can be observed.[2] AIROA is thus sensitive to the carotenoid arrangement; tight "card-pack" H-aggregates exhibiting a blue-shift if compared to the monomer, whereas loose "head-to-tail" J-aggregates are characterized by a red-shift of the absorption band.[1]

To understand the observation, we performed molecular dynamics (MD) simulations of (3*S*,3'*S*)-AXT dimers and decamers in mixed solvents (acetone/water, in 1:9 and 3:7 ratios) and subsequent quantum chemical calculations of ECD spectra for MD snapshots. Indeed, the calculated spectra of AXT aggregates in the 1:9 and 3:7 solutions reproduced some experimental trends observed for the H and J-aggregates. For both the 1:9 and 3:7 systems a dimer MD model provided a positive ECD couplet of the main absorption band consistent with the experimental results.[2,3]

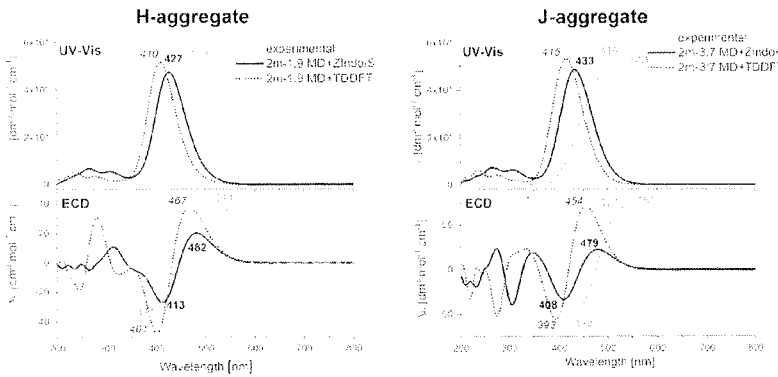

Figure.1 Theoretical and experimental absorption and ECD spectra of the H and J (3S.3'S)-AXT aggregates.

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Acknowledgement
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O IDN 41

VISUAL EXPLORATION OF THE VIBRATIONAL CHIROPTICAL PROPERTIES

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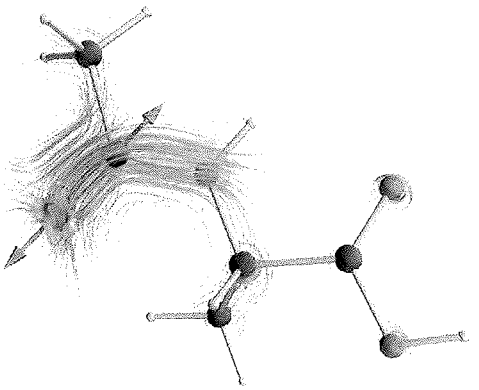
Characterization of chiral compounds is a central issue in several fields, such as catalysis, materials and life science. Over the last years, vibrational analysis supported by Density Functional Theory (DFT) calculations have had considerable successes in assigning the absolute configuration (AC) and evaluating the conformational properties of many molecular systems, organometallics included.(1,2) In this contribution, we will show some strategies to achieve accurate simulations of IR and vibrational circular dichroism (VCD) spectra beyond the harmonic approximation.(3) For large systems like transition metal complexes, a convenient approach is to reduce the dimension of the system to a set of normal modes directly related to the region of interest of the spectrum.(4) In fact, a careful definition of the reduced dimensionality (RD) scheme can lead to very good results in the reproduction of target features of the spectrum, at a fraction of the computational cost of the full calculations. Moreover, vibrational transition current density (VTCD)(5) maps allow an evaluation of the electron flow associated to the molecular vibration. A proper graphical representation can significantly help the pattern recognition process, highlighting the portions of the molecule more electronically involved in the transition. This can give insights on the nature of the chiroptical properties and on the origin of the band-shape, information that are generally lost when only numerical values are considered. All these aspects will be addressed in this contribution through the presentation of user-friendly dedicated tools aimed at analyzing and interpreting the different features in the spectra.(6,7)



Vibrational Transition Current Density of 4th normal mode of AcAla

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O IDN 42

ISOTOPICALLY ENGENDERED CHIRALITY FROM ENZYMATIC NAPHTHOYL-RING REDUCTION STUDIED BY VIBRATIONAL CIRCULAR DICHROISM

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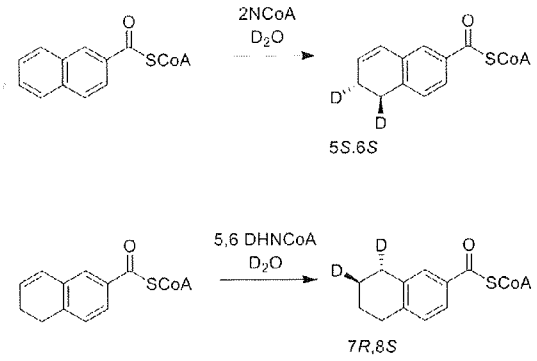
The reduction of aromatic hydrocarbons (e. g. Birch reductions) depends on alkali metals, ammonia, and cryogenic reactions conditions and has generally low selectivity.[1] In contrast, reductions of aromatic ring systems catalyzed by arylcarboxyl-coenzyme A (CoA) reductases follow a highly defined reaction path.[2] To study such mechanisms it is useful to elucidate the stereoselectivity of the enzymatic reaction;however, if the product is not chiral such an analysiscan be challenging.

We performed conversions of naphthoyl-CoA catalyzed by the microbial enzymes 2-naphthoyl-CoA (2-NCoA) reductase and 5,6-dihydro-2-NCoAreductase (5,6-DHNCoA) in D_2O. In the course of the enzymatic reduction deuterium atoms from the solvent are added to the ring system, which leads to dihydro -and tetrahydronaphthoyl-CoA products with isotopically engendered chirality (Scheme 1). We used vibrational circular dichroism (VCD) spectroscopy and quantum chemical calculations for the determination of the absolute configuration of (5*S*,6*S*)-5,6-dihydronaphthalene-2-carboxylic-5,6-d_2 acid and (7*S*,8*S*)-5,6,7,8-tetrahydronaphthalene-2-carboxylic-7,8-d_2 acid (Figure 1). The molar difference absorptivity ($\Delta\varepsilon$) of the observed and the calculated spectra was comparable, which indicates a large enantiomeric excess and demonstrates the high enantioselectivity of both enzymatic reactions. Our results are consistent with a two-electron reduction mechanismwith a Meisenheimer complex-analogous intermediate for the 2-NCoA-catalyzed reduction and an unprecedented cationic transition state for the 5,6-DHNCoA-catalyzed reduction.



Scheme 1. Generation of isotopically engendered tetrahydronaphthoyl-CoA through enzymatic reductions.

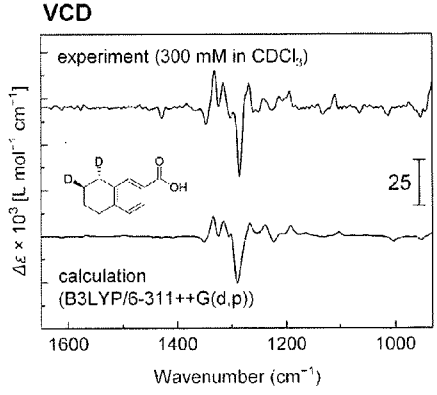


Figure 1. VCD-assignment of the absolute configuration of 5,6,7,8-tetrahydronaphthalene-2-carboxylic-7,8-d2acid.

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O IDN 44

DrawMol and DrawSpectrum: new programs to visualize and interpret (optically active) vibrational spectra

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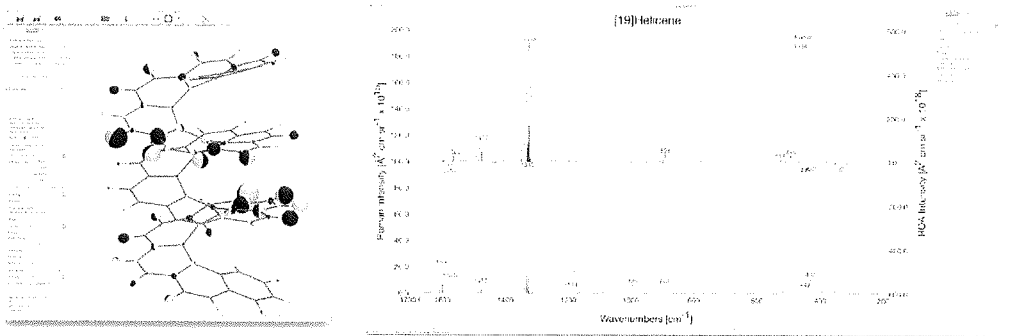
Vibrational spectroscopies are powerful tools to study the structures of molecules, polymers, self-assembled monolayers, interfaces, ... Indeed, each normal mode of vibration provides information about their structure: the composition, the configuration, the conformation, or the supramolecular arrangement. Last but not least, there exists a broad range of vibrational spectroscopies: Infrared (IR), Raman, Vibrational Circular Dichroism (VCD), Raman Optical Activity (ROA), Hyper-Raman, Resonant Raman (RR), Sum Frequency Generation (SFG), which all provide specific signatures.

In many cases, there is no simple relationship between the structure and the pattern observed on the experimental spectra or, for many new techniques like ROA, simple rules of thumb still need to be worked out. This is where theoretical chemistry can help by unraveling the different signatures and by relating these to the specific structure. That's why I have recently developed a suite of two new programs called DrawMol (www.unamur.be/drawmol) and DrawSpectrum (www.unamur.be/drawspectrum) that are available on sale on the Mac App Store since November 2016. DrawMol is a full-featured program to build molecular structures from scratch (and to generate the input files for Gamess-US and Gaussian quantum chemistry packages) as well as to visualize molecular properties. In addition to the visualization of the structures, the molecular orbitals and the dipole moments that are commonly found in other programs, DrawMol also represents the polarizability and hyper-polarizability using the unit sphere representation, the vibrational normal modes together with the IR vectors, the NMR chemical shifts, and the magnetically induced current density. The decomposition scheme [1] introduced by Hug that divides the intensity into group coupling matrices (GCMs) or atomic contribution patterns (ACPs) and the interface to analyze the coupling between normal modes of two similar molecules [2, 3] has also been implemented into DrawMol. DrawSpectrum is a program that plots IR, Raman, VCD, ROA, UV, ECD as well as SFG spectra from molecular properties calculated in a quantrum chemistry package. Experimental data can be plotted as well.

In this contribution, I will present some of these and I will demonstrate that more insight on the ROA signatures can be gained from using them.



DrawMol showing the vibrational normal mode at 1383 cm^{-1}(left) and DrawSpectrum showing the Raman

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O IDN 45

EXPLICIT SOLVATION OF CARBOXYLIC ACIDS FOR VCD STUDIES: LIMITING THE COMPUTATIONAL EFFORTS WITHOUT LOOSING ACCURACY

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The formation of hydrogen bonds in solution is a well-known and important factor in various chemical processes. IR and VCD spectroscopy are excellent tools to observe hydrogen bonding as vibrational transitions are very sensitive to even small conformational changes.[1] This was already shown for single molecules in solute-solvent interactions like small dipeptides, where strong hydrogen bonds can significantly alter the IR and VCD spectral signatures.[2]

To deepen our understanding of these interactions on a molecular level and further develop general rules for taking hydrogen bonds into account during simulations, several solute-solvent systems where investigated.[3] Spectra of three different carboxylic acids (α-methoxyphenyl-acetic acid (MPAA), 2-phenylpropionic (PPA) acid and 3-phenylbutyric acid (PBA)) in four different solvents of different polarity (chloroform, acetonitrile, dimethylsulfoxide and methanol) where simulated and recorded. This also offered the opportunity to examine other properties, like distance dependence and acid strength.

In the typical concentration range employed for VCD studies, all investigated carboxylic acids were found to prefer the formation of dimers in chloroform. In other investigated solvents, hydrogen bonded solute-solvent clusters have to be considered explicitly for the spectral analysis, with solvent polarity playing an important role on the magnitude of spectral changes. In this contribution, the origin of the solvent-dependence of the VCD spectra of the different carboxylic acids is discussed, along with the correlation of spectral response with hydrogen bonding strength, acid strength and the effect of distance dependence between the hydrogen bond and the stereogenic center.

