Berlin, June 12 - 17, 2010

ibbi 2010

isolated biomolecules and biomolecular interactions

Isolated Biomolecules and Biomolecular Interactions

Fritz-Haber-Institut der Max Planck-Gesellschaft
and
Tagungsstätte Harnack-Haus

12-17 June 2010, Berlin, Germany

Welcome

The Isolated Biomolecules and Biomolecular Interactions 2010 (IBBI 2010) conference is the continuation of a series of successful meetings held in Les Houches, France (2000), Wildbad Kreuth, Germany (2002), Exeter, UK (2004), Prague, Czech Republic (2006) and Valladolid, Spain (2008).
We are very pleased to host the 2010 edition in Berlin. The conference program is dense and is comprised of 27 invited, 15 “hot topic” and more than 80 poster presentations. Nonetheless, you should find plenty of time between presentations to engage in scientific exchange.
We all hope that you will enjoy your stay in Berlin and a stimulating conference! If you need any help or have any questions, please contact the local organizing staff.

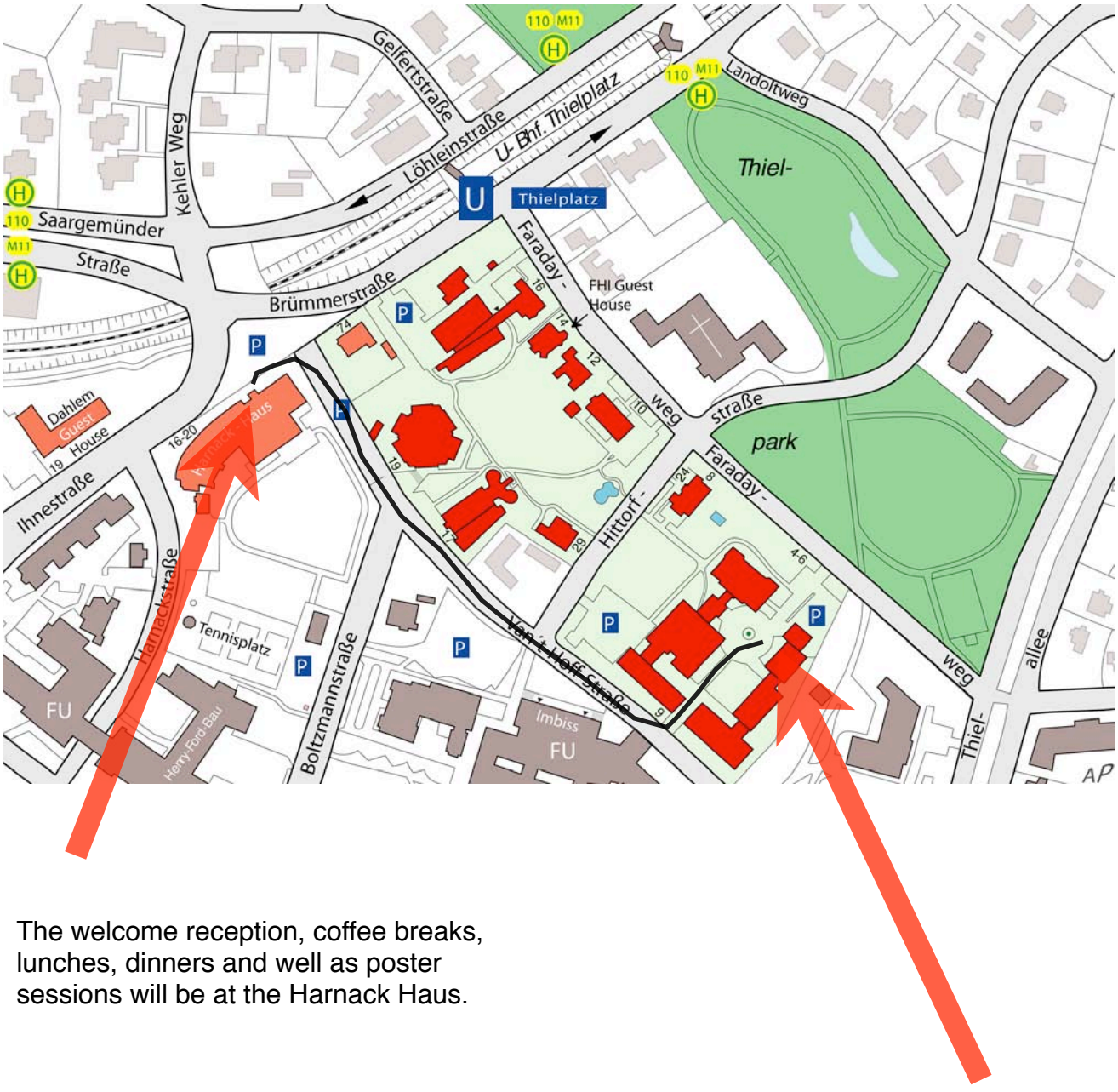
The local organizing committee:
Gert von Helden (Chairman)
Volker Blum
Matthias Scheffler
Gerard Meijer

The IBBI scientific committee:
Michael Bowers (University of California Santa Barbara, USA)
Charles Desfrancois (University of Paris-Nord, France)
Pavel Hobza (Academy of Sciences, Prague, Czech Republic)
Jean Pierre Schermann (University of Paris-Nord, France)
John Simons (Oxford University, UK)
Rainer Weinkauf (University of Düsseldorf, Germany)
José L. Alonso (Universidad de Valladolid, Spain)

Support is provided by:

General Information

Location:



The welcome reception, coffee breaks, lunches, dinners and well as poster sessions will be at the Harnack Haus.

The lectures will be at the lecture hall of the Fritz-Haber-Institut.

Map of the surroundings:

The Harnack Haus is indicated as “1”, the location of the lecture room as “2”.
Within walking distance, you can also find:

3) the park “schwarzer Grund” for a short walk,
4) the restaurant and Biergarten “alter Krug”,
5) the restaurant and Biergarten “Luise”,
6) the open air museum and farm “Domäne Dahlem”,
7) a supermarket,
8) the ethnological museum,
9) the botanical garden.

Close by 5) and 7), there are also two banks as well as a pharmacy.

Further Information:

- Public transport:
Schedule information can be found on the website http://www.bvg.de. The FHI and Harnack Haus are at the stop "Thielplatz" of the subway U3. The nearest exit is in train direction (coming from the city). Single fares within Berlin are 2,10 € (zone AB), valid for subway and busses. Short distances, "Kurzstrecke", (up to three stops of the subway or six stops of a bus, no changeover allowed) are 1,30 €. You can get tickets at the vending machines in the subway stations or from the bus driver. **Tickets obtained from the vending machines need to be validated (stamped, "entwertet") before the ride.**

- Excursion:
The excursion is on Tuesday and will be a boat tour on the Spree river through Berlin. The boat will leave from near "Schloss Charlottenburg" at about 19:00 and return there around 23:00. Details can be found on a handout.

- Soccer:
Please note that the 11th of June is the start of the soccer world championship in South Africa. On Sunday evening, after the poster session, there is the opportunity to watch the World Cup soccer game Germany - Australia in the Harnack Haus on a big screen.

- WLAN:
Eduroam access is provided at both, the FHI and the Harnack Haus. Non eduroam users can access the internet via the Wi-FHI guest network. For guest WLAN access in the Harnack Haus, contact the Harnack Haus front desk.

-Posters:
Formal poster sessions will be held on Sunday and Monday. The posters can stay on the boards during the entire conference. Presenters should be at their posters on Sunday for posters with an even number, and on Monday for posters with an odd number.

Program

Sunday, 13 June

9:00	**Opening**	
9:15	J.-P. Schermann	A brief review of spectroscopic studies of biomolecular structures from gas-phase to living cells
10:00	N.C. Polfer	Peptides chasing their tails – what infrared spectroscopy can tell us about peptide dissociation chemistry
10:30	HT: M.T. Rodgers	Infrared multiphoton dissociation spectroscopy of protonated uracil and thiouracils: effects of thioketo-substitution on gas-phase conformation
10:50	**Break**	
11:30	O.V. Boyarkin	Photofragmentation spectroscopy of protonated gramicidin S
12:00	R.A. Jockusch	Fluorescence and photodissociation spectroscopy of mass-selected ions
12:30	B. Paizs	Cyclization and rearrangement reactions of fragment ions of protonated peptides: IRMPD and theoretical studies
13:00-14:30	**Lunch**	
14:30	M. Bonn	Label-free, real-time studies on intermolecular interactions at model membranes using surface vibrational spectroscopy
15:00	M.P. Gaigeot	DFT-based molecular dynamics simulations for the interpretation of gas phase IR-MPD experiments of floppy peptides and for condensed phase IR experiments
15:30	**Break**	
16:10	HT: P.B. Armentrout	Threshold collision-induced dissociation measurements of protonated peptides
16:30	HT: M. Rossi	Stability and (un)folding of a peptide helix in the gas phase from first-principles: Ac-$Ala_{15}LysH^+$
16:50	HT: J. Oomens	Structure of anionic peptides and their CID fragments
18:00	**Dinner**	
20:00	Poster I	

Monday, 14 June

9:00	A.J.R. Heck	Native mass spectrometry in viral structural biology and molecular systems biology
9:45	B. Brutschy	Macromolecular protein assemblies from the membrane and solution studied with LILBID-laser mass spectrometry
10:15	HT: A. Lübcke	Towards fs time-resolved photoelectron spectroscopy of biomolecules in aqueous solutions
10:35	**Break**	
11:15	D. van der Spoel	Protein structure in the gas phase
11:45	J.A. Loo	Probing the fidelity between gas phase and solution phase protein structures with top-down mass spectrometry
12:15	L. Konermann	Protein structure and function studied by mass spectrometry
12:45-14:30	**Lunch**	
14:30	N.P. Ernsting	Low-frequency vibrations due to biomolecular recognition of duplex DNA enhanced by solvent
15:00	C. Ochsenfeld	Intermolecular interactions in molecular systems with 1000 and more atoms — a challenge for quantum chemistry
15:30	**Break**	
16:10	HT: M. Schwell	VUV spectroscopy of biological molecules produced by vaporization of nanoparticles: Bringing fragile neutrals to the gas phase
16:30	HT: I. Compagnon	UV spectroscopy of gas phase proteins
16:50	HT: M.S. de Vries	Photochemical selection in prebiotic chemistry of nucleobases
18:00	**Dinner**	
20:00	Poster 2	

Tuesday, 15 June

9:00	M.T. Bowers	Amyloid aggregation: the latest news
9:45	C. Wu	Predicting structures of small non-amyloid and amyloid proteins using molecular dynamics simulation in implicit water
10:15	HT: K. Pagel	Alternate dissociation pathways identified in charge-reduced protein complex ions
10:35	**Break**	
11:15	R.M.A. Heeren	Ion mobility and molecular histology: New glasses for the doctor!
11:45	G. Grégoire	Probing the specific interactions and structures of gas-phase vancomycin antibiotics with cell-wall precursor through the combination of ion mobility mass spectrometry and IRMPD spectroscopy
12:15	B.T. Ruotolo	Development of ion mobility-mass spectrometry as a high- throughput approach for structural genomics
12:45-14:30	**Lunch**	
14:30	J.S. Klassen	Structure and stability of protein-ligand complexes in the gas phase
15:00	HT: K.B. Bravaya	Electronic structure of the ionized DNA bases clusters: the effects of H-bonding and stacking interactions.
15:20	HT: S.V.K. Kumar	Low energy electron interaction with duplex supercoiled and relaxed, and single stranded plasmid DNA
16:00	**Excursion**	

Wednesday, 16 June

9:00	J. Simons	Isolated carbohydrates and carbohydrate interactions
9:45	J.A. Leary	Ion mobility investigations of carbohydrate:protein:metal non- covalent complexes
10:15	HT: P. Çarçabal	100 keV proton irradiation of Halo-Uracils in the gas phase: Specific fragmentation channels revealed by coincidence measurements
10:35	**Break**	
11:15	J. Bredenbeck	Mixed IR/VIS multidimensional spectroscopies: chemistry and biophysics in realtime
11:45	M. Gerhards	IR/UV investigations on hydrated and aluminum containing peptides
12:15	Y. Xu	Spectroscopy of chiral molecules: from the gas phase to solution
12:45-14:30	**Lunch**	
14:30	J.L. Alonso	Watching conformations of biomolecules: a microwave spectroscopy approach
15:00	E. Nibbering	Ultrafast generation of aqueous carbonic acid
15:30	**Break**	
16:10	HT: E.F. Aziz	On the enzymatic activity of catalase: an iron L-edge X-ray absorption study of the active centre
16:30	HT: D.M. Benoit	Molecular conformation from vibrational spectra: anharmonicity is key!
16:50	HT: P. Kupser	Catching proteins in liquid helium droplets
17:10	t.b.a.	Closing remarks
18:00	**Dinner**	

Invited Presentations

A Brief Review of Spectroscopic Studies of Biomolecular Structures from Gas-Phase to Living Cells

Jean-Pierre Schermann

Department of Biophysics and Chemical Biology, WCU Seoul National University, Korea and LPL-CNRS, Université Paris 13, Villetaneuse, France

Structure and function of biomolecules are intimately related. In living cells, biomolecules interact and act in a highly concentrated, crowded and inhomogeneous medium. For simplicity, their structures are usually studied under homogeneous and diluted conditions. It is usually accepted that the 3-D structure of a biomolecule contains the information and thus a tremendous effort is devoted for example to the experimental determination of native structures of proteins through NMR or X-ray crystallography. Gas-phase studies that provide intrinsic structures in absence of any environment also emphasize the determination of well-defined and rigid conformations of a variety of biomolecular systems at very low temperature. However, a huge fraction of proteins are not structured and nevertheless play crucial roles due to their molecular recognition abilities, for example in cellular signalling.

Spectroscopic experiments conducted at room temperature in gas-phase strongly lack the conformer selectivity achievable in low-temperature studies but can sometimes be closer to the biological reality as long as not only structure but also dynamical flexibility is taken into account. Today, some experimental studies aim to combine the structural selectivity of ion mobility, the information brought by infrared spectroscopy and the possibility of varying temperature from near 0 K up to room temperature.

Water plays an essential role and hydration is thus widely investigated. Two extreme situations have mostly been considered. In low-temperature cluster studies, step-wise addition of water molecules emphasize preferential hydration sites corresponding to the most strongly bound species but the first hydration layer is then only very crudely approximated. On the contrary, spectroscopic investigations (IR, NMR, CD …) conducted in bulk water at room temperature provide an average but more realistic picture. Unfortunately, they most often do not distinguish between the very different situations encountered by water molecules, for example on biomolecular surfaces accessible to solvent or embedded in hydrophobic pockets. The role of temperature and hydration described in the preceding remarks can be illustrated in the case of the gas-phase and aqueous phase structures of the acetylcholine neurotransmitter. A drug-design point of view is then adopted through introduction of a pharmacophore model that is also used for nicotine and other drugs mimicking the biological role of acetylcholine. In particular, information brought by hydrated clusters and bulk studies may be compared in order to investigate the influence of hydration of nicotine in its receptor pocket.

Biomolecules can today be investigated under real biological conditions in living cells through NMR and spectroscopy. The obtained structures can then be compared to those deduced from aqueous phase studies. It is also possible to monitor in real time the fate of living cells until their death.

Peptides chasing their tails – what infrared spectroscopy can tell us about peptide dissociation chemistry

Nick C. Polfer, Xian Chen, Marcus Tirado
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Jos Oomens, Jeffrey D. Steill
FOM Institute 'Rijnhuizen', Nieuwegein, The Netherlands

Peptides are dissociated in mass spectrometers to derive their amino acid sequence. In collision-induced dissociation (CID), abundant amide backbone cleavage is observed, resulting in N-terminal **b** and C-terminal **y** fragments. While **y** fragments adopt a normal peptide structure, **b** fragments exhibit a C-terminal amide C=O that must be stabilized by a nucleophilic attack. It was generally assumed that another carbonyl oxygen engages in this attack, resulting in a five-membered ring oxazolone structure. This has been confirmed by infrared photodissociation spectroscopy [1]. However, peptides exhibit other nucleophiles, such as side-chain groups, and the N-terminal amino group. When the latter group takes part in a "head-to-tail" nucleophilic attack, this gives rise to a macrocycle structure, where the N- and C-terminal parts of the molecule are fused together. Re-opening of this structure at a different amide bond results in sequence permutation [2], thus potentially leading to misidentification of the sequence. Once again, vibrational spectroscopy can yield insights for the presence of such macrocycle structures, based on diagnostic vibrations [3]. Recent results on the competition between oxazolone and macrocycle formation will be presented for a number of peptide systems. The trends so far suggest that the propensity to form the macrocycle structure increases with chain length of the fragment [4]. Moreover, some residues are shown to play an important role in dis/favoring macrocycle formation. It is expected that these studies will shed light on the processes that promote sequence permutation in CID, thus establishing how prevalent this phenomenon is.

[1] Polfer *et al., J. Am. Chem. Soc.* **2005**, 127, 17154.

[2] Harrison *et al., J. Am. Chem. Soc*. **2006**, 128, 10364.

[3] Polfer *et al., J. Am. Chem. Soc*. **2007**, 129, 5887.

[4] Chen *et al., J. Am. Chem. Soc*. **2009**, 131, 18272.

Photofragmentation Spectroscopy of Protonated Gramicidin S

Natalia S. Nagornova, *Thomas R. Rizzo and Oleg V. Boyarkin*
Laboratoire de Chimie Physique Moléculaire, École Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

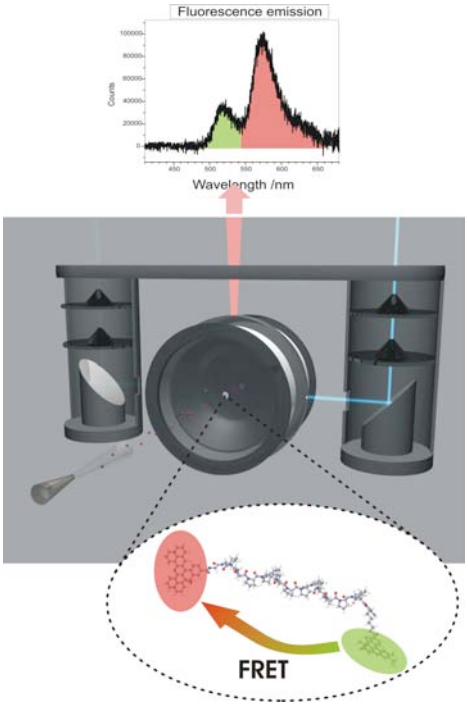
Specific biological functions of proteins are largely determined by the 3-D structures that they adopt in *vivo*. Calculation of these complex structures requires experimental verification and, perhaps, gradual adjustments of the employed models. Vibrational spectroscopy can provide a "fingerprint" of a molecule by revealing its characteristic pattern of infrared transitions, which is intimately related to molecular structure. Comparison of this pattern with that calculated for a few pre-selected, the most stable structures provides a mean for selecting truly structures of experimentally observed conformers. This strategy however fails for large molecules (9-10 and more amino acids), in particular, because of timely calculations. Additional, experimentally derived structural constraints may shorten the calculations by narrowing a pre-selection to a few structures prior to lengthy calculations of their vibrational spectra. Here we employ a UV and an IR-UV laser double resonance photo-fragmentation approaches to measure electronic and, subsequently, conformer-selective IR spectra of protonated decapeptide, gramicidin S, in the gas-phase.[1,2] Cooling ions to T~12K in a 22-pole linear ion trap and a use of narrow linewidth UV and IR lasers allows vibrational resolution in both electronic and vibrational spectra. In addition to vibrational "fingerprints" in 7-5.5 μm and 3.5-2.5 μm regions we have derived some qualitative constraints that predetermine structure of the most stable conformer of doubly protonated gramicidin S.[3] These spectroscopic data serve as a benchmark for challenging computations of gramicidin S structure.

1 O. V. Boyarkin, S. R. Mercier, A. Kamariotis, and T. R. Rizzo, J. Am. Chem. Soc. **128** (9), 2816 (2006).
2 J. A. Stearns, S. Mercier, C. Seaiby, M. Guidi, O. V. Boyarkin, and T. R. Rizzo, J. Am. Chem. Soc. **129** (38), 11814 (2007).
3 Natalia S. Nagornova, Thomas R. Rizzo and Oleg V. Boyarkin, J. Am. Chem. Soc. online publication March 4, 2010 (Communication)

Fluorescence and Photodissociation Spectroscopy of Mass-Selected Ions

Rebecca A. Jockusch
Department of Chemistry, University of Toronto, Toronto, Canada M5S 3H6

Characterization of biomolecules and biomolecular complexes in a highly-controlled gas-phase environment allows valuable simplification of complex biological systems and provides a route to elucidate the effects of specific non-covalent interactions. We have recently built a flexible interface for doing optical spectroscopic experiments on gaseous molecular ions and clusters, formed by electrospray ionization (ESI), mass selected and stored in a quadrupole ion trap mass spectrometer (QIT-MS). [1] Recent results from fluorescence and photodissociation action spectroscopy of several small molecular ions and fluorophore-labeled peptides will be presented. These include the intrinsic behavior of a model chromophore of the green fluorescent protein.[2] In addition, dispersed fluorescence spectra and fluorescence lifetime measurements showing fluorescence resonance energy transfer (FRET) in gaseous polyproline-based peptides will be presented. The effect of molecular charge on peptide conformation is explored using measured FRET efficiency and computations. The effect of molecular charge on peptide conformation is explored using measured FRET efficiency and computations. The gas-phase FRET studies presented here provide a new route to probe the intrinsic structure of biomolecules, both in isolation and in well-defined micro- environments.



[1] Q. Bian, M. W. Forbes, F. O. Talbot and R. A. Jockusch, (2010) “Fluorescence Excitation and Emission Spectroscopy of Trapped, Mass-Selected Gas-Phase Ions,” *Phys. Chem. Chem. Phys.*, *12*, 2590-2598.

[2] M. W. Forbes and R. A. Jockusch (2009) “Deactivation Pathways of a GFP Chromophore Studied by Electronic Action Spectroscopy,” *J. Am. Chem. Soc.*, *131*, 17038-17039.

Cyclization and Rearrangement Reactions of Fragment Ions of Protonated Peptides: IRMPD and Theoretical Studies

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Computational Proteomics Group, German Cancer Research Center, Heidelberg, Germany

Philippe Maître
Laboratoire de Chimie Physique, Université Paris-Sud 11, Paris, France

Peptide sequencing in proteomics is mainly achieved by tandem mass spectrometry (MS/MS) of protonated peptides. In these experiments peptide ions are excited by collisions with inert gases (collision-induced dissociation (CID)) to induce fragmentation and the resulting product ion spectra are used to decipher the sequences. The product ion spectra of protonated peptides are usually dominated by sequence informative *b*, *a*, and *y* fragments, which are formed in a complex reaction cascade [1]. To facilitate rapid processing of the large number of spectra routinely produced in high-throughput proteomics experiments, various bioinformatics tools have been developed. These programs utilize fragmentation models to generate theoretical spectra for candidate sequences and various mathematical measures to assess similarity between these theoretical spectra and the experimental MS/MS spectra. One of the basic assumptions inherent to the current implementation of this strategy is that peptide ions or their fragments dissociate on *direct* fragmentation pathways, which do not introduce rearrangements of the original sequences.

Recent studies [2-4] indicate that the dissociation chemistry of *a and b* ions cannot be universally described by considering only *direct* fragmentation chemistries. For example, linear *b* structures can undergo head-to-tail cyclization to form a macrocyclic isomer which can open up at any amide bond to regenerate linear isomers. This chemistry in all but the case where the original sequence is regenerated leads to linear *b* isomers with scrambled sequences. IRMPD and theoretical studies on this 'scrambling' chemistry of *b* ions and rearrangement pathways of *a* fragments will be reviewed in this presentation.

[1] Paizs, B.; Suhai, S. *Mass Spectrom. Rev.* **2005**, *24*, 508.

[2] Harrison, A. G.; Young, A. B.; Bleiholder, B.; Suhai, S.; Paizs, B. *J. Am. Chem. Soc.* **2006**, *128*, 10364.

[3] Bleiholder, C.; Osburn, S.; Williams, T. D.; Suhai, S.; Van Stipdonk, M.; Harrison, A. G.; Paizs, B. *J. Am. Chem. Soc.,* **2008**, *130*, 17774.

[4] Erlekam, U.; Bythell, B.J.; Scuderi, D.; Van Stipdonk, M.; Paizs, B.; Maitre, P. *J. Am. Chem. Soc.* **2009**, *131*, 11503.

Label-free, real-time studies on intermolecular interactions at model membranes using surface vibrational spectroscopy

Mischa Bonn
FOM-Institute AMOLF, Science Park 104, 1098 XG Amsterdam, The Netherlands

Sum frequency generation (SFG) vibrational spectroscopy is a technique that provides the vibrational spectrum of the outermost monolayer of molecules at an interface. As such, it has proven itself to be a very powerful technique in the study of molecular structure of surfaces and interfaces in different chemical environments. It is particularly well-suited for the study of biomolecular interactions at model biological membranes. It provides information on the organization and confirmation of lipids, the water hydrating the lipids, and proteins embedded in, or interacting with the model membrane.

We have performed SFG studies on lipid monolayers, aimed at elucidating the intermolecular interactions that give rise to membrane functionality. We will report on the interaction of lipids with cholesterol and DNA, reveal the molecular signatures of an antimicrobial peptide destabilizing both the lipids and the membrane bound water, and report on the specific interactions between the large protein choleratoxin and GM1 lipids.

Molecular level details revealed by SFG in these studies show that SFG can provide unique insights on the interactions between lipid monolayers and DNA, peptides and proteins in real time, in situ, in an intrinsically label-free manner.

DFT-based molecular dynamics simulations for the interpretation of gas phase IR-MPD experiments of floppy peptides and for condensed phase IR experiments

M.-P. Gaigeot

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Finite temperature DFT-based ab initio molecular dynamics simulations are presented for the calculation of infrared spectra in relation with IR-MPD experiments (InfraRed MultiPhoton Dissociation exps). Illustrations are taken from our recent works on flexible peptides of increasing size and complexity in relation with IR-MPD experiments. A special emphasis will be put forward on the importance of taking the effect of conformational flexibility into account in the calculation of the spectra as well as taking into account vibrational anharmonicities, all properties that are naturally included in molecular dynamics simulations.

We also present our new method for extracting "Effective Normal Modes" from the dynamics, more specifically with the goal of assigning the active vibrational modes from the simulations in terms of internal movements. Illustration of the method for extracting mode couplings anharmonicities will also be presented.

We will also show how all the methodology can be applied to liquid phase spectra calculations with illustrations from our works on peptide models, as well as on solid/liquid interfaces.

Recent references :

M.-P. Gaigeot
Perspective paper in Phys. Chem. Chem. Phys., Special issue: Biomolecular structures, from isolated molecules to living cells, **12**:3336-59 (2010)

A. Cimas, M.-P. Gaigeot
Phys. Chem. Chem. Phys., **12**:3501, 2010

A. Cimas, T. D. Vaden, T. S. J. A. de Boer, L. C. Snoek, M.-P. Gaigeot
J. Chem. Theor. Comput., **5**:1068, 2009

M.-P. Gaigeot
J. Phys. Chem. A., **112**:13507, 2008

G. Grégoire, M.P. Gaigeot, D.C. Marinica, J. Lemaire, J.P. Schermann and C. Desfrançois.
Phys. Chem. Chem. Phys., **9**:3082-3097, 2007.

M.P. Gaigeot, M. Martinez, R. Vuilleumier.
Mol. Phys., **105,** 2857-2878, 2007, Special Issue dedicated to Peter Pulay

Native Mass Spectrometry in Viral Structural Biology and Molecular Systems Biology

Albert J. R. Heck

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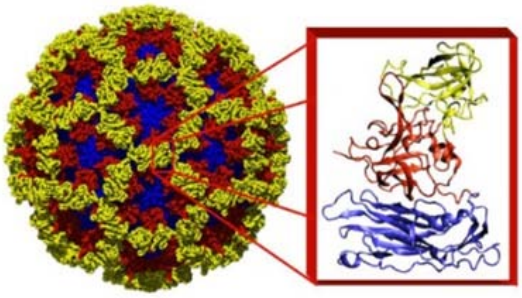
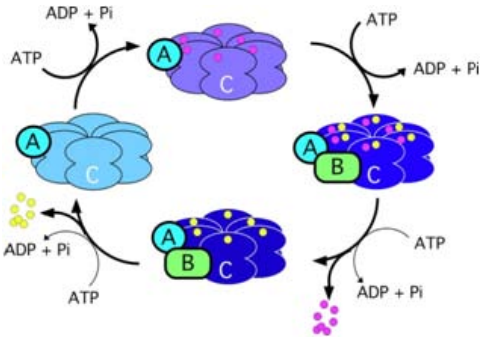
The development of electrospray ionization coupled to mass spectrometry has enabled the analysis of very large intact protein complexes even when they are held together by non-covalent interactions. Together with equally spectacular advances in mass spectrometric instrumentation a new field has emerged, termed native protein mass spectrometry that focuses on the structural and functional analysis of the dynamics and interactions occurring in protein complexes. Native mass spectrometry allows the topological investigation of intact protein complexes with high sensitivity and a theoretically unrestricted mass range. This unique tool provides complementary information to established technologies in structural biology.

Using such mass spectrometry based technologies we have begun to study the biophysical properties of virus structure and assembly, focusing on the important HBV and norovirus human pathogens. The masses of HBV (3-4 million Da) and the noro virus (over 10 million Da) create significant challenges on any structural method to characterize these particles with considerable resolution, are some of the largest particles ever analyzed by high resolution mass spectrometry. For these viruses we have been able to probe several distinct assembly intermediates, which are generally low abundant and therefore difficult to monitor by other techniques. Several biophysical parameters such as self-assembly, stability and shape of the virus particles were monitored as well as their dependence on pH, ionic strength and temperature.



