ABSTRACTS

OF ORAL & POSTER PRESENTATIONS

Current Trends in Computational Chemistry 2002

Jackson, Mississippi
November 1-2, 2002

Enzyme Targetted Herbicide Design: A Molecular Modelling Studies

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Inhibition of biosynthesis of aromatic amino acids such as phenylalanine, tyrosine and tryptophan, in plants, many bacteria and microbes leads to the disruption of proliferation of these systems. This is the origin of the discovery of potent herbicide. Commercially important herbicides should have the properties that satisfy the compatibility of environment. One such herbicide is glyphosate which provides the herbicidal performance needs of the market place and it exhibits very low mammalian toxicity and environmentally friendly characteristics. Recently, it was shown that glyphosate inhibits the growth of the pathogenic parasites Plasmodium falciparum (malaria), Toxoplasma gondii and Cryptosporidium parvum. Further, glyphosate is a non-selective herbicide spectrum that controls most of the problematic weeds. It is non-toxic to birds, fish, insects and most bacteria and is readily broken down by microbes and hence ammonia, inorganic phosphate and carbon dioxide are produced.

It is evident from the studies of physiological, biochemical and genetic experiments that glyphosate controls weeds by inhibiting the plant enzyme 5-enolpyruvylshikimate 3 – phosphate (EPSP) synthase (EC 2.5.1.19). Glyphosate is a prime target for this enzyme (EPSP) synthase, which is the key enzyme for the production of plant aromatic amino acids and important metabolites that are needed for plant growth. These derivatives are derived through the Shikimate pathway. As this pathway is absent in mammals, fish, birds, reptiles and insects, it can be considered as an important pathway in the herbicide research as this will not biologically affect the species mentioned above. Hence, research on designing herbicide based upon this pathway is expected to yield potent and commercially important and successful herbicides. Recent studies strongly suggest that the only commercially relevant compound to be an inhibitor of the enzyme EPSP synthase is glyphosate.

The enzyme EPSP synthase catalyses the reaction involved in transfer of enolpyruvyl moiety from phosphoenol pyruvate (PEP) to shikimate-3-phosphate (S3P) forming the products EPSP and inorganic phosphate (P_i). Glyphosate inhibits this enzyme in a slowly reversible reaction, which is competitive with PEP and uncompetitive with shikimate-3-phosphate (S3P).

Numerous studies using solution, solid state NMR, florescence and differential scanning calorimetry demonstrate that glyphosate preferentially forms a stable ternary complex with the enzyme EPSP synthase and S3P (EPSPS.S3P.Glyphosate). This ternary complex most likely represents the actual enzyme – bound form of glyphosate, which is responsible for its herbicidal activity in plants.

The specificity of PEP as well as glyphosate for the same enzyme, EPSPS, leads to competitive behavior. Even a minor conformational change induced upon glyphosate dramatically reduces enzyme affinity, thereby making the unavailability of glyphosate binding domain. Hence, a detailed analysis of the structure and function of both glyphosate and its target, the molecular mode of action with its target and the modeling of its various analogs has been the subject of recent studies. In this paper we have presented the preliminary results of conformational studies on this herbicidal compound.

A Theoretical Study of Structure and Properties of Uric Acid: A Potent Antioxidant

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A detailed study of tautomeric properties of uric acid and its different anions were performed at the Density Functional Theory level employing B3LYP functional. Initially, the relative stability of various possible neutral tautomers were determined using 3-21G(d,p) basis set and this was followed by computation with 6-31G(d,p) basis set for selected stable tautomers. To determine the different possible anions of uric acid the basis set 6-31++G(d,p) was used. The effect of aqueous solvation on the relative stability of the neutral and anionic species was considered using Tomasi's polarized continuum model. The keto form of the molecule was found to be the most stable in the gas phase and in aqueous medium. Among monoanions, the anion obtained by deprotonation of the N3 site is the most stable, while among dianions, the anion obtained by deprotonation of both N3 and N7 sites is the most stable both in the gas phase and in aqueous medium. Different properties of neutral tautomers, neutral transition states, and anionic form of the uric acid in the gas phase and in aqueous media were studied. The radical species were also investigated for their various properties in both media.

Substituent Effects on the Cyclopentadienyl Cation

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We have investigated the changes in geometry and ground-state energy for the singlet and triplet states of the cyclopentadienyl cation (Cp^+) as substituents are added. The substituents studied include chlorine, fluorine, the amino group, the methyl group, and the silyl group. The number of substituents added to the ring ranged from one to five. Derivatives of Cp^+ in which a carbon was replaced by boron and nitrogen were also studied. Geometry optimizations were carried out at the B3LYP/6-31G* level, followed by single-point energies at the CCSD(T)/ccPVDZ level. For all the substituted Cp^+ compounds studied, the alternation in bond lengths around the ring was considerably more marked for the singlet state than for the triplet state. This difference in bond-length alternation between the singlet and the triplet state was noticeably less pronounced for the heterocyclic compounds. The resonance Hammett constant (σ_R^0) was used as a measure of the relative electron-donating or electron-withdrawing ability of each substituent. The resonance Hammett constant was plotted versus several parameters: (1) the triplet-singlet energy gap, (2) the carbon-carbon bond length opposite the site of single substitution, (3) the HOMO-LUMO gap, (4) the average bond length in the ring, and (5) the π-electron density. In most of these cases, the correlation for single substitution was fairly good, but the correlation for multiple substitution was poor.

Does Deterministic Chaos Play a Role in Chemistry?

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The lecture summarizes author's teaching experience in the field of non equilibrium deterministic chaos of chemical reactions. Deterministic chaos is understood in the sense of extreme sensibility to initial conditions. It is shown that Verhulst's logistic model of population serves as the basis of interpretation of the simplest auto-catalytic reaction: A+X⁄2X. Oscillating reactions, dissipative structures, bifurcations and deterministic chaos are reviewed in this framework.

Visual Recurrence Analysis of Nonlinear Vibrational Dynamics in H_3^+ Molecule

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In 1954 E. Fermi, J. Pasta and S. Ulam (FPU) performed numerical simulation of the planar motion of a one dimensional anharmonic chain of 64 particles with fixed ends [1]. To their surprise, instead of finding rapid redistribution of energy among the normal modes, they could observe a variety of manifestly non-equilibrium and non-equipartition behaviors. Recently, Casetti et al. [2] performed extensive numerical calculations and found that there is a threshold energy, below which the dynamics appears to be regular and above stochastic. Similar behavior has been found in the numerical studies of the Henon-Heiles Hamiltonian [3],

$$H = \tfrac{1}{2}(\dot{x}^2 + \dot{y}^2) + \tfrac{1}{2}(x^2 + y^2) + x^2 y - \tfrac{1}{3} y^3,$$

where depending on the value of energy, a fully developed chaos, a coexistence of regular and chaotic regions of phase space, or only regular trajectories are observed.

