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BOOK OF ABSTRACTS

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LC-SPE (CRYO)NMR APPROACH TO THE IMPURITY PROFILING OF 7-ETHYLTRYPTOPHOL

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7-Ethyltryptophol, 2(7-ethyl-1H-indol-3-yl)ethanol, is a key starting material in the synthesis of Etodolac, a non-steroidal anti-inflammatory drug. Depending on the synthetic pathway for 7-ethyltryptophol, commercially available material comprises many different impurities which can cause formation of coproducts in the synthesis of Etodolac thus complicating the purification of the final product.[1] Therefore, to develop an optimal purification procedure of Etodolac, it is important to know the structures of impurities in 7-ethyltryptophol. Classical methods for separation and isolation of impurities, such as preparative or semi-preparative liquid chromatography, are time and solvent consuming. Nowadays, hyphenated NMR techniques are becoming faster, more efficient and more sensitive tool for determination of impurities and degradation products in pharmaceuticals and natural products. [2,3]

In this study LC-SPE (cryo)NMR methodology was used to identify impurities in 7-ethyltryptophol. Chromatographic separation was achieved on Waters XBridge Phenyl and C18 columns (150 mm x 4.6 mm; 3.5 μm) using a combination of gradient and isocratic elution. Compounds were trapped on HySphere Resin GP cartridges in a SPE multitrapping mode. ^{1}H, COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC NMR spectra and MS spectra were recorded to determine the structures of impurities. In this way 17 compounds were identified. These results show a good potential of LC-SPE (cryo)NMR technique in an identification and structural characterization of low level impurities and degradation products in pharmaceuticals.

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DOSY NMR TECHNIQUE IN STUDIES OF IONIC-LIQUID GELS AND AGGREGATION OF ASPHALTENES

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Diffusion ordered spectroscopy (DOSY) is a two-dimensional NMR technique, where one dimension reveals conventional chemical shifts and another dimension diffusion coefficients that can be correlated with molecular properties such as size, weight, shape, charge, etc. and that depend on molecular surrounding (temperature, viscosity, aggregation state) [1]. Moreover, the DOSY technique gained popularity in analysis of complex mixtures not only because of the non-destructive nature of NMR spectroscopy itself, but also due to its ability to perform the analysis without any prior separation of different components. Therefore the main two applications of the DOSY technique involve identification of different components in a complex mixture and determination of aggregation size.

In one DOSY application it will be discussed how a high ionic conductivity of supramolecular ionic-liquid gels correlates with its cation and anion diffusion coefficients depending on gelator concentration (Figure 1) [2].

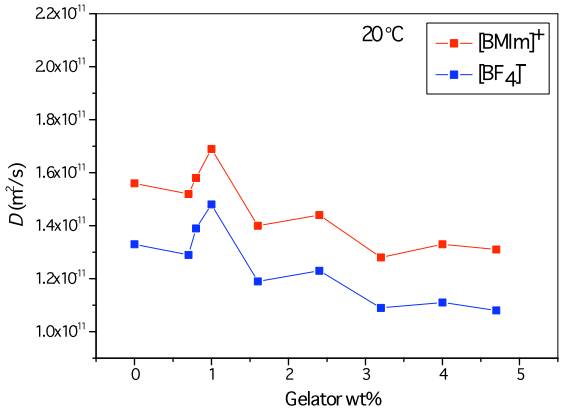

Figure 1. Cationic and anionic diffusion coefficients at 20 °C of the neat [BMIm][BF_4] and ionogels as a function of gelator concentration.

Another DOSY application presented will be a study of asphaltene aggregation in samples of crude oil and residues from atmospheric and vacuum distillation of crude oil.

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THE ROLE OF THE AMINO ACID CHIRALITY AS THE POTENTIAL PROMOTER OF DIFFERENT TYPES OF TURNS IN FERROCENE PEPTIDES

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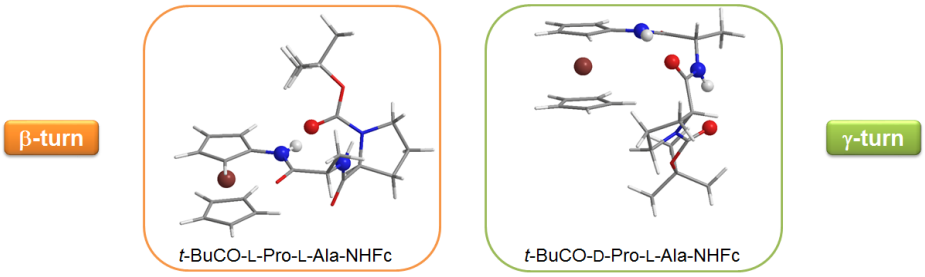
Ferrocene and its derivatives have attracted much attention in recent years due to their specific structural properties and applications in bioorganometallic and bioanalytical chemistry. Ferrocene peptides show potential to mimick secondary structures of proteins. The distance of 3.3 Å between two cyclopentadienyl rings promotes intramolecular hydrogen bonding between peptide chains. [1] Recently, a series of mono- and disubstituted ferrocene peptide derivatives have shown the self-assembly and gelation behaviour. [2]
A series of monosubstituted ferrocene peptides bearing homo- and heterochiral Pro-Ala sequence were described. A change of the Pro amino acid chirality can affect the secondary structure. A homochiral derivatives of *t*-BuCO-Pro-Ala-NHFc favour β-turns, and a disruption of the secondary structure, observed in their heterochiral analogues in solution, is ascribed to formation of γ-turns according to the computational study. In comparison to ferrocene conjugates, their non-ferrocene analogues comprised of the same amino acid sequences showed β-turn as the most preferred structural motif. Thus, a ferrocene unit could act as a potential promoter of γ-turns in heterochiral derivatives. The X-ray determined crystal structures of heterochiral derivatives show preference for β-turns. The calculated interaction energies pointed out the significance of the intermolecular hydrogen bonds favourable enough to overcome rearrangement of a single molecule from the most stable conformer to the one adopted in the solid state. The current research confirms the potential of the investigated compounds for the fine tuning of their conformational properties by variation of the chirality of constituted amino acids.



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MODELING THE STRUCTURE AND REACTIVITY OF ORGANIC COMPOUNDS USING A NEW CLUSTER-CONTINUUM SOLVATION METHOD

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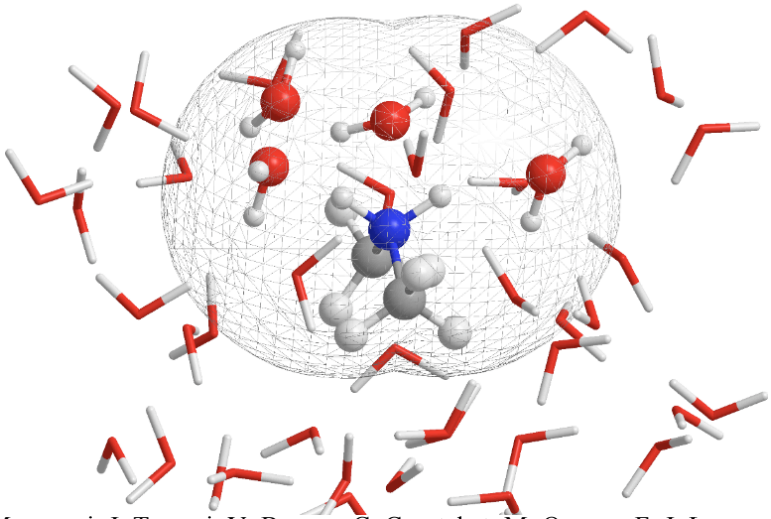
Despite the advancement of implicit solvent models, explicit solvation – or rather, cluster-continuum methods – are still necessary for the accurate description of most polar reactions. We attempt to answer two important problems: "How many (explicit solvent molecules are needed)?" and "Where (to put them)?"