Moreover, we used native mass spectrometry to probe the regulation of a cyano-bacterial circadian clock, which is regulated by the interplay of protein assembly and protein phosphorylation, involving three proteins; KaiA, KaiB and KaiC. Native mass spectrometry was used to measure the real-time assembly properties of this self-organizing system and provided the missing link needed to construct a full theoretical molecular model to describe the rhythm, stability and regulation of this clock.



Macromolecular Protein Assemblies from the Membrane and Solution Studied with LILBID-Laser Mass Spectrometry

Bernd Brutschy

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Biological molecules in membranes often form highly functional macromolecular assemblies, such as the complexes of the breath chain (I to V), ion-channels, transporters etc. Since they are partially hydrophobic their analysis represents a great challenge to mass spectrometry (MS). Nevertheless they are of greatest relevance and in their majority important drug targets. Solvable protein assemblies on the other hand are less demanding from the point of preparation but also often form highly functional, complicated macromolecular complexes or nanomachines such as ribosomes, polymerase, efflux pumps or oligomers of proteins such as those formed from Aβ–amyloid causing Alzheimer´s disease.
LLILBID (laser induced liquid bead ion desorption) allows to analyse biomolecules from on demand micro droplets (R=50 μm) in vacuum by laser ablation of preformed ions from solutionby means of a pulsed IR laser (3μm). The strength of interaction can be varied by the laser intensity. At low intensity large membrane molecules, solubilised in micelles from detergent, can thus be made "flying" and analyzed by TOF mass spectrometry (MS). At higher intensity noncovalently bound assemblies (complexes) may be fragmented into their subunits, allowing the analysis of their covalent building blocks. The method is very sensitive and requires only μl of solution at μM concentration for an analysis. Moreover it is tolerant to alkali salts, different buffers, detergents. doubly charged ions, pH etc. Therefore the ions may be studied in a more or less native environment, which is in general crucial for the formation of specific functional assemblies.
The talk will give an overview of the method, discuss results from complex I, from ATPases (complex V), and other nano machines and findings for the Aβ–oligomers and other soluble protein complexes etc.

References.

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A Novel Approach to Analyze Membrane Proteins by Laser Mass Spectrometry: From Protein Subunits to the Integral Complex J. Am. Soc. Mass Spectrom. 18,1429-1438

N.Morgner, J. Hoffmann, H-D. Barth, T. Meier, B. Brutschy (2008)
LILBID mass spectrometry applied to the mass analysis of RNA polymerase II and a F1Fo-ATP synthase
Int. J. Mass Spectr. 277, 309-313

N.Morgner, V. Zickermann, S. Kerscher, I. Wittig, A. Abdrakhmanova, H-D. Barth, B. Brutschy, U. Brandt (2008)
Subunit Mass Fingerprinting of Mitochondrial Complex I , BBA-Bioenergetics 1777, 1384-1391

Protein structure in the gas phase

David van der Spoel
Dept. of Cell and Molec. Biol., Uppsala University

The gas-phase provides a hostile environment for biological specimens, like proteins. Nevertheless mass spectrometry routinely probes proteins and peptides outside their native environment. In order to facilitate and strengthen interpretation of such experiments we provide a structural underpinning based on simulations. We find in general that solution structures of proteins are largely maintained upon complete dehydration [1,2]. Encapsulation of proteins inside thin water layers or lipds or detergent micelles further stabilizes the native structure [3,4].

[1] A. Patriksson, E. Marklund and D. van der Spoel, Biochemistry 46 (2007) 933 [2] E. Marklund, D.S.D. Larsson, A Patriksson, D. van der Spoel and C. Caleman, Phys. Chem. Chem. Phys. 11 (2009) 8069 [3] Y. Wang, D.S.D. Larsson and D. van der Spoel, Biochemistry 48 (2009) 1006 [4] R. Friemann, D.S.D. Larsson, Y. Wang and D. van der Spoel, J. Amer. Chem. Soc. 131 (2009) 16606

Probing the Fidelity between Gas Phase and Solution Phase Protein Structures with Top-Down Mass Spectrometry

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Mass spectrometry (MS) has been used to characterize higher order structure and assembly states of solution phase proteins and protein complexes. Implicit in this application of MS is the assumption that elements of the structural details of the solution phase protein molecule are preserved in the gas phase molecule. Despite numerous studies that have been published, there is some skepticism among the biophysical/biochemical community that this application of MS has utility for understanding solution phase protein structures.

We have used electrospray ionization mass spectrometry (ESI-MS) not only for detecting noncovalent protein-ligand complexes [1], but also to define the sites of ligand-protein interactions. We are attempting to develop top-down protein MS for measuring the sites of noncovalent protein-ligand binding. We have discovered that electron capture dissociation (ECD) dissociates only covalent bonds of noncovalent protein-ligand complexes, i.e., the noncovalent ligand interaction is retained [2]. Therefore, an ESI-ECD-MS/MS strategy of native protein-ligand complexes may reveal the contact interface for protein-ligand interactions.

Moreover, because electrostatic interactions are significantly strengthened in the absence of solvent, these types of interactions can withstand energetic gas phase processes, such as collisionally activated dissociation (CAD). The sites of ligand binding can be probed by CAD-MS/MS for protein-metal and protein-nucleotide complexes [3]. Increasing the multiple charging (i.e., supercharging) of noncovalent proteins increases the efficiency of top-down MS [4]. Enhanced charging and dissociation of native protein complexes have been observed for a variety of supercharging reagents, including sulfolane.

We show that top-down MS is able to determine the sites of protein-ligand interactions, such as adenylate kinase-ATP, interactions of protein profilin and KabC (a naturally occurring toxin) with the hydrophobic pocket of the actin protein, and calcium ions with the EF-hands of calmodulin. These studies demonstrate that the structures of the solution phase complex have not been significantly perturbed upon transition to the gas phase.

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Protein Structure and Function Studied by Mass Spectrometry

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Proteins act as biological nano-machines that carry out a myriad of functions inside living organisms. In order to perform these tasks, the linear amino acid chain of each protein has to fold into a highly specific three-dimensional structure. Once a protein has reached this native state, conformational dynamics play a key role for energy transduction, signaling, enzyme catalysis and many other processes. Electrospray ionization (ESI) mass spectrometry (MS) provides a number of exquisitely sensitive strategies for exploring protein structure, folding, and dynamics [1]. Our laboratory employs a combination of "native" ESI-MS, on-line rapid mixing, H/D exchange (HDX), as well as covalent labeling for studies in this area [2]. We will discuss how "bottom-up" HDX can provide detailed insights into the mechanism of bacterial signal transduction. Another focus are "top-down" HDX measurements with electron capture dissociation (ECD), an approach that represents a novel strategy for probing protein H-bonding networks [3]. Exciting new developments in microsecond hydroxyl radical labeling provide information on the folding mechanisms of water-soluble and membrane proteins [4, 5]. The information gained using these techniques is complementary to that obtainable by traditional structural biology tools such as NMR spectroscopy and X-ray crystallography.

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Low-frequency vibrations due to biomolecular recognition of duplex DNA enhanced by solvent

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The bis-benzimidazole dye Hoechst 33258 binds to A:T-rich regions in the minor groove of duplex DNA. Low-frequency oscillations of such recognition sites, when several phosphodiester residues move coherently, were not observed until now in aqueous solutions. They are reported here as depending on solvent. Following optical excitation of the ligand, we monitor its entire fluorescence band with 80 fs time resolution using broadband fluorescence upconversion and, independently, broadband stimulated emission. Weak oscillations of the dynamic Stokes shift reflect supramolecular vibrational modes, as determined by molecular dynamics simulations. Oscillations are stronger in (aqueous) ethylene glycol compared to water. The THz dielectric loss band of water offers frictional forces which dampen out coherent oscillations of the biopolymer in that frequency range. If it is reduced by a cosolvent, low-frequency vibrational spectroscopy of DNA becomes possible even in aqueous solutions.

Intermolecular Interactions in Molecular Systems with 1000 and More Atoms — A Challenge for Quantum Chemistry

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Quantum chemistry has evolved over the last decades to become a versatile tool for studying structures and properties of molecular systems. Despite this success, the applicability to large molecules is hampered by the strong polynomial increase of the computational effort with molecular size M. Therefore a central goal of our work is to overcome this scaling wall and to develop linear-scaling methods, which allow for quantum-chemical studies of molecular systems with 1000 and more atoms at Hartree-Fock (HF), Density-Functional Theory (DFT), and Møller-Plesset (MP2) levels. At the same time our methods guarantee fully-controlled numerical accuracies, so that no reliability is lost. While in general HF and todays DFT approaches provide often useful results for describing many molecular properties (e.g., NMR), they fail for the calculation of intermolecular interaction energies, since dispersion-type effects are not or not sufficiently accounted for. However, such interactions are crucial for many chemical and biochemical processes. Here, our new MP2 method for reducing the $\mathcal{O}(M^5)$ scaling to linear offers new possibilities, since it allows for the calculation of large systems such as, e.g., an RNA system with 1664 atoms and 19 182 basis functions. The presentation will give an overview on new possibilities of quantum-chemical methods for studying complex systems. Furthermore, examples for a fruitful interplay between theory and experiment will be presented, which allows to gain new insights into molecular processes: the calculation of intermolecular interactions within molecular recognition processes, RNA-catalyzed Diels-Alder reactions, and receptor-virus interactions.

Amyloid Aggregation: The Latest News

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Amyloid formation is associated with many serious diseases, including Alzhimer's, Parkinson's and type 2 diabetes. In recent years it has been shown the proximate toxic agents. In these diseases is in the early oligomer states, not in the amyloid fibrils themselves. These states are very difficult to study since they come to rapid steady state and cannot be separately isolated. Consequently traditional spectroscopic methods, including x-ray crystallography, are not effective. For the past several years we have been applying ion mobility based mass spectroscopy (IMS-MS) methods to a number of these systems. In this talk I will give brief descriptions of the diseases and their impact on human health, a discussion of the methods we use and recent results on Alzheimer's (the Abeta peptide) and type 2 diabetes (the IAPP peptide) and potential drug candidates we are currently working on.

Predicting structures of small non-amyloid and amyloid proteins using molecular dynamics simulation in implicit water

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It is still a grand challenge to predict protein structures using physics-based models given the sequence information. Yet, more and more successful examples start to emerge as a result of significant improvements in Molecular Mechanics force field and conformation sampling technique (e.g. Replica Exchange Molecular Dynamics/REMD). In the first part of this talk, I will talk about our recent work (JCTC, in press) on assessing performance of popular Quantum Mechanics and Molecular Mechanics methods using MP2/ccPVTZ results of 100 tetrapeptide structural models. In the second part, I will present our recent successful modeling of several small non-amyloid and amyloid proteins by using AMBER force field (ff96) plus an implicit solvent model (iGB=5) and Replica Exchange Molecular Dynamics (REMD). The examples include an alpha/beta fold protein and two amyloid peptides (a prion fragment and amylin). The predicted results are verified by experimental techniques (Ion Mobility Mass Spectroscopy, CD and others).

Ion mobility and molecular histology: New glasses for the doctor!

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The analysis of biological surfaces with imaging mass spectrometry is an analytical science that experiences a rapid growth as a result of many new fundamental insights and instrumental innovations. The prospect of a capability to directly analyze biomolecular distributions related to societal relevant diseases incited a huge interest by a number of new disciplines. Among those are biomedical sciences, molecular biology, genomic, proteomics and even systems biology. They all share a common interest: obtaining the quantitative spatial distribution of as many biomolecules as possible on a tissue surface preferably on a cellular level. Unfortunately there is no single technique that can provide all of this detail in concert. New, innovative methods are investigated that bring together experimental results from different imaging MS approaches, for example SIMS and MALDI. Combined they provide new molecular visualization tools for medical researchers.

The common histological tools typically only provide generic morphological information unless immunohistochemistry is used to determine the distribution one specific known protein. Imaging mass spectrometry has evolved to bring these two disciplines, mass spectrometry and histology. This approach, sometimes referred to as molecular histology, can take great benefit from the use of either high resolution mass spectrometry or gas-phase ion mobility separation. Both approaches combined with imaging mass spectrometry can reveal new tissue details that remain hidden with conventional molecular imaging approaches. In this contribution we will discuss the development and applications of these new chemical microscopes.

Probing the specific interactions and structures of gas-phase vancomycin antibiotics with cell-wall precursor through the combination of Ion Mobility Mass Spectrometry and IRMPD spectroscopy

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Vancomycin is a naturally occurring glycopeptide antibiotic active against Gram-positive bacteria and is considered as a drug of last resort for the treatment of penicillin-resistant *Staphylococcus aureus*. Vancomycin binds to the bacteria cell-wall peptidoglycan precursor through noncovalent interactions with the C terminal part containing the ^{D}Alanyl-^{D}Alanine sequence. Vancomycin and its peptide receptor analogues $Ac_2{}^{L}K^{D}A^{D}A$ have been widely used as model systems for investigating biomolecular recognition processes through pure mass spectrometric approaches. In particular, the energetics of dissociation of vancomycin-receptor complexes strongly change in positive and negative ion modes although no direct structural investigation has been yet carried out. We are thus mostly concerned with the binding site of the receptor peptide to vancomycin and more precisely to question whether the structure known in the condensed phase is preserved upon desolvation during electrospray.

Biomolecular recognition of vancomycin antibiotics with its cell-wall precursor analogue $Ac_2{}^{L}K^{D}A^{D}A$ has been investigated in the gas phase through a combined laser spectroscopy (IRMPD), ion mobility mass spectrometry (IMS) and theoretical modeling approach. The two experimental methods are highly complementary: the global shape of the system is probed by ion mobility, and IRMPD spectroscopy is directly sensitive to the intra and inter molecular interactions. Structural assignment has been achieved through comparisons with the low-energy conformers obtained from replica-exchange molecular dynamics simulations, for which IR spectra were calculated using a hybrid quantum mechanics/semi-empirical (QM/SE) method at the DFT/B3LYP/6-31+G*/AM1 level.[1] Both theoretical and experimental findings provide strong evidence that the native structure of the $V+Ac_2{}^{L}K^{D}A^{D}A$ complex is only preserved in the deprotonated species and is lost in protonated complex.[2,3]

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Development of Ion Mobility-Mass Spectrometry as a High-throughput Approach for Structural Genomics

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The field of structural genomics is ultimately concerned with determining high-resolution structures for all the functional macromolecules within living cells and tissues and one of the chief bottle-necks in this ambitious endeavour is the technology available for determining the structures of multi-protein assemblies. Ion mobility-mass spectrometry (IM-MS) is an attractive approach for assessing protein topology, as measurements can be acquired for transient assemblies, at low concentrations and in the context of complex mixtures. Recent efforts in our laboratory have been aimed at generating high-throughput IM-MS methods that are capable of determining the topology, organization, and stability of disease-associated protein complexes in an automated fashion. A rate-limiting step in the acquisition of IM-MS data for protein complexes is the identification of optimal parameters, both in solution and in the gas-phase, for attaining the maximum number of IM measurements that can be related easily to solution-phase dimensions and distances. Often, the optimal conditions for topology model generation represent several distinct solution conditions and instrument settings that must be discovered after a protracted period of trial and error. Here, we describe an extensive, ongoing screen of solution additives and ion-molecule reaction chemistries aimed at modulating ion charge state, improving gas-phase structural stability, and maximizing the intensity of protein sub-assemblies for down-stream model building. We will also describe our recent efforts to develop these screens into basic rules and best-practices that can be used to automate protein topology assignment from IM-MS data in a high-throughput framework.

Structure and Stability of Protein-Ligand Complexes in the Gas Phase

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The structure and stability of a number of desolvated protein-ligand complexes have been investigated using experimental and computational methods. Time-resolved blackbody infrared radiative dissociation (BIRD) measurements, implemented with Fourier-transform ion cyclotron resonance mass spectrometry, were combined with a functional group replacement (FGR) strategy to probe the nature of the stabilizing intermolecular in three protein-ligand complexes: a single chain variable fragment of the monoclonal antibody Se155-4 and specific trisaccharide ligand Gal[Abe]Man, the high affinity interaction between the homotetrameric protein streptavidin and biotin, and the hydrophobic interactions between bovine β-lactoglobulin and saturated, unsaturated and branched fatty acids. Comparison on the interactions identified in the gas phase by BIRD-FGR with those present in aqueous solution indicates that specific interactions are generally preserved upon transfer from solution to the gas phase with electrospray ionization. Furthermore, the strengths of individual intermolecular interactions measured in the gas phase are found to be in good agreement with calculated or experimental values reported for model systems. Deuterium kinetic isotope effects measured for select complexes reveal a late dissociative transition state, wherein the ligand is fully removed from the binding cavity. Finally, the first direct comparison of the Arrhenius parameters for the dissociation of protein-ligand complexes in their solvated and desolvated states was carried out. Notably, the differences in the activation parameters measured in solution and the gas phase can be quantitatively explained by the differential hydration of the ligand in the bound state and in the putative transition state.

ISOLATED CARBOHYDRATES AND CARBOHYDRATE INTERACTIONS

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The interaction between carbohydrates and proteins is a key factor in many biological processes but the factors dictating selective carbohydrate–protein interactions are not easily discerned. Selectivity must depend in part upon the conformational structures of the interacting carbohydrate ligands and their receptors but because of their flexibility and the universality of hydrogen-bonded interactions in aqueous environments, their structures and interactions may also be influenced by explicit hydration, dehydration, or the direct involvement of water at the receptor site. Understanding carbohydrate structural choice and the consequences of carbohydrate interactions with water, with proteins or with both, presents a notoriously complex challenge. Characterizing their *intrinsic* three dimensional structures is a key starting point on the road towards meeting it – a necessary first step on the way to investigating and understanding the consequences of their interactions with other molecules, not least water. The lecture will review recent [1, 2] and current spectroscopic and computational investigations of a range of carbohydrates that are important in Nature, initially isolated in the gas phase and subsequently, interacting with other molecules, particularly water and peptides. They have been selected not just because they *are* 'do-able' but because of the physical and biochemical issues they address.

Acknowledgments. A debt of gratitude is owed to Prof Ben Davis for his deep involvement in all the work which will be presented; the post-docs and students who did it, particularly, Emilio Cocinero, Pierre Çarçabal, Tim Vaden and Conor Barry; and the agencies who funded it, EPSRC, STFC, the Royal Society and the Leverhulme Trust.

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Ion Mobility Investigations of Carbohydrate:Protein:Metal Non-Covalent Complexes

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Ion Mobility MS can be used to investigate changes in conformation of various biological molecules. This presentation will focus on how both arrival time distribution and collision cross section changes when metal ions and other ligands non-covalently coordinate to proteins. Electrostatic interactions and metal ion coordination cause proteins to shift from elongated to more compact structures. Chemotactic proteins MCP1 and MCP2 show shifts to a more compact structure with ligand (oligosaccharide and Ca^{2+}) binding. Shifts to a more compact or more elongated structure also occur depending on the radial and axial distance of the nanospray tip to the cone. While the MCP-1 dimer exhibited an unfolded structure at high collision energy in the trap cell of, the metal coordinated dimer exhibited a a more compact structure. Also observed was heparin octasaccharide, bound to MCP-1 dimer, which caused the formation of two ion conformation populations within the ion mobility spectrum.

Mixed IR/VIS Multidimensional Spectroscopies: Chemistry and Biophysics in Realtime

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Multidimensional experiments, daily business in the field of NMR, have been demonstrated only relatively recently in IR spectroscopy [1]. Similar as nuclear spins in multidimensional NMR, molecular vibrations are employed in multidimensional IR as probes of molecular structure and dynamics, albeit with femtosecond time resolution.

Our use of mixed IR/VIS pulse sequences considerably extends the potential of multidimensional IR spectroscopy, enabling studies of ultrafast nonequilibrium processes as well as surface specific, highly sensitive experiments. A UV/VIS pulse preceding the IR pulse sequence can be used to prepare the system under study in a nonequilibrium state. 2D-IR snapshots of the evolving nonequilibrium system can be taken to monitor structural changes, for example during a light triggered reaction or during the photocycle of a light sensitive protein. Transfering the system to a nonequilibrium state by electronic excitation during the IR pulse sequence allows for correlating states of reactant and product of the light triggered process via their 2D-IR cross peaks – a nonequilibrium 2D-IR version of exchange spectroscopy. Introduction of a non-resonant VIS pulse at the end of the IR part of the experiment selectively upconverts the infrared signal of interfacial molecules to the visible spectral range by sum frequency generation, enabling femtosecond surface 2D-IR spectroscopy with submonolayer sensitivity [2].

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IR/UV investigations on hydrated and aluminum containing peptides

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Secondary structures play an important role to explain the function of proteins and the interplay with metal ions is of high interest to obtain information on e.g. ion transport or induction of diseases. To investigate the interactions of proteins with metal ions and water molecules on a molecular level the analysis of isolated model systems in a molecular beam experiment is an ideal starting point. The influence of water or metal ions on secondary structures of isolated peptides is analyzed by mass selective IR or IR/UV spectroscopy.

In order to figure out different binding motifs in metal/peptide clusters the attachment of Al^{+} and Al^{3+} cations to the backbone of different protected amino acids and dipeptide models is investigated by means of mass selective IR photodissociation spectroscopy. In case of clusters with very strong bonds between the aluminum cation and a peptide containing an aromatic chromophore a combined IR/UV technique is applied in order to yield the vibrational spectra in the NH stretching region. The comparison with extensive ab initio and DFT calculations lead to suggestions for structural arrangements. The aluminum cations are attached to the carbonyl groups and lead to strong changes of the backbone conformation. The structures are discussed with respect to their stability, spin state and the influence of the aromatic chromophore.

Furthermore the influence of a successive back-bone hydration is investigated by attaching one to three water molecules to the backbone of the neutral protected amino acid Ac-Phe-OMe. The structures of the resulting species are investigated by the mass- and isomer selective IR/Resonant 2-photon ionisation technique which is applied in the region of the OH and NH stretching vibrations as well as in the region of the amide I and II modes. Two isomers are observed both for the mono- and dihydrated cluster. For all isomers the β_L backbone conformation of the monomer is almost conserved. In case of the trihydrated cluster only one isomer is obtained with a strong change of the backbone conformation compared to the monomer. This change is driven by the possibility to form a hydrogen-bonded network (a first solvation shell) including all water molecules as well as the CO and NH groups of the backbone.

Spectroscopy of chiral molecules: from the gas phase to solution

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In our laboratory, we use experimental spectroscopic techniques and *ab initio* calculations to quantitatively characterize the phenomena of chirality and chiral recognition on the molecular level. I will present a series of high resolution rotational and vibrational spectroscopic studies of propylene oxide and its binary adducts with ethanol, glycidol, and itself. Using the experimentally established structures and stability ordering, complemented with the *ab initio* calculations, we examine the chiral discriminating forces at play in these molecular systems. In the second part of the talk, I will discuss our two-pronged approach to study the effects of solvent-solute hydrogen-bonding on chiroptical measurements using both high resolution spectroscopy and vibrational circular dichroism (VCD) spectroscopy. We observed that some vibrational bands of an achiral molecule, such as water, can show significant VCD strength through hydrogen-bonding to a chiral molecule. This effect, termed chirality transfer, will be discussed.

Watching Conformations of Biomolecules: A Microwave Spectroscopy Approach

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Microwave spectroscopy, considered the most definitive gas phase structural probe, can distinguish between different conformational structures since they have unique spectroscopic constants and give separate rotational spectra. However it suffers a serious limitation: it has been limited to molecular specimens having an appreciable vapour pressure. In general, large molecules, in particular those of biological importance, have low vapour pressures and tend to undergo thermal reactions and degradation upon heating, making them out of reach for structural studies in the gas phase. Recently, rotational studies of biomolecules have entered in a new stage with the LA-MB-FTMW experiment. It combines laser ablation with Fourier transform microwave spectroscopy in supersonic jets overcoming the problems of thermal decomposition associated with conventional heating methods. To date different α- and β-amino acids [1] have been studied using this technique, making possible the characterization of their preferred conformations. Even in conformationally challenging systems these can be identified by rotational spectroscopy, as has been illustrated with the assignment of seven low-energy conformers in serine [2] and threonine [1], six in cysteine [3] and aspartic acid [4], and nine in γ-amino butyric (gaba). The nucleic acid bases uracil [5], thymine [6], cytosine and guanine [7] have also been studied and their preferred tautomeric forms determined. Among the neurotransmitters the most stable conformers of ephedras [8] and adrenaline have also been investigated.

This technique has been successfully applied to the study of monosaccarides. Three conformers of the prototype α-D-glucose have been characterized for the first time in the gas phase.

After the first experimental observation of the monohydrated cluster of glycine [9], complexes between amino acids and nucleic acid bases with water have also been investigated to obtain information on the changes induced in the conformational or tautomeric preferences by the addition of solvent molecules.

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Ultrafast generation of aqueous carbonic acid

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Exploring the acid-base chemistry of bicarbonate, HCO_3^-, in aqueous solution, and the conversion to aqueous carbon dioxide, CO_2, is of utmost importance in understanding the chemical reactivity of these molecular species in contexts as diverse as blood physiology, chemical weathering, ocean acidification, and carbon dioxide sequestration strategies. Under conditions of pH < 8.5 it is assumed that CO_2 first becomes hydrated, forming carbonic acid (H_2CO_3), which subsequently dissociates into HCO_3^- and H_3O^+. Direct observation of aqueous H_2CO_3, however, has proven to be elusive. Protonation of HCO_3^- should in principle lead to H_2CO_3, that, however, generally is assumed to be unstable, as prompt water catalysed decomposition into CO_2 and H_2O is believed to occur. Only recently it has been shown that H_2CO_3 can be detected as isolated molecules in the gas phase [1], or in ice matrices [2]. H_2CO_3 in aqueous solution in contrast has – until now – remained uncharacterized. Rapid mixing techniques have only provided access to the overall time scale for the hydration and subsequent deprotonation (or the reverse protonation/dehydration) kinetics of the reaction [3]. We present femtosecond infrared spectroscopic results showing unequivocal support for the existence of deuterated carbonic acid, D_2CO_3, under aqueous conditions, formed after ultrafast protonation of DCO_3^- dissolved in D_2O, and its persistence for nanoseconds. Here we photoexcite at 330 nm a photoacid, 2-naphthol-6,8-disulfonate (2N-6,8S), with a 50 fs pump pulse. We follow the aqueous bimolecular deuteron transfer by monitoring IR-active vibrational marker modes of 2N-6,8S with femtosecond time resolution. We use the Szabo-Collins-Kimball approach to describe bimolecular reaction dynamics subject to the Debye-von Smoluchowski diffusional motions, and derive on-contact proton transfer reaction rates between HCO_3^- and 2N-6,8S that follow the Marcus correlation between free energy and the proton transfer rates found for a large class of aqueous proton transfer of photoacid dissociation and photoacid-base neutralization reactions [4]. This Marcus free energy correlation supports an associated pK_a of 3.45 ± 0.15 for carbonic acid (in bulk water at 25°C, zero ionic strength, atmospheric pressure), substantially lower than the value of 6.35 commonly assumed on the basis of the overall CO_2 to bicarbonate equilibrium.

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Hot Topic Presentations

Infrared Multiphoton Dissociation Spectroscopy of Protonated Uracil and Thiouracils: Effects of Thioketo-substitution on Gas-Phase Conformation

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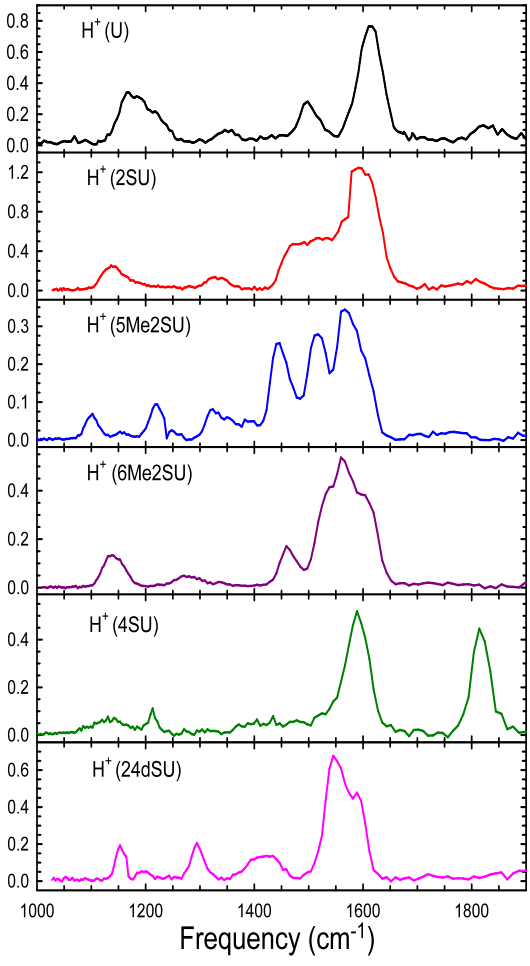
The gas-phase structures of protonated complexes of uracil (U) and five thiouracils including: 2-thiouracil (2SU), 5-methyl-2-thiouracil (5Me2SU), 6-methyl-2-thiouracil (6Me2SU), 4-thiouracil (4SU), and 2,4-dithiouracil (24dSU) are examined via infrared multiple photon dissociation (IRMPD) action spectroscopy and theoretical electronic structure calculations. The IRMPD action spectra of these six protonated complexes exhibit both similar and distinct spectral features over the range of ~1000 to 1900 cm^{-1} such that the complexes are easily differentiated by their IRMPD action spectra (see Figure). Absence of the carbonyl stretch at ~1825 cm^{-1} in the IRMPD spectra for the H^+(U), H^+(2SU), H^+(5me2SU), and H^+(6Me2SU) complexes suggests that the binding of a proton reduces the carbonyl functional groups in these complexes. In contrast, the intense band at ~1825 cm^{-1} in the IRMPD action spectrum of H^+(4SU) indicates that the carbonyl group is not reduced in this complex. Measured IRMPD action spectra are compared to linear IR spectra calculated at the B3LYP/6-31G* level of theory to identify the structures accessed in the experimental studies. On the basis of these comparisons and energetics derived from the calculations, it is clear that binding of a proton stabilizes a minor tautomer of the nucleobase in the H^+(U), H^+(2SU), H^+(5me2SU), and H^+(6Me2SU) complexes, where the diketo, thioketo-oxo, dithioketo groups are reduced by proton binding and transfer of the N3H proton. In contrast, the proton preferentially binds at the 4-thioketo position to the canonical oxo-thioketo tautomer in the H^+(4SU) complex. Additional bands are present in the IRMPD action spectra of the H^+(U) and H^+(4SU) complexes that suggest that a small population of excited low-energy conformers are also accessed in the experiments.