The many coupling and resonances in even small molecules and the possible existence of FPU-like behavior in molecular systems, has been intriguing and persistent question for a long time [4]. The aim of this work is to study the vibrational dynamics of the simplest polyatomic molecule, H_3^+, known as a strongly anharmonic with a large amplitude motion, and to show that it exhibits similar features like that observed in FPU and Henon-Heiles systems.

For these purposes we have used classical trajectory method as implemented in the DRC routine introduced by Stewart et al. to follow steepest descent paths efficiently on the semiempirical MNDO potential surface [5] and subsequently extended to an ab initio wave functions and implemented into the electronic structure program package GAMESS [6]

Recurrence plots (RPs) are relatively new technique for the qualitative assessment of time series [7]. With RPs one can graphically detect hidden patterns and structural changes in data or see similarities in patterns across the time series under study. To expand a one-dimensional signal into an d-dimensional phase space, one substitutes each observation in the original signal X(t) with vector y(i)={x(i), x(i+T), x(i+2T),..., x(i+(d-1)T)}, where i is the time index, d is the embedding dimension and T represents the time delay. As a result, we have series of vectors Y = [y(1), y(2), y(3), ..., y(N-(d-1)T)], where N is the length of the original series. Proper choice of the time delay and the embedding dimension is critical for this type of phase space reconstruction. Once the dynamical system is reconstructed, RP can be used to show which vectors in the reconstructed or original space are close and far from each other. Distance matrix D_{ij} between vectors y(i) and y(j) in the reconstructed series is given by

$$D_{ij} = \sqrt{(x(i) - x(j))^2 + (x(i+T) - x(j+T))^2 + ... + (x(i+(d-1)T) - x(j+(d-1)T))^2}\ .$$

The next step is to choose a threshold corridor [δ_l, δ_h]. Once the threshold corridor has been chosen, it is used to generate a thresholded recurrence matrix

$$B(i,j) = \begin{cases} 1 & \text{if } \delta_l \le D(y_i, y_j) \le \delta_h \\ 0 & \text{otherwise} \end{cases}\ .$$

Finally, the RP is generated by darkening all pixels (*i*, *j*) that correspond to nonzero entries in matrix *B*. The examples of the RPs are shown in Figure 1.

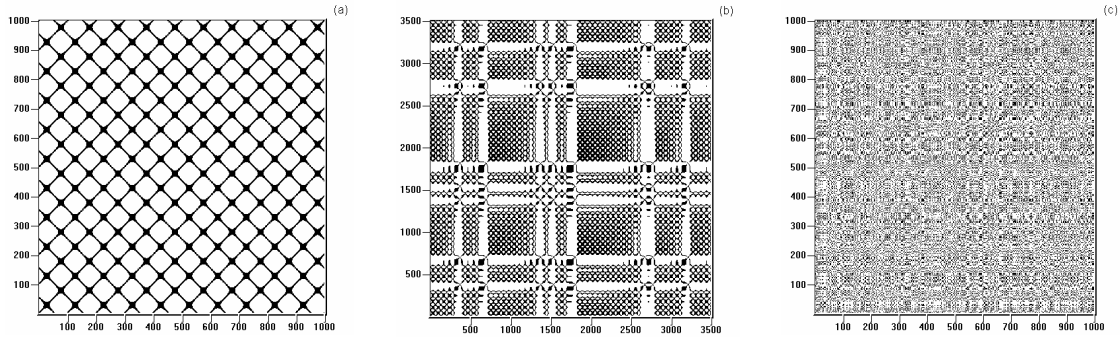

Fig. 1. *Recurrence plots of (a) a time series derived by sampling the function sin(t), (b) a time series of a deterministic chaotic signal (Lorenz system), and (c) a time series of a fully random signal (white noise).*

To examine behavior of H_3^+ vibration dynamics depending on the amount of vibrational energy supplied, we performed DRC calculations at the HF/6-311G** computational level. As the initial conditions of DRC calculations, the same amount of vibrational energy ranging from 0.2 to 4.5 vibrational quanta $h\nu_i$ was given in the positive direction to all normal modes. In every case, the time step was set equal to 0.05 fs and simulation was carried out over 5ps. Representative results of our extensive classical trajectory calculations are shown in the Figure 2.

In the case of regular vibration motion (Fig. 2.a) skeleton of RPs has a structure of regular lattice. This structure is similar to RP of a time series of sampled function sin(*t*) (Fig. 1.a), indicating periodic character of vibration motion. As the energy increases, this lattice becomes more and more dense and distorted due to presence of higher modulation frequencies. When the transition from regular to stochastic vibration motion occurs, lattice becomes at first slightly deformed (Fig. 2.b, c) and when the motion becomes fully stochastic, skeleton of RPs displays a very complicated pattern (Fig. 2.d), similar to chaotic (Fig. 1.b) or even stochastic systems (Fig. 1.c). This behavior is also evident from the Fourier transforms, which changes from sharp peaks, to a broad band spectra corresponding to chaotic motion. DRC calculations performed with 20 different values of vibrational energy supplied to all normal modes revealed transition from regular to stochastic motion at energy slightly higher than zero point vibrational energy. The threshold of this transition is lying close to $0.6\sum_{i=1}^{3} h\nu_i$. This behavior of H_3^+ molecule resembles the dynamics of the FPU-model and Henon-Heiles Hamiltonian, indicating that an order-to-chaos transition might be characteristic feature of Hamiltonians describing also real molecules. We performed similar calculations for the molecule of water (which is in contrast with $H_{3,}^+$ known as a prototype of a harmonic molecule) up to the energy $6\sum_{i=1}^{3} h\nu_i$, but we have not observed any similar phenomena.