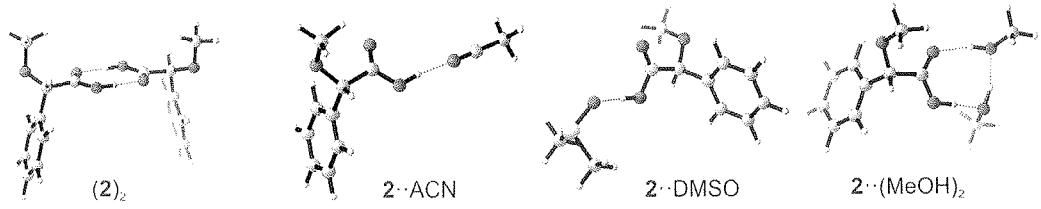

Fig. 1. MPAA as dimer in chloroform (left) and with interacting solvent molecules: acetonitrile, DMSO and methanol (from second left to right).

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O IDN 46

Molecular specificity in resonance ROA – B_{12} vitamin case

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Many of key physiological processes and biological molecules are chiral and Raman Optical Activity (ROA) appears an exceptionally suitable tool to study them. The main problem in such studies in real systems is the fact that ROA is hampered by low sensitivity. The way to circumvent this issue is exploiting resonance enhancement. A few examples demonstrating resonance signal enhancement were presented before, for example by Bouř and co-workers.[1] We have recently shown that aggregation-induced resonance ROA (AIRROA) for carotenoids can be obtained in mixed (water: organic solvent) solutions at the concentration as low as 510^{-6} mol dm^{-3}.[2]

Nevertheless, although resonance enhancement enables working in conditions closer to physiological (relatively low concentrations), a new issue has been raised, i.e. suggested lack of molecular specificity of RROA. As the single electronic state theory of RROA shows[3], RROA spectra obtained via excitation of a single electronic state are monosignate and closely resemble resonance Raman (RR) spectra. In this way the richness of information provided by classical bisignate ROA is lost and no additional advantage of RROA versus RR is obtained besides recognition of optical isomers.

In our new study, based on resonantly enhanced RROA spectra of various B_{12} vitamin derivatives, we clearly demonstrate increased molecular specificity of RROA compared to RR. Our data show that not only information provided by RR and RROA differ (differences between respective RR and RROA spectra), but only RROA (and not RR) enables distinguishing between B12 derivatives with various substituents, partially due to the fact that obtained RROA spectra are bisignated. In general non-resonant ROA yields enriched information compared to RS and, due to its increased sensitivity relatively to ROA, challenges ECD as a chiroptical method of studying the molecular structure in detail.

In general, ROA is a more informative method compared to Raman spectroscopy. Our results show that also RROA may yield enriched information compared to RR and, due to increased sensitivity of RROA relatively to ROA, it may challenge ECD as a chiroptical method of studying the molecular structure in detail.

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O IDN 47

Spectrometer for measurement of Raman optical activity in the extended spectral range

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Raman optical activity (ROA) is most often recorded in the spectral range of 200-2400 cm^{-1}, with only few exceptions (1,2). ROA in the low and high wavenumber areas is difficult to measure due to the intense Raman signal, its strong polarization and resulting high susceptibility to artifacts, both for solute and solvent, including water. Measurement is also hampered by the fact that the spectrograph has a lower sensitivity in the peripheral areas of the spectrum, due to lower efficiency of diffraction grating and vignetting of optics.

We tried to solve the above mentioned problems by designing a spectrometer capable of recording ROA spectra in the range of 80-3800 cm^{-1} without loss of spectral resolution.

Depolarized bands from intermolecular interactions and delocalized normal modes dominate in the low wavenumber range below 200 cm^{-1}. Their interpretation and assignment is difficult, but we think they carry useful information about the conformational properties of studied molecular systems.

Hydrogen stretching vibrations are the main source of Raman scattering in the high wavenumer range above 2800 cm^{-1}. ROA signal of these vibrations is very weak, the circular intensity difference (CID) is often below 10^{-5}. However, we believe that measured data are important for tests of *ab initio* simulations outside the harmonic approximation. In addition, Raman signal from water stretching vibrations is very useful indicator for monitoring of the sample temperature, especially in the relatively long measurements required for ROA.

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O IDN 48

A Partial Spectrum Approach in Infrared Absorption and Vibrational Circular Dichroism

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Obtaining theoretical IR and VCD spectra requires computing electric/magnetic tensors in addition to the computationally expensive construction of the force constant matrix. Even Density Functional Theory (DFT) calculations may be overwhelming if one is interested in large and flexible systems. We will present an alternative approach in which only a selected region of the spectra is considered at a higher level of theory, while the 'basis' spectra are first calculated at a much faster level. This significantly reduces the overall computational cost of such calculations if only small ranges of the spectra are needed.

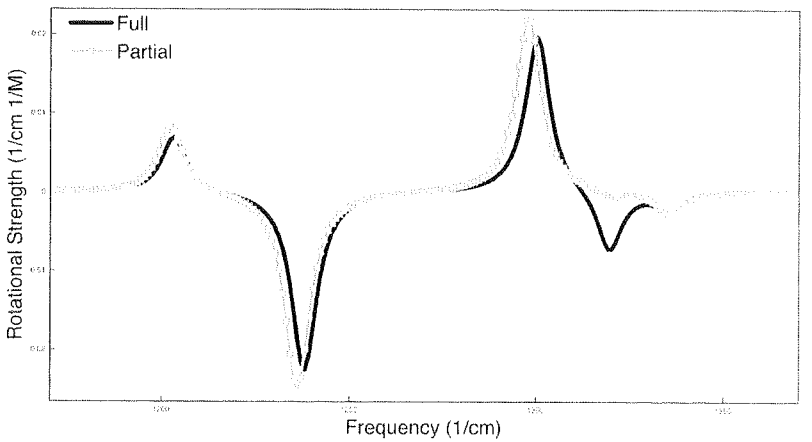

Figure 1 – VCD spectra of alanine as obtained in a full DFT calculation and in the partial spectra approach

O IDN 51

An efficient technique to calculate vibrational circular dichroism spectrum

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The vibrational circular dichroism (VCD) spectroscopy is a highly useful technique for predicting the three-dimensional structure of molecules. Based on the VCD spectrum, the absolute configuration of chiral molecules can be identified (1). The theoretical calculation of VCD spectrum is advantageous in the understanding of experimental observations since it can easily indicate the intensity-peak of the spectrum with the corresponding stretching of the bonds. The calculations of the atomic axial tensor (AAT) and the atomic polar tensor (APT) are required to obtain VCD spectra (2). In general, the ab-initio calculation of APT and AAT tensor is computationally expensive since it needs to solve response equations for all the nuclear displacements. Recently, Coriani et al. (3) have derived an alternative method to compute the AAT and APT tensor where the nuclear displacements response calculations are avoided. The alternative approach is an efficient approach to simulate a VCD spectrum when a computationally low-cost Hessian result is available. Our current objective is to implement the alternative formulation of the AAT and APT in the Amsterdam Density Functional (ADF) software. In ADF, the low-cost Hessian methods, for example, density functional tight binding (DFTB) Hessian, are available [4]. By combining the alternative method for the atomic tensors and a low-cost Hessian for normal modes, a high speed-up in the total calculation of VCD spectrum can be achieved.

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O IDN 56

BIOFLUID ANALYSIS – A CHALLENGE TO CHIROPTICAL SPECTROSCOPY

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Although many of essential biomolecules exhibit chirality, which makes them ideal candidates for chiroptical analysis (1), the studies of biomolecules in their natural biofluid environment have been very limited. The complexity of biofluids along with low concentrations of clinically relevant moieties represent the major drawbacks, which negatively influence the execution and outcome of any experiment involving chiroptical techniques (2). To address the aforementioned issues, we developed measurement procedures for a smooth analysis of two most commonly utilized biofluids, blood plasma and urine, by methods of vibrational and electronic optical activity (3,4). A combination of ultrafiltration, fluorescence quenchers (sodium iodide, activated charcoal) and photobleaching was successfully used to minimize the extremely high background fluorescence of blood plasma during the simultaneous Raman and Raman optical activity (ROA) measurements using the 532-nm excitation. This procedure also contributed to 50% lower time requirements per analysis and a significant improvement of the signal-to-noise ratio within the resulting spectra (by an average factor of 3.3). A four-fold dilution of blood plasma with sterile phosphate buffer mimicking the natural biological conditions allowed for the electronic circular dichroism (ECD) analysis in the deeper ultraviolet region, thereby facilitating the detection of all bands within the protein-like spectral pattern. To avoid the strong absorption of water generally limiting the experiments with vibrational circular dichroism (VCD), a 6-μm path length was used enabling us to observe bands related to protein secondary structure within the amide I and amide II spectral regions. In addition, chiroptical spectroscopy proved its inherent sensitivity to molecular structure (1) during the ECD analysis of urine, in which we were able to detect even slight, yet diagnostically significant urinary protein levels. Within all acquired spectra, we observed several bands that are specific for essential plasmatic biomolecules, especially proteins accompanied by lipids, amino acids, glycoproteins or nucleic acids. In fact, within our pilot studies, we were also able to detect differences in the plasmatic and urinary spectral profile of healthy and diseased individuals. Therefore, we believe that chiroptical spectroscopy is a powerful tool for the monitoring of changes within biomolecule structure and properties upon various physiological and pathological conditions.

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O IDN 58

Resonance-Induced Enhancement of Solvent Vibrational Raman Optical Activity

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The enhancement/induction of solvent Raman Optical Activity is sometimes observed for solutes strongly absorbing the excitation radiation (1). The solute molecule probably enhances the signal similarly as a colloid particle during surface-enhanced Raman scattering. This phenomenon can be potentially used for applications in analytical chemistry, structural studies and chemical imaging of biomolecular systems.

The theory of resonance phenomena is very complex and available computational tools do not allow for quantitative predictions. Currently, we used the transition polarizability model (TPM) method for basic understanding of the spectra. The method is based on the matrix-perturbation formalism which was previously applied for SERS, SEROA and induced circularly polarized luminescence (2, 3).

We applied this method on the Nickel complex (fig. 1) solvated by various solvents (chloroform, methanol, etc.). The results provide a qualitative insight to the solute-solvent interactions and induction of vibrational optical activity.

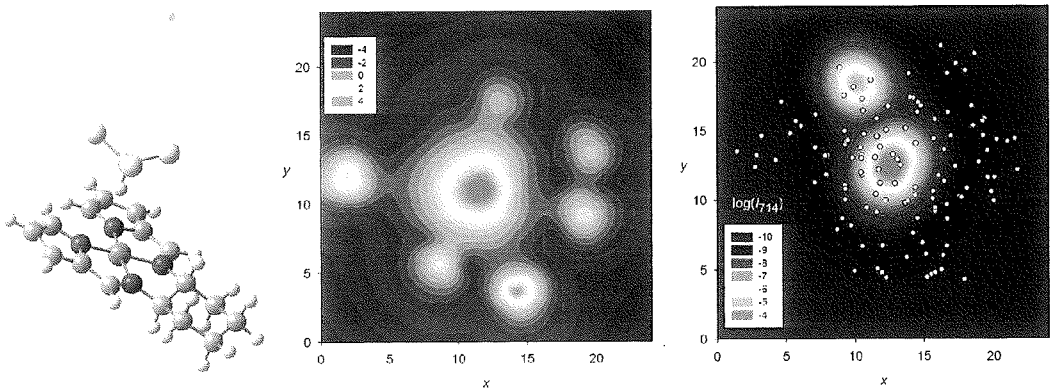

Figure 1: The Nickel complex interacting with chloroform (left) and atoms in and Ni complex/chloroform cluster (yellow circles) and intensity of the enhanced electric field in a cross-section plane calculated by TPM, for the excitation ω_0 = 532 nm (middle) and a chloroform-scattered frequency ω_i = 741 cm^{-1} (left).

