7th International Conference on Vibrational Optical Activity (VOA7)

August 7 – 11, 2022

University of Alberta, Edmonton, Alberta, Canada

Welcome to the *7th International Conference On Vibrational Optical Activity*

University of Alberta, Edmonton, Alberta, Canada

August 7 – 11, 2022

On behalf of the Local Organizing Committee and the International Steering Committee, we welcome you all to the 7th International Conference on Vibrational Optical Activity (VOA7). The VOA conference series aims to present the cutting edge in research and development in the field of vibrational optical activity (vibrational circular dichroism and Raman optical activity) and related spectroscopies, highlighting both experimental and theoretical advances. At VOA7, we will feature a large portion of invited presentations by graduate students, postdoctoral fellows and early career researchers, in addition to leading scientists in the field. We look forward to exciting presentations and stimulating discussions about the newest trends and applications of this diverse family of techniques.

For some of us this might be the first in-person meeting since the begin of the pandemic, and we thank you for your cooperation to help us to run VOA7 in the safest possible way without compromising the in-person atmosphere.

We wish you all a scientifically productive and personally enjoyable meeting at which new friendships can be made and old ones renewed.

Yunjie Xu and Wolfgang Jaeger

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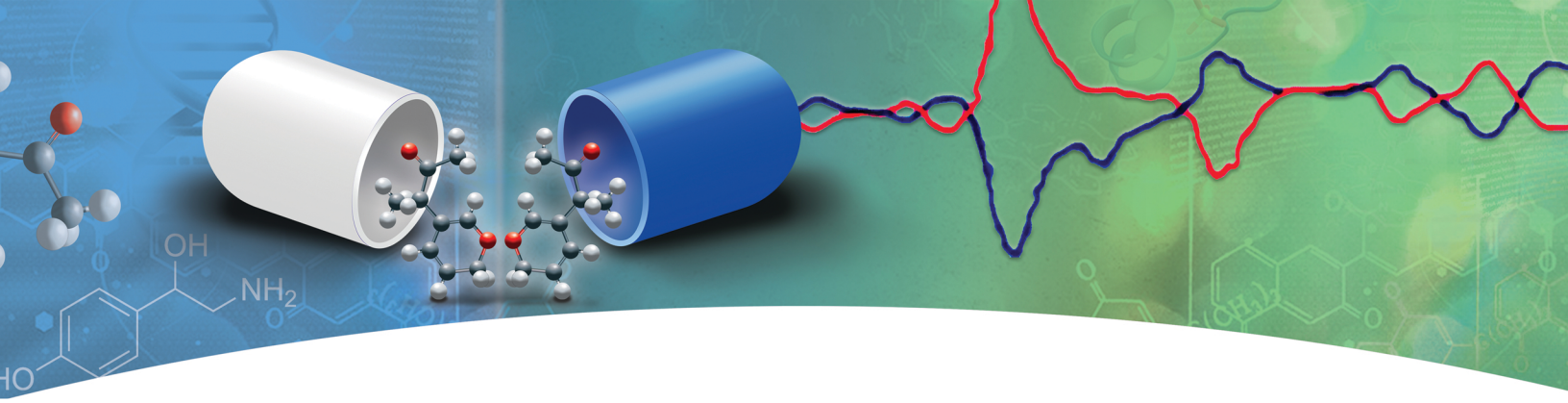

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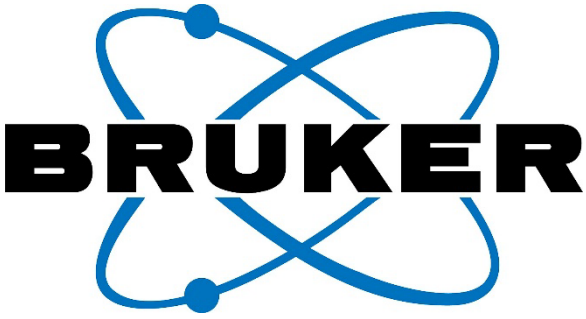

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7th Vibrational Optical Activity Conference, VOA7

Aug 07 – 11, 2022, Edmonton, AB, CANADA

Sunday, Aug. 07, 2022			**Chair: Yunjie Xu, University of Alberta**
17:00	–	19:00	Registration
19:00	–	22:00	Get-together party: with food and drinks
20:00	–	20:05	Welcome messages: Yunjie Xu
20:05	–	20:10	Information: Wolfgang Jäger
20:10	–	20:20	VOA conference series: Larry Nafie

Monday, Aug. 08, 2022			**NRE 2-001**
			Assistant Tech Chair: Alex N. Mort, University of Alberta
			Chair: Rina Dukor, BioTools
8:30	–	9:10	Carin Rae Lightner PJS1
9:10	–	9:30	Mallory Green CT1
9:30	–	10:05	Jan Helbing IT1
10:05	–	10:25	Justin Neil CT2
10:25	–	11:00	**Bruker Coffee Break**
			Chair: Julien Bloino, Scuola Normale Superiore
11:00	–	11:35	Marco Fusé IT2
11:35	–	12:10	Sandra Luber (on-line) IT3
12:10	–	12:30	Josef Kapitan (on-line) CT3
12:30	–	14:00	**BioTools Lunch**
			Assistant Tech Chair: Colton Carlson, University of Alberta
			Chair: Mohamad Al-Jabiri, University of Alberta
14:00	–	14:35	Sérgio Domingos IT4
14:35	–	14:55	Jiarui Ma CT4
14:55	–	15:30	Tohru Taniguchi IT5
15:30	–	16:05	Agnieszka Kaczor IT6
16:05	–	16:40	**BrightSpec Coffee Break**
			Chair: Wybren Jan Buma, University of Amsterdam
16:40	–	17:15	Reinhard Schweitzer-Stenner IT7
17:15	–	17:35	Aleksandra Wajda CT5
17:35	–	18:10	Shunai Che (on-line) IT8
18:10	–	19:10	Int. Steering committee meeting
18:10			**Tour of UofA and Hawrelak Park**

Tuesday, Aug. 09, 2022			**NRE 2-001**
		Assistant Tech Chair: Arsh Hazrah, University of Alberta	
		Chair: Tim Keiderling, University of Illinois Chicago	
8:30	– 9:10	Guojie Li	PJS2
9:10	– 9:45	Joanna Rode	IT9
9:45	– 10:05	Mutasem Alshalalfeh	CT6
10:05	– 10:25	Grzegorz Zając	CT7
10:25	– 11:00	**Schrödinger Coffee Break**	
		Chair: Sergio Abbate, Università di Brescia	
11:00	– 11:35	Jiří Kessler	IT10
11:35	– 12:10	Pavel Michal (on-line)	IT11
12:10	– 12:30	Martin Brehm (on-line)	CT8
12:30	– 14:00	**Jasco Lunch**	
		Assistant Tech Chair: Jiarui Ma, University of Alberta	
		Chair: James Cheeseman, Gaussian	
14:00	– 14:35	Sascha Jähnigen	IT12
14:35	– 15:10	Wybren Jan Buma	IT13
15:10	– 15:30	Julien Bloino	CT9
15:30	– 16:00	**Coffee Break**	
		Chair: Agnieszka Kaczor, Jagiellonian University	
16:00	– 16:35	Christian Merten	IT14
16:35	– 16:55	Ernesto Santoro	CT10
16:55	– 17:30	Feng Wang (on-line)	IT15
		Chair/Security: Wolfgang Jäger, University of Alberta	
18:00	– 20:00	**UofA drinks/finger food: Poster Session**	

Wednesday, Aug. 10, 2022			**NRE 2-001**
			Assistant Tech Chair: Guojie Li, University of Alberta
			Chair: Jan Helbing, University of Zürich
8:30	–	9:05	Patrick Vaccaro IT16
9:05	–	9:25	Yanqing Yang (on-line) CT11
9:25	–	9:45	Piero Lafiosca (on-line) CT12
9:45	–	10:20	Valentin Paul Nicu IT17
10:20	–	10:55	**Coffee Break**
			Chair: Christian Merten, Ruhr-University Bochum
10:55	–	11:30	João M. Batista Jr. IT18
11:30	–	11:50	Monika Krupova CT13
11:50	–	12:10	Amin Moazeni CT14
12:10	–	12:30	Giovanna Longhi CT15
12:30	–	13:30	**Gaussian lunch**
			Conference Excursion
14:00	–	14:15	**Bus ride to Fort Edmonton Park**
14:15	–	17:30	Tour the park
17:30	–	20:30	**Gala dinner/ BioTools Poster prize and PCCP book prize winners**
20:30			**Bus ride back to Lister Center**

Thursday, Aug. 11, 2022			**NRE 2-001**
			Assistant Tech Chair: Mutasem Alshalalfeh, University of Alberta
			Chair: Arsh Hazrah, University of Alberta
8:30	–	9:05	Reinhard Dötzer IT19
9:05	–	9:40	Emilio J. Cocinero IT20
9:40	–	10:15	**Coffee Break**
			Chair: João M. Batista Jr., UNIFESP
10:15	–	10:50	Fan Xie (on-line) IT21
10:50	–	11:10	Chiara Sepali (on-line) CT16
11:10	–	11:25	Closing remarks & invitation to VOA8 2024
Thank You for Attending VOA7 2022, Edmonton, Alberta!			

Instrumentation and Artifacts in Raman Optical Activity

Carin R. Lightner, Hannah Niese, Stefan A. Meyer, Robert C. Keitel, Daniel Gisler*, David J. Norris

Optical materials Engineering Laboratory ETH Zurich

*Istituto Ricerche Solari Locarno (IRSOL), Università della Svizzera italiana (USI)

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Raman optical activity (ROA) is a powerful chiroptical technique with the ability to determine absolute configuration of chiral molecules and to study protein structure in biologically relevant solvents. Despite its promise, experimental ROA studies are still much less common than studies with vibrational circular dichroism (VCD), a closely related technique. Much of this difference relates to the greater complexity of ROA instruments, and the problem of artifacts in ROA. ROA measurements require careful control of both the incident and scattered polarization states, as well as needing spatial rather than point detection systems to resolve the full spectrum. The standard of modern ROA instruments was set by Werner Hug in 1991, and the impact of artifacts was further reduced by Hug's development of the virtual enantiomer system in 2002. (1,2) Despite these advances, the complexity of ROA instrumentation and the problem of artifacts still prevents ROA from widespread use. We have constructed a new ROA instrument based on high-frequency polarization modulation. (3) Our instrument has greatly reduced complexity while performing on-par with instruments based on Hug's design. We couple high-frequency polarization modulation with a spatial detector using the Zurich imaging polarimeter (ZIMPOL). Additionally, we have developed an expanded method of understanding and identifying artifacts in ROA measurements. Together these advances push ROA instrumentation closer to the more widely used domain of CD and VCD instruments. It is our hope that our advancements in instrumentation will allow researchers to fully exploit the potential of ROA measurements.

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Imaging the Photoelectron Circular Dichroism in the Photodetachment of Deprotonated 1-Indanol Anion

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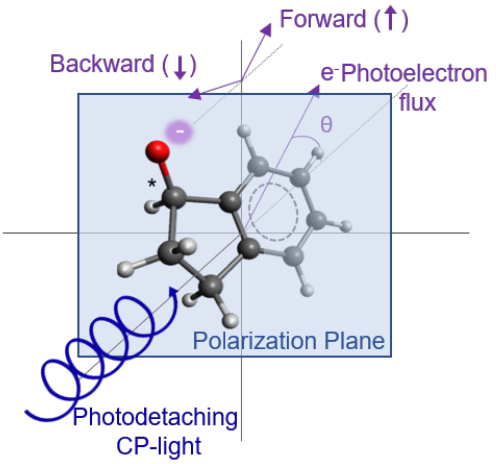
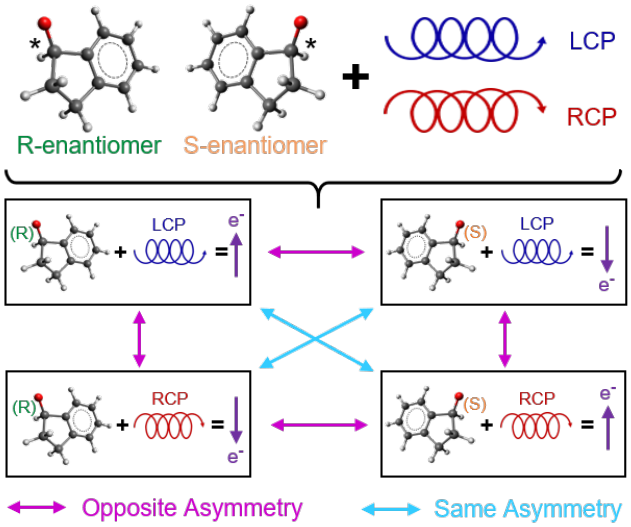
Photoelectron Circular Dichroism (PECD) is a method of chiral discrimination, which can aid in our fundamental understanding of electron dynamics and holds promise for future analytical techniques of chiral compounds. In PECD, irradiation of a non-racemic sample by circularly polarized light, resulting in the detachment of an electron, leads to a forward-backward asymmetry of the photoelectron angular distribution. This technique has significant advantages over other optical CD methods, such as absorption circular dichroism, as sensitivity to the molecular chirality can manifest within the electric-dipole approximation, bypassing the need for observation of weak interactions with a molecule's magnetic moment. Additionally, the use of anions for this technique would allow for mass-selectivity and eliminate the need for X-ray based ionization sources, thus leading to a potentially robust analytical tool for chiral discrimination of dilute multicomponent gas-phase samples. PECD as it pertains to neutral chiral species has flourished over the past two decades, evident by the many theoretical and experimental works now available.[1] However, PECD of anions has only been observed within the last year, in an experiment lacking in mass selection and energy resolution.[2] By coupling the PECD technique with pre-photodetachment mass selection and velocity-map imaging, we are able to provide an energy-resolved PECD signal for the isolated species of deprotonated 1-indanol anion. We have identified a maximum PECD signal of approximately 10% for an enantiomeric pure sample, which is similar to what has been seen for neutral indanol.[3]





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UV-Labelling Instead of Isotope Labelling for Transient Circular Dichroism Spectroscopy of Biomolecules

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IR transition dipole moments, their couplings and hence vibrational circular dichroism (VCD) signals are intrinsically weak and their detection requires rather high sample concentrations, in particular when isotope labels are used to obtain local structure information. These high concentrations make it very difficult to excite a sufficient fraction of the sample in time-resolved VCD experiments[1]. We discuss an alternative approach, where we seek information on local conformation changes of the peptide backbone by a combination of transient UV-circular dichroism and -labelling. Ultrafast transient CD-spectroscopy has recently been extended to cover the deep UV (250-350 nm) with broad-band femtosecond laser pulses[2]. Single-atom substitutions of backbone carbonyls with thio-carbonyls give rise to localized absorption and CD signals in this spectral window, which are more than twenty times stronger than their mid-IR ($^{13}C=O$ stretch) analogues. It has thus become possible to observe the coupling of localized electronic transitions and its change in time[3,4].