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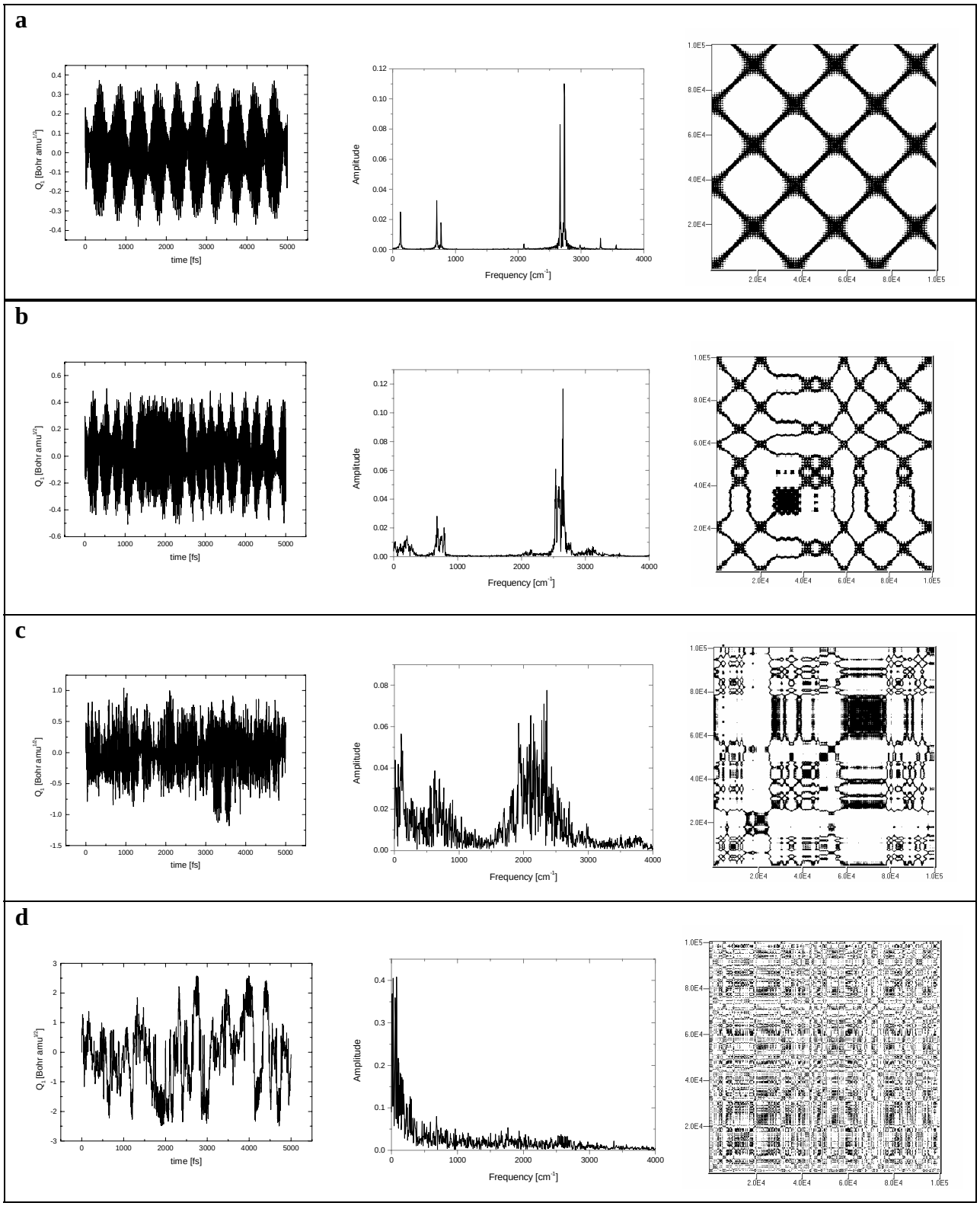

Fig.2. *Time dependences of normal mode coordinates (left column), their Fourier transforms (middle column) and their recurrence plots (right column) for various amount of energy* $\alpha\sum_{i=1}^{3} h\nu_i$ *supplied to the normal modes: (a) α = 0.5; (b) α = 0.75; (c) α = 1.5; (d) α = 3.5.*

Modified Genetic Algorithm to Model Crystal Structures Allowing Molecular Geometry Relaxation

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Introduction

In recent years the field of crystal engineering, whose goal is to design solids with specific properties,[1] has received significant contributions from advances in computer modeling of organic materials.[2] Organic crystalline materials are prevalent in many industries, including pharmaceuticals, agrochemicals, pigments, dyes, explosives and specialty chemicals and modeling techniques that can predict their structures and properties are highly desirable.

Polymorphism is one of the greatest challenges in crystal engineering today, increasingly, the experimental evidence shows that organic crystals may exist in a number of polymorphs that can fall within a narrow range of energies. This is not a well-understood phenomenon; therefore it is necessary to develop a better understanding of the conditions under which organic solids can crystallize in different polymorphic forms. This is important because different polymorphs can exhibit very different properties such as shelf life, bio-availability, solubility, morphology, vapor pressure, density, color, and shock sensitivity.

Practical methods that can lead to accurate crystalline structures in an effective manner are required to make significant advances in crystal engineering. Finding the global energy minima of complex systems such as proteins[3] and molecular and atomic clusters[4] is a NP- (non polynomial)- hard problem. Similar difficulties have been encountered in optimizing crystalline structures.

Many studies have attempted to generate good starting points for local energy minimizations using techniques such as: common coordination geometries, close-packing arguments and statistical correlation.[5,6] A Monte-Carlo simulated annealing process has also been considered,[7] as well as molecular dynamics.[8] Recently, Lommerse et. al.[9] published a test of crystal structure prediction of small organic molecules. This paper provides a description of almost all existent methods for crystal structure prediction. Their performance was tested by calculating the structures of crystals whose experimental structures had not been published at the moment of the test. The resulting structures were compared with the experimental ones showing the prediction quality for each method

In our previous work using modified genetic algorithms for the prediction of crystal structures we used the "fix molecular geometry approximation." This approximation can be justified for relatively rigid molecules like aromatic hydrocarbons,[10,11] but many organic crystals contain much more flexible molecules, which may exhibit different conformations for different polymorphs. Here we describe the new functionality added to the package MGAC (Modified Genetic Algorithm for Crystal and Cluster structures)[10,11] to model the structures of organic crystals allowing relaxation of the molecular geometries.

Methodology

Genetic Algorithms[12,13] are a family of search techniques rooted on the ideas of Darwinian biological evolution. These methods are based in the principle of survival of the fittest,

considering that each string or *genome* represents a trial solution candidate of the problem, at any generation the *genomes* or "individuals" compete with each other in the population for survival and produce off-strings for the next generation by prescribed propagation rules. One of the advantages of genetic algorithms is that they can provide not only a global minimum, but also information on other states with energies close to the minimum. Also GAs are able to search large complex spaces with relatively efficiency.