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O IDN 59

Is it Possible to Enhance Vibrational Circular Dichroism Signals with Tailor-Made Gold Nano-Antennas?

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At frequenciesneartheir electronic resonances,metalnanostructures can amplifythe incident electric field 'seen'by nearby molecules by orders of magnitude, and dramatically enhance signals and increase the sensitivity of spectroscopic measurements.Unfortunately, however, the local field direction is often ill-definedand difficult to reproduce, which can be very problematic for polarization-sensitive chiral spectroscopies like circular dichroism (CD) or Raman optical activity (ROA).In order to better control the local fieldswe have used e-beam lithography to deposit multiple patches of exactly parallel, but randomly distributed (to avoid electronic coupling effects) gold nano-antennas on CaF_2 substrates.[1] The antennas were 200 nm wide and 100 nm thick, and their length varied around 2500 nm, resulting inresonances in the vibrational fingerprint region.The substrates were subsequently spin-coated with binaphthol solution.

A femtosecond laser-based polarization-division spectrometer[2] allowed us to tightly focus the mid-IR light and sample multiple spots inside and outside theantenna regions (for background measurements). Thanks to our single-shot detection, itwas also possible to precisely align the antennas parallel to the polarization of (the more intense) arm of the interferometer. This turned out to be crucial for eliminating the effect of the enormous linear dichroism of the antennas. Indeed, measuring VCD with a commercial spectrometer and a rotating sample (anespecially large 5x5 mm antenna patch) yielded only a large artefact, identical for both binaphthol enantiomers (Fig.1, left).It is very similar tothe absorption spectrum, showing the broad contribution from the antenna with dips due to the vibrational bands of the molecules. The polarization division interferometer, on the other hand, gave rise to a relativelyflat baseline (Fig. 1, right). Unfortunately, however, signals due to molecular vibrations were only recorded for a few samples, and must probably be attributed to the linear birefringence of binaphthol crystals that had started to form on the substrates[3,4].

(V)CD signals depend only linearly on the local electric field, which makes themmuch less sensitive to electric field enhancement thanabsorption ($\sim E^2$), Raman ($\sim E^4$), or other higher order spectroscopies. Even with our tailor-made antennas, the field enhancement was not larger than 10. This resulted in a sizable absorption of the spin-coated substrates (x100), but could not compensate for the low concentration of molecules in the vicinity of the gold nanostructures.

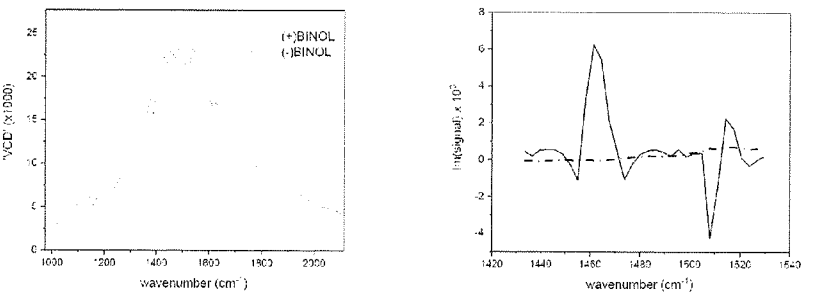

Fig. 1: Left: VCD artefact recorded with a rotating sample in a commercial spectrometer. Right: well-aligned sample in the femtosecond polarization division spectrometer(dashed) and signal probably due to crystal formation(solid).

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O IDN 60

VOA of Aqueous Solutions: Hydrogen Bonding vs. Conformational Flexibility

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We present a computational methodology based on a polarizable Quantum Mechanical (QM)/Molecular Mechanics (MM) (1) approach based on Fluctuating Charges (FQ) (2-4) coupled to classical Molecular Dynamics (MD) to accurately compute Vibrational Optical Activity (VOA) spectra of chiral systems in aqueous solution. This approach is applied to the calculation of Infrared (IR), Vibrational Circular Dichroism (VCD), Raman and Raman Optical Activity (ROA) spectra of (L)-methyl lactate and (S)-glycidol (5-7). Remarkable agreement between calculations and experiments is reported, showing the reliability and accuracy of the methodology, especially with respect to standard continuum solvation approaches.

Such discrepancies are not only due to the inaccurate description of Hydrogen-Bonding interactions in the continuum approach, but also to a different sampling of the Potential Energy Surface resulting from the static continuum or dynamic QM/FQ + MD approaches.

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O IDN 64

Resonance Raman optical activity of human serum transferrin

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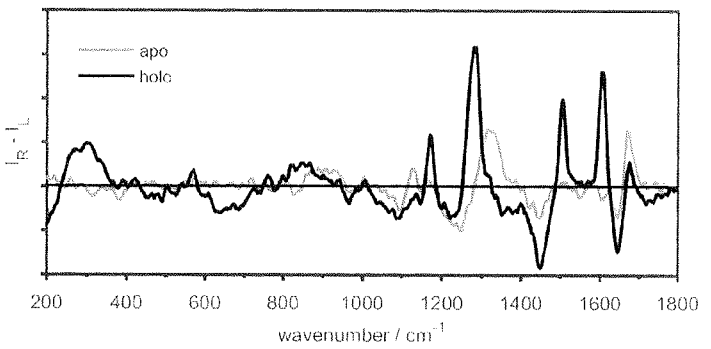
Cancer has become an ever increasing risk in our aging Western world. As a consequence of a rise in diagnosed cancer cases, in combination with the limitations and side effects caused by conventional cancer treatments, new therapies with high efficiency and targeted delivery to limit these side effects are much sought after. The glycoprotein human serum transferrin represent itself as the ideal candidate as it has recently been studied, in vitro, as a transporter of small molecules into cells, more specific, into malignant cells as they overexpress the transferrin receptor on their surface.

Transferrins are responsible for the iron transport into cells of higher order organisms. They have two specific, high-affinity Fe(III) binding sites. The Fe^{3+} ion is bound very tightly in an octahedral coordination involving two tyrosines, one histidine, one aspartic acid and one bidentate (e.g. CO_3^{-2}). The most striking feature of this property is that this binding is reversible with the decrease of pH. Thus, transferrin can appear in different forms: The holo-form of transferrin is fully saturated with bound iron. When not bound to iron, this form is referred to as apotransferrin.

In this contribution, Raman optical activity (ROA) was employed to investigate human serum transferrin. The Raman spectrum of the holo form reveals four resonance enhanced bands which are assigned to phenolate vibrational modes.[1] The corresponding ROA bands are all positive. Nevertheless, a small couplet in the amide I region, centered around 1662 cm_{-1}, is observed. The apo-form, on the other hand, results in an off-resonance ROA spectrum and hence providing information about the secondary structure.



As mentioned above, human serum transferrin has recently been studied, in vitro, as transporter of small molecules into cancer cells. One of these small molecules is the well-known anti-malaria drug artesunate and when bound to human serum transferrin, it is located very close to the amino residues which interact with Fe(III).[2] Therefore, electronic circular dichroism (ECD) together with resonance ROA was performed on different ratios between human serum transferrin and artesunate to investigate to influence of this binding both on the electronic transition causing the resonance effect and the secondary structure of the

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O IDN 66

Complementarity in Chiroptical Spectroscopy: divide and conquer molecular flexibility

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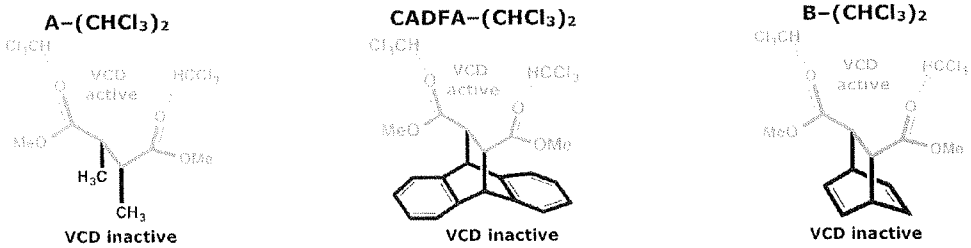
A series of studies[1-3] performed by Polavarapu et al. have shown that in order to fully characterize the molecular structure of chiral compounds it may often be necessary to consider more than one chiroptical spectroscopy technique. Since this complementary character has very important implications for the interpretation of the various chiroptical spectra it is necessary to explore the underlying mechanisms responsible for it. Using a few illustrative example molecules[3-5], in this presentation, the differences between the predictions made with three different spectroscopic techniques (VCD, ECD and ROA) are rationalized in terms of known chiroptical properties and phenomena. For example, the general coupled oscillator VCD mechanism can be used to identify the VCD-active/-inactive sites of a molecule. This will not only prevent the over-interpretation of the information contained in the VCD spectra, but will also explains why ECD and VCD spectra may often contain different structural information. In addition, it is shown that a priori knowledge of the VCD-active/-inactive molecular site may also be used to simplify the computation of VCD spectra. On the other hand, ROA spectra affected by pre-resonance effects associated to the single excited state resonance ROA phenomenon may contain information about low-populated conformers, which cannot be retrieved from VCD and/or ECD spectra.



***Figure's Caption**: By reducing the size of the VCD-inactive fragment (in black) of the chiral adduct of dimethyl fumarate and anthracene (CADFA) it is demonstrated that VCD can discriminate poorly (if at all) between structures that have similar VCD-active sites (in grey).*

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O IDN 72

Explicitly solvating small molecules with a Monte Carlo approach

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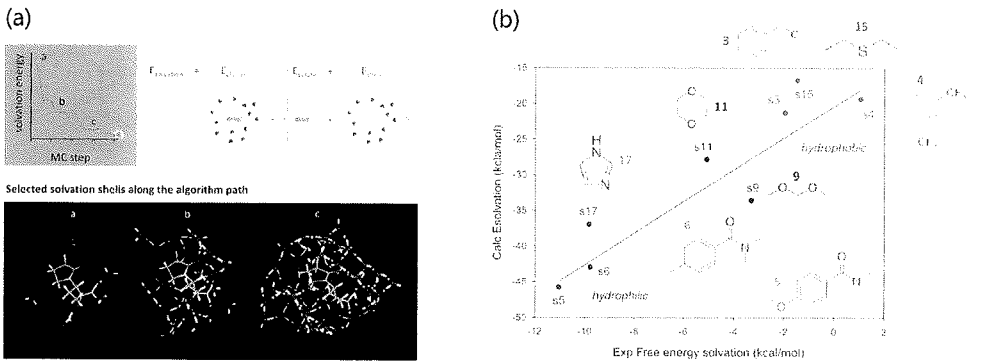
Dealing with solvation effects in quantum chemical calculations is an active research field (1-4). The efforts principally aim at finding a computationally effective way to account for the effects of solvent molecules surrounding the solute. This foster the interpretation of molecular spectra recorded in solution state. This important experimental condition allows gathering information on molecular structures and it is frequent in vibrational and electronic spectroscopy. When the solute-solvent interaction is strong enough, the use of PCM schemes (3) including explicit solvent molecules (4) is successful in describing the spectroscopic response of the solute under the influence of the solvent. The essential input of any explicit solvation scheme is the definition of representative clusters composed by the solute and selected solvent molecules. Such clusters could be difficult to devise, especially when the solute is flexible and/or possesses several groups which may sustain hydrogen-bonds with the solvent. This may often happen for pharmaceutical drug molecules in water environment.

In this work, we propose an explicit solvation scheme based on a Monte Carlo approach. It is implemented through the OpenBabel library (5). The solvation shell is determined by subsequent addition of solvent molecules, optimally selecting those which maximize the interaction energy with the solute (Fig 1a). The important role of the solvation energy, which was selected to bias our Monte Carlo algorithm, is well recognized in the thermodynamic description of solvation (6).

We successfully tested the algorithm on a set of small molecules solvated in water (Fig 1b), reproducing a satisfactory correlation of the calculated energies of solvation vs. the measured solvation free energies (7). After this validation of the algorithm and its parametrization, we aim at making the code freely available to the community as a tool which may help in the interpretation of spectroscopic data recorded in solution.