Threshold collision-induced dissociation measurements of protonated peptides

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The "pathways in competition" model has significantly improved our understanding of peptide fragmentation reactions and allows prediction of activation barriers for generation of key sequence ions for small model peptides. In this study, threshold collision-induced dissociation (TCID) on a guided ion beam instrument and variable time ion trap CID experiments were used to study the fragmentation of a group of protonated tripeptides. Our focus was on formation of b_2^+ and y_1^+, and the influence of peptide sequence on the relative threshold energies for generation of these product ions. In addition, density functional theory (DFT) calculations were used to predict structures and energies for relevant minima, including reaction intermediates, post-reaction complexes and proton-bound dimers, and transition states.

Tripeptides (GGG, GAG, and GGA) were either purchased or synthesized using Wang resin and conventional Fmoc chemistry. Protonated ions were generated using electrospray ionization. Ion trap CID was performed using a ThermoFinnigan LCQ-Deca mass spectrometer with He as the bath/collision gas. A guided ion beam tandem mass spectrometer was used to measure kinetic-energy-dependent cross sections for CID of the same peptides. Density functional theory calculations (B3LYP/6-31+G(d,p) level) were performed using the Gaussian 03 program.

Ion trap CID of the peptides generates nearly exclusively b_2^+. Initial experiments with AGG, GAG and GGA (using variable energy and variable time ion trap CID experiments) suggest that energy required to produce b_2^+ is sensitive to the position of the A residue, with an observed trend GGA > AGG > GAG. These qualitative conclusions were then examined using the guided ion beam instrument where a more diverse group of product ions, including a_3^+, y_2^+, a_2^+, and a_1^+, were generated from the respective peptides. Thresholds for generation of the various product ions have been measured for GGG, GAG, and GGA. In GGG, the threshold for generation of b_2^+ is lower by ~ 1 eV (center of mass frame) compared to other products such as a_3^+, y_2^+, and y_1^+, consistent with the lower energy (multiple collision) ion trap CID experiments. For GAG, the b_2^+ threshold shifts down another 0.3 eV, a_2^+ shifts down ~1 eV, and other products retain similar energy profiles. For GGA, the b_2^+ threshold is comparable to that for GGG, but now the y_1^+ threshold is very similar and much lower than for GGG and GAG.

The trends with respect to how easily the b_2^+ ion is generated, both in the ion trap and guided ion beam experiments, are consistent with the relative energies for transition states and products predicted by DFT calculations. For GGG, the transition state for generation of b_2^+ is 30-50 kJ/mol lower than those for the b_3^+ and y_2^+ pathways. This supports the observation of b_2^+ as the dominant fragment in the low energy ion trap CID experiments, and the relative thresholds for the respective products in the guided ion beam experiments. Predictions of transition state and product energies for the other peptides examined are also consistent with both the ion trap and guided ion beam measurements.

Stability and (un)folding of a peptide helix in the gas phase from first-principles: Ac-Ala$_{15}$LysH$^+$

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Peptides in vacuo offer a unique, well-defined test bed to match experiments directly against first-principles approaches that predict the intramolecular interactions governing peptide and protein folding. In this respect, the polyalanine-based peptide Ac-Ala$_{15}$-LysH$^+$ is particularly interesting, as it is experimentally known to form helices in vacuo, with stable secondary structure up to ∼750K [1]. Room-temperature folding and unfolding timescales are usually not accessible by direct first-principles simulations, but this high T scale allows a rare *ab initio* view. We here use van der Waals (vdW) corrected [2] density functional theory in the PBE generalized gradient approximation as implemented in the all-electron code FHI-aims [3]. We show by long Born-Oppenheimer *ab initio* molecular dynamics that Ac-Ala$_{15}$-LysH$^+$ indeed unfolds rapidly (within a few ps) at T=800K and 1000K, but not at 500K. Most importantly, the observed stability depends critically not just on a correct inclusion of H-bonds and the designed termination effects, but also on vdW interactions. If these are *not* properly included, the helix unfolds already at 700K and the strcutural stability at 500K is mostly 3_{10}-helical, in disagreement with experiments; when vdW is included, the temperature stability is raised and the α-helical structure is stabilized at lower temperatures.

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Structure of anionic peptides and their CID fragments

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While peptide sequencing by collision induced dissociation tandem mass spectrometry (CID MS) has found wide application in biochemistry, the underlying reaction chemistry remains an issue of lively debate. In recent years, the application of infrared (IR) spectroscopy to CID fragment ions has provided important new information on the molecular structures of CID fragment ions, for which several isomeric forms had been suggested.

Peptide sequencing via tandem MS in negative ion mode (*i.e.* on the deprotonated peptide) is not nearly as popular as its positive ion mode counterpart, although additional information from the deprotonated peptide could obviously increase the sequence coverage. For instance, ***c***-type ions are commonly observed in CID of peptide anions [1]. However, the dissociation modes of deprotonated peptides appear to be more complex and have often been reported to be more residue-specific.

In this contribution, we investigate the structure of selected anionic peptides and their CID fragments obtained through IR spectroscopy using the free electron laser FELIX in combination with an ESI FTICR mass spectrometer. This method has recently been applied to identify the deprotonation site in amino acids [2], which had been under much debate for tyrosine and cysteine in particular. Though different structures have been hypothesized, peptides lacking acidic residues have generally been assumed to deprotonate on the C-terminus. Our IR spectra of the conjugate base of tri-alanine, compared to calculated spectra at the DFT level, indeed provide strong support for a carboxylate structure.

More intriguing questions relate to the charge site in CID fragments. While carboxylate structures are lowest in energy for C-terminal fragments, the location of the negative charge in anionic N-terminal fragments remains more of a mystery to date. Using IR spectroscopy, we show that deprotonation on an amide N-atom forming an amidate anion is the most likely structure for anionic *a*-type peptide fragments lacking acidic residues [3]. Amidate structures are substantially more stable than tautomeric enolate structures as is further verified by spectra of the conjugate base of N-metylacetamide.

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Towards fs time-resolved photoelectron spectroscopy of biomolecules in aqueous solutions

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The combination a liquid microjet with fs time-resolved photoelectron spectroscopy (TRPES) allows for the direct observation of transient electronic structure of molecules in solution. Photophysical processes in solvated chromophores are initiated by ultraviolet fs laser pulses and probed by time-delayed photoionization of valence electrons. We will present first TRPES studies of adenine and adenosine, which were excited by a 100 fs, 200 nm (6.20 eV) pulse and ionized by a 100 fs, 265 nm (4.65 eV) pulse. As an example, we show in Figure 1 the time-dependent photoelectron spectrum of a 2 mM aqueous solution of adenine. A detailed analysis of our data will be given and results will be discussed.

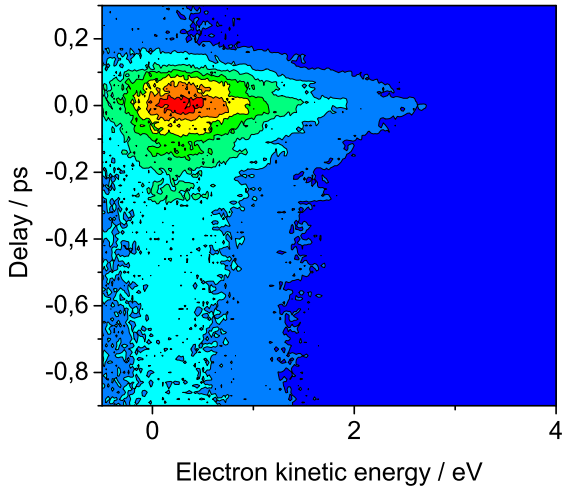

Figure 1: Time-resolved photoelectron spectrum of a 2mM aqueous solution of adenine.

VUV spectroscopy of biological molecules produced by vaporization of nanoparticles: Bringing fragile neutrals to the gas phase

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We will present a new aerosol source implemented inside the SAPHIRS molecular beam chamber which is a versatile and permanent endstation of the DESIRS VUV beamline at SOLEIL. The very first scientific results obtained on 2 amino acids will be presented too.

It has been shown in 2006 that the thermodesorption of biological nanoparticles (containing one pure substance) is a soft vaporisation method that produces gas phase neutrals within a tiny vapour plume (few mm^3) [1]. This kind of source is ideally adapted to the brilliant light of 3rd generation synchrotron light sources. Thermally fragile neutral molecules, like amino acids, can be studied in this manner in the gas phase, for example using VUV photoionization electron spectroscopy, or mass spectrometry. The advantage of tuneable VUV light is to induce a "soft ionization", where the photon energy can be adjusted so as to avoid dissociative ionization, thus yielding fragment-free mass spectra. This method is perfectly suited to study the electronic structure and corresponding fragmentation dynamics of the thermodesorbed, unfragmented neutrals.

Here we present a newly built aerosol source where special emphasis has been laid on the design and the characterization of an aerodynamic lens system (ALS) and a thermodesorber. This system has been implemented inside the SAPHIRS chamber, which is equipped with an imaging photoelectron-photoion coincidence spectrometer that has been described earlier [2]. It combines velocity map imaging of the photoelectrons with a Wiley-McLaren TOF-MS.

The ALS is used to focus nanoparticles, produced by nebulisation of a liquid solution, into the vacuum by forming a highly collimated beam [3]. This beam is introduced into the ionization region of SAPHIRS, via a differential pumping stage chamber. An optical detection unit, which is composed of a cw solid-state laser at 532 nm (15 mW) and a photomultiplier, is used to detect scattered light of the particles at the ALS outlet in order to align the aerosol beam, and to control the stability of the source. The theoretical performances of the ALS and the characterization of the produced particle beam by nanophase threshold photoelectron spectroscopy (TPES) will be presented.

A heater is inserted between the extraction plates of the ionisation region in order to vaporise continuously the nanoparticles of the beam. The neutral molecules of the resulting vapour plume can then be ionized by the brilliant VUV radiation of the DESIRS

beamline. We will show that this heater does not perturb significantly the imaging of the photoelectrons. The temperature of the heater can be adjusted and thus one can tune the thermal energy of the gas phase neutrals produced.

Finally, we will present first results on thermally-desorbed biomolecules (tryptophane, phenylalanine) [4]. We were able to record TPEPICO energy scans, where the internal energy of the parent ion was scanned with a 25 meV resolution. To our knowledge, this has never been achieved before. The recording time of the spectra is several hours showing thereby the high stability of this new source.

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UV spectroscopy of gas phase proteins

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UV spectroscopy of a variety of trapped anions ranging from the amino-acid to the entire protein was performed by means of photoinduced electron detachment. It is shown that photoinduced electron detachment spectroscopy overcomes the current limitations of photofragmentation and extends the range of UV spectroscopy of trapped species to very large systems.[3-4] The influence of a negative charge on the optical spectrum of aromatic amino-acids is discussed.[1-2]

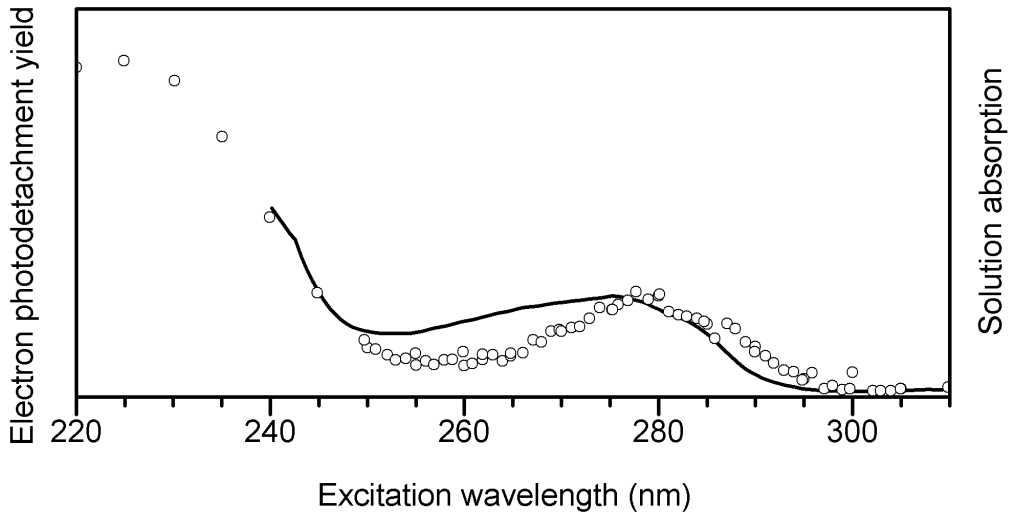

Fig. UV spectroscopy of Ubiquitin protein. (open circles: electron photodetachment in the gas phase; full line: absorption in solution)

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Photochemical Selection in Prebiotic Chemistry of Nucleobases

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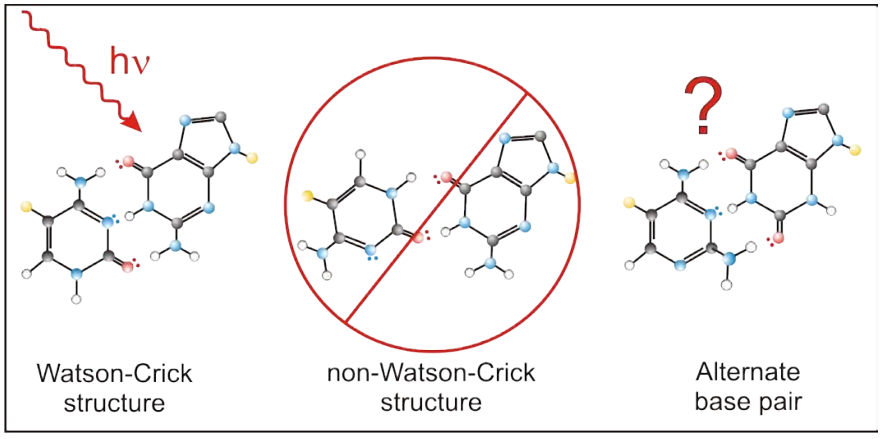
From a chemical perspective one may define the origin of life as the synthesis of the first macromolecule with a replication scheme, such as RNA. Once such a replicating, or autocatalytic, macromolecule exists, evolution can be called on as the model for further development of life. Today such synthesis is mediated by an extensive biochemical machinery, involving complex proteins and enzymes, which however would not have existed on a prebiotic earth. Therefore we investigate the fundamental properties of nucleobases without the contemporary biological environment by studying them as *isolated* molecules and clusters, in the gas phase.

Most of the heterocyclic compounds that today are involved in replication exhibit UV photochemical stability, due to fast internal conversion, while other derivatives of *the same compounds* often do not. This diffusion of electronic energy is mediated by conical intersections, as modeled by a growing number of quantum calculations. Yet more surprisingly, in many cases the biologically most relevant tautomeric form or even specific base pair structure exhibit this mechanism, while other tautomers or structures of the same base pair are vulnerable to UV radiative damage.

We study the excited state dynamics of isolated nucleobases and their clusters by a combination of double resonant spectroscopy, pump-probe measurements and detection of hot ground state molecules that result from rapid internal conversion. For comparison we also study these properties in alternate bases that could potentially have led to alternate genetic alphabets to evaluate if UV photochemical selection could have played a role in arriving at the biochemistry of life as we know it today.



Alternate Dissociation Pathways Identified in Charge-Reduced Protein Complex Ions

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Tandem mass spectrometry (MS) of large protein complexes has proven to be capable of assessing the stoichiometry, connectivity, and structural details of multi-protein assemblies [1]. While the utility of tandem MS is without question, a deeper understanding of the still controversially discussed mechanism of protein complex dissociation will undoubtedly drive the technology into new areas of enhanced utility and information content.

We present here the systematic analysis of the charge state dependent decay of the non covalently associated complex of human transthyretin (TTR), generated by collision induced dissociation (CID). A crown ether-based charge reduction approach was applied to generate intact transthyretin tetramers with charge states ranging from 15+ to 7+. These nine charge states were subsequently analyzed by means of tandem MS and ion mobility spectrometry. Three different charge-dependent mechanistic regimes were identified: 1) Ions with a charge above 12+ followed the commonly observed CID dissociation pathway resulting in highly charged, unfolded monomers and compact, charge-stripped trimers [2]. 2) Tetramers with charge states between 11+ and 9+ still dissociated into monomer and trimers, but the expelled monomers were carrying fewer charges and retained their compact, native-like conformation. 3) 9+ and 8+ ions primarily yielded C-terminal peptide fragments which were cleaved from intact and fully folded TTR tetramers. Ions with a charge below 8+ were virtually indestructible in the instrument and neither showed signs of dissociation nor unfolding.

Taken together, the results presented highlight the potential of charge state modulation as a method for directing the course of gas phase dissociation and unfolding of protein complexes. Particularly noteworthy is the fact that under certain conditions the remaining stripped complex, as well as the departing subunit, retain compact, native-like structures. This has implications for various gas phase-spectroscopic and structural biology experiments in which maintaining conformations close to the native state is of paramount importance.

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Electronic structure of the ionized DNA bases clusters: the effects of H-bonding and stacking interactions.

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Electron hole formation is the primary step of DNA oxidative damage and charge transfer causing distant mutations in the DNA sequence. Ionization energies of the nucleic-acid bases (NAB) in their natural environment are decreased in comparison to those of isolated bases due to stabilization of open-shell cation through hydrogen bonds formation, stacking interaction with neighboring bases and electrostatic interactions. Isolated dimers of the A, T bases and $(AT)_2$ tetramer are considered as model systems. The influence of the H-bonding and stacking interactions on the vertical ionization energies of the NAB monomers and dimers, electronic structure of produced cations is analyzed using equation-of-motion coupled-cluster (EOM-IP-CCSD). IP-CISD and DFT methods are employed to study ionization of the $(AT)_2$ tetramer. It is shown that inter-fragment interactions affect ionized states of the NAB dimers via two distinct mechanisms: hole delocalization and electrostatic interactions. H-bonding and stacking interactions have profound impact on ionization energies of NAB in dimers: ionization energies in dimers can be decreased by as much as 0.4-0.5 eV. Both factors are also found to contribute to the strong decrease in ionization energy of the tetramer. The hole is found to be delocalized over two A bases, which results in 0.45 eV decrease of the ionization energy. H-bonding between AA and TT stacked pairs leads to further stabilization of the ionized state by 0.24 eV.

Low Energy Electron Interaction with Duplex Supercoiled and Relaxed, and Single Stranded Plasmid DNA

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The energy transfer from ionizing radiation to molecules generates large quantities (~10^5/MeV) of low energy electrons (LEE, <30 eV). It is surmised that such copiously produced LEE mediate strand breakages in DNA. In order to get insights that are biologically relevant, we have analyzed strand breakages in supercoiled and relaxed plasmid duplex DNA and compared the same with single stranded circular DNA plasmid forms. Efficient conversion to relaxed form of DNA from highly purified supercoiled plasmid DNA preparations was generated by the action of *Drosophila* Topoisomerase-I. Most studies in this field so far have focused on only supercoiled plasmid [1] and to the best of our knowledge, none on other forms of DNA. Therefore, our studies in the electron energy range 10 to 25 eV report first-time observations along these lines. The results indicate that LEE induces strand breakages on both supercoiled as well as relaxed duplex plasmid DNA. The efficiencies were comparable in both cases. Unraveling strand nicks in the latter involved gel analyses of DNA following duplex denaturation by alkali treatment. We uncovered discernible strand breakage products from relaxed form of DNA only following duplex denaturation, thereby revealing single strand nicks being generated by LEE. Therefore, supercoiling energy was not mandatory for imparting strand breakages. Most surprisingly, the same conditions of LEE exposure yielded no strand nicks in single-stranded plasmid DNA. It is pertinent to point out that LEE interaction with ssDNA [2] shows larger electron capture compared to double stranded DNA. Hence, it is necessary to distinguish between electron capture and strand breaks when considering LEE induced damage to DNA and obviously necessitates detailed experiments need to be performed to unravel these aspects of LEE interaction. We believe that any strand breakage model on LEE – DNA interactions must involve DNA double helix chemistry; although several previous studies have revealed neutral and ionic desorptions [*e.g.* Ref. 3] resulting from dissociative electron attachment / dissociative ionization steps and intrinsic hydration water in layered DNA samples consisting of either single (Oligos) or double stranded DNA on solid surfaces.

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100 keV proton irradiation of Halo-Uracils in the gas phase: Specific fragmentation channels revealed by coincidence measurements.

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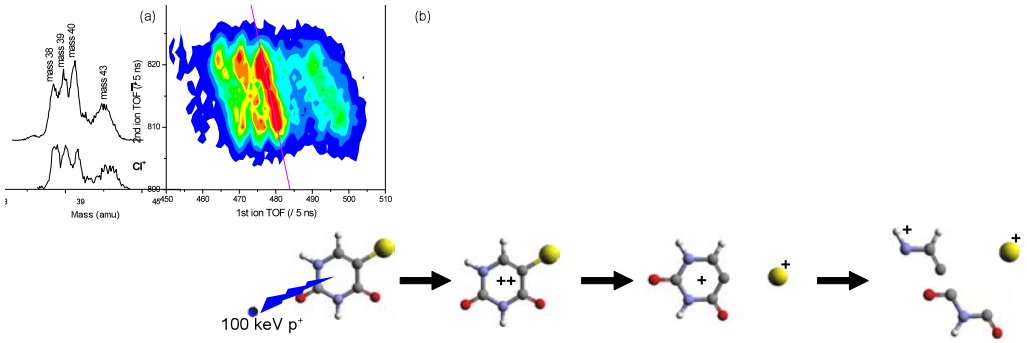
The ubiquitous role of ionizing radiations, on one hand used in medical treatments but on the other hand known as having potential harmful long term effects puts them at the confluence of several disciplines such as physics, chemistry, biology and medicine.
5-Halo-Uracil molecules (5XU, X = F, Cl, Br, I) are used in treatment of cancer as chemotherapy agents and they also act as radio-sensitizer in concomitant radio- and chemotherapies. Radio-sensitization is an increase of the macroscopic biological effect (tumoral cells death due to DNA mutations and breakages) of the ionizing radiation (X rays or high energy protons) on the targeted tissues. Surprisingly, although the advantages of radio-sensitizing substances is established, there is little knowledge on the microscopic fundamental physical and chemical mechanisms underlying radio-sensitization and, more generally, on the interaction between ionizing irradiation and molecular systems.
We have undertaken a study of the direct effects (ionization, fragmentation, molecular rearrangement) of 100 keV proton irradiation on 5XU in the gas phase. The energy potentially deposited into the target molecules being very high, it could be expected that all dissociation pathways are statistically open and that these molecules, differing one to another by one atom only, should lead to similar fragmentation patterns. Interestingly, our experiments relying on a coincidence detection of the fragments have enabled the disentanglement of complex sequential dissociation pathways and specific pathways have been revealed. For instance, ion products of mass 38, 39 and 40 amu are associated to the transient formation of the de-halogenated uracil cation and their intensities are very sensitive to the nature of the primarily ejected halogen. It suggests that specific de-hydrogenation states are explored while these fragmentations occur. We will present these results as well as the latest results obtained from a similar experiment where energy controlled electrons are used as irradiation source to better appreciate the amount of energy absorbed by the parent molecules.



On the enzymatic activity of catalase: an iron L-edge X-ray absorption study of the active centre

Nora Bergmann[a], Sébastien Bonhommeau[b], Kathrin M. Lange[c], Stefan Eisebitt[d,c], Frank de Groot[e], Majed Chergui[f] and Emad F. Aziz[c,*]

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Phys. Chem. Chem. Phys. 12, 4827 - 4832 (2010)

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Catalase and methaemoglobin have very similar haem groups, which are both ferric, yet catalase decomposes hydrogen peroxide to water and oxygen very efficiently, while methaemoglobin does not. Structural studies have attributed this behaviour to their different distal environments. Here we present Fe $L_{2,3}$-edge X-ray absorption spectra of these proteins in physiological solutions, which reveal clear differences in their electronic structures, in that πback-donation of the Fe atom occurs in catalase, which confers on it a partial ferryl (Fe^{4+}) character, while this is not the case in methaemoglobin (1). The origin of the Fe^{4+} character stems from the proximal tyrosine residue. We also find that both systems are in a high spin state. Temperature effects influence the spectra of catalase only weakly, in agreement with previous studies of its chemical activity. We conclude that the high activity of catalase is not only determined by its distal environment but also by its partial ferryl character.

Reference:

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Molecular conformation from vibrational spectra: anharmonicity is key!

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Molecular structure determination from vibrational data is still a very difficult problem, mostly due to the large number of close-lying transitions that occur for systems of a chemically relevant size. As experimental investigations become more complex and the size of the systems studied increases, there is a pressing need for a reliable theoretical framework that can help assign the lines observed by spectroscopists and thus facilitate structure elucidation from vibrational data.

Unfortunately, the current standard theoretical model of molecular vibrations, namely the harmonic approximation, is unable to capture some of the key vibrational phenomena. Indeed, most of the modern spectroscopic experiments that deal with energy transport, conformational transitions, non-linear spectra, or dissociative excitations fall outside the remit of this approximation.

Over the years, we have developed a series of theoretical techniques [1–5] that go beyond the harmonic approximation and allow us to perform fast and accurate quantum mechanical vibrational calculations on molecular systems, using interaction potentials computed directly by electronic-structure programs and grid-computing technology.

In this contribution, we focus on the determination of the conformation of small biological molecules and model proteins with the aim of understanding the subtle balance of weak interactions leading to the formation of nano-scale biostructures. We use our latest methodology to interpret high-resolution spectra of gas-phase biomolecules, and highlight the importance of anharmonicity for a reliable determination of molecular conformations from vibrational data.

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Catching proteins in liquid helium droplets

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The isolation of foreign species in liquid helium nano-droplets is of fundamental interest and has found important applications in molecular spectroscopy. Helium clusters have an internal equilibrium temperature of ~0.37 K, which is maintained by evaporative cooling.

Liquid helium is optically transparent from the deep UV to the far IR and superfluid helium droplets can serve as gentle matrices to provide an isothermal environment for embedded molecules at cryogenic temperatures. Further, due to the weak interactions of liquid helium, molecules embedded in helium nanodroplets can rotate freely and their optical spectra show narrow linewidths.

For studying molecules in helium droplets, a prerequisite is the ability to bring the intact molecule into the gas phase. For many interesting species such as most larger biomolecules, this can not be done via evaporation. Pulsed laser desorption is one other possibility, doing so, however, yields low concentrations in the gas phase as well as frequently a mixture of species that additionally contains decomposed molecules and matrix molecules. More promising would be to use established techniques, as for example electrospray ionization followed by mass separation, and to incorporate those mass/charge selected ions into helium droplets.

We here present an experimental approach in which mass/charge selected ions that are stored and accumulated in an ion trap are picked up by helium droplets traversing the trap. The approach is conceptually similar to pickup experiments of neutrals from gas cells, however a crucial difference is that in the case of the ion trap, use is made of the high kinetic energy of the heavy helium droplets, which allows ions only to leave the trap once they are inside a droplet.

It is demonstrated that droplets can be efficiently doped with a mass/charge selected amino acid as well as with the much bigger m ≈ 12 000 amu protein Cytochrome C in selected charge states. The sizes of the ion-doped droplets are determined via electrostatic deflection. Under the experimental conditions employed, the observed droplet sizes are very large and range, dependent on the incorporated ion, from 10^{10} helium atoms for protonated Phenylalanine to 10^{12} helium atoms for Cytochrome C.

Poster Presentations

Identification of the C_7 and C_5 Peptide Conformations in Alanine and Proline Derivatives

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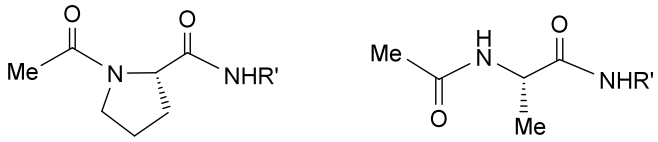
Rotational spectra of the smallest peptide systems derived from alanine (Ala) and proline (Pro), namely the amino acids blocked at the *N*- and *C*-termini with amide groups (RCO-Ala-NHR', RCO-Pro-NHR'; R = Me, R' = Me or H, Figure 1), have been examined with laser ablation molecular beam Fourier transform microwave (LA-MB-FTMW) spectroscopy [1]. The experimental rotational and ^{14}N nuclear quadrupole coupling constants have been compared to *ab initio* theoretical predictions. The C_7 and C_5 peptide conformations (intramolecularly hydrogen-bonded seven- or five-membered cycle, respectively) have been unequivocally identified in the supersonic expansion.
The ability to identify peptide conformations suggest that it soon may be possible to explore the structures of larger peptides using LA-MB-FTMW spectroscopy.



RCO-Pro-NHR' RCO-Ala-NHR'

Figure 1. Structure of the alanine and proline derivatives investigated (R' = Me or H).

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Threshold collision-induced dissociation measurements of protonated peptides

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The "pathways in competition" model has significantly improved our understanding of peptide fragmentation reactions and allows prediction of activation barriers for generation of key sequence ions for small model peptides. In this study, threshold collision-induced dissociation (TCID) on a guided ion beam instrument and variable time ion trap CID experiments were used to study the fragmentation of a group of protonated tripeptides. Our focus was on formation of b_2^+ and y_1^+, and the influence of peptide sequence on the relative threshold energies for generation of these product ions. In addition, density functional theory (DFT) calculations were used to predict structures and energies for relevant minima, including reaction intermediates, post-reaction complexes and proton-bound dimers, and transition states.