As an answer, we present an unbiased, widely applicable, accurate and efficient method for cluster continuum solvation modeling. The presented method provides a recipe for finding and selecting solvent molecules which are important for the accurate description of the modeled solute. This recipe is, in principle, the same for all solutes, including reaction intermediates and transition structures, and applicable to any solvents.

The most important feature of this method is a novel approach for the generation of clusters, in which only important solvent molecules are added to the solute. This approach is based on the concept of functional group solvation basins (FGSB), which are constructed by combining solvation spheres centered on functional groups. Solvation sphere radii are defined by analyzing radial distribution functions of solvent molecules around solute functional groups, which enables the elimination of molecules unperturbed by the solute. Also, the presented method implements a procedure for simple, effective and unbiased generation of geometries with a selected number of solvent molecules. This is achieved by sorting the solvent molecules according to their interaction energy.



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THE INVESTIGATION OF ANILINE AND HYDROXYLANILINE MICROSOLVATION USING A NEW CLUSTER-CONTINUUM METHOD

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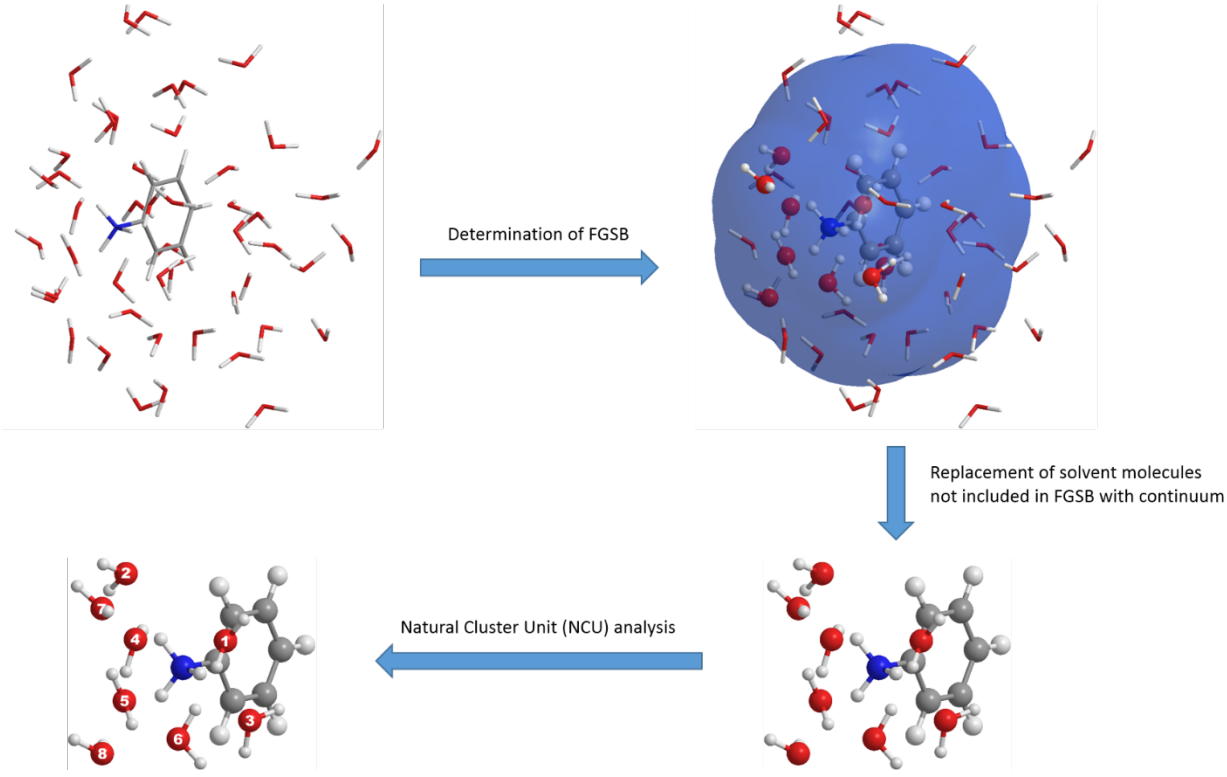
In this work, a new cluster-continuum solvation method was tested. Based on the initial clusters, radial probability distribution functions for oxygen atoms of water molecules around the functional groups of the solute were created. They were used in order to construct functional group solvation basins, in which all the potentially important explicit solvent molecules for consideration of microsolvation are located. Afterwards, the solvent molecules most tighty bound to the solute were determined using NCU analysis.

Aniline, phenylhydroyxlaniline and their protonated species were chosen as model systems. Structural patterns of the most stable clusters with 1, 2 and 3 water molecules were studied at the SMD/ωB97XD/6-311+G(2df,2p) level of theory. Results show significant improvements in comparison with those produced only by using the implicit solvent.



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We gratefully acknowledge the financial support to this work from the Croatian Science Foundation, grant no. 7444, project ORGMOL.

Enhancing the resolution of NMR spectra by interrupted acquisition

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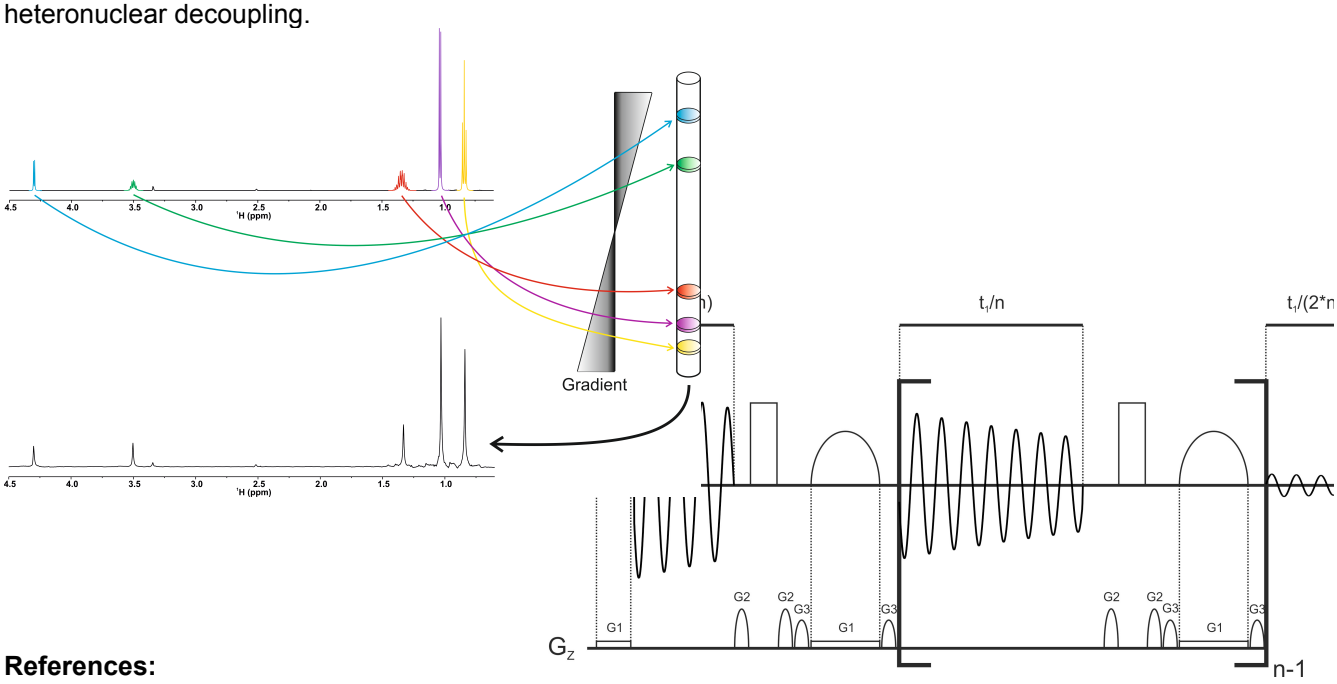
Protons are the most often used nuclei for NMR structure elucidation of organic and biological molecules. Compared to other NMR detectable nuclei, ^{1}H spectra typically suffer from low resolution and severe signal overlap, mainly due to extensive scalar coupling between protons. Homonuclear broadband decoupling (pure shift spectra), which leads to a collapse of ^{1}H signals into singlets vastly increases the resolution, which in some cases corresponds to a theoretical signal dispersion of NMR spectrometers at several GHz [1]. One of the approaches for homonuclear broadband decoupling in the indirect dimension of two- and multidimensional NMR spectra uses frequency-selective pulses during a weak gradient field [2]. We recently reported an adaption of this method to achieve homonuclear broadband decoupling during acquisition [3]. Scalar coupling information, which is often key in analyzing chemical structures, is of course completely lost in such experiments. Two methods, which constitute a compromise between pure-shift spectra and fully coupled spectra will also be presented: real-time SERF spectra [4] and real-time J-scaled proton spectra. With the first of these, 1D spectra are obtained which contain scalar coupling to one selected signal only, while J-scaling allows the recording of proton spectra with reduced coupling constants, reminiscent of off-resonance heteronuclear decoupling.



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COMPUTER SIMULATIONS OF URETHANE-INDUCED CARCINOGENESIS

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The carcinogenesis of urethane (ethyl carbamate), a byproduct of fermentation that is consistently found in various food products, was investigated with a combination of kinetic experiments and quantum chemical calculations. The main objective of the study was to find $\Delta G^{\ddagger}$, the activation free energy for the rate-limiting step of the S_N2 reaction among the ultimate carcinogen of urethane, vinyl carbamate epoxide (VCE), and different nucleobases of the DNA. In the experimental part, the second-order reaction rate constants for the formation of the main 7-(2-oxoethyl)guanine adduct in aqueous solutions of deoxyguanosine and in DNA were determined. A series of ab initio, density functional theory (DFT), and semiempirical molecular orbital (MO) calculations was then performed to determine the activation barriers for the reaction between VCE and nucleobases methylguanine, methyladenine, and methylcytosine. Effects of hydration were incorporated with the use of the solvent reaction field method of Tomasi and co-workers and the Langevine dipoles model of Florian and Warshel. The computational results for the main adduct were found to be in good agreement with the experiment, thus presenting strong evidence for the validity of the proposed S_N2 mechanism. This allowed us to predict the activation barriers of reactions leading to side products for which kinetic experiments have not yet been performed. Our calculations have shown that the main 7-(2-oxoethyl)deoxyguanosine adduct indeed forms preferentially because the emergence of other adducts either proceeds across a significantly higher activation barrier or the geometry of the reaction requires the Watson−Crick pairs of the DNA to be broken. The computational study also considered the questions of stereoselectivity, the ease of the elimination of the leaving group, and the relative contributions of the two possible reaction paths for the formation of the 1,N2-ethenodeoxyguanosine adduct.

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AROMATIC DINITROSO COMPOUNDS AS SUPRAMOLECULAR BUILDING BLOCKS

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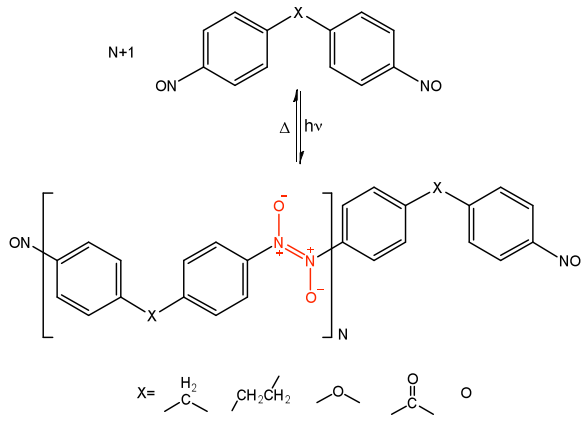
Aromatic C-nitroso compounds can exist in three different forms, as monomers, *Z*- or *E*- dimers (azodioxides). Nitroso compounds also exhibit photochromic and thermochromic behavior in solid state. Azodioxides dissociate under UV irradiation at low temperatures and again dimerize at elevated temperatures.[1]

Aromatic nitroso compounds with two or more nitroso groups could be used as supramolecular building blocks. Wuest et al. utilized tetranitroso bocks for construction of covalent organic networks (COFs) by polymerization.[2] Supramolecular structures with azodioxides groups could be disassembled or reassembled by applying external stimuli such as UV radiation or heat. Our goal was to prepare aromatic dinitroso compounds with various spacers between two aromatic rings and to investigate their polymerization properties in solid state. Most of the examined dinitroso compounds form oligomers in the solid state which are mainly in *E*- configuration. Diphenyl-ether derivative doesn't form dimers because of the quinoid resonance structure, while diphenylmethane derivative forms *Z*- oligomers. In the case of diphenylmethane derivative, *Z*- conformers are stabilized by favorable aromatic ring π-π stacking.

Monomers are generated upon UV irradiation at cryogenic temperatures. Monomers dimerize by heating the samples to ~150 K. Methane, ethane, biphenyl and benzophenone derivatives form *E*-oligomers upon redimerization. In the case of diphenylmethane, *E*- dimers isomerize to thermodynamically more stable *Z*- conformation upon further heating.



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AROMATIC C-NITROSO COMPOUNDS AS BUILDING BLOCKS FOR NEW SUPRAMOLECULAR ASSEMBLIES

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Aromatic C-nitroso compounds can exist in two different forms, as monomers or dimers (azodioxides).[1] Formation of azodioxide bond strongly depends on the conditions of the environment. The predominant species in solution at ambient temperature are monomers whereas lowering of temperature or crystallization favors dimerization. In solid state, dimerization is dependent not only on electronic factors but also on topochemical effects. If the molecules are favorably oriented in crystal lattice with their nitroso groups in the vicinity they readily form azodioxides. Such azodioxides can undergo photodissociation to monomers in crystal at cryogenic conditions and in turn, by warming above some critical temperature, redimerization occurs.

In our recent studies, we tried to expand the current knowledge about the dimerization of aromatic C-nitroso compounds by exploring if it can occur on two-dimensional gold surface through formation of ordered self-assembled bilayers (SABs).[2,3] SABs could be formed by interactions of nitroso groups exposed at the interface of self-assembled monolayer (SAM) and those present in solution via azodioxide bonds. We have prepared nitrosoaromatic derivatives with one and two nitroso groups functionalized with sulfur headgroups for adsorption on Au(111) surface. Layers of nitrosoaromatic derivatives on Au(111) surface were studied by scanning tunneling microscopy (STM) and atomic force microscopy (AFM). STM and AFM images revealed that in addition to self-assembly into monolayers, the nitrosoaromatic derivatives are also able to form ordered bilayers.

In addition, we examined the ability of aromatic C-nitroso compounds to dimerize on the three-dimensional surface of Au nanoparticles.[3] We have prepared Au nanoparticles capped with nitrosoaromatic derivatives with one and two nitroso group and characterize them by FTIR spectroscopy, UV-Vis spectroscopy and transmission electron microscopy (TEM). It was found that nitroso molecules are present in dimeric form on the gold surface leading to interlinking of Au nanoparticles through azodioxide bonds and their subsequent aggregation.