(a) Scheme of the proposed explicit solvation Monte Carlo algorithm. (b) Correlation between experimental solvation free energies of selected small molecules (7) and the corresponding calculated energies of solvation.

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O IDN 74

Molecular Structure Analysis of Pantolactone Using Chiroptical Spectroscopies

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Various techniques of chiroptical spectroscopy have been widely used for the molecular structure analysis of chiral compounds. Electronic circular dichroism (ECD) is by far the most commonly employed technique for investigating chiral substances. ECD, which is associated with electronic transitions in the ultraviolet to visible regions, is often used for secondary structure estimation of proteins, and for structural analysis of chiral molecules. The commercial instrument for ECD has a history over 50 years. On the other hand, vibrational optical activity (VOA) can be used to determine the absolute configuration of chiral compounds in combination with molecular orbital calculations.[1-4] VOA consists of two different techniques of chiroptical spectroscopy, vibrational circular dichroism (VCD) and Raman optical activity (ROA). Today, VOA is a useful tool for the molecular structure analysis of chiral molecules.

In this presentation we wish to demonstrate the application of molecular structure analysis of D-Pantolactone[5] using various chiroptical spectroscopies. We performed the measurements of D-Pantolactone to show the high sensitivity and accuracy of our chiroptical spectroscopy instruments. As a result, examples of successful determination of the absolute configuration by technique of measured versus calculated VCD and ROA spectra will be provided.

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O IDN 75

PROBLEMS WITH INTERPRETATION OF CHIROPTICAL SPECTRA BY USING QUANTUM CHEMICAL CALCULATIONS

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Chiroptical spectroscopy methods supported by the quantum mechanical calculations are powerful tool for example in assignment of absolute configuration, monitoring structural changes in chiral molecules, and conformational analysis. However, several problems arise when the chiroptical spectra are modelled. First, reproducing the spectra of a flexible molecule requires a proper evaluation of its conformational space. This problem is even more pronounced when the barriers heights between the conformers are lower than or comparable to the energy of thermal motions at 300 K. Moreover, for some compounds, pairs of different conformers exhibit almost mirror image spectra.[1,2] Hence, the proper estimation of the conformer population is crucial for the correct interpretation of the chiroptical spectra. Second, reproducing surrounding of solvent is especially important for molecules forming hydrogen bonds with the environment.[3,4] Then, usually at least the first solvation sphere needs to be explicitly taken into account by consideration of a few solvent molecules and the next solvation spheres can be mimicked using a continuous solvent model. Third, use of a proper DFT functional and an adequate basis set is also esential.[5]

The solid-state measurements could overcome the conformational and solute-solvent interactions problems as the molecular conformation is fixed and univocal in the solid state (unless polymorphs or a disorder occur). The reproduction of the experimental solid-state chiroptical spectra is a challenge even if the X-ray structure is determined. The most often, the spectrum is simulated for the single molecule cut out from the crystal. If the agreement with the experimental data in not excellent, taking a few molecules bound as they are in the crystal, can lead to better concordance. In this presentation problems with interpretation of example experimental VCD and ECD spectra of molecules with significant conformational lability and ability for formation of intermolecular bonds in solutions and solid state will be discussed.

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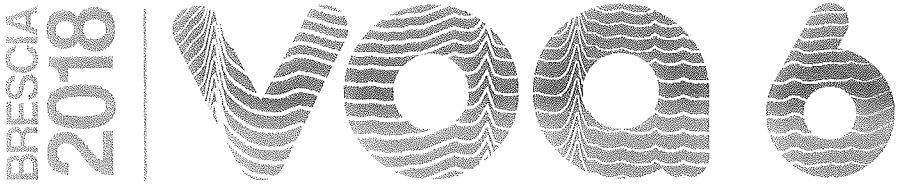
POSTER PRESENTATIONS



P IDN 8

Novel chiral architectures by oxophilic interaction of metals with Homochiral sulfoxide containing *o*-OPEs

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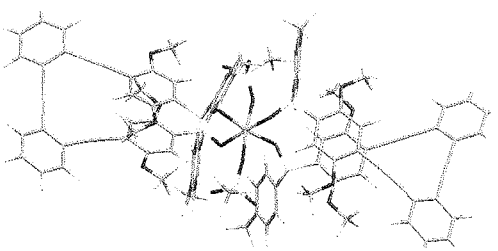
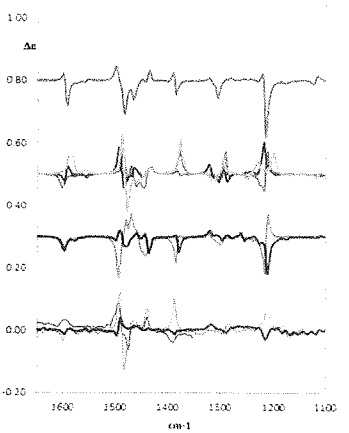
Chiral organic compounds show interesting chiroptical properties due to their intrinsic dissymmetry. It is well known that chiral fluorescent molecules are able to emit light with some degree of circular polarization. This property is usually described as circularly polarized luminescence or CPL. (1)

Nowadays, developing simple organic monomolecular emitters with high dissymmetry factors is very attractive, because of their up-and-coming applications. For example, they have been suggested as crucial for developing new luminescent materials, biosensors or devices for encrypting information. (2)

Vibrational circular dichroism (VCD) is very useful for conformational analysis, since the vibrational chiroptical response can reflect local differences and may be heavily dependent on hindered torsions. Therefore, VCD gives relevant structural information about the sample in solution, which, in many cases, cannot be inferred by other spectroscopic techniques. We have recently synthesized a new homochiral sulfoxide containing ortho-oligo(phenylene)ethynylenes (*o*-OPEs). (3) This family of compounds has demonstrated OFF/ON switching of CPL in the presence of metals. VCD has been a valuable technique to determine their structures in solution. Complementary to VCD, Raman spectroscopy in the 2000–2300 cm^{-1} region provides information on the interaction of CC triple bonds with metal atoms.



Homochiral sulfoxide containing o-OPE backbone with metal



VCD spectra

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REVISITING ELECTRONIC AND VIBRATIONAL CIRCULAR DICHROISM INTENSITIES BY THE ANALYSIS OF THE ELECTRIC-MAGNETIC POLARIZABILITY

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We have written a computer code (polar) that numerically computes the frequency-dependent dipole-dipole polarizabilities of any selected molecular system by a sum-over-states approach, starting from the regular output of time dependent density functional theory calculations carried out with the popular Gaussian code. This allows one to express the electronic circular dichroism signal as the real part of the trace of the electric-magnetic dipole-dipole polarizability tensor ($\boldsymbol{\alpha}_{em}$). Such an effort mimics the theoretical approaches to the simulation of UV-Vis absorption spectra in terms of the electric-electric molecular polarizability, which led to elegant applications to non-linear optics when the hyperpolarizability is considered (1).

In a similar way, it is also possible to address the contributions to $\boldsymbol{\alpha}_{em}$ given by vibrational transitions instead of electronic transitions. This naturally leads to the expression of vibrational circular dichroism (VCD) intensities through the trace of the real part of the vibrational component of the electric-magnetic polarizability tensor ($\boldsymbol{\alpha}_{em}^{vib}$). We have thus suitably extended the polar code to compute $\boldsymbol{\alpha}_{em}^{vib}$, which allows one to simulate VCD spectra straightforwardly from the formatted checkpoint file of a typical Gaussian frequency calculation.

The aim of such developments is the embedding of the quantum-mechanical details of the chiroptical spectroscopic response of a molecule ($\boldsymbol{\alpha}_{em}$) within the simulation of the electromagnetic field distribution at the surface of plasmonic devices. Such simulations are crucial in the interpretation of the experimental spectra measured from devices designed to enhance chiroptical interactions by the surface plasmon resonance of metal nanostructures.

We acknowledge funding from the Italian Ministry of Education, Universities and Research (MIUR) through the PRIN 2015 program (Project No. 2015FSHNCB "Plasmon-enhanced vibrational circular dichroism").

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PLASMON-ENHANCED VIBRATIONAL CIRCULAR DICHROISM

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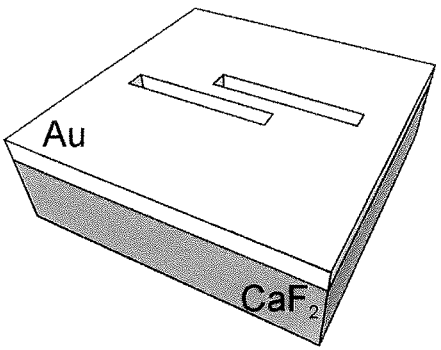
Recently, novel 'superchiral' approaches have been proposed to enhance the CD signal by tailoring the properties of the electromagnetic field through the control of the associated optical chirality (1). In this framework, plasmonic chiral sensing holds exciting perspectives (2,3) but several challenges have also been discussed (4-6). In particular, it has been pointed out that losses prevent the establishment of magnetic resonances in plasmonic nanostructures at visible wavelengths, which represents a possible limitation for plasmon-enhanced superchirality and justifies the recent proposals to move to dielectric materials for superchiral electronic spectroscopies (5,6).

Along this line, one can argue that the mid-infrared spectral range, where metals behave as very good conductors and can sustain strong magnetic resonances, holds interesting promises for superchiral vibrational circular dichroism. We discuss the perspective application and the preliminary results exploiting chiral plasmonic slits, previously introduced in the literature (7), to enhance the chiroptical activity in the mid infrared.



A sketch of the chiral slit arrangement considered for the exploitation of superchiral near fields in the mid infrared (7).

The research leading to these results has received funding from the Italian Ministry of Education, Universities and Research (MIUR) through the PRIN 2015 program (Project No. 2015FSHNCB "Plasmon-enhanced vibrational circular dichroism").

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P IDN 19

MONOSACCHARIDE CONFORMATIONS STUDIED BY RAMAN OPTICAL ACTIVITY AND NMR

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Monosaccharides are biologically important compounds, function of which depends on their conformational behaviour. Conformational analysis usually starts with generation of potential energy surfaces (PES) reflecting energetics of rotations of individual exocyclic groups. PES profiles generated by molecular dynamics or by a systematic scanning of corresponding torsion angles then leads to identification of low-energy conformations and their populations according to the Boltzmann distribution. We have found, however, that the results may differ significantly depending on the theoretical level used in molecular modelling.

We focused on conformations of exocyclic groups in a set of five β-methyl D-glycosides (glucose, galactose, mannose, fucose and N-acetyl glucosamine) based on validation of the PES results with NMR data (particularly ^{13}C chemical shifts) and Raman optical activity spectra (ROA). Selected geometries of low-energy conformers found at the PES obtained from molecular dynamics simulations were optimized at the DFT level for all orientations of C6-CH_2OH, C1-OCH_3 and C2-acetamido groups. In the next step, the ^{13}C and ^{1}H chemical shifts and both Raman/ROA spectra were calculated for all optimized geometries. A fit to experimental values provided the conformer populations. The protocol can be generally used for analysis of Raman and ROA spectra of other saccharides (Fig. 1, ref. 1).

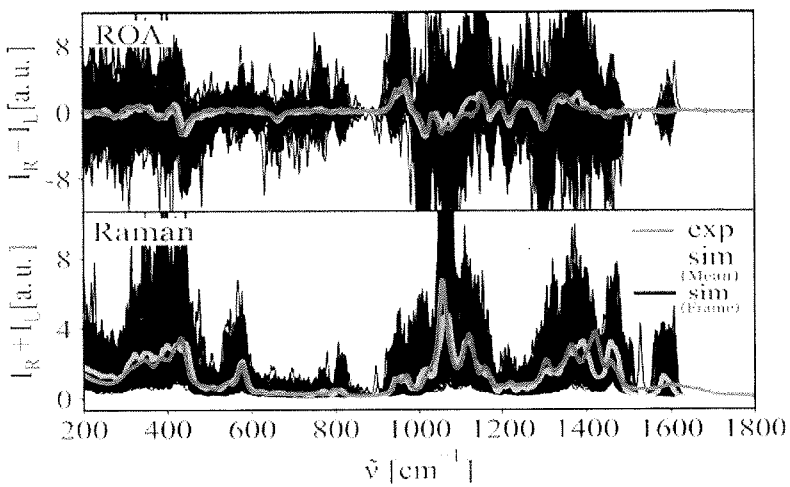

Figure 1. Comparison of experimental and simulated Met-α-GlcA Raman and ROA spectra.