We investigate light-induced folding and unfolding of *β*-hairpin model peptides (Tryp-zippers), where different pairs of peptide bonds have been labeled by thio-carbonyls. Conformational change is induced by trans-cis isomerization of an azobenzene derivative which replaces two amino-acids in the turn region[3]. While clear differences between the CD-signals of the labels in the folded and unfolded states are promising, we also observe significant effects on hairpin stability, which depend on the position of the thio-substitution. An extension of the experiments to observe tryptophan coupling changes near 220 nm will also be discussed.

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Quantitative, Rapid Chiral Analysis by Molecular Rotational Resonance Spectroscopy

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Determination of the absolute configuration and enantiomeric excess of small chiral molecules, both in pure analytical samples and in mixtures, is an area of broad interest in industry and research. Chiral chromatography (gas, liquid, or supercritical fluid) is a powerful tool for enantiomer separation and quantitation, but requires enantiomeric standards in order to confidently determine the elution order. Meanwhile, vibrational circular dichroism and Raman optical activity can determine absolute configuration via comparison of experimental spectra to quantum chemistry calculations, but are not effective at determining enantiomeric excess without a reference or at direct analysis in mixtures. Molecular rotational resonance (MRR) spectroscopy with chiral tagging can serve as an effective complement to these techniques. In this method, a small chiral molecule is used to convert spectroscopically equivalent enantiomers into resolvable diastereomers through noncovalent gas-phase complexation.[1,2] Both absolute configuration and enantiomeric excess, on pure samples and in mixtures, can be performed. In this talk, I will present applications of chiral analysis by MRR within the pharmaceutical, chemical, and consumer products industries. Many of these chiral measurements can also be performed in a rapid measurement enabling routine analysis of analytes.

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Computational tools for VCD analysis

Marco Fusè

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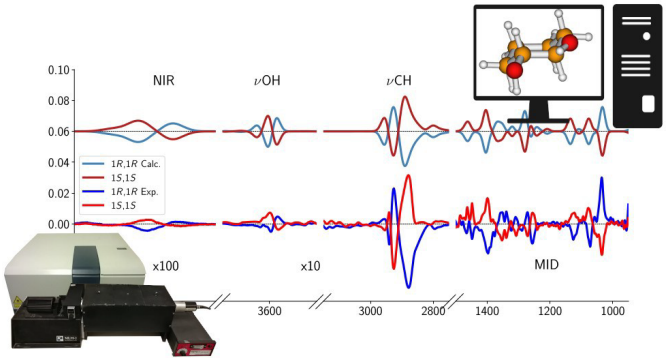

Over the years, chiroptical spectroscopy supported by Density Functional Theory (DFT) calculations has gained considerable success in assigning the absolute configuration and in evaluating the conformational properties of many molecular systems, organometallics included.[1,2,3] Vibrational spectroscopy is particularly appropriate to directly extract structural and physico-chemical information on the ground states. Inclusion of the anharmonic treatment is often still overlooked, but it is mandatory in some regions of the spectra, where the harmonic approximation is known to fail. Indeed, taking into account anharmonicity allows evaluation of the contributions of overtone and combination bands.[4]

Accurate simulations require several steps which start with a careful exploration of the conformational landscape of the systems up to the inclusion of anharmonic corrections. Flexible molecules are characterized by closely spaced energy minima, all contributing to the overall spectrum. Herein, we present a set of procedures which can be employed to achieve accurate simulation of the experimental spectra. Meta-heuristic algorithms are used in two-stage QM/QM′ (Quantum Mechanical) exploration/refinement strategy to achieve a cheap yet complete exploration of the conformational space.[5] The low-energy structures are subsequently evaluated at higher level of theory, including anharmonic corrections, allow one to compare experiments and simulation without the need for empirical scaling factors.[6] Nonetheless, the application to large and flexible systems remains challenging and *ad hoc* models are needed. In this contribution we will also discuss some tools to sustain anharmonic calculations, taking into account large amplitude motions and the presence of resonances.

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Forefront dynamic methods for chiral spectroscopy in gas and condensed phase

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I will give an overview about our developments for computational approaches for chiral systems with emphasis on dynamic methodologies.

I will discuss our efficient approach based on density functional perturbation theory for the accurate calculation of vibrational Raman optical activity (VROA) spectroscopy, which has been used to compute the first VROA spectra from density functional theory-based molecular dynamics [1,2]. Moreover, novel analysis methods have provided important insight for molecules in gas phase as well as condensed phase systems such as (ionic) liquids [3,4]. In addition, we have recently presented a pioneering implementation using nuclear velocity perturbation theory based on velocity-dependent atomic basis functions and magnetic field perturbation theory in the CP2K program package, thus allowing to compare those two approaches on equal footing for the first time [5].

Other research directions have concerned real time propagation methods and their extension to chiral systems [6]. I will present our efforts for electric circular dichroism [7], discuss the importance of the choice of gauge and presentations for property operators, and show our pioneering calculations for VROA [8]. The latter has allowed to obtain entire excitation profiles including off-, pre- and on-resonance effects within one set of simulations and has very recently been extended from gas to condensed phase systems obeying periodic boundary conditions [9], giving unprecedented insight into the complex behaviour of chiral molecules in solution.

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On the usefulness of measuring the degree of circularity in Raman scattering

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A quantity called the degree of circularity (DOC), measured in Raman scattering when excited by circularly polarized radiation, was first promoted in a paper by Werner Hug in which it was used as a measure of the susceptibility of Raman optical activity (ROA) bands to artifacts.[1]

We try to review also other important areas in which the degree of circularity is essential.

It can be shown that the DOC can be used to reliably distinguish in measured circular intensity difference (CID) spectra whether the observed spectral bands originate from a Raman scattering or luminescence.[2] This is possible because Raman scattering is a two-photon process sensitive to the polarization of the excitation radiation. In contrast, circularly polarized luminescence (CPL) consists of two one-photon processes, and the information about the polarization of the excitation radiation is primarily lost.

The degree of circularity also plays a prominent role in the phenomenon arising from the interaction of electronic circular dichroism with polarized Raman scattering (ECD-Raman), which also manifests itself as a spurious signal when measuring the Raman optical activity of absorbing substances exhibiting circular dichroism.[3] However, just as importantly, we can reliably simulate the ECD-Raman signal using DOC, ECD, and absorption measurements and subtract it from the measured CID spectra in order to obtain a pure resonance ROA signal.[4]

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A rotational perspective on the recognition problem for chiral molecules

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Since the dawn of the chirped-pulse era [1], broadband rotational spectroscopy has become a foundation for new methods to explore beyond conventional spectroscopy and attain next-level tracing and even acquire control over molecular properties. The improved sensitivity of the technique has unlocked studies of increasingly more complex molecular species, including molecular motors [2], and large molecular complexes [3,4]. With the intrinsically narrow line widths of rotational transitions, microwave spectra are molecular fingerprints that grant unambiguous assignment of exact three-dimensional structures, and even allow identification and quantification of enantiomers using recently developed strategies. In this scope, microwave three-wave mixing [5,6] and chiral tag rotational spectroscopy [7,8] have both become very competitive methods for sensing and quantification of enantiomeric samples in the gas phase, challenging the precision and accuracy of other established analytical standards. Using the results from recent investigations, we will discuss these chiral-sensitive measurements, their underlying concepts, and their reach beyond the realms of analytical science.

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Chiral-Tag Molecular Rotational Resonance Spectroscopy of Methyl Lactate Dimers

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Methyl lactate, one of the simplest chiral easters, has been an important research object for chiral recognition using low resolution jet-cooled Fourier transform infrared spectroscopy [1,2]. The methyl lactate monomer has the ability to form a strong intramolecular hydrogen bond between the hydroxy group and carbonyl group and its aggregates show a robust competition between intra- and intermolecular hydrogen bonding interactions. Rotational spectra of the most stable monomeric conformer and its many isotopologues were reported previously, as well as the tunneling splittings associated with the ester methyl and the α-carbon methyl internal rotors.[3,4]

In the current study, we applied broadband chirped-pulse Fourier transform microwave spectroscopy to detect binary aggregates of methyl lactate in the 2-12 GHz range. Rotational spectra of several binary conformers of methyl lactate were assigned, with the aid of a conformational searching tool, i.e., CREST, and subsequent DFT calculations. The high resolution nature of the experiments allows one to obtain structural and energetic details of individual conformers, examine the associated conformational landscape and the influence of additional intermolecular interactions on the splittings of the internal rotors, and also discuss the relative constitutions of different forces to the chirodiastaltic energy, i.e., the energy responsible for chirality recognition.

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Molecular Structural Analysis Using VCD Spectroscopy in the 2400-1900 cm^{-1} Region

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Common biomolecules do not show strong absorption in the 2400-1900 cm^{-1} region. Vibrational chromophores such as alkyne, nitrile, isonitrile, azido, allene, carbodiimide, and C-^{2}H bond have been known to exhibit characteristic IR absorptions in this biomolecularly transparent region. Some of these chromophores have been utilized as vibrational probes in biomacromolecular IR and Raman studies (*e.g.*, studies for oligonucleotide conformations, protein fibril formation, and drug-protein interactions). However, applications of these chromophores for structural analysis using VCD spectroscopy have not been studied in detail. We have introduced these chromophores to various chiral molecules and observed their VCD signals. Through the studies of these chromophores, this paper discusses three topics (1)-(3) shown below.

(1) Chromophores for observing a VCD couplet in the 2400-1900 cm^{-1} region

We previously reported that two carbonyl groups in a chiral molecule yield a strong VCD couplet whose shape reflects the relative orientation of these groups.[1] High signal intensity achieved by this approach should be useful for structural analysis of biomacromolecules. We examined the applicability of alkyne, nitrile, isonitrile, and azido groups for observing a VCD couplet. We chose a chiral binaphthyl as a model scaffold and synthesized binaphthyls possessing two of these chromophores. VCD measurements of these molecules found that the 2400-1900 cm^{-1} VCD signals originating from alkyne were too small. Meanwhile, nitrile and isonitrile exhibited moderately strong VCD signals; however, their signals are largely affected by anharmonic contributions, which make a proper interpretation of the VCD signals difficult. Azido groups showed the strongest VCD couplet and its interpretation was feasible with using theoretical calculations.[2] Application of azido groups for biomolecules has also been demonstrated.

(2) Extraction of local stereochemical information by one chromophore

VCD couplet approach requires introduction of two chromophores to suitable positions. We found that, in a suitable case, one chromophore is sufficient to extract local stereochemical information in the presence of various substituents and stereocenters in other moieties.[3]

(3) Chromophores with axial chirality

Allene and carbodiimide were excluded from the studies (1) and (2) because of their axially chiral structures. The axial chirality of carbodiimide was predicted in 1932, but the preparation of carbodiimide with one-handed axial chirality had not been reported. We showed that the use of a conformationally restrained cyclic structure provides carbodiimides with one-handed axial chirality, as proven by VCD.[4]

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Vibrational Optical Activity as a unique tool to study biological and artificial supramolecular systems

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Due to exciton coupling, supramolecular chirality is a source of a very intense chiroptical signal, giving the opportunity to use vibrational optical activity (VOA) methods, which show superb molecular sensitivity over electronic chiroptical techniques, but are inherently hindered by their low sensitivity compared to their vibrational 'parent' techniques (IR and Raman spectroscopies). Exploring resonance enhancement due to carotenoid aggregation, we addressed the issue of chiral organization of carotenoids in model membranes (liposomes), micelles, and in conjunction with the protein (**Fig. 1**). Spectacular examples of supramolecular architectures that give extraordinarily intense chiroptical signal are protein fibrils; hence, we used VCD combined with microscopic methods to determine the structure, microstructure, and polymorphism of amyloid fibrils obtained from several common proteins. Last, but not least, we analyzed metal complexes designed to function as stereodynamic probes enhancing the chiroptical readout of small chiral co-ligands. Our research confirm that VOA is a unique tool for characterizing a variety of chiral supramolecular assemblies.