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Deuterium NMR – a powerful tool in studying molecular order

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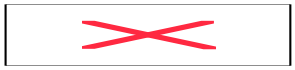
The analysis of deuterium NMR (^{2}H-NMR) spectra depends on the way the quadrupolar hamiltonian is averaged by molecular motions. In the presence of fast, anisotropic molecular motions the quadrupolar interaction is averaged to a non-zero value, which results in a doublet of Lorentzian lines characterized by a splitting $\Delta\nu$. In the general case of fast uniaxial motions around a local symmetry axis denoted by $\vec{n}$, the splitting is given by:



(1)

in which $P_2(\vartheta)$ is the second order Legendre polynomial:

(2)

$\vartheta(t)$ is the instantaneous angle between the C−D bond and the local axis $\vec{n}$, Ω is the angle between $\vec{n}$ and the static magnetic field B. The overbar denotes a time averaging over motions faster than the characteristic time ν_q^{-1}. The factor $\overline{P_2(\vartheta)}$ is the local orientational order parameter which describes the degree of motional anisotropy of the C−D bond with respect to the symmetry axis. For C−D bonds in $-CD_2-$ or $-CD_3$ groups,  . In the fast motion limit, the line width of each component of the doublet depends on the relaxation time T_2 and is generally small or comparable to the value of the splitting. This leads to well resolved spectral lines. In a disordered system, the resulting spectrum is the superposition of such doublets, and the resulting line shape is thus directly related to the distribution of residual interactions in the system. In a macroscopically oriented system, the spectrum is a doublet, which gives a direct measurement of the macroscopic order parameter. Based on measured splitting values and the known value of macroscopic angle Ω, the mean degree of orientational order parameter (S) can be calculated as:

(3)

Some typical ^{2}H-NMR spectra of various anisotropic systems will be presented and analyzed.

Simplification of structure elucidation in organic chemistry by real-time J-up and down-scaled NMR

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NMR spectroscopy is one of the most frequently used techniques for the structural characterization of small to medium sized organic and biomolecules. Because of its high natural abundance, widespread occurrence and high sensitivity, ^{1}H nuclei are often used in this process. Their resonance frequencies and scalar coupling patterns can provide important structural information. Despite the clear advantages of ^{1}H NMR spectroscopy, proton signals are often overlapped since they are found in a narrow spectral region of only ~10 ppm. Scalar coupling information is often used for organic structure elucidation, but is also one major source of signal overlap of proton signals. We developed a new technique [1] to obtain spectra without homonuclear scalar coupling which simplifies proton spectra of organic molecules. All multiplets collapse into singlets, which significantly enhances the resolution. In other cases, a higher resolution of the multiplet structure is desired to understand the chemical environment of the coupling partners. For that purpose J-upscaling [2] can be used to enlarge coupling constants by factors up to 20, in order to allow very accurate determination of signal splittings. This approach sometimes even enables the determination of coupling constants which are unresolved in regular NMR spectra.

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OPTIMIZATION, INTERPRETATION AND SELECTION OF MOLECULAR DESCRIPTORS IN STRUCTURE-PROPERTY MODELS

Bono Lučić

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In development of novel structural descriptors different optimization procedures can be applied, in order to improve their relevance and descriptive potential in establishing structure-property/activity models. Examples of commonly-used optimizations are those based on finding or definition of different weighting schemes (or methods) for calculating charges or electronegativites of atoms, or different bond weighting schemes. One such example is also the optimization of molecular connectivity index (of order one) introduced by Randić in 1975 [1], also named the product-connectivity index, which is a distance-based topological index belonging to the class of Zagreb indices introduced by Gutman and Trinajstić in 1972 [2]. Recently, Gutman reviewed twenty formulations of connectivity index that are based on different weighting schemes of vertex degrees (representing C atom valence counting only neighbouring C atoms), and compared them in modelling the standard heats of formation and normal boiling points of acyclic octanes. I will analyze some novel procedures for optimization of connectivity index in an attempt to (1) improve physico-chemical interpretation of connectivity index as a molecular descriptor, (2) test and improve the quality of different formulations of connectivity index in estimation and prediction of several properties of larger sets of alkanes, and (3) compare the quality of these relationships with the best ones obtained using the large pool of descriptors calculated by the computer program Dragon [4]. Based on these three criteria, suggestions for the selection of proper optimization procedure in the use of connectivity indices in structure-property/activity modelling will be given.

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Introducition of new tripple resonance system for analysis of fluorine molecules

Naoyuki Fujii and Satoshi Sakurai

JEOL comp. presentation

We would like to introduce new triple resonance system by using a unique probe. This system should be very useful for analysis of fluorine molecules.

Participants: Mr. Naoyuki Fujii (or Mr. Satoshi Sakurai)

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NMR STUDIES OF TETRAHELICAL G-RICH DNA STRUCTURES

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Great interest in guanine-rich nucleic acids and G-quadruplexes is stimulated by their occurrence in telomeric regions and gene promoters. Bioinformatic studies suggest that G-quadruplexes may act as cis-acting regulatory elements for a large portion of human genes. G-quadruplexes are formed in the presence of cations such as K^+ and Na^+ ions. These non-canonical four-stranded structures are composed of stacked layers of G-quartets, which are formed by four guanine residues connected by Hoogsteen-type hydrogen bonds.

G-quadruplexes are structurally highly polymorphic. High-resolution X-ray crystallographic and NMR structures have provided valuable insights into the effects of cation size and charge on G-quadruplex structures. Solution-state NMR studies have demonstrated that cations undergo dynamic exchange between coordination sites in the interior of a G-quadruplex and bulk solution.

Many G-quadruplex structural features indicate that even for relatively simple G-rich DNA sequences possible structural motifs are still not known entirely.[1-3] It is impossible to unequivocally predict folding topology from oligonucleotide sequence and assess its thermodynamic stability at the current state of knowledge. Both are however crucial for understanding biological functions of G-quadruplexes as well as for the use of these noncanonical structures as targets in development of new anticancer and antiviral drugs and in nanotechnological applications. Our recent study[4] has shown that protonation–deprotonation equilibrium can control reversible transformations and can serve as a conformational switch.

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New high dimensionality experiments for intrinsically disordered proteins

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Studies of biomolecular structure and dynamics by NMR spectroscopy at atomic resolution require acquisition of multidimensional spectra. However, the recording time of sufficiently resolved multidimensional spectra is often very long due to the sampling limitations. A variety of different methods was proposed to overcome this limitation in multidimensional NMR spectroscopy. They could be utilized in two different ways, either to shorten the experiment duration without loss of resolution, or to perform experiments that are not obtainable conventionally, i.e. with significantly improved resolution and/or of high dimensionality. Most often first of these two, so called "Fast NMR" approach, is shown as the example of the utility of these methods, as it saves expensive spectrometer time. However, in many cases spectra featuring extraordinary resolution and high number of dimensions may be more interesting from scientific point of view as they reveal effects that are hidden, when spectral lines are broad, or enable resolving spectral ambiguities when peaks are overlapped. This second approach we refer to as "Accurate NMR". Its full potential is manifested when the overall experiment time is less important than a new information available from spectra of high dimensionality (4-6D) or of high resolution approaching natural line-width. The new methods were applied for NMR studies of intrinsically disordered proteins, where the structural disorder in combination with highly repetitive amino-acid sequences causes severe peak overlap in the spectra. Recently, several novel 4-6D pulse sequences are proposed. The new experiments employ non-uniform sampling that enables achieving high resolution in indirectly detected dimensions. The experiments facilitate resonance assignment of intrinsically disordered proteins.