The method provided reliable populations of *gg*, *gt* and *tg* rotamers for all exocyclic functional groups and may be in addition used for improvement of molecular dynamics force fields.

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Binding of Lanthanide Complexes to Histidine-Containing Peptides Probed by Raman Optical Activity Spectroscopy

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Lanthanide complexes are used as convenient spectroscopic probes for a variety of biomolecules.[1] Their binding to proteins is believed to be enhanced by the presence of histidine in the protein sequence, perhaps due to a π-π interaction histidine and lanthanide ligands, but the strength of the interaction significantly varies across different systems..

To understand the role of the histidine environment and the peptide sequence in the binding, we synthesized short histidine-containing peptides (His-Gly, His-Gly-Gly, His-Gly-Gly-Gly, Gly-His, Gly-His-Gly, His-His, and Gly-Gly-His). Their circular polarized luminescence (CPL) induced at the $[Eu(DPA)_3]^{3-}$ complex was measured using a Raman optical activity (ROA) spectrometer (Fig. 1). The ROA technique enabled us to detect weak CPL bands invisible to conventional CPL spectrometers. Based on the CPL intensity, relative binding strengths can be estimated and correlated with molecular dynamics (MD) calculations.

We found that longer peptides, low pH, and histidine residue close to the N-peptide terminus favor the binding.[2] The spectroscopic data were qualitatively explained by MD simulations. In the future we want to explore the specificity of lanthanide binding and induced optical activity for probing secondary and tertiary structures of larger peptides and proteins.

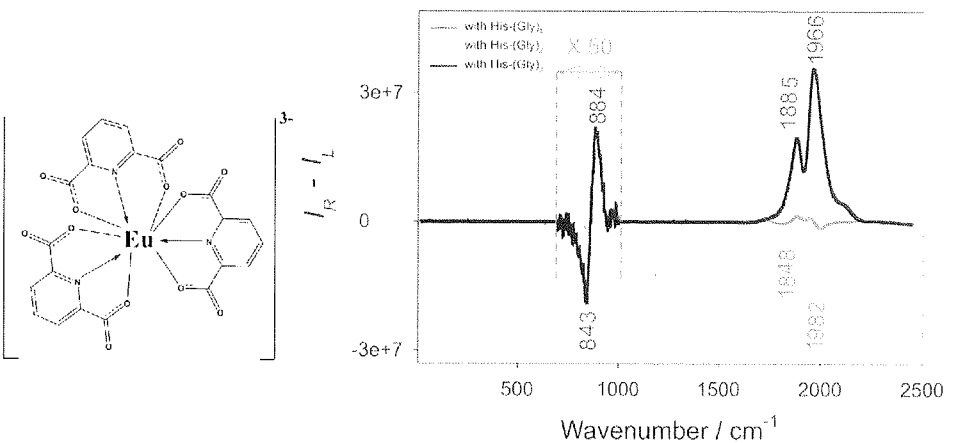

Figure 1: $[Eu(DPA)_3]^{3-}$ ion (left) and CPL spectra of $[Eu(DPA)_3]^{3}$ chelating with His-$(Gly)_n$ (n = 1, 2, and 3).

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P IDN 28

IR/VCD spectral signatures of 1,2-diols: relative and absolute configurations from acetonide derivatives

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In a previous work, we have demonstrated that the relative and absolute configurations of 1,3-diols could be readily determined from IR and VCD spectra, respectively, of acetonide derivatives.[1] In the present work we investigate whether this simple spectra-structure relationship can be applied to the acetonides of 1,2-diols. To that end, acetonides of representative compounds containing both *syn* and *anti* vicinal diol moieties were prepared (Figure 1). Initial empirical analyses revealed two distinct IR spectral markers for *syn* and *anti* relative configurations of the acetonides at around 1220 and 1385 cm^{-1}. In contrast to what was observed for 1,3-diols,[1] however, the VCD analysis of the acetonides of 1,2-diols revealed a couplet-like signal at around 1385 cm^{-1} for both *syn* and *anti* configured molecules. These markers were corroborated by quantum chemical calculations. Despite the lack of specificity of the VCD features identified, the combination of IR and VCD can be used to determine the absolute configuration of 1,2-diols. Once the relative configuration of the acetonide derivative is determined from the IR spectrum, the absolute configuration can be assigned based on the +,- or -,+ VCD couplet. Further studies are under way to confirm the generality of these findings.

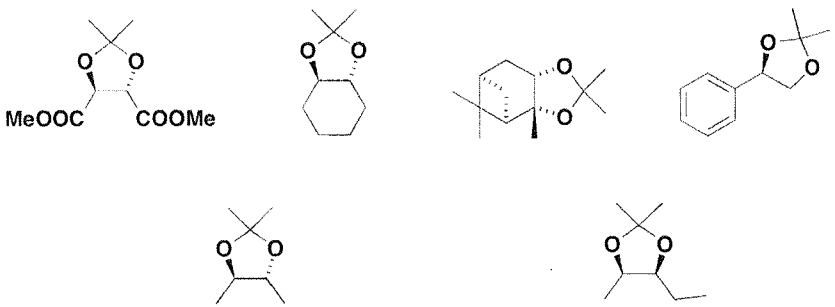

Figure 1. Representative acetonide derivatives of 1,2-diols investigated.

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Characterization of Solvent Interactions of Camphorquinone Oxime

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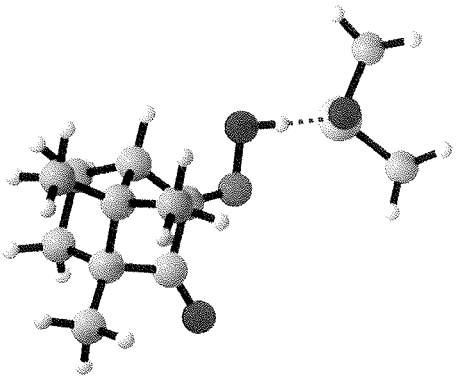
Intermolecular interactions with solvent molecules can significantly influence vibrational absorbance and circular dichroism signatures of chiral molecules. The extent of this influence depends on the strength of the interaction, and the IR and VCD spectral analysis may become very complicated. Consequently, it is often necessary to consider solute-solvent clusters explicitly in the quantum chemical calculation to draw reliable conclusions on the absolute configuration of the target compound.[1-4]

In order to systematically investigate the effect of solute-solvent interactions on different functional groups, we selected camphorquinone oxime as model structure for the oxime group. Being a derivative of camphorquinone, the target molecule is quite rigid and conformational changes can only occur in the oxime group. Solvation is investigated in different organic solvents (chloroform, methanol and dimethyl sulfoxide). By comparing the experimental spectra with calculated ones, we show that camphorquinone oxime prefers the formation of dimers in chloroform. In strong hydrogen bonding donor or acceptor solvents, the explicit consideration of solute-solvent clusters is necessary to theoretically describe the experimental spectra.



Intermolecular interaction of camphorquinone oxime with dimethyl sulfoxide

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P IDN 34

Taming conformational heterogeneity in VCD spectroscopy

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Vibrational circular dichroism (VCD) relies strongly on computations. These are usually performed with density functional theory (DFT). However, it is well known that DFT energies have uncertainties of up to a few kcal/mol. Since VCD is so sensitive to the conformation of the studied molecule, comparison of experimental and theoretical spectra suffers significantly from this uncertainty, in particular for systems with many low-energy conformations.

Here, we present results of studies on the highly flexible citronellal molecule. We show that using the computed energies to weight the different conformations leads to the same level of agreement with the experiment as simply averaging over the low-energy conformations with equal weights. Using Boltzmann weights from DFT calculations is thus a very poor model to simulate the experiment for systems with many low energy conformations. To solve this, we have developed a genetic optimization algorithm that optimizes conformational energies to the experimental spectrum with the energy uncertainty as boundary condition. We show that this approach provides not only a much better agreement between experiment and calculation, but also provides more insight in the effects of the uncertainty in energies. Moreover, we show that it allows for an unambiguous check on the reliability of the assignment of the absolute configuration given the uncertainties in conformational energies.

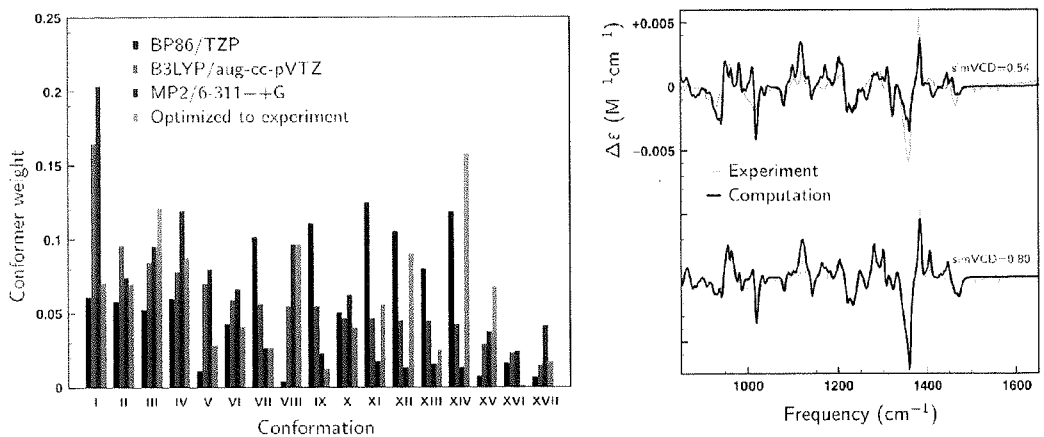

Figure 1. Left: Boltzmann weights for citronellal gained at different levels of theory together with the weights that are optimized to experiment. Right: comparison of the experimental VCD spectrum with the Boltzmann weighted (top) and optimal weighted (bottom) spectrum using an energy restriction of 1 kcal/mol.