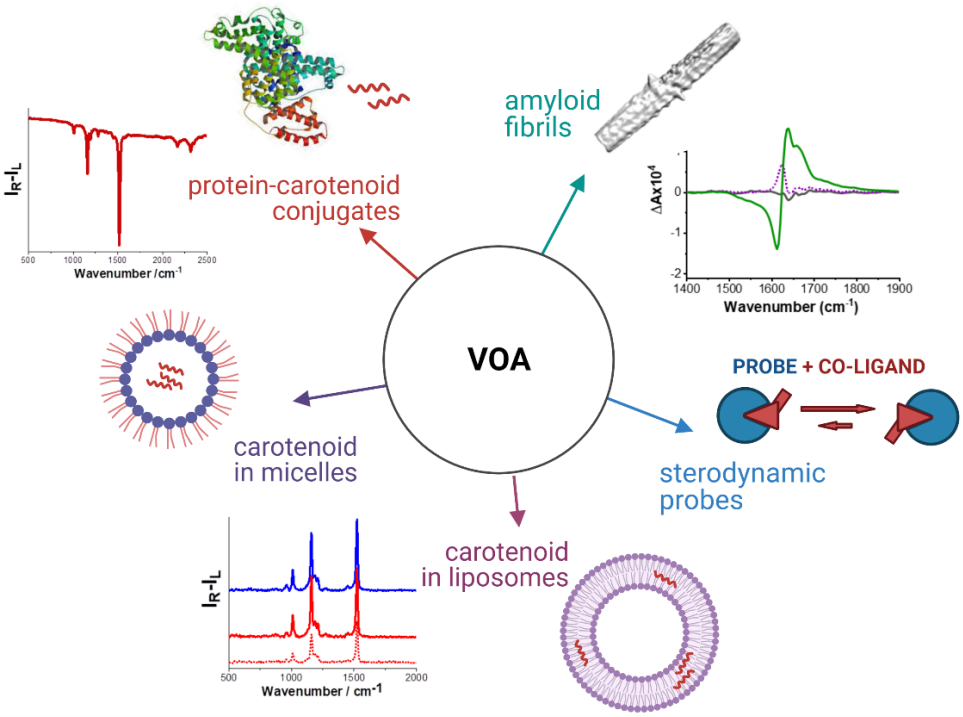

Fig. 1. *Schematic representation of various supramolecular systems analyzed using VOA (created with Biorender.com).*

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Vibrational Circular Dichroism Spectroscopy as a Tool for Exploring Conformational Distributions of Oligopeptides.

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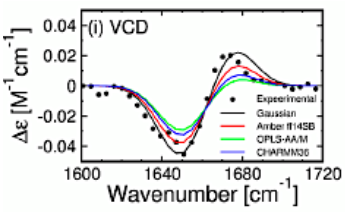
While UV circular dichroism spectroscopy is an established tool for exploring the structure of peptides and proteins in solutions vibrational circular dichroism spectroscopy is still somewhat of a rarity in the field of Biospectroscopy. We have utilized the enormous structural sensitivity of amide I VCD to explore the conformations of unfolded peptides as well as the large scale self-assembly of short peptides into long fibrils on a nano- and even micrometer scale. Our research group has combined VCD with IR, polarized Raman and NMR spectroscopy to obtain Ramachandran distributions of non-terminal amino acid residues in tri-, tetra and pentapeptides. We showed (a) that the Ramachandran plots are side chain specific, (b) that amino acid residues predominantly sample the upper the left quadrant of the Ramachandran plot where they differ with respect to their polyproline II (pPII)–β-strand ratio[1] and (c) that a residue's conformational distribution depends on the conformational preferences of its neighbors.[2–4] Recent force field developments for molecular dynamics simulations have focused on reproducing the exceptionally high pPII propensity of alanine residues. We recently tested the capability



of some of these new releases to reproduce a series of J-coupling constants and the amide I' VCD profile of the cationic GxG peptides (x represents different amino acid residues) in D_2O. The inserted figure compares the experimental VCD spectrum of GAG (dotted) with signals obtained with CHARMM 36 (blue), OPLS-AA/M (green), Amber ff14SB and an empirical model based on the superposition of two-dimensional Gaussian distributions (black).[5] None of the investigated force fields reproduces the pronounced VCD couplet of GAG and other GxG peptides as well as the fit of our empirical Gaussian distribution model.[6] Among the force fields Amber ff14SB produces the best results for GAG and AAA.[5]

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Polymorphism of amyloid fibrils studied using chiroptical spectroscopies combined with microscopic methods

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Amyloid fibrils are mostly known as pathological protein aggregates in human neurodegenerative diseases. However, due to their exceptional properties, there is a growing interest in the application of amyloid fibrils as advanced and versatile nanomaterials. The possibility to synthesize functional nanomaterials from proteins is very attractive due to the simplicity of the *in vitro* reaction, their natural origin and low cost of the reagents. Natural biopolymers, such as amyloid fibrils, can be a future alternative to synthetic materials causing plastic global pollution.

In this work, the *in vitro* process of amyloid fibrils formation was controlled and characterized by chiroptical spectroscopies: VCD (Vibrational Circular Dichroism) and ECD (Electronic Circular Dichroism), as well as microscopic methods: TEM and cryo-EM (Transmission Electron Microscopy). We observed a remarkable diversity of amyloids fibrils structures, that underlie amyloid polymorphism, depending on the specific aggregation conditions. We have shown that homolog native proteins may have a very different unique signatures of mature fibrils (**Fig. 1**). Numerous fibrils' architectures were investigated and systematic analysis of their properties enabled a better understanding of fibrils' stability and the mechanism of their formation, what is important both for the amyloidosis prevention as well as for better control of the process of artificial fibril formation. Our results contribute to optimization of amyloid materials in order for successful functionalization using specific biomacromolecules, fluorophores, nanoparticles, nanowires, etc., for novel applications.

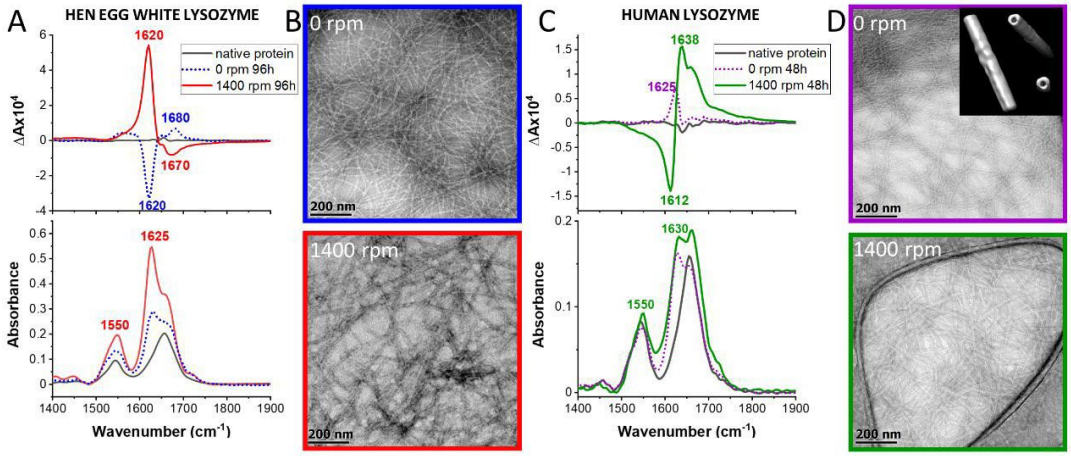

Fig. 1. *Different architectures of fibrils obtained from lysozyme homologs. VCD/IR spectra (**A, C**) and TEM images of fibrils (**B, D**). Conditions: 60 mg/ml, pH 2, 60°C, agitation (0 rpm or 1400 rpm).*

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Enantiomeric Discrimination by SERS-Chiral Anisotropy of Chiral Nanostructured Gold Films

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Abstract: As one of the typical route of enantiomeric discrimination, chiral detection and quantification is of critical importance in many areas of analytical sciences, chemical biology, and the development of pharmaceuticals and pesticides. Multiple theoretical concepts and chiroptical spectroscopic techniques, such as optical rotation (OR) and circular dichroism (CD), have been developed based on the selective interaction between enantiomers and circularly polarized electromagnetic waves to identify the absolute configuration and composition of enantiomers. However, these methods are impossible to use for racemates and enantiomers with weak optical interactions; thus, finding a new chiral response effect remains a challenge. Here, we report a surface-enhanced Raman scattering-chiral anisotropy (SERS-ChA) effect that combines chiral discrimination and surface Raman scattering enhancement on chiral nanostructured Au films (CNAFs). Right- and left-handed CNAFs (R/L-CNAFs) composed of antipodal Boerdijk- Coxeter-Bernal helical Au nanofibres were grown perpendicularly on various substrates with N-Acetyl-S/R-Cysteine (S/R-NAC) as symmetry breaking agents. The SERS-ChA effect was validated by identifying over a hundred pairs of enantiomers with different electric dipole configurations, sizes, chromophores, concentrations, and *ee* values. On R- CNAFs, sinister (S) molecules exhibited remarkably higher Raman enhancement factor than their rectus (R) analogues. The enhancement factor was linearly correlated with the *ee* value of enantiomeric percentage. Except for the molecules with mesomeric species in the same amount of chiral centres, all of the enantiomers tested can be quantified with a high *anisotropic* factor (*g*-factor) ranging between 1.34 and 1.99. Selective resonance coupling between the induced electric and magnetic dipoles due to co-operative spin polarization between the enantiomers and chiral plasmonic modes of CNAF was speculated to be responsible for the SERS-ChA effect. These findings open the door to a promising strategy within enantiomeric discrimination technologies and new horizons for chiral responses in chemistry, physics and biology.
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Keywords: chiral mesostructure; chiral anisotropy; inorganic materials; enantiomeric discrimination; SERS

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Discovery of a New Type of Chiral Raman Spectroscopy

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Resonance Raman optical activity (RROA) measures the small intensity difference between the scattered right circularly polarized light, I_R, versus scattered left circularly polarized light, I_L, when a randomly polarized light is scattered off and is also in resonance with a chiral molecule. Researchers have explored RROA as a mean to significantly enhance the weak ROA response for the past two decades, although the progress has been severely hampered by the lack of agreement between theoretical and experimental RROA spectra so far.

In 2019, we reported chiral Raman measurements of a resonating chiral Ni complex, where extremely large chiral Raman responses of a range of achiral and chiral solvents were detected.[1] These large chiral Raman pattens (relative intensity and signs) could be reproduced by treating the resonating Ni system as quantum plasmons, although the predicted magnitude was much smaller compared to the experiment. In 2020, after examining a series of light-matter events which could occur simultaneously under a typical RROA experimental condition, we discovered a new form of chiral Raman spectroscopy, eCP-Raman---a combination of electronic circular dichroism (ECD) and circularly polarized Raman (CP-Raman).[2] All the experimental chiral Raman features of solvents could be well reproduced by this eCP-Raman mechanism. One year later, Further analyses of the experimental $I_R - I_L$ spectra of three resonating chiral solute molecules revealed that they could also explained by the novel eCP Raman mechanism without any detectable contributions from natural RROA.[3] The discovery of eCP-Raman allows one to extract true RROA contribution from the $I_R - I_L$ signal obtained under resonance to facilitate the current theoretical RROA development. Furthermore, eCP-Raman offers a new way for sensitive chirality detection of molecular systems in biology and chemistry.[4]

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Knotty spectroscopy of chiral atropisomeric naphthalenediimides

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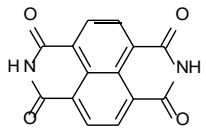
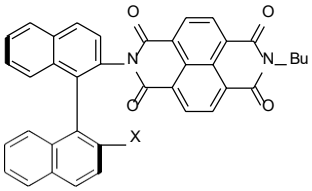
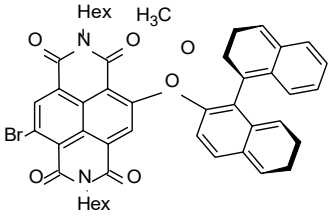
Naphthalenediimide (NDI) moiety is an important core for modern low molecular weight organic semiconductors and other applications. Chiral NDIs provide amazing supramolecular structures, but monomers are studied less frequently. Recently, we synthesized a series of atropisomeric NDI derivatives, axially chiral due to the hindered rotation of the binaphthyl (B) rings. The chiral substituent was attached both to the N and C-atoms (N,C-NDIB):



NDI



(*S*)-N-NDIB-X (X= NH_2, $NHCH_3$, OH, OCH_3)



(*S*)-C-NDIB

N-NDIB-X exhibited a weak ECD band nearby 532 nm - Raman optical activity (ROA) excitation line [1,2]. Unexpectedly, instead of the resonance ROA bands of studied molecules, the spectra were dominated by solvent bands. The sign was the same as that of the resonating ECD band and the observation was related to ECD combined with circularly polarised (CP) Raman scattering [2- 5]. We showed that the signal in this relatively recently discovered spectroscopy (ECD-Raman or eCP-Raman) can be modulated by a careful selection of the substituent or solvent. The π-electron donor-acceptor properties of the substituent, its bulkiness, and the ability to form intermolecular hydrogen bonds with the solvent affect the resonance conditions and sign of the resonating ECD band. Despite the rigidity of N-NDIB-X molecules, the interpretation of their ECD spectra required calculations with a complete hybrid explicit-implicit solvation model. The conformational flexibility of the in-core substituted C-NDIB derivatives further complicated the analysis.

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Two-Cells Raman Optical Activity Experiments: Mechanism of Chiral Raman Signals of a racemic Europium Salt and a Complex with a Near Resonance Transition Ni Complex

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Chiral lanthanide complexes often exhibit strong circularly polarized luminescence (CPLu) signals and have been studied extensively for their binding and sensing applications.[1] While CPLu is typically measured using a CPLu spectrometer,[2] a recent new development is to utilize a Raman optical activity (ROA) spectrometer to measure CPLu spectra, [3] illustrating the versatile applications of such an instrument.

In this work, we examined the $I_R - I_L$ signal of a mixture of a racemic Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium complex [Eu(fod)$_3$] with a chiral Ni transition metal complex[4] which is in (near) resonance with the 532 nm laser source using an ROA spectrometer. The goal was to understand and evaluate the contributions of different chiroptical events to the observed $I_R - I_L$ signal detected at the luminesce bands of [Eu(fod)$_3$]. More specifically, we evaluated whether chemical contact with a resonance chiral Ni metal complex, the excited state CPLu, and/or electronic circular dichroism of the Ni complex[5] are the dominant contributors or not. To achieve this goal, we applied both one-cell and two-cell measurements[5] and compared to the results with a related achiral Eu salt. The relative importance of different mechanisms contributed to observed $I_R - I_L$ signal will be discussed.

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Resonance Raman optical activity (RRROA): measurement challenges and how to deal with them

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Raman optical activity (ROA) is a great chiroptical tool for biomedical study. ROA can be used to study e.g. the absolute configuration and conformational equilibrium of chiral compounds, as well as secondary and tertiary structure of proteins. The most commonly used form of ROA (SCP-ROA) measures the intensity difference in Raman scattering of right- and left-circularly polarized light. However, the non-resonance ROA signals are rather weak, 3-4 orders of magnitude weaker than the classical Raman. In order to measure good ROA spectra, highly concentrated samples, long accumulation times and high laser power are needed.