TOPOLOGICAL COORDINATES FOR BAR POLYHEX CARBON STRUCTURES

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Very often the basic information about a nanostructure is a topological one. Based on this topological information, we have to determine the Descartes coordinates of the atoms. In the present talk, we review first the previous results obtained by drawing graphs with the help of various matrices as the adjacency matrix [1,2], the Laplacian matrix and the Colin de Verdiere matrix [3]. We explain why they are applicable if the atoms are on spherical surfaces. We have found a matrix **W** which could generate the Descartes coordinates for fullerenes, nanotubes and nanotori and also for nanotube junctions and coils as well [4]. Here will be shown with examples of bar polyhex structures that using the matrix elements of smaller structures the **W** matrix of larger structures can be generated[5].

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Simple graph-theoretical model for flavonoid binding to P-glycoprotein

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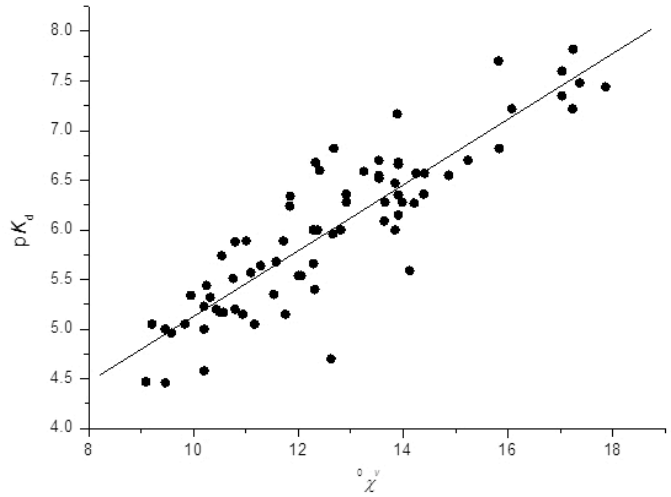
Abstract

Three sets of flavonoid derivatives (N = 32, 40, and 74) and logarithms of their dissociation constants (log K_d) that describe flavonoid affinity toward P-glycoprotein were modelled using six connectivity indices ($^0\chi^v$…$^5\chi^v$). The best results were obtained with the zero-order valence molecular connectivity index ($^0\chi^v$) for all three sets. Standard errors of the calibration models were around 0.3, and that of the constants from the test sets even a little lower, 0.22 and 0.24. Despite using only one descriptor, our model proved better in internal (cross-validation) and especially in external (test set) statistics than much more demanding methods used in previous 3D QSAR modelling [1,2,3]



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MOLECULAR EXTENDED GRAPH SIGNATURES AND DESCRIPTORS QSAR OF IONIC LIQUID TOXICITY

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Applied are molecular extended valence graph signatures and molecular descriptors for qualitative structure activity relations (QSAR) for prediction of toxicity levels of several classes of ionic liquids (ILs). First, second and third order graph signatures are calculated for comparative study with the descriptors for a comparative study of QSAR prediction accuracy. The signatures and descriptors are separately determined for each of the cations and anions and adjoined into a single record for each of ILs combinations. Correlation matrices of the descriptors and signatures are compared and singular decomposition is applied for dimension reduction. Focus of the modeling is importance classification of the signature and descriptors information extracted from applied models. The models are based on extreme gradient boosted ensembles (forests) of decision trees. The models are derived for combinations of the following cations: imidazole, pyridinium, quinolinium, ammonium, phosphonium; and anions: BF_4, Cl, PF_6, Br, CFNOS, NCN_2, $C_6F_{18}PBF_4$, Cl, PF_6, Br, CFNOS, $C_6F_{18}P$. ILs Toxicity levels are based on E_{50} concentrations on enzyme *acetycholinesterase* inhibition. Based on evaluated importance lists of the graph signatures and descriptors constructed are individual decision trees optimized by the genetic algorithm (GA). The derived models are validated by ten fold cross validation resulting in 10% average errors by individual decision trees, and considerable improved prediction accuracy, when compared to single tree and standard chemometric models, were obtained by random forest predictors for toxicity classification at error level 2% and for E_{50} with Pearson regression coefficient R^2=0.992.

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A WALK-THROUGH SEVERAL RULES OF AROMATICITY

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Many of the quintessential aromatic compounds present high symmetry. Although not all aromatic species are symmetric, the most archetypal aromatic compounds are highly symmetric and possess degenerate highest-occupied molecular orbitals. These orbitals can be fully occupied resulting in a closed-shell structure or can be same-spin half-filled. This closed-shell or same-spin half-filled electronic structure, which provides an extra stabilization, is the origin of several rules of aromaticity such as the Hückel 4n+2 rule,[1-4] the lowest-lying triplet excited state Baird's rule,[5,6] the Soncini and Fowler extension of Baird's rule,[7] or the 4n rule followed by monocyclic conjugated hydrocarbons in a Möbius-type conformation.[8,9] These rules of (anti)aromaticity, which can be strictly applied to monocyclic conjugated hydrocarbons, are nicely summarized in the so-called Ottosson's cube.[10] In the case of polycyclic conjugated hydrocarbons (PCH) the above mentioned rules do not necessarily apply. One of the most successful attempts to generalize Hückel's rule to benzenoid PCH is the so-called Clar's π-sextet rule.[11] This simple rule has been widely validated both experimentally and theoretically. In 1984, Glidewell and Lloyd (GL) reported an extension of this rule to polycyclic conjugated hydrocarbons having rings with any even number of carbon atoms in their structure. Examples of the analysis and applications of these rules performed in our group will be discussed and the validity of some of these rules will be assessed. Finally, we will briefly refer to the connection between Hückel's rule and the 4*n*+2 Wade-Mingos' rule of *closo* boranes[12,13] and we will refer to the lack of rules in the case of octahedral aromatic compounds.[14]

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Graph-Theoretical Approaches in Drug Discovery*

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This presentation is dedicated to the 80th birthday of Professor Nenad Trinajstić with whom I have a longstanding scientific collaboration, numerous joint publications and who inspired my research work presented here

Abstract: We have developed new methodological solutions for prediction and study of protein binding sites, based on graph theoretical approaches, combined with molecular dynamics simulations. Protein binding sites have been subject of intensive research, due to their key role in binding of drugs, and also, because they allow us to understand biochemical processes of a cell. For efficient drug development, one should know structure of the binding site and its dynamics, that is, one should be able to predict how the process of binding a molecule will change the binding site. The research of protein binding sites is also driven by scientific field named structural genomics, whose goal is to determine three-dimensional structures of representatives of all known proteins and their biochemical functions. Because biochemical functions of proteins are closely related to protein binding sites, further development of computational approaches to predict protein binding sites is needed.

We have developed a freely available ProBiS web tools enabling the discovery of molecules relevant to pharmaceutical research. This new tools will enable researchers to predict molecules that will bind to their investigated proteins using ProBiS, and molecular dynamics will provide a quantitative measure of how firmly the predicted molecules will bind to a protein.

Here, we review these algorithms and their use in pharmaceutical discovery.
In particular:

• **ProBiS Algorithm**: for detection of structurally similar protein binding sites by local structural alignment [1]

ProBiS enables binding sites & ligands prediction based on detection of similar evolutionary patterns in proteins.

• **ProBiS-CHARMMing Web Server** @ http://probis.nih.gov for prediction and energy optimization of ligands [2]

ProBiS-CHARMMing predicts & minimizes ligands for any protein and can be used to generate holo protein structures from apo proteins (or prepare ligand-receptor complex for molecular dynamics simulation).