P IDN 35

VIBRATIONAL CIRCULAR DICHROISM SIGNATURES OF THE CF_3 CHROMOPHORE

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Fluorine is widely used in medicinal chemistry and in the design of drug molecules. Spectroscopic approach helps to appreciate the main chemico-physical properties of the CF-stretching modes. In particular the IR and VCD spectra of several compounds containing CF_3 substituent are considered and analyzed. Different pharmaceutically relevant molecules have been evaluated by the point of view of IR and VCD bands relative to the symmetric and antisymmetric stretching CF3 modes. We discuss a configuration assignment rule which arises from CF-stretching normal modes in the range of 1100-1150 cm^{-1} (the CF-stretching modes are the most IR-intense [1,2]). In the cases we have examined (Figure 1) the VCD sign appears to correlate to the molecule AC: (-) ↔ (R) and (+) ↔ (S). DFT calculations confirm these conclusions. This rule is also tested on a new compound, N-tert-butanesulfinyl-1-(quinoline-4-yl)-2,2,2-trifluoroethylamine (**8**), containing two chiral centers: a sulfur atom (as sulfoxide moiety), whose configuration is known, and a carbon atom bearing the CF3 moiety of unknown configuration. A similar instance, i.e. compound **9** in Figure 1, line C, had been treated in the recent literature [3]

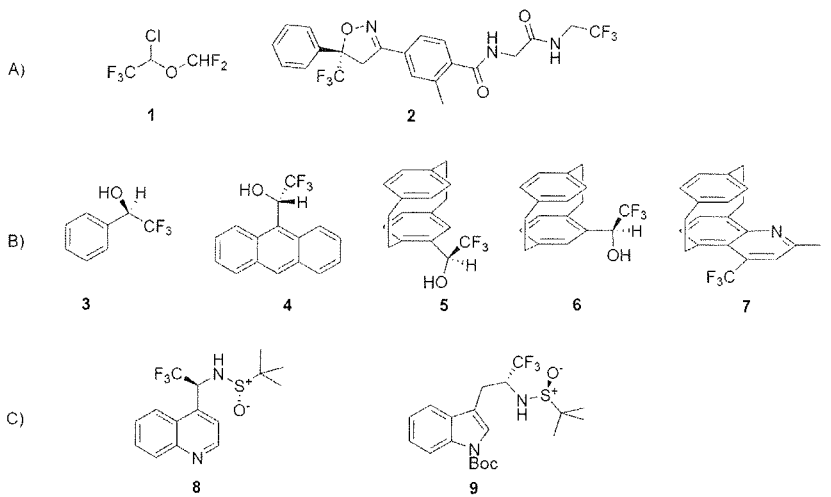

Figure 1. Molecule structures of studied compounds

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INTERPRETATION OF VCD SPECTRA OF *l*-STERCOBILIN AND *d*-UROBILIN IN SOLUTION WITH COMBINED MD AND DFT CALCULATIONS

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In this work we deal with two chiral bile pigments, *d*-urobilin and *l*-stercobilin. In the past, the interpretation of ORD and ECD data had led Moscowitz et al. [1,2] to introduce to seminal concept of inherently dissymmetric chromophore: indeed the ECD spectra in chloroform was defined by an electronic transition, at ca. 490 nm, taking place over an extended and bent molecular portion, with P shape for *d*-urobilin and M shape for *l*-stercobilin. A sign reversal in the ECD spectrum was noticed in CH_3OH by decreasing temperature [2]. To enquire on this aspect and on newly recorded VCD spectra in CD_2Cl_2, we rand DFT/PCM calculations, which it is revealed partly satisfactory. To improve the predicted spectra an MD-QM/MM approach [3,4] was undertaken and results were found to improve and will be reported in this communication. A MD simulation was run in CD_2Cl_2, followed by a clustering. The average conformation of each cluster was used to perform a two-layers ONIOM calculation: a 6 Å solvent shell is treated MM (GAFF Force Field), *l*-stercobilin hydrochloride is treated at DFT level of theory, whole in IEF-PCM environment to taking care of long-range solvation effect. This approach, although suffer of the limitations of MD, allows to analyzed the effect of chlorine ion on *l*-stercobilin conformation and the effect of explicit solvent.

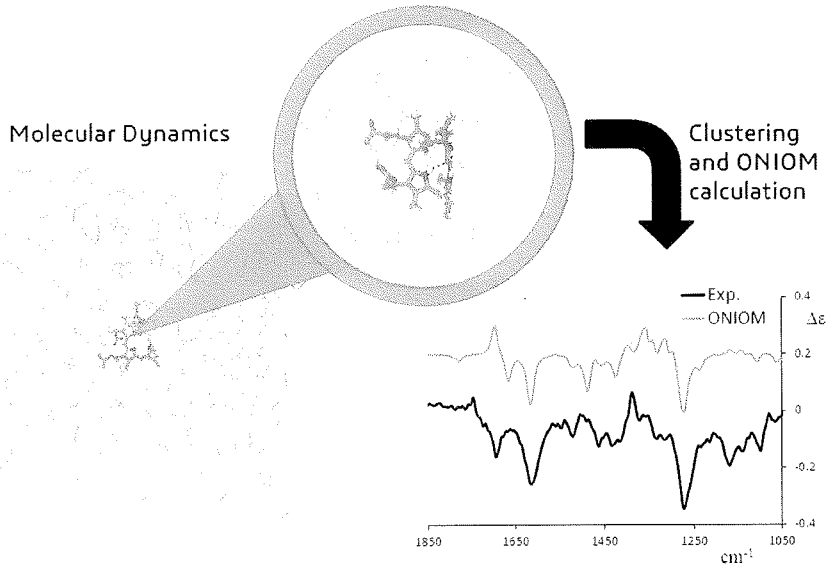

Figure. *Typical snapshot of MD from which the system to be simulated by ONIOM method is derived (see magnified image). On the latter VCD spectra are calculated to be compared with experiment*

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VCD SPECTRA OF DIMERS OF (*R*)-CARVONE, (*R*)-PINO-CARVONE AND (-)-MENTHOL

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Recently Taniguchi and Monde [1] revamped the interest in exciton CD, by applying it to the vibrational case, namely to VCD (VDEC model). The vibrational exciton model had been known for quite a while and was previously remembered under different names, like the Coupled Dipole model or the Coupled Oscillator model [2-3]. However the number of cases compared in ref. [1] was quite considerable and the arguments produced there important together with a systematic examination of coupled C=O stretchings. Later on, limits of applicability and further cases were presented [4-7], not strictly limited to particular vibrational modes. Of peculiar interest was the study at ref. [4], dealing with covalent dimers, as for example dicamphors; the latter model molecules are particularly attractive, due to the C_2-symmetry element, which is always a favorable condition for the acquisition of VCD spectra. Herein we further examine C2-dimers of natural products (Figure 1, **1** and **3**) and of ad-hoc synthesized dimer of (*R*)-pinocarvone Figure 1, **2**), a molecule which had been synthesized in 1995 and whose structure had been defined by X-ray diffraction data [8]. The experimental results provide important indications on the conformer populations, especially using the data in the region of the carbonyl stretching for **1** and **2**.

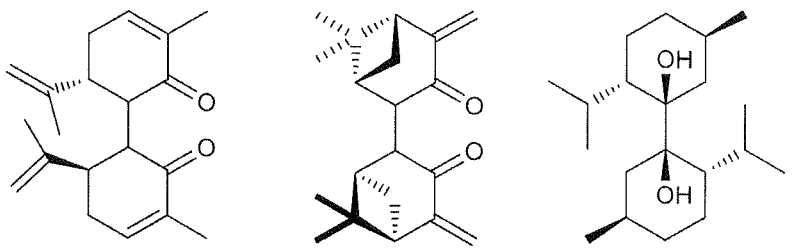

Figure 1. *The organic molecules dimers of the present study: di-(R)-carvone (**1**), di-(R)-pinocarvone (**2**), di-(1R)-menthol (**3**).*

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P IDN 40

Simulation of the Vibrational Chiral Spectra of Artemisinin at the Anharmonic Level

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Artemisinin, a famous active ingredient in Chinese medicine (青蒿素, qinhaosu), has gained renewed interest from the scientific community since the Nobel Prize in Physiology or Medicine awarded to professor Youyou Tu in 2015.(1) More than 10 drugs based on arteminin havealready been developed, due to its high efficient for the treatment of malaria and several cancers. These properties have a close relation to the peroxide bridge (reaction site). Therefore, spectroscopy can help understanding the bio-activity more deeply,by probing the vibrations related to this bridge and the neigbor chiral centers (recognition site).

For such a kind of study, chiral spectroscopies are well adapted, however their sensitivity poses a challenge for theory. As a result, the setup of a computational protocol is critical to reach a sufficient accuracy. Beyond the problem of the choice of the electronic structure calculation method, the description of the nuclear motions has to be addressed. For instance, the harmonic approximation can be insufficient, due to the systematic overestimation of transition energies and the impossibility to reproduce the intensity of non-fundamental bands. Scaling factors can partly correct some of those issues. However, the improvement is not systematic and rely onempirical studies. A correct approach requires a proper inclusion of the anharmonicity, which represents a steep increase of the overall computational cost, which has made such models impractical except for small molecules. This situation has changed in the recent years, and methods based on vibrational second-order perturbation theory (VPT2) have been shown to be applicable even on medium-to-large molecule system.(2) However, a known problem of VPT2 is the impact of resonances, namely Fermi and Darling-Dennison, which can strongly impact the reliability of the calculated vibrational transition energies and intensities, hence the spectral band-shape.(3,4) Arteminsinin represents an interesting challenge due to its size and vibrational structure. In this presentation, we will illustrate the impact of the level of calculations on simulated vibrational spectra, namely infared, vibrational circular dichroism (VCD), Raman, Raman optical activity (ROA). In particular, we will focus on the description of the vibrations, and the effect of resonances when accounting for the anharmonic effect at the VPT2 level. We will present strategies to overcome this issue, in order to reach a sufficient level of reliability and accuracy.

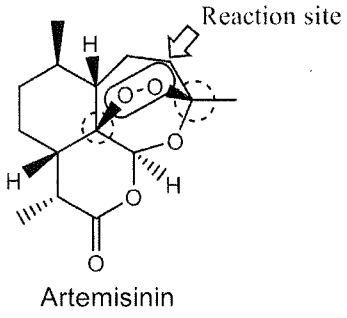

Figure: The structure of Artemisinin

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P IDN 49

COMPARISON OF DFT METHODS IN THE STRUCTURAL ANALYSIS OF HEROIN

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Heroin, a semi-synthetic alkaloid, is one of the often abused hard drugs all around the world. Morphine, the basic ingredient for heroin synthesis, is found in the seed pods of several representatives of the poppy family, which are primarily cultivated in Afghanistan, Pakistan or Iran. In 2015, more than 4.5 tons of heroin were seized in the European Union, accompanied by 8.4 tons in Turkey and Norway (1). Nowadays, the samples exhibit higher purity than those in the previous years (1,2). Therefore, the knowledge of the spatial structure of heroin in solution (as the best *in vivo* condition) plays the main role in the detailed understanding of the effect and metabolism of this substance within the human body.

As heroin is optically active, it is possible to use methods of chiroptical spectroscopy for the structural analysis thereof. Chiroptical methods together with quantum-mechanical calculations represent effective tools for the investigation of the 3D structure of chiral molecules. The presented work compared different types of density functional theory (DFT) calculations for the determination of the molecular structure of heroin in solution. Vibrational (VCD) and electronic circular dichroism (ECD), supported by conventional infrared (IR) and ultraviolet (UV) absorption spectroscopies, were applied and the spectroscopic results were supplemented by *ab initio* calculations.

Eighty-one starting geometries were optimized at the HF/6-31** level with the conductor-like continuum solvent model implemented in the polarizable continuum model. Selected conformers were further reoptimized at the cam-B3LYP/aug-cc-pVDZ level. Different calculation levels were used for the simulation of the spectra and the achieved results were compared via similarity index using the CDSpecTech program. The best result for the IR and VCD spectra was obtained for the B3LYP/6-311++G** level. For UV and ECD spectra, the cam-B3LYP/aug-cc-pVDZ level yielded the highest similarity index. Very good agreement between the simulated and the experimental spectra was achieved, which enabled us to describe the structure of heroin in solution at the atomic level.

This work was supported by the Ministry of the Interior of the Czech Republic (MVO/VI20172020056), Operational Programme Prague – Competitiveness (CZ.2.16/3.1.00/24503 and /21537), National Program of Sustainability (NPU MSMT: LO1601 - 43760/2015) and Specific University Research MSMT No. 21-SVV/2018 (A2_FCHI_2018_042).

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P IDN 50

STRUCTURE ANALYSIS OF NEW SYNTHETIC DRUGS METHYLONE, BUTYLONE AND PENTYLONE IN SOLUTION

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New psychoactive substances (NPS) are nowadays a very popular alternative to the illicit narcotics and psychotropic substances. The NPS imitate their structure and effects of the new substances are often even stronger than the original narcotics. The availability of the NPS is increasing as well as the total number of drugs detected every year. The EU Early Warning System is now monitoring over 670 substances (1). This system helps the EU legislative to respond quickly to the occurrence of new NPS in Europe. The current trends in the identification and controlling of such substances demand a fast and reliable analysis. Moreover, the methods for detailed study of their structure are required. Vibrational spectroscopy represents one of the effective tools for the identification and analysis of the NPS, and the chiroptical methods are able to provide further information on their 3D structure, which is the key e.g. for the understanding of their biological activity (2).