While as discussed above, many organic molecules exhibit relatively rigid molecular structures that may be considered fix in the optimization of the crystalline structure. A more common situation is to have molecules with much less rigid structures. In this case the molecular geometry and conformation can be highly dependent of the phase of the material. This is to say that large geometry or conformational changes may be observed between gas, liquid and solid phases, even different crystalline phases may have different molecular structures. This is the case when the difference in the intramolecular energy between different molecular conformations is comparable to the intermolecular interactions among molecules in the crystal. For first case, due to the weaker intermolecular interactions, it is possible to encode the crystal structure using the crystallographic parameters, the position of the center of mass of each molecule and the relative orientation between molecules in the crystalline cell. Therefore, the number of free variables is: $N_{die}.N_{mol}+6N_{mol}+6$, where N_{mol} and N_{die} are the number of molecules and dihedral angles between single bonds in the asymmetric unit. This approximation was used in our previous MGAC work. When this approximation is not valid, it is necessary to encode the crystalline structure using the crystallographic parameters, $\{a,b,c,\alpha,\beta,\gamma\}$ and the Cartesian coordinates of N atoms belong to the asymmetric unit in an array of dimension 3N. Therefore the number of free variables to optimize is 3N+6, which is much larger than $N_{die}.N_{mol}+6N_{mol}+6$, consequently increasing the search space for the crystalline structure.

GA optimization

The GA was programmed using GASPlib[3,4] and GALib.[14] The initial population is created randomly with N_{pop} individuals. The energy optimization of each individual (crystals) in every generation is made employing the CHARMM code.[15] The GA operations of mating (crossover), mutation and selection are used to evolve one generation into the next. The best individuals (50% of the population) are copied directly into the next generation. The remaining of the population is generated by recombination and mutation. In order to choose the parents of these new individuals from the previous population, they are characterized by a fitness probability. Finally, this group of $N_{pop}/2$ evolved individuals is added to the best $N_{pop}/2$ individuals of the original population to produce the next generation of N_{pop} individuals. This procedure is repeated until the algorithm reaches a maximum number of generations defined at the beginning of the running.

Calculations

In order to test the capabilities of the outlined method we choose the L-Alanine and D-Alanine crystals. The initial population consists of 20 individuals that evolve during 20 generations. The crystal structure were optimized both under the "fix molecule approximation" and allowing the relaxation of the molecular geometry. The differences and coincidences between the corresponding evolutions are discussed in the presentation.

The population's statistics for every generation in the evolution of the crystal structures are presented for the complete evolution. The histograms of the evolution for the crystal structures are also discussed. Finally the X-ray diffraction powder spectra calculated for the experimental and predicted structure are compared.

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Modeling of Atomic Clusters Structures by Means of the Genetic Algorithm Using Semiempirical Methods

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Introduction

The structure and physical properties of atomic and molecular clusters are an extremely active area of research, not only in fundamental but also in applied science, because their size scale is currently being approached by the present miniaturization trend in microelectronics.[1]

The optimization of structures containing more than a few atoms is a crucial problem, due to the explosive appearance of possible isomers with the increase in the number of atoms in the cluster. Global geometry optimization becomes very difficult for large clusters.[2,3] Several reasons justify the increasing interest on the structures and properties of mixed Si_nX_m clusters. First, many of them have been observed, i.e. SiC, SiC_2, SiC_4, which play important roles in chemical reactions in the interstellar medium.[4] Second, Si-C clusters are involved in technological applications, as the manufacture of SiC thin films.[5] Third, metal-doped silicon clusters, i.e. Si_nCu, Si_nMo, etc., are relevant in modern electronic devices.

The difficulties present in finding the global minima on the potential energy surface may be summarized as:

1- Ab-initio methods are very expensive to model structures of medium size clusters. Even those clusters with more than ten atoms produce so many isomers that also a parallel technique combined with ab-initio methodology would demand tremendous cpu time to arrive at the minima.
2- Ab-initio methods present N^3 algorithm complexity, with N the number of basis functions.
3- The bonding nature in silicon metal clusters is different from the chemical bonding found usually in Organic or Inorganic Chemistry. Because of that it is very difficult to model a proper interaction potential to reproduce the interatomic interactions in these clusters.

The aim of this contribution is to present an algorithm for finding the structures corresponding to the global minima and their closets local minimum for mixed silicon clusters Si_nX_m (X=Al, C). The interest on X=C is to test the method, since there are extensive studies on the geometry and properties of these clusters.[6,7] The aluminum has been chosen because it is one of the dopants that reduce the surface reactivity respects to pure silicon cluster,[8] for clusters with more than thirty atoms. To our knowledge the Si_nAl_m clusters have not been deeply studied. There are no experimental or theoretical reports about the structure of small size Si-Al clusters. We consider that their study is useful to get another insight into the mechanism of the silicon-metal bonding

Methodology

There are several methods available for finding the global minima, but the genetic algorithm (GA),[9,10] and basin hopping Monte Carlo (BHMC)[11,12] are probably the best current approaches for finding the global minima in the energy potential surface of molecular and atomic clusters.[9]

We have employed the GA to model the structures of the mixed clusters and then relaxed them by using more accurate, but computationally more demanding density functional theory (DFT)[13] methods. Genetic algorithms[9,10] are a family of search techniques rooted on the ideas of Darwinian biological evolution. These methods are based in the principle of survival of the fittest, considering that each string or *genome* represents a trial solution candidate of the problem. At any generation the *genomes* or individuals compete with each other in the population for survival and produce off-strings for the next generation by prescribed propagation rules. One of the advantages of the genetic algorithm is that they can provide not only a global minimum, but also rich information on other states close to the minimum. Operators analogues to crossover, mutation and natural selection are employed to perform a search mechanism able to explore the multidimensional parameter space and determine which regions of that space provide good solutions for the problem. We coded the cluster structure in real-valued vectors that represent the *genome* for the structure. Optimization runs begin with random initial configurations, i.e. parent structures that are combined to form off-strings, and then compete with the parents and each other to survive in a selection process. Over successive generations the population evolves to include increasingly optima structures, ultimately containing the global minima.