Being a much more sensitive method, Resonance Raman optical activity (RROA) can be used to measure biomolecules in much lower concentrations, but its measurement and spectral analysis is still challenging. Recently it has been reported that RROA spectra may be masked by other spectroscopic effects such as electronic circular dichroism (ECD) in combination with circularly polarized Raman scattering (ECD-Raman). [1] We demonstrate here on a series of vitamin B12 analogues, how to recognize true, not attenuated RROA and how to minimize or subtract the ECD-Raman effect from measured RROA signal. [2]

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Modelling of protein vibrational optical activity

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Protein conformations are extensively studied in order to understand their behavior and biological functions, including protein roles in neurodegenerative diseases. Vibrational optical activity (VOA) can be used to monitor the structure of peptides and proteins in solutions. Quantum-chemical calculations are conveniently used to interpret the spectra and obtain the link between geometry and spectral patterns. However, due to their high computational demands, direct calculations have been often limited to relatively small systems.

We therefore applied a multi-level computational strategy to large proteins, to explain the spectral response of protein fibrils (α-synuclein[1], polyglutamic acid[2]) or low frequency Raman optical activity of poly-L-alanine[3]. The geometry was taken from x-ray or molecular dynamics simulations, the spectroscopic properties were obtained from the density functional theory on smaller fragments and transferred to the larger system. For fibrils, the periodicity can be used in a crystal-like model.

Satisfactory agreement of calculated VOA spectra with the experimental ones was obtained (e.g. Fig. 1), indicating that the method can be generally used for biomolecular conformational studies.

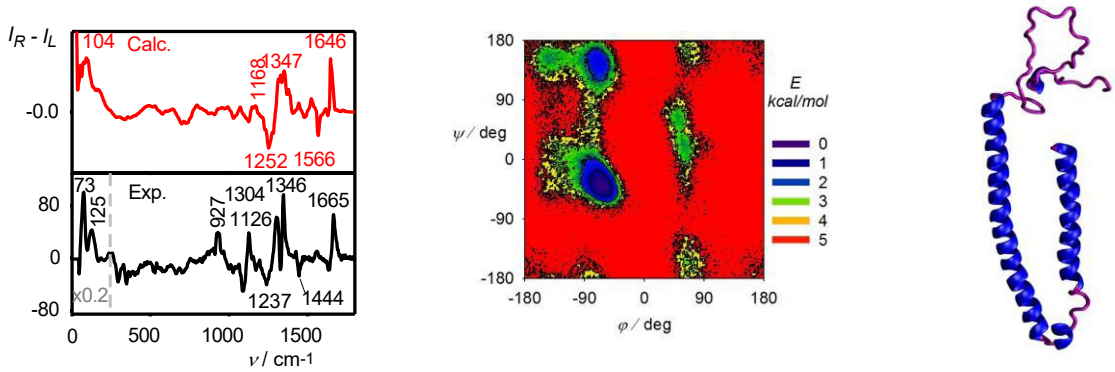

Fig 1. Simulated and experimental ROA and Raman spectra of α-helical conformation of α-synuclein (left), its Ramachandran plot (middle) and the structure (right)

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Accurate determination of enantiomeric excess by Raman optical activity

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The knowledge of the optical purity of a chiral sample is of great importance, especially in the analytical chemistry and pharmaceutical industry. In recent years, vibrational optical activity has emerged as a sensitive and non-invasive technique for the analysis of chiral molecules in solution. Despite this, the relatively limited accuracy of enantiomeric excess (EE) determination in the range of 1–2% reported in previous studies may be considered insufficient in some situations.[1,2]

For this reason, we attempted to propose a new methodology for the determination of enantiomeric excess using Raman optical activity (ROA), which would achieve higher accuracy. It was necessary to use algorithms for Raman baseline correction, ROA intensity normalization, and systematic error elimination. Higher accuracies of 0.05% for neat α-pinene and 0.22% for an aqueous solution of alanine were achieved within ~6 hours of signal accumulation for each enantiomeric mixture. These results confirmed that ROA is a valuable tool for the quantitative analysis of enantiomeric mixtures.[3]

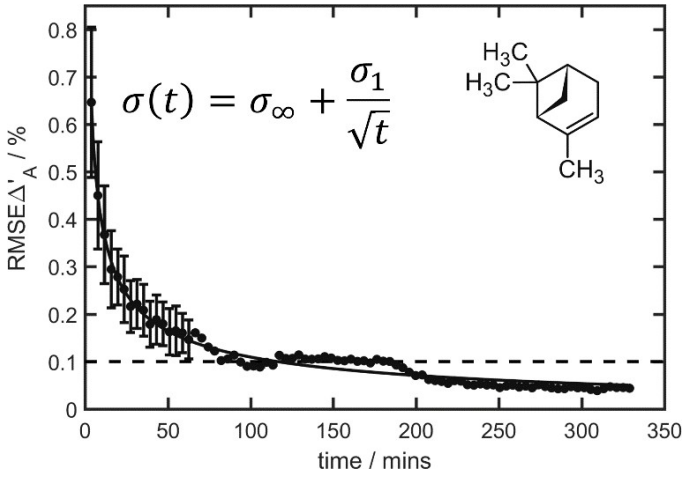

Fig 1. Dependence of the accuracy of the enantiomeric excess determination on the measurement time of one α-pinene mixture.

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Computing Bulk Phase VCD and ROA Spectra from *ab initio* Molecular Dynamics Simulations

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We present our newly developed methodology for computing Raman optical activity (ROA) spectra of liquid systems from *ab initio* molecular dynamics (AIMD) simulations [1]. The predicted spectra capture the full explicit solvent effect and show realistic line shapes when some anharmonicities *(hydrogen bonds, etc.)* are present. The method is built upon our recent developments to obtain magnetic dipole moments from AIMD [2] and to integrate molecular properties by using radical Voronoi tessellation [3]. Large and complex periodic bulk phase systems can easily be treated, since only AIMD simulations are required as input, and no time-consuming perturbation theory is involved. The approach relies only on the total electron density in each time step and can readily be combined with a wide range of electronic structure methods. To the best of our knowledge, this is the first protocol to predict ROA spectra of periodic bulk phase systems. Even large and flexible molecules can be treated by our approach. As an example, the experimental ROA spectrum of *N*-acetyl-L-cysteine (NALC) in water is reproduced well *(see Figure 1)* [6].

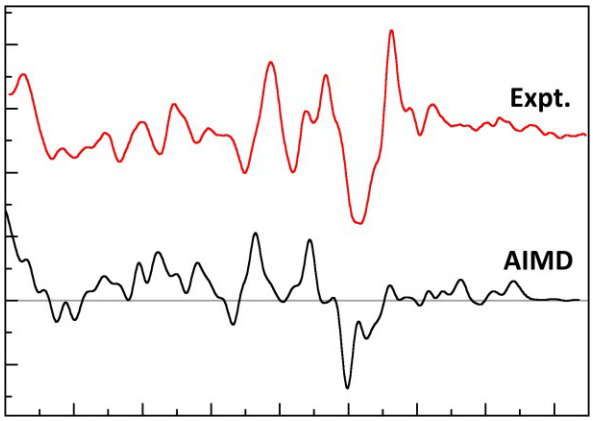

Figure 1: Experimental and predicted ROA spectrum of *N*-acetyl-L-cysteine in water [6].

Together with our previous work on infrared, Raman, resonance Raman, and VCD spectroscopy [2-5], the full set of vibrational spectra is routinely accessible for complex periodic bulk phase systems now through an unified protocol. The methods are all implemented in our freely available open-source program package TRAVIS [7-8], and a step-by-step tutorial is available online [9].

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[9] `https://brehm-research.de/spectroscopy`

Computation of Vibrational Circular Dichroism in the Periodic Gauge

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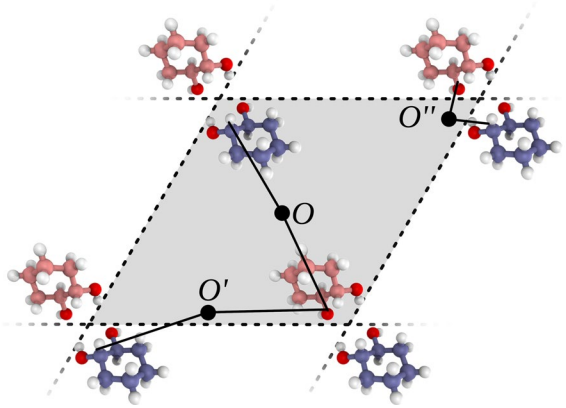
Solid-state VCD is becoming ever more popular in academic research as well as in pharmaceutical industry. It circumvents the necessity of substrate solubility since the measurements are carried out directly on (powdered) microcrystals dispersed in a matrix material. At the same time, the molecules, closely packed, have low conformational flexibility, thus exhibit sharper, more intense VCD signals than in solution. [1] In addition, packing effects that show as non-local contributions gain large influence on the spectrum, which endows VCD with the capacity to distinguish polymorphs.

In this talk we discuss the computation of solid-state VCD and point out the limitations of the conventional theoretical framework used for the definition of VCD in solution or gas phase. A solid-state model resorts to repeating structural units of the molecular crystal sample (e.g., unit cells) and is therefore fully periodic, which renders the absolute position of atoms, charges or electrons ill-defined due to the lack of a universal reference point (origin). Applying the prevalent computational protocol, the VCD spectrum turns out differently depending on the choice of origin – although it should, as a physical observable, be origin invariant. We show that it is possible to formulate VCD with an explicit account for periodicity, which re-connects the theoretical model to the (finite) physical system. [2]

Several applications are presented together with the general workflow to obtain a solid-state VCD spectrum from computed molecular properties, for which we employ our python package *ChirPy*. [3] As a special extra, we introduce our recent implementation of magnetic dipole moments into a polarisable force field, which dramatically reduces the computational cost of VCD calculations.



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Good Vibrational Circular Dichroism on bad and ugly molecular systems

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Vibrational Circular Dichroism (VCD) has proven to be a powerful means to determine the stereochemistry of chiral molecular systems. In furthering its applications, a number of challenges need to be met. Firstly, the molecules that have been investigated, have been largely restricted to rigid systems with relatively few low-energy conformations. Nature is, however, not rigid but flexible, and very often exploring large conformational landscapes. Another issue is that so far molecules have been considered with only a few chiral centres. In practice, there is, however, a plethora of systems with many chiral centres, and also for such systems one would like to be able to get a grip on their absolute configuration. Finally, until now predominantly relatively small molecular systems have been studied. Being able to apply VCD to larger molecular systems would be extremely rewarding, and provide access to polymeric systems and novel molecular architectures. In this lecture I will discuss novel approaches that we have developed and applied in recent years to meet these challenges[1-6].

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On the accurate prediction of VOA spectra: recent progresses, successes and remaining challenges

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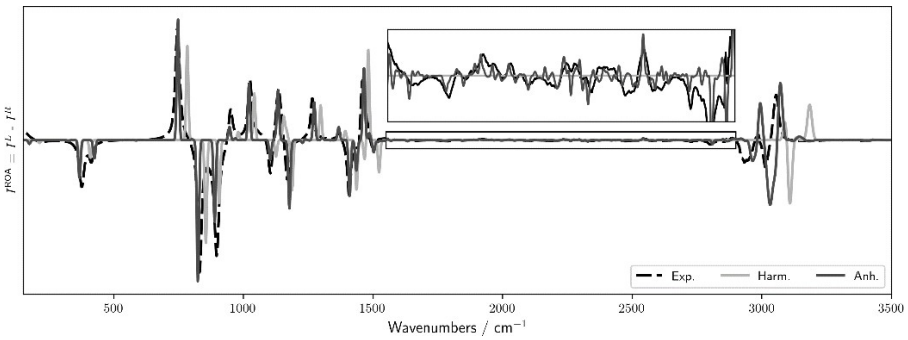
With new experimental setups and instruments capable of achieving unprecedented levels of resolution and revealing new details on vibrational spectral band-shapes, limitations in current computational protocols become more glaring. Common coping mechanisms, such as frequency scaling schemes, offer limited solutions, as newly revealed peaks often involve non-fundamental transitions. These limitations become even more evident on chiroptical spectroscopies. The availability of mirror-image spectra helps identify more clearly low-intensity bands. However, the sensitivity of such techniques, and the need to accurately predict multiple properties and their interaction pose serious challenges to the definition of reliable computational protocols, applicable to wide ranges of molecular systems.

In principle, accounting for the anharmonicity in vibrational motions can provide better predictions of the energies and intensities of fundamental bands, but also reproduce the finer features in the spectral band-shapes. However, this comes at a significant computational price. Perturbative methodologies, like the second-order vibrational perturbation theory, offer an appealing balance between cost and accuracy.[1,2] However, this is achieved by introducing new approximations, especially the so-called resonances,[3] hindering the adoption of such approaches in standard computational protocols.

In this contribution, we show recent developments on automated procedures to address the problem of resonances, leading to band-shapes close to the most detailed experimental spectra on prototypical molecules. These results have shown the need to review standard density functional theory-based protocols used to predict VOA spectra. More comprehensive benchmarks are thus needed to achieve reliable and accurate computational protocols.[4] This work paves the way to tackling larger biomolecules. To this end, ongoing works on dealing with molecular size and structure flexibility will be illustrated.