Tripeptides (GGG, GAG, and GGA) were either purchased or synthesized using Wang resin and conventional Fmoc chemistry. Protonated ions were generated using electrospray ionization. Ion trap CID was performed using a ThermoFinnigan LCQ-Deca mass spectrometer with He as the bath/collision gas. A guided ion beam tandem mass spectrometer was used to measure kinetic-energy-dependent cross sections for CID of the same peptides. Density functional theory calculations (B3LYP/6-31+G(d,p) level) were performed using the Gaussian 03 program.

Ion trap CID of the peptides generates nearly exclusively b_2^+. Initial experiments with AGG, GAG and GGA (using variable energy and variable time ion trap CID experiments) suggest that energy required to produce b_2^+ is sensitive to the position of the A residue, with an observed trend GGA > AGG > GAG. These qualitative conclusions were then examined using the guided ion beam instrument where a more diverse group of product ions, including a_3^+, y_2^+, a_2^+, and a_1^+, were generated from the respective peptides. Thresholds for generation of the various product ions have been measured for GGG, GAG, and GGA. In GGG, the threshold for generation of b_2^+ is lower by ~ 1 eV (center of mass frame) compared to other products such as a_3^+, y_2^+, and y_1^+, consistent with the lower energy (multiple collision) ion trap CID experiments. For GAG, the b_2^+ threshold shifts down another 0.3 eV, a_2^+ shifts down ~1 eV, and other products retain similar energy profiles. For GGA, the b_2^+ threshold is comparable to that for GGG, but now the y_1^+ threshold is very similar and much lower than for GGG and GAG.

The trends with respect to how easily the b_2^+ ion is generated, both in the ion trap and guided ion beam experiments, are consistent with the relative energies for transition states and products predicted by DFT calculations. For GGG, the transition state for generation of b_2^+ is 30-50 kJ/mol lower than those for the b_3^+ and y_2^+ pathways. This supports the observation of b_2^+ as the dominant fragment in the low energy ion trap CID experiments, and the relative thresholds for the respective products in the guided ion beam experiments. Predictions of transition state and product energies for the other peptides examined are also consistent with both the ion trap and guided ion beam measurements.

Cation Aza-Crown Complexes: Determination of Structures and Bond Dissociation Energies Using Guild Ion Beam Tandem Mass Spectrometry and Quantum Chemical Calculations

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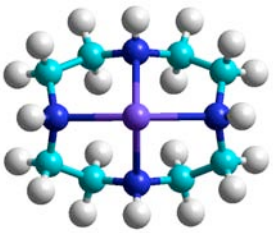
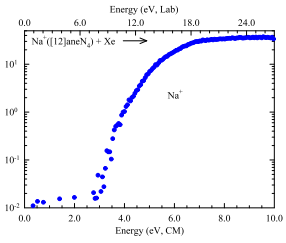
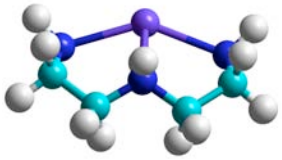
Macrocycle complexes have been useful in understanding many systems encountered in biology along with having widespread use in analytical, pharmaceutical, and synthetic chemistry. In the present study, we examine the noncovalent interactions between alkali metal cations (Li^+, Na^+, K^+, Rb^+, and Cs^+) and the nitrogen or aza crown ether, (1,4,7,10-tetraazacyclododecane, [12]aneN_4). Guided ion beam tandem mass spectrometry techniques are used to characterize the kinetic energy dependence of the collision-induced dissociation (CID) of these cation-aza-crown complexes. In all cases except Li^+([12]aneN_4), only simple CID resulting in loss of the intact crown ether is observed over the range of collision energies examined as shown below for the Na^+([12]aneN_4) complex. Quantitative thermochemical analysis of the experimental CID cross sections is used to extract accurate bond dissociation energies (BDEs) of these cation-aza-crown complexes. As a result of the size of these systems, the lifetime of the dissociating complex must be included in the thermochemical analyses to achieve accurate BDEs. Density functional theory calculations are employed to characterize the structures and stabilities of the isolated cations and aza-crown ether as well as the noncovalently bound complexes comprised of these species. The ground state and stable low-energy structures of the alkali metal cation–[12]aneN_4 complexes have been investigated in detail and as a function of symmetry. Both the ground state geometry (shown below for the Na^+([12]aneN_4) complex) and the binding energies of these complexes are found to depend strongly on the size of the alkali metal cation. The theoretical calculations and experimental studies find that the binding energies decrease monotonically with increasing size of the metal cation, indicating that the binding in these complexes is indeed primarily noncovalent in nature. The trends in the structures and binding energies as a function of the alkali metal cation are examined and discussed in detail.





Na^+([12]aneN_4)



Force-dependent redox potentials of disulfide bonds

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The influence of thermodynamic effects, such as the influence of temperature and pressure on chemical reactions are indisputably accepted. However, little is known on the consequences of mechanical stress on reactions such as bond cleavage. We aim at understanding the influences of tension on redox energies. Here, we present a first insight on the effect of tension upon redox reactions. Forces as small as a few 100 pN significantly alter and mostly increase the redox potential. We compare the effects on redox energies originated by mechanical forces to the effects arising from the changes in chemical surrounding. We find that both types of effects have the equal capacity to alter redox potentials.

Towards understanding the oxidation processes of methionine-containing polypeptides: from the addition of OH radicals to the 2-center 3-electron radical cations.

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We focused our attention on the earlier steps of the oxidation process of Methionine (Met), which is a target of oxidizing free radicals in peptides or proteins. The first step is supposed to be the addition of OH radicals on the sulphur atom of methionine, followed by OH^--elimination and formation of a radical cation. Then the sulphur-centred radical cation can complex with oxygen, nitrogen or another sulphur atom from a neighbouring residue or from a peptidic bond.

In order to study the first step of oxidation, we have compared the stability of the resulting OH radical adducts of Met, Tyr and Phe, which are targets in competition in the Methionine Enkephaline (the sequence of which being Tyr-Gly-Gly-Phe-Met). The thermodynamical and the activation energies of the addition were computed with the DFT method.

For the next step of complexation, we have investigated the stabilization of the radical cations of three peptides containing the Methionine (MetGly, Gly and Met) by formation of intramolecular S∴X (X = S, N, O) bonds. Several stable structures of 5 to 10 member-cycles were isolated in vacuum and in water. The absorption wavelengths λ, corresponding to the $\sigma \rightarrow \sigma^*$ transition, were calculated with the TD-DFT method for each stable complex. The λ variations, from the near UV to the green visible, are related to the different nature of the S∴X bonds (pure 2c-3e bonds or electrostatic) that were characterized using the ELF and the AIM topological analyses.

IR/UV investigations on aluminum/peptide cations

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Secondary structures play an important role to explain the function of proteins. In this case the interplay with metal ions is of high interest to obtain information on e.g. ion transport or induction of diseases. To investigate the interactions of proteins with metal ions on a molecular level the analysis of isolated model systems in a molecular beam experiment is an ideal starting point. The changes of the secondary structure of an isolated peptide by adding a metal ion is analyzed by mass selective IR or IR/UV spectroscopy.

In order to figure out different binding motifs in metal/peptide clusters the attachment of Al^+ and Al^{3+} cations to the backbone of different protected amino acids and dipeptide models is investigated by means of mass selective IR photodissociation spectroscopy. In case of clusters with very strong bonds between the aluminum cation and a peptide containing an aromatic chromophore a combined IR/UV technique is applied in order to yield the vibrational spectra in the NH stretching region. The comparison with extensive ab initio and DFT calculations lead to suggestions for structural arrangements. The aluminum cations are attached to the carbonyl groups and lead to strong changes of the backbone conformation. The structures are discussed with respect to their stability, spin state and the influence of the aromatic chromophore.

Anomalous gas-phase photoabsorption profile of the Retinal: a high level *ab initio* study

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Experimental and theoretical studies of the gas-phase photoabsorption of the biological chromophores provide extremely useful information about the intrinsic properties of the light-absorbing cofactors of the photoactive proteins. Such knowledge helps to shed light on the fundamental role played by proteins in the ultrafast reaction dynamics of biological photoreceptors. The primary light-induced reaction of the retinal isomerization in the photocycle of visual pigments and specific mechanisms that make color tuning possible are of particular interest.

The present study is aimed at high-level *ab initio* modelling the unique photophysical properties of the isolated biological chromophore of Rhodopsin. The unique sensitivity of the photoabsorption of the protonated Schiff-base 11-*cis* retinal may be traced to the flexibility of its conjugated double-bond chain and, in particular, to the influence of the floppy β-ionone ring, being a part of a π-conjugated system. Moreover, the local topology of the ground-state potential energy surface with respect to the rotation angle has been found to have a significant impact on the gas-phase absorption profile of the first S_0-S_1 transition, which has been experimentally found remarkably broad with an essentially flat top extending from 530 nm to 610 nm. In the present study the remarkable features of the experimental photoabsorption profiles of the low-lying transitions have been interpreted by solving the one-dimensional quantum rotational nuclear motion problem using the corresponding ground state adiabatic MP2/cc-pVTZ and PBE0/cc-pVDZ potentials. Given the quantum mechanical probability of a given initial nuclear configuration, the broadening of the S_0-S_1 and S_0-S_2 absorption lines has been estimated by the semiclassical Lax's approach. The final shape of the integrated spectrum results from the temperature-averaged nuclear density function spread over the rotational levels populated at a given temperature. The ground state rotational temperature and the S_0-S_1 and S_0-S_2 transition electric dipole moment dependence on the nuclear position are discussed. The vertical excitation energies have been calculated using the original version of the multistate multireference perturbation theory approach XMCQDPT2. All calculations have been carried out in the frame of the Firefly computational package.

This work is supported by the RFBR grant (project 08-03-00914-a) and the grant from the President of Russian Federation for young scientists (MK-64815.2010.4).

Electronic structure of the ionized DNA bases clusters: the effects of H-bonding and stacking interactions.

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Electron hole formation is the primary step of DNA oxidative damage and charge transfer causing distant mutations in the DNA sequence. Ionization energies of the nucleic-acid bases (NAB) in their natural environment are decreased in comparison to those of isolated bases due to stabilization of open-shell cation through hydrogen bonds formation, stacking interaction with neighboring bases and electrostatic interactions. Isolated dimers of the A, T bases and $(AT)_2$ tetramer are considered as model systems. The influence of the H-bonding and stacking interactions on the vertical ionization energies of the NAB monomers and dimers, electronic structure of produced cations is analyzed using equation-of-motion coupled-cluster (EOM-IP-CCSD). IP-CISD and DFT methods are employed to study ionization of the $(AT)_2$ tetramer. It is shown that inter-fragment interactions affect ionized states of the NAB dimers via two distinct mechanisms: hole delocalization and electrostatic interactions. H-bonding and stacking interactions have profound impact on ionization energies of NAB in dimers: ionization energies in dimers can be decreased by as much as 0.4-0.5 eV. Both factors are also found to contribute to the strong decrease in ionization energy of the tetramer. The hole is found to be delocalized over two A bases, which results in 0.45 eV decrease of the ionization energy. H-bonding between AA and TT stacked pairs leads to further stabilization of the ionized state by 0.24 eV.

Gas-Phase Structural Biology: Measuring and Interpreting Collision Cross Sections

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Ion mobility and mass spectrometry (IM-MS) can provide detailed insights into the structures of macromolecular assemblies, including those that are most challenging for condensed-phase techniques. Applications of IM-MS have exploded with the recent availability of commercial instrumentation, but there are a number of concomitant and poorly characterized aspects of these experiments: collision cross sections (CCS) are often not determined directly from measured drift times, but indirectly through calibration; CCS calibration standards in the literature are of significantly higher mobility and lower mass than the macromolecular assemblies of greatest interest; experiments are normally performed in N_2 gas and then calibrated to He; and measured CCS can be difficult to assign to specific structures.

Significant progress towards characterizing and reducing the errors associated with measurements of collision cross sections (CCS) using travelling-wave IM-MS instrumentation has been achieved. Here, CCS values were measured directly using a modified Synapt HDMS (Waters) in which the travelling-wave ion mobility cell has been replaced with an 18 cm ion mobility cell that has a uniform electric field along the axis of ion transmission and RF confinement along the perpendicular axes. CCS were determined from the slopes of drift time versus reciprocal drift voltage plots, using drift voltages ranging from 50–200 V in ~2.5 Torr of either He or N_2 gas. Absolute CCS for denatured peptides and proteins, and buffered proteins and protein complexes, enable the calibration of travelling-wave ion mobility drift time data through use of calibration standards with similar masses and mobilities, and whose accurate CCS were determined on instrumentation with essentially the same geometry, conditions, and time scales. Travelling-wave CCS errors determined for protein complexes calibrated using other protein complexes are significantly less than those calibrated using denatured proteins. This database indicates that He and N_2 CCS can be well correlated for large protein complexes, but that errors for smaller ions can be more significant.

A robust coarse-grained modelling approach using polyhedral shapes has been developed to calculate the projection approximation collision cross sections of protein complexes and other ions. Values obtained using this method correlate well with projection approximation results for atomic structures. Many macromolecular assemblies have polyhedral architectures, enabling their representation with very few parameters. This approach has great potential for hypothesis driven investigations of ions with poorly characterized structures.

Ab initio Study of π-Stacked DNA Base Conformations Allowing Charge Migration

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Charge transfer reactions are a key process in the propagation and detection of DNA damage caused by oxidizing agents and ionizing radiation[1]. DNA charge transfer has proven to be mediated by π-π interactions between the bases and, as such, to be sensitive to DNA conformation and stacking, with only certain base conformations being charge transfer active[2,3]. *Ab initio* high-level quantum mechanics methods, including state-averaged CASSCF/MRCI and RASSCF/RASPT2, are used to characterize, in gas phase, the very specific conformations of the DNA stacking of two consecutive guanines, the most easily oxidized nucleic acid base, required for charge transfer to occur. The topology of the potential energy surfaces of the electronic states governing the charge transfer between the bases has been studied in terms of all intermolecular geometrical parameters of the complex. Relative translational motions of both guanines in their molecular planes are demonstrated to have an important influence on the charge migration between the bases and five stationary point conformations are characterized along the reaction path by which the event occurs[4]. We show that these conformations are recurrently found in DNA and RNA X-ray structures, often in particular conformations such as quadruplexes, or at the interface with proteins, ligands or metal ions. The model system for which the electronic structure is calculated is extended to a sequence of three stacked guanines demonstrating that the charge transfer proceeds in a multi-steps fashion, from one base to another following a mechanism governed by the relative motions of both bases. Finally, the effects of the DNA-protein interface are considered by investigating the approach of an arginine. The implications for understanding the role played by the H-bond/cation-π stair motifs recurrently found at protein/DNA interfaces on DNA-mediated charge transfer are discussed in light of these results.

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Structure and infrared spectrum of the Ag^+- $(pyridine)_2$ ionic complex: probing metal-ion-mediated artificial DNA base pairing in the gas phase

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Apart from the biological relevance, natural deoxyribonucleic acid (DNA) and its derivatives are very popular building blocks and precursors for numerous applications in synthetic organic chemistry, medicine, biotechnology, and material science. Nowadays, active research is aiming at incorporating different non-natural base pairs into DNA to expand the natural four letter genetic alphabet for wider range of applications. One of the recently established methods is the site specific functionalization of DNA by metal-mediated base pairing, in which the metal ions form coordinate bonds to the natural or artificial nucleobases at the required positions. Very recently, the solution-phase DNA double helix structure of Ag(I) mediated base pair using imidazole nucleoside has been characterized by NMR spectroscopy [1]. Pyridine (Py) containing nucleoside has also been used, and it was confirmed that Ag^+ ions introduce higher stability to DNA than other transition metal ions (Cu^{2+}, Ni^{2+}, Pd^{2+}, Hg^{2+}) [2].

We report the infrared (IR) spectrum of Ag^+-Py ionic complex in the fingerprint range. The IR spectrum is recorded by IR multiphoton dissociation using the tuneable IR-FEL at CLIO coupled to a modified Bruker APEX-Qe mass spectrometer [3]. The experimental IR spectrum is compared to quantum chemical calculations carried out at the B3LYP level. Py offers two binding sites to Ag^+, namely, the π electron density of the aromatic ring (π-bond) and the nitrogen lone pair (σ-bond). Inspection of the IR spectrum suggests the formation of the σ-bonded structure. The predicted planar structure of the Py-Ag^+-Py ionic complex with D_{2h} symmetry is attributed to the preferred binding motif of such metal-mediated base pairs in DNA. The effect of Ag^+ complexation on charge delocalization, geometry, and vibrational modes of the Py moiety in the complex is significant and analyzed in detail.

Acknowledgments

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Structures and Binding Energies of Noncovalent Complexes of Peptidomimetic Protonated Nitrogen Bases with 18-Crown-6

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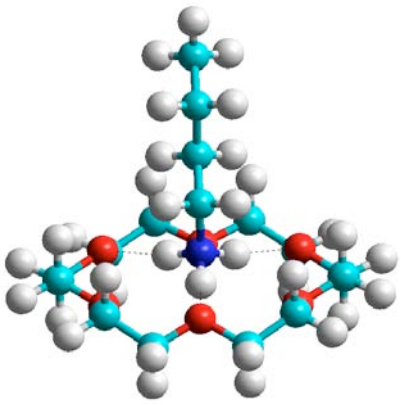
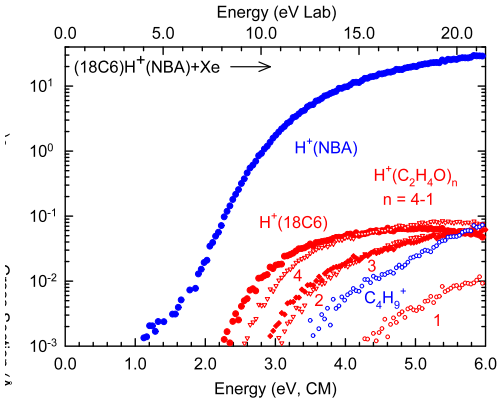
The absolute 18C6 binding affinities of six protonated nitrogen bases that serve as mimics for the n-terminal amino group and the side chains of the basic amino acids (histidine, lysine and arginine) were determined by guided ion beam tandem mass spectrometry. The nitrogen bases examined in the present study include: imidazole (IMID), 4-methylimidazole (4MeIMID), n-butylamine (NBA), 1,5-diamino pentane (DAP), isopropylamine (IPA) and methylguanidine (MGD). The kinetic-energy-dependent cross sections for collision-induced dissociation (CID) of these $(18C6)H^+(B)$ complexes are analyzed using an empirical threshold law to extract absolute 0 and 298 K bond dissociation energies (BDEs) after accounting for the effects of multiple collisions, kinetic and internal energy distributions of the reactants, and unimolecular dissociation lifetimes. Structures were optimized and frequency analyses were performed using density functional theory at the B3LYP/6-31G* level of theory. The optimized structure of the $(18C6)H^+(NBA)$ complex is shown below. Relative energetics as well as the theoretical BDEs were determined at the B3LYP/6-311+G(2d,2p) and MP2(full)/6-311+G(2d,2p) levels of theory. In all systems, CID results in loss of the intact crown ether producing $H^+(B)$ as the lowest energy dissociation pathway, allowing the $(B)H^+-18C6$ BDEs to be extracted. The measured $(B)H^+-18C6$ BDEs exhibit good agreement with MP2 theory, whereas B3LYP theory systematically underestimates the BDEs by ~30 kJ/mole. Present results indicate that the of side chain of lysine is the preferred binding site for 18C6 complexation based upon the large BDE determined for the corresponding NBA mimic. Minor production of the protonated crown, $H^+(18C6)$, in competition with the protonated base, $H^+(B)$ is observed in the $(18C6)H^+(NBA)$ and $(18C6)H^+(IPA)$ systems. CID cross sections for the $(18C6)H^+(NBA)$ complex are shown below. The potential energy surfaces for the observed dissociation pathways in these systems indicate that formation of $H^+(18C6)$ involves a tight transition state that decelerates the dissociation process. Therefore, the thresholds for the $H^+(B)$ and $H^+(18C6)$ CID cross sections do not reflect their relative proton affinities. The $H^+(18C6)$ was observed as a competitive dissociation product in the $(18C6)H^+(IMID)$ and $(18C6)H^+(4MeIMID)$ systems. Based on the relative thresholds for dissociation in these two systems, we derive a revised value for the PA of 18C6 of 934.5 ± 7.1 kJ/mole. The PA value derived here exhibits good agreement with both MP2(full) and B3LYP estimates for the proton affinity of 18C6, where values of 943.3 and 924.3 kJ/mole, respectively are found.





Microsolvation of polyalanine-based peptides

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Microsolvation is an important method to approach the interaction of peptides with individual solvent molecules. We study two small peptides whose structures in *vacuo* (without solvent) have been the subject of experiments in the recent years: Ac-Ala5-Lys-H^+ [1] and Ac-Phe-Ala5-Lys-H^+[2]. The aim of this work is to theoretically identify the lowest-energy conformers of these peptides and carry out microhydration studies to find the preferred water binding sites. A basin hopping search with the OPLS-AA force-field potential in the TINKER package is first used to scan the potential energy surface for a wide variety of candidate conformers. Then the all-electron electronic structure code FHI-aims [3] is used to follow up the lowest energy structures with van der Waals corrected [4] density functional theory (PBE) to determine the energy hierarchy. Short replica exchange runs with *ab initio* molecular dynamics are added to further probe the vicinity of the identified structures. Our findings indicate that both helical and "non-helical" conformers are present among the low-energy conformers of Ac-Phe-Ala5-Lys-H^+, similar to the case of Ac-Ala5-Lys-H^+. For both Ac-Phe-Ala5-Lys-H^+ and Ac-Ala5-Lys-H^+, the first few water molecules are found to bind to the protonated lysine end in the lowest energy conformer. We address the accuracy of the pre-screening forcefield compared to DFT-vdW as well as dependence of the energy hierarchy within DFT itself on the functional being used.

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Conformational Flexibility of Tropane alkaloids: Tropinone, Scopine and Scopoline

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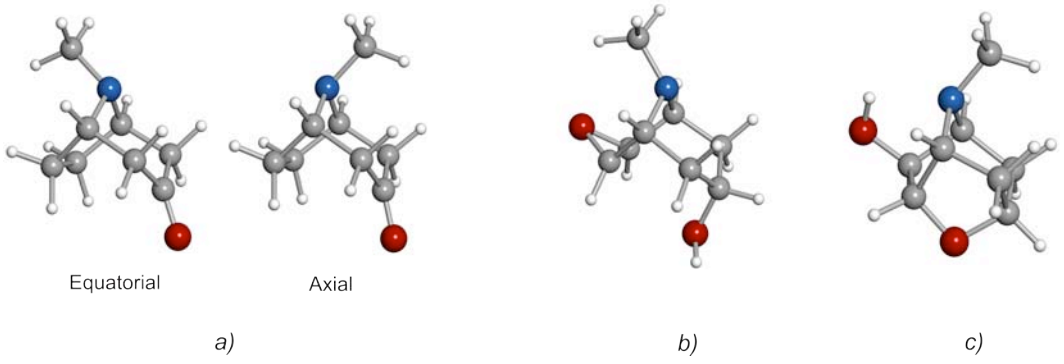
The tropane bicycle is the common structural motif of a series of relevant alkaloids used as antocholinergics and neurostimulants, including both natural compounds (i.e., atropine, scopolamine and cocaine) and synthetic analogues used in medicinal Chemistry. Structure-activity-relationship studies have revealed correlations between the biological properties and several aspects of ligand conformation, including not only the nature, position and orientation of the aryl substituents of tropane but also different connections between stereochemistry and bioactivity.

In order to elucidate the conformational landscape of several tropane alkaloids we report a microwave study using the new Balle-Flygare-type Fourier-transform Microwave Spectrometer built at the *Universidad del País Vasco*. For tropinone two conformers (axial and equatorial) were identified in the rotational spectrum, detecting all ^{13}C-monosubstituted isotopomers in natural abundance (1.1%) for both conformers. Furthermore, isotopomers containing ^{15}N (0.4%) and ^{18}O (0.2%) were also observed for the equatorial species. Finally, the effective and substitution structures were determined for both conformers of tropinone.

The investigation of scopine gave an intense spectrum, but it was inconsistent with the structural models expected for this molecule. The carrier of the new spectrum was later identified as scopoline, generated *in situ* by an intramolecular reaction at the moderate temperatures of the nozzle. A single conformation was detected for scopoline, with an ether bridge seriously distorting the tropane motif.



a) Tropinone (equatorial and axial); b) Scopine; c) and Scopoline.

UV spectroscopy of gas phase proteins

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UV spectroscopy of a variety of trapped anions ranging from the amino-acid to the entire protein was performed by means of photoinduced electron detachment. It is shown that photoinduced electron detachment spectroscopy overcomes the current limitations of photofragmentation and extends the range of UV spectroscopy of trapped species to very large systems.[3-4] The influence of a negative charge on the optical spectrum of aromatic amino-acids is discussed.[1-2]

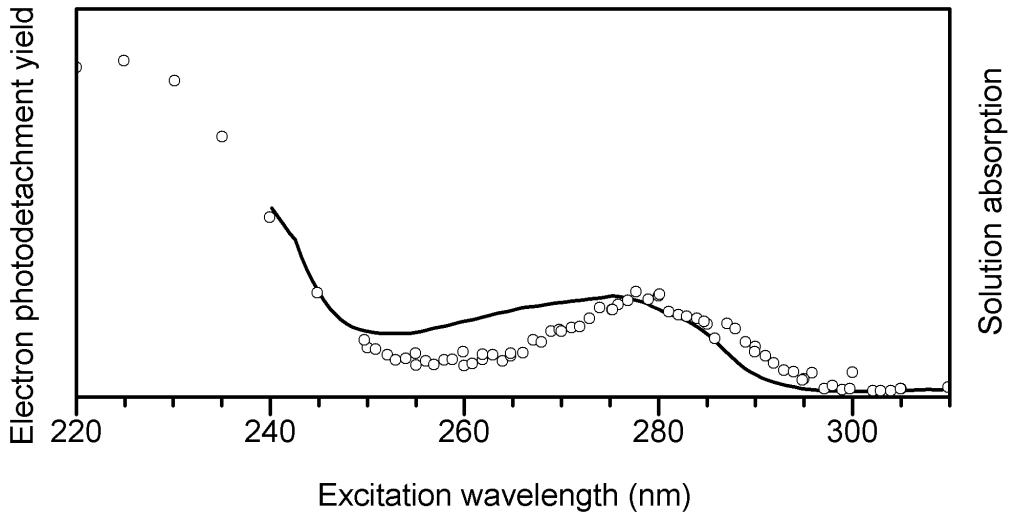

Fig. UV spectroscopy of Ubiquitin protein. (open circles: electron photodetachment in the gas phase; full line: absorption in solution)

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UV spectroscopy of isolated metal-peptides complexes

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UV spectroscopy of trapped metal-amino acids and metal-peptides complexes is presented. It is shown that the optical properties of an aromatic amino-acid can be tuned by addition of a metal ion[1-2] or a metal cluster.[3] Charge transfer type of excitation may lead to absorption in the visible range, while the presence of a cluster results in the enhancement of the optical absorption by several orders of magnitude. In the case of small peptides, the effect of the metal on the conformation is presented.[4] The role of metal ions in biologically relevant peptides is discussed in terms of optical and conformational effects.[5]

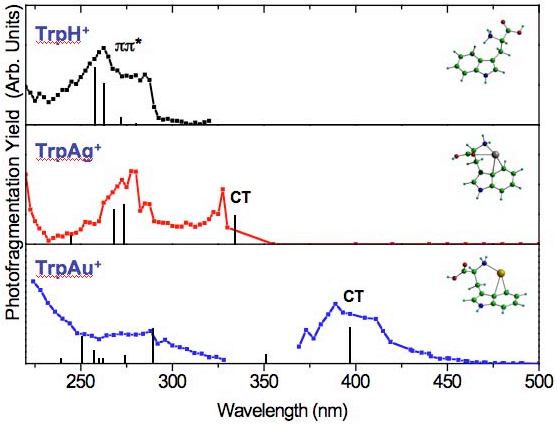

Fig. UV photofragmentation spectra of tryptophan cations.

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Vibrational and electronic spectra of protonated and metalated biomolecular building blocks: Geometric and electronic structure

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The geometric and electronic structure of mass-selected ions and cluster ions of biological interest are characterized in the gas phase by photodissociation spectroscopy in the IR and UV/vis spectral ranges. The species of interest are produced in a variety of ion sources, including chemical and electrospray ionization, as well as laser desorption. Photodissociation spectra are obtained using a variety of tandem mass spectrometers (multipole, ICR, time-of-flight) and laser sources (IR-OPO, UV/vis-OPO, dye, IR-FEL). The spectra are analyzed by comparison to quantum chemical calculations. The systems investigated recently include

(i) protonated neurotransmitters (dopamine, histamine, serotonine, nicotinamid)

(ii) protonated xanthine derivatives (caffeine, theophylline)

(iii) complexes of Ag^+ with phenol, pyridine, and a variety of PAH molecules

(iv) complexes of Zn^{2+} with histidine analogues

These systems are relevant for a large variety of biophysical interactions and processes, such as signal transduction (protonated neurotransmitters and xanthines), enzymatic phenomena (Zn^{2+}-histidine complexes), and biotechnology (metal ion mediated DNA engineering). An example for the latter topic includes the unusually strong Ag^+-pyridine interaction used for engineering of DNA-bearing material via metal-ion mediated artificial base pairing.

The information extracted from the IR and electronic spectra include geometric parameters, such as binding sites for ligands (π– and H-bonding), protons, metal ions (π– and σ–bonding) and corresponding bond lengths, binding energies and bond strengths, and electronic structure (charge distribution). Comparison with the properties of the corresponding isolated neutral molecules reveals the effect of protonation, metalation, and microsolvation on the geometric, vibrational, and electronic structure of the biomolecular building blocks. Recent selected results will be presented.

Acknowledgments

These studies were supported by DFG (DO 729/2-5), FCI, and EU. We also appreciate the support of the teams at the FELs at CLIO and FELIX facilities, as well as collaborations with the groups of J. Oomens (Amsterdam), K. Asmis (Berlin), and P. Maitre (Paris).

Microsolvation of Anesthetics in Supersonic Expansions: The Propofol Water System

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Interaction between anesthetics and the receptor active site is driven by non-covalent forces, which are difficult to describe by computational methods, either ab initio, or non-ab initio (DFT, semiempirical, force fields…, etc.). Besides, the anesthetic docking process is a competition between the salvation by the extracellular medium and the interactions in the active pocket. Thus, understanding the whole docking process requires of a good knowledge of the salvation process and of the non-covalent interactions between the anesthetic and the receptor.

Propofol (2,6-diisopropylphenol) recently became sadly famous as the dead of Michael Jackson is thought to be due to an overdose of this substance. It is a short-acting, intravenously administered hypnotic agent, structurally related to phenol, although its two isopropyl substituents in *para* with the OH group strongly hinder the hydroxyl group ability to establish hydrogen bonds. In addition, the relative orientation of the methyl groups raises five possible conformational isomers. In this work we report a spectroscopic study of the propofol and of its complexes with up to three water molecules. Using a supersonic expansion, the molecules are cooled to a few K, to favor the formation of non-covalent aggregates, and are probed with the aid of up to three tunable lasers, using a number of mass-resolved experimental techniques, in order to extract information about the excitation energy, vibrational modes, number of isomers and relative stability. Comparison with calculations conducted using MP2 and DFT methods allow a full characterization of the system under study.

Conformer separation, alignment, and orientation of neutral molecules for coherent diffractive imaging experiments

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In 2009 the first X-ray Free-Electron Laser (FEL) , the Linac Coherent Light Source (LCLS) at the Stanford Linear Accelerator Center (SLAC), became operational. One envisioned application with such novel hard X-ray FELs is the diffractive imaging of isolated, non-crystallizable bio-molecules in the gas phase. Because a single X-ray laser pulse will completely destroy the molecule, its diffraction pattern needs to be recorded in a single shot. The (electronic) structure of the molecule must not significantly change on the timescale of the laser pulse (<100 fs) in order to obtain unperturbed diffraction patterns. In order to benchmark radiation damage and the structure retrieval algorithms, we will perform first studies on ensembles of small molecules (e. g. diiodobenzene) at LCLS in 2010. In order to observe the diffraction pattern, samples of identical (i. e., oriented) molecules must be prepared. Furthermore, if the target molecules occur as different structural isomers, the individual isomers need to be spatially separated. We have demonstrated the spatial separation of individual strucutral isomers [1, 2] and very strong 1D and 3D laser-alignment and mixed field orientation of such molecules [3, 4]. Here, we will discuss how such targets can be prepared, using quantum-state-selection techniques, and applied for X-ray diffraction experiments.

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The elusive question of tautomerism in cytosine: quantum chemical and matrix isolation spectroscopic investigations

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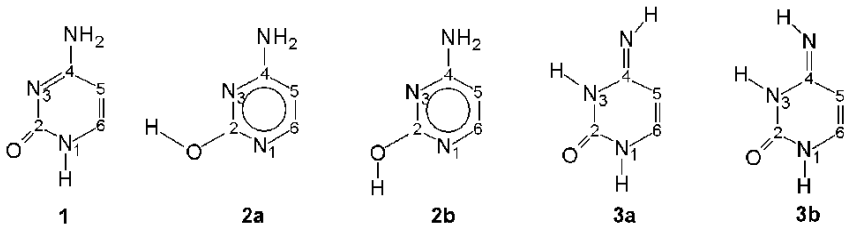
The biological importance of possible tautomerization of nucleotide bases has been recognized from the beginnings of molecular genetics. Still, there is much uncertainty about the relative abundance of tautomers. Specifically about cytosine, there is general consensus that it exists in the "canonical" amino-oxo form (**1**) in condensed phases. In the gas phase, however, all spectroscopic and theoretical studies indicate that two or three tautomers coexist, with a dominance of the amino-hydroxy form (**2**). High level quantum chemical calculations predict free energies of only $\Delta G \leq 1$ kcal/mol for **1** and, more surprisingly, also for the imino-oxo form **3a**, relative to **2b** [1]. This would imply abundances of up to 20% for both. Gas-phase spectroscopic studies do „see" these isomers but with much smaller abundance. Accepting that crystalline cytosine consists of molecules of tautomer **1** (connected by hydrogen bonds), and the barrier to unassisted tautomerization is very high (all calculations put it to around 40 kcal/mol), a fundamental question is how tautomerization can take place during evaporation in the gas-phase experiments. Traces of water may play a crucial role as water reduces the barrier by about a half. The possibility of various, differently H-bonded dimer transition states, leading to various different tautomers [2,3] cannot be ruled out, either.

Recently we have calculated the electronic spectrum, including vibrational structure, of tautomer **1** and analyzed the published experimental spectra on the basis of this form [4]. Among several discrepancies, even the number of electronic transitions is uncertain. For the present study we have thus re-measured the UV-VIS and IR spectrum of cytosine in Ar and Kr matrices with better quality than found in previous studies. The computations have been extended to tautomers **2** and **3** and include now the third A' excitation. On this basis, we try to interpret the spectra as composite spectra of various tautomers/isomers. Structures and transition state barriers for three possible dimers have also been computed.



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Evidence for catechol ring – induced conformational restriction in neurotransmitters

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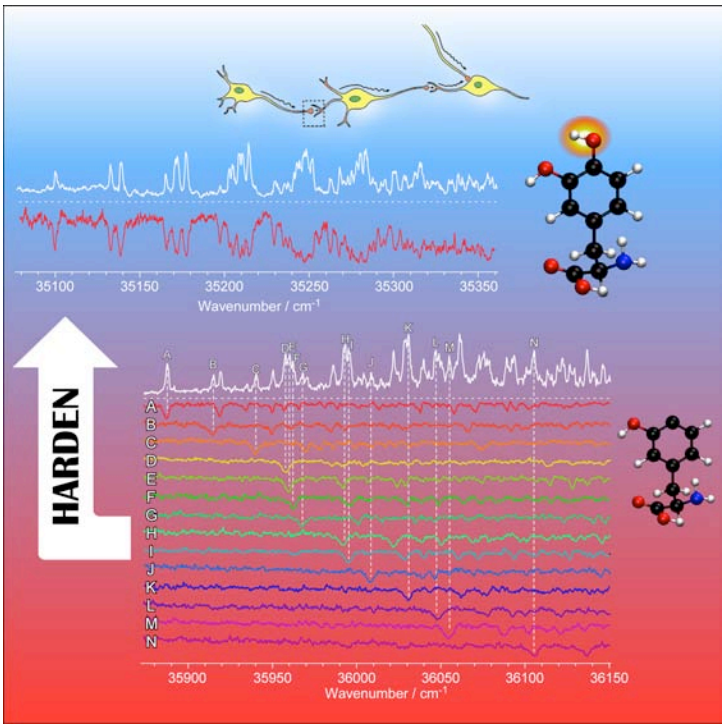
In the neurotransmission process, a specific neurotransmitter binds to a specific receptor in a "Key and Lock" recognition process. Neurotransmitters, such as the catecholamines, are flexible molecules that can change their shape easily in principle. However conformations of both the "key" and "lock" must be quite limited to achieve high selectivity. We have investigated the conformational diversity of catecholamines and related molecules by laser spectroscopy. Molecules of the tyrosine family, which contain a phenolic aromatic chromophore, exist as several conformers. In contrast, a single conformer is observed in dopa and other catecholamines, which contain two hydroxyl groups on the benzene moiety (catechol). This demonstrates that the presence of a catechol ring restricts significantly the number of stable conformations.

Ref : H. Mitsuda et al., J. Phys. Chem. Lett. 2010, 1, 1130–1133



Theoretical modelling of ESI electrospray ionisation mechanisms : thermodynamical stability of mesoscopic charged droplets.

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Although ESI has become the ionization method of choice for routine mass spectrometric analyses, relatively little is known about its mechanistic details, in particular the ion formation from charged nano-droplets continues to be a matter of debate, as acknowledged by several world-leading groups[1-3]. The mechanisms of ion formation in ESI are pivotal, since the structure and charge states of the biomolecules are likely to be affected by the desolvation process. A related question yet to be answered is the relationship between the structure and chemical composition of solution-phase analytes and the corresponding gas-phase ions, or in other words, how can ESI transfer biomolecules and non-covalently bound complexes into the gas-phase while preserving their solution-state?

We present here our first results on the modeling of ESI phenomena of charged nano-droplets and embedded ions based on Monte-Carlo (MC) and Molecular Dynamics (MD) simulations, using a mesoscopic highly coarse-grained representation of the particles. Our general aim is to provide a comprehensive view of the thermodynamics and kinetics of charged nano-droplets and embedded analytes (typically proteins & non-covalently bound protein complexes) with a direct access to the ESI mechanisms and changes in structure- and charge-states along the evaporation processes.

The following points will be emphasized in the present presentation :

- Location of the analytes within the droplet, i.e. interiror *vs* surface, as a function of total charge.
- Rayleigh limit and the total charge sustained by a given droplet.
- Structure of the droplets depending on the temperature, in relation with the Thomson model.
- Dynamics of evaporation.

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VIBRATIONAL STUDY OF POLYETHER-CATION COMPLEXES

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Infrared Multiphoton Dissociation coupled to an Electrospray Ionization-Fourier Transform ion cyclotron resonance mass spectrometer at the beamline of the free electron laser FELIX are employed to investigate the gas-phase conformations of linear and cyclic polyethers complexes with different cations at the vibrational level [1-3]. Conformational assignment is supported by quantum chemical calculations (DFT and MP2). Complexes of both achiral and chiral crown ethers, of aza-derivatives and of linear polyethers are considered, in combination with singly and doubly charged cations. Optimum backbone conformations maximize oxygen-action interactions while minimizing the overlap between the lone pairs of the oxygens, commonly leading to non-trivial symmetry groups and chiral atropoisomeric structures (see Fig. 1). The presence of a heteroatom in the aza-crowns and the introduction of divalent cations provide information on the roles played by the disruption of the ring geometry and by the polarizability of the cavity. We expect these results to be useful for the comprehension of the mechanisms involved in *guest-host* Macrocyclic Chemistry.

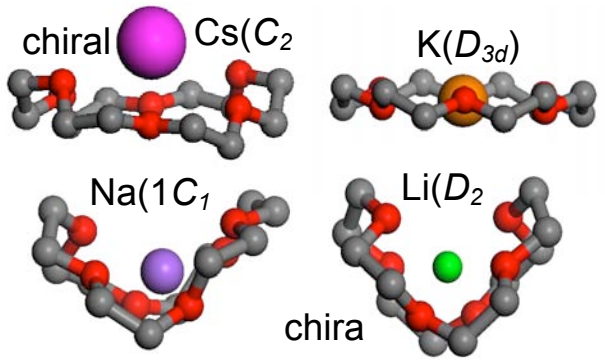

Fig. 1: Symmetric and chiral conformations of 18-crown-6 alkali cation complexes

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FAST PASSAGE ACQUIRED ROTATIONAL COHERENCE: INSTANT CAPTURE OF MULTI-CONFORMATIONAL LANDSCAPES

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Extended molecular systems with two or more structural groups, linked by σ-bonds, might and will adopt a multitude of shapes. Often, when directed by subtle intramolecular interactions, the conformational behavior is not obvious. Especially if long range interactions are involved, a priory guesses are difficult to make and calculations become increasingly unreliable. Supersonic-jet rotational spectroscopy will reveal the situation with unrivaled precision and clarity, even in difficult cases. However, since employing a high-Q Fabry-Perot type resonator, the short-stimulus excitation Fourier-transform technique is quite narrow banded and surveying large spectral ranges - as required to capture the spectral signatures of flexible molecules - can become very time-consuming.

The alternative In-phase/quadrature-phase-Modulation Passage-Acquired-Coherence Technique (IMPACT) overcomes existing limitations in Fourier Transform Microwave (FTMW) spectroscopy. This new method is ideally suited to unravel dense spectra of conformationally flexible, large molecules - a situation often encountered in biomolecular systems. We illustrate the performance and capabilities of the intrinsically simple set-up with the case of nicotine: Two conformations have been observed using the IMPACT-FTMW spectrometer implemented in Valladolid.

Nicotinoid alkaloids consist of two ring systems connected via a $C-C$ σ-bond: Joining pyridine either with a (substituted) pyrrolidine or piperidine ring system, pyrrolidinic or piperidinic nicotinoids are formed. Nicotine itself, consisting of pyridine and N-methylpyrrolidine, exhibits three sites that allow for conformational flexibility: (I) puckering of the pyrrolidine ring (Eq./Ax. positions of the pyridine), (II) inversion of the N-methyl group (Eq./Ax. positions of the hydrogen), and (III) relative orientation of the two rings (Syn-Anti). The preferred conformations are characterized by an equatorial (Eq.) pyridine moiety and equatorial (Eq.) $N-CH_3$ stereochemistry. The planes of two rings are almost perperdicular with respect to each other while exhibiting two low energy conformations, Syn and Anti, that differ by a 180 rotation about the $C-C$ σ-bond. The Eq.-Eq. conformational preference is likely due to a weak hydrogen bond interaction between the nitrogen lone pair at the N-methylpyrroline and the closest hydrogen in pyridine.

While presenting this case study, emphasis will be taken on the implementation of the technique as a generalized method to not just capture wide-spread spectral signatures from large amplitude motions and other origins in bio-molecular systems - but capture it rapidly.

Site of Peptide Ion Cleavage is Directed by Low-Energy Backbone-Protonated Isomers

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According to the popular "mobile proton model" for peptide ion fragmentation in mass spectrometry, peptide bond cleavage is typically preceded by intramolecular proton transfer from basic sites to an amide nitrogen in the backbone. If the intrinsic barrier to dissociation is the same for all sites, the fragmentation propensity at each amide bond should reflect the relative stability of the corresponding N-protonated isomer. This hypothesis was tested by using ab initio and force-field computations on several polyalanines and Leu-enkephalin. It was found that backbone N-protonation is most favorable near the C-terminus, indicating that fragmentation should also occur near the C-terminus. This is consistent with previously reported experimental and computational reports that fragmentation near the C-terminus is preferred, thus supporting the hypothesis. In the case of polyalanines, the preference for C-terminal N-protonation, which is stronger for longer peptides, may be understood in terms of the well known "macrodipole" in the corresponding helical conformations. In contrast, the opposite stability trend is found for peptides constrained to be linear. Their preference for N-protonation near the N-terminus may also be understood in terms of simple amide dipoles. Computational mutation of the polypeptides into polyketones erases the stability trends, thus supporting the dipole model.

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Laser Desorption Supersonic Jet Spectroscopy of Tri-Peptide; Z-Pro-Leu-Gly-NH_2

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Introduction Molecular recognition process plays a crucial role in information propagation and strage in biological body. In order to clarify the process in the neural transmission from the spectroscopic view, we are investigating conformations and structures of neurotransmitters. In this study, we focused on tripeptide; Pro-Leu-Gly (PLG). This peptide is a partial sequence of oxytocin, which is a well-known neuropeptide. In this work, we investigated capped peptide, whose C-terminal was amidated and N-terminal was modified by benzylcarboxy group (Z-group). We applied laser desorption supersonic jet technique to Z-Pro-Leu-Gly-NH_2 (ZPLG), and measured double resonance spectra to investigate number of conformational isomers and their structures under the ultra-cold and isolated condition in the gas phase.

Experimental A fundamental of YAG laser (1064 nm) was employed to desorb the ZPLG. Vaporized ZPLG was jet-cooled by free-jet expansion of Ar gas (3-4 MPa) introduced through a pulsed valve. To the supersonic molecular beam of ZPLG, tunable UV lasers and an IR laser were irradiated. Ionized ZPLG was detected by a TOF MASS.

Results and Discussions By monitoring a mass-channel of $ZPLG^+$ and scanning the UV laser, we measured a resonance enhanced multi-photon ionization (REMPI) spectrum (Fig. 1a). At the origin region of the spectrum (Fig. 1b), number of sharp bands are observed, which suggests the co-existence of some conformational isomers. To distinguish the electronic transitions of each isomer, we applied UV-UV hole burning (HB) spectroscopy, in which two tunable UV laser, ν_p and ν_b, are employed. By fixing ν_p to an arrowed band and monitoring the REMPI signal intensity, which is proportional to the population of a specific species at the ground state giving the arrowed electronic transition. Previous to the ν_p, the ν_b is irradiated and scanned. If the ν_b corresponds to the electronic transitions of the specified species by the ν_p, the intensity of REMPI signal is reduced. Thus, the conformer- selected electronic spectrum can be measured as a depletion spectrum shown Fig. 1c. At least 2 bands (indicated * in the figure) observed only in the REMPI spectrum. This result means that these bands come from other conformers than the specified one by the ν_p. However, the intensity of these bands is much weaker than the arrowed band, it means that these are minor conformers. Therefore it was found that ZPLG has a single major conformer in the gas phase. The IR spectrum and the results of theoretical calculations will be presented in the poster.

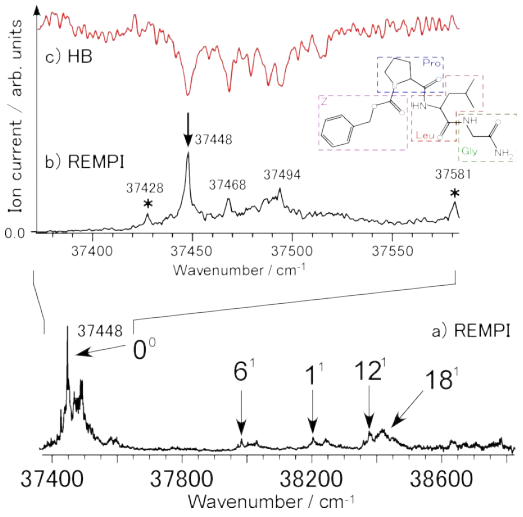

Fig. 1 a) REMPI spectrum of ZPLG, b) whose origin region, and c) HB spectrum by fixing ν_p to arrowed band of b).

Structural Analysis of F_0F_1-ATPase active site mimics by IR spectroscopy

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Nature makes wide use of biomolecular motors, which drive many essential processes of life. To this end, they convert chemical energy (ATP) into directed mechanical motion. An example of such a biomolecular motor and the focus of this research is F_0F_1-ATPase. Its biomolecular motion is initiated by conformational changes at the active site, and is induced by the association and hydrolysis of ATP. Experimental studies and molecular dynamics simulations have given insight in the modus operandi of these motors, however, they lack information on the conformational dynamics at the molecular level. This is because up to now, the experiments are performed on the complete protein, where the active site is hidden by the protein environment.

To understand the conformational dynamics at the active site of the ATPase biomolecular motor, we will first develop a model system of this active site. It is known that only four residues of the binding pocket are important for binding and recognizing ATP, the so-called arginine-finger. Here, we will focus on the position of glutamic acid (Glu) and arginine (Arg). These Glu and Arg residues are important for recognition and efficient binding of ATP. Therefore, the distance between these residues in the active site mimic have to be determined and optimized.

The required detailed view of the active domain will be obtained by using IR spectroscopy on internally cooled biomolecules in the gas phase. This enables us to study the intrinsic properties of biomolecules in absence of interactions with the natural environment (e.g. solvent molecules). In this project, REMPI and IR-UV ion-dip spectroscopy are performed on Z-Glu-OH, Z-Arg-OH and Z-Glu-$(Ala)_n$-Arg-NHMe (n = 0, 1, 3, 5) in the gas phase. The Free-Electron Laser for Infrared eXperiments (FELIX) is used as the IR source to obtain IR spectra in the 1000 cm^{-1} – 1800 cm^{-1} range. In this region, the Amide I and II bands can be monitored, which are very sensitive to hydrogen bonding, as well as the fingerprint region, which can be used to determine the backbone conformation. Together with quantum chemical calculations, the secondary and tertiary structure of these active site mimics will be determined revealing the optimal position of Glu and Arg.

Vibronic spectroscopy of indazole dimer isotopomers

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The doubly hydrogen-bonded indazole dimer can be regarded as a model molecule mimicking the characteristics of nucleic acid base pairs. This study continues our previous investigations on indazole [1], deuterated indazole [2] and its self- and water complexes [3] cooled in a supersonic jet. Near UV spectra (291-293 nm) of three indazole dimer isotopomers, Ia_2-*hh*, Ia_2-*hd*, and Ia_2-*dd*, were measured by laser induced fluorescence excitation, dispersed fluorescence (DF), and mass-selected resonance enhanced two photon ionization spectroscopies. Structure optimizations and frequency calculations were carried out at TPSS/aug-cc-pVTZ level for the S_0 state and at B3LYP/cc-pVTZ level for the S_1 state.

All three isotopomers are planar in the S_0 and S_1 states. The Ia_2-*hh* and Ia_2-*dd* homodimers have C_{2h} symmetry, but the Ia_2-*hd* heterodimer has C_s symmetry. Interaction between the monomer moieties gives rise to two exciton states split by $\sim$25 cm^{-1}. The transitions to the exciton states are $\sim$325 cm^{-1} redshifted from the $S_1 \leftarrow S_0$ origin band(s) of the monomer(s). For homodimers, the lower exciton state has A_g symmetry and the upper exciton state has B_u symmetry; thus only the $B_u \leftarrow A_g$ transition is allowed. For Ia_2-*hd* transitions, both exciton states are allowed.

Indazole dimer's six intermolecular vibrations, representing the relative motions of the monomer moieties, have frequencies from 15 cm^{-1} to 130 cm^{-1}. The progression of intermolecular vibrations in the excitation and DF spectra are dominated by the shearing, the stretching and the cogwheel mode. In the excitation spectra of the homodimers, the totally symmetric shearing and stretching fundamentals belong to the upper exciton state, but the b_u cogwheel fundamental belongs to the lower exciton state, so that the resulting vibronic symmetry is always B_u.

In the higher frequency part of the DF spectra beyond 600 cm^{-1}, intramolecular vibrations and their combinations with intermolecular vibrations appear. Each monomer vibration gives rise to two intramolecular vibrations of the dimer, which are close in frequency, but have different symmetry. Their symmetry is rigorously a_g and b_u for homodimers. Each a_g fundamental appears directly in the spectra, but its b_u counterpart is combined with the cogwheel fundamental, forming a $\sim$44 cm^{-1} blue-shifted band.

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Identifying Neutral and Ionic Small Molecule Complexes in Solution by Electrospray Ionization Mass Spectrometry

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While electrospray ionization mass spectrometry (ES-MS) is widely used to detect and quantify protein-ligand complexes in solution, a significant challenge for the quantification complexes of small molecules (molecular weight <1-2 kDa) is distinguishing specific small molecule complexes (formed in solution) from nonspecific complexes (formed during the ES process). In the present study, a new methodology named nonspecific probe method for distinguishing specific small molecule complexes from nonspecific complexes observed in the mass spectrum was developed. The nonspecific probe method involves addition of a macromolecular probe (PNS) to the solution. The relative abundance of nonspecific complexes formed by PNS and clusters of small molecules during the ES process is compared to the expected statistical values. To validate the method, it was applied to several homogeneous and heterogeneous small molecules complexes including metal-EDTA, peptide-antibiotics and amino acid clusters.

Electronic Structure and Dynamics of Cytosine

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Three cytosine tautomers have been observed in the gas phase: the enol, keto, and keto-imino forms [1]. Existing sub-nanosecond time-resolved data in the literature were measured with an excitation wavelength of 250-267 nm and cannot be assigned to a single tautomer. Nevertheless, a large body of theoretical work is based on the questionable assumption that the reported data can be assigned to the biologically relevant keto tautomer. We disentangled the relaxation dynamics of the keto and enol tautomers by time-resolved mass [2] and electron spectroscopy with photoexcitation wavelengths in the range of 260 to 290 nm.

We observed three ionic transients with lifetimes of femtoseconds to hundreds of picoseconds for the biologically relevant keto tautomer. The electron spectra show broad, unstructured bands. The data could be assigned to internal conversion and excited-state tautomerization or intersystem crossing. Only two transients with femtosecond and picosecond lifetimes were identified for the enol or keto-imino tautomer and were assigned to internal conversion processes.

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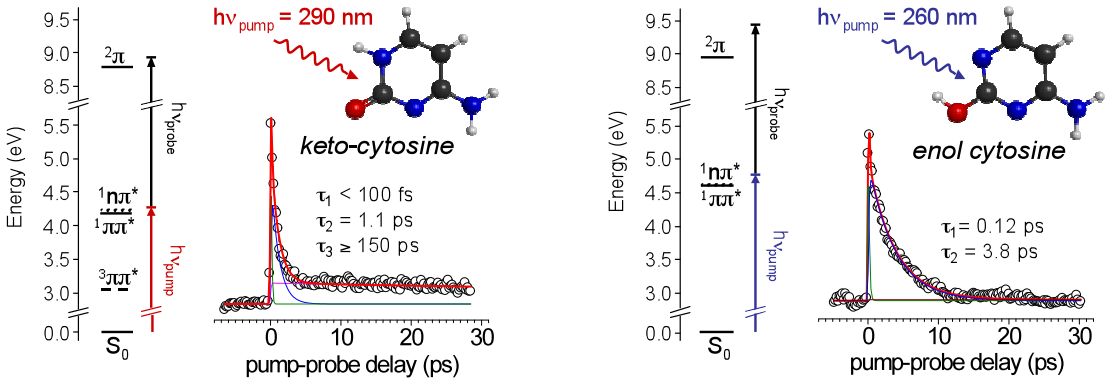

Information from the molecular frame

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Chemistry naturally occurs in the molecular frame, and many novel investigations aim at providing information directly from the molecular frame. These include, for example, ultrafast X-ray or electron diffraction and studies of the directional effects in reaction dynamics (stereodynamics). In order to experimentally obtain such data from molecular ensembles, one has to rigidly connect the laboratory and molecular frames.

Over the last years, we have developed the necessary techniques to perform such experiments: We have demonstrated the quantum-state and conformer-selection of large molecules using inhomogeneous electric fields [1]. We have successively demonstrated unprecedented degrees of laser alignment and mixed (dc-electric and laser) field orientation of these samples [2], rigidly linking molecular and laboratory frame.

We have now exploited these state-selected and oriented samples to measure photoelectron angular distributions in the molecular frame (MFPADs) from non-resonant femtosecond-laser photoionization. The obtained MFPADs show rich structure which provide information about the charge distribution and electrical properties of the molecule. Moreover, these MFPADs could provide detailed information on ultrafast molecular dynamics in future pump-probe experiments.

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Infrared spectroscopy of human bone marrow: evidence of structural changes during acute leukemia

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Fourier transform infrared (FTIR) spectroscopy was explored as a means to distinguish newly diagnosed of acute lymphoblastic leukemia from disease free bone marrow samples. Characteristic bands alterations were identified in both healthy and diseased samples arising from cellular protein, lipid and DNA. There were specific changes that affected the secondary structure of proteins that appeared in the FTIR spectra and confirmed with the second derivative analysis. The overall protein structure in the control sample consists primarily of α-helix, whereas in ALL sample it has a relatively high proportion of anti-parallel β-sheet protein constituents presumably due to leukemia. Different absorbance's ratios for specific bands were calculated and plotted versus the patient samples. There are significant fluctuations in the ratios under investigation which can be attributed to the changes in the biomolecular structure between normal and leukemia samples. Our results indicate that the absorbance of amide A and B are in the range 3,340-3,000, the lipid/protein ratio and the phosphate/amide II ratio are all yielding statistically significant differences parameters, that it can be used as a biomarker in differentiating acute leukemia from leukemia free bone marrow.

Keywords: FTIR spectroscopy; acute lymphoblastic leukaemia; human bone marrow; structural changes; quantitative analysis; infrared spectroscopy; biomolecular structure; biomarkers.

Catching proteins in liquid helium droplets

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The isolation of foreign species in liquid helium nano-droplets is of fundamental interest and has found important applications in molecular spectroscopy. Helium clusters have an internal equilibrium temperature of ~0.37 K, which is maintained by evaporative cooling.

Liquid helium is optically transparent from the deep UV to the far IR and superfluid helium droplets can serve as gentle matrices to provide an isothermal environment for embedded molecules at cryogenic temperatures. Further, due to the weak interactions of liquid helium, molecules embedded in helium nanodroplets can rotate freely and their optical spectra show narrow linewidths.

For studying molecules in helium droplets, a prerequisite is the ability to bring the intact molecule into the gas phase. For many interesting species such as most larger biomolecules, this can not be done via evaporation. Pulsed laser desorption is one other possibility, doing so, however, yields low concentrations in the gas phase as well as frequently a mixture of species that additionally contains decomposed molecules and matrix molecules. More promising would be to use established techniques, as for example electrospray ionization followed by mass separation, and to incorporate those mass/charge selected ions into helium droplets.

We here present an experimental approach in which mass/charge selected ions that are stored and accumulated in an ion trap are picked up by helium droplets traversing the trap. The approach is conceptually similar to pickup experiments of neutrals from gas cells, however a crucial difference is that in the case of the ion trap, use is made of the high kinetic energy of the heavy helium droplets, which allows ions only to leave the trap once they are inside a droplet.

It is demonstrated that droplets can be efficiently doped with a mass/charge selected amino acid as well as with the much bigger m ≈ 12 000 amu protein Cytochrome C in selected charge states. The sizes of the ion-doped droplets are determined via electrostatic deflection. Under the experimental conditions employed, the observed droplet sizes are very large and range, dependent on the incorporated ion, from 10^{10} helium atoms for protonated Phenylalanine to 10^{12} helium atoms for Cytochrome C.

Matrix Isolation Infrared Spectroscopic Investigation of the Thermal Decomposition of the Skin-Softening Agent Glyoxyldiureide

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Glyoxyldiureide (also known as allantoin) is a product of purine metabolism and known since long ago to exist in nature, for example, in allantoic and amniotic fluids, in fetal urine and in many plants and bacteria. Glyoxyldiureide is active in skin-softening and rapid skin cells regeneration. It removes corneocytes by loosening the intercellular kit or the desmosomes (protein bridges) that maintain the adhesion of corneocytes to each other. It then exfoliates dry and damaged cells and boosts the radiant appearance of the skin, whose surface becomes smoother and softer. Due to these properties, glyoxyldiureide has been used in cosmetic industry in several forms (*e.g.*, lotions, creams, suntan products, shampoos, lipsticks, and various aerosol preparations), as well as in topical pharmaceutical preparations for treatment of skin diseases for many years. From a more fundamental perspective, glyoxyldiureide is also an interesting compound, in which different types of intra- and intermolecular H-bond interactions can be expected to be relevant in determining its structural preferences, spectroscopic properties, and reactivity. In particular, the fragmentation reactions exhibited by the compound appeared to us particularly appealing for investigation since the structure of the glyoxyldiureide ring, with two sequential –C(=O)–N(H)– fragments, looked a good candidate to act as a precursor of isocyanic acid, a well known biologically pernicious substance that can easily react with amino terminus residues of proteins (or side chains of lysine and arginine residues) to form carbamoylated proteins, which have been observed in several states of disease. Hence, in the present investigation we have studied the thermal fragmentation of the compound taking place upon sublimation. The identification of the decomposition products was made by using matrix isolation infrared spectroscopy and quantum Density Functional Theory based calculations. In addition, we obtained and assigned the room temperature infrared spectrum of the compound. This enabled us to get information on the most relevant intermolecular interactions that stabilize the *g'C* conformer of the compound in this phase over the thermodynamically most stable *gC* conformer.

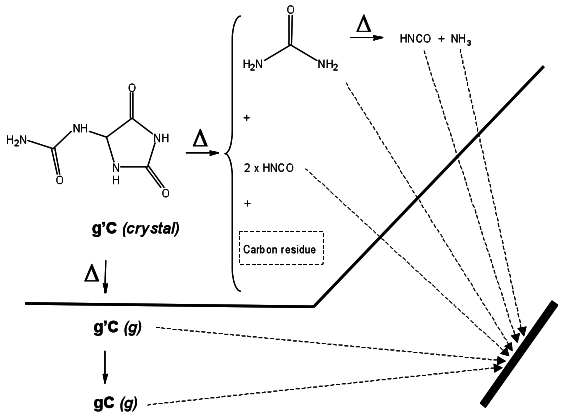

Figure 1.
Schematic representation of the observed thermal fragmentation processes and conformational isomerization of glyoxyldiureide.

IRMPD spectroscopy and quantum chemical calculations of protonated neurotransmitters in the gas phase: dopamine

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Neurotransmitters are chemical messenger compounds, which are responsible for signal transmission, enhancement and modulation between neurons via synapses. The catecholamine dopamine is one representative of the group of neurotransmitters. It affects brain processes that control movement and emotional response. At physiological pH (e.g. 7.4 in the blood) dopamine exists in its protonated form [1]. In the aqueous phase at pH 7, experiments and calculations indicate a nearly equal mixture of extended trans and folded gauche conformers, whereas in the gas phase calculations for neutral and protonated dopamine prefer the gauche conformation [2]. In contrast, the analysis of the crystal structure [3] and IR spectra of neutral dopamine [4] yield a trans conformation.
We present the first IR spectrum of isolated protonated dopamine in order to evaluate the preferred protonation site and the conformational structure in the gas phase. The IR spectrum was measured in the fingerprint range (570-1880 cm^{-1}) by means of IR multiple photon dissociation (IRMPD) using the free electron laser FELIX. The spectrum was recorded in a FT-ICR-MS equipped with an ESI source. This study is complemented by quantum chemical calculations at B3LYP and MP2 levels of theory using the cc-pVDZ basis set.
Several low-energy isomers with protonation at the amino group were predicted in the energy range 0-50 kJ/mol. The best agreement between the measured IRMPD spectrum and the calculated linear absorption spectra is observed for the conformer lowest in energy at both levels of theory. In this folded gauche structure, one of the three protons of the ammonium group is pointing toward the catechol subunit, thereby maximizing the interaction of the positive charge with the aromatic ring.
The calculated energetically preferred neutral structure of dopamine also possesses a gauche conformation. In contrast to the protonated species, the interaction with the aromatic ring is smaller, due to the smaller electrostatic interaction, and thus leading to longer bond distances between the proton of the amino group and the ring.

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IRMPD Spectroscopy on Protonated Purine Alkaloids in the Gas Phase

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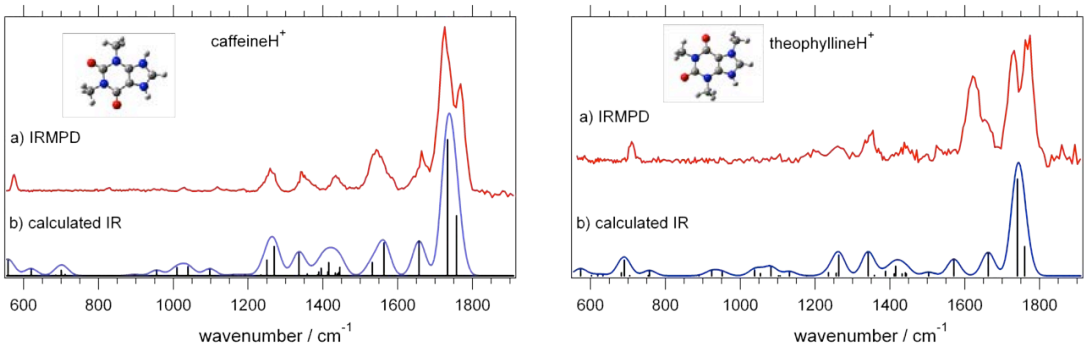
Caffeine is known as a psychoactive stimulant drug acting by blocking the adenosine receptors which are responsible for the protection of neurocytes to be overstrained. Theophylline, a demethylated derivate and degradation product of caffeine, shows pharmacological efficiency as active component, e.g., for relaxing the bronchial muscle (asthma). In solutions at acidic as well as basic pH values they can also be existent in the protonated state [1].

In this contribution we present the IR multiphoton dissociation (IRMPD) from the protonated caffeine and theophylline in the gas phase. The ions are produced via electrospray ionization, selected and trapped in a FTICR spectrometer before interacting with the IR free electron laser FELIX. The photodissociation spectra of the products and the depletion of the parent as function of the wavelength were measured simultaneously in the ICR cell.



The photodissociation process in caffeineH^+ leads to the loss of fragments having the masses 57 and 85 u. Both fragments can be associated to the rupture of the 6 ring system (57=$CONCH_3$ and 87=$CONCH_3CO$). In theophyllineH^+, we find 3 channels corresponding to losses of 57 ($CONCH_3$), 17 (OH, NH_3), and 102, indicating more complex rearrangements. In the figure the total fragment ion yields obtained for caffeineH^+ and theophyllineH^+ are presented. The structure of the parent species was identified by performing MP2 and B3LYP calculations at the cc-pVDZ level and comparing theoretical IR spectra of different isomers with the experimentally measured spectrum. The results confirm the protonation in caffeine and theophylline on the N(9) position, which corresponds to the formation of the energetically lowest-lying isomer.

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Supersonic Jet-Spectroscopy of the Deoxythymine Tautomers 5-Methyl-2-Hydroxypyrimidine and 5-Methyl-2-Pyrimidinone

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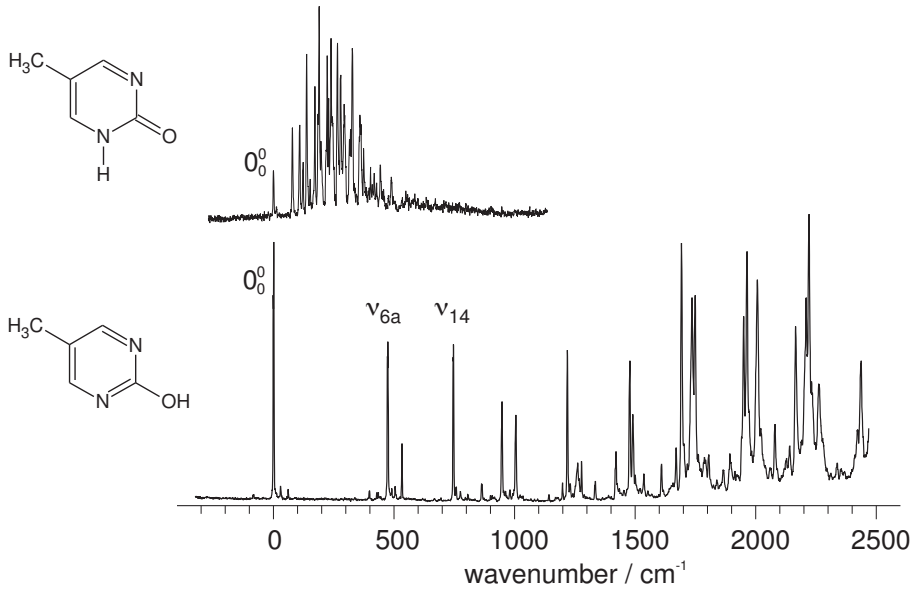
We have investigated the absorption spectra of supersonic jet-cooled 5-methyl-2-hydroxypyrimidine (5M2HP) [1][2] and 5-methyl-2-pyrimidinone (5M2P), the two tautomeric forms of deoxythymine, using two-color resonant two-photon ionization (R2PI) spectroscopy. Unlike uracil and thymine, which exhibit structureless optical spectra [3], the vibronic spectra of 5M2HP and 5M2P are well-structured with narrow vibronic bands, allowing to probe the excited state of a thymine analogue. The spectrum of 5M2HP shows strong in-plane benzene-type vibrations, extended progressions and combination bands up to $> 3\ 600\ \mathrm{cm}^{-1}$ whereas the spectrum of 5M2P breaks off $\sim 500\ \mathrm{cm}^{-1}$ above the electronic origin.



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Two Conformers of Acetyl Salicylic Acid in the Gas Phase

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The emergence of laser ablation molecular beam Fourier transform microwave (LA-MB-FTMW) spectroscopy has rendered accessible the gas-phase rotational study of solid biomolecules with high melting points, such as amino acids [1], neurotransmitters [2] or nucleic acid bases [3]. Among the molecules to benefit from this technique there are common important drugs never observed in the gas phase through rotational spectroscopy. We present here the results on a LA-MBFTMW study of acetyl salicylic acid, commonly known as aspirin. The polymorphism of aspirin is still an enigma despite numerous experimental studies [4] and its structure in the gas phase was still unknown. We have observed two stable conformers of aspirin which interestingly are stabilized by n-π* interactions. The barrier to internal rotation of the methyl group has been determined for both conformers from the analysis of the A-E splittings due to the coupling of internal and overall rotation.

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Towards fs time-resolved photoelectron spectroscopy of biomolecules in aqueous solutions

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The combination a liquid microjet with fs time-resolved photoelectron spectroscopy (TRPES) allows for the direct observation of transient electronic structure of molecules in solution. Photophysical processes in solvated chromophores are initiated by ultraviolet fs laser pulses and probed by time-delayed photoionization of valence electrons. We will present first TRPES studies of adenine and adenosine, which were excited by a 100 fs, 200 nm (6.20 eV) pulse and ionized by a 100 fs, 265 nm (4.65 eV) pulse. As an example, we show in Figure 1 the time-dependent photoelectron spectrum of a 2 mM aqueous solution of adenine. A detailed analysis of our data will be given and results will be discussed.

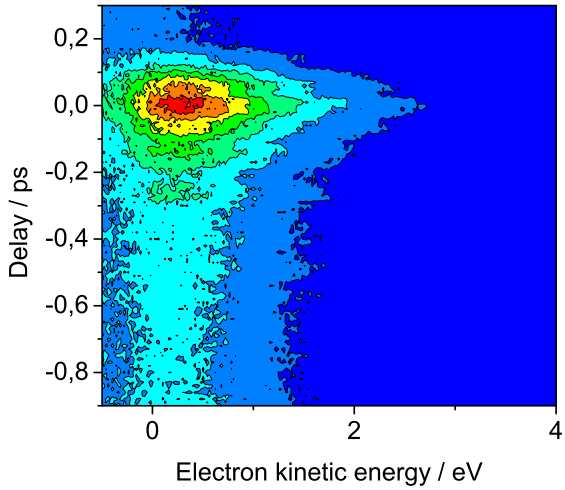

Figure 1: Time-resolved photoelectron spectrum of a 2mM aqueous solution of adenine.

Combining IRMPD spectroscopy and ion mobility mass spectrometry to improve structural insights on isolated Amyloid-β protein strands

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Amyloid-β protein strands are found in the brain of people affected by some neurodegenerative diseases such as Alzheimer's one. These strands can aggregate to form small toxic oligomers and then evolve into mature fibrils in which molecules have a β-sheet structure. A promising approach to tackle these diseases is to inhibit the formation of a β-sheet seed, it is thus crucial to improve insights on the structural properties of small oligomers and monomers. To date, most studies have dealt with amyloid-β strands in solution, which is the native environment of these systems. However, gas-phase techniques such as mass spectrometry allow controlling their stoichiometry and can give access to their intrinsic molecular properties. Most of the experimental gas-phase studies of amyloid-β protein have been carried out with ion mobility spectrometry (IMS) [1,2], which is very powerful but probes the global shape of the molecular system. Therefore, our approach is to combine IMS data with the results of Infra-Red Multi-Photon Dissociation (IRMPD) spectroscopy, which is directly sensitive to inter- and intramolecular interactions. Moreover, we interpret these data by means of molecular modeling, collision cross-section calculations and simulations of IR absorption spectra. Since DFT calculations are unaffordable for amyloid-β strands, we used a hybrid QM/SE method that we found to be reliable for the prediction of IR spectra of peptides [3]. The effects of charge state and molecule size on the structure of amyloid-β strands in the gas phase will be presented.

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Photoelectron spectroscopy of multiply negatively charged Cytochrom C

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UV photoelectron spectroscopy is a versatile tool to examine electronic structures of isolated and mass-selected anions without the perturbing influence of a matrix.

Multiply charged Cytochrom C in the gas phase was generated by electrospray ionization from a solution in methanol/ water. After desolvation of the solvent in a stainless steel capillary, the ions were transmitted through an electrodynamic ion funnel and accumulated in a hexapole ion trap for 33 ms. After passing the reflectron, mass-selected ions were decelerated before entering the detachment region of a magnetic bottle photoelectron spectrometer. Here they were irradiated with the fourth harmonic of a Nd:YAG (4.66 eV, 266 nm) . Arrival time distributions of the emitted electrons were measured and converted to energy spectra.

We present photoelectron spectra of the Cytochrom C with four up to twelve negative charges. From these spectra the adiabatic electron affinity and the repulsive Coulomb barrier can be directly extracted. Watching the evolution in the adiabatic electron affinity as a function of the charge state we could observe unfolding processes in the proteins. Our findings could be confirmed by comparing the experimental results with MD simulations.

Raman Spectral Signatures as Conformational Probes of Biomolecules

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A first application of ionization-loss stimulated Raman spectroscopy (ILSRS) for monitoring the spectral features of four conformers of a gas phase neurotransmitter (2-phenylethylamine) is reported. The Raman spectra of the conformers show bands that uniquely identify the conformational structure of the molecule and are well matched by density functional theory calculations. The measurement of spectral signatures by ILSRS in an extended spectral range, with a relatively convenient laser source, is extremely important, allowing enhanced accessibility to intra- and inter-molecular forces, which are significant in biological structure and activity.

ON-SPECTROMETER OPTIMISATION OF SOLID STATE NMR EXPERIMENTS USING SELF-LEARNING ALGORITHMS

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Nuclear Magnetic Resonance (NMR) spectroscopy relies on radio frequency (RF) pulse sequences to manipulate nuclear spin systems and extract structural information from the studied materials. Our first focus is the decoupling of protons in solid state alanine and glycine, since these model systems contain two of the strongest proton-proton couplings known. A combination of magic angle spinning and complex phase modulation of RF fields is able to narrow spectral line widths from two hundred to several kHz, revealing splittings that elucidate molecular structure in the solid state.

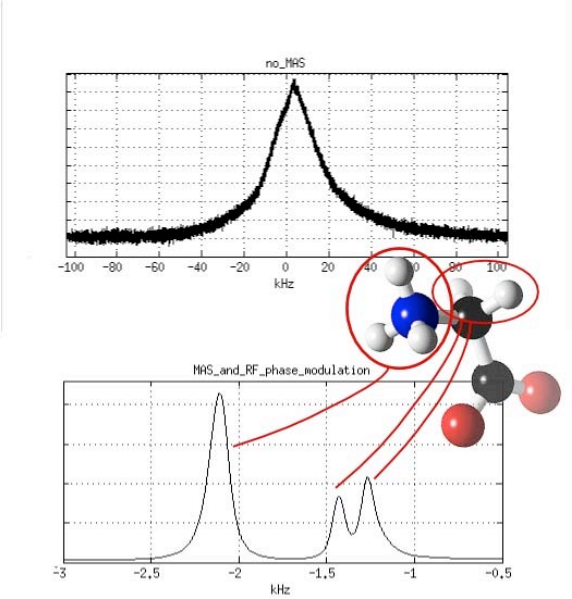

Figure 1 The resulted spectrum (below) of an optimization ^{1}H-windowed detection experiment on glycine. This optimization takes approx. 3 hours.

The complex multi-parameter nature of this problem inspired us to use evolutionary algorithms that are well suited to avoid local optima. Furthermore, an on-spectrometer approach gives valuable information on the role of experimental imperfections. We present our on-spectrometer optimization approach to enhance the performance of proton-proton decoupling RF sequences.

Peptide bond formation induced by slow multiply charged ions

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Recently, the study of irradiation damages induced in biomolecular systems has become a subject of special interest in the fields of physics and biology. In particular, ion-induced fragmentation of small biomolecules evaporated in the gas phase was studied with precise mass-spectrometric methods.

As amino acids constitute the building blocks of proteins, the study of the dissociation pathways of amino acids is a first important step for the understanding of more complex systems. Ion induced dissociation of such systems has been studied using highly charged ions delivered by the ARIBE facility at GANIL. A dedicated set-up is used for the irradiation of single biomolecules and clusters of biomolecules in the gas phase. The products of the reaction are mass over charge analysed using a time-of-flight spectrometer.

Recent experimental results concerning both alpha and beta alanine clusters have shown that chemical reactions may be induced by the interaction with highly charged ions. Especially, the formation of peptide bonds has been observed in the case of beta alanine clusters. However, this synthesis of stable protein molecules from amino acids clusters can only occur in very specific conditions (clusters size, configuration of the single molecule and of the molecules inside the clusters). Model calculations of the cluster configuration of both alpha and beta alanine could explain that peptide bond formation is only observed in the case of beta alanine.

Gas phase folding of a two-residue model peptide chain: interplay between experiment and theory

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Capitalizing on state-of-the-art techniques in laser spectroscopy and quantum chemistry, we have carried out a joint experimental/theoretical investigation on a flexible test molecule, aiming at an assessment of emblematic quantum chemistry techniques.

The 2-residue Ala-based model peptide chosen, Ac-$(Ala)_2$-OBzl (where Ac- and -OBzyl stand for N-acetyl and benzylester respectively), is short enough that it can still be tractable theoretically, whilst also containing both a ring phenyl and a flexible chain that allows it to experience dispersive effects and conformational diversity.

Two forms of comparable abundances, one folded and one fully extended, have been detected in the supersonic expansion after laser desorption, and characterized experimentally using UV and IR/UV spectroscopy.

The simultaneous observation of such very different conformations has led us to conclude the need to carefully consider three main effects when computing energies and conformations of such isolated peptides:

i) a good treatment of electronic correlation, required to handle dispersive interactions, for instance with M06-2X at the DFT level, or by empirical corrections, using a DFT-D approach (e.g. B97-D)

ii) intramolecular BSSE corrections, which account for the use of limited basis sets

iii) thermodynamic corrections at non-zero temperatures (~ 300 K), for a realistic comparison with experimental abundances.

Clearly, because of a large intramolecular BSSE, MP2 alone is shown not to be suitable for benchmarking energy surfaces and structures of such biological systems and should therefore not be taken as a reference method, especially when designing new generation force fields for biomolecules.

Analysis of big macromolecular soluble and membrane protein complexes for ESI-MS

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In recent years MS evolved into a powerful method to analyse the stoichiometry and connectivity of multiprotein complexes. This is usually achieved by controlled disassembly of the complex, either in solution or in the gas phase. However, with growing size and complexity of the assembly it gets increasingly difficult to obtain analysable datasets, not only for the complex itself but also for its constituting subcomplexes and subunits. A common approach to overcome these problems is to improve instrumentation in order to yield spectra of higher informational content. However, an often underestimated component is the quality data analysis. We present here a novel data analysis technique which can be used to obtain structural information about complicated and highly heterogeneous protein assemblies.
Experimental conditions were optimized to obtain spectra that contain variing sets of subcomplexes, by means of different solution disruption or CID conditions. For the thorough spectra analysis, a novel LabVIEW based software tool (*Mass*ign)is used, with which simulated spectra can be produced to resemble the experimental spectra. Peak series can be detected and compatible subcomplexes determined, taking subunit masses into account as well as mass shifts or differences in behaviour of soluble and membrane complexes. Dependencies of the charge state distributions of parent complexes, dissociated subunits and subcomplexes can be included or where applicable known restraints regarding allowed/forbidden subunit combinations.
The approach of producing mass spectra of large complexes and their subcomplexes and simulating them with *Mass*ign has been very successful for different biological systems. Up to now several macromolecular assemblies - soluble as well as membrane complexes - have been analysed this way, such as different ATPases, Polymerases or the spliceosomal U1snRNP. The simulations can be used for qualitative, and where applicable, quantitative analysis of the spectra. Simulation of the spectra enables a more complete analysis of all subcomplexes than is possible with standard programs. Even peak series with low intensity and/or considerable overlap with other species can be extracted from an experimental data set. Considering charge state distributions of parent complexes, CID sub complexes and dissociated subunits is often the only way to assign a peak series to the correct subcomplexes, particularly where several possible subunit combinations differ in mass by less than can be resolved. Compositional changes depending on time, collision energy etc can be followed automatically over spectra series. The dissociation pathways of different complexes could be determined for several VoV1 as well as FoF1 ATPases as well as Polymerase I and III. Conclusions about assembly pathways could be drawn and information about the stoichiometry and connectivity of subunits could be deduced, where not known before. Such an interpretation was not possible using standard software packages.

Spectroscopy of isolated and solvated forms of protonated gramicidin S in the gas phase

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We employ an IR-UV laser double resonance photo-fragmentation approach to measure conformer-selective IR spectra of protonated natural antibiotic gramicidin S (GS), isolated in the gas phase. Cooling ions to ~10K greatly suppresses thermal congestion and allows us to measure vibrationally resolved UV spectra and highly-resolved, conformer-specific IR spectra of singly and doubly protonated bare GS as well as its complexes with up to 14 water molecules. The obtained spectroscopic data indicate significant difference in the structures of the bare singly and doubly protonated GS, suggesting a highly symmetrical (C_2) structure of the doubly protonated species. The constraints provided by our highly-resolved spectra serve as a challenging benchmark for the computations of peptides structures.

Gradual solvation of GS in water results in a distinct alternation of spectroscopic signatures of these species. Nevertheless, even for the largest studied complex with 14 H_2O molecules frozen on GS the measured spectra exhibit, in main, vibrationally resolved structures. The detailed analysis of these spectra, which is still under way and which requires a great computational support, may shed some light on the key to the field question of relevance of the gas-phase spectroscopy to peptide structures in solutions.

Molecular dynamics and elementary processes involved in damage induced by synchrotron radiation in the soft X-ray regime on biomolecules

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Biological consequences of ionizing radiation on living organisms result from physical processes taking place in the early stages following exposure. The identification and the understanding of these primary physical events are important for the building up of knowledge in radiobiology.

A novel research program, concerning the interaction between gas phase biomolecules and soft X-rays delivered by the synchrotron light source SOLEIL, will be carried out on the PLEIADES beamline.[1]

Although not best suited to radiation therapy, soft X-rays have been shown to be a unique tool to understand the early stages of DNA damage by ionizing radiation. Tuning the photon energy enables either to target specific DNA atoms and/or to select the energy of the secondary (Auger associated to various thresholds and photo-) electrons emitted. Synchrotron radiation, with its continuous spectrum over a wide photon energy range is thus the appropriate light source for such studies. Due to the increase by a factor two of the yield of inner-shell ionizations in DNA, Fayard et al. have shown for example that soft X-rays above the C-K threshold are twice more efficient at cell killing than below it.[2] Moreover, atomic inner-shell relaxation in biomolecules creates localized ballistic electron sources via the production of Auger electrons. Studies have shown that such electrons, even with kinetic energies as low as 3 eV, can efficiently induce single and double strand breaks in DNA. In addition, specific fragmentation of the core ionized molecule may occur.

The sophisticated spectroscopic tools and methodologies available on the beamline, like photoelectron spectroscopy or Auger electron/ion coincidences, combined with tunable soft X-rays delivered by SOLEL will make possible the determination of the energy distribution of the ejected electrons for a specific dissociation channel of the biomolecule, or the different electronic states involved in this break down. Those measurements should be very helpful as new inputs in radiation damage models. Stability of elementary bricks of DNA or polypeptides will be investigated together with the resonant processes or the opening of new dissociation channel that will be quantified.

Preliminary results on the fragmentation of Uracil molecule around different thresholds will be shown. Let's also emphasize that experimental data on such complex systems need molecular dynamics simulations for an accurate interpretation.

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Alternate Dissociation Pathways Identified in Charge-Reduced Protein Complex Ions

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Tandem mass spectrometry (MS) of large protein complexes has proven to be capable of assessing the stoichiometry, connectivity, and structural details of multi-protein assemblies [1]. While the utility of tandem MS is without question, a deeper understanding of the still controversially discussed mechanism of protein complex dissociation will undoubtedly drive the technology into new areas of enhanced utility and information content.

We present here the systematic analysis of the charge state dependent decay of the non covalently associated complex of human transthyretin (TTR), generated by collision induced dissociation (CID). A crown ether-based charge reduction approach was applied to generate intact transthyretin tetramers with charge states ranging from 15+ to 7+. These nine charge states were subsequently analyzed by means of tandem MS and ion mobility spectrometry. Three different charge-dependent mechanistic regimes were identified: 1) Ions with a charge above 12+ followed the commonly observed CID dissociation pathway resulting in highly charged, unfolded monomers and compact, charge-stripped trimers [2]. 2) Tetramers with charge states between 11+ and 9+ still dissociated into monomer and trimers, but the expelled monomers were carrying fewer charges and retained their compact, native-like conformation. 3) 9+ and 8+ ions primarily yielded C-terminal peptide fragments which were cleaved from intact and fully folded TTR tetramers. Ions with a charge below 8+ were virtually indestructible in the instrument and neither showed signs of dissociation nor unfolding.

Taken together, the results presented highlight the potential of charge state modulation as a method for directing the course of gas phase dissociation and unfolding of protein complexes. Particularly noteworthy is the fact that under certain conditions the remaining stripped complex, as well as the departing subunit, retain compact, native-like structures. This has implications for various gas phase-spectroscopic and structural biology experiments in which maintaining conformations close to the native state is of paramount importance.

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Low-energy electrons breaking molecular bonds in phospholipids

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Owing to the vast number of metabolic processes that can lead to potentially damaging radiation effects, the cell membrane with its highly ordered structure and complex functionality presents an important target in radiobiology (for example, DPPC is a major component of the highly radiation sensitive lung tissue,) and a perfect "live model" of a biosensor. Low-energy electrons are proved to be the most abundant secondary species created in the irradiation of the living tissue by high-energy ionizing radiation (X- and γ – rays, ions, etc), creating reactive molecular fragments from nucleic bases [1] and breaking the strands of the DNA [2], but also proved to be an efficient tool in production of bio-chips on the SAM structure [3]. We are seeking information about the suitability of the phospholipid films as a potential substrate for deposition of another set of molecules, such as amino-acids, short peptides and oligonucleotides, all of which are basic constituents of the cell.

Chemical changes in phospholipid (DPPC – 1,2-dipalmitoyl-sn-glycero-3-phosphocholine) monolayer films deposited on a solid substrate are studied in an X-ray photoelectron spectroscopy experiment. DPPC films have been irradiated by a monoenergetic electron beam in the energy range from 5 to 200 eV. The shifts in the binding energy of C 1s, O 1s, P 2p, and N 1s atoms, as well as the change in their intensity, were observed before and after electron irradiation. We show that the electrons with energy between 20 and 100 eV have the largest effect on DPPC, mostly stripping off the protons from the tails and breaking the COO- bond in the head of the molecule, but also releasing methyl group from the choline group (N-$(CH_3)_3$). The least effect of electron irradiation is shown on the P 2p band, regardless of the incident energy, which may be linked to the orientation of the DPPC molecules and additional intramolecular bonding.

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Using differential ion mobility for conformer selection in cold ion spectroscopy

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As the size of biological molecules increases, their electronic spectra become increasingly complex, making the implementation of conformer specific IR-UV double-resonance spectroscopy difficult. A major source of this complexity comes from the presence of multiple stable conformations that have different but partially overlapping electronic spectra. If one could manage to separate conformers before performing spectroscopic measurements, it would allow the extension of spectroscopic techniques to much larger molecules.

Toward this end we use Field Asymmetric Ion Mobility Spectrometry (FAIMS) as a filter to select certain conformations of peptides before putting them into a cold ion trap for spectroscopic analysis. FAIMS separates conformers on the basis of the difference of their ion mobility at high and low electric field [1]. Previous work using H/D exchange has demonstrated that FAIMS is able to separate conformers of doubly charged bradykinin [1, 2]. We present here our most recent results using electronic spectroscopy of doubly charged bradykinin in a cold 22-pole ion trap to evaluate the ability of FAIMS to separate conformers and hence simplify the spectrum.

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Photofragmentation dynamics of small protonated biomolecules

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UV photofragmentation is used to characterize physico-chemical properties of molecules containing chromophore. Our group is involved in Photo-Induced Dissociation of small protonated biomolecules.

After a 263 nm UV laser irradiation, protonated molecules formed by ElectroSpray can dissociate following several pathways. These pathways are generally identified in mass spectrometry using mass measurement of ionic species. However, the detection of only final ionic fragments doesn't give mechanistic and dynamic (< 1 µs) information. With our experimental set-up, for each channel, ionic and neutral(s) fragments are detected in coincidence. It is possible to determine whether the fragmentation takes place in one or several steps and step timings are evaluated from nano- to microsecond time scale.

We recently developed an interpretation of various fragmentation pathways of small peptides (di- and tripeptides) similar to a previous work on protonated tryptophan [1]. Laser induced fragmentations can be explained by two types of mechanisms: statistical fragmentation occurring in the ground state after internal conversion or direct fragmentation, specifically photo-induced, triggered by photo-active electron migration and followed by a proton transfer [2].

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Water In-take Mechanism Observed in Secretory Phospholipase A_2

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Secretory phospholipase A_2 ($sPLA_2$), an enzyme implemented in several human diseases, cleaves the *sn*-2 acyl ester bond of glycerolphospholipids to produce free fatty acids and lysophospholipids [1,2]. The enzyme is also able to hydrolyze a range of phospholipid analogues at different rates [3-5]. The molecular origin for the observed different catalytic efficiencies is not well understood. To gain further insight, it requires studying the individual steps in the reaction pathway of the enzyme-catalyzed reaction. In the present study, we focus on the molecular machinery enabling water conductance in $sPLA_2$. A series of molecular dynamics (MD) simulations on $sPLA_2$ complexed with the enzyme's natural substrates or chlorambucil phospholipid prodrug were performed and the water path into the active site was mapped. The MD simulations revealed that a hydrogen bonding network connected to a hydrophobic channel is important for the access of water molecules. An aspartic acid residue (Asp^{91}), which is part of a hydrogen bonding network, provides electrostatic attraction for water molecules. Once entering the protein structure, water molecules diffuse into the hydrophobic channel where the highly conserved aromatic residues Phe^5 and Tyr^{51} were found to play an important role. The orientation of the aromatic rings diverts the flow direction of incoming water molecules towards the catalytic residue His^{47}. In the $sPLA_2$-prodrug complex simulations, the size of the hydrophobic channel is slightly increased due to the relatively bulky drug covalently attached to the *sn-2* position of the phospholipid. The widening of the channel does not affect the orientation of Phe^5, and hence water molecules can freely reach the catalytic site. These observations suggest that all substrates should be efficiently hydrolyzed by $sPLA_2$, which is shown to be in good agreement with experimental data comparing the hydrolysis of the natural substrates and phospholipid prodrug by human $sPLA_2$. Thus, the MD simulations suggest a molecular mechanism behind the water flow towards the catalytic site involving highly conserved amino acid residues, and this knowledge is essential in guiding future efforts in phospholipid-prodrug design.

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Large-Amplitude Vibrations of an N-H$\cdots\pi$ Hydrogen Bonded Cis-Amide - Benzene Complex

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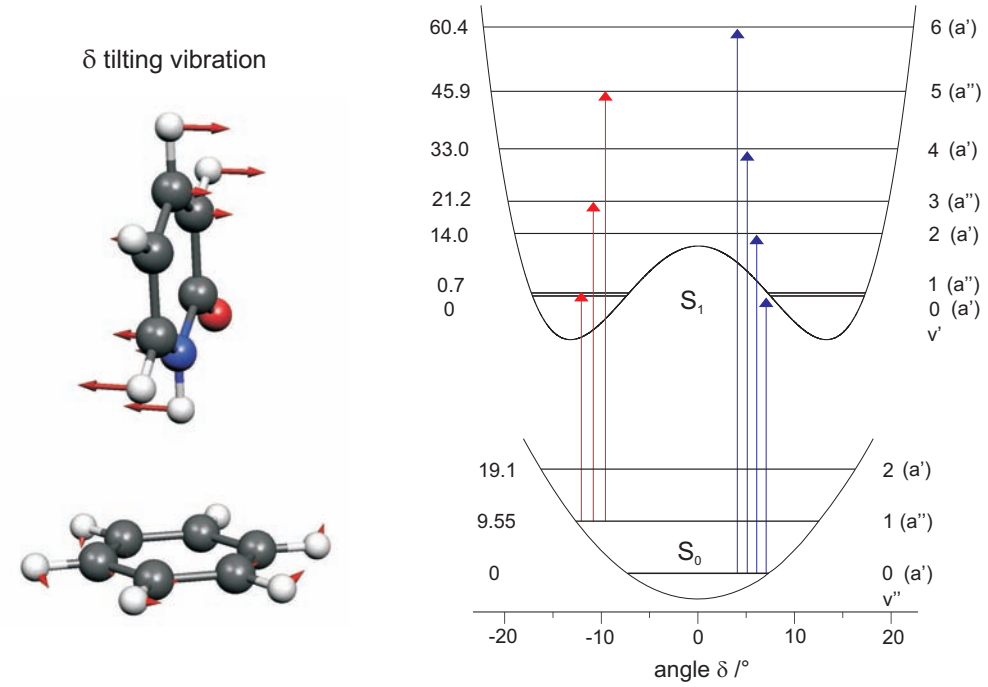
We have investigated the large-amplitude vibrations of supersonically cooled 2-pyridone·benzene in the S_1 state, using two-color resonant two-photon ionization spectroscopy. RI-CC2 and SCS-RI-CC2 calculations of the S_1 state predict a tilted T-shaped structure with an N-H$\cdots\pi$ hydrogen bond to the benzene ring, similar to the S_0 state [1]. The vibronic band structure up to 60 cm^{-1} above the electronic origin is dominated by large-amplitude δ tilting excitations, reflecting a change in the tilt angle. The S_0 and S_1 state δ potentials were fitted to experiment, yielding a single minimum in the S_0 state and a double-minimum S_1 potential with $\delta_{min}= \pm 13$ degrees. Weaker excitations of the second large-amplitude vibration, the θ twisting or benzene internal-rotation mode, are also observed.



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Folding patterns within long chained peptide systems.

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The secondary structure of a protein has a significant effect on its overall shape and function. In recent years many studies have investigated the secondary structure of proteins by concentrating on short peptide chains in a gas phase environment [1]. Similar systems were investigated a number of decades ago in solution, however, these recent gas phase studies allow the role that local interactions play in the folding of these peptide chains to be investigated in solvent-free environment expected to more closely represent the hydrophobic medium found within a protein interior or lipid membrane.

In the current work IR/UV double resonance spectroscopy has been utilized to investigate gas phase intra-molecular interactions within long chained peptides. Owing to the flexible nature of these long chained peptides a number of significant minima are accessible and so state-of-the-art quantum chemical calculations have been employed to aid in the assignment of the experimentally observed conformers. Knowledge of the conformers present allows interactions important in the folding of the peptide chain to be determined.

The results of this work extend the wealth of data on short peptide chains and allows the folding patterns within longer peptide chains to be observed emphasizing the importance of fundamental interactions in determining the secondary structure of proteins.

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Specific interactions between Vancomycin antibiotic and a cell-wall precursor in the gas phase probed by IRMPD spectroscopy and ion mobility mass spectrometry

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Vancomycin is a naturally occurring glycopeptide antibiotic active against Gram-positive bacteria and is considered as a drug of last resort for the treatment of penicillin-resistant *Staphylococcus aureus*. Vancomycin binds to the bacteria cell-wall peptidoglycan precursor through noncovalent interactions involving its C-terminal part containing the ^{D}Alanyl-^{D}Alanine sequence. Vancomycin and its peptide receptor analogue $Ac_2{}^{L}K^{D}A^{D}A$ have been widely used as a model system for investigating biomolecular recognition properties through pure mass-spectrometric approaches. In particular, the fragmentation energetics of these complexes strongly changes from protonated to deprotonated species, although no direct structural investigation has been yet carried out. We are thus mostly concerned with the binding site of the receptor peptide to vancomycin and more precisely to question whether the structure known in the condensed phase is preserved upon desolvation during electrospray.

Biomolecular recognition of Vancomycin with its cell-wall precursor analogue $Ac_2{}^{L}K^{D}A^{D}A$ has been investigated in the gas phase through a combined laser spectroscopy (IRMPD), ion mobility mass spectrometry (IMS) and theoretical modeling approach. The two experimental methods are highly complementary: the global shape of the system is probed by ion mobility, and IRMPD spectroscopy is directly sensitive to the intra- and inter-molecular interactions. The low-energy conformers obtained from replica-exchange molecular dynamics (REMD) simulations were filtered by the ion mobility data. Structural assignment has been achieved through comparisons between the IRMPD spectra and scaled harmonic normal mode frequencies calculated using a hybrid quantum mechanics/semi-empirical (QM/SE) method at the B3LYP/6-31+G*:AM1 level [1]. Both theoretical and experimental findings provide strong evidence that the native structure of the $V+Ac_2{}^{L}K^{D}A^{D}A$ complex is only preserved in the deprotonated species and is lost in protonated complexes [2,3].

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Adsorption geometry of thymidine on Au (111) surface: experiment and computational modeling

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The chemical properties of DNA and DNA subunits (such as nucleobases, nucleosides and nucleotides) on surfaces are of great interest from nano-technology point of view. They can be consider as a potential candidates as a building blocks of molecular systems of "nano-electronics" [1]. In the present studies the electronic structure and absorption geometry of thymidine molecules (dT) on a gold surface were investigated at different coverage, i.e. mono-and multi-layers. The structure of thymidine consists of the thymine base linked to a sugar molecule (deoxyribose) via a C-N glycosidic bond. The changes of chemical states were identified by measuring of valence and X-ray photoelectron (XPS) spectra of thymidine deposited onto the Au (111) crystal. In addition near-edge X-ray absorption fine structure spectroscopy (NEXAFS) allowed a determination of the adsorption geometry and the empty state electronic structure of this complex. Moreover computational modeling of thymidine on Au (111) crystal has been performed by using Adsorption Locator module included in Accelrys Software Inc. Analysis of experimental results and geometries obtained from calculations has shown that the thymine moiety strongly interacts with Au surface while the sugar moiety not so significantly.

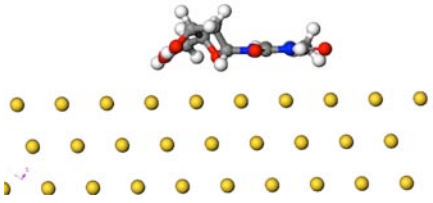

Fig.1 Adsorption geometry of Td on Au (111)

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Charge transfer in neutral peptides:
the appearance of salt bridge structures

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The biological function of a protein is determined by its three-dimensional structure, which results from a subtle combination of intrinsic conformational preferences and interactions with its biological environment. To fully understand the biological function, the intrinsic properties of isolated parts of proteins -single amino acids and small peptides- have extensively been studied in the past few years, mainly by vibrational spectroscopy. Particularly, the combination of IR-UV ion-dip spectroscopy with laser-desorption molecular beam techniques has recently yielded detailed insights in their secondary and tertiary structure. Additionally this technique offers the possibility not to only study the isolated peptides, but also to controllably add elements of the environment such as water or metal ions. For example, metal-ion complexation and the formation of salt bridge structures play an important role in proteins, enzymes and other amino acid based biomolecules. Peptide-metal complexes are a key factor in processes such as structural support, catalytic cycles and the function of ion channels.

A crucial discrepancy between the gas-phase structure of isolated peptides and their biologically relevant counterparts is the transition from the non-zwitterionic, canonical, to the zwitterionic form. Whereas neutral, isolated peptides have always been found in their canonical form, in their natural environment charge-separated structures play an important role. Recently, it has been shown that it is possible to generate and investigate such neutral charge-separated structures in the gas phase (i) by specific peptide design and (ii) by alkali metal ion complexation that gives rise to salt bridge structures. At the same time, by controllably adding metal ions, we can study there influence on the conformational structure of the peptide.

To reveal the presence of zwitterionic structures and to elucidate the influence of the biological environment, IR ion-dip spectroscopy is used on individual, isolated peptides and their clusters with various metal ions. Ground state vibrational spectra in the mid-IR region are sensitive to the hydrogen-bonding network present in the peptide via the frequencies and intensities of the Amide I (C=O stretching) and Amide II (NH bending) vibrations. Additionally, the presence of zwitterions can directly be probed by IR spectroscopy, since the free C=O stretching mode in the 1740 to 1800 cm^{-1} region offers an unambiguous signature of the group being present in the carboxylic acid (C=O) form or the carboxylate (COO^-) form. To elucidate the conformational structure of the peptides, the IR spectra are compared with quantum chemical calculations.

Conformer-specific spectroscopy and fragmentation dynamics of helical peptides in a cold ion trap

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Recent work in our laboratory has focused on conformer-specific spectroscopic studies of helical peptides in a cold, 22-pole ion trap [1, 2]. In this work, spectroscopic detection is achieved by detecting photofragments subsquent to UV absorption, or in the case of IR-UV double resonance, by an IR-induced decrease in the photofragmention signal. In some cases we use IRMPD to assist the fragmentation process [3].

We present here an analysis of possible mechanisms of UV-induced fragmentation and explore the basis on which this fragementation signal is enhanced by IRMPD. We also examine the mechanism of IR-UV double resonance by examining small helical peptides with multiple chromophores.

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Stability and (un)folding of a peptide helix in the gas phase from first-principles: Ac-Ala$_{15}$LysH$^+$

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Peptides in vacuo offer a unique, well-defined test bed to match experiments directly against first-principles approaches that predict the intramolecular interactions governing peptide and protein folding. In this respect, the polyalanine-based peptide Ac-Ala$_{15}$-LysH$^+$ is particularly interesting, as it is experimentally known to form helices in vacuo, with stable secondary structure up to ∼750K [1]. Room-temperature folding and unfolding timescales are usually not accessible by direct first-principles simulations, but this high T scale allows a rare *ab initio* view. We here use van der Waals (vdW) corrected [2] density functional theory in the PBE generalized gradient approximation as implemented in the all-electron code FHI-aims [3]. We show by long Born-Oppenheimer *ab initio* molecular dynamics that Ac-Ala$_{15}$-LysH$^+$ indeed unfolds rapidly (within a few ps) at T=800K and 1000K, but not at 500K. Most importantly, the observed stability depends critically not just on a correct inclusion of H-bonds and the designed termination effects, but also on vdW interactions. If these are *not* properly included, the helix unfolds already at 700K and the strcutural stability at 500K is mostly 3_{10}-helical, in disagreement with experiments; when vdW is included, the temperature stability is raised and the α-helical structure is stabilized at lower temperatures.

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Alkali metal cationized aliphatic amino acids: charge-solvation becomes more favorable with increasing ion size

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Structures of alkali metal cationized amino acids fall in two main categories, being charge-solvated (CS), where the charge is solvated by the Lewis basic sites of the amino acid, or salt-bridge (SB), where the amino acid adopts a zwitterionic structure and the metal ion interacts predominantly with the negative carboxylate moiety. The thermodynamic balance between these two motifs has been the subject of many investigations, recently involving also IR ion spectroscopy. As a general trend, it was found that most amino acid alkali metal ion complexes possess a CS structure. Moreover, the SB structure becomes more favorable with increasing metal ion size. Here we show that this latter trend is opposite for aliphatic amino acids.

Infrared ion spectra of alkali metalized amino acid complex ions are recorded via IR multiple photon dissociation using the wavelength tunable free electron laser FELIX (1000 to 1800 cm^{-1}). The experimental IR spectra are compared to DFT calculated spectra for different candidate structures to identify the structure present. IR spectra for the series of alkali metal ions Li^+ through Cs^+ with proline and *N*-methyl alanine were recorded.

The IR spectra of both series of complexes show similar trends. The complexes with Li^+ and Na^+ exhibit a single strong band in the 1600-1800 cm^{-1} range, which is due to the anti-symmetric stretch mode of a carboxylate moiety, indicating the presence of an SB isomer. For complexes with K^+, a second band appears as a blue-shifted shoulder and the relative intensity of this shoulder increases for complexes with Rb^+ and Cs^+. This band is due to the CO stretch of a carboxylic acid moiety, diagnostic for a CS structure. Hence, for small metal ions exclusively SB structures are formed while for increasing metal ion size, a CS structure becomes gradually more favorable. This trend is opposite to what has been observed for functionalized amino acids.

The opposite trends in stability are explained by two competing effects. The decreasing polarizing effect of metal ions with increasing size tends to favor the stability of CS structures for larger metal ions, as is observed here for the aliphatic amino acids. On the other hand, efficient charge-solvation by the Lewis-basic groups of a functionalized amino acid is sterically more favorable for a smaller cation, explaining the trend observed for amino acids with a heteroatom or aromatic moiety in their side chain.

NOVEL ASPECT

Stability trend of charge-solvated versus salt-bridge structures in alkali metal cationization is reversed for aliphatic versus functionalized amino acids

VUV photodissociation and keV ion-induced dissociation of protonated leucine enkephalin

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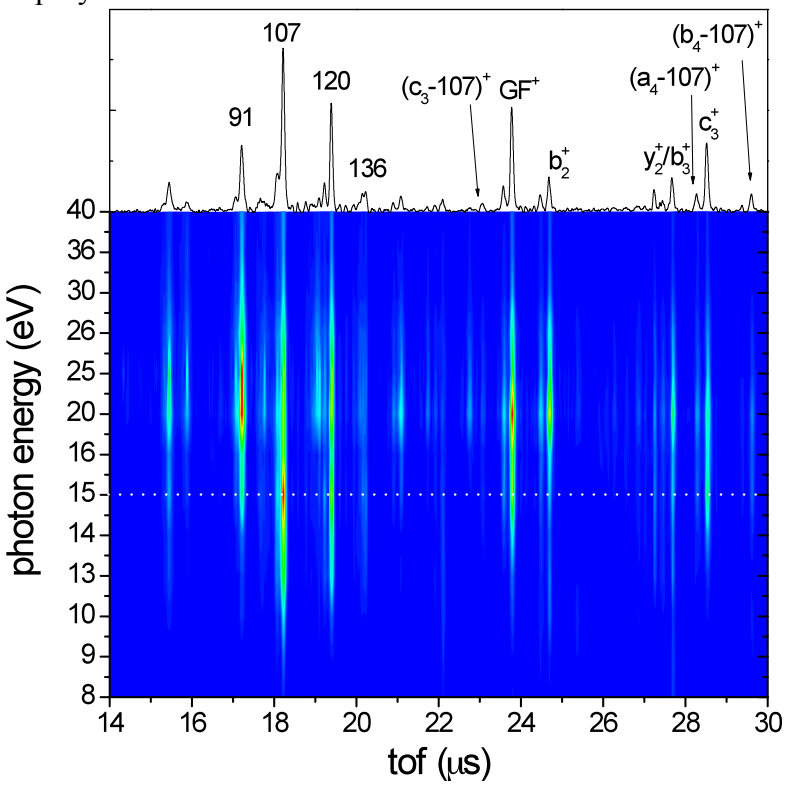
Dissociation of mass-selected peptide ions is a basic technique for peptide sequencing and protein identification by means of mass spectrometric techniques. To drive the dissociation processes, excitation by multiple collisions with inert gas atoms (collision induced dissociation, CID) or surfaces (surface induced dissociation, SID), by electron capture (electron capture dissociation, ECD) and by blackbody infrared radiation or laser light has been employed.



Time of flight spectra of leucine enkephalin photodissociation products. The spectrum on the top corresponds to the 15 eV dotted white line.

We have developed a new apparatus in which protonated leucine enkephalin ions produced in a home built electrospray ionization are transported and mass-filtered by two RF-quadrupoles and subsequently collected and cooled in a Paul trap to accumulate sufficient target density. The trapped biomolecular ions are then irradiated with keV ions or with VUV photons from the U125/NIM beamline at the BESSY II synchrotron. Interaction products are extracted into a time-of-flight mass spectrometer to investigate the ionization and fragmentation pattern.
In contrast to conventional excitation techniques, sidechains dominate the fragment mass spectrum for both VUV photons and keV ions [1]. Backbone scission is a relatively weak channel. A pronounced dependence of the fragmentation pattern on the electronic structure of the projectile ions as well as on the photon energy can be attributed to electron removal from localized molecular orbitals.

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Relating vibrational spectra and conformational structures of small model peptides: From gas phase to microclusters

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Biopolymers such as peptides and proteins are known to exist in a huge number of conformational structures, even for rather short sequences of amino acids. Typically, these molecules exhibit meta-stable behavior with large but rare jumps between different basins of the underlying potential energy surfaces. A microscopic understanding for the driving force of bio-molecular conformations is often hampered by the coexistence of intra- and intermolecular forces. In recent years, the advent of gas phase experiments of small peptides with a controllable number of attached solvent molecules, accompanied by corresponding computer simulations, opens the way to detect meta-stable bio-molecular conformations to separate effects from intra- and intermolecular interactions.

In our present work, the tri-peptide Z-Aib-Pro-NHMe is chosen as a model system with almost iso-energetic β- and γ-turn structures coexisting even at low temperatures. In UV/IR double resonance experiments vibrational spectra (mainly amide I, II, III modes) were obtained for individual conformations [1]. Quantum-chemical DFT and MP2 methods have been used to locate a large number of minimum energy structures exhibiting different H-bonding patterns as well as transition states connecting the different minima. The transition between the γ-turn structure preferred in gas phase and the β-turn structure preferred in solution is found to occur in our micro-solvation studies already upon going from one to two solvent particles [2].

In addition, trajectories based simulations are used to extract information on molecular conformations at higher temperatures. While conventional molecular simulations of Z-Aib-Pro-NHMe suffer more (AMBER) or less (MMFF) from the quality of the underlying force fields, *ab initio* molecular dynamics simulations (AIMD) lend themselves as an alternative [3]. For the system under investigation, DFT-based trajectories of a few pico-seconds length could be generated for different temperatures. Meta-stable molecular conformations with corresponding lifetimes and free energies could be extracted by means of various geometric and dynamic clustering techniques [3].

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The benzene dimer – a floppy symmetric top

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Interactions between aromatic systems are nowadays known to play an essential role in determining protein and DNA stability and DNA-protein interaction. In particular, two competing structures of aromatic complexes are observed in nature: the so-called edge-to-face and the (offset-)stacked one. Their relative stability is crucial in explaining the preference of specific protein structures in nature.
The benzene dimer can be seen to be the prototypical system to study such interactions between aromatic systems, which are governed by dispersion forces. It exhibits two competing low-lying equilibrium structures, a T-shape one (corresponding to an edge-to-face arrangement) and a parallel-displaced one (corresponding to a stacked arrangement). Both the subtle binding energy difference between these two structures and the complex intramolecular dynamics are particularly challenging and have received much attention. By now, both experimentalists and theorists agree that the T-shape structure is the global minimum on the extremely flat potential energy surface of the benzene dimer. However, its complex internal dynamics is not understood to date.

We are approaching this using a tight combination of high-resolution rotational spectroscopy, permutation-inversion group theory and high-level ab initio bound-state calculations of the vibration-rotation tunneling states. In agreement with the only other microwave study existing in the literature, we find a group of microwave transitions, which fit a symmetric-top Hamiltonian. It consists of a quartet fine structure with a characteristic intensity and splitting pattern originating from the rich internal dynamics of the benzene dimer. Our study is complemented by additional Stark effect measurements to analyze the torsional components and to determine the dimer's dipole moment. To better understand the complex internal dynamics, we extend the work to the isotopologue C_6H_6-C_6D_6. On the poster, we will present our recent results and shed new light onto the complex internal dynamics of the benzene dimer.

CRASY: Correlated Rotational Alignment Spectroscopy

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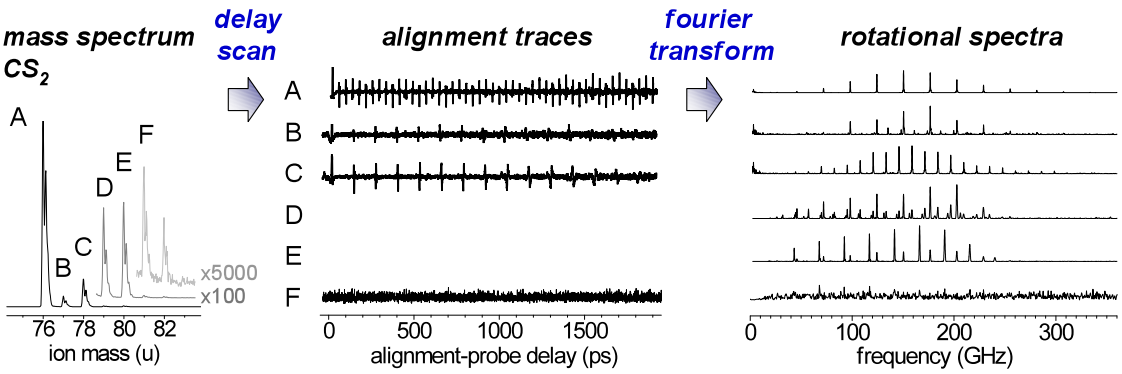
Femtosecond time-resolved pump-probe-spectroscopy allows the observation of photochemical reactions in real time: Photoexcitation of an initial state in a chromophore creates an excited state population at a well-defined moment in time. A time-delayed projection of the evolving excited state onto an observable final state creates a signal which reflects all excited state processes. We perform pump-probe ionization spectroscopy of isolated molecules and clusters. The detection of ion masses allows the characterization of chromophore composition and fragmentation processes, while the measurement of electron kinetic energies allows the assignment of the evolving electronic states. The investigation of increasingly complex (biological) systems, however, is hampered by the abundance of structural isomers, tautomers and isotopes in larger systems.

We developed a CRASY spectroscopic method to overcome this limitation. Our method combines rotational spectroscopy in the time domain with femtosecond-pump-probe experiments. An infrared pulse generates a coherent rotational wave packet by means of non-adiabatic alignment. After a variable delay, we probe the wave packet dynamics by ultraviolet pump-probe ionization. Due to the time-dependent molecular alignment, all ionization signals are intensity modulated with the characteristic ground-state rotational Raman frequencies. A Fourier-transformation extracts rotational Raman spectra for every detected species. Mass-CRASY and electron-CRASY experiments (with respective mass and electron detection) thereby provide structural information about the initial state and allow the explicit assignment of structure-dependent properties

We illustrate the power of CRASY spectroscopy in experiments with a natural sample of CS_2. In a single experiment, we resolved rotational spectra and fragmentation propensities for 9 natural isotopes down to abundances of 10^{-5}. Rotational frequencies of rare isotopes were extracted without the expensive synthesis of enriched isotopic mixtures. Future experiments with enhanced resolution will investigate tautomer- and isomer- specific photochemical processes in DNA bases and clusters.



VUV spectroscopy of biological molecules produced by vaporization of nanoparticles: Bringing fragile neutrals to the gas phase

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We will present a new aerosol source implemented inside the SAPHIRS molecular beam chamber which is a versatile and permanent endstation of the DESIRS VUV beamline at SOLEIL. The very first scientific results obtained on 2 amino acids will be presented too.

It has been shown in 2006 that the thermodesorption of biological nanoparticles (containing one pure substance) is a soft vaporisation method that produces gas phase neutrals within a tiny vapour plume (few mm^3) [1]. This kind of source is ideally adapted to the brilliant light of 3rd generation synchrotron light sources. Thermally fragile neutral molecules, like amino acids, can be studied in this manner in the gas phase, for example using VUV photoionization electron spectroscopy, or mass spectrometry. The advantage of tuneable VUV light is to induce a "soft ionization", where the photon energy can be adjusted so as to avoid dissociative ionization, thus yielding fragment-free mass spectra. This method is perfectly suited to study the electronic structure and corresponding fragmentation dynamics of the thermodesorbed, unfragmented neutrals.

Here we present a newly built aerosol source where special emphasis has been laid on the design and the characterization of an aerodynamic lens system (ALS) and a thermodesorber. This system has been implemented inside the SAPHIRS chamber, which is equipped with an imaging photoelectron-photoion coincidence spectrometer that has been described earlier [2]. It combines velocity map imaging of the photoelectrons with a Wiley-McLaren TOF-MS.

The ALS is used to focus nanoparticles, produced by nebulisation of a liquid solution, into the vacuum by forming a highly collimated beam [3]. This beam is introduced into the ionization region of SAPHIRS, via a differential pumping stage chamber. An optical detection unit, which is composed of a cw solid-state laser at 532 nm (15 mW) and a photomultiplier, is used to detect scattered light of the particles at the ALS outlet in order to align the aerosol beam, and to control the stability of the source. The theoretical performances of the ALS and the characterization of the produced particle beam by nanophase threshold photoelectron spectroscopy (TPES) will be presented.

A heater is inserted between the extraction plates of the ionisation region in order to vaporise continuously the nanoparticles of the beam. The neutral molecules of the resulting vapour plume can then be ionized by the brilliant VUV radiation of the DESIRS

beamline. We will show that this heater does not perturb significantly the imaging of the photoelectrons. The temperature of the heater can be adjusted and thus one can tune the thermal energy of the gas phase neutrals produced.

Finally, we will present first results on thermally-desorbed biomolecules (tryptophane, phenylalanine) [4]. We were able to record TPEPICO energy scans, where the internal energy of the parent ion was scanned with a 25 meV resolution. To our knowledge, this has never been achieved before. The recording time of the spectra is several hours showing thereby the high stability of this new source.

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IR/UV investigations on an isolated cyclopeptide and its monohydrated cluster

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Cyclopeptides are a widespread class of substances in nature with the antibiotic valinomycin being one the most famous representatives. Their physiological effects are frequently based on the tendency to form bioactive conformations. Therefore the investigation of their structure is of great importance for understanding their functionalities. The mass-, isomer- and state-selective IR/R2PI spectroscopy represents an ideal tool for the structural investigation on isolated molecules in the gas phase. With the help of this spectroscopic method the cyclic tetrapeptide $(Pro\text{-}Tyr)_2$ and its complexes with water are investigated. In combination with DFT calculations we are able to assign a structure with two intramolecular hydrogen bonds for the electronic ground state of the cyclopeptide. For the monohydrated cluster two isomers have to be discussed: In one of them the water molecule is simply attached to the assigned monomer structure as hydrogen donor whereas the second isomer is characterised by a water molecule which is inserted into one of the intramolecular hydrogen bonds.

Population transfer spectroscopy of protonated biological molecules in a cold ion trap

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Biological molecules are fluxional rather than static, and thus their function depends both on their structure and their conformational dynamics. We thus study not only the stable conformations of isolated biological molecules but also the barriers that separate them, since the dynamical behavior depends upon the connectivity between minima. These studies provide a fundamental understanding of the isolated molecule that serves as a benchmark for theoretical studies.

We produce biomolecular ions in the gas phase *via* nanospray, mass-select them and guide them into a cold 22-pole cooled ion trap where we use a variety of laser techniques to study them spectroscopically.[1]

We start by measuring electronic spectra of the parent ions by recording the photofragment ion signal as a function of the UV laser wavelength. Using this vibrationally resolved electronic spectrum, we then record infrared-ultraviolet double resonance spectra of single conformations of the trapped biomolecular ions. The conformational assignment is done by comparing these measured infrared spectra with DFT calculations.[2] Having identified different conformers, we then perform population transfer experiments using IR excitation of the NH stretches as well as the Amide I and II vibrations.

We present here the results of these experiments using molecules of increasing size, starting with a seven amino acid helical peptide Ac-Phe-$(Ala)_5$-Lys[3] and going to the twelve amino acid peptide containing glycine, Ac-Phe-$(Ala)_3$-$(Gly)_4$-$(Ala)_3$-Lys.

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Photoinduced migration of water in acetoanilide-water cluster

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Migration of water plays an important role in functions of biological molecues such as enzymes and proteins. The investigation of migration of water at the molecular level is important to understand the biological functions. Here we propose acetoanilide-water (AA-H_2O) cluster as a model system of water migration in biological molecules. In the gas phase two isomers of AA-H_2O will be observed since two binding sites NH and CO groups exist in AA. Actually, we observed the S_1-S_0(0-0) transtions of AA(NH)-H_2O and AA(CO)-H_2O at 35902 and 36050 cm^{-1}, respectively. We also observed the IR-dip spectra of these isomers in the S_0 state. The ionization potentials of AA(NH)-H_2O and AA(CO)-H_2O aredetermined to be 66962 and 67704 cm^{-1}, respectively. On the basis of these results we carried out the measurement of photoionization of the two isomers via the $S_1(v'=0)$ state. The IR spectra of products are displayed in Fig. 1. Two IR spectra measured by ionizing the two isomers are very similar, indicating the formation of $[AA(NH)\text{-}H_2O]^+$ by a migration of water from the CO site to the NH site in the D_0 state (Fig. 2). The creation of plus charge on the CO site by photoionization of AA(CO)-H_2O may induce repulsion between the water and the CO site, promoting the water migration. Molecular dynamics simulation suggests that the oxgen atom of water molecule directs towards the molecular plane of AA during the migration, and time scale of this process is estimated to be 1.5 ps. This study clearly shows the change of the nature of the CO site from hydrophilic to hydrophobic due to the ionization.

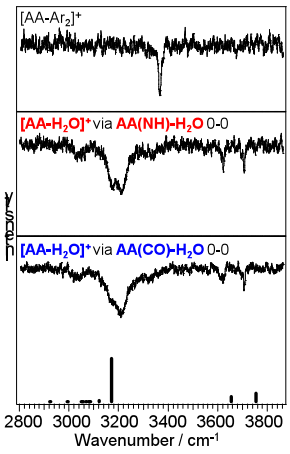

Fig. 1 IR-dip spectra of $[AA\text{-}Ar_2]^+$ (upper), $[AA\text{-}H_2O]^+$ via the NH site (middle) and the CO site (lower) together with a calculated IR spectrum.

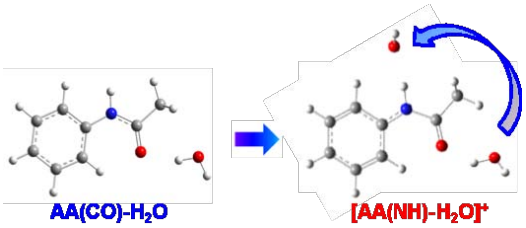

Fig. 2 Photoionization of AA(CO)-H_2O promotes the water migration.

First observation in the gas phase of the ultrafast electronic relaxation pathways of the S_2 states of heme and hemin

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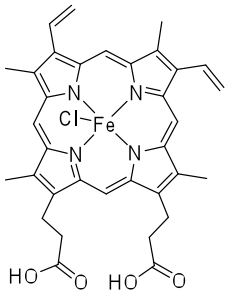
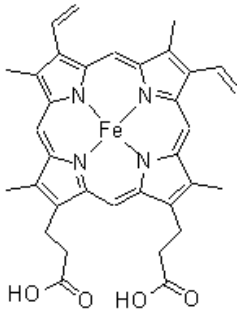
The time evolution of electronically excited heme (iron II protoporphyrin IX $Fe^{II}PP$) and its associated salt hemin (iron III protoporphyrin IX chloride, $Fe^{III}PPCl$), has been investigated for the first time in the gas phase by femtosecond pump-probe spectroscopy. The porphyrins were excited at 400 nm in the S_2 state (Soret band) and the relaxation dynamics was probed by multiphoton ionization at 800 nm. We have compared this time evolution with that of excited state of zinc protoporphyrin IX (ZnPP). The S_2 excited state of ZnPP decays to S_1 likely through a conical intersection in less than 100 fs to the long lived S_1 state. In turn, in the case of $Fe^{II}PP$ and $Fe^{III}PPCl$, the key event is interpreted as an ultrafast charge transfer from the porphyrin excited orbital π^* to a d vacant orbital on the iron atom (Ligand to Metal Charge Transfer LMCT). This intermediate LMCT state then relaxes to the ground electronic state within 250 fs. We also report on the ability that laser desorption provides to prepare iron II protoporphyrin IX Fe^{II} PP in the gas phase.



Hemin
Iron^{III} Protoporphyrin IX Chloride
[Fe ^{III} PP-Cl]



Heme
Iron^{II} Protoporphyrin IX
[Fe ^{II} PP]

Efficient Excited-State Deactivation of Peptides via an Electron-Driven Proton-Transfer Process

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Very recently, the electronic and vibrational spectra of various conformers of several tripeptides with an aromatic chromophore, such as Trp-Gly-Gly, Phe-Gly-Gly, and Gly-Phe-Ala, have been obtained by double-resonance spectroscopy in supersonic jets.[1-4] The assignment of the spectra to specific conformers has become possible by comparison with accurate ab initio calculations.[1-4] Unexpectedly, the conformers with the lowest energy (according to the ab initio calculations) were not observed in the resonant two-photon ionization (R2PI) spectra. Here we present excited state ab initio calculations on proton transfer processes in peptides.[5,6,7] We have identified a mechanism which is responsible for efficient radiationless decay from the excited state to the ground state and therefore for a very short lifetime. While similar mechanisms have previously been found for other hydrogen-bonded systems like DNA base pairs, this is the first time that the electron-driven proton-transfer mechanism has been found in peptides. This mechanism may be essential for the photostability of proteins.

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Direct spectroscopy of contact charge transfer states: Possible consequences for tryptophan excited-state deactivation pathways by O_2 and formation of reactive oxygen species

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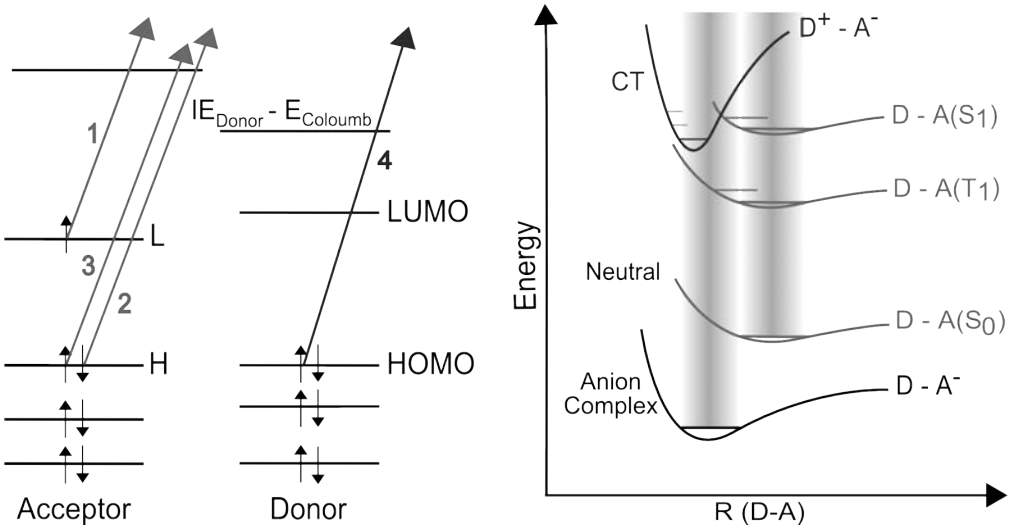
In this poster we demonstrate that photodetachment photoelectron spectroscopy (PD-PES) of non-covalently bound heteromolecular anion clusters allows direct access to neutral contact charge transfer (CCT) states. The bithiophene·indole cluster is investigated as a model system in such way that both chromophores have similar optical excitation cross-sections and hence the PD-PES shows the signature of both molecules. For the complexes O_2·stilbene, O_2·indole and O_2·*N*-methylindole the optical cross-sections of the conjugated chromophores are much larger than that of O_2. This forces most of the anion-to-neutral photoexcitation into the CCT state. The CCT states lie below S_1 for bithiophene·indole and O_2·stilbene or even below T_1 for O_2·indole and O_2·*N*-methylindole. Significant differences are found between the PD-PES of O_2 with indole and *N*-methylindole indicating that different collision sites may have different CCT state energies and as a result different $^1\Delta_g$ oxygen formation efficiencies. We discuss the possible consequences of the energetics and the geometry changes for the excited-state deactivation of tryptophan *via* the CCT state O_2^-·tryptophan$^+$.



Molecular orbital (left side) and electronic state scheme (right side) for the donor acceptor complex indole·O_2

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Probing the Structures of Unfolded Proteins by Ion Mobility-Mass Spectrometry: Effects of Solution versus Gas-Phase Formation of Monomeric Ions from Homomeric Complexes

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Gaining a detailed understanding of how proteins unfold in the gas phase is an intriguing yet challenging goal due to the transient nature of the process and the intermediate species formed. The coupling of ion mobility (IM) technology to mass spectrometry (MS) provides a two-dimensional separation of ions by both their mass over charge ratio (*m*/*z*) and shape. IM-MS has been used to explore the conformation and unfolding pathways of several natively monomeric proteins in the gas phase.[1] More recently, researchers have shown that collisionally activated protein complexes can populate partially folded intermediate states that are stable on millisecond time scales.[2]

We are keen to develop a detailed understanding of the unfolding process of monomeric ions from large homomeric protein complexes. Monomeric ions are generated via two pathways: 1) denaturation of the complexes in solution and 2) collision-induced dissociation (CID) of the complexes in the gas phase, which typically results in the loss of protein monomer ions that have disproportionately large charge states.[3] IM measurements are used to determine the collision cross sections (CCS) of these ions, which provide insights into their structures. These CCS values enable direct comparisons between ions formed by the two pathways, and with models of unfolded and partially folded species.

These results indicate that the CCS of monomer ions formed from solution denaturation and gas-phase CID increase as a function of charge state, but that increases at very high charge states are very small. At low charge states, the CCS for ions from both methods are similar, but at higher charge states these values can deviate significantly. Finally, for some protein complexes, both folded and unfolded monomer protein ions are observed as dissociation products, indicating that there is still a great deal to understand about protein complex unfolding and dissociation in the gas phase.

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Conformational Studies on Esters using Molecular Beam Fourier Transform Microwave Spectroscopy and Quantum Chemical Methods

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The motivation to study the molecular structure of odor substances traces back to the ancient time where the philosophers predicted that good smelling substances must have round surfaces and, in the opposite, the acidic substances have rough surfaces or needle form. Since then, numerous studies on odor structure have been done. With our contribution in microwave spectroscopy we could determine the structure of many esters, which are also well known for their abundance in fruit odor.

The method we use is Molecular Beam Fourier Transform Microwave (MB-FTMW) spectroscopy in the frequency region of 3-40 GHz. In this poster we will present ethyl pivalate[1] which has only three relevant conformers and no free methyl rotor. We observed all conformers and the analysis yielded a set of three rotational constants and five quartic centrifugal distortion constants. The conformers were identified by comparing the experimental rotational constants with those obtained by ab initio calculations at MP2/6-311++G** level. One conformer has C_s symmetry, the other one forms a pair of enantiomers with C_1 symmetry.

Moreover, we'll present ethyl *iso*-valerate[2] where more conformers were expected than in ethyl pivalate. The present of more conformations involving three torsional hollows has brought higher complexity in our structure analysis. The rotational and centrifugal distortion constants of the most abundant conformer were determined. However, the theoretical results obtained at MP2/6-311++G** level did not agree very well with the experimental results. Thus, a comparison between different quantum chemical methods was undertaken to assign the conformer observed in the molecular beam. The results obtained by *ab initio* calculations at MP3/6-311++G**, MP4/6-311++G**, and CCSD/6-311++G** level and B3LYP/6-311++G** agree much better with the spectroscopy data. It is therefore not possible to assign the correct conformer of ethyl *iso*-valerate with MP2 calculations.

In the past we have also successfully assigned numerous acetic acid ester, like methyl acetate[3], ethyl acetate[4], iso-propyl acetate[5], *iso*-propenyl acetate[6], allyl acetate[7], iso-amyl acetate[8], and other esters, like ethyl n-butyrate[9] and methyl propionate[10].

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[3,5,6,8,9,10] to be published

Is β-homo-proline a dependable pseudo-γ-turn forming element of β-peptides?

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There is an increasing interest in the synthesis and structural analysis of peptides containing β-amino acids. β-amino acids in peptides can yield physiologically highly active compounds. They are considered as important potential peptidomimetics, because, similarly to peptides containing α-amino acids, β-peptides can form a number of stable secondary structures such as sheets and helices, and they are considerably resistant to widespread proteolytic enzymes.

In order to test the pseudo-γ-turn forming capability of β-homo-proline (β^3-HPro) its derivative, Ac-β^3-HPro-NHMe was synthesized and its potential energy landscape was investigated by infrared (IR) and vibrational circular dichroism (VCD) spectroscopy. Based on the analysis of experimental spectra aided by density functional computations three different pseudo-γ-turn-like *trans* conformers and a *cis* conformer were identified in cryogenic Ar and Kr matrices. In contrast to its α-Pro analogue, the room-temperature abundance of the *cis* conformer is significant; it is above 10% in the isolated phase. Furthermore, solution-phase vibrational spectra and computations show that the *cis* conformer is predominant in polar solvents. This result indicates that β^3-HPro is significantly less apt to form pseudo-γ-turns when compared to the γ-turn forming tendency of α-proline. The present study also proves the advantages of matrix isolation VCD (MI-VCD) technique [1] over the conventional solution-phase VCD spectroscopic measurements.

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Interrogating viral capsid assembly with ion mobility mass spectrometry: from sheet- to sheath-like structures

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The viral coat proteins of the important human pathogens Hepatitis B virus (HBV) and norovirus spontaneously produce capsids with morphologies identical to the native virion under the right conditions. The underlying mechanism of self-assembly is still little understood, although it has been suggested that certain small transient oligomers may act as nucleation intermediates. The nucleus and larger intermediates in viral capsid assembly are therefore low abundant and difficult to characterize. Here, we monitored small oligomers of HBV and norovirus under equilibrium conditions using native ion mobility mass spectrometry. The hyphenation between ion mobility mass spectrometry and computational modeling enabled us, for the first time, to identify structural features of these potential intermediates. Instead of closed icosahedral capsids or more globular shaped proteins the oligomers exhibit sheet-like structures suggesting that they are indeed assembly competent. Based on the obtained data, we propose a pathway for capsid formation of both viruses based on the observed features.

VitAL: Viterbi Algorithm for *de novo* Peptide Design

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Drug design against proteins to cure various diseases has been studied for several years. Numerous design techniques were discovered for small organic molecules for specific protein targets. The specificity, toxicity and selectivity of small molecules are hard problems to solve. The use of peptide drugs enables a partial solution to the toxicity problem. There has been a wide interest in peptide design, but the design techniques of a specific and selective peptide inhibitor against a protein target have not yet been established.

A novel *de novo* peptide design approach is developed to block activities of disease related protein targets. No prior training, based on known peptides, is necessary. The method sequentially generates the peptide by docking its residues pair by pair along a chosen path on a protein. The binding site on the protein is determined via the coarse grained Gaussian Network Model. A binding path is determined. The best fitting peptide is constructed by generating all possible peptide pairs at each point along the path and determining the binding energies between these pairs and the specific location on the protein using AutoDock. The Markov based partition function for all possible choices of the peptides along the path is generated by a matrix multiplication scheme. The best fitting peptide for the given surface is obtained by a Hidden Markov model using Viterbi decoding. The suitability of the conformations of the peptides that result upon binding on the surface are included in the algorithm by considering the intrinsic Ramachandran potentials.

The model is tested on known protein-peptide inhibitor complexes. The present algorithm predicts peptides that have better binding energies than those of the existing ones. Finally, a heptapeptide is designed for a protein that has excellent binding affinity according to AutoDock results.

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*** The web-server is forthcoming. The server will allow users to provide their target proteins as input and obtain a binder peptide sequence as an output.

MOGADOC - A Database for Properties of Free Molecules

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In order to facilitate the access to structural and structure-related properties of free molecules the group Chemical Information Systems (formerly Section for Spectra and Structure Documentation) at the University of Ulm has compiled and critically evaluated for almost four decades the literature in the field of gas-phase electron diffraction, microwave spectroscopy and molecular radio astronomy. On this basis the MOGADOC database (the acronym stands for Molecular Gas-phase Documentation) has been established for Windows personal computers.

MOGADOC enables the user to trace literature

- for gasphase electron diffraction back to 1930
- for microwave spectroscopy back to 1945
- and for molecular radio astronomy back to 1965.

The hierarchically constructed database contains now over 34,500 bibliographic references for about 10,000 inorganic, organic and organometallic compounds including 7,800 numerical datasets with bond lengths and angles. Among the compounds there is a series of simple biomolecules such as aminoacids (glycine, alanine, proline, etc.), nucleobases (uracil, thymine, adenine, etc.), carbohydrates (glyceraldehyde, dihydroxy-propanone, etc.), alkaloids (caffeine, nicotine, etc.) etc..

The standard retrieval features of the HTML-based database, which runs by means of the Microsoft Internet Explorer or Mozilla Firefox, have been described elsewhere in detail [1]. An implemented Java-based structure editor enables the user to retrieve structural formulas and their fragments [2-3]. Here the user has the choice to take into account or to ignore *cis-trans*-isomerism in cyclic compounds and (*E*)-(*Z*)-isomerism at double bonds. Moreover, a Java-based applet has been developed, which enables the user to visualize the molecular structures three-dimensionally [4]. The user can interactively rotate, shift and scale the displayed 3D structure by moving the mouse. One can allow or suppress the display of bond orders, atom labels (which are necessary to assign the corresponding geometrical parameters in that entry) and the principal axis system of inertia.

The project has been supported by the Dr. Barbara Mez-Starck Foundation.

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Comparative study of interaction of poly-A and poly (dA-dT) with single wall carbon nanotubes

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An interest to the problem of interaction between single-wall carbon nanotubes (SWCNT) and nucleic acids is connected with perspectives of biotechnological applications, e.g., separation of nanotubes from a bungle and their characterizations by different nucleotide sequences, creation of various biosensors, etc. Despite of the experimental data about evidence of nucleic acid interaction with carbon nanotubes, until now is not clear the mechanism of the DNA interaction. The most known model was proposed by Smalley et al, in which DNA or other polymer wraps around the nanotube [1]. Our previous SEIRA (surface enhanced infrared absorption) spectroscopy experiment has shown that the DNA structure, when interacting with SWCNT, is converted into a new unknown form [2].

This study is focused on the interactions between SWCNT surfaces with DNA, poly-A, poly (dA-dT) to clear up the conformation changes in these complexes. New spectroscopic technique based on the effect of enhancement of infrared (IR) absorption by rough metal surface (SEIRA) together with surface enhanced Raman spectroscopy (SERS) and atomic force microscopy (AFM) for registration of structural changes in carbon nanotubes and DNA/carbon nanotubes complexes were applied.

The probe of SWCNT (produced at the Institute of General Physics, RAN) with poly A (Fluka) (pH=5.5) or poly (dA-dT) (Sigma) was prepared in aqueous solution by mixing in ultra sound mixer and further centrifugation under 30 000 turn/min.

We have registered in poly-A (poly(dA-dT)) and nanotubes complexes the following spectroscopic features: i)an enhancement of sugar vibrations, ii)increase of the intensity of phosphate bands and their shift, iii) drastic decrease of stretching OH close to 3400 cm-1, iv)decrease of intensity of adenine band. We have registered a number of H-bonds breaks, redistribution of the H-bond net, adenine interaction with carbon nanotube fragments. We have indicated cites of the interaction of the biomolecules with nanotubes. The important point that the most of the cites in the biomolecules was occupied by water molecules before. A reason of drastic difference of nanotube interaction with poly A in comparison with poly (dA-dT) are described.

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Studying Candida antarctica lipase B in organic solvents at fixed water activities using molecular dynamics simulations

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We present a molecular dynamics (MD) study of Candida antarctica Lipase B (CALB) in organic media. This enzyme is used as catalyst in numerous industrial applications, often in organic solvents at rather dry conditions [1]. It has been observed experimentally that the type of organic solvent affects e.g. activity, selectivity and stability, and hence careful selection of solvent can be very beneficial. It is therefore highly desirable to gain a better understanding of how enzymes behave in organic media. In this study, we focus on the flexibility and hydration level of the CALB in different solvents, including acetone, tert-butanol, methyl tert-butyl ether and hexane, under varying hydration conditions. While only minor structural differences are seen in the different media, we do observe that the flexibility, characterized by the root-mean square fluctuations, increases with increasing hydration level. The hydration level is in turn affected by the organic solvent properties. We observe that in polar solvents, more water molecules are necessary to be included in the simulation to attain the same hydration levels of CALB as monitored in non-polar solvents.

In order to investigate the effects on flexibility purely originating from the organic solvent species, we compare simulations of CALB in different solvents, where the hydration levels of the enzyme are similar. In experiments, one often accomplishes this by fixing the (thermodynamic) water activity [2]. In order to make our calculations more compatible with such experiments, we will present a scheme for conducting MD simulations at specified water activity.

We have also extended our studies to include the effect of solvent on the stability of the Michaelis-Menten complex, formed by CALB and an ester substrate. Results for near-attack conformation populations for forming the tetrahedral intermediate will be discussed.

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UV-irradiation of caged compounds: Analyzing the first step of the mechanism by ESI-MS

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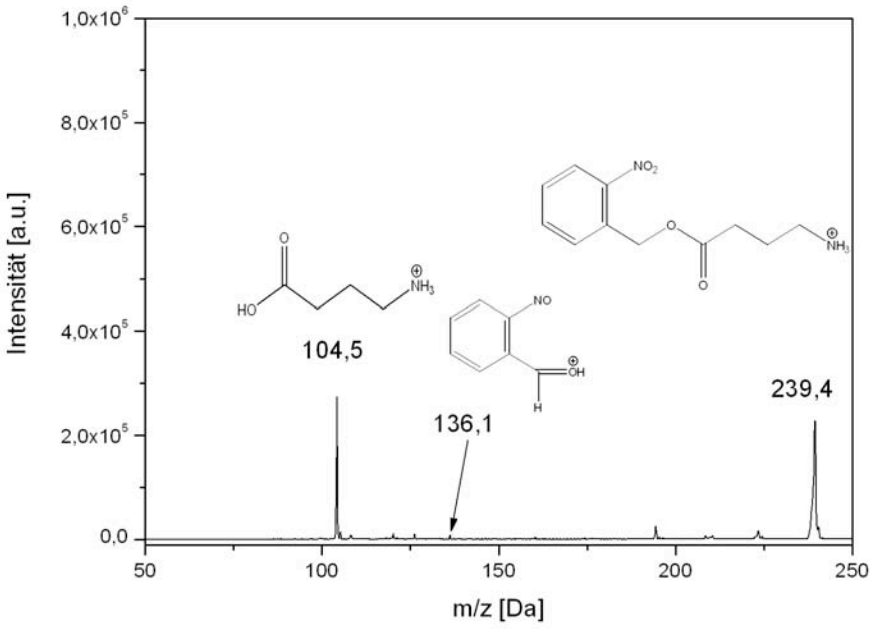
Caged compounds are interesting for different fields in medicine, biochemistry and biophysics. They are specific substances with a photo labile protective group which can be split off under UV irraditation. When the substance gets activated at a certain time it can release enzymes, drugs or active pharmaceutical compounds in cells immediately. Interesting for us was the mechanism of the release of the protective group: it is believed that H transfer precedes the final bond cleavage. In this poster we discuss the question whether the molecule for the H transfer needs a protic solvent or can occur by an intramolecular shift of a proton. In this work we used 2-nitrobenzyl-4-aminobutanoate as an example for a caged γ-glycine. The substance was first irradiated with UV-light in a protic solution with a neutral pH-value and then analyzed with an ESI mass spectrometer. By alkalinizing the solution and then repeating the irradiation and the analysis under same conditions we can get hints for the mechanism.



Successfully split off of the protective group (136,1 Da) and release of the active γ-glycine (104,5 Da) after UV-irradiation

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Characterizing Hydration-Induced Folding in Dicarboxylate Dianions using Gas Phase Vibrational Spectroscopy

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Dicarboxylate dianions $^{-}O_2C\text{-}(CH_2)_m\text{-}CO_2^{-}$ play important roles in natural environments, e.g., as charge carriers in proteins and in organic aerosols in the troposphere. The hydration of these dianions is particularly intriguing, because the two hydrophilic centers are separated by a flexible hydrophobic aliphatic chain. Anion photoelectron spectra combined with molecular dynamics simulations suggested that the dianion is either quasi-linear and the two charge centers are separately solvated, or folded, with a single water cluster forming around the carboxylate groups, depending on the degree of hydration.[1]

We employ gas phase vibrational spectroscopy to characterize the structure of microhydrated dicarboxylate dianions of different chain length *m* in order to shed light onto the mechanism governing the solvent-mediated folding process. Infrared photodissociation (IRPD) spectra of $^{-}O_2C\text{-}(CH_2)_m\text{-}CO_2^{-}(H_2O)_w$ (m=2,4,6,8; w=0-40) ions, thermalized at 15 K, were measured from 1300-1750 cm^{-1}, the region of the carboxylate symmetric and antisymmetric stretching bands. Up to eight water molecules comprise the first solvation shell of the two carboxylate groups. Additional water molecules add to the outer hydration shell and result in an abrupt decrease of the intensity of the symmetric stretching band above a specific number of water molecules, which depends *m*. Ab initio calculations confirm that this abrupt decrease in intensity is directly linked to the conformational change from a quasi-linear to a folded dianion.

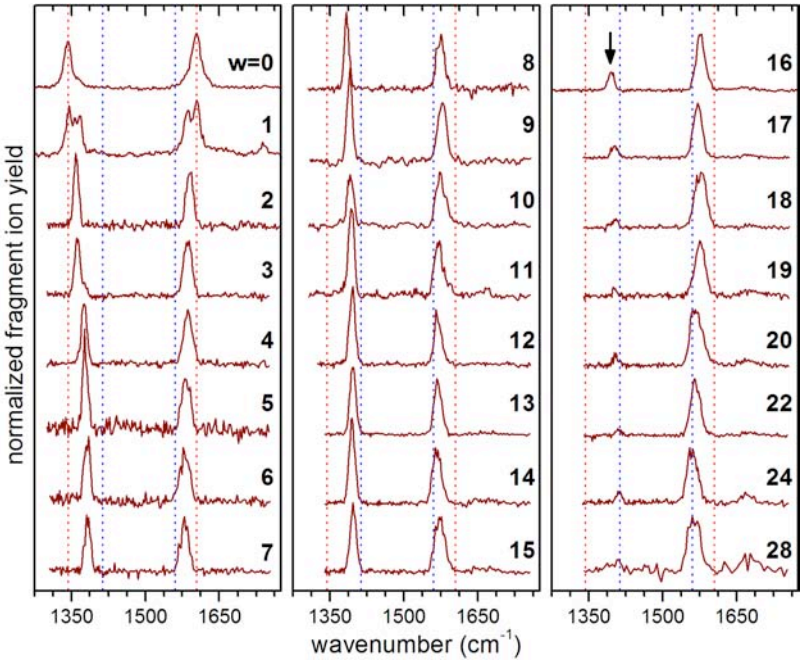

Figure: IRPD spectra of $[^{-}O_2C\text{-}(CH_2)_6\text{-}C_2O^{-}](H_2O)_w$

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Infrared Spectroscopy of Protonated Water Clusters: The Effects of Argon Tagging and Deuteration

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Protonated water clusters of the form $H^+(H_2O)_n$ and $D^+(H_2O)_n$ are produced in a supersonic molecular beam using a pulsed discharge source. These complexes and their analogues "tagged" with argon atoms are mass selected in a reflectron time-of-flight mass spectrometer and investigated with infrared laser photodissociation spectroscopy. The comparison of measured IR spectra to those predicted by computational studies reveals the hydrogen bonding structures produced and the presence of different isomeric structures at certain cluster sizes. For some clusters, spectra can be measured with versus without argon tagging to investigate the effects of complexation on the structures and spectra. Deuterated clusters are found to form mainly the same isomeric structures as their all-H counterparts.

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