We have employed our Modified Genetic Algorithm to model Cluster and Crystal Structures (MGAC),[14,15] implementing a very important modification: we have not employed any empirical potential to model the interatomic interaction. We have used a semi-empirical molecular orbital program, MSINDO[16] to evaluate the energy of each cluster in each cycle of the genetic evolution. MSINDO is a modification of the original SINDO1 method.[17] We consider that the employment of a semiempirical method is a reasonably choice in view of the compromise between accuracy and computational requirements to produce the clusters' structures.

Calculations

The **GA** operations of mating (crossover), mutation and selection are used to evolve one generation into the next. The best individuals (50% of the population) are copied directly into the next generation. The remaining population part is generated by recombination and mutation. In order to choose the parents of these new individuals from the previous population, they are characterized by a fitness probability. Finally, this group of $\mathbf{N_{pop}}/2$ evolved individuals is added to the best $\mathbf{N_{pop}}/2$ individuals of the original population to produce the next generation of $\mathbf{N_{pop}}$ individuals. This procedure is repeated until the algorithm reaches a maximum number of generations defined at the beginning of the running.

The initial population consists of 10 individuals that evolve during 20 generations. We applied the GA method to model the structures of small Si_nC_m and Si_nAl_m clusters with n+m=5**.**

We present evolutionary plots for each cluster and corresponding histograms to detect not only the global minima but also other structures close to it.

The best candidate was relaxed to a better structure employing the B3PW91 DFT method[18,19] and a 6-31g* basis set. For each structure the complete set of harmonic force constants and the associated frequencies where evaluated at the same theoretical level in order to verify that the global minima is a stationary state. The best structures for mixed Si-C clusters are compared with results reported in the literature[6,7]. The stability of each final structure is discussed in the presentation. These calculations on the global minima were performed using the G98 suite of programs.[20]

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Theoretical Studies of Air Force Material Projects

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Recently, a series of platinum-containing oligomers [e.g. *trans*-bis(tri-n-butylphosphine)bis(alkynyl)Pt] have been synthesized in our laboratories. These molecules are non-linear absorbers and show forbidden singlet-triplet peaks in the visible region. We have performed Time-dependent Density Functional Theory (TDDFT) calculations on the model compound *trans*-bis(acetylene phenyl)bis(trimethylphosphine)Pt, among others. We have characterized the $S_0 \rightarrow S_1$ and $S_0 \rightarrow T_1$ transitions, which play the critical role in the NLO properties. Eventually, we plan to study dimers, trimers, and the polymeric forms of these species, comparing our results to experiment.

We have also studied the dumbbell-shaped molecules, C_{122}, which are two buckyballs connected by an acetylene bridge. We have studied the types of bridging (e.g. face-face, edge-edge, and vertex-vertex) and the electron affinities of these species at the AM1 and Density Functional levels of theory.

Comparative Study of Small Silicon Clusters with Cu, Sc and Y Dopants

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Silicon is known to play the most important role in microelectronic technology and its properties can be dramatically modified by the presence of metal impurities. Currently, there is a continuing trend for the miniaturization of electronic devices, and the structures and properties of these reduced systems are known to be very different from their bulk counterparts, which makes it important to study the structures and properties of small silicon clusters with metal dopants. The novel properties revealed in these clusters can be exploited in developing new cluster-assembled materials with clusters as building blocks.

In this contribution, the interaction of small silicon clusters with Cu, Sc and Y atoms is studied in a comparative way using a hybrid density functional technique (B3LYP). The charge transfer in these clusters is found to proceed from the metal to the Si atoms. The most pronounced difference between the transition-metal (TM) impurities (Sc and Y) and Cu lies in the much stronger participation of the valence d shell of the TM species in the interaction between the metal atom and its Si environment than found in the case of Cu. It is found very important to examine several electronic configurations for each initial structure in order to determine the ground-state electronic configuration.

Acknowledgment

This work is supported by the National Science Foundation (NSF) through the CREST program under HRD-9805465.

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Conformational Studies of *cis* - and *trans* - Cycloundecenes by Dynamic NMR Spectroscopy and Computational Methods.

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A mixture of *cis* - cycloundecene and *trans* - cycloundecene, obtained by partial reduction of the 1,2 - diene, showed evidence in the low - temperature ^{13}C NMR for a C_1 conformation for the cis isomer and a predominant C_2 conformation for the trans isomer, with one or more minor conformations not yet observed for the trans. Calculations at the HF / 6-311G* level have been carried out for both isomers. The results obtained by ab initio calculations are in good agreement with the experimental results and predict a conformation of C_1 symmetry to be lowest in free energy for the *cis* - isomer, followed by a conformation of C_s symmetry with a relative free energy of 0.58 kcal/mol at - 180 ^0C. For the *trans* - isomer, the ab initio calculations predict a conformation of C_2 symmetry for the global minimum., with the next - most stable conformation having C_1 symmetry and a relative free energy of 1.8 kcal/mol.

Acknowledgement

This work was supported by NSF - CREST Grant No. HRD - 980 5465.

Polarizability and Hyperpolarizability

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The polarizability alpha of a molecule describes the linear response ofits dipole moment to an applied electric field. General properties of alpha will be described and it will be shown how electronic degeneracy or the application of a magnetic field leads to antisymmetric components. Linear natural optical activity arises from the electric dipole induced by an oscillating magnetic field (and the magnetic dipole induced by an oscillating electric field). The computation of vibrational circular dichroism and Raman optical activity will be discussed. Hyperpolarizabilities describe the nonlinear response of a molecule to a strong electric field. The first hyperpolarizability beta gives the dipole proportional to the square of an applied electric field and leadsto frequency doubling and sum-frequency generation which generally require an oriented sample. Beta vanishes for centrosymmetric systems. Chiral molecules have an isotropic beta which can give rise to sum-frequency generation by liquids or gases. The second hyperpolarizability gamma gives the dipole proportional to the third power of an applied electric field and leads to third-harmonic generation and four-wave mixing; it is exhibited by all samples. The hyperpolarizabilities are sensitive to the outer reaches of the charge cloud and their computation therefore requires large and diffuse basis sets. This sensitivity implies that these properties are particularly vulnerable to intermolecular forces. The computation of beta for simple chiral molecules will be discussed.

Some Aspects of cis/transplatin Coordination to the DNA Bases and a Comparison of the Pt and Pd Complexes: Quantum Chemical Computational Studies

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Interactions of the square planar Pt(II) complexes with DNA bases, base pairs and their models were examined.