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Recent advances in the application of vibrational circular dichroism spectroscopy for the characterization of asymmetric catalysts

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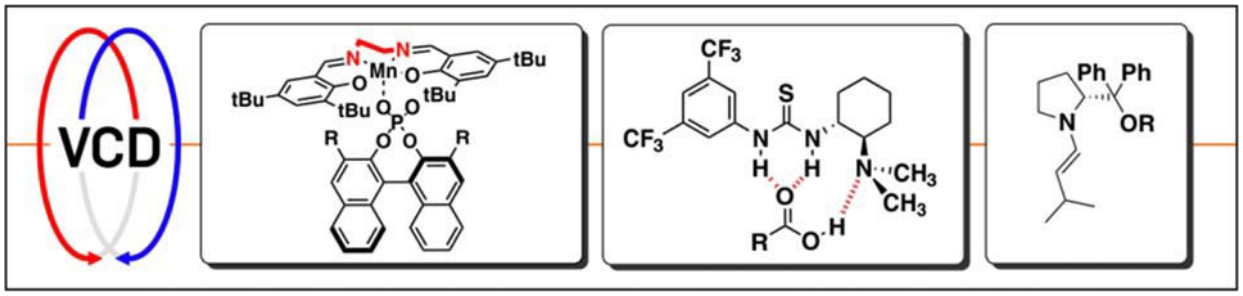
Vibrational circular dichroism (VCD) spectroscopy, the chiroptical version of IR spectroscopy, has become a frequently used method for the determination of absolute configurations.[1-3] It has furthermore been recognized to be extremely sensitive to conformational changes, often much more than a compounds parent IR spectrum. Therefore, we have begun to utilize VCD spectroscopy for the characterization of conformational preferences of asymmetric catalysts and complexes, that are formed upon interaction or reaction of a catalyst with substrates. This talk will showcase some of our activities in this research direction. We will discuss how VCD spectra of a chiral ion pairing catalyst could be used to confirm a conformational shifting mechanism that determines the catalyst's enantioselectivity.[4] Furthermore, we will see that both conformational preferences of the a thiourea catalyst as well as of its hydrogen-bonded complexes with substrates[5] can be obtained from a detailed VCD spectra analysis. Challenges of using VCD spectroscopy for the characterization of *in-situ* generated species will be discussed for examples from enamine-/iminium-catalysis.[6, 7] Finally, recent results on a hypervalent iodine(III) catalyst will be presented that serve as prime example for the capabilities of VCD spectroscopy in revealing structures of active catalysis in solution phase,[8] that cannot be obtained from other techniques.



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7-Azaindole breaks carboxylic acid dimers and simplifies VCD spectra analysis

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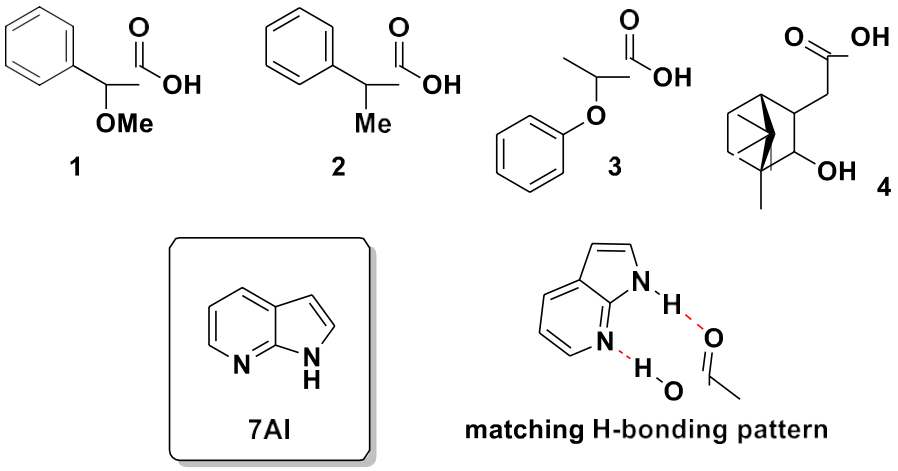
Vibrational circular dichroism (VCD) is defined as the differential absorbance, ΔA, of a chiral molecule for the left and right circularly polarized radiation, A_L-A_R in the infrared (IR) region, and is emerging as one of the most powerful and used tool for the study of optically active compounds with the comparison of the computed counterpart [1]. In the presence of carboxylic acid functional groups, the efficacy of accounting for explicit solvent effects has been proven in our group [2], but this usually means a more demanding computationally effort. In addition, carboxylic acids can form dimers in solvent like chloroform that needs to be taken into account by building and computing them. Either solvent or dimerization influences only arises after computation of the monomer or the experiment are not matching quite well. To overcome such problems, we introduce here the use of a complementary structural base as 7-azaindole (7AI) that provides a basic site interaction N, that binds -OH moiety, and the NH that binds the =O moiety. This interaction prevents the formation of the dimeric species simplifying the computational analysis. We present the application over four model compounds [scheme 1], showing not only the absence of the deprotonation, occurring in the case of using a generic amine, but also the applicability to a more complex, nature-like compound such as 4. Compound 4 also present an additional –OH group in the vicinal position that is not involved in the complexation with 7AI. Instead, in the case of a standard complexation with a base/amine or dimerization, the additional –OH group needs to be considered. The use of 7AI does not involve any chemical structural change meaning that the analyzed compound can be retrieved and this is a key feature in dealing with natural compounds that are not always easy to handle, due to a usually high flexibility and a low amount at our disposal [3].



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Structure, Conformation and Chirality of Compounds Using Computational Molecular Spectroscopy

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Computational molecular spectroscopy serves a general tool for experimental molecular spectroscopic measurements and beyond. In this presentation, I will outline computational molecular spectroscopic research development at Swinburne University of Technology (Australia) for characterisation of various medium size molecular systems. I will use a few examples where computational and experimental molecular spectroscopic studies work together to achieve the discovery. The examples including the characterization of tetrahydrofuran structure using electron momentum spectroscopy (EMS)[1]; the core electron ionization energy of dipeptides [2], model aromatic compounds[3] and recently hydrogen storage materials such as ammonia borane using X-ray emission spectroscopy (XPS); conformation determination of ferrocene (Fc) using inferred (IR) spectroscopy[4]; optical properties of cis-resveratrol using vibrational circular dichroism (VCD) and Raman optical activity (ROA) spectra[5]. And very recently, we employed simulated optical spectrum such as UV-Vis and fluorescence spectra to study conformer of 4-anilinoquinazoline derivatives based epidermal growth factor receptor (EGFR) tyrosine kinases inhibitors (TKIs)[6] as well as nuclear magnetic resonance (NMR) spectroscopy to study chirality of a recently approved drug (R)-lorlatinib. I will finish with the development of a robust quantum mechanical (QM) conformational sampling method for optical reporting of EGFR-TKI (AG-1478)[7] which is capable of calculating hundreds of conformers in the search for potent conformation under different environments. This robust method is able to reduce the research time from years to weeks.

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Nuclear Contributions to Dispersive Electronic Optical Activity: Vibrational Motion as a Mediator of Intrinsic Chiroptical Response

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The dispersive phenomena of electronic circular birefringence (ECB), which rotate the state of optical polarization for non-resonant light propagating through an isotropic chiral medium, long have been used to elaborate stereochemical configuration and to assess enantiomeric purity. Although the resulting chiroptical response stems primarily from interactions of electronic origins, the influence of large-amplitude (conformational) and small-amplitude (vibrational) nuclear degrees of freedom cannot be discounted. Indeed, seemingly innocuous vibrational motion – oftentimes mediated by strong solute-solvent coupling – has been shown capable of markedly affecting both the magnitude and the sign of measured optical rotatory dispersion (ORD or wavelength-resolved ECB) even for conformationally rigid chiral species.

Synergistic experimental and theoretical efforts designed to unravel the putative roles of nuclear dynamics on dispersive chiroptical signatures will be presented, with particular emphasis directed towards the elucidation of vibrational effects on ORD spectral profiles. An important guidepost for these endeavors can be found in the *intrinsic* response evoked from chiral molecules that are devoid of significant *extrinsic* perturbations from their surroundings. Requisite measurements of such isolated-molecule behavior have been made possible by our continuing development of cavity ring- down polarimetry (CRDP), an ultrasensitive (long-pathlength) chiroptical probe that has enabled ECB studies be conducted in rarefied gaseous media.[1] Quantum-chemical analyses built on the linear-response frameworks of density-functional and coupled-cluster theory will be used to interpret experimental findings quantitatively, thereby revealing the fundamental nature and the practical repercussions of interactions taking place between electronic and nuclear degrees of freedom.

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Conformational Analysis and Non-covalent Interactions of Tetrahydro-2-furoic acid by Using Vibrational Circular Dichroism Spectroscopy

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Vibrational circular dichroism (VCD) spectroscopy is a powerful spectroscopic tool for determination of structural properties of chiral molecules directly in solution, including their absolute configurations and conformations. More recently, the matrix-isolation (MI) technique which allows substantial control over the sample(s)/carrier gas ratio(s) and deposition conditions has been combined with VCD. It can avoid the solute-solvent interactions and have the molecular target largely in its isolated monomeric form. The MI technique generally yields much narrower IR and VCD bandwidths than those obtained in solution, providing the opportunity to investigate possible conformations of the target molecules in considerable details.

THFA is an important intermediate in the production of pharmaceuticals such as Alfuzosin, Faropenem and Tecadenoson. The THFA monomer exhibits an interesting conformational landscape with a range of possible conformers and has been studied through a variety kind of spectroscopic tools. In the previous studies by using rotational spectroscopy and MI-VCD spectroscopy, THFA is favored to adopt the *trans*-COOH configuration which tend to form the intramolecular hydrogen(H)-bond.[1,2,3] On the other hand, THFA, like many other carboxylic acids, is more favor to adopt the *cis*-COOH configuration. For example, two *cis*-COOH THFA subunits are bonded through a double H-bonded ring in $CDCl_3$ [4] and *cis*-COOH THFA are bonded with water molecules under different pH environments. In the current study, we will present a full report on the investigation of the non-covalent interactions THFA molecule, ranging from gas phase to solution and finally to the rare gas matrix. The analysis will be mainly focused on the interesting observations of the unusual THFA dimer species by using MI-VCD spectroscopy.

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Towards Effective Approaches for Spectral Properties of Large Embedded Systems

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The computational simulation of chiroptical spectroscopies can be a viable tool to unravel the structural information of chiral biomolecules in their natural environment. The modelling of such systems is however a challenging task, due to the large number of atoms involved. Most effective approaches resort to multiscale models, in which the system is divided into different regions. In this work, we focus on Quantum Mechanics/Molecular Mechanics (QM/MM) approaches, in which the classical part is treated by means of the polarizable Fluctuating Charges (FQ) force field, that has been successfully applied to the treatment of large solvated systems. [1,2]

In order to deal with very large biomolecules, semiempical quantum-mechanical methods are mandatory.[3] The Density Functional Tight-Binding (DFTB) approach, which is an approximate DFT-based model that allows for the calculation of molecular properties on systems composed by thousands of atoms, [4-6] is particularly effective. DFTB has recently been coupled with the FQ force field [7], and in this work we further extend it to the simulation of Vibrational Circular Dichroism spectra of chiral molecules of biological interest.

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Artificial intelligence algorithms for chiroptical spectroscopy

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Human beings are biased by nature and have a limited capacity to deal with complexity. Machine learning techniques do not suffer from these shortcomings, however, to yield sensible results, they need to be tailored for the problem at hand. The challenge is to fine-tune the fitness function used by the artificial intelligence algorithm. In this lecture I will discuss how novel and robust protocols for analysing molecular structures and spectra can be developed by employing clustering and genetic algorithms. Using a data base developed in-house, I will illustrate the ability of these protocols to 1) identify common patterns in the chiroptical spectra and associate them to structural motifs, 2) identify the VCD-active/-inactive site of a molecule, and 3) make absolute configuration assignments that are immune to the uncertainties associated with the Boltzmann factors predicted by DFT calculations.

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Facilitating Stereochemical Analysis of Natural Products: a Quest for VOA Spectral Markers

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The use of vibrational optical activity (VOA) methods for the stereochemical analysis of natural product molecules has faced a tremendous increase over the last two decades.[1,2] The availability of dedicated commercial instrumentation has contributed to raise awareness of the advantages of VOA over other well-established methods, such as X-ray crystallography and NMR. The need of quantum chemical calculations to simulate VOA spectra, however, has hampered the widespread use of these chiroptical methods by the natural product community. As a result, most of the vibrational circular dichroism (VCD) and Raman optical activity (ROA) investigations on chiral molecules from natural sources come from few specialized VOA research groups. In order to facilitate and expand the use of VOA methods by non-specialists, our research group has been focused on the identification and validation of VCD spectral markers[3-6] for reliable stereochemical assignments of different classes of secondary metabolites. In this talk, the most recent approaches applied to natural products spectral analysis ranging from visual inspection to machine learning based methods will be presented, along with their main advantages and drawbacks. Analyses will be mainly focused on cyclic peptides and terpene molecules.

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Conformational Studies of Cyclic Hexapeptides with Vibrational Circular Dichroism: Experimental and Theoretical Approach

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Growing antibiotic resistance is becoming one of the world's most urgent public health problems, with wide implications also for food security and development. A growing number of bacterial infections are getting harder to treat since the antibiotics are becoming less effective. Therefore, efforts to develop new classes of compounds with antimicrobial activity and reduced risk of triggering antibiotic resistance, such as antimicrobial peptides, are accelerating.

Antimicrobial peptides (AMPs) are short and mostly positively charged peptides that can be found in a variety of organisms with direct and indirect (immunomodulatory) antimicrobial activity. In this work, we use vibrational circular dichroism (VCD) spectroscopy and theoretical modelling to study the structure and conformation of four cyclic hexapeptides with potential to be used as AMPs.

Cyclic hexapeptides possess a significant conformational flexibility that makes theoretical interpretation of experimental VCD spectra especially challenging. Identification of possible conformations of a molecule, as well as determination of the relative Boltzmann populations of individual conformers, is a crucial step in simulation of VCD spectra of flexible molecules.

In this talk, we present a comparison of two methods for conformational sampling in simulation of VCD spectra of cyclic hexapeptides in water. The first method is based on the molecular dynamics (MD) simulations, while the second approach is using the Conformer-Rotamer Ensemble Sampling Tool (CREST)[1-3] to identify the most stable conformations. Both methods sample conformational space quite well, producing a large number of unique conformers. While MD conformational sampling can better capture the solvent-solute interactions and their influence on conformation, CREST approach provides reasonable results with low computational cost.

