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**BOOK OF**

**ABSTRACTS**

**Editors: Hrvoj Vančik and Jerzy Cioslowski**

# NOVEL STATISTICAL PARAMETERS FOR MODEL QUALITY ESTIMATION

**Bono Lučić,<sup>a</sup> Jadranko Batista,<sup>b</sup> Viktor Bojović,<sup>a</sup> Mario Lovrić<sup>c,d</sup>**

<sup>a</sup>*NMR Centre, Ruđer Bošković Institute, Zagreb, Croatia, lucic@irb.hr*

<sup>b</sup>*Faculty of Science and Education, University of Mostar, Mostar, Bosnia and Herzegovina*

<sup>c</sup>*Srebrnjak Children's Hospital, Srebrnjak, Zagreb, Croatia*

<sup>d</sup>*Know-Center, Inffeldgasse 13/6, AT-8010 Graz, Austria*

The choice of model quality evaluation parameters is a very important decision in selecting the best model developed in an attempt to relate property/activity of molecules with their structure described by molecular descriptors. Quality evaluation parameters are statistical parameters, like correlation coefficient ( $R$ ) or standard error of estimate ( $S$ ) together with other analogous parameters, calculated between an experimental set of values and those estimated or predicted by the model. The size of data set (i.e. the number of compounds in data set) and the number of optimized parameters in the model determine the number of degrees of freedom of the problem, which is further used in assessing the significance of statistical parameters and confidence interval. However, in many problems in chemistry or life sciences, the distribution of data is drastically skewed, having in data set only a few active compounds and a lot of inactive ones. In that case, standard model quality evaluation parameters ( $R$ ,  $S$ ) could be over-optimistic. If the data set is very large, the obtained parameters will be highly significant. To overcome this problem the concept of chance correlation is introduced. Because standard parameters like  $R$  or  $S$  do not include information about the chance accuracy, novel parameters are defined that take it into account. Their values give information about the real contribution of the model over the most probable chance accuracy. An overview and comparison of these parameters will be given and their usefulness will be illustrated on several two-state classification problems. Possibility of generalization of these parameters to classification problems with more than two classes will be analyzed.

**Acknowledgement:** This research is supported by the Croatian Ministry of Science and Education through basic grants given to their institutions and by the Croatian Government and the European Union through the European Regional Development Fund – the Competitiveness and Cohesion Operational Programme (KK.01.1.1.01) The Scientific Centre of Excellence for Marine Bioprospecting – BioProCro.

# DEPENDENCE OF THE TOTAL PHENOLIC CONTENT MEASUREMENT VALUES ON THE PROCEDURE USED FOR DETERMINATION OF CALIBRATION CURVE

Drago Bešlo,<sup>a</sup> Suzana Kristek,<sup>a</sup> Dražen Vikić-Topić,<sup>b,c</sup> Bakhtiyor Rasulev,<sup>d</sup> Bono Lučić<sup>b</sup>

<sup>a</sup>J. J. Strossmayer University of Osijek, Faculty of Agrobiotechnical Sciences Osijek, Osijek, Croatia,  
*dbeslo@fazos.hr*

<sup>b</sup>NMR Centre, Ruđer Bošković Institute, Zagreb, Croatia, *lucic@irb.hr*

<sup>c</sup>Department of Natural and Health Sciences, J. Dobrila University of Pula, Pula, Croatia

<sup>d</sup>North Dakota State University, Department of Coatings and Polymeric Materials, Fargo, ND, USA

The total phenols are determined by the modified Folin-Ciocalteu method in such a way that the Folin-Ciocalteu reagent (a mixture of phosphotungstate and phosphomolybdic acid), in reaction with phenolic components reduces and changes color to blue [1]. During the measurement of the total phenolic content, the concentration is determined by using the calibration curve of gallic or ascorbic acid. Depending on the choice of the reference compound for determination of calibration curve and on the theoretical approach used for determination of calibration curve, the results may vary considerably. Through the measurement of the total phenolic content of the same type of honey (e.g. acacia), it appears that the total phenolic contents of the same type of honey vary depending on the geographical dispersion, the influence of climatic factors in the current year, the difference between the time of sampling and the time of measurement, etc. However, in addition to these expected and normal variations, the increased disagreement between the measurements in different laboratories could be also due to differences in the process of determination of calibration curve. Namely, analyzing results in the most frequently cited papers [1-3], significant differences in total phenolic contents were observed. These discrepancies are primarily related to the minimal and maximal range of measurement of gallic or ascorbic acid concentrations in which the calibration curve is determined, comparing with the total phenolic contents of samples. Thus, it is possible to produce a calibration curve passing through the starting point, while some authors provide the calibration curve without including the starting point. The influence of these factors is investigated in analysis of total phenolic contents of 99 honey samples from the South-Eastern European region.