This work presents the systematic study of three structurally similar new psychoactive substances methylone, butylone and pentylone in aqueous solution. The methods of vibrational (VCD) and electronic circular dichroism (ECD), infrared (IR) and ultraviolet (UV) absorption were supported the *ab initio* calculations at B3LYP/6-311++G(d,p) and B3PW91/6-311++G(d,p) level, including solvent effects. Stable conformers of individual substances were found: 5, 6, 9 for methylone, butylone, pentylone, respectively. For each conformer the relative abundances based on the Boltzmann distribution were determined. Very good agreement between the experimental and the simulated ECD, VCD, IR and UV spectra was achieved, which allowed the assignment of the absolute configuration and the description of the detailed molecular structure of individual conformers. This approach can be helpful for future studies of biological activity, binding properties, metabolism, transport or distribution of NPS in organism.

The work was supported by the Ministry of the Interior of the Czech Republic (MV0/VI20172020056), partial support provided by Operational Program Prague – Competitiveness (CZ.2.16/3.1.00/24503 and CZ.2.16/3.1.00/21537), National Program of Sustainability (NPU MSMT – LO1601; 43760/2015) and the Specific University Research (MSMT No 21-SVV/2018).

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P IDN 52

Chriroptical study of natural and model supramolecular chiral systems

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Chirality at the supramolecular level is ubiquitous in Nature. The clear proofs of this are macromolecules of biological importance, including DNA and proteins. Phenomena like aggregation of xanthophylls is also related with the proper functioning of essential biological systems like photosynthetic apparatus and lipid bilayers[1].

In this study we focus on natural carotene crystals exposing supramolecular chirality and characteristic helical arrangement. Carotene crystals come from crystalline chromoplasts of carrot root and consist mainly of achiral β-carotene with a small contribution of chiral α-carotene and lutein[2], so most probably their optical activity might be driven by the process of chirality induction. Here, we describe the chiroptical study of natural carotene crystals as well as aggregate model systems with the use Electronic Circular Dichroism (ECD) and Raman Optical Activity (ROA) spectroscopy.

It is commonly known that xanthophyll molecules show ability to aggregate in hydrated organic solvents. Many of such species exhibiting supramolecular chirality depend primarily on the chirality of a single component molecule[3-5]. However, the supramolecular chirality may be derived not only from chiral elements, but also from achiral ones that are ordered by structurally similar chiral molecules. In such supramolecular systems noncovalent interactions like π-π stacking or hydrogen bonding stabilize the helical structure and also allow for non-symmetric transfer of chiral information. According to 'sergeant and soldier' effect, when a small amount of chiral compound (the 'sergeant') is added to achiral one (the 'soldiers'), a strong optical activity signal may obtained, similar to that observed for the 'sergeant' alone[1,6]. For this purpose we used two structurally similar xantophylls: astaxanthin (chiral) and β-carotene (achiral) as a model system in order to understand more about the structure and optical properties of carotene crystals.

Our results proved that astaxanthin and β-carotene create together a supramolecular chiral assembly in a way that achiral β-carotene molecules are forced to form a chiral arrangement by chiral addition of astaxanthin like in 'sergeant and soldiers' effect. Moreover, as the absorption range of formed supramolecular assemblies coincides with the ROA excitation wavelength, thus the registration of resonance ROA spectra of aggregates were possible.

To sum up, the study has been carried on in order to obtain a deeper understanding of the chirality induction process, the supramolecular chemistry of xantophyll assemblies, as well as the resonance enhancement of ROA signal through aggregation process. It is important that data recorded for the model systems can be extrapolated and related to biological ones like natural carotene crystals.

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This work was supported by National Science Centre (UMO-2017/25/B/ST4/00854).

P IDN 53

CHIROPTICAL AND VIBRATIONAL SPECTROSCOPY IN IDENTIFICATION AND STRUCTURE ANALYSIS OF COLOURED COCAINE-METAL COMPOUNDS

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Cocaine, belonging to the family of tropane alkaloids, is historically one of the most famous illegal psychoactive substances in the world. It is produced mostly in South America from where it is distributed worldwide. In 2016, more than 70 tons of cocaine were seized in the European Union within 98 thousand police seizures and the estimated amount of its lifetime users in Europe is approximately 17 million (1). In order to fight the drug-related crime effectively, various analytical methods have been developed and optimized to enable fast and reliable identification of cocaine in suspicious samples. Scott's test, a colorimetric method commonly used by customs officers for a preliminary check for the presence of cocaine, is based on the reaction of the drug with cobalt thiocyanate, which is accompanied by a visible colour change. The inventive drug smugglers and distributors, however, seek the ways of hindering the identification of the narcotic in their shipments and one of these methods is transportation of cocaine in the form of its coloured compounds with metal ions, which provide a negative result of the Scott's test and may easily confuse trained police dogs (2). With respect to the described situation, it is necessary to develop analytical methods, which would enable a reliable identification of cocaine in such masked forms. In this work, the methods of chiroptical and vibrational spectroscopy were used for the characterization of the coloured cocaine compounds (Co^{2+}, Cu^{2+}, Fe^{3+} and others) and the potential of the selected methods for the identification of the masked cocaine was discussed. Cocaine is a chiral molecule with four stereogenic centres and thus chiroptical spectroscopy was also applied for the investigation of the cocaine-metal interactions. Chiroptical methods provide an excellent tool for the investigation of the 3D structure of chiral molecules in a solution (3) and they were successfully used for the detailed description of the cocaine conformations in aqueous solution recently (4). Cocaine was reliably identified in all the studied samples by electronic circular dichroism (ECD) and vibrational circular dichroism (VCD) and the nature of the cocaine-metal interaction was discussed. In addition, the potential of infrared (IR) spectroscopy in identification of such masked forms of cocaine was examined as the application of portable IR spectrometers may present a suitable tool for the preliminary tests of suspicious materials during customs inspections.

This work was supported by the grant of Ministry of Interior of the Czech Republic (VI20172020056) and partially by Operational Programme Prague – Competitiveness (CZ2.16/3.1.00/24503 and /21537), National Program of Sustainability I (NPU MSMT: LO1601 - 43760/2015) and Specific University Research MSMT No. 21-SVV/2018 (A2_FCHI_2018_042)

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P IDN 55

SPECTROSCOPIC IDENTIFICATION OF COUNTERFEIT PHARMACEUTICALS FOR ERECTILE DYSFUNCTION TREATMENT

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The production and distribution of counterfeit pharmaceuticals is one of the actual problems for the modern society worldwide. It not only causes economic loss to the pharmaceutical companies, it also presents a serious public health risk mostly due to the unknown composition of the counterfeits. Some of them may contain different amount of the active substance or diverse undeclared, generally cheaper, excipients. In the special cases, counterfeits with completely different active substance or even preparations containing toxic additives were reported (1). The situation is especially troubling in the case of phosphodiesterase type 5 (PDE-5) inhibitors used for the erectile dysfunction treatment. The most famous PDE-5 inhibitors Viagra® (sildenafil), Cialis® (tadalafil) and Levitra® (vardenafil) belong to one of the most commonly falsified class of drugs, because patients often prefer to buy them anonymously from unverified sources (mostly from various Internet drug stores) rather than to consult a doctor, as PDE-5 inhibitors are prescription-only pharmaceuticals (2). To ensure the effective fight against the distribution of these counterfeits, it is necessary to develop analytical methods enabling fast and reliable identification of suspicious samples.

In this work, basic physical parameters of the set of suspicious Viagra®, Cialis® and Levitra® tablets such as appearance, weight or size were examined and the more detailed characterization by means of Raman, VCD and ECD spectroscopies followed. The potential of the selected spectroscopic methods for the reliable identification of counterfeit tablets was discussed. In addition, ab initio calculations were combined with the experimental results to describe the 3D structure of chiral tadalafil in a solution. Raman spectroscopy was chosen as it seemed to be a suitable tool for the identification of counterfeit PDE-5 inhibitor drugs, because it provided a fast, relatively cheap and non-destructive analysis. Another advantage is the availability of portable Raman spectrometers discussed in this work. After interpreting the spectra of the suspicious tablets, it was possible to reliably differentiate counterfeit from genuine preparations and the missing or additional excipients were identified in some cases. While sildenafil and vardenafil are achiral, the tadalafil molecule possesses two stereogenic centres and thus ECD and VCD spectroscopies (3), which are inherently sensitive to the 3D structure of chiral molecules, were applied for the study of its conformations in a solution. DFT calculations were performed and four stable conformers of tadalafil were revealed. The solvent effects were considered via the polarizable continuum model for all the calculations. Excellent agreement between the simulated and experimental spectra was found, which enabled a detailed interpretation of the experimental data.

This work was supported by the grant of Ministry of Interior of the Czech Republic (VI20152020048) and partially by Operational Programme Prague – Competitiveness (CZ2.16/3.1.00/24503 and /21537), National Program of Sustainability I (NPU MSMT: LO1601 - 43760/2015) and Specific University Research MSMT No. 21-SVV/2018 (A2_FCHI_2018_042)

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P IDN 57

CHIROPTICAL PATTERN OF GASTROINTESTINAL TUMORS

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Gastrointestinal tumors largely contribute to the globally increasing number of cancer deaths. Despite intensive research, the diagnosis remains unreliable and, in many cases, too late making the prognosis highly unfavorable (1). Due to minimal invasiveness, blood-based analysis is considered a prerequisite for future large-scale screening of populations at risk. Blood and its derivatives contain a number of biomolecules, the concentration and structure of which vary according to the current health status of an individual. In addition, many of these biomolecules are chiral and, thus, their structural alterations may be observable by chiroptical spectroscopy (2,3). To reveal the disease-specific spectral pattern, we examined blood plasma samples of patients suffering from different gastrointestinal tumors, specifically pancreatic, colon and hepatocellular cancers. Raman optical activity (ROA) and electronic circular dichroism (ECD) were complemented by unpolarized techniques of molecular spectroscopy (Raman and infrared absorption). The obtained spectra were compared to those of a control group and disease-specific spectral patterns were observed. The major differences between patients and controls were identified in the spectral regions corresponding to protein secondary structure, which suggests a pathology-induced misfolding or conformational changes of plasmatic proteins. Not only the spectra of individual cancers varied from the control subjects, but the combination of spectroscopic methods also allowed for the discrimination between particular cancer types. A statistical model based on linear discriminant analysis of all spectroscopic data was created to assess the accuracy of our approach with respect to the clinical diagnosis. High values of sensitivity and specificity after cross validation suggest great potential of the combination of chiroptical and conventional vibrational spectroscopies in the clinical diagnostics of gastrointestinal tumors.

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P IDN 61

Chiral Enhancement Factor: Determining the chiral component of nearfield enhancement in plasmonic surfaces.

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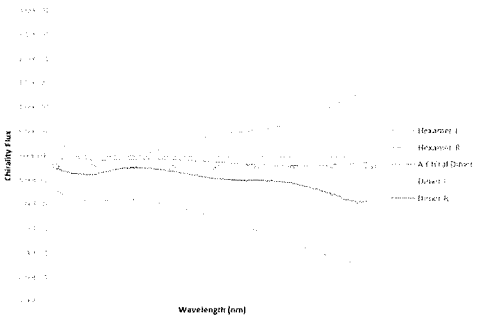
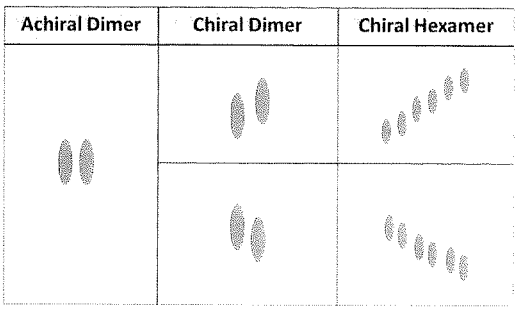
Vibrational optical activity (VOA) measurements can distinguish between molecular enantiomers and resolve complex tertiary structures but these techniques suffer from low signal, limiting their application. Plasmonic surface enhancement has the potential to do for VOA what it has done for equivalent 'achiral' vibrational techniques as in surface-enhanced IR spectroscopy (SEIRA) and surface-enhanced Raman spectroscopy (SERS), but as of yet the chiral contribution of typical SEIRA and SERS substrates has been poorly understood. Here, we present a technique, optical chirality flux spectroscopy (OCFS)[1] which can be used to probe the chiral component of near field enhancement, and to define a 'chiral enhancement factor'.