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Competition Between Halogen- and Hydrogen-Bonding Interactions: Iodine with Two Halogen Bond Acceptors with Carbonyl and Thiocarbonyl Groups in Solution

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Halogen-bonding interactions,[1] defined as the attractive interactions between an electrophilic region on a halogen bond donor and a nucleophilic region in a halogen bond acceptor, are studied in a series of solutions containing iodine as halogen bond donors, and 4-benzyl-1,3-thiazolidine-2-one (NOS) or 4-benzyl-1,3-thiazolidine-2-thione (NSS) as halogen bond acceptors (Figure1) using multiple spectroscopic tools including vibrational circular dichroism.

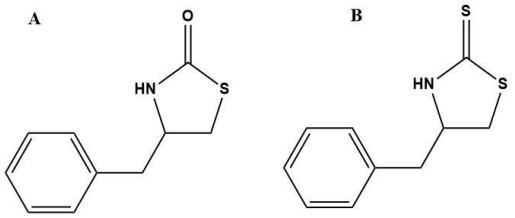

Figure 1. Chemical structures of (A) 4-benzyl-1,3-thiazolidine-2-one (NOS), and (B) 4-benzyl-1,3-thiazolidine-2-thione (NSS).

In the current study, we focus on the competition of halogen bonds with hydrogen bonds in the solution, a subject of great interest to many experimental and theoretical chemists.[2,3] The model halogen donors selected for the current study, namely NOS and NSS, contain potential sites for halogen-bonding, hydrogen-bonding and π-bonding interactions. The titrations of NOS/NSS with I_2 have been monitored with UV-Vis absorption, infrared, and vibrational circular dichroism (VCD) spectrospcopies, as well as NMR. Spectral signatures associated with the halogen-bonding and hydrogen-bonding interactions are identified in these solutions. To explain the observed spectra, we have also carried out systematic conformational searches of the corresponding hydrogen and halogen bonded binary aggregates and the related gd3bj empirical dispersion calculations. Comparison between the experimental and simulated IR and VCD spectra provides detailed information about the co-existence of the hydrogen-bonding and halogen-bonding interactions in the NSS-I_2 pair. A new halogen/hydrogen-bonding motif has been identified for the NSS-I_2 interaction, different from the one proposed before in similar compounds.[3]

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VCD as a tool to monitor molecular interactions in solution

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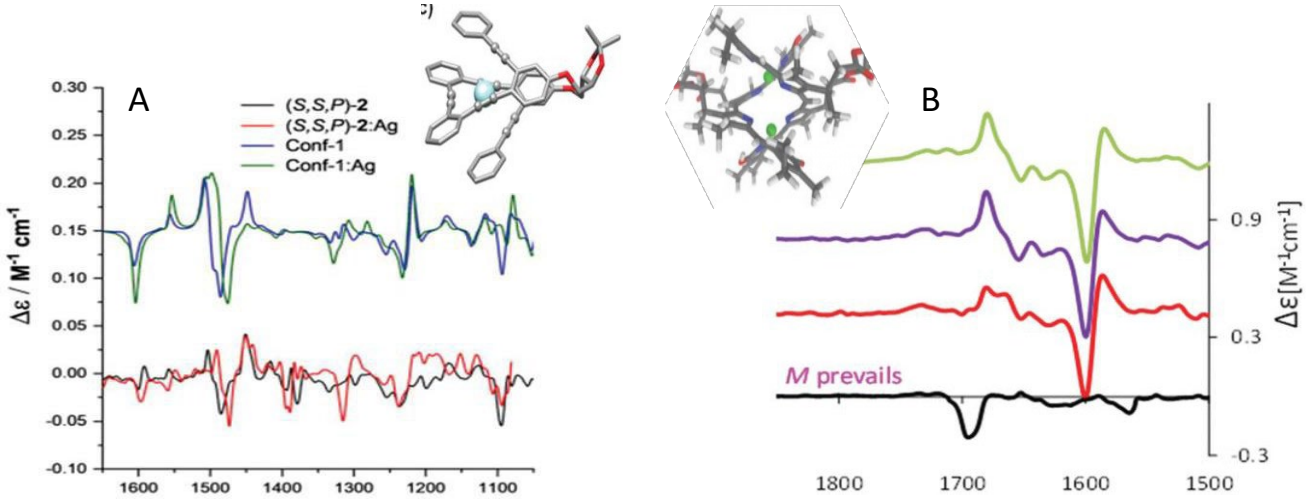
Vibrational Circular Dichroism (VCD) is the form of VOA which had been developed first. Due to small VCD signals, normally of the order of 10^{-5}-10^{-4} with respect to total absorption, in the earliest days of VCD most measurements were carried out in the liquid state [1]. Even nowadays, when instrumentation has greatly advanced [2], measurements are carried out in fairly concentrated solutions. The technique has shown particular sensitivity to environment: this fact enhances on one side the potentiality of the technique and on the other side calls for quite challenging theoretical treatments. In this note we will review some examples, combining experimental results and computational studies, considering three types of compounds: the first set comprising model compounds like pantolactone [3], the second one comprising heme-catabolites like biliverdin and stercobilin derivatives [4], and the third and last one for organic compounds used in material chemistry [5]. VCD, used in conjunction with ROA and ECD, reveals quite useful in monitoring the interactions of the studied compounds not only with the solvent but also with other partner molecules, allowing to study aggregation phenomena and/or interaction with metal ions. By way of example, we report a figure composed from refs. [4] and [5]; theoretical treatment of complexity inversely proportional to the size of the studied compounds were successfully employed.



A: comparison of theoretical and experimental VCD spectra of ortho-phenylene ethylene-based helical systems with and without Ag(I). Adapted from [6] B:VCD spectra of biliverdin chiral derivative (black) with added triflates of zinc (red line), nickel (purple line) and silver (green line). Adapted from [4]

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Rotational Spectroscopy (FT-MRR) in Industrial Analysis

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Broadband rotational spectra are highly characteristic of analytes, since they consist of a large number of spectral lines with precise frequencies. Most importantly, they can differentiate isomers and even isotopomers in a precise and conclusive manner. Structural assignments are made through comparison with literature spectra, if available, or else by matching with simulated spectra based on quantum chemical calculations of rotational parameters.

While rotational spectroscopy as such has been available, and its general analytical value known, for a long time, only the Fourier transform variant („FT-MRR“) developed by Pate et al.
[1] has rendered the recording of broadband rotational spectra fast enough to be attractive for industrial use.

The value of FT-MRR technology is augmented by its ability to identify enantiomers and determine their optical purity [2]. This is typically achieved by the formation of non-covalent diastereomeric complexes of chiral analytes with an optically pure auxiliary („chiral tag“) [3].

Examples for the identification, quantification and enantiomeric excess determination of organic chemicals from industrial process chemistry by FT-MRR, elaborated in close cooperation between BASF and BrightSpec and U VA scientists, are given.

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Microwave and laser spectroscopies as a tool for chiral discrimination

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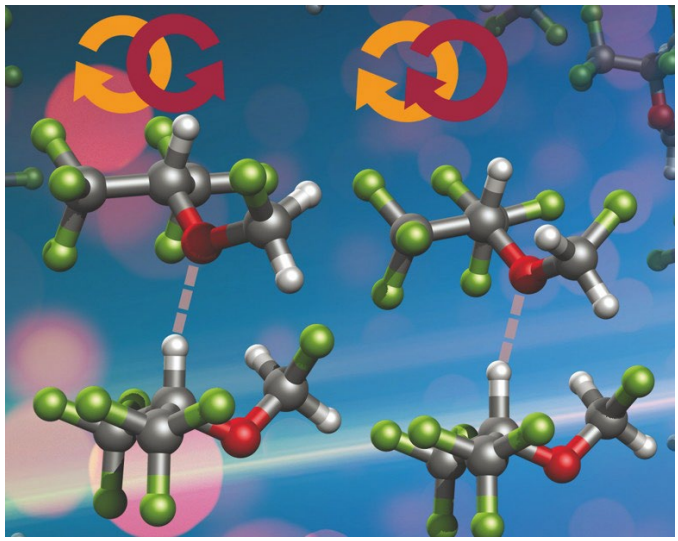
Several studies on biomolecules (carbohydrates and glycopeptides) and several applications, exploiting an experimental strategy which combines microwave and laser spectroscopies in high resolution, NMR, computation and synthesis. Laser spectroscopy offers high sensitivity and selectivity, making it ideal for studying biochemical systems of medium-large size.[1,2] Moreover, microwave spectroscopy provides higher resolution and direct access to molecular structure. [3,4] This combined approach provides not only accurate chemical insight on conformation, structure and molecular properties, but also benchmarking standards guiding the development of theoretical calculations. In order to illustrate these possibilities several examples will be presented.[2-7]



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Chiral Recognition Motif between Vicinal Diols and Diamines Revelled by Molecular Rotational Resonance Spectroscopy

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The chirality dependent intermolecular recognition patterns between trans-1 2-cyclohexanediol (DOH) and trans-1,2-Diaminocyclohexane (DA) were investigated via chirped pulse Fourier transform microwave (CP-FTMW) spectrometers[1,2] at 2-12 GHz[3] and 18-26 GHz[4] frequency region with the support of theoretical calculations. Three types of H-bond networks: 4 H-bonded Cage, three 3 H-bonded Zigzag, and 2 H-bonded Cyclic topologies were identified. They are in close analogy to the dimer structure of vicinal diols that were previously studied via FTIR and Raman jet spectroscopy[5,6], where an energetically unrivaled S_4-symmetric Cage heterochiral diol dimer was found to be dominating the spectra. The corresponding less symmetric homochiral Cage diol dimer was 10 kJmol^{-1} less stable and invisible on spectra. In the case of DOH-DA dimers, we found that such a strong heterochiral preference for Cage dimers disappeared, the homochiral and heterochiral Cage dimers are almost non-distinguishable in energy. Instead, a Zigzag heterochiral dimer was assigned to the strongest dimer peak, the corresponding 5 kJmol^{-1} less stable homochiral Zigzag dimer is invisible on the spectrum. This work provides further insights into the origin of chirality dependent structure preference in molecular systems containing both hydroxy and amine groups.

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Raman Optical Activity of Serine and Cysteine in Aqueous Solution: A Computational Study

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Raman Optical Activity (ROA), the chiral analogous of Raman spectroscopy, has recently emerged as a valid analytical technique due to its structural sensitivity [1]. The interpretation of ROA spectra benefits from the comparison with reliable computational reference data. A possible solution consists of exploiting QM/classical approaches, which retain the atomistic nature of the whole system, such as in Quantum mechanical (QM)/Molecular mechanics (MM) methods [2]. In this contribution, we present a novel QM/MM approach to accurately model ROA of systems in solution. The method is based on polarizable QM/Fluctuating Charge (FQ) [3] and QM/Fluctuating Charge and Fluctuating Dipole (FQFμ) [4] models. The performances of both approaches are tested against the reproduction of ROA spectra of solvated amino acids, in particular L-Serine and L-Cysteine in aqueous solution [5]. In all cases, experimental data are nicely reproduced, thus highlighting the potentiality of these methods for the reliable description and prediction of ROA spectra of molecular solutes.

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Vibrational Spectroscopy of Homo- and Heterochiral Amino Acid Dimers: Conformational Landscapes and Chirality Recognition

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Homochirality of biological life is a well-known, yet unexplained phenomenon.[1] To probe the fundamental forces that prefer homochirality and the possible interactions between chiral species, molecular chiral recognition tools are needed. In this study we use Infrared Multiple-Photon Dissociation (IRMPD) spectroscopy, a tool that utilizes mass spectrometry and IR spectroscopy to bring together both detection sensitivity and structural sensitivity to probe protonated amino acid dimers of homo- and heterochiral asparagine with serine and with valine. To aid our experimental study we devised a three-tiered computational approach to aid in experimental assignment. The conformational landscapes were probed systemically to filter the conformational space of all four dimer species and as a result, 8 to 14 final conformational geometries were identified within a 10 kJ mol^{-1} window of the global minimum structure found of each species. The structures were further grouped on their intermolecular binding topologies and subunit configuration into type I, II, III, and ZW categories. Comparison between experimental IRMPD spectra and simulated harmonic IR features allowed for identification of the types of structures responsible for observed features. Final abundances of structures within our categories and observation are viewed through the lens of kinetically controlled dimer formation.

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Chirality discrimination at binary organic/water interfaces by interfacial tension measurements and MD simulations

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Chirality discrimination/recognition is one of the most subtle aspects of molecular recognition[1-3]. Can interfacial tension measurements illustrate such recognition at a liquid-liquid interface? By judicially select the appropriate solvents and chiral solutes used and design the essential controlled experiments, we aim to extract concrete evidence of chirality discrimination at a binary toluene (organic)/water(aqueous) interface with such measurements and further support the experimental findings using molecular dynamics simulations. Serine and 2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl (Tol-BINAP were selected as the aqueous and organic solute respectively. The interfacial tension measurements were carried out by using different chirality combination of the two chiral solutes. In addition, controlled experiments were performed by omitting the chiral solute used in one of the phases. Molecular dynamics (MD) simulations were also implemented to provide molecular insight into the chirality recognition phenomena at the interface. Experimental interfacial measurements exhibit a clear chirality-controlled difference when a homochiral versus a heterochiral enantiomeric pairs are introduced at the interfaces. The related molecular dynamics simulations support the experimental results and provide further molecular insight of intermolecular interactions at the interfaces. The results indicate that preferential interactions exist between different pairs of enantiomers at the binary interfaces which can be captured directly by using interfacial tension measurements.