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BEYOND SLATER DETERMINANTS: A GENERAL SCHEME TO CONSTRUCT REALISTIC WAVE FUNCTIONS

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Many-body Hilbert space is a vector space in which the vectors are wave functions. For identical fermions, the wave functions must be antisymmetric. The Slater determinants are a complete basis for this antisymmetric-function Hilbert space, which they span as a linear space over the complex numbers, as is well known. On the other hand, wave functions are just complex functions, which can be naturally multiplied by any symmetric function to give new antisymmetric functions. But if functions are vectors, multiplying functions is vector multiplication, which naturally gives the Hilbert space the mathematical structure of an algebra. Like the Lie algebras of group theory, this Hilbert-space algebra is finite-dimensional, i.e. it has a finite number of generators. In simple technical terms, if the complex coefficients, which multiply the Slater determinants in the usual formulation, are generalized to symmetric functions, then the sum spanning the whole Hilbert space is no longer infinite. Exactly $N!^{d-1}$ antisymmetric functions are sufficient to span the whole N-fermion Hilbert space in d dimensions, with symmetric-function coefficients. Of course, the antisymmetric functions which appear in this expansion — the basis vectors of the algebra — are not arbitrary, but can be generated by an operative algorithm. They are called shapes. Shapes are true generalizations of the ground-state Slater determinant in more than one dimension. They provide a new language to discuss a number of open problems in physics, chemistry, and materials science, all centered around the construction of realistic wave functions for strongly correlated systems.

WHAT KIRCHHOFF *REALLY* DID CONCERNING SPANNING TREES IN ELECTRICAL NETWORKS AND ITS RELATIONSHIP TO MODERN GRAPH-THEORETICAL WORK

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In 1845, as a 21-year-old undergraduate, Gustav Robert Kirchhoff (writing under the pseudonym '*Studiosus*' Kirchhoff) published, as '*Mitglied des physikalischen Seminars zu Königsberg*' at the Albertina University, a classic paper[1] in which he stated his Laws I and II of electrical circuits — laws which, for more than a century, have been 'well-known to every schoolboy'. Two years later, in a second paper[2] in the *Annalen der Physik und Chemie*, he examined the mathematical foundations of these laws and it is this paper which is still of interest to modern Graph Theorists. This is because it has deep implications for the theory of linear equations[3], and it was also the first paper to consider, if only implicitly, the idea of the spanning trees of a graph.[4,5] The speaker has long had an interest in the enumeration of spanning trees[6,7] and this talk evaluates what Kirchhoff actually did in his much-cited paper of 1847, and how this relates to modern work.[5–7]

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Spectroscopic networks: small molecules as complex systems

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Several research fields in chemistry, including high-resolution molecular spectroscopy as well as thermochemistry and reaction kinetics, handle an extreme amount of data, most of which is deposited in information systems. In all these areas there is a strong ongoing activity to gather new data (preferentially via specifically designed new experiments yielding the most useful information), critically evaluate and validate them (with respect to all the available data), improve the overall quality of the resulting information system (to always provide the best existing data for, for example, engineering and scientific applications), and thus turn information into knowledge in the most efficient way. To ease these activities use of the language and the algorithms provided by network (graph) theory is recommended.

For individual molecules quantum mechanics (QM) offers a simple, natural and elegant way to build large-scale (complex) networks: quantized energy levels are the nodes, allowed transitions among the levels are the links, and transition intensities supply the weights. QM networks are characterized experimentally via spectroscopy; thus, realizations of QM networks are called spectroscopic networks (SN). As demonstrated most clearly for the SN of $H_2{}^{16}O$, involving the largest experimental SN studied containing some 200 000 transition entries and about 20 000 rovibrational energy levels and the largest *ab initio* SN containing 200 000 nodes and half a billion of links, both the measured and certain first-principles computed one-photon absorption and emission networks appear to have definitely top heavy and likely scale-free degree distributions, with a scaling parameter slightly above 2. The proposed novel view of high-resolution spectroscopy and the observed scaling of the degree distribution of SNs have important practical consequences: appearance of hubs among the energy levels, arguments about assortativity, robustness, error tolerance, and an "ultra-small-world" property of SNs. A data reduction facility via a minimum-weight spanning tree approach, which can assist high-resolution spectroscopists to improve the efficiency of the assignment of measured spectra, is a consequence of this view.

Inversion of the measured transitions to yield experimental energy levels, based on the concept of SNs, is called MARVEL (*m*easured *a*ctive *r*otational-*v*ibrational *e*nergy *l*evels). Efficient algorithms developed allow to carry out a least-squares analysis of large SNs within a fraction of a second. MARVEL has been used to analyse high-resolution spectroscopic data for $^{12}C_2$, nine isotopologues of water, for three isotopologues of H_3^+, for $^{14}NH_3$, and for parent ketene. The special role of results from "fourth-age" quantum chemical techniques during the spectroscopic analysis is emphasized.

FREE RADICAL SCAVENGING POTENCY OF PHLORETIC ACID: THERMODYNAMICS OF $2H^+/2e^-$ PROCESSES

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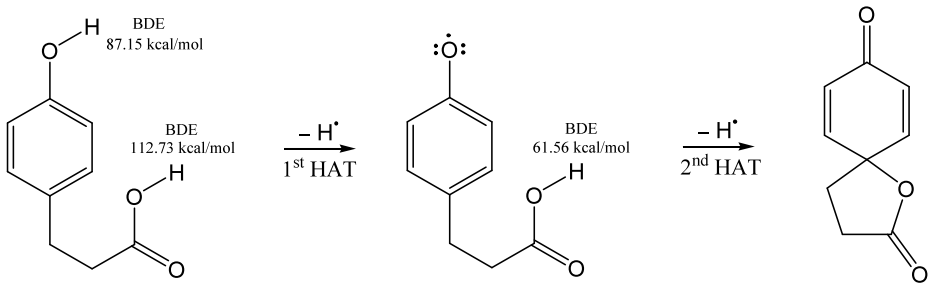
Phloretic acid (3-(4'-hydroxyphenyl)propanoic acid) is one of the most abundant colon metabolites of various classes of polyphenols (e.g., polymeric proanthocyanidins, tea catechins, and ellagitannins). Its concentration in fecal water may reach value of 210 μmol/L [1], which could be high enough to exert at least *in situ* antioxidant activity [2].

Thermodynamics of $2H^+/2e^-$ free radical scavenging mechanisms of phloretic acid was studied by DFT method using Gaussian 09 package [3]. Geometry optimizations and frequency calculations were carried out using the M06-2X/6-311++G(d,p) level of theory, in conjunction with the SMD continuum solvation model.

For the first time direct involvement of carboxylic group in free radical scavenging mechanisms was investigated considering double hydrogen atom transfer (HAT), double single electron transfer–proton transfer (SET–PT) and double sequential proton loss electron transfer (SPLET) processes producing dienone lactone [4].



Obtained results indicate that phloretic acid possesses potential for inactivating free radicals of different characteristics ($HO^•$, $HOO^•$, $CH_3O^•$, $CH_3OO^•$, $CH_2{=}CH{-}O{-}O^•$, $PhO^•$, $Cl_3COO^•$ etc.) by direct scavenging *via* double HAT and double SPLET mechanisms. In this way, because phloretic acid is produced in high μM concentrations and it is usually better absorbed than its precursor molecules, it may contribute to health benefits associated with regular intake of polyphenol-rich diet.

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UV-VIS SPECTRA OF SOME PHENOLIC SCHIFF BASES: EXPERIMENTAL AND THEORETICAL STUDY

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Schiff bases represents important class of synthetic compounds which was first synthesized in condensation reactions of aldehydes and aromatic amines [1]. Phenolic Schiff bases found wide application in medicine and pharmacy. These compounds exhibit good antitumor, antiviral, antifungal and antibacterial activity [2]. Due to these biological properties Schiff bases were used for the synthesis of many drugs [3]. Ten phenolic Schiff bases were put under examination of their UV-Vis properties. The solutions of all compounds were prepared in methanol, and the UV/Vis measurements were performed in the area of 200-500 nm range. The quantum-chemical interpretation of UV-Vis spectra of these compounds has become a crucial support for experimental data. The time-depend density functional theory (TDDFT) appear to be an effective tool to estimate UV-Vis absorption of medium sized π-conjugated compounds. Gaussian program package [4] was used for simulation of UV-Vis spectra of examined compounds and calculation were performed at the B3LYP/6-311+G(d,p) level of theory. To provide better understanding of distribution of electron density, natural bond orbital (NBO) analysis was used. NLMO clusters were constructed and they represent a part of a molecule characterized with eminent electron density. Synergism between the TDDFT and NBO theory helps for better understanding of electronic transitions engaged in the UV-Vis light absorbtion of the examined compounds. The Kohn−Sham orbitals can be replaced with NLMO clusters since they are described with specified energies and shapes. NLMO clusters provide delocalization over the definite part of molecule, while the Kohn-Sham orbitals are delocalized through the whole structure.

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STRUCTURAL AND ANTIOXIDATIVE FEATURES OF CHLOROGENIC ACID

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Chlorogenic acid (5-O-caffeoylquinic acid, **5CQA**) shows pharmacological and nutritional properties, such as antitumor [1], antidiabetic [2], antihypertensive [3], antiatherosclerotic [4], anti-inflammatory, hypolipidemic [2] and antioxidative [5] activities.

This work contributes to clarification of **5CQA** structure by comparing the experimental and simulated IR, Raman, ^{1}H-NMR, ^{13}C-NMR, and UV spectra. For this purpose, a comprehensive conformational analysis of **5CQA** was performed to reveal its most stable conformations in the gas-state and solution. The lowest-energy conformers were used to predict the spectra by means of density functional theory. Very good agreement between all experimental and simulated spectra indicates correct arrangement of the atoms in the **5CQA** molecule. The quinic moiety is characterized with directed hydrogen bonds, where the carboxylic hydrogen is not oriented towards the carbonyl oxygen of the carboxylic group, but towards the oxygen of the proximate hydroxyl group.

In addition, the bond dissociation enthalpies, proton affinities, electron transfer enthalpies, ionization potentials, and proton dissociation enthalpies for **5CQA** and caffeic acid were used for thermodynamic consideration of the major antioxidative mechanisms: HAT (Hydrogen Atom Transfer), SPLET (Sequential Proton-Loss Electron-Transfer), and SET-PT (Single Electron Transfer – Proton Transfer). Both compounds are characterized with very similar values of each enthalpy, suggesting that they will exhibit comparable antioxidative activities. This assumption is in perfect accord with the experimental findings. HAT may be the predominant mechanism in nonpolar solvents, while HAT and SPLET are competitive pathways in polar media. Mechanistic investigation of the HAT and SPLET pathways are under intensive scrutiny.

References:

[1] Y. J. Liu, C. Y. Zhou, C. H. Qiu, X. M. Lu, Y. T. Wang, *Mol. Med. Rep.* **8 (**2013) 1106–1110.

[2] K. W. Ong, A. Hsu, B. K. Tan, *PLoS One* **7** (2012) e32718.

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THE "ANTHRACENE PROBLEM": REACTIVITY-BASED AROMATICITY STUDY OF BENZO-ANNELATED ANTHRACENES

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The so called "anthracene problem" refer to the phenomena that the different aromaticity indices predict different order of aromaticity of anthracene rings. The aromatic nature of the hexagonal rings of anthracene was assessed by studding the reaction mechanism of the bromine addition. The obtained results were compared with several different aromaticity indices, namely, the energy effect (ef), multicenter delocalization indices (MCI), harmonic oscillator model of aromaticity (HOMA) index, and nucleus independent chemical shifts (NICS). The reactivity based study of aromaticity was further applied to analyze the effect of benzo-annelation on the aromaticity of the central ring in anthracene derivatives. It was shown that the distribution of the bromination products depends on the local aromaticity of the individual rings. This way, it was shown that the aromaticity indices can be used to assess the reactivity of the studied molecules.

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MOLECULAR DYNAMICS SIMULATIONS IN BIOLOGICALLY RELEVANT SYSTEMS

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In this talk, basic principles of molecular dynamics simulations and other computational techniques relevant for biologically important systems will be outlined with aim to reveal molecular details of the processes occuring at the nanosecond timescale. In particular, several interesting problems, such as behavior of membranes under oxidative stress conditions [1] and cell penetrating peptide translocation [2], will be presented. Finally, a case study of theoretically predicted attractive interactions between positively charged guanidinium cations in water will be described [3]. This unusual and counterintuitive interaction still lacks a direct experimental verification and it is suggested that NMR technique might be well suited for this purpose.

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In addition, the bond dissociation enthalpies, proton affinities, electron transfer enthalpies, ionization potentials, and proton dissociation enthalpies for **5CQA** and caffeic acid were used for thermodynamic consideration of the major antioxidative mechanisms: HAT (Hydrogen Atom Transfer), SPLET (Sequential Proton-Loss Electron-Transfer), and SET-PT (Single Electron Transfer – Proton Transfer). Both compounds are characterized with very similar values of each enthalpy, suggesting that they will exhibit comparable antioxidative activities. This assumption is in perfect accord with the experimental findings. HAT may be the predominant mechanism in nonpolar solvents, while HAT and SPLET are competitive pathways in polar media. Mechanistic investigation of the HAT and SPLET pathways are under intensive scrutiny.

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From Superacid Chemistry to '*in silico*' Chemistry

Selected Topics of Experimental and Computational NMR Spectroscopy of Carbocations

28th MC2 Conference
June 20–26, 2016, Dubrovnik, Croatia

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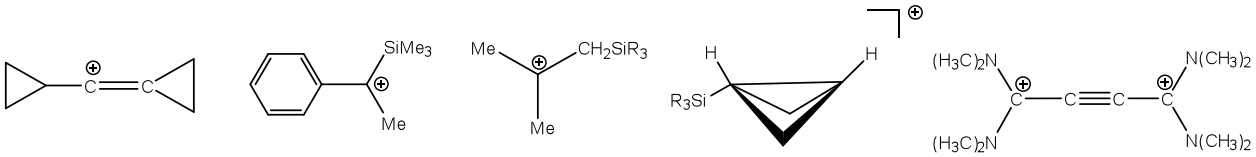
In this contribution some retrospective and recent results on experimental and computational NMR Spectroscopy of highly reactive carbocations will be presented.

Selected examples such as the experimental and computational characterization of vinyl cations, the effect of silyl groups on carbocations, a "simple" solution of the conundrum of the $C_4H_7^+$ cation problem and other topics will be presented. It will be demonstrated that the accurate calculation of magnetic parameters such as ^{13}C-NMR chemical shifts and J_{CC} and J_{SiC} spin-spin coupling constants are a useful tool for a detailed understanding of hyperconjugation and hypercoordination in carbocations.



