

Shedding Light on Molecular Recognition Mechanisms

New experimental approaches are unveiling the weak non-covalent forces between molecules that historically have been challenging to study in the arduous terahertz spectral region.

Molecular recognition, the mechanisms by which biological macromolecules interact either with each other or with other various small substrates with high specificity and affinity to form specific molecular complexes, constitutes the foundation for all processes in living organisms. Proteins, the most important class of biological macromolecules, all realize their vital biological specific functions through the association to other molecules.

Knowledge of the detailed mechanisms responsible for molecular recognition phenomena and an accurate quantification of the energetics, which drive the association processes, will therefore help to facilitate the discovery, design, and development of new drugs.

“The *intra*-molecular vibrational ‘fingerprints’ of stable molecules, kept together by covalent chemical bonds, are usually detected in the infrared (IR) spectral region. However, as the

non-covalent intermolecular forces stabilizing weakly bound molecular complexes normally are 10-100 times weaker than covalent bonds ($\sim 5-50 \text{ kJ}\cdot\text{mol}^{-1}$), the *inter*-molecular vibrational modes introduced by the complexation between molecules are detected in the less accessible terahertz (THz) spectral region”, says Associate Professor René Wugt Larsen, who is in charge of the THz cluster spectroscopy group at DTU Chemistry.

The accurate interaction strength, directionality and cooperativity of the weak “contacts” associated with non-covalent intermolecular forces can be probed *directly* via these large-amplitude modes arising from the now hindered rotational and translational motion of the subunits relative to each other. These resulting THz spectral signatures are thus crucial in order to characterize with unprecedented accuracy the intermolecular potential energy surface spanned by the subunits and yield rigorous experimental benchmarks to validate or improve quantum chemical methodologies.

However, the relevant part of the spectrum is denoted the “THz gap” as historically it has been challenging to produce intense radiation with these wavelengths. The only high-brightness sources of broadband THz radiation are offered by large-scale synchrotron radiation facilities as Canadian Light Source, Synchrotron SOLEIL (Paris), Australian Synchrotron and recently at the free-electron laser facility FELIX (Nijmegen).

“There is a fundamental need for experimental approaches which are able to investigate the intermolecular energy balances associated with the interplay of weak non-covalent forces such as directional intermolecular hydrogen bonds and dipole-dipole interactions, non-directional long-range van der Waals forces and steric repulsion between molecules”, says René Wugt Larsen.

Soft “Quantum Crystals”

The demand for THz spectral signatures of weakly bound molecular van der Waals complexes has urged for the development of complementary experimental approaches employing conventional radiation sources, where the experimental sensitivity is governed by significant number densities of transient molecular systems trapped in ultra-cold inert environments.

The research group of Associate Professor René Wugt Larsen has recently demonstrated that highly enriched *para*-H₂ “quantum crystals” of >99,95 % purity offers multiple advantages as a host for low-temperature THz cluster spectroscopy arising from the unique “quantum nature”.

The H₂ molecule exists as two spin isomers: *para*-H₂ with paired nuclear spins or *ortho*-H₂ with unpaired nuclear spins, where the latter has a “reactive” magnetic moment. In the ground state of this soft material, the *para*-H₂ molecules provide an almost

Other Research Activities

The THz cluster spectroscopy group of Associate Professor René Wugt Larsen has recently established fruitful internal collaborations with the DTU Chemistry molecular material research groups of Associate Professor Kasper S. Pedersen and Associate Professor Martin Nielsen concerned with the spectroscopic characterization of novel metal-organic frameworks and organometallic complexes. In addition, a close external collaboration with the Danish Hydrocarbon Research & Technology Centre (DHRTC) has recently been established related to spectroscopic investigations of fluid-fluid and surface-fluid association mechanisms.

field-free host medium, where the large-amplitude zero-point lattice motion offers significantly free space for embedded guest molecules and the crystal behaves as an “extremely cold gas”.

In newly developed experimental setups the research group of Associate Professor René Wugt Larsen has been able to characterize in great detail the large-amplitude vibrational motion of weakly bound molecular van der Waals complexes embedded in enriched *para*-H₂ at 4 K.

Proof-of-Concept at DTU Chemistry

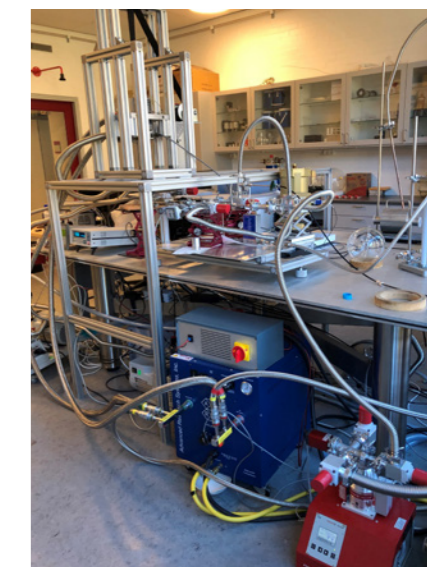
The project was initiated in 2013, when René Wugt Larsen obtained a 5-year Sapere Aude Research Leader grant from the Independent Research Fund Denmark / Natural Sciences (FNU). Later, the Danish Hydrocarbon Research and Technology Centre (DHRTC) has provided further funding. The “proof-of-concept” has recently been published in the journal *Physical Chemistry Chemical Physics*.

“In this work, we have revealed interesting molecular recognition processes and we have managed to trap a variety of exotic molecular systems. These molecular systems are formed due to the kinetics associated with the mobility of molecules

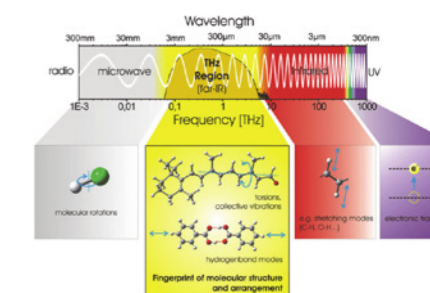
in the soft *para*-H₂ medium and would never form under ambient conditions”, says Associate Professor René Wugt Larsen. “The observed THz signatures and intermolecular force fields provide challenging experimental benchmarks even for the most sophisticated quantum chemical methodologies”, he continues.

The PhD Students Dmytro Mihrin and Alexandre Vouste have developed a fully-automated cryogen-free *para*-H₂ synthesis apparatus based on a temperature controlled closed-cycle helium cryo-cooler for these studies and the workshop at DTU Chemistry has constructed many vital parts for these new experimental facilities.

A future aim is to address one of the most fascinating phenomena in nature referred to as the “homochirality of life”. The chemistry of life is built almost exclusively on left-handed amino acids and right-handed sugar molecules. Often one chiral form of a drug is active, while the other(s) are either inactive or have severe adverse effects. It has been argued, that a true breakthrough in our understanding of these molecular chirality recognition phenomena can be achieved by accurate THz spectroscopic investigations of chiral drug-receptor model systems.



The new THz cluster spectroscopy experiment for investigations of weakly bound molecular van der Waals complexes doped in *para*-H₂ “quantum crystals” at 4 K.



The electromagnetic spectrum and the variety of spectroscopies (MW, THz, IR and UV) associated with the different quantum states of molecular systems [adapted from *Anal. Bioanal. Chem.* 2010, 397, 1009-1017].

The large-amplitude hindered internal rotational motion for a kinetically formed “exotic” conformation of the ternary CS₂-(H₂O)₂ van der Waals complex in *para*-H₂.