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Determining the Nanostructure and Fibril Axis of Gly-X_{Ar}-Gly Using the Amide I' Bands in their FTIR and VCD Spectra

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Recently, our group has identified a novel class of peptides with the general motif GXG (X being a variable residue) that can act as ultra-low molecular weight gelators.[1,2] A subset of these peptides that are currently of high interest include GFG, GWG, and GHG, which all contain a central aromatic residue ($GX_{Ar}G$). These peptides can self-assemble into exceedingly long fibrils which form highly dense sample spanning networks that underly very strong hydrogels. The amide I' profiles of the vibrational spectra for these systems suggest sheet structures differing from canonical β-sheets. Refined crystal structures were obtained for the crystalline fibrils of each system using powder x-ray diffraction (PXRD) and Rietveld refinement. Orthorhombic unit cells forming a $P2_12_12_1$ space group were obtained for both GFG and GWG and a monoclinic crystal system belonging to the $P2_1$ space group for GHG. The central residue of GFG and GWG adopt unusual structures that occupy the "forbidden" region of the Ramachandran plot. Comparisons of simulated and experimental FTIR and vibrational circular dichroism (VCD) amide I' (AI') profiles corroborate the PXRD structures. Our experimental set-up reduced the sample to a quasi-two-dimensional network of fibrils which we exploited to identify the main fibril axis. Simulations assignable to the delocalized AI' modes were carried out by employing a classical Coupled Oscillator model that describes the coupling between excited eigenstates of harmonic oscillators. Each amide group is treated as a vibrating oscillator with an intrinsic wavenumber and local transition dipole moment (TDM). To account for the reduced dimensionality of our system we calculated the projections of electronic and magnetic excitonic transition dipole moments onto the axes of a coordinate system aligned with the basis vectors x, y, and z of the unit cell. We then considered three (simplifying) cases in which the rotating Jones vector of the incident light lies either in the xy-, xz-, or yz-plane by solely considering the TDM projections onto these planes. Using this method, we validated the obtained crystal structures of GFG and GWG fibrils. The preliminary GHG structure is currently being investigated. We demonstrate that PXRD, vibrational spectroscopy, and amide I simulations provide a powerful toolset for secondary structure analysis of peptide fibrils and that VCD can play a pivotal role in fibril axis determination.

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Calculation of rotational circular dichroism for diamagnetic and paramagnetic molecules

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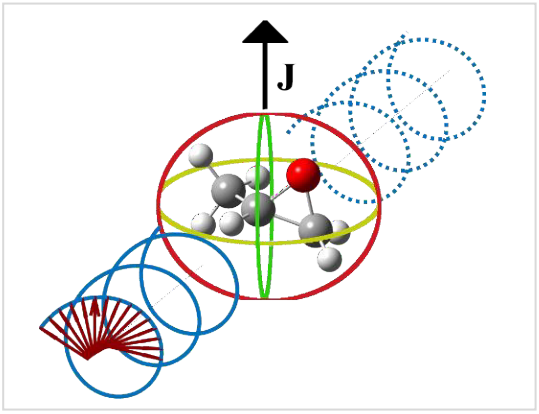
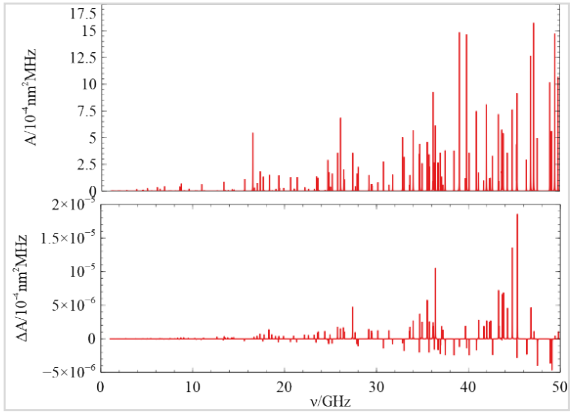
Circular dichroism (CD) techniques are invaluable for conformational and enantiomeric analyses of optically active molecules. While CD spectra are routinely measured for electronic and vibrational transitions (ECD and VCD), rotational transitions (RCD) give much weaker signal and they have not been detected so far. To guide future experiments, it may be convenient to identify molecules with high spectral intensities. Salzman [1-4] performed RCD calculations for six small diamagnetic molecules (d1, d2, d3-oxiranes, methyloxirane, methylthiirane, transdimethyloxirane), using the rigid rotor Hamiltonian. Here, we extend on his theory and also calculate RCD spectra for a more biologically relevant molecule, the L-alanyl-L-alanine dipeptide. We show that the quadrupole contribution is zero, while paramagnetic molecules give enhanced RCD signal. Dipole and rotational strengths of the six diamagnetic molecules are investigated up to high rotational quantum numbers ($J \sim 120$), and trends of spectral intensities in dependence on transition frequency and J are analyzed. In general, dipole strength remains constant with growing J, while rotational strength rises. In paramagnetics, however, the rotational strength peaks at the start of the trend and remains constant throughout.





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Prediction of VCD and ECD Spectra by a Combined Use of DFT and a Neural Network

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It is often assumed that computational prediction of ECD and especially VCD spectra requires generation of a large number of conformations in order to achieve a satisfactory agreement with experimental spectra. Since large and flexible molecules possess a prohibitively large number of conformations, it is crucial for the computational efficiency and for the accuracy of the simulated spectra to be able to select a fairly small number of relevant (low energy) conformations, before these structures are passed to resource-demanding DFT calculations. Thus, an accurate and computationally-inexpensive ranking of conformations becomes an important step in a spectra prediction workflow.

We demonstrate that a recently developed neural network QRNN[1] which was trained to simulate DFT energetics outperforms a force field and semi-empirical methods at the task of ranking conformations by energies. We use the neural network for geometry optimizations of large drug-like molecules and for selection of their conformers, and report on the implications for the generated ECD and VCD spectra. We report the time savings produced as a result of computationally cheaper operations driven by QRNN and demonstrate the quality of the resulting spectra.

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VCD Spectroscopy of Chiral Cage Compounds

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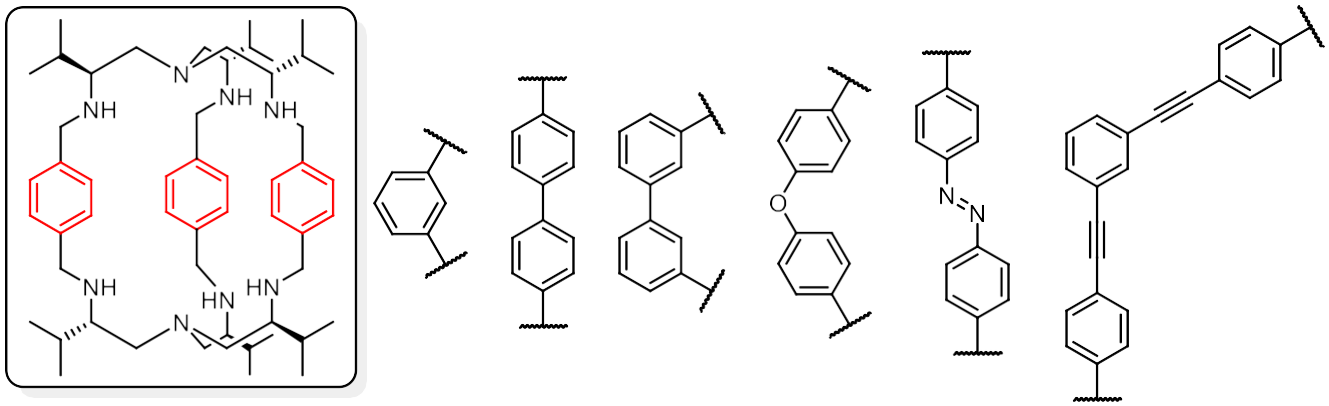
Azacryptands are macrocyclic cage compounds first synthesized by Lehn and co-workers.[1] Chiral versions of these systems are not known in literature so far. In this work, we present the synthesis of novel chiral azacryptands obtained by condensation of chiral TREN (tris(2-aminoethyl)amine)[2] units, derived from valine, with different aldehydes. Our synthetic procedure is suitable to access a large scope of linker groups. Starting from a simple phenyl linker, different arylic linker groups with diverse substitutions patterns have been examined. A diazobenzene cage compound has been synthesized to investigate its photoswitching behaviour. The introduction of more diverse functional groups in the linker group is under investigation to probe for example charge-transfer processes.



VCD spectra of cage compounds are to this point little known in literature.[3] The VCD spectra of the novel azacryptand cages have been recorded and compared with spectra obtained by DFT-based methods. Short linker groups as the phenyl linker group show a rigid conformation. By increasing the length of the linker groups, the cryptands become more twisted and adopt a helical conformation. Azacryptands are known to bind metal ions and anions as guest molecules and thus are used for sensing and recognition.[4] In our study, transition metal ions have been introduced into the cavity and the IR and VCD spectra of these complexes have been measured and compared to computed spectra as well. Several anions could be encapsulated in these cationic complexes and their conformational preferences have been elucidated.

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Halogen-Bonding Interactions of Iodopentafluorobenzene with Carbonyl and Thiocarbonyl Functionalities in solution

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Halogen-bonding interactions[1], defined as the attractive interactions between an electrophilic region on a halogen bond donor and a nucleophilic region in a halogen bond acceptor, are studied in a series of solutions containing iodopentafluorobenzene (F_5BnI) as halogen bond donors, and 4-benzyl-1,3-thiazolidine-2-one (NOS) or 4-benzyl-1,3-thiazolidine-2-thione (NSS) as halogen bond acceptors (Figure1). These systems have been selected for their potentials to form intermolecular contacts in solution which have mainly the hydrogen, halogen, and π bonding characters.

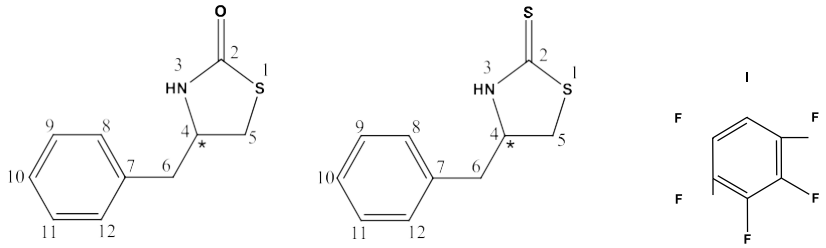

Figure 1. Chemical structures of NOS and NSS (left) and F_5BnI (right).

Multiple spectroscopic tools have been utilized including UV-Vis, electronic circular dichroism, NMR, Infrared (IR) and vibrational circular dichroism (VCD) to characterize the systems experimentally[2]. Extensive conformational searches were carried out for the possible binary aggregates which are formed utilizing mainly the hydrogen, halogen, and π bonding interactions. Subsequent geometry optimizations and harmonic frequency calculations have also been performed to simulate all the IR and VCD spectra of possible binary aggregates using gd3bj empirical dispersion. Comparison between the experimental and theoretical data provides the detailed information about the competition between the hydrogen-bonding and halogen-bonding interactions in the NSS- F_5BnI and NOS- F_5BnI pairs.

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Solvent Effects in Chiral Cyclic Amides

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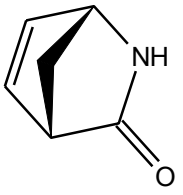
Solvent environment is known to alter the population distribution of chiral molecules by facilitating solute-solvent interactions.[1–4] In some cases, this can have a noticeable effect on the experimental and simulated vibrational spectra, however an empirical rule to predict the extent of the solvent effect is not known. Therefore, the creation of a library of how different functional groups are affected by the solvent environment is a useful tool to assist in the prediction of solvent-based phenomena.

In this study, we present the solvent effects of three chiral cyclic amides that range in conformational complexity: from a single conformer structure (**1**) to two pyrrolidone derivatives (**2** and **3**) that differ in side chain structure. Combining spectroscopic methods with computational modelling of the monomeric and dimeric structures of these chiral cyclic amides can assist in the future prediction and treatment of amides, and other hydrogen bonding functional groups, in different solvent environments.



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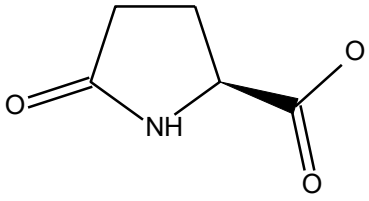

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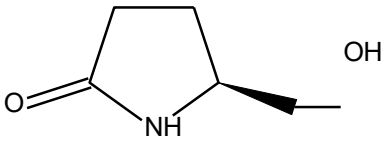

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Stereochemical Outcome of Deoxyfluorination of Unsaturated Alcohols

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Fluorinated organic compounds have been used especially in pharmaceutical chemistry[1] because fluorine is known to increase pharmaceutical bioavailability due to its high lipophilicity and metabolic stability. For example, almost 50% of drugs recently approved by FDA contain fluorine atoms[2]. A general method to introduce fluorine atoms into organic molecules is deoxyfluorination, which is easily proceeded by reagents such as DAST, XtalFluor, PyFluor, etc[3]. Since the mechanism of this reaction is generally presumed to be S_N2, the chirality of the fluorinated products has been believed to be inverted. However, we found that deoxyfluorination of some of biological unsaturated alcohols proceeded with stereochemical retention. Because accurate stereochemical information is essential for applying fluorinated molecules to medicinal chemistry, their chirality should be studied in detail. In this work, we performed deoxyfluorination of a series of unsaturated alcohols using various reaction conditions, and then analyzed the stereochemistry of fluorinated products by VCD spectroscopy and chiral HPLC. We also discuss a plausible mechanism deduced from reaction intermediates.

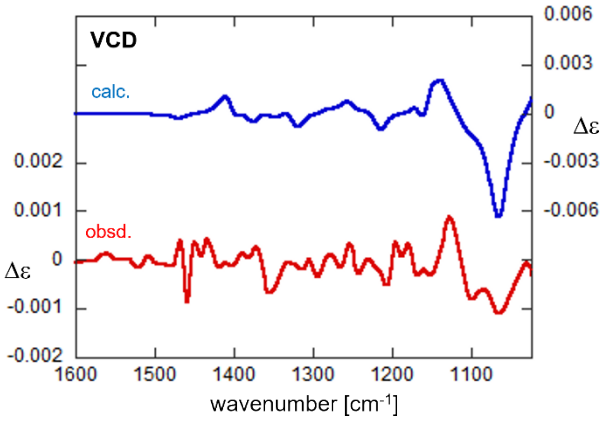
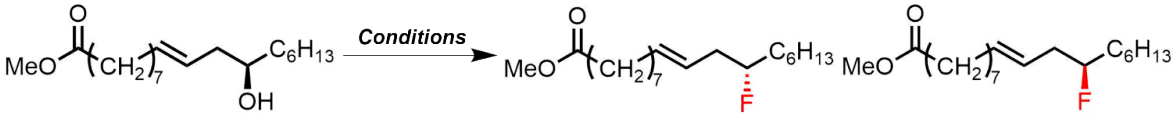


Figure 1. Comparison of calculated and observed VCD spectra of methyl ricinelaidate fluorinated by XtalFluor-E.