The influence of the platinum complexes on tautomeric forms of guanine and adenine was established[1]. It was found that the adenine imino-tautomer is better stabilized under the influence of (2+) charged $[Pt(NH_3)_3]^{2+}$ cation. However, this preference was eliminated for (1+) charged $[PtCl(NH_3)_2]^{+}$ and neutral $PtCl_2(NH_3)$ adduct, giving a similar energy difference between imino- and amino-form of adenine like for the non-metalated adenine tautomers. On the contrary, guanine keto-form is further stabilized over enol-form under platination. The energy preference about 15 kcal/mol in the case of (2+) Pt adduct is reduced with decreasing charge of the complexes. The value for neutral Pt complex resembles situation in non-metalated guanine. Thus, it can be suggested that there is no substantial influence on the adenine and guanine tautomeric balances in a real solvent where an efficient charge screening have to be taken into consideration.

A base pair enhancement under platination was also explored[2]. Platination causes some distortion in the H-bond arrangement. Basically, it can be said that pyrimidine bases rotates around its center of mass under the Pt influence. This effect was also observed for other metals.[3,4] It was shown that no (pairwise) base pair enhancement was observed for AT pair. Nevertheless, platinated guanine base exhibits slightly more firmly connection with cytosine.

Solvation effects were studied for cis/transplatin, $[Pt(NH_3)_4]^{2+}$ cation, $[PtCl_4]^{2-}$anion[5]. These investigations were performed using very accurate approach and it was found that $Pt(NH_3)_2(OH)_2$ together with $[Pt(NH_3)Cl(OH)_2]^{-}$ complex represent the most stable species on the hydration energy surface. This conclusion is partially in accord with experimental findings since $Pt(NH_3)_2(solvate)_2$ is the expected hydrated form of cis/transplatin which should interact with the DNA helix. Trans conformers are generally more stable in neutral and cationic forms, e.g. $Pt(NH_3)_2(OH)_2$ and $Pt(NH_3)_2Cl_2$, and cis conformers represent better stabilized structures in the case of negatively charged systems (e.g. $Pt(NH_3)Cl(OH)_2]^{-}$).

A similar hydration energy surface was also calculated for corresponding square planar Pd(II) complexes.[6] Obtained energies (heats of solvation) clearly show that the different metal reactivity (Pt(II) versus Pd(II)) to DNA bases is not caused by different thermodynamical properties of these both metals but due to other (kinetical) reaction factors which under development[7].

Model study on Pt-bridges of the purine DNA bases shows weaker adenine coordination in accord with the other studies in this branch. In dependence on base (guanine or adenine), symmetrical or non-symmetrical arrangement was observed.[8]

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Pseudopotential DFT Plane-wave Calculations on Unit Cell Structures for Energetic Organic Compounds

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Unit cell optimizations have been performed for several energetic compounds including RDX, HMX, CL20, and nitromethane using DFT pseudopotential plane-wave methods as implemented in the VASP suite of codes. Use of the very popular PW91 exchange-correlation functional is seen to produce unit cell lengths for these crystals that differ significantly from experiment even with large plane-wave expansions. The cell lengths are seen to have a strong dependence on the size of plane-wave expansion (i.e, kinetic energy cutoff E_{cut}), and appear to converge (as a function of E_{cut}) on structures that differ from experiment by as much as 8%. Optimization of isolated molecular structures (in a super-cell approximation) with these same methods gives internal molecular coordinates in good agreement with experiment and AO based DFT calculations, suggesting that the error in cell length are due to a poor description of the intermolecular forces due most likely to the choice of exchange-correlation functional. Results will be presented demonstrating these points.

Analytical Second Derivatives of the MP2 Energy for Molecules in Solution: A Formulation within the Polarizable Continuum Model.

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The study of the molecular electronic structure and properties of molecules in solution is now feasible thank to the recent extensions of the ab-initio methods to the continuum solvation models. In this effort the attention has been mainly focused on the Hatree-Fock/DFT level of the theory for the energy and for its analytical derivatives. Less advanced is the evolution to the quantum mechanical continuum solvation at level of the second order Moller-Plesset theory (MP2). In this communication we present an analytical algorithm for the MP2 energy second derivatives within the Polarizable Continuum Model (PCM)[1]. The methods is based on the extension of the MP2 Z-vector formalism to molecule interacting with a dielectric medium [2] and benefices of the semi-direct algorithm of MP2 second derivatives [3]. Numerical applications of the method complete a detailed description of the theory.

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Conformational Studies of *trans* - Cycloheptene, *trans* - Cycloheptene Oxide and *trans* - Bicyclo [5.1.0] Octane

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The conformations of *trans* - cycloheptene (**1**), *trans* - cycloheptene oxide (**2**), and *trans* - bicyclo [5.1.0] octane (**3**) were studied by ab initio calculations. At the MP2/6-31G* level, a global_minimum of C_1 symmetry was found for each of the three compounds. In addition, a local minimum of high energy and C_2 symmetry was found in each case. The extent of twisting and bending about the double bond in **1** (29.0 and 33.7^o, respectively) will be compared with the literature values for this alkene and for *trans* - cyclooctene. The geometry for **1** obtained in the present calculations will be compared with the MM3 geometry calculated by Saunders and Jimenez - Vazquez.

Acknowledgement

This work was supported by NSF - CREST Grant No. HRD - 980 5465.

Conformational Studies of Cyano Formate (HCO_2CN) and Related Compounds

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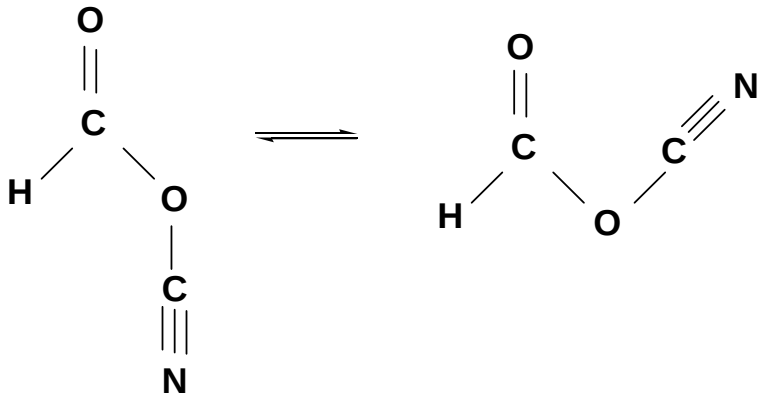
The E - Z conformational equilibria for cyano formate (**1**), cyano thiolformate (**2**), and N - cyanoformamide (**3**) were studied by ab initio calculations at the MP2 / 6-311+G(df, pd) level, as part of a study to determine the effect of electron - withdrawing groups in esters and related compounds.