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Aromaticity – One of the Central Concept of Chemistry, Revisited

Milan Randić

In 1865 August Kekulé proposed cyclic structure of benzene, the prototype of aromaticity, the formula of which involves alternating CC single and double bonds. He suggesting that aromaticity be defined in terms of molecular structural characteristics. It was only in 1930 that Erich Hückel (a physicist) has shown that monocyclic C_nH_n systems are aromatic if they have $4n+2$ π-electrons and non aromatic if they have $4n$ π-electrons. This explaines why benzene C_6H_6 is aromatic and cyclooctatetrene C_8H_8 is not aromatic, which was a great mystery up to that time. Hückel $4n+2$ Rule has been one of the greatest successes of quantum chemistry, and generalizations of the Hückel $4n+2$ Rule to polycyclic systems remained one of the greatest challenges for theoretical chemistry for the following decades. With arrival of Chemical Graph Theory there war renewed interest in unsolved problems of chemistry of the past. Thus in 1976, which is 110 years after Erlenmayer introduced three Kekulé valence structures for naphthalene, were found conjugated circuits, which, almost 50 years after Hückel, lead to the generalization of the Hückel $4n+2$ Rule to polycyclic systems in 1977. This allowed Cyvin and Gutman to prove a theorem that shows that all benzenoid hydrocarbons are aromatic, while the generalized Hückel $4n+2$ Rule shows that among nonbenzenoid systems there are aromatic, less aromatic, and no aromatic systems. In 1972 Eric Clar advanced his "Aromatic Sextet" theory to explain why some benzenoid hydrocarbons are more aromatic then others. However, Clar "Aromatic Sextet" theory, expressed in terms of aromatic sextet rings, migrating sextet rings, and "empty" rings, remained a qualitative model till 2014, when it was cast into numerical representation using the concept of *ring bond orders*, which are based on Pauling bond orders of 1935, and could have been introduced eighty years ago – but were not! With generalized Hückel $4n+2$ Rule and quantitative Clar "Aromatic Sextet" theory, aromaticity of conjugated benzenoid and nonbenzenoid hydrocarbons is no longer the problem. Observe that interest in Kekulé valence structures, which has been always present in Chemical Graph Theory, lead to conjugated circuits, and ring bond orders. The problem that remains is general unfamiliarity of chemists at large with the notion of conjugated circuits. We end the lecture with brief comparison of calculation of ring currents in conjugated hydrocarbons by enumeration of contribution of conjugated circuits and by exact quantum chemistry approach.

ROBUST VALIDATION OF APPROXIMATE 1-MATRIX FUNCTIONALS WITH FEW-ELECTRON HARMONIUM ATOMS

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A simple comparison between the exact and approximate correlation components U of the electron-electron repulsion energy of several states of few-electron harmonium atoms with varying confinement strengths provides a stringent validation tool for 1-matrix functionals. The robustness of this tool is clearly demonstrated in a survey of 14 known functionals, which reveals their substandard performance within different electron correlation regimes. Unlike spot-testing that employs dissociation curves of diatomic molecules or more extensive benchmarking against experimental atomization energies of molecules comprising some standard set, the present approach not only uncovers the flaws and patent failures of the functionals but, even more importantly, also allows for pinpointing their root causes. Since the approximate values of U are computed at exact 1-densities, the testing requires minimal programming and thus is particularly suitable for rapid screening of new functionals.

Structural characterization of the toxin-coregulated pilus H (TcpH) protein by liquid-state NMR

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Cholera is an acute intestinal infection disease which is still present in developing countries. Based on malnutrition and poor sanitary conditions the ingestion of food or water contaminated with the bacterium *Vibrio cholerae* leads to water diarrhea. This can result in death by dehydration within few hours if treatment is not promptly given.

The two main virulence factors of *Vibrio cholerae* are the cholera toxin, which causes massive loss of water and the toxin-coregulated pilus which is necessary for colonization in the intestine. The regulation of both of these factors is provided by the transcription factor ToxT. ToxT on its part is regulated by the membrane-bound transcription factors ToxR and TcpP. The interaction partner of TcpP is TcpH that protects it from proteolytic degradation and thereby significantly influences the regulation [2]. TcpH is a 16.3 kDa membrane protein and consist of 2 domains: an N-terminal membrane domain which is embedded in the plasma membrane and a most likely unstructured C-terminal domain which is extends into the periplasm and interacts with TcpP.

Calculating the structure of all proteins of the cascade would not only give exact insights in the mechanism of cholera toxin regulation but also potential treatment targets.

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ENUMERATION OF DIAGONALLY CONVEX POLYOMINOES

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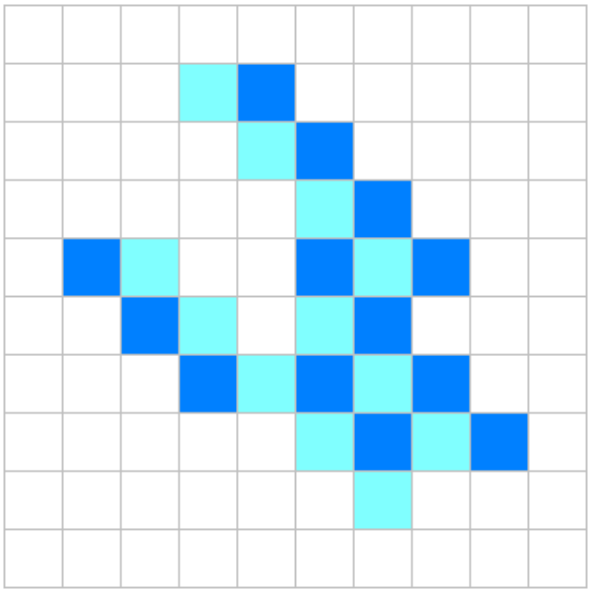

Already 20 years ago, column-convex polyominoes and directed diagonally convex polyominoes were well explored models. By contrast, nothing was known about general (*i.e.*, undirected) diagonally convex polyominoes. So in her habilitation thesis, published in 1996, Mireille Bousquet-Mélou wrote: “En comparant aux tableaux précédents les nombreux travaux effectués, on est d’abord frappé par le fait que la convexité diagonale n’a été que peu étudiée…” In the meantime, things have not changed. Combinatorialists somehow got used to this gap in their knowledge.

But in the present lecture, the gap will be filled (at least partly). Namely, we have enumerated diagonally convex polyominoes by perimeter. The perimeter generating function is very complicated and satisfies an algebraic equation of degree eight. The Taylor series expansion of that generating function is

$$x^4 + 2x^6 + 7x^8 + 28x^{10} + 122x^{12} + 556x^{14} + 2618x^{16} + 12634x^{18} + 62128x^{20}$$

$$+ 310212x^{22} + 1568495x^{24} + 8014742x^{26} + 41323641x^{28} + 214719610x^{30} + \ldots$$

FUNCTIONAL AND STRUCTURAL STUDIES OF THE BACTERIAL TOXIN LdrD

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Several Toxin/Anti-Toxin (TA) systems have been described in different prokaryotic species including *Escherichia coli*. The TA system *LdrD* codes for two open reading frames of 35 and 28 codons. *LdrD*-35 is a 35 aminoacid peptide which causes growth inhibition and changes in the cell physiology [1]. Until now the mode how *ldrD*-35 exerts its toxic effect is unknown; besides, there is no evidence of the expression of the full length *ldrD* peptide although its mRNA is very stable and constitutively expressed under experimental conditions. We therefore aimed to find a cellular target for the *LdrD* peptide in order to further understand its toxic mechanism inside the cell.

We studied the post-transcriptional events coupled to the expression of the *ldrd*-35 peptide in order to understand the mechanism of action in the cell and to elucidate why the peptide is not expressed, we also performed structural studies over the synthetic peptide to gain further hints about the possible targets of the peptide which could lead to the toxic effects exerted by this gene. In this work we found strong evidence supporting that the LdrD peptide interacts with ribosomal elements including the protein L4 in the ribosomal tunnel. The structural studies showed a high helical propensity in the peptide which is a common feature between the so called stalling peptides [2]. We present here the first functional/structural study of LdrD and propose a new mechanism for the activity of type I Toxin/Anti-toxin systems where the toxin element acts as a ribosome stalling peptide.

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Ontological status of chemical formula

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In papers about the philosophy of science, and especially in philosophy of chemistry, the discussion focused to the meaning of chemical formula appeared frequently in recent years. The main question is about the role of chemical formula as a possible barrier of deeper information. There are two opposite opinions of which the first argues that the formula is only the working symbol derived from the corresponding nomenclature, while the second propose the explanation that formula represents an un-ended origin of chemical information.

I will represent here the short history of chemical formula, the ideas behind it, and the role of chemical formula in the construction of basic chemical concepts.