Methyl ricinelaidate — **inversion** — **retention**

PyFluor, DBU, toluene, rt, o.n.	**>99%**	<1%
XtalFluor-E, Et_3N-3HF, 0 °C→rt, o.n.	27%	**73%**

Figure.2 Deoxyfluorination of methyl ricinelaidate.

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Chiral ECD-Raman spectroscopy of vitamin B_{12} analogues and atropisomeric naphthalenediimides

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There is no doubt that resonance Raman optical activity (RROA) is a method with enhanced vibrational sensitivity, which was shown recently for several biomolecules such as carotenoid aggregates, cytochrome c, or vitamin B_{12} derivatives. Under the resonance regime, for diluted samples, it is possible to detect strong monosignate or bisignate RROA spectra with CIDs $\sim 10^{-3}$-10^{-2} in a very short time and with low laser power. The bisignate RROA spectra are rich in structural information about the molecule, compared to single signed RROA spectra that are highly similar to the parent Raman spectrum (apart from the sign).

Although RROA reveals its enormous potential, is still a constantly developing field of science. Very lately it has been reported that true RROA spectra of colorful and resonating compounds may be altered by other effects, such as electronic circular dichroism (ECD) in combination with circularly polarized (CP) Raman (ECD-Raman effect)[1]. The ECD-Raman effect has been probably ignored in many previously RROA measurements which could result in the inappropriate interpretation of experimental data. Moreover, this phenomenon was observed not only for solvent signals[2] but also in those from chiral, light-absorbing solutes[3]. In our study, we show that ECD-Raman effect is the dominant factor over the natural Raman optical activity in a series of atropisomeric naphthalenediimides and vitamin B_{12} derivatives.

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Alternating 1-Phenyl-2,2,2-Trifluoroethanol Conformational Landscape with the Addition of Common Co-Solvents: A Rotational Spectroscopic and Ab Initio Study

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Over the past few decades, the use of fluorinated compounds in the agrochemical, pharmaceutical, and biomedical fields have significantly increased largely due to the unique combination of steric and polar effects exhibited by fluorine. In particular, the self-aggregation of fluorinated alcohols enables them to enantioselectivity catalyze organic reactions, such as the epoxidation of olefins. However, this catalytic activity is drastically reduced upon the addition of common co-solvents such as water and 1,4-dioxane. In this work, the reduction in catalytic activity was probed by investigating alterations in the conformational landscape of the stereochemically active fluorinated alcohol (*R*)-1-phenyl-2,2,2-trifluoroethanol (PhTFE) upon the addition of a single water or 1,4-dioxane molecule with rotational spectroscopy and *ab initio* calculations.

PhTFE itself was previously reported to have three conformations, **I** (*gauche*+), **II** (*trans*), and **III** (*gauche*-), however, only the most stable conformer, *gauche*+, was experimentally observed [1]. Interestingly, two conformers of both the 1:1 binary adducts of PhTFE with 1,4-dioxane, PhTFE···1,4-dioxane, and PhTFE with water, PhTFE···H_2O, were experimentally observed [2, 3]. For the case of PhTFE···1,4-dioxane, both observed conformers exhibited PhTFE in its *trans* configuration. In the PhTFE···H_2O case, one observed conformer has PhTFE in its *gauche*+ configuration, whereas the other has it in the *trans* configuration. To fully understand the stabilizing and destabilizing intermolecular interactions present in these complexes, their structures were analyzed within the quantum theory of atoms in molecules (QTAIM), non-covalent interactions (NCI), and symmetry adapted perturbation theory (SAPT) frameworks. Furthermore, we will discuss the barrierless large amplitude motions (LAMs) which sample several minima identified theoretically and the implication of LAMs in simulating vibrational optical activity (VOA) spectra.

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Effect of seeding on formation of amyloid fibrils

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The amyloid fibrils yield the most intense VCD signals, reported up to now, with the dissymmetry factors of 10^{-2}-10^{-3} [1]. Several common neurodegenerative diseases such as Alzheimer's or Parkinson's disease are related with the formation of pathogenic amyloid fibrils in living tissues. An important factor in the formation of amyloid fibrils is the destabilization of the native conformation of the protein. This process can be caused *in vitro* by the change of certain parameters, including pH, temperature, centrifugation or change of salinity. To accelerate fibrils' formation, the process of seeding can be applied. In our study, we confirmed that a small amount of seeds significantly change the fibril structure and increase the rate of their formation (Fig. 1). Interesting observations were also made regarding the structure of formed fibrils, as we noticed that the structure of "daughter" fibrils may not be always controlled by the "mother" fibril structure, as previously reported [2,3]. Further studies are needed to verify if our observations can be generalized for other proteins than lysozyme.

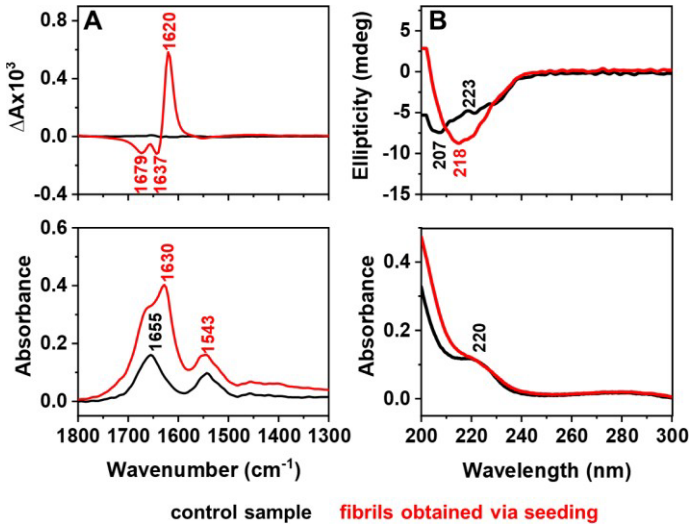

Fig. 1. VCD/IR (A) and ECD/UV-vis (B) spectra of hen egg white lysozyme fibrils without agitation (**control sample**) and hen egg white lysozyme incubated without agitation (**fibrils obtained via seeding**) in water, initial conditions: pH 2, 60 mg·ml^{-1}, incubation for 24h at 60°C. Seeds obtained with agitation, pH 2, 60 mg·ml^{-1}, incubation for 72h at 60°C.

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Raman optical activity of nucleotides: experimental and theoretical study

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Nucleotide conformational flexibility affects their biological functions. Although the spectroscopy of Raman optical activity (ROA) is well suited to structural analysis in aqueous solutions[1], the link between spectral shape and nucleotide geometry is not fully understood. Here, we investigated the conformational dynamics of nucleotides by measuring the Raman and ROA spectra of common nucleotides (AMP, GMP, CMP, dTMP) and interpreting them on the basis of molecular dynamics (MD) combined with density functional theory (DFT). MD yielded information about the sugar puckering and other coordinates affecting the ROA signal of the nucleotides. Analysis of the internal hydrogen bonds revealed, for example, that the H-bonds between sugar the C3' hydroxyl and phosphate group strongly influence the sugar puckering. The simulated spectra from the combined MD/DFT modelling correlated well with the experimental data and provided insight into the dependence of the spectral shapes on conformational dynamics.

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Chirality Synchronization in Binary Adducts of 3,3,3-Trifluoro-1-Propanol

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The conformational landscapes of the monomer and dimer of 3,3,3-trifluoro-1-propanol (TFP) were investigated using Fourier transform chirped pulse microwave spectroscopy in tandem with quantum chemical calculations. We focus on understanding transient chirality, atropisomer chirality and chirality synchronization in the TFP monomer and dimer, phenomena with practical importance [1]. The configurations of the TFP monomer are defined by the CCCO and CCOH dihedral angles, with *G+*, *G-* and *T* associated with the heavy atom frame and *g+*, *g-* and *t* with the OH orientation directions. This leads to four mirror-imaged configurations, i.e., *G+g+*/*G-g-*,*G+t*/*G-t*, *G+g-*/*G-g+*, and *Tg+*/*Tg-* which are (transiently) chiral, and one achiral *Tt* configuration. It is convenient to classify the above monomeric conformers into the folded (*G*) and flat (*T*) conformer families which are expected to cool separately to the most stable conformer in a jet because of the low and high torsional barriers associated with the OH and backbone torsion motions, respectively. Experimentally, rotational spectra of the parent and ^{13}C isotopologues of chiral *G+g+/G-g-* and achiral *Tt* were observed in a jet expansion and assigned. The isotopic data clearly established the heavy atom frames of the two monomeric conformers.

There are a large number of possible binary conformers of TFP and the 12 most stable ones (**I** to **XII**) can be classified into two types: ***Type 1*** (**I** – **VII**) which consist of two folded TFP monomer units and ***Type 2*** (**VIII** – **XII**) which consist of one folded and one flat monomer subunits. Both types were detected experimentally. In the previous study of the related trifluoroethanol (TFE) dimer, an abundance ratio of 10:1 favouring the heterochiral dimer was reported and the unusually large abundance difference was attributed to chirality synchronization in a jet expansion [2,3] even though both binary conformers are energetically comparable. Of particular interest here is the observation of homochiral **I** and heterochiral **III** dimers, of ***Type 1***, with an abundance ratio of 5:1, much larger than their relative energy difference would support. This suggests that the ***Type 1*** TFP dimers show chirality synchronization as well. The origin of such synchronization in a jet expansion will be further discussed.

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Matrix effects in MI-VCD spectra: The effect of temperature and concentration

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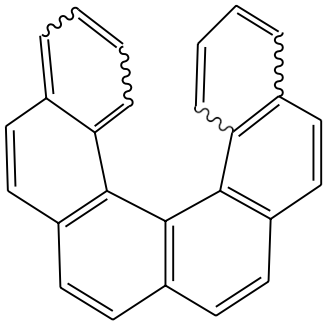
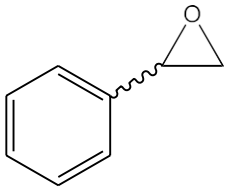
In Matrix Isolation (MI)[1] the compound of interest is trapped in an inert gas at cryogenic temperature to avoid dimerization and/or thermal relaxation. In combination with Infrared (IR) spectroscopy, MI gives a broad choice of studies from isomerism to photochemistry or aggregate clustering. Vibrational Circular Dichroism (VCD) spectroscopy is the chiral version of IR spectroscopy and measures the difference between left and right circular polarized IR light absorbed by a chiral molecule. Typically employed to solution phase measurements, the sensitivity of VCD has been shown to be of added benefit for the investigation of intermolecular interactions[2]. Both IR and VCD spectra need to be compared with computations to determine if the expected structure is the one experimentally obtained. VCD coupled to MI (MI-VCD)[3] offers a better resolution than VCD solution thanks to the narrow line width. In turn, it is also much more prone to matrix cage effects[4], which can hardly be predicted computationally.

Our group already encountered MI-VCD specific matrix effects and was able to explain it by distortion around the lowest energy conformer[5]. These effects cannot be predicted and can only be treated individually. To further investigate such matrix site effects and to give some experimental guidelines on how to avoid them, we studied two compounds having different sizes. Despite the bulkiness of hexahelicene **1**, 5 K difference during the deposition is enough for the VCD spectra to be different in Argon. Besides an influence of the temperature, we also found the concentration of styrene oxide **2** to influence the spectral quality. Under different experimental conditions, it shows such matrix effects in Argon, but not in Nitrogen matrix. In both cases, the IR spectra are not affected. In this contribution, we report the MI-IR and MI-VCD spectra of **1** and **2** and discuss the effects of the deposition conditions.



1



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A combined broadband rotational spectroscopic and theoretical study of hydrated *cis* and *trans* (-)-carveol

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Carveol, a primary constituent in spearmint and peppermint oil, is a monocyclic monoterpenoid alcohol that is produced in nature by the photooxidation of limonene.[1] Structurally, carveol contains two chiral centers with three substituents (methyl group, hydroxyl group, and propylene group) attached to its cyclohexane ring. The combination of the three flexible substituents, ring puckering, and two chiral centers introduces a complex conformational topography. As an atmospherically relevant molecule, it also has a high probability of interacting with other atmospheric species, such as water. The formation of a hydrogen-bonded complex with water will further increase the conformational complexity of the system. Five monomers for *cis* and *trans* (-)-carveol have been assigned in a previous study,[2] but a spectroscopic analysis of the monohydrate is still lacking. A detailed study of the topology and energetics of hydrated carveol may provide further insights into complex conformational dynamics, as well as chirality recognitions studies. Chirped-pulse Fourier transform microwave spectroscopy (CP-FTMW) is an excellent tool for such investigation as it is able to unambiguously distinguish structural conformers within a complex mixture.[3] A broadband spectrum with rotational transitions of *cis* (-) and *trans* (-)-carveol monohydrate was recorded using a chirped pulse Fourier Transform microwave spectrometer in the 2-6 GHz region.[4] To aid in experimental assignment the Conformer–Rotamer Ensemble Sampling Tool(CREST)[5] was utilized. The CREST results include 36 monohydrate conformations for *trans* (-)-carveol, and 47 monohydrate conformations for *cis* (-)-carveol. Using these results, a total of three monohydrate conformers were experimentally assigned, with the likelihood of additional monohydrates or dihydrates being present in the spectrum. For the *trans*-monohydrate, two conformers were identified, which correspond to the two monomer conformers assigned in the previous study.[2] A single monohydrate was assigned for *cis* (-)-carveol, consistent with the lowest energy equatorial monomer conformation from the monomer study.

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