**Acknowledgement:** This research is supported by the Croatian Ministry of Science and Education through basic grants given to their institutions and by the Croatian Government and the European Union through the European Regional Development Fund – the Competitiveness and Cohesion Operational Programme (KK.01.1.1.01) The Scientific Centre of Excellence for Marine Bioprospecting – BioProCro.

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## Similarity Based Approach for Elucidation of Drug-Kinase Binding Affinities

**Davor Oršolić<sup>a</sup>, Bono Lucić<sup>b</sup>, Višnja Stepanić<sup>c</sup>, Tomislav Šmuc<sup>d</sup>**

<sup>a</sup>Ruder Bošković Institute, Bijenička cesta 54, 10000 Zagreb, davor.orsolic@irb.hr

<sup>b</sup>Ruder Bošković Institute, Bijenička cesta 54, 10000 Zagreb, bono.lucic@irb.hr

<sup>c</sup>Ruder Bošković Institute, Bijenička cesta 54, 10000 Zagreb, visnja.stepanic@irb.hr

<sup>d</sup>Ruder Bošković Institute, Bijenička cesta 54, 10000 Zagreb, tomislav.smuc@irb.hr

Protein kinases catalyze the phosphorylation of proteins which is probably the most important regulatory mechanism in all living organisms, meaning their deregulation is a contributing factor in an increasing list of diseases including cancer [1,2]. Therefore, mapping the kinase target space for drugs and drug-like compounds, including marine organisms and their byproducts, and extending the druggability of the human kinome space is of huge clinical interest [3,4].

To address this challenge we have developed similarity based approach for elucidation of drug-target interaction profiles [5]. Predictive methodology used relied on ensemble learning methods, Random Forest and Xgboost algorithms in R [6,7]. This framework was used to predict interaction profiles, or binding affinities, for dedicated drug-like compounds and kinases, using fingerprint based and sequence based similarity features, respectively.

Findings from our experiments show that the approach based on similarities is promising approach for the treatment of large and diverse sets of compounds and targets, and that learning methodology should be capable to capture highly non-linear and very localized interactions. In that respect models trained based on smaller number of samples in close proximity of test samples (learning in the neighborhood or proximity of the actual tested interaction pairs) gave more accurate predictions than learning from large, non-localized training set.

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# **Classification of fungicides based on the mode of action (MOA) with extension to DrugBank molecules**

**Ozren Jović, Bono Lučić, Višnja Stepanić, and Tomislav Šmuc**

*Ruđer Bošković Institute, Bijenička cesta 54, 10 000 Zagreb, Ozren.Jovic@irb.hr*

Approximately 215 fungicides have been sorted based on their mode of action (MOA) in the biochemical pathways of plant fungal pathogens, in the Fungicide Resistance Action Committee (FRAC) MOA Code List 2019 [1]. The FRAC grouping is made according to processes in metabolism (such as nucleic acid metabolism), respiration, sterol biosynthesis in membranes, etc. So far, 377 fungicides have been approved for use [2], and only some of them have already been classified according to MOA. In addition, there are antifungal compounds other yet unapproved with unknown mode of action [1,3]. The goal of this research was to establish a model for classification of unknown compounds to fungicide or non-fungicide group and to assign fungicide group to corresponding MOA, which is of importance also for bioprospecting of novel bioactive marine compounds. Partial-least squares regression discriminant analysis (PLS-DA), uninformative variable elimination PLS-DA (UVE-PLS-DA) and Random Forest algorithms were [4] applied in modeling on fungicide sets of compounds with 1D and 2D Padel Descriptors [5]; 2/3 samples were taken for calibration and 1/3 for validation. The obtained model was used to classify each of the rest yet unclassified antifungal compounds into 11 broad MOA classes (models with fewer classes were considered too). Additionally, prioritized compounds with unknown activity mode from DrugBank database (all DrugBank molecules considered) were classified too. Prioritization of DrugBank compounds for the MOA classification was based on specific regression and descriptor rule criteria which were inferred to determine whether the candidate compound has basic characteristics of an antifungal agent.