OCFS can be used to measure the chiral asymmetry in enhancement from plasmonic surfaces. This can elucidate unintended chirality in standard SERS and SEIRA substrates and also guide design of so called chiral plasmonics. This enhanced understanding will help the field of VOA utilize the full potential of plasmonic enhancement.



Optical chirality flux measurements of different plasmonic structures.



Cartoon of different plasmonic structures measured.

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P IDN 62

Investigating of a chiral thiourea bifunctional catalyst

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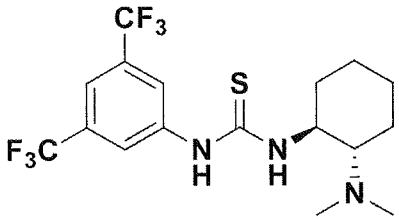
In the past, thioureas were mainly used as a reducing agent or as a source of sulfide in the organic synthesis. Since 1998, when Jacobsen et al. discovered the catalytical properties of thioureas, chiral thioureas are frequently used as hydrogen bonding organo-catalysts in a variety of organic reactions, especially in the asymmetric catalysis.

In a previous study, we investigated the interaction-induced preferences of a chiral thiourea model compound, bis(α-phenylethyl)thiourea (PETU), by vibrational circular dichroism spectroscopy and identified solvent-induced conformational changes in non-polar and polar solvents. Furthermore, we studied the binding topology between the thiourea-moiety and an acetate anion as a model reactant. (2) In the PETU study, we already showed that this binding is more complex compared to the predicted C2-symmetry in literature.

The aim of this work was to transfer these observations to the bifunctional thiourea catalyst developed by Takemoto (Scheme 1). (3) We started to investigate conformational changes caused by binding properties of different carboxylates.

The biggest challenge investigating the real thiourea catalysts is that they often contain CF_3 groups to acidify the hydrogens of the thiourea-moiety. In comparison with the experimental IR and VCD spectra, the harmonic frequencies of the CF stretching vibrations predicted with common hybride functionals such as B3LYP were found to be heavily misplaced. In this contribution, we also show that the M06-2X functional provides harmonic C-F stretching frequencies with an accuracy sufficient for a reliable spectra analysis. (4)



Takemoto

Scheme 1: Chemical structure of investigated chiral thiourea.

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P IDN 65

Raman Optical Activity of 3-aminoquinuclidine

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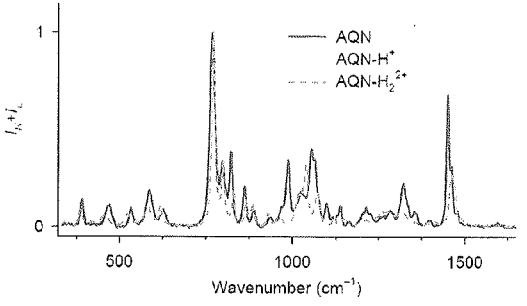
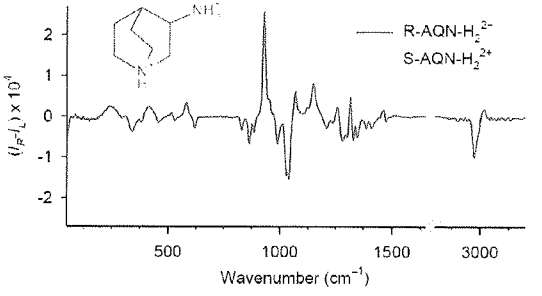
3-aminoquinuclidine (AQN) is an important pharmacophor having role in many different 5-HT3 and 5'-HT1A receptor modulators (ion channels mediating depolarization and excitation of neurons in the central and peripheral nervous system), agents displaying neuronal activity, and medicaments which help to bypass resistance to some cancer drugs. AQN is a chiral molecule and information on its absolute configuration and enantiomeric purity is crucial to the use of AQN in drug synthesis. AQN contains both primary and tertiary amine group and depending on pH value it can be found in three differently charged forms.

In our contribution we present thorough vibrational characterization of AQN based on Raman and ROA spectroscopy and DFT spectral simulations. From pH dependent Raman spectral series we determined dissociation constants associated with transitions between AQN's protonated states (pKa_1=7.2 for tertiary amine group, and pKa_2=10.6 for primary amine). At three chosen pH values (each dominated by particular protonated state) we have recorded ROA spectra in the full range of fundamental molecular vibrations (50 to 4000 cm^{-1}) on new ROA spectrometer build and currently fine-tuned by J. Kapitán in Olomouc. Despite low circular intensity difference of AQN (2.10^{-4} at max) where acquired fine spectra for both enantiomers including the C-H stretching region. In DFT calculations we have studied manifestations of various protonation in AQN's spectra and effects of molecular flexibility on the quality of the simulated spectral profiles. We have found that in equilibrium there is weak twist of quinuclidine (QN) skeleton caused by presence of primary amine. Further, we observed that the rotation of primary amine affected the spectral shape mostly in the low frequency (< 500 cm^{-1}) and C-H stretching regions, while twist of QN's skeleton in one or another sense led to the rapid spectral changes in the fingerprint region. Finally, we have also studied the improvement of the simulated spectral profiles upon the inclusion of the explicit solvent molecules into the calculated system.



Raman spectra of differently protonated states of AQN.



ROA spectra of double protonated AQN (pH=5.02)

P IDN 68

A New ICP-ROA Spectrometer at Scaldis Spectroscopy

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Instrument development in the field of Raman Optical Activity (ROA) has been relatively limited in recent years, with only a few research groups developing their own spectrometers, or exploring new frontiers in ROA.[1-6] An important reason for this state of affairs is the availability of a commercial ROA instrument, which has opened up ROA as a technique to the scientific community, without the requirement of developing a research instrument in-house.

Nevertheless, developing and constructing a home-built ROA spectrometer has many advantages. There are of course the advantages of flexibility and extensibility. Having full control of both the optical layout as well as the acquisition software of the instrument makes it possible to not only extend the instrument, but to fully explore the effect of each component on both the throughput of the instrument and also on the polarization artefacts that are a constant issue in ROA measurements.

When building a new spectrometer, it is also possible to benefit from the advances that have been made in both the field of optics, detectors and lasers in recent years. It is clear that while developing a new spectrometer is challenging and time-consuming, there are major benefits to this approach that should result in a high-performance, easily extendible, and thus future-proof instrument.

Within the last few years, ROA spectroscopy has become an important field of research for Scaldis spectroscopy (Molecular Spectroscopy group at the University of Antwerp and Quantum Chemistry group at Ghent University combining their chiroptical expertise). As a result, there is an ever increasing demand for ROA measuring time, as such it was decided to invest in a second spectrometer. Given the advantages of a home-built instrument listed above, we decided to build our own Incident Circular Polarization (ICP) ROAspectrometer. The instrument is based on the classic back-scattering ROA spectrometer, and builds on all the advances that have been made in ICP-design over the years. The instrument uses state-of-the-art components throughout in a bid to push this tried and tested technique to new limits.

In this poster presentation we present our new home-built ROA spectrometer operating at 532 nm, and show the first spectra acquired with this instrument.

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P IDN 71

ELECTRONIC AND VIBRATIONAL EXCITON COUPLING IN CHIRAL POLYIMINE MACROCYCLES

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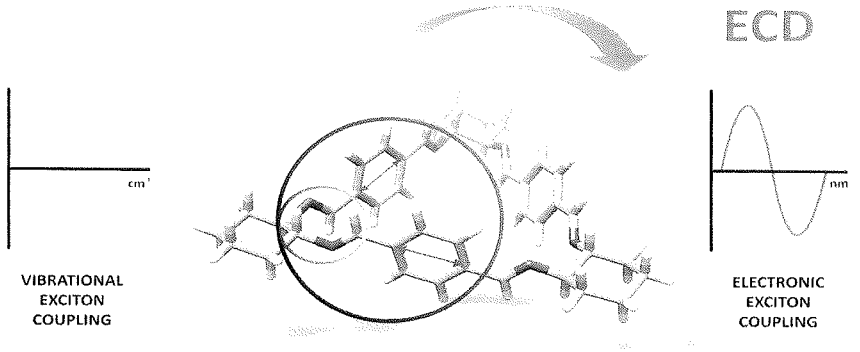
Readily available chiral macrocycles and their (poly)oxygenated congeners represent an unique class of macrocyclic rigid compounds optimal for test of electronic and vibrational circular dichroism exciton chirality methods (1). Information available from both methods, supported by DFT calculations, allow to determine absolute stereochemistry of given molecular systems (2,3).

Electronic and vibrational circular dichroism spectra of macrocyclic congeners are strongly affected by polar substituents in macrocycle skeletons. Double substitution by OH groups in each aromatic fragment of the macrocycle caused sign reversal of the exciton couplet in the region of the strongest UV absorption. On the other hand, ECD spectrum of the macrocycle having two methoxy groups shows two exciton couplets – the long-wavelength positive and negative, observed at the shorter wavelengths.

VCD spectra of macrocyclic triangular imines show vibrational exciton couplets in the region of C=N stretches. The signs of these couplets are positive and the opposite of the diamine chirality. For trianglimine macrocycles the interpretation of VCD spectra in terms of excitons is much more convincing than for electronic circular dichroism spectra.



Vibrational and electronic exciton coupling in polyimine macrocycles.

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AUTHORS' INDEX

	SUNDAY, Sept. 9th	MONDAY, Sept. 10th	TUESDAY, Sept. 11th	WEDNESDAY, Sept. 12th	THURSDAY, Sept. 13th
MORNING part I	-	08.30 am secretariat desk opening 09.00 am I SESSION "PAST, PRESENT and FUTURE of VOA"	08.30 am secretariat desk opening 09.00 am V SESSION "ROA/VCD Experimental Old&New"	08.30 am secretariat desk opening 09.00 am IX SESSION "APPLICATIONS of VOA – proteins, sugars, Lipids and Nucleic Acids; fibrils" part A 10.00 am POSTER SESSION	08.30 am secretariat desk opening 09.00 am X SESSION "General Aspects of Chirality and VOA"
COFFEE BREAK	-	10.30 am	11.00 am	11.00 am	10.30 am
MORNING part II	-	11.00 am II SESSION "VCD&ROA EXPERIMENTAL"	11.30 am VI SESSION "ROA and non-linear spectroscopies"	11.30 am CHIROPTICAL SPECTROSCOPIES AND ASTROCHEMISTRY "IN FRONT OF THE MIRROR: THE SEARCH OF CHIRAL MOLECULES IN THE UNIVERSE" part A	11.00 am XI SESSION "APPLICATIONS of VOA – proteins, sugars, Lipids and Nucleic Acids; fibrils" part B
LUNCH	-	12.50 pm	01.00 pm	01.15 pm	12.20 pm 01.20 pm CHIROPTICAL SPECTROSCOPIES AND ASTROCHEMISTRY "IN FRONT OF THE MIRROR: THE SEARCH OF CHIRAL MOLECULES IN THE UNIVERSE" part B 03.30 pm Closing Remarks
AFTERNOON part I	-	01.50 pm III SESSION "VCD&ROA Theory and Ab-Initio Calculation"	02.00 pm VII SESSION "APPLICATIONS of VOA - materials" 03.20 pm POSTER SESSION	02.30 pm SOCIAL PROGRAMME Guided visit to Santa Giulia Museum	
COFFEE BREAK	-	04.00 pm	04.20 pm	-	-
AFTERNOON part II	03.30 pm participants registration 05.00 pm opening ceremony 05.15 pm Stephens Award	04.30 pm IV SESSION "VCD&ROA: MD simulations (QM/MM and some address to Aggregation, Band-shape, etc.)"	04.50 pm VIII SESSION "APPLICATIONS of VOA – natural products and drugs"	-	-
EVENING	06.00 pm WELCOME COCKTAIL	-	-	07.30 pm SOCIAL DINNER Ristorante Vedetta, Brescia	-

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