Dipole moments were also obtained for each of the structures. The cyano group decreases the preference for the Z isomer from ca. 5 kcal/mol for methyl formate to 1.5 kcal/mol for **1**. The E - isomers of **2** and **3** are calculated to be preferred over the Z - isomers. Results for the compounds with the cyano group replaced by ethynyl will also be described.

Acknowledgement

This work was supported by NSF - CREST Grant No. HRD - 980 5465 and NIH - MBRS Grant No. GM08047.

First-principles Molecular Dynamics: Current Achievements and Perspectives

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Since its introduction more than 15 years ago first-principles molecular dynamics has significantly influenced the field of electronic structure calculations for solids, liquids and molecules. Current implementations use a plane-wave pseudopotential approach based on density functional theory at the generalized gradient approximation level. In this talk I will illustrate the status of the field in terms of a few examples of applications which stress the unique advantages of a combined molecular dynamics and electronic structure scheme. Finally, I will discuss new perspectives that are made possible by re-formulating the approach in terms of maximally localized Wannier functions.

Conformational Analysis of the Acyl Pocket Loop in Acetylcholinesterase Computed by Monte Carlo Methods with a Generalized Born Model of Solvation

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Acetylcholinesterase (AChE) catalyzes the hydrolysis of the neurotransmitter, acetylcholine and is the target of organophophorus acid anhydride (OP) nerve agents. In the X-ray crystal structures of AChE, the acyl pocket loop (APL; residue 287 to 290; Ile Phe Arg Phe) exists in at least two conformations, the native conformation (2ACE state) and a conformation that interacts with an irreversible inhibitor, diisopropylphosphorofluoridate (2DFP state). The backbone of Phe 288 has a left-handed helix conformation in 2ACE and a beta strand conformation in 2DFP. This study investigated the structure, conformations and energy landscape of the APL in the native state environment by using Monte Carlo methods.

Eight computed states of the APL, which included the 2ACE and 2DFP states, were computed and characterized. The free energy of the 2DFP state was 4 kcal/mol higher than that of the 2ACE state. Overlays of backbone and side-chain atoms on the X-ray structures gave rise to root-mean-square deviations of 0.6Å and 1.8Å for 2ACE, and 1.7Å and 5.1Å for 2DFP. Arg 289 was predicted to play a key role in the APL stability. The GB solvent polarization energy for the interaction of Arg 289 with the rest of the protein was –56, for the native state, and between 82 and 115 kcal/mol, for alternative states. The inter-residue conformational energy of Arg 289 favored the non-native states by between 128 and 166 kcal/mol. A balance between solvation free energy and internal conformational energy determined the stable loop conformation. The computed information should be useful in the development of antidotes against biological and chemical warfare agents that target AChE.

Macromolecular Simulations Using Continuum Solvent Models

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It is often useful in computer simulations to use a simple description of solvation effects, instead of explicitly representing the individual solvent molecules. Continuum dielectric models often work well in describing the thermodynamic aspects of aqueous solvation, and approximations to such models that avoid the need to solve the Poisson equation are attractive because of their computational efficiency. I will discuss on approach, the generalized Born model, which is simple and fast enough to be used for molecular dynamics simulations of proteins and nucleic acids. Strengths and weaknesses will be discussed, both for fidelity to the underlying continuum model, and for the ability to replace explicit consideration of solvent molecules in macromolecular simulations. The focus will be on versions of the generalized Born model that have a pairwise analytical form, and therefore fit most naturally into conventional molecular mechanics calculations. I will discuss both static energetic analysis and molecular dynamics simulations using the new methods.

Regioselectivity of Nucleophilic Addition to α,β Unsaturated Carbonyl Compounds with a π-Deficient Aromatic Substituent Attached to the β-Carbon

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Florida International University

Nucleophilic attack at an α,β-unsaturated carbonyl compound usually results in conjugate addition at the β carbon (1,4 or Michael addition), but recently addition at the α carbon has been observed when strongly electron-withdrawing groups are positioned at the β carbon relative to a carbonyl group [e.g., methyl 3,3-bis(trifluomethyl)propenoate and ethyl 3-(2,4-dinitrophenyl)propenoate (**1**)]. In recent work, we have demonstrated preference for attack by cyanide anion at the α-carbon for series of model compounds on the basis of HF/6-31+G(d) and B3LYP//HF/6-31+G(d) calculations. Here we demonstrate that π-deficient aromatic rings attached to the β-carbon can be effective in redirecting regioselectivity to the α-carbon.

Conformational Preferences of Small Polypeptides from Calculated and Experimental NMR Chemical Shifts

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Conformational preferences (free energy differences between conformations) of small peptides in solution are difficult to study. These molecules do not fold and their NMR shifts are a Boltzmann average of various conformations.

NMR chemical shifts of nuclei in similar environment can be accurately predicted by first principles calculations. For instance ^{1}H shifts can be predicted to ~ 0.1 ppm in peptide analogues in solution. Comparison of the observed shifts and their temperature dependence with Boltzmann averages of calculated shifts can determine the free energy differences between conformers. We have calculated the NMR shifts of all nuclei in CH_3CO-Gly-Ala-Gly-NH_2 except for the glycines on the ends as a function of the center φ, ψ conformational angles and plotted a complete map of the φ, ψ space in 30° increments. The calculations to model the temperature dependence are on the way. The investigation will be extended to CH_3CO-Ala-Ser-Ala-Val-Ala-NH_2, a prospective molecule in the research for 'mad-cow' disease.

Oxidative Damage to Cytosine: Implication for Radiation Induced Damage in DNA

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A radical observed in irradiated single crystals of cytidine, 3'-CMP and 5'-dCMP is characterized by three anisotropic proton hyperfine couplings and is called the 3αH radical. The 3αH radical shares properties with the allyl-like radical observed in thymine derivatives. The goal of the present work is to show that the previously observed 3αH radicals are cytosine base radicals formed on 5-methyl cytosine impurities in these crystals. Ab initio electron propagator calculations in the Partial Third Order (P3) approximation with the 6-311G(d,p) basis set have been used to show that these 5-methyl cytosines are excellent hole traps, having an ionization potential comparable to guanine. The importance of these cytosine oxidation sites to the radiation chemistry of DNA is discussed.