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# A NEW ALGORITHM FOR FINDING LARGEST SMALL POLYGONS

Charles Audet,<sup>a</sup>, Pierre Hansen,<sup>b</sup> and Dragutin Svrtan<sup>c</sup>

<sup>a</sup> Ecole Polytechnique de Montreal, Canada , Charles.Audet@gerad.ca

, HEC Montreal , pierre.hansen@gerad.ca

<sup>c</sup> Faculty of Science, Departement of Mathematics, Zagreb, Croatia, dragutin.svrtan@gmail.com

## Abstract:

A small polygon is a convex polygon ( in the euclidean plane ) of unit diameter. The problem of determining the largest area of small n-gons was already studied almost 100 years ago by Reinhardt . He showed that regular n-gons are optimal when n is odd and kites with unit length diagonals are optimal when n=4. For n=6 the largest area is a root of a degree 10 polynomial with integer coefficients having up to 6 digits. . This is the famous Graham's largest little hexagon (1975). R.L.Graham (with S.C.Johnson) needed factoring a 40-degree polynomial with up to 25- digit coefficients. Graham introduced the diameter graphs by joining the vertices at maximal distance. For n=6 (resp.8 ) there are 10 (resp. 31) possible diameter graphs. The case n=8 was attacked in 2002 by C. Audet, P.Hansen, F.Messine and J.Xiong via global optimization (10 variables and 20 constraints) which produced (an approximate) famous Hansen's little octagon.

In this talk we report on a new optimization algorithm which uses complex arithmetic and Laurent polynomials ( instead of rational functions). By iterated discriminant computations and symbolic factorizations we obtain minimal equation F8 (of degree 42) for the area of the largest small axially symmetric octagon . Similar explicit equation F10 we have obtained for the largest small axially symmetric decagons has degree 152, but in that case we have encountered intermediate polynomials with coefficients having enormous size (up to 2893 digits !).

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# 1, 3-H-SHIFT – A NEW ROUTE TO STATIC BICYCLOBUTONIUM IONS

## Further Answers to the Conundrum of the Structure of C<sub>4</sub>H<sub>7</sub><sup>+</sup> Cation

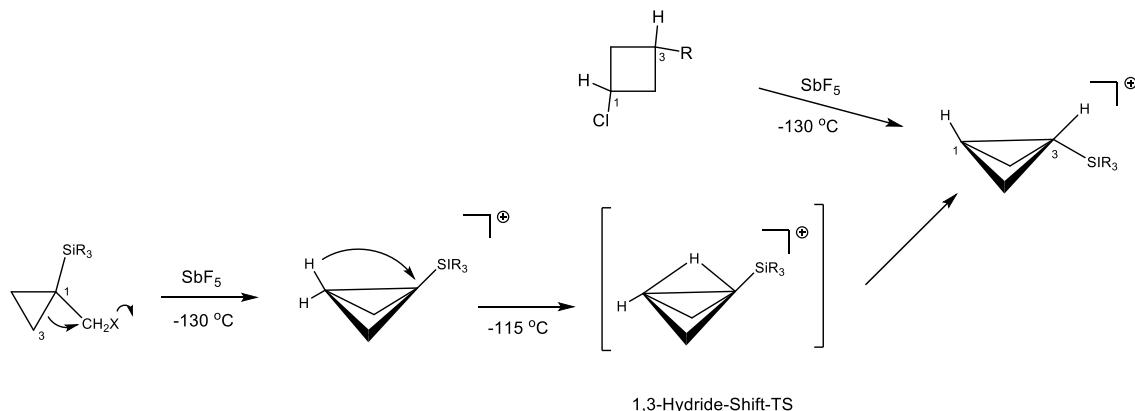
**Hans-Ulrich SIEHL**

*Ulm University, D-89069 Ulm, Germany*  
*Ullrich.siehl@uni-ulm.de*

The cyclobutyl/cyclopropylmethyl cation system (C<sub>4</sub>H<sub>7</sub>)<sup>+</sup> has most likely been the focus of more studies than any other carbocation system except the 2-norbornyl cation. Over a timespan of more than half a century practically all the tools of experimental physical organic chemistry and numerous computational methods have been utilized to shed light on the structure and dynamics of these type of carbocations. The current consensus for the parent C<sub>4</sub>H<sub>7</sub><sup>+</sup> cation seems to be that two isomeric structures each threefold degenerate and of nearly equal stability equilibrate on a very flat potential energy surface. The fast interconversion prevented a straightforward structural assignment in solution.

Recently we have shown that **static** substituted bicyclobutonium cations can be generated using appropriate silyl-substituted cyclobutyl precursors.

We now describe a new pathway to generate static 3-silyl substituted bicyclobutonium cations via 1,3-Hydride shift.



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# Interdisciplinary Study of Dipeptidyl Peptidase III – Keap1 Interactions

**Sanja Tomić,<sup>a</sup> Sara Matić,<sup>a</sup> Filip Šupljika,<sup>b</sup> Mihaela Matovina,<sup>a</sup> Ferenc Bogar<sup>c</sup>  
and Marko Tomin<sup>a</sup>**

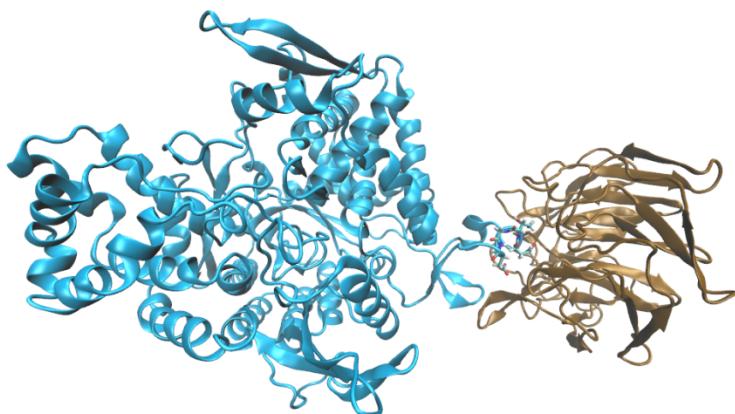
<sup>a</sup> Division of Organic Chemistry and Biochemistry, Ruder Bošković Institute, Bijenička cesta 54, 10000 Zagreb, Croatia, [sanja.tomic@irb.hr](mailto:sanja.tomic@irb.hr)

<sup>b</sup> Faculty of Food Technology and Biotechnology, University of Zagreb, Zagreb, Croatia, [fsupljik@irb.hr](mailto:fsupljik@irb.hr)  
<sup>c</sup> MTA-SZTE Biomimetic Systems Research Group, University of Szeged, Hungarian Academy of Sciences  
[bogar@sol.cc.u-szeged.hu](mailto:bogar@sol.cc.u-szeged.hu)

Human dipeptidyl peptidase III (hDPP III) is a cytosolic, zinc dependent exopeptidase, widely distributed in mammalian tissue and considered to participate in the final steps of the protein degradation, but also in many other physiological processes. So, there is a clear evidence of its involvement in the cytoprotective Keap1/Nrf2 pathway, most probably by binding to Keap1, a negative regulator of the nuclear erythroid 2–related factor 2 (Nrf2), in the oxidative stress conditions [1].

With the aim to better understand involvement of human DPP III in the Keap1- Nrf2 pathway and in this way its role in the oxidative stress regulation, we studied its binding to the Keap1 protein. Like Nrf2, hDPP III binds to the Kelch domain of the Keap1 protein via the ETGE motif. Although located in a flexible loop, this motif is firmly attached to the DPP III protein body and we have not noticed its translocation during extensive MD simulations [2, 3].

Based on the results of our studies, experimental and computational, we could conclude that the ETGE loop translocation is an energetic barrier in the process of the hDPP III – Keap1 binding.



hDPP III (cyan) – Kelch (ochre) complex obtained after 330 ns of MD simulation.

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# SOME OBSERVATIONS ON TRIPLET GROUND-STATES IN THE CONTEXT OF ‘TOPOLOGICAL’ (HLPM) RING-CURRENTS IN CONJUGATED SYSTEMS

T. K. Dickens & R. B. Mallion

Peterhouse, Cambridge CB2 1RD, England, United Kingdom

When the quasi graph-theoretical Hückel–London–Pople–McWeeny (HLPM) approach<sup>1–4</sup> is used to calculate ‘topological’  $\pi$ -electron ring-currents and bond-currents in conjugated hydrocarbons, a problem is identified that occurs whenever application of the *Aufbau* process<sup>5</sup> gives rise to a triplet  $\pi$ -electronic ground-state configuration. This circumstance seems to occur only rarely and, when it does, the generally somewhat *outré* molecular graphs in question appear unlikely to represent extant or viable conjugated systems. The molecular graphs of four examples are used to illustrate this ‘triplet ground-state’ problem, only one of which represents a hydrocarbon that has actually been synthesised. It is pointed out that the triplet ground-state problem does constitute an intrinsic limitation of the HLPM approach. It is, however, also a limitation that is necessarily inherent in other equivalent (though ostensibly different) methods of calculating magnetic properties due to  $\pi$ -electron ring-currents — methods that are likewise founded on the Hückel molecular-orbital conventions.<sup>6</sup> When a triplet ground-state arises, topological ring-currents and bond-currents cannot be calculated by the HLPM method. Infinite paramagnetism is formally predicted in such situations.<sup>7,8</sup>

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# UNOCCUPIED NATURAL ORBITALS IN ATOMS AND MOLECULES

**Jerzy Cioslowski**

*Institute of Physics, University of Szczecin, Wielkopolska 15, 70-451 Szczecin, Poland  
jerzy@wmf.univ.szczecin.pl*

The existence of unoccupied natural orbitals (UNOs) in Coulombic systems of interacting particles is of fundamental importance to electronic structure theory. If confirmed, it would invalidate core assumptions behind many approximate treatments of the electron correlation problem, such as the 1-matrix functional theory (DMFT) and the extended Koopmans' theorem (EKT). Whereas systematic search for UNOs in arbitrary many-electron atoms and molecules is not facile, it can be productively carried out in the case of two-electron species thanks to the simple structure of their singlet ground-state wavefunctions.

The appearance of UNOs in two-electron harmonium atoms at certain magnitudes of the confinement strength has been unequivocally proven in the course of recent investigations in which sign patterns of the natural amplitudes have been rigorously analyzed. In the study described in this talk, an analogous approach, which involves juxtaposing the sign patterns at the united-atom and dissociation limits, is applied to the H<sub>2</sub> molecule. Its reliability hinges upon high accuracy of the natural amplitudes {λ<sub>nl</sub>} pertaining to the ground state of the helium atom that are obtained from calculations employing the Nakatsuji generators and exact numerical quadratures.

Employment of these quadratures results in an efficient algorithm for calculation of {λ<sub>nl</sub>} and the corresponding natural orbitals (NOs). The results of such calculations are presented for the total of 600 NOs pertaining to the ground state of the helium atom. The benchmark-quality values of {λ<sub>nl</sub>} computed for 1 ≤ n ≤ 100 and 0 ≤ l ≤ 5 reveal gross inaccuracies in the previously published data. In particular, the dependence of {λ<sub>nl</sub>} on n is found to follow very closely a simple power-scaling that, contrary to previous claims, varies only weakly with l. Even more importantly, the high accuracy of the present calculations makes it possible to state with almost certainty that in the case of the ground state of the helium atom the only positive-valued natural amplitude is that pertaining to the strongly-occupied orbital, i.e {λ<sub>10</sub>}.

# The Chemistry Development Kit (CDK): A Java Library for Chemo- and Bioinformatics

**Mehmet Aziz Yirik,<sup>a</sup> Christoph Steinbeck<sup>a</sup>**

<sup>a</sup>*Institute for Inorganic and Analytical Chemistry,  
Friedrich-Schiller-University,  
Jena, Germany*

MAY: [yirik.mehmetaziz@uni-jena.de](mailto:yirik.mehmetaziz@uni-jena.de) CS: [christoph.steinbeck@uni-jena.de](mailto:christoph.steinbeck@uni-jena.de)

The Chemistry Development Kit is a widely-used open source cheminformatics library developed since the year 2000 with contribution of now more than 100 scientists. It is a collection of modules covering an object-oriented model of chemical graphs, input and output of structure information in many popular formats, ring searching, aromaticity detection, descriptor calculation, structure diagram generation, rendering and more. Due to its LGPL license, the CDK can be easily integrated with both open-source and proprietary projects. The library is now available in version 2.1 with vastly improved computational performance. The CDK code is maintained with quality control measures such as regular code review. The toolkit is continuously extended with many new algorithms and implementations such as computer-assisted structure elucidation methods, mathematical chemistry, chemical image generation and so on.

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# INVERSE MOLECULAR DOCKING AS A POWERFUL NEW APPROACH IN DISCERNING PROMISCOUS MODE OF ACTION OF NATURAL COMPOUNDS

**Urban Bren,<sup>a</sup> Veronika Furlan,<sup>a</sup> Katarina Kores,<sup>a</sup> Janez Konc<sup>a</sup> and Matevž Bren<sup>b</sup>**

<sup>a</sup> Faculty of Chemistry and Chemical Technology, University of Maribor, Smetanova 17, SI-2000 Maribor, Slovenia, [urban.bren@um.si](mailto:urban.bren@um.si)

<sup>b</sup> Institute of Mathematics, Physics and Mechanics, Jadranska 19, SI-1000 Ljubljana, Slovenia, [matevz.bren@um.si](mailto:matevz.bren@um.si)

Research efforts are placing an ever increasing emphasis on identifying signal transduction pathways related to the chemopreventive activity of natural compounds such as curcumin and resveratrol. Using a novel inverse molecular docking approach, we sought to find new potential targets of these two polyphenols. Docking of curcumin and resveratrol into each ProBiS predicted binding site of >38 000 nonredundant protein structures from the Protein Data Bank was performed, and a number of their new potential targets was successfully identified. These explain known actions or predict new effects of both curcumin and resveratrol. We firmly believe that our computational results will complement and direct future experimental studies on their anticancer activity as well as on their therapeutic effects against neurodegenerative disorders.

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# Explicitly correlated wavefunctions in quantum chemistry

**Filip Pratnicki<sup>a</sup>**

<sup>a</sup>*Institute of Physics, University of Szczecin, Wielkopolska 15, 70-451 Szczecin, Poland,  
filip.pratnicki@gmail.com*

One of the basic challenges of quantum chemistry is the search for the solutions of the time-independent Schrödinger equation, which is particularly complicated for many-body systems. Constituting the basis for calculations of electronic properties of atoms, molecules and extended systems, these solutions, i.e. many-electron wavefunctions, provide information of great importance to many branches of chemistry. What appears to be crucial is the choice of the proper method that can provide very high accuracy with relatively low computational cost. A whole group of such fast converging methods comprises the formalisms that employ the explicitly correlated wavefunctions.

During the first part of this talk a theoretical concept of correlation effects in electronic wavefunctions will be presented and analyzed using simple systems such as He atom and H<sub>2</sub> molecule as an example. This will include a review of different types of correlation, cusp conditions, convergence rates and methods, allowing for inclusion of the approaches to electron correlation problem such as configuration-interaction (CI), coupled-cluster (CC) and Møller-Plesset (MP) theories.

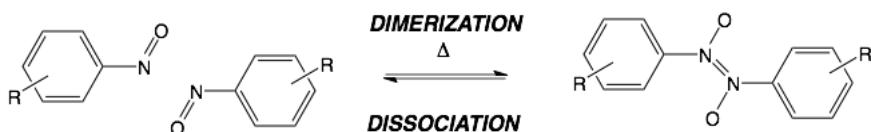
The second part of the lecture will be devoted to the overview of the whole family of explicitly correlated wavefunctions, whose history is ninety years old, starting with the Hylleraas-type wavefunctions, through Gaussians (ECGs, GTGs and GGn methods), and up to the R12 and F12 theories. Both the description of different variants of the formalisms and the issues concerning their potential computational problems and efficiency for systems of diverse sizes will be mentioned.

# Concept of thermal solid-state reaction mechanisms

Hrvoj Vančik

Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac  
102A, 10000 Zagreb, Croatia, vancik@chem.pmf.hr

Three types of organic solid-state reactions, dimerizations, dissociations, and *Z*–*E* isomerizations were investigated by using the transformations of aromatic C-nitroso compounds in crystalline solids as a convenient molecular model. Here we propose a conceptual frame for solid-state organic reaction mechanisms by examining activation parameters obtained from kinetic measurements under specific experimental conditions. The possibility of the appearance of a sort of short-lived intermediate liquid-like phase that constitutes a critical condition for initiating chemical reaction in crystalline solids, similarly to the mechanism for the thermal solid-state reactions proposed by Paul and Curtin is discussed. The analogy of the proposed concept with the recent hypothesis about the variable rigidity/softness of the reaction cavity in the enzyme reactions, and with the newest molecular dynamic simulation studies of solid phase transformations was considered.



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