Molecular Descriptors Family on QSAR Modeling of Quinoline-based Compounds Biological Activities

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Motivation

- Structure – activity relationships allow explaining of biological activities and can suggest the synthesizing of new active compounds.

Idea

- The idea is to create a unitary approach, based on a minimal set of well-known truths, capable to generate an efficient model of activity behavior depending on molecular structure.

Material

- A set of 15 Quinoline based compounds was taken into study.
- Quinolines, heterocyclic compounds, are an aromatic nitrogen compounds characterized by a double-ring structure contains a benzene and a pyridine, with antiseptic, antipyretic, and antiperiodic properties, widely used as a parent compound to make drugs.
- Mutagenicity and cytotoxicity of quinolines in Salmonella typhimurium was used as investigated activities.

Method

- A new original set of molecular descriptors, called Molecular Descriptors Family (MDF) was used to make the Quantitative Structure - Activity Relationship study.
- The MDF is of pure structural nature and take into account both geometrical and topological model of molecules. The MDF use sets of atomic properties, distance metrics, interaction descriptors, overlapping descriptors methods, molecular fragmentation criterions, overall fragmental descriptors superposing methods, and linearization procedures in order to produce a number of 787968 MDF members with different calculation formulas.

The MDF

It use sets of object oriented properties and methods as follows:

- Atomic property (p) can be one of: M (mass), Q(charge), C(cardinality), E(electronegativity), G(group electronegativity);
- Distance metric (d) can be one of: t(topological) and g(geometrical);
- Interaction descriptor (implies two participants) can be one of: D(d), d(1/d), O(p_1), o(1/p_1), P(p_1p_2), p(1/p_1p_2), Q($\sqrt{p_1p_2}$), q(1/$\sqrt{p_1p_2}$), J(p_1d), j(1/p_1d), K(p_1p_2d), k(1/p_1p_2d), L(d$\sqrt{p_1p_2}$), l(1/d$\sqrt{p_1p_2}$), V(p_1/d), E(p_1/d^2), W(p_1^2/d), w(p_1p_2/d), F(p_1^2/d^2), f(p_1p_2/d^2), S(p_1^2/d^3), s(p_1p_2/d^3), T(p_1^2/d^4), t(p_1p_2/d^4);

- The overlapping descriptors interaction can be one of: R and r (threat descriptors as scalars, compute resultant relative to a given atom j and respectively conventional origin), M and m (first calculate and then use the property center similarly to well-known mass center calculations), and D and d (threat descriptors as Cartesian vectors);
- Molecule fragmentation are made on pairs of atoms using one of: m (minimal fragments), M (maximal fragments), D (Szeged distance based fragments) and P (Cluj shortest paths based fragments);

- Molecular descriptor cumulates overall fragmental descriptors values by using one of:
  - Conditional group: m (smallest), M (highest), n (smallest absolute), N (highest absolute);
  - Averages group: S (sum), A(average of all valid values), a(S divided by number of all fragments), B (average first by atom and then my molecule), b (by bond);
  - Geometric group: P (multiplication), G(geometric mean, valid fragments), g (adjusted G), F (by atom and then by molecule), f (by bond);
  - Harmonic group: s (harmonic sum), H (harmonic mean, valid fragments), and similarly to above h, I, and i.

MDF formulas and names

- MDF values enter in QSAR modeling after a transformation (linearization procedure, one of: **I** (identity, no change), i (inverse), A (absolute), a (inverse of absolute), L (logarithm of absolute), l (logarithm). The mathematical formula of the calculation is like:

$L_D(S_F(\{I_M(A_P,D_O,D_F(A_P,D_O),f)\ |\ f \text{ is from } F_C(Molecule)\}))$

where L_D is linearization descriptor, S_F is overall superposing formula, I_M is interaction model, A_P is atomic property, D_O is distance operator, D_F is descriptor formula and F_C is fragmentation criteria.

- As result, a number of 787968 MDF members are calculated:

  $2(D_O)*6(A_P)*24(D_F)*6(I_M)*4(F_C)*19(S_F)*6(L_D)$

- Labeling obey the construction of the descriptor. Thus, AiPdtQt are from:

$D_O = t, A_P = Q, D_F = t, I_M = d, F_C = P, S_F = i, L_D = A$

- Not all MDF members has real (computable) and not identical values. More, not all of them are distinct each from other. A procedure to clean the MDF set was implemented and applied.

Data set

Name of the compounds	Mutagenicity	Cytotoxicity
8-methyl-quinoline	-0.71	-3.39
8-aminoquinoline	-0.24	N/A
8-hydroxyquinoline	0.79	-2.30
8-chloroquinoline	0.37	-2.38
8-ethylquinoline	0.40	-2.73
8-cyanoquinoline	-0.46	-3.59
8-ureidoquinoline	-1.93	-3.71
8-fluoroquinoline	-0.55	-3.67
8-sulfonamidoquinoline	-2.82	-4.45
8-benzyloxyquinoline	0.92	-1.41
quinoline	0.09	-3.12
8-methoxyquinoline	-1.50	-3.75
8-ethoxyquinoline	-1.05	-3.42
8-quinolinol acetate	-0.26	-2.62
N-8-quinolinyl acetamide	-1.09	-3.64

Results

- For the Quinolines set, only 319867 (all 15, Mutagenicity) and 319827 (14 of 15, Cytotoxicity) has real and not identical values and only 102608 (15) respectively 103411 (14) are distinct each from other. The selected members (102608 for Mutagenicity and 103411 for Cytotoxicity) enter into multiple linear regression analysis. Mono-varied and bi-varied models were applied. At the end of all pair's computations (for bi-varied model, 5264149528 pairs for Mutagenicity), the best QSAR models were selected and presented.

MDF QSARs for Mutagenicity of Quinolines

No	QSAR	r, r^2, r^2_{adj}	F, p%	$r^2_{cv\text{-}loo}$	Remarks
1	4.63 - 6.58·*iHPMdCg*	0.8, 0.65, 0.62	23.8, $3 \cdot 10^{-2}$	0.57	Mono-varied model, n = 15
2	-4.49 +8.35·*INDRLQt* +1.96·*lHPmTMt*	0.99, 0.98, 0.97	250, $1.7 \cdot 10^{-8}$	0.96	Bi-varied model, n = 15 r^2(*INDRLQt, lHPmTMt*) = 0.63 r^2(*INDRLQt*) = 0.123 r^2(*lHPmTMt*) = 0.03

MDF QSARs for Cytotoxicity of Quinolines

No	QSAR	r, r^2, r^2_{adj}	F, p%	$r^2_{cv\text{-}loo}$	Model remarks
1	-4.14 $+8.39\cdot10^{-3}\cdot aAmrKQt$	0.845, 0.715, 0.692	30, $1.4\cdot10^{-2}$	0.573	Mono-varied model, n = 14
2	$-7.18\cdot10^{-1}$ $+2.25\cdot10^{-1}\cdot lsMrSQg$ $+9.87\cdot10^{-2}\cdot ASPrVQg$	0.98, 0.96, 0.95	125, $2.7\cdot10^{-6}$	0.928	Bi-varied model, n = 14 $r^2(lsMrSQg, ASPrVQg) = 0.38$ $r^2(lsMrSQg) = 0.06$ $r^2(ASPrVQg) = 0.004$
3	-1.58 $+2.06\cdot10^{-1}\cdot lNMrSQg$ $+9.3\cdot10^{-2}\cdot ASPrVQg$	0.98, 0.96, 0.95	122, $3.1\cdot10^{-6}$	0.934	Bi-varied model, n = 14 $r^2(lNMrSQg, ASPrVQg) = 0.34$ $r^2(lNMrSQg) = 0.004$ Best cross-validation score
4	-1.6 $+3.37\cdot10^{-1}\cdot lNMrEQg$ $+9.47\cdot10^{-2}\cdot ASPrVQg$	0.98, 0.96, 0.95	119, $3.5\cdot10^{-6}$	0.933	Bi-varied model, n = 14 $r^2(lNMrEQg, ASPrVQg) = 0.35$ $r^2(lNMrEQg) = 5\cdot10^{-5}$

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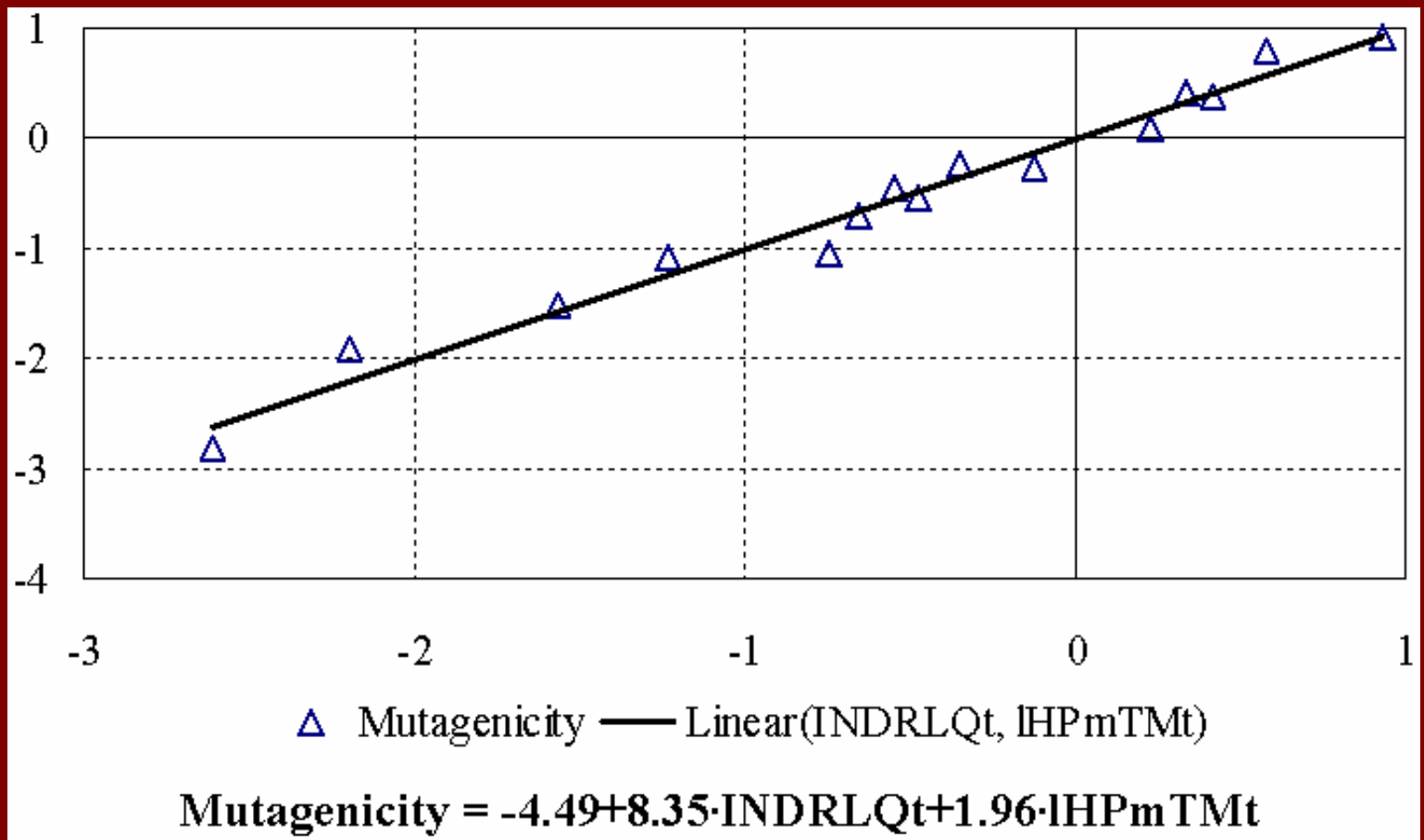
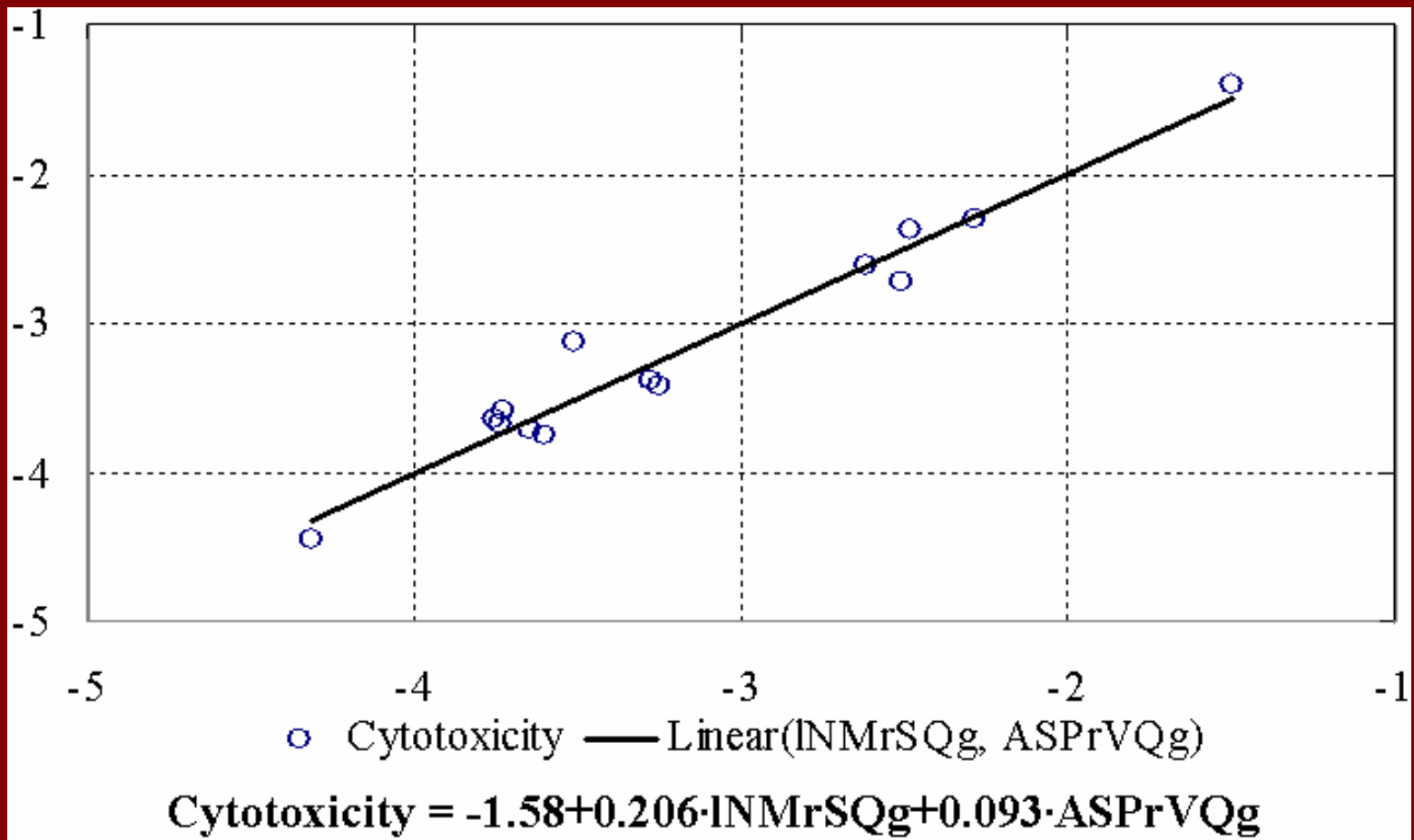
Plot of best MDF QSAR for Mutagenicity of Quinolines



Mutagenicity = -4.49+8.35·INDRLQt+1.96·lHPmTMt

Plot of best MDF QSAR for Cytotoxicity of Quinolines



Remarks

1. As are expected, a pair of MDF members provides significantly better explains of the activity (mutagenicity and cytotoxicity) compared with single member. More, comparing with previous reported results (*):
   - Mutagenicity, n = 13 - two Quinolines omitted, r^2 = 0.87 vs. 0.98 (our result with MDF members)
   - Cytotoxicity, n = 13 - one Quinoline omitted, r^2 = 0.8 vs. 0.96 (our result with MDF members)

   the MDF produces better explanation of structure-activity relationship.

(*) Smith J.C., Hansch C., Morton J.M., QSAR treatment of multiple toxicities: the mutagenicity and cytotoxicity of quinolines, Mutation Research, 1997, 379, p. 167-175.

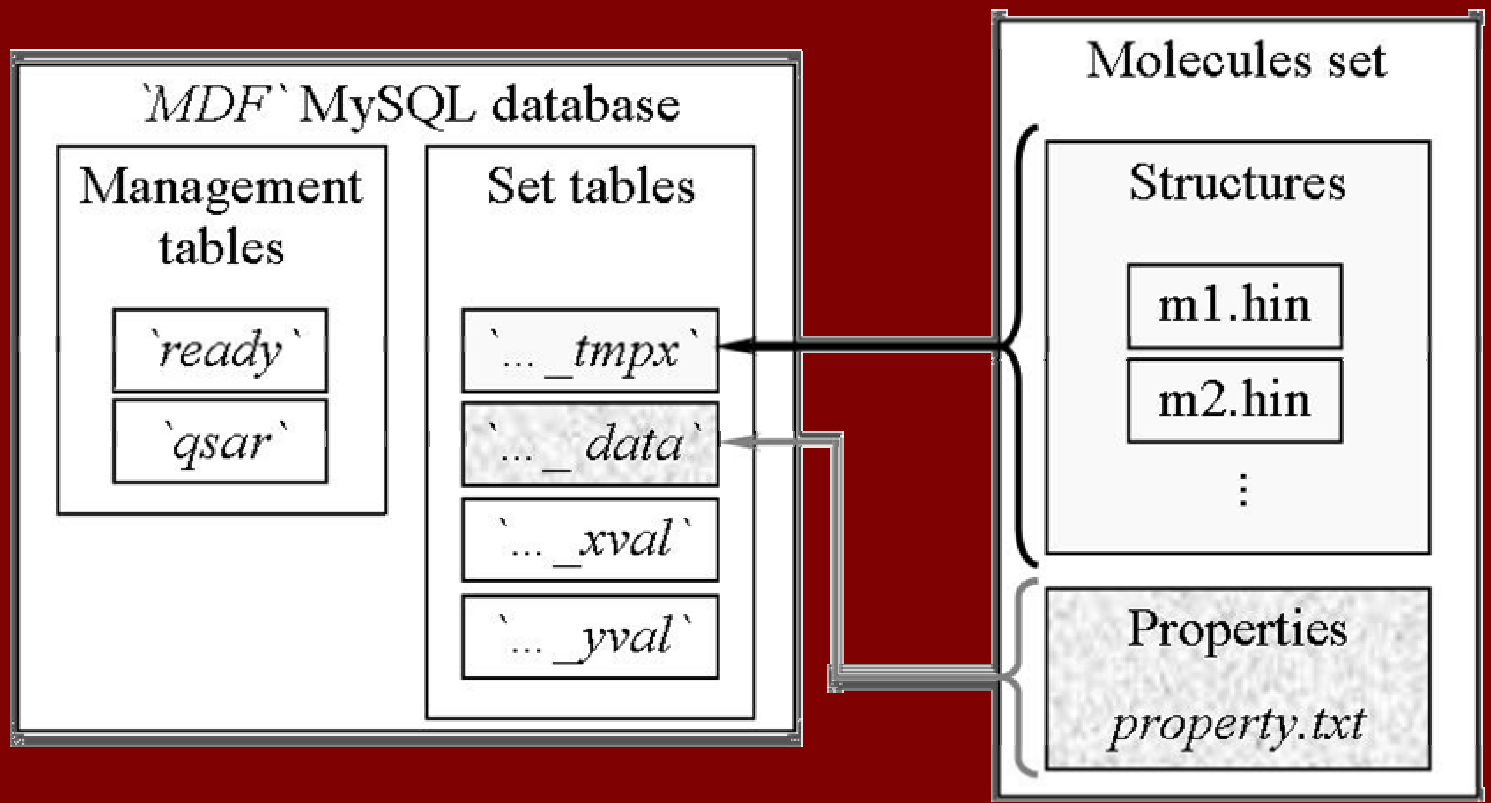
2. The absence of the best descriptor from the mono-varied model from the pair(s) of best bi-varied model, the almost null correlation between every single descriptor from bi-varied model and activity, and the presence of statistically significant link between descriptors from the best bi-varied pairs demonstrates that it is no link between using of orthogonal descriptors (Principal and/or Dominant Component Analysis) and QSAR modeling.
3. In bi-varied QSARs, when is more than one model that obtains the same values of correlation coefficient, the cross-validation score allows to choose the best model.

4. Even if using of MDF in QSAR modeling is time consuming, it has doubtless advantages, such as better QSAR and a much closer structure activity explanation.
5. Best bi-varied QSAR model of Mutagenicity uses the INDRLQt and lHPmTMt members, and is statistically significant ($p = 1.7 \cdot 10^{-8}$ %).
6. All three best of bi-varied QSARs of Cytotoxicity use members which consider the geometrical shape (g) as well as the atomic property represented by the partial change (Q) and are statistically significant ($p \approx 3 \cdot 10^{-6}$ %).
7. The obtained QSAR models allow making of important remarks on structural nature of Mutagenicity and Cytotoxicity activities.

Conclusions

- Mutagenicity of Quinolines is almost of molecular topology nature and is strongly dependent on both atomic mass and partial atomic charge (99% for bi-varied MDF QSAR model with INDRL**Qt** and lHPmT**Mt** members).
- Cytotoxicity of Quinolines is strongly dependent on the partial change atomic property and its behavior is almost of molecular geometry nature (98% for bi-varied MDF QSAR model with lNMrS**Qg** and ASPrV**Qg** members).

The End.



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Abstract Book

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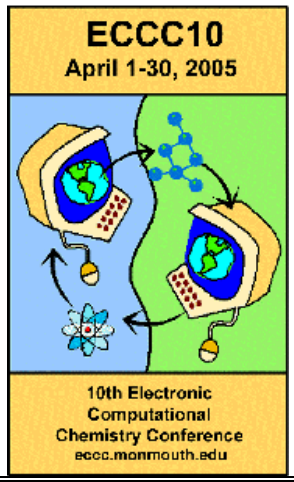

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The prizes for the ECCC10 Award winners are provided by Parallel Quantum Systems (PQS), Schrodinger, Inc. and SimBioSys Inc.

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Highlights of ECCC10

- Keynote presentation by Prof. Truhlar of University of Minnesota
- Fifty-three submitted presentations
- 260 registered participants
- Month-long online discussion
- Publication of an online Abstract Book
- Proceedings published in a special issue of Theoretical Chemical Accounts
- Five presentations win the Outstanding Scientific Presentation Award and one presentation wins the Best Multimedia Presentation Award
- Prize for each winner worth over $2000 provided by PQS, Schrodinger and SimBioSys

The Tenth Electronic Computational Chemistry Conference (ECCC10) was held April 1-30, 2005 on the Internet at http://eccc.monmouth.edu. The ECCC series is open to any interested parties, with free registration, to submit abstracts, view presentations or participate in discussion.

About 260 participants take part in the month-long virtual conference, centered on computational chemistry but also including presentations covering computational molecular biology, computational and theoretical molecular and atomic physics, visualization, chemo-informatics, and all related fields. One invited keynote presentation by Prof. Donald G. Truhlar and 53 submitted presentations were contributed to ECCC10 by scientists from around the world. The ECCC10 was a truly international conference, as the presentations come from 24 countries or regions: Bulgaria, Romania, Poland, India, Russia, Latvia, Austria, Mauritius, UK, Taiwan, France, China, Australia, Sweden, Mexico, Uzbekistan, Switzerland, Japan, Italy, Hungary, Canada, Croatia, Netherlands, and USA.

Abstracts for all contributions to ECCC10 were reviewed by the Scientific Organizing Committee (SOC) to insure novelty, scientific value, and appropriateness for inclusion in the conference. The members of the ECCC10 SOC are: Robert Topper (Chair), Frederick R. Bennett, David Chatfield, Olga Dmitrenko, Guangyu Sun, Mark Tuckerman, and Amir Weitz.

New to the ECCC series is the introduction of a keynote presentation, this time given by Prof. Donald G. Truhlar of University of Minnesota. Prof. Truhlar gave an excellent review on the history, current status and future direction of the combined quantum mechanical/molecular mechanical (QM/MM) calculations.

Also new is the establishment of the Award program. Five presentations were chosen as the Outstanding Scientific Presentations and one as the Best Multimedia Presentation by the SOC. Each Award winner received a set of scientific software ranging from QM, MM, to docking, which are generously sponsored by Parallel Quantum Systems, Schrodinger and, SimBioSys. The winners of the Outstanding Scientific Presentations are #5, #8, #16, #50 and #51, while the winner of the Best Multimedia Presentation is #49.

The ECCC10 Proceedings will be published in a special issue of Theoretical Chemistry Accounts. An abstract book containing all presentations is published online by ECCC10.

The ECCC10 committee thanks all authors, participants, and Prof. Truhlar for their time and effort for making the ECCC10 a successful conference.

Scientific Organizing Committee (SOC), ECCC10
May 19, 2005

Abstracts of

The Tenth Electronic Computational Chemistry Conference

(ECCC10)

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Keynote Presentation

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100. QM/MM: What have we learned, where are we, and where do we go from here?

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This paper will briefly review the current status of the most popular methods for combined quantum mechanical/ molecular mechanical (QM/MM) calculations, including their advantages and disadvantages. There will be a special emphasis on very general link atom methods and various ways to treat the charge near the boundary. Mechanical and electric embedding will be contrasted. Then we will review some recent tests and applications from our work and that of other groups and summarize what we learn about QM/MM from these studies. We will also discuss some available software. Finally, we will present a few comments about future directions of research in this exciting area.

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Presentations

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1. Theoretical and Linear-Dichroic Infrared Spectral Analysis of Aromatic Dipeptides and Their Protonated Salts

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Keywords: phenylalanine, tyrosine and tryptophan containing dipeptides, dipeptide salts, ab initio calculations, linear-dichroic infrared spectral analysis

The three-dimensional structures of aromatic L-phenylalanine (Phe), L-tyrosine (Tyr) and tryptophan (Trp) dipeptides and their protonated forms were obtained by ab initio calculations employing 6-31G** basis set at Hartee-Fock level of theory. The stereo-structural changes as a result of protonation processes were carried out. The theoretical results were compared with the experimental ones received by linear-dichroic infrared spectral analysis using an orientation solid-state original technique as nematic liquid crystal suspension. The detailed experimental frequency characterization of both non- and protonated forms of the dipeptides studied were also carried out by an application of the so-call step-wise reduction procedure for polarized spectra interpretation.

2. Computational Studies on [1,7]-H Shift in Thermal Previtamin D/Vitamin D Isomerization. Simulations of the Kinetic Isotope Effect

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Keywords: vitamin D, hydrogen shift, kinetic isotope effect, B3LYP

The lowest energy eight ground state conformers of 3-desoxy-previtamin D, four conformers of 3-desoxy-vitamin D and four transition structures (TS) have been fully optimized and characterized at the B3LYP/6-31G(d) level. The optimized transition structures differ in the conformation of A-ring (3beta-hydrogen can be axial or equatorial) and helicity of the triene system [right-handed (RH) and left-handed (LH)]. The calculated activation enthalpy is in fair agreement with experiment (20 kcal/mol vs 19 kcal/mol). It has been found that calculated activation entropy has twice smaller absolute value than experimental (-9 e.u. vs -20 e.u.). Almost decade ago, Okamura reported that transformation of previtamin D3 to vitamin D3 has temperature dependent primary kinetic isotope effect (KIE=11.4 at 298.15 K and 6.2 at 353.15 K), whereas KIE for [1,7]-H shift in 1alpha,25-dihydroxyprevitamin D3 is only modestly temperature dependent (7.5 and 5.5 at 298.15 K and 353.15 K). In order to understand this difference, we performed KIE simulations using different models and approaches. All the data (including experimental studies in different media) suggest that the KIE may have a marked entropy contribution, which depends on the variety of external (media, temperature) and internal (structural modification) factors in a complex way. Thus, the gas-phase calculations are unable to predict correctly KIE for these thermoconvesions.

3. An *ab Initio* Study of the Potential for the Interaction of the Isotopes and Ions of Hydrogen with Ethane

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Keywords: methyl transfer, ethane, reaction potential

Alkyl transfer is involved in many reactions such as synthesis, catalysis, polymerisation and isomerisation of hydrocarbons. These reactions have come under increasing scrutiny in recent years as computational methods have allowed direct probing of some of the dynamic features. To provide more insights on methyl transfers, reactions of the isotopes and ions of hydrogen with ethane were studied by ab initio methods. The interaction energy of these reactions was computed at several levels of theory such as HF, MP2, MP3, QCISD, and with various basis sets such as 6-31G*, 6-311G* and 6-311++G**. Also the IRC method was used to investigate the interaction of hydrogen atom and its ions with an ethane molecule. The range of interaction considered was between 1.0000 Å and 5.0000 Å. The results indicate that the charge on the hydrogen atom combined with the choice of basis set and level of theory influence the interaction potential curve to a large extent. However, within the framework studied, the isotopes of hydrogen do not affect the energetics of the transfer reactions. Further, the enthalpy of the S_N2 reaction between ethane and hydrogen is found to be larger compared to those between ethane and the ions of hydrogen, which are almost zero.

4. Molecular Descriptors Family on QSAR Modeling of Quinoline-based Biological Activities

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Keywords: QSAR model, Quinolines, Molecular Descriptors Family, MLR

The use of a new original set of molecular descriptors, called Molecular Descriptors Family (MDF) into a Quantitative Structure-Activity Relationship study on Mutagenicity and Cytotoxicity of Quinoline based compounds are presented. The MDF is of pure structural nature and takes into account both geometrical and topological model of molecules.

The MDF uses sets of atomic properties, distance metrics, interaction descriptors, overlapping descriptors methods, molecular fragmentation criterions, overall fragmental descriptors superposing methods, and linearization procedures in order to produce a number of 787968 MDF members with different calculation formulas. Starting with a given set of molecules, not all MDF members has real (computable) and not identical values. For the Quinolines set taken in this study, only 319867 (all 15, Mutagenicity) and 319827 (14 of 15, Cytotoxicity) have real and not identical values and only 102608 (15) respectively 103411 (14) are distinct each from other. The selected members (102608 for Mutagenicity and 103411 for Cytotoxicity) enter into multiple linear regression analysis. Mono-varied and bi-varied models were applied. At the end of all pair's computations (for bi-varied model, 5264149528 pairs for Mutagenicity), the best QSAR models were selected and presented here. The MDF QSAR model of Mutagenicity use 15 compounds and of Cytotoxicity use 14 compounds. The plots of the best bi-varied QSAR model of Mutagenicity for Quinolines with MDF members and of the selected best bi-varied QSAR model of Cytotoxicity for Quinolines with MDF members are presented.

Comparing with previous reported results (Mutagenicity, n = 13 - two Quinolines omitted, r^2 = 0.87; n = 13 - one Quinoline omitted, r^2= 0.8) the MDF produces better explanation of structure-activity relationship. Even if using of MDF in QSAR modeling is time consuming, it has doubtless advantages, such as better QSAR and a much closer structure activity explanation. The obtained QSAR models allow one to make important remarks on the structural nature of mutagenicity and cytotoxicity activities of quinolines. Mutagenicity is almost of molecular topology nature (99%) but is strongly dependent on both atomic mass and partial atomic charge; Cytotoxicity is strongly dependent on the partial change atomic property and its behavior is almost of molecular geometry nature (98%).

5. The Application of Composite Energy Method to n-Butyl Radical beta-scission Reaction Kinetic Estimations

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Keywords: Butyl, CBS, RRKM, Reaction Rate

Traditional electronic structure energy calculations consist of a single calculation. However, a calculation at a very accurate level of theory can be time and resource intensive. In an effort to achieve high accuracy results at less computational cost, several model chemistries have been defined as a series of calculations combining their results for predicting an energy value for the molecule under investigation. Even though multiple calculations are run, their total computational cost is still significantly less than that of the single, high-accuracy model which they are designed to approximate. These methods are called composite energy methods or compound methods.

In this work, a modified composite energy method (CBS-RAD(MP2)) is created as a modification of the CBS-RAD method which has proven to give accurate energetics for free radical reactions. It replaces the time-consuming QCISD(fc)/6-31g* method in the geometry optimization and frequency calculation steps with

MP2(full)/6-31g* level calculations. The accuracy of the new CBS-RAD(MP2) method is compared with the widely used G2, G3, and CBS-QB3 composite methods for predicting heats of reaction and activation barriers of 15 hydrocarbon cracking reactions. We find that the new CBS-RAD(MP2) method has the least RMS error for both heats of reaction and activation energy calculations. In addition, the CBS method is drastically less demanding of computer resources so this method is recommended for other large systems where high quality reaction energetics and rates are necessary. The kinetics of hydrocarbon cracking reactions are very difficult to measure experimentally due to many types of side reactions taking place at high temperature. Further work using Transition State Theory and RRKM theory were done to estimate the rate constants for n-butyl radical beta-scission reaction. The CBS-RAD(MP2) model proves to have good agreement with the experimental data, indicating it is a good method for studying other hydrocarbon cracking reactions involving large species. A kinetic model of the reaction with pressure and temperature effects is proposed which can be easily applied to different reaction conditions without performing additional costly calculations.

6. Conformational Preferences of the Plant Polypeptide Hormone Systemin

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Keywords: Protein folding, energy landscape, clustering, bioactive conformation, receptor binding

Systemin, the first plant polypeptide hormone to be discovered, is an 18-amino acid polypepide which binds to a membrane receptor kinase to signal wound response. Biochemical evidences point to its N-terminal 14 residues as important for binding and C-terminal 4 residues for signal activation. Substitution of Pro at position 13 with Ala nearly abolishes its activity. Despite a few spectroscopic studies, detailed understanding of the conformational characteristics of systemin is lacking. We have undertaken multiple copy simulated annealing and replica exchange molecular dynamics studies of systemin under a Generalized Born solvent approximation. From the simulation studies it appears that the polypeptide hormone exists in aqueous solution as an ensemble of beta turns and coiled conformations. This is in general agreement with previous NMR and CD spectroscopic studies. Comparison of the conformational preferences of systemin with that of systemin substituted with Ala at position 13 suggests possible reasons for its loss of function.

7. The Influence of Solvent Molecules on NMR Spectra Studied on Barbituric Acid in the DMSO Solution

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Keywords: barbituric acid, NMR spectroscopy, chemical shifts, theoretical calculations

This work shows modifications of chemical shifts in barbituric acid (BA), caused by the dimethylsulphoxide (DMSO) molecules. The reason of discussed changes are the H-bonded complexes created by barbituric acid with this solvent in solution.

In order to examine the shift changes the authors take into consideration the barbituric acid alone, the cluster of BA with two DMSO molecules and two different clusters with four DMSOs units. The chemical shifts of these systems have been calculated and the obtained results have been compared with experimental data. Theoretical calculations predict a significant downfield shift for protons involved in intermolecular N-H···DMSO H-bonds. The influence of the solvent molecules on other nuclei chemical shifts, especially protons of barbituric acid methylene group, is also reported.

The calculations have included Hartree-Fock and several Density Functional Theory methods. All methods correctly describe experimental 1H and 13C NMR spectra of barbituric acid. The best consistence between experiment and theory is observed for the BLYP functional. Four approximations of magnetic properties calculations embedded in the Gaussian'98 package have been tested. The results of the performed calculations indicate that from practical point of view the GIAO method should be preferred.

8. Study of H-Bonded Cluster Characteristics of Sub- and Supercritical Methanol by Computer Simulations

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Keywords: supercritical methanol, hydrogen-bonded clusters, computer simulation

We report the results of our analysis of the effect of thermodynamic parameters of state on methanol H-bonded cluster (HBC) characteristics (geometric, energetic, and topological ones). Within the framework of these studies, extensive Molecular Dynamics (MD) simulations of various phase lines near methanol saturation curve and critical point have been performed. Computer simulations demonstrated that despite of expected different behavior of the HBC characteristics calculated along different phase lines, as functions of state parameters, the functional type of the correlation between some of HBC characteristics and the mole fraction of H-bonded molecules does not depend on phase path methanol passes on at transition to

supercritical state. In the present study, an attempt has been also made to estimate the mean H-bonds number per methanol molecule by combining the DFT Single Point calculations on classical MD configurations with Natural Bond Orbital analysis. Using our computational scheme, which is somewhat similar to the Wood's ABC/FEP approach [J. Chem. Phys. 1999, 110, 1329], we tried to evaluate the degree of hydrogen bonding in bulk methanol from the wave functions of separate (contained up to 600 atoms) electronic subsystems.

9. Lewis Acid Sites in Boralites

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Keywords: zeolite, boron substitution, L-sites, water, ammonia, ethene, carbon monoxide, DFT

There has been much discussion on the nature of Lewis acid sites (L-sites) in zeolites. To date it has been established using both experimental [Catal. Today. 1988, 3, 367] and theoretical [Russ. J. Phys. Chem. (Eng. Ed.) 2003, 77, 1340; J. Chem. Phys. 2004, 120, 10263] techniques that coordination unsaturated aluminum atoms at structural defects of the zeolitic lattice can account for certain types of Lewis acidity observed. The substitution of framework aluminum by boron, which is a method for controlling the acid catalyst properties of zeolites, gives rise to L-sites at boron atoms. Unlike their aluminum counterparts, boralitic L-sites are formed as readily as by mild dehydration [Appl. Catal. 1990, 66, 111], which can happen during activation of a boralitic catalyst. However, data on the properties of such L-sites is even scarcer than that on conventional zeolitic L-sites, in spite of their possible role in catalytic reactions.

The present work is aimed at density functional modeling of a boralitic L-site within a cyclic cluster including 3 T-atoms, 2 Si and 1 B. A similar cluster was used earlier as a successful model for a zeolitic L-site. This allows us to perform the direct comparison of the properties of the two L-sites. It is shown that the boralitic L-site is rather weak. Unlike its zeolitic counterpart, it cannot bind a molecule of ethene or carbon monoxide. Only a base as strong as ammonia can form a stable 1:1 complex with the boralitic L-site. In agreement with experiments on the structure of dehydrated and rehydrated boralites, water is found to bind to the L-site only if not less than two its molecules are interacting with the model cluster. As water loading increases, the geometry of the BO_3 fragment undergoes gradual changes indicative of facile hydrolisys of the boralite lattice.

10. Metal Binding Induced Conformational Interconversions in Xylopyranosides

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Keywords: B3LYP, metal-ion binding sites, conformation, sugars, methyl xylopyranoside

The binding of divalent metal ions (Mg^{2+}, Ca^{2+}, Zn^{2+}, and Cd^{2+} to methyl-ß-D-xylopyranoside is investigated with density functional theory (B3LYP/LANL2DZ) calculations. As usual, the uncomplexed sugar exists preferentially in the $^4C_1$ conformation. Binding of the metal to this ring conformation occurs mainly between the hydroxyl groups attached to C-3 and C-4. Owing to the possible triple coordination of the metal ion, in the metal complexes, the $^1C_4$ ring conformation is considerably more stable. Complex stabilities follow the order Mg > Zn > Cd > Ca, i.e. complex stabilities are inversely related to the corresponding ionic radii.

11. Quantum Chemical Investigation of Phenylacetylene Iodination by Carbon Tetraiodide

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Keywords: AM1; phenylacetylene; carbon tetraiodide; radical reaction

The mechanism of iodination process was studied by AM1 semiempirical method as implemented in MOPAC 6 program. It was shown that molecule of CI_4 in excited triplet state T_1 serves as a source of iodine radical. Approaching of iodine radical to molecule of phenylacetylene was carried out using reaction coordinate method. The possibility of the stable intermediated complex formation has been shown. The selectivity of reaction is dependent on attack direction of second iodine radical. The approaching of this one from the another side of molecular plane leads to the reaction with formation of 1,2-diiodo-1-phenylethene molecule. However, if the both iodine radicals are located at the same side of phenylacetylene plane formation of iodine molecule (I_2) occurs. The both reactions occur spontaneously, but the phenylacetylene iodination reaction is more energetically advantageous in comparison with iodine molecule formation at ~25 kcal/mol. The mechanism of polyiodinated oligomers is suggested.

12. Studies of Electron and Proton Affinities of Fluorine Derivatives of Methylethynyl Radicals and their Anions

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Keywords: Electron affinity, proton affinity, DFT, DZP++, methylethynyl, radicals, anions,fluorine

The fluorine derivatives of the methylethynyl radical (•C≡C-CH_3) and methylethynyl anion (-:C≡C-CH_3)have been studied using density functional theory

(DFT) with DZP++ basis sets. Electron affinities (adiabatic and ZPVE-corrected) and proton affinities for radicals and anions respectively have been computed using six different DFT functionals, i.e., BHLYP, BLYP, B3LYP, BP86, BPW91 and B3PW91. The adiabatic electron affinity of •C≡C-CH_3[experiment = 2.718 ± 0.008 eV; BHLYP (2.60 eV), BLYP (2.57 eV), B3LYP (2.72 eV), BP86 (2.74 eV), BPW91 (2.60 eV) and B3PW91 (2.67 eV)] and proton affinity of -:C≡C-CH_3[BHLYP (16.93 eV), BLYP (16.70 eV), B3LYP (16.82 eV), BP86 (16.73 eV), BPW91 (16.84 eV) and B3PW91 (16.92 eV)] have been compared with those of their fluorine derivatives to determine the effect of the electronegative fluorine on the electron affinities and proton affinities of the substituted methylethynyl radicals and anions respectively. The B3LYP predicted electron affinities are 3.31 eV (•C≡C-CH_2F), 3.86 eV (•C≡C-CHF_2) and 4.24 eV (•C≡C-CF_3) and the B3LYP proton affinities of these fluorine anionic derivatives are 16.23 eV (-:C≡C-H_2F), 15.81 eV (-:C≡C-CHF_2)and 15.52 eV (-:C≡C-CF_3). The results are analysed in terms of the electron withdrawing effect of fluorine and negative hyperconjugation. It is found that electron affinity values increase and proton affinity values decrease as the number of substituting fluorine atom increases.

13. Quantum Chemical Studies on Structure Activity Relationship of Natural Product Polyacetylenes

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Keywords: antimycobacterial activity, polyacetylenes, falcarindiol, logP

An extract of the roots of Levisticum officinale L. (Apiaceae) exhibited significant antimycobacterial activity against Mycobacterium fortuitum. 3(R)-falcarinol [3(R)-(-)-1,9-heptadecadien-4,6-diin-3-ol] and 3(R)-8(S)-falcarindiol [3(R)-8(S)-(+)-1,9-heptadecadien-4,6-diin-3,8-diol] were identified as the active components in this extract [Schinkovitz, 2005, submitted]. 3(R),8(R)-dehydrofalcarindiol and 1,3R,8R-trihydroxydec-9-en-4,6-yne were isolated from different sources and surprisingly these polyacetylene exhibited no anti-mycobacterial activity [J Nat Prod, 2004, 67, 892]. Additionally, a whole series of furanocoumarin ethers of falcarindiol exhibited anti-proliferative properties [Bioorg Med Chem Lett, 1998 8, 93]. We have studied the relationship between the electronic properties and biological activity of these structurally related compounds and a good correlation between logP and activity has been established.

14. The Role of Small Molecule – Small Molecule Interactions in Overcoming Biological Barriers for Antibacterial Drug Action

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Keywords: multidrug resistance, MDR, antibiotic activity, MDR modulators, intermolecular interactions, GRID

The ineffectiveness of antibiotics against bacteria can be caused by multidrug resistance pumps (MDRs) or by the presence of an outer membrane which restricts the penetration of amphipathic compounds into Gram-negative bacteria. In a paper by Tegos et al. [Antimicrob Agents Ch, 2002, 46, 3133], a panel of plant antimicrobials was tested against a series of MDR bacteria and showed remarkable activity in the presence of two different MDR modulators (INF271 and MC207110). Our previous studies suggested that inhibitors of MDR may have affinity for substrates of efflux transporters, and that they may form complexes which could have a number of roles in the mechanism of MDR inhibition. These complexes may facilitate entry of drugs into the cell and secondly the drug in such a complex may be hidden from MDR transporters [Bioorg Med Chem Lett, 2004, 14, 881].

In this study we have modelled antimicrobials and MDR modulators reported and evaluated the interaction energies between them. We have demonstrated that complex formation is feasible and confirmed that modulation activity against the efflux pump NorA in Staphylococcus aureus correlates with the interaction energies between MDR modulator INF271 and antibacterials. Additionally, the change of logP of complexes might be responsible for overcoming the impermeability of the outer membrane in Gram-negative bacteria and increasing the antibacterial activity of plant antibacterials in the presence of MC207110.

15. Molecular Dynamics Simulations of Proteins with Modified Disulfide Bonds

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Keywords: Disulfide bond, molecular dynamics, protein modification

Protein based medicines are the fastest growing class of new medicines entering the clinic. Their biological activity is mediated in the extracellular environment. Therefore, therapeutically relevant proteins usually have a small number of disulfide bonds which help to maintain their tertiary structure in the circulation. Chemically, the disulfide bond serves to covalently link spatially separated cysteine residues to form a polypeptide macrocycle. In many proteins, the macrocycle can be very large. For example, interferon-a 2a has two disulfide bonds with one linking cysteines 1-98 and the other linking cysteines 29-138. These are both large macrocyclic substructures which contribute to maintaining the protein's tertiary structure. It is known that interferon can retain most of its activity when the disulfide bond between the cysteines 1-98 is reduced to liberate the free thiols for the two cysteines. To try and exploit the site specific reactivity of thiols, we have studied the effects of incorporating a 3 and 5 carbon methylene bridge between the two cysteines in each of the disulfide bonds of interferon-a 2a. Disulfide bridging was studied by two different molecular simulation protocols: (i) molecular dynamics (solvated protein), and (ii) stochastic dynamics (implicit solvent). We have shown that the disulfide bonds in interferon and other clinically relevant proteins can be reduced and chemically modified with a 3 carbon methylene bridge whilst still retaining the protein's tertiary structure.

16. Oxygen Diffusion in Minihemoglobin from Cerebratulus lacteus – a Locally Enhanced Sampling Study

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Keywords: Minihemoglobin, locally enhanced sampling, molecular dynamics

Heme proteins may serve as a source of oxygen in nerve tissue during anoxia. Recently an interesting structure of 109 residue minihemoglobin (CerHb) present in worm *Cerebratulus lacteus* (1KR7) has been published [Structure, 2002, 10, 725]. The detailed route of a ligand from cytosol to the heme pocket is not known. It would be very interesting to know which particular residue affect CerHb performance the most. Results of molecular dynamics simulations of dioxygen diffusion within the CerHb protein matrix are presented. The Locally Enhanced Sampling method (LES) [J Amer Chem Soc 1990, 112, 9161; J Chem Phys, 1992, 97, 7838] as implemented in the NAMD [J Comp Phys, 1999, 151, 283] code was used for simulations of CerHb with 1, 5, 10 and 15 copies of O_2, immersed in a box of TIP3 waters. LES trajectories on 1 ns time scale gave thus information equivalent to data from an order of magnitude longer classical simulations. The results were graphically analyzed using the VMD code [J Molec Graphic, 1996, 14, 33]. Several alterative routes of O_2 diffusion were found in LES simulations. The dominant path consists of two steps. Firstly, ligand move from the heme pocket to different cavity through the barrier define by residues Phe10 and Tyr48. The heme pocket is composed of Tyr11, Leu14, Phe15, Phe25, Gln44, Thr48 and Phe10 residues. Secondly, the ligand leaves the protein passing the next and more complex barrier situated between the E/F loop and the H helix. We note that the number of paths observed depends on a number of LES copies of oxygen ligands.

17. Withdrawn

18. Relationship Between Diameter and Indices for Infinite Armchair Single Wall Carbon Nanotubes

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Keywords: single wall carbon nanotube, CC bond length, diameter, PM3, DFT.

CC bond lengths and diameters of infinite armchair single wall carbon nanotubes (SWCNTs) from (4,4) to (15,15) have been calculated using semiempirical PM3 and PM5 and density functional PBEPBE and B3LYP methods. The CC bonds are found to be elongated comparatively to those in graphene sheet, 1.421 Å. The two kinds of bonds in armchair SWCNT, directed nearly along the nanotube axis and directed along the nanotube circumference, are elongated in different ways. The smaller the nanotube index, the larger the bond elongation. However, even for the (5,5) nanotube, the elongation does not exceed 0.008 Å (0.6 % relative to the graphene sheet value). Thus, the value of 1.44 Å, which is often used for the CC bond length in armchair SWCNTs, is an overestimation. Due to the fact that a real nanotube is not cylindrical, but polyhedral, the theoretical relationship between the nanotube diameter, indices and bond length is broken. We suggest new theoretical relationship between these nanotube parameters. Knowing the diameter, the band positions in the Raman and optical spectra of the nanotube can be calculated.

19. Analysis of a Set of 2.6 Million Unique Compounds Gathered from the Libraries of 32 Chemical Providers

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Keywords: Chemoinformatics, chemical databases, screening, drug-like, lead-like, fingerprints, diversity

3.8 million compounds from structural databases of 32 providers has been gathered and stored in our

database. Once the duplicates are removed using the INChI, 2.6 million compounds remain. The 32 databases and the whole database were studied in term of uniqueness, diversity, frameworks, drug-like and lead-like properties. This study shows that there are more than 87 000 frameworks in our database. Among the unique compounds 1.9 million are drug-like and more than 900 000 are lead-like. The druglikeness and leadlikeness are estimated using in house scores using functions to estimate convenience to properties rather than cut-off values. The compounds are stored in a MySQL database and the code to manage this database is in Java. In consequence, we have a free and easily updatable system for chemical databases management and screening sets generation.

20. Withdrawn.

21. Mapping the Orbital Wavefunctions into Momentum Space: Orbital Topologies and Bonding Mechanisms in the Outer Valence Shell of n-Butane Conformational Isomers

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Keywords: Orbital momentum distributions, n-butane conformers, orbital topologies, outer valence shell, chemical bonding mechanism

Orbital topologies and orbital based bonding mechanism in the outer valence shell of the four most significant structures of n-butane on the conformational potential energy surface are presented. The orbital electron density distributions and orbital momentum distributions are studied in r-space and k-space, respectively, using quantum mechanical calculations. The conformational isomers are produced due to torsional motion about the n-butane central C-C bond, that is, the anti-butane isomer A, two eclipsed-butane (B and D) and the gauche-butane (D). The orbital wavefunctions of the lowest energy electronic states of the conformers are calculated using the RHF/TZVP model. The quantum mechanically generated orbital wavefunctions of the species are directly mapped into their orbital momentum distributions using plane wave impulse approximation for orbital momentum distributions. The orbital topologies of the conformers are presented and outer valence orbital electron distributions and momentum distributions are analyzed in detail to reveal the orbital based bonding mechanism for n-butane. This paper demonstrates that a combined information from both configuration space and momentum space is able to contribute to a comprehensive and detailed understanding of the orbital bonding mechanism in particular for isomerization of molecules.

22. Theoretic Investigation of the Size and Charge Effects in Photochemistry of Heteroaromatic Azides

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Keywords: aromatic azide, photodissociation, PM3, HF, B3LYP.

Structures of linear cata-condensed heteroaromatic azides from azidopyridine to azidoazahexacene (the size of aromatic pi-system from 6 to 26 e) in neutral and protonated forms are calculated by semiempirical (PM3), ab initio (HF/6-31G*) and DFT (B3LYP/6-31G*) methods. In the ground (S_0) state, the azido group in all azides is characterized by a quasi-linear geometry and possesses rather large positive charge at two terminal nitrogen atoms. The azide photoactivity, as established in earlier work, is defined by the nature of molecular orbital (MO) that is filled in the lowest singlet excited (S_1) state. If the antibonding $sigma_{NN}$*-MO is filled, the azide is photoactive (photodissociation quantum yield phi > 0.1). The filling of the $sigma_{NN}$*-MO is found to depend on the size and charge of aromatic pi-system of azide. For the initial members of the investigated series of azides, the $sigma_{NN}$*-MO is filled both in neutral and in protonated forms, and these azides are photoactive, in full accordance with experimental data. With the pi-system size increasing, the energy gap between the highest occupied MO and the lowest unoccupied MO (LUMO) decreases, whereas gap between the $sigma_{NN}$*-MO and LUMO increases. As a result, when the size of the pi-system increases above certain threshold, the $sigma_{NN}$*-MO ceases to be filled in the S_1 state, and the azide becomes photoinert (phi drops below 0.01). The threshold is calculated to be 22 and 18 pi-electrons for the neutral and positively charged azides, respectively.

23. Computer-Aided Design of Original COX2-Inhibitors: Docking Protocols and Virtual Screening under Pharmacophoric Constraints

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Keywords: Docking, pharmacophore, scoring functions, consensus, lead-like databases, virtual screening

Cyclooxygenase is catalysing the first committed step in arachidonic-acid metabolism. High prostaglandin concentrations, emanating from this transformation, trigger inflammation deseases. Prostaglandin synthase exists under two isoforms: COX-1, which is constitutively expressed in most of tissues and COX-2, the targeted one, induced by cytokins, endotoxins and responsible for inflammation phenomenon.

We aimed to develop a model to screen lead-like (900 000 compounds) databases and to sort out novel compounds selective on COX-2 with some specific

features. To assess and predict the inhibition character of new selective non-steroidal anti-inflammatory inhibitors (NSAIDs), we carried out docking analysis using FlexX-Pharm. This new FlexX docking module, coupled with scoring functions, offers the possibility to include, before docking, pharmacophoric constraint acting as a prior filter.

24. Replica Exchange Simulation of the Preferred Conformations of 2-Thiouridine

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Cytoplasmic transfer RNA (tRNA) molecules display a large diversity of posttranscriptionally modified nucleosides at the anticodon wobble at position 34 and 3' to the anticodon triplet at position 37. Some of these modifications appear to play an important role in the recognition of the correct codon on the ribosome. In particular, the modified nucleoside 2-thiouridine at position 34 in $tRNA^{Lys}$ discriminates between AAA and AAG on one hand and AAU and AAC on the other, in contrast to uridine which does not discriminate. It has been suggested that these modifications work by regulating the conformational rigidity/flexibility of the nucleosides at those positions. To explore this hypothesis, we present here the results of a preliminary replica exchange molecular dynamics study where we compare the conformational characteristics of uridine and 2-thiouridine in aqueous solution.

25. Theoretical Study of the C-C Coupling Reactions of the Vinyl, Phenyl, Ethynyl and Methyl Complexes of Palladium and Platinum

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Keywords: C-C coupling, platinum, palladium, DFT.

The main factors controlling the C-C reductive elimination reactions of vinyl, phenyl, ethynyl and methyl ligands from the Pd and Pt complexes were studied with a density functional method. Both symmetrical $R_2M(PH_3)_2$ and asymmetrical $RR'M(PH_3)_2$ complexes were considered (where M= Pd and Pt). The barrier of C-C coupling from the symmetrical $R_2M(PH_3)_2$ complex decreases in the order: R = methyl > ethynyl > phenyl > vinyl, and the exothermicity of reaction increases in the same order. The methyl-methyl coupling is the most energy demanding, while the vinyl-vinyl coupling is the least among the complexes studied. For the asymmetrical $RR'M(PH_3)_2$ complexes, the activation and reaction energies are found to be approximately average of the corresponding parameters of symmetrical coupling reactions. The major thermodynamic and kinetic factors determining the C-C coupling in these complexes will be presented and discussed.

26. Relative Raman Intensities in C_6H_6, C_6D_6, and C_6F_6: A Comparision of Computed Values

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Keywords: *ab initio*, Raman, intensity, Hartree-Fock, MP2, DFT, ccsd, CAS-SCF

The accuracy of various quantum chemistry methods (Hartree-Fock, MP2, ccsd, CAS-SCF, and several types of DFT) for predicting relative intensities in Raman spectra for C6H6, C6D6, and C6F6 were compared. The predicted relative intensities for the two a1g breathing modes were compared with carefully measured relative intensities. While none of these methods excelled at this prediction, Hartree-Fock with a large basis set was most successful for C6H6 and C6D6, while PW91PW91 was the most successful for C6F6.

27. A PM3(tm) Semiempirical Study on Complexes of Transition Metal with Aminoacids

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Keywords: transition metal complex, semiempirical methods, PM3(tm)

We have studied several complexes of transition metals (Co, Ni, Zn, Cu) with glycine and phenylalanine via the PM3(tm) semiempirical hamiltonian. Full geometry optimization was performed in the gas phase and we have also considered solvent effects. We discuss some trends in the behavior of these metals towards complexation with glycine and phenylalanine.

28. Potential Oxygen-Carrying Complexes by Design

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Keywords: oxygen carrier, semiempirical methods, dioxygen, transition metal complex

Our group has studied computationally the potential as oxygen carriers of several complexes of salen with Co, Cu, Fe, Ni. We have performed full geometry optimizations in the gas phase for the complex, its active form with DMSO as ligand, and with

dioxygen complexated with the active form. We discuss energetic and orbital features.

29. Ligand Receptor Interaction and QSAR Study of Estrogens

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Keywords: Estrogen, PM3, Klopman atomic softness, ligand receptor interaction

Softness values En‡ of Estrogen derivatives and Softness values Em‡ of receptors Lysine, Histidine, Tyrosine and Cystein have been evaluated by Klopman equations. The required parameters for the solution of Klopman equation have been calculated with the help of semiemperical PM3 parameterization. The DEnm‡ (difference between En‡ and Em‡) has been derived and highest DEnm‡ values which is for tyrosine is taken as one descriptor with Qmin (highest negative charge), DHf0 (heat of formation), ET (total energy) and EE (electronic energy) as second descriptor for multiple linear regression analysis. The estrogen derivatives have been divided into four different sets on the basis of their structural similarities, and their biological activity taken from literature in terms of Relative Binding Affinity. The regression analysis shows that, DEnm‡ values in combination with second descriptors provide very good relationship with biological activity and with the help of these values the prediction of biological activity of any unknown compound is possible. The results also indicate that carbonyl oxygen is the specific functional group of receptors proteins involved in interaction with estrogen derivatives.

30. Differences in Electrostatic Potential Around DNA Fragments Containing Guanine and 8-oxo-Guanine

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Keywords: DNA damage, 8-oxo-guanine

Changes of electrostatic potential (EP) around the DNA molecule resulting from chemical modifications of nucleotides may play a role in enzymatic recognition of damaged sites. Effects of chemical modifications of nucleotides on the structure of DNA have been characterized through large scale computations. Quantum mechanical structural optimizations of fragments of three pairs of nucleotides with and without 8-oxo-guanine were performed at the density functional level of theory with a B3LYP exchange-correlation functional and 6-31G** basis sets.

The electrostatic potential around the DNA fragments was projected on a surface around the double helix. The 2D maps of EP of intact and damaged DNA fragments were analyzed to identify modifications of the EP that result from the occurrence of 8-oxo-guanine. It was found that distortions of phosphate groups and displacements of the accompanying countercations are clearly reflected in the EP maps.

31. PM3/CM2 and DFT Calculated Charge Distributions in the Molecule of 2,3-Trimethylene-3,4-dihydro-4-quinazolinone

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Keywords: PM3, DFT, charge model 2, 2,3-trimethylene-3,4-dihydro-4-quinazolinone

The theoretical calculations on distribution of a charge on frontier orbitals and on atoms of 2,3-trimethylene-3,4-dihydro-4-quinazolinone and its derivatives are carried out. The calculations were realized using Mulliken (qM) and Charge Model 2 (qCM2) models by PM3 in the gas phase and with taking into account the solvation effect (EtOH and H2O) using the SM5.42R solvation model in the AMSOL 7.0. Furthermore, in B3LYP/6-31G (d, p) level has been calculated the distribution of a charge on atoms by Mulliken model. The 2,3-trimethylene-3,4-dihydro-4-quinazolinone and its derivatives have been selected based on high biological activity and presence of extensive base of experimental data on reactivity of studied compounds. This is allows to estimate accuracy of a theoretical computational method for the estimation of the electronic density redistribution for related compounds.

32. Fast and Scriptable Molecular Graphics in Web Browsers without Java3D

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Jmol (http://www.jmol.org/) is a versatile Java applet that provides fast rendering of small molecules, protein, crystal structures, vibrations and animations without the need of Java3D and a scripting language making molecule webpages interactive.

33. Withdrawn

34. Quantum-Chemical Study of Hydrogen Abstraction from Methane and Benzene by Triplet Nitrosooxide

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Keywords: B3LYP, potential energy surface, nitroso oxides, exited electronic state, photochemistry

The paper describes recently obtained results on quantum chemical modeling of a hydrogen atom abstraction from methane and benzene by nitroso oxides in the triplet state. The potential energy surfaces for the abstraction have been built by means of B3LYP/6-31G(d) calculations. It was shown that the most probable reaction path is the abstraction by triplet nitroso oxides having the triangular O-N-O fragment. The transition state structure has been found. The calculated activation energy of the abstraction estimated to be 67.6 kJ/M for CH4 and 45.4 kJ/M for benzene. Heat effect is 58.0 kJ/M and 38.6 kJ/M, corresponding.

35. *Aconitum* and *Delphinium* Alkaloids. "Drug-Likeness" Descriptors Related to Toxic Mode of Action

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Keywords: *Aconitum* alkaloids, *Delphinium* alkaloids, QSAR, "drug-likeness", toxicity

Diterpenoid alkaloids found in plants of the genera *Aconitum* and *Delphinium* have been the targets of considerable interest of medicinal chemists for a broad range of pharmacological properties demonstrated: arrhythmogenic (neurocardiotoxic), local anaesthetic, antiarrhythmic, curariform, analgesic, hypotensive, anti-inflammatory, spasmolytic, neurotropic and psychotropic. Early studies have shown that these alkaloids act as neurotoxins and can be subdivided into two main groups. Group one is represented by compounds with curarelike (curareform) activity – neuronal nicotinic acetylcholine receptor binders. Group two is comprised of alkaloids – neurotoxins acting at voltage-gated Na+ channel. It is very intriguing that despite of having very similar molecular skeletons, these alkaloids exhibit principally different (in some cases antagonist) actions varying from poisonous to therapeutic. Large series of *Aconitum* and *Delphinium* alkaloids have been investigated by means of QSAR analysis. Descriptors related to "drug-likeness" of molecules were selected to discriminate between "drugs" and "non-drugs" amongst diterpenoid alkaloids studied. A usefulness of such approach has been assessed and it proved to give reliable results on whether a particular diterpenoid alkaloid is likely to be poison or drug. A number of QSAR models with "drug-likeness" descriptors have also been obtained and discussed in terms of their relativity to the mode of toxic action exhibited by alkaloids of two groups mentioned.

36. NMR And Molecular Modelling Investigations Of Dynamic Phenomena Observed In Alkaloid Berberal

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Keywords: isoquinoline alkaloids, NMR, molecular modelling, conformer, rotamer

Isoquinoline alkaloids is one of the most widespread group of alkaloids that serve as a good source for promising therapeutics. Berberal is a unique representative of a series of isoquinoline alkaloids that contains phthalide residue attached to nitrogen atom. Earlier we have reported the 1H and 13C NMR analysis results for this molecule [Khim.prirod.soed., 1993, 6, 869]. In this paper we present results of combined NMR and molecular modelling investigations of a dynamical phenomena observed in berberal molecule. In particular, the chemical shift of H-9 proton of lactone ring appeared to be of 7.97 ppm instead of expected 6-6.5 ppm. Further, a widened form of the signal could possible been observed because of the dynamic transitions between several conformers. Temperature – dependant NMR investigations have been carried out aiming to identify the presence of conformers. There are two dynamical processes that take place in molecular structure: inversion of cycle B (resulting in two conformers) and rotation of phthalide residue around the bond N-C9 (resulting in two rotamer forms). The geometry and its energy for each conformer and rotamer have been carefully examined by means of molecular mechanics (MM+) and semiempirical AM1 methods. Our investigations suggest that rotation of N-C9 bond is most probable reason for the abnormal H-9 shift observed. The later is also well-explained by the results of temperature-dependent NMR studies.

37. Stable Free Radicals - A Density Functional Theory Calculation of Structure and Reactivity

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Keywords: nitroxides, reactive oxygen species, computer simulation, scavengers

Nitroxides have been recently recognized as an important, new class of antioxidants. Several computational methods have been previously employed in order to predict the redox potentials of nitroxyl radicals and to better understanding of the catalytic cycle, antioxidant and/or scavenging potency of different nitroxides derivatives. In this work, the redox behavior of a series of nitroxyl radicals was analyzed in parallel with computational studies to extend our knowledge of the structural features necessary for anticipating the nitroxides scavenging abilities against ROS (reactive oxygen species). Quantum chemical calculations on some typical nitroxyl radicals and corresponding oxo-ammonium cations were performed at the unrestricted level of hybrid density functional theory. Nitroxide oxidation via ROS to the cation was

treated as adiabatic reaction and both the starting structure and the oxidized one were fully optimized using the 6-31+G* basis set. Electron and spin densities, electrostatic potentials and thermodynamic properties were obtained from single point calculations using 6-311+G* basis set. Similar calculations were performed for hydrated molecules: solvent effects were evaluated by the polarizable continuum model.

38. Computing Metallofullerenes: Gibbs Energy Treatment of Ca@C_{72}, Ca@C_{72}, Ca@C_{82}, Ca@C_{82}, La@C_{82}, La@C_{82}, and Sc_3N@C_{80}, Sc_3N@C_{80}

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Various endohedral cage compounds have been suggested as possible candidate species for molecular memories. One approach is built on endohedral species with two possible location sites of the encapsulated atom while another concept of quantum computing aims at a usage of spin states of N@C_{60}. In this work, four systems related to the first approach are simulated computationally, combining the treatments of quantum chemistry and statistical mechanics. Relative concentrations of five isomers of Ca@C_{72}, nine isomers of Ca@C_{82}, four isomers of La@C_{82}, and two isomers of Sc_3N@C_{80} are computed using the Gibbs energy.

Evaluations of fullerenes require entropy inclusion owing to very high synthetic temperatures. An illustration is supplied on two recently observed endohedral system - Ca@$C_{72}$and Ca@C_{82}. Five isomers are considered for Ca@C_{72}: IPR-related cage (a), two non-IPR C_{72} cages (b) and (c), a structure with one heptagon (d), and a species with two heptagons (e). For Ca@C_{82}, the isomers derived from the nine IPR structures are treated: C_{3v}(a), C_{3v}(b), C_{2v}, C_2((a), C_2((b), C_2((c), C_2((a), C_s(b), C_s(c). The analytical harmonic vibrational analysis is carried out at the B3LYP level in a combined basis set: 3-21G for C atoms and a dz basis set with the effective core potential on Ca. Electronic excitation energies are evaluated by TD DFT at the same level and also by the ZINDO method. The separation energetics is computed at the B3LYP/6-31G* level.

Relative concentrations (mole fractions) x_i of *m* isomers can be expressed through their partition functions q_i and the enthalpies at the absolute zero temperature or ground-state energies $\Delta H^o_{0,i}$ (i.e., the relative potential energies corrected for the vibrational zero-point energies) by a compact formula:

$$x_i = (q_i \exp[-\Delta H^o_{0,i}/(RT)])/(\sum_{j=1}^{m} q_j \exp[-\Delta H^o_{0,j}/(RT)]), \quad (1)$$

where R is the gas constant and T the absolute temperature. Eq. (1) is an exact formula that can be directly derived from the standard Gibbs energies of the isomers, supposing the conditions of the inter-isomeric thermodynamic equilibrium. Rotational-vibrational partition functions are constructed from the calculated structural and vibrational data using the rigid rotator and harmonic oscillator approximation. No frequency scaling is applied as it is not significant for the x_i values at high temperatures. The electronic partition function was constructed by directed summation. The symmetry and chirality contributions are included accordingly.

In the Ca@C_{72} system, the (b) and (c) non-IPR species represent major isomers while the IPR-related structure (a) comes as a minor species. Five structures show significant populations at higher temperatures for Ca@C_{82}: C_{2v}>C_s>C_2>C_{3v}>C_s.

39. Dual Space Analysis of the Electronic Structure of Adenine Tautomar Imino form

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Keywords: Dual space analysis,outer valance shell, binding energy,geometry optimization, orbital momentum distribution.

The study of the DNA basis Adenine is interesting because of its tautomerism. The electronic structure of the imino form of the two adenine tautomers is studied here using the dual space analysis method. The SAOP model is implemented to calculate the outer valence orbital energies and compared with the RHF/TZVP and B3LYP/TZVP results, and available experimental data. The optimized geometry of both tautomers in imino form with different configurations are examined. The changes in the dipole moments due to the $N_{(9)}$ to $N_{(7)}$ proton transfer is not as significant as that observed in the case of the amino form, as reported by Wang et al [J Theo Comput Chem, accepted].

40. The Conformational Mobility of the Aliphatic Chains in the Isobutyl Silsequioxanes

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Keywords: octakis(Isobutyl)octasilsesquioxane, phase transition, conformational mobility, molecular dynamics simulations

Polyhedral oligomeric silsesquioxanes (POSS) are a class of condensed three dimensional oligomeric organosiliceous compounds with cage frameworks having different degrees of symmetry. The term silsesquioxane derives from the stoichiometry of the compound where each silicon atom is bonded to one-and-a-half oxygen (sesqui-) and to an hydrocarbon (-ane) by a condensation reaction leading to ($RSiO_{1,5}$) bond units. The differential calorimetric profile of the octakis(Isobutyl)octasilsesquioxane indicates that a

phase transition occurs at about 330 K. Combined Raman and X-ray powder diffraction data suggested that this transition is related to a change in the conformational freedom of the isobutyl chains bonded to the silsesquioxane cage. To confirm this hypothesis, we characterized the conformational mobility of the octakis(Isobutyl)octasilsesquioxane molecule by molecular dynamics simulations, employing the Macromodel software as implemented in the Schrodinger (www.schrodinger.com) program suite.

41. First Principles Study of the Metallicity of Small Diameter Single Walled Carbon Nanotubes

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Keywords: carbon nanotubes, density functional theory, electronic properties

We present a first principles study of the metallicity of several different small diameter single walled carbon nanotubes (SWCNTs). Calculations were carried out with the Vienna *ab initio* Simulation Package (VASP 4.6) employing density functional theory, using local density approximation (LDA) within the framework of the projector augmented-wave (PAW) method. The metallicity of small diameter SWCNTs is largely influenced by high curvature effects, which is taken into account in our calculations. The results of our investigations include the expected opening of a small secondary gap in those non-armchair nanotubes, which would be metallic in zone folding approximation, and the also expected vanishing of both primary and secondary gaps at very small diameters due to rehybridization of sigma and pi bands. The latter effect appears at different critical diameters for tubes with primary gaps and tubes with secondary gaps, and some chirality dependence is observed as an indication of strong individuality of different SWCNTs. Results are discussed, and the need for including many-electron effects in determining the quantitative value of the band gap is addressed.

42. Systematic and exhaustive software tools for structure based rational drug design

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Keywords: Rational drug design; Ligand docking; de novo Design; VHTS; Scoring function

Scientific advancements during the past two decades have altered the way pharmaceutical research produces new bio-active molecules. Traditional 'trial and error' drug discovery efforts are gradually being replaced by structure based rational drug design. A key technique is the use of methods including X-ray crystallography and NMR for the determination of the 3-dimensional structure of a target protein followed by various modelling techniques for the design of small molecule ligands that could interact with the target structure. The first generation of the software tools were limited to energy calculations and molecular dynamics simulations based on simple force field models. More automated methods, like flexible ligand docking and de novo ligand design programs have emerged in the 90s. However, many of these software systems relied on stochastic algorithms to perform the search, effectively performing a computerised 'trial and error' search.

SimBioSys provides ligand design and docking tools that are systematic, exhaustive, rely on rational rules, heuristics and dynamic knowledge bases. The novel algorithms designed and optimised to solve the specific problems greatly outperform the general random methods. The presentation gives a brief overview of the efficient algorithms behind the SPROUT (de novo ligand design) and eHiTS (flexible ligand docking and virtual high throughput screening) software tools. Validation test results are presented to demonstrate the effectiveness of these tools for the solution of practical drug design problems.

43. Structures and Electronic Properties of Aromatic Nitrile Hydratase Substrates and Products – A DFT Study

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Keywords: NHase, DFT, B3LYP, aromatic nitriles, aromatic amides

Nitrile hydratase (NHase) is an important enzyme widely used in biotechnology. NHase converts nitriles to the corresponding amides. Its active site contains non-heme low spin Fe(III) or low spin non-corrinoid Co(III). Although structures of some NHases are known since 1997 [Structure, 1997, 5, 691], the catalytic mechanism is not fully recognized. In the literature [Nature Biotechn, 1998, 16, 733] at least three models of the catalysis were postulated, but none has been verified, yet. Theoretical modeling may help to elucidate observed selectivity of certain NHases, but the details of molecular and electronic structure of substrates and products have to be determined first. We investigated selected aromatic substrates of NHase (nicotinonitrile, o-, m-, p-methylbenzonitrile [Appl. Microbiol. Biotechnol. 2004, 64, 76] - Fig. 1) and the corresponding products (nicotinamide, o-, m-, p-methylbenzamid). Such studies could provide an insight into molecular basis of catalytic reaction and answer which of the postulated catalytic mechanism do occur in the protein. Optimum geometries of all compounds were obtained using density function theory (DFT) method with B3LYP 6-31(d,p) functional implemented in Gaussian98 code. An analysis of the effect of bulky methyl group on the nitrile and amide group properties will be presented, and molecular electrostatic maps will be discussed.

44. *Ab initio* MP2 Level Study of Annulation Effects on the Valence Isomerism of [6]Paracyclophanes

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The isomerizations of 2,3-annulated [6](1,4)Dewar-cyclophanes to the corresponding annulated [6]paracyclophanes have been studied using high level MP2 *ab initio*. The special focus of this work was the effect of ring size of the annulation. Smaller rings decrease the exothermic character of the Dewar Benzene Isomerization. Larger Rings have no effect since the strain on the Dewar benzene is similar to having no annulation.

45. N-aminopeptides as Peptidonucleic Acids Building Blocks : A DFT and AIM study

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Keywords: AIM, Intramolecular hydrogen bonding, N-amino peptides, peptidonucleic acids.

In our laboratory, peptidic synthesis is carried on on N-aminopeptides in order to synthesize peptidonucleic acids based on an N-aminopeptidic backbone. In the present study, peptidonucleic acids building blocks have been optimized at the HF/STO-3G//B3LYP/6-31G(d,p) level in various conformations and their electronic density has been studied by means of the AIM methodology, in order to assess intramolecular bonding and thus discuss the stability of the conformers. The studied oligomers are built from two nucleic bases linked by an amido arm to an N-aminopeptidic backbone.

46. NMR-based Structural Studies of the MUC1 Tandem Repeat Glycopeptides

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Keywords: MUC1, glycopeptides, GalNAc, NMR

MUC1 is an integral membrane glycoprotein that is expressed on the epithelial cell surface of various organs which include colon, pancreas, breast and lungs. The extracellular domain of MUC1 consists of a variable number of tandem repeat of 20 amino acids. This tandem repeat (AHGVTSAPDTRPAPGSTAPP) domain of MUC1 is heavily O-glycosylated. O-glycosylation in the tandem repeat domain is catalyzed by a family of enzymes called GalNAc transferases. In vitro studies using tandem repeat peptides containing the DT to ES substitution have shown that O-glycosylation at specific sites by GalNAc transferases require prior glycosylation at other sites. In this study, we used NMR and computational methods to study the conformational changes that take place following initial glycosylation of the tandem repeat peptides. The three peptides that were studied are 1) AHGVT*SAPESRPAPGSTAPPA 2) AHGVTSAPES*RPAPGSTAPPA 3) AHGVTSAPESRPAPGST*APPA (*=αGalNAc). These three peptides were designed to mimic the underglycosylated form of MUC1 found on the surface of tumor cells. Comparison of conformational features of the glycosylated peptide segments VTSA, PESR and GSTA with their corresponding nonglycosylated counterparts showed that O-glycosylation causes subtle changes in the conformation of the peptide backbone at sites proximal to the site of O-glycosylation. However, O-glycosylation does not cause changes in the conformation at distant sites.

47. Influence of the Aqueous Solvent Microstructure on the Behavior of the Mobile-free Counterions on the Protein-Solvent Interface

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Keywords: proteins, protein-protein association, electrostatics, ionic strength effects, dielectric heterogeneity

It is become obvious that molecules of the aqueous solvent play crucial role in protein folding, conformational adaptabilities, as well stability and the function of proteins. In the framework of the continuum electrostatic model, we have shown that the aqueous solvent microstructure, particularly the correlated orientational Debye polarization of the water molecules, leads to new electrostatic effects at the protein-solvent interface, particularly, determines the spatial heterogeneity of the dielectric properties of solvent and protein at the interface (Ninth Electronic Computational Chemistry Conference (ECCC9), 2003. http://bims.unmc.edu/ECCC9/article33/; Biophys. J. 2004.87:1544-1557). This heterogeneity is significantly different from that obtained by the generally accepted classical approaches, which consider solvent as the uniform dielectric medium of the high dielectric constant. From a physical standpoint this heterogeneity should influence on the behavior of the mobile-free counterions in solvent and change the ionic strength effects near the interface. These effects are very important for adequate estimations of the electrostatic interactions in proteins as well as protein-protein and protein-ligand association. At the present work we used the concept of nonlocal electrostatics for model interface between a protein and an aqueous solvent as well as a phenomenological theory of polar solvent to analyze the electrostatic interaction energy between a point charge placed in the solvent and the dielectric boundary arising at the solvent-protein interface. Our asymptotic and numerical analysis revealed that the charge undergoes

more strong effective repulsion at the grater distances from the interface in contrast to classical solvent model. The molecular recognition in a long-distance range is discussed.

48. Withdrawn

49. Automated Docking of Estrogens, Antiestrogens and SERMs Into an Estrogen Receptor Alpha and Beta Isoform Using the PMF Forcefield and the Lamarckian Genetic Algorithm

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Keywords: estrogen receptor, PMF, Lamarckian genetic algorithm, SERM, estradiols, docking

A diverse set of estrogens, antiestrogens and SERMs (Selective Estrogen Receptor Mediators) whose relative binding affinities (RBA) with respect to 17b-estradiol are known, are automatically docked into a particular estrogen receptor alpha and beta (ER-α and ER-β) in silico, utilizing the Lamarckian genetic docking-algorithm and the PMF (potentials of mean force) force field. After division into distinct classes (estrogens, antiestrogens, SERMs), the ligands are ranked based upon the calculated ligand:receptor interaction energies, as well as experimental RBAs. Comparison of both rankings shows good agreement within the distinct ligand classes. The presented results indicate that PMF may be applied to the estrogen receptor:ligand complexes, and the ranking of ligands within distinct classes is a very useful pre-screening-tool for development of novel estrogen receptor ligands.

50. The Electronic Structure and Intrinsic Redox Properties of [2Fe-2S]+ Clusters with Tri- and Tetra-Coordinate Iron Sites

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In biological electron transport chains, [2Fe-2S] units in electron transfer proteins have versatile electrochemical properties with reduction potentials ranging from -450 to –150 mV vs. NHE for the $[Fe_2S_2]^{2+/1+}$ redox couple for standard ferredoxins and from about –100 to +400 mV for Rieske-type proteins, serving as important electron carriers in a wide variety of biological processes. Although it has been proposed that in addition to changes of the hydrogen-bonding network around the cluster, the variation in reduction potentials between the high- and low-potential Rieske proteins also depend on the degree of coupling between cluster oxidation state and histidine protonation state, the influence of the intrinsic factors on reduction potential of the [2Fe-2S] clusters, in particular on the pH-independent low-potential Rieske proteins, is not fully understood. Using potentially bidentate ligands (-$SC_2H_4NH_2$), we produced $[2Fe\text{-}2S]^+$ species of different coordination geometries by fission of $[4Fe\text{-}4S]^{2+}$ complexes. Even though the ligands are monodentate in the cubane complexes, both mono- and bidentate complexes were observed in the [2Fe] fission products through self-assembly due to the high reactivity of the tri-coordinate iron sites. The structure, electronic structure, and redox property of the [2Fe] and [4Fe] species were probed using photoelectron spectroscopy (PES) and broken-symmetry density functional theory (DFT) calculations. It was found that tetracoordination significantly decreases the electron binding energies of the [2Fe] complexes, thus increasing the reducing capability of the $[2Fe\text{-}2S]^+$ clusters.

51. Vibrational Properties of Infinite Carbon Chains

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Keywords: Polyyne, carbyne, cumulene, vibrational, phonon dispersion, ab initio, optic

Infinite carbon chains and their oligomers have been the focus in materials science and astronomy. An infinite linear carbon chain can be alternating as in polyyne or carbyne, or equidistant, as in the case of cumulene. Vibrational spectroscopy is an important characterization tool to detect the existence and investigate the structures of these systems. Although polyyne and cumulene have long been serving as classical models of lattice vibration in solid state physics, and their vibrational spectroscopy has been studied and utilized extensively in the literature, there still exists controversy regarding some fundamental vibrational properties of long carbon chains. In this work, a series of ab initio calculations are performed on linear carbon chains based on both oligomer and periodic boundary condition (PBC) methods, with special attention paid to the connection and interplay between them. A consistent phonon dispersion is obtained with all the techniques used in this work, including the PBC phonon calculation, scaled quantum mechanical oligomer force field (SQMOFF) method, and our newly developed k-dependency extraction from oligomer frequencies method. The phonon dispersion pattern reported in this study is different from previous results found in the literature. After comparison with experimental vibrational data of oligoynes, the Raman active bond length alternation mode, or the longitudinal optic mode of polyyne is determined to be around 1900 cm^{-1}, in contrast with the widely accepted values falling in the 2000-2300 cm^{-1} range. The infinite equidistant carbon chain, cumulene, should have no vibrationally active bands in principle, in contrast to various values

reported in the literature. Our results should aid the identification of various linear carbon chains occurring in the chemistry of carbon.

52. Nonlinear Transformation Methods for Accelerating the Convergence of Coulomb Integrals Over Exponential Type Functions

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Keywords: Nonlinear transformations, Extrapolation methods, Numerical integration, Molecular integrals, Slater type functions, B functions

It is well known that in any ab initio molecular orbital (MO) calculation, the major task involves the computation of molecular integrals, among which the computation of Coulomb integrals are the most frequently encountered. As the molecular system gets larger, computation of these integrals becomes one of the most laborious and time consuming steps in molecular systems calculation. Improvement of the computational methods of molecular integrals would be indispensable to a further development in computational studies of large molecular systems. The atomic orbital basis functions chosen in the present work are Slater type functions. These functions can be expressed as finite linear combinations of B functions which are suitable to apply the Fourier transform method.

The difficulties of the numerical evaluation of the analytic expressions of the integrals of interest arise mainly from the presence of highly oscillatory semi-infinite integrals. In this work, we present a generalized algorithm based on nonlinear transformations methods, for a precise and fast numerical evaluation of molecular integrals over Slater type functions and over B functions. Numerical results obtained for the two-center Coulomb integrals over Slater type functions and over B functions, with a series of molecules show the efficiency of the approach presented in this work. Comparisons with numerical results obtained using existing codes and from the literature are listed.

53. Modeling of Complex Hydrides: An *ab initio* and Molecular Dynamics Approach

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The aim of this research project is to get an insight into structural and dynamical details of hydrogen (un)loading processes, phase segregation, and stability and dynamics of phase boundaries. Coupled to this is to get a better understanding of hydrogen interaction with host matrix elements. We intend to achieve this by simulating large clusters containing NaH,Na3AlH6, NaAlH4 and Al phases, plus catalysts atoms. MEAM parameters derived from DFT calculations will be used to describe the solid state reactions and phase separations of interest in hydrogen (de)sorption in alanates. Key problem: Timescales at which structural changes occur maybe orders of magnitude above that accessible in MD simulations. Trick: Use rare-event dynamics (A.F. Voter et al Annu. Rev. Mater. Res. 32,321(2002)).

54. Semiempirical Study of Supramolecular Bis-porphyrin "Molecular Tweezers"

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Keywords: AM1, porphyrins, complexations, supramolecular

In this paper, semiempirical study of a series of space separated bis-porphyrin "molecular tweezers" 1 using AM1 method will be presented [J Mol Model 2000, 6, 318]. It was found that bis-porphyrine systems such as 2 are significantly less rigid than previously thought [PCC. 2001, 3, 4488]. Variation of metal-metal separation distance does not cause significant energy change thus enabling these molecules to easily adjust to the optimal bonding distance required for complexation of various pyridyl ligands.

55. Development of a TIP5P Consistent Carbohydrate Force Field

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The inclusion of zero-mass point charges around electronegative atoms, such as oxygen, within molecular mechanical force fields is known to improve hydrogen bonding directionality. In parallel, inclusion of lone-pairs in a water model, TIP5P, increased the ability of the water model to reproduce both gas phase and condensed phase properties over its non-lone pair containing predecessor, TIP3P. In general, the parameters in the force field relevant for modeling the solvent are developed independently of and differently from those for the biomolecules due to the molecular size of the latter component. Therefore, a different ansantz has to be implemented to derive the most optimal lone-pair position in each type of molecule.

Currently the GLYCAM carbohydrate force field computes partial charges via fitting the classical molecular electrostatic potential (MEP) to the quantum mechanical MEP. Application of this methodology to optimize the lone pair placement is therefore consistent with the current parameters and is straightforward to implement. The bond, angle, torsion, and Lennard-Jones force field parameters are based on atom type, while the partial charges are unique to each atom. Previously, biomolecular lone pair models employed the same lone-pair placement for all oxygen atom types regardless of their chemical environment. Here, we present an atom

type specific lone-pair model, which leads to the most optimal placement for each atom type and notably results in reproduction of the lone pair placement present in TIP5P. Development of a lone-pair inclusive carbohydrate force field in conjunction with a lone-pair containing water model, such as TIP5P, is necessary to ensure the compatibility between these two models. Implementation of this lone-pair model into the GLYCAM force field improves the geometry for a series of hydrogen bonded clusters over the non-lone pair containing force field and is shown to reproduce condensed phase solution properties for mono- and disaccharides.

56. Characterization of the Conformational State and Flexibility of Free Form gp120

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Keywords: HIV-1, gp120, molecular dynamics simulations, potential-mean-force

The free form gp120 structure, which is crucial to intervention of HIV-1 infection, is resistant to experimental characterization. In order to gain such detailed structural knowledge, we performed a series of molecular dynamics (MD) simulations: (a) classical MD simulations on gp120 core domain from CD4-cocrystal structure; (b) PMF simulations to explore the unfolding pathways; (c) classical MD simulations on conformations with bridging sheet unfolded. Results show that gp120 populated a conformation with loose interactions among the inner domain, the outer domain and -strands 20/21 part of the bridging sheet. - strands 2/3 part of the bridging sheet displayed high flexibility and are able to switch between folded and unfolded conformations.

Based on the refolding simulations and the minimum at the PMF surface, an atomic detail model for the unbound state gp120 is proposed, which may be targeted for AIDS therapy.

57. Natural Resonance Structures and Aromaticity of the Nucleobases

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Keywords: nucleobase, DFT, natural bond orbital, natural resonance theory, aromaticity, and nucleus-independent chemical shift (NICS)

Natural resonance theory (NRT) and nucleus-independent chemical shift (NICS) analyses have been applied to the molecular electron densities of the five common nucleobases (adenine, guanine, cytosine, uracil and thymine) that were obtained from density functional theory calculations. Compared with the dominance of the two Kekulé structures of benzene, the structural modifications in the form of heteroatoms within the rings and the exo-substituents introduce large amount of charge separation in nucleobases. As a result, the leading resonance structures for cytosine, uracil and thymine are still covalent structures, but their weightings decrease to 30-40% in the NRT expansion. For adenine and guanine, several ionic NRT structures have weightings of about 10%, which is as large as that of their covalent NRT structures. We present the calculated NICS at the ring center as an indication for aromaticity of the nucleobases and of many intermediate structures starting from benzene and pyrrole. The effects of different structural modifications on the overall aromaticity in nucleobases are thus examined.