On the Intermolecular ^{15}N NMR Chemical Shielding Surface for Nucleic Acids

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There has been an eminent interest in understanding the factors which govern the magnitudes and orientations of the NMR chemical shielding tensors of ^{15}N nuclei in biological macromolecules [1]. We have previously analyzed the modulation by hydrogen bonding of the chemical shielding tensors of the imino ^{15}N and ^{1}H nuclei in the base pairs of nucleic acids [2], [3] and discussed the quantum chemical results in the context of several approaches of relaxation control in NMR experiments [4]. Most recently, we have applied several *ab initio* methods to study an influence of stacking interactions on the chemical shielding of ^{1}H, ^{13}C, and ^{15}N nuclei in model dimers [5].

In the present work, for the uracil trimer characterized by the length of the hydrogen bond, *rHB*, $rHB \in \langle 2.65; 3.50 \rangle$ Å, and the vertical stacking separation, *rST*, $rST \in \langle 3.00; 4.60 \rangle$ Å, we have established the five-parameter chemical shift surface for the stacked and hydrogen-bonded N3 nucleus, $\delta(rHB, rST; c_{1\ldots5})$, and the seven-parameter N3 chemical shielding anisotropy surface, $CSA_a(rHB, rST; c_{1\ldots7})$. These surfaces will be presented together with method-related issues. Currently this approach is being applied to systems exhibiting the Watson-Crick base pairing.

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Acknowledgement

This research has been supported by the Grant Agency of the Academy of Sciences of the Czech Republic, Grant AVOZ4050913. Time allocation in the Czech Academic Supercomputer Centre is gratefully acknowledged.

Time Dependent Hartree Fock hyperpolarizabilities Calculations on Conjugated Chiral Nonlinear Optical Molecules. Correlation with Measurements by Hyper-Rayleigh Scattering(HRS)

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The measurements of the components of the hyperpolarizability tensor using Hyper-Rayleigh scattering are compared with the Time Dependent Hartree Fock (TDHF) dynamic hyperpolarizabilities computations (1,2).

We use for these calculations the Mopac program 93 of Fujitsu Limited and the Spartan program (wave function version 5) for the full optimized geometry. The geometries were obtained with two DFT methods DFT/SVWN-6-31G and DFT/BP86-6 31G** in order to detect an eventual geometric effect, but we do not find a great effect.

We have studied 2 chiral molecules MolA , camphorquinone structure and MolB, polycyclic steroid structure(3,4) as shown in Fig 1. A pseudo tensor contribution to the β tensor in chiral dyes can be expected to lead to macroscopic second harmonic generation in poled polymer materials axialled aligned by Corona effect.

According to group theory, this tensor can be described in part by rotationally invariant scalar figures of merit and this hyperpolarizability tensor β can be decomposed into four rotationally irreducible tensor parts : β^{1ss}, β^{1mm}, β^{2mm} , and β^{3ss} We have in cartesian representation of the rank 3 , the irreducible form of β :

$$\beta_{ijk} = \beta_{ijk}^{(3s)} + \beta_{ijk}^{(2m)} + \beta_{ijk}^{(1s)} + \beta_{ijk}^{(1m)} \quad (1)$$

where the superscript indicates the tensor rank and the permutation symmetry(s=symmetric and m=mixed symmetry). Each of these components (figures of merit) can be obtained by HRS experimental technique with an elliptically polarized laser beam to the 1064nm wave length.
In this work, we have studied the correlation between the sum of these 4 components and the theoretical values obtained by TDHF computations. If we consider the table 1, we can consider that this correlation is acceptable.

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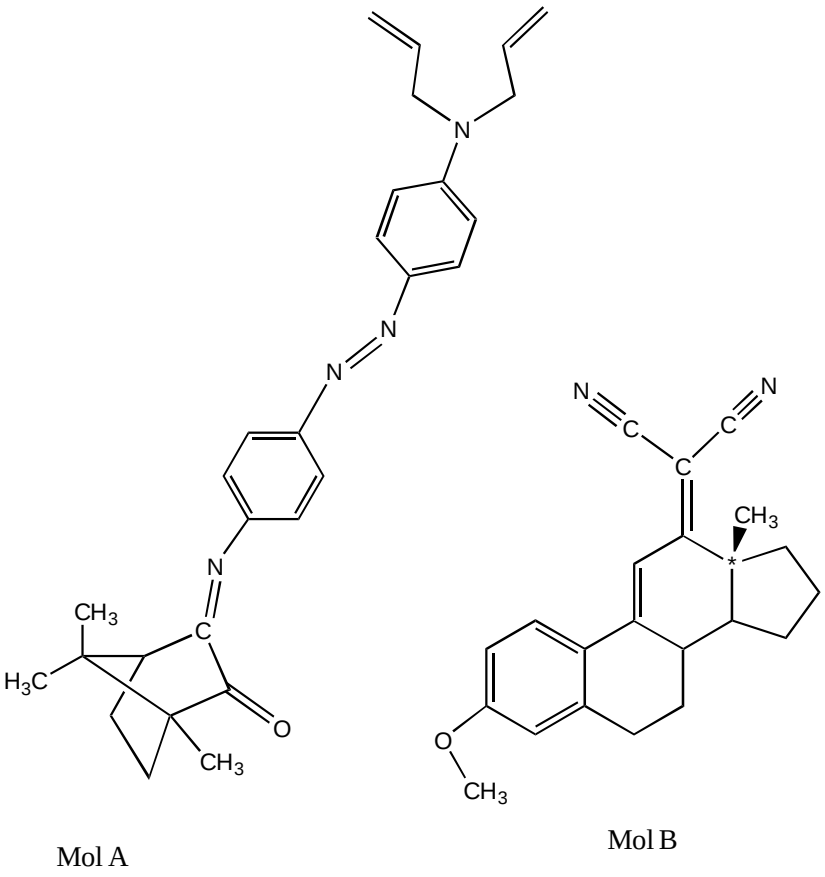
Acknowledgements

We acknowledge Y.Delage, S.Bourdais, F.Calvayrac and Y.Labaye for assistance in order to resolve graphics, printing,computer connection and other system problems.

Table 1

	Method for full optimized geometry	TDHF calculation SHG β in 10-30esu to 1064nm	Measurements of the components of the Hyperpolarizability tensor β in 10-30esu to 1064nm				
			β1ss	β1mm	β2mm	β3ss	βsum
MolA	DFT/SVWN DFT/BP86	290,9 212,2	110	26,8	15,7	70	222,5
MolB	DFT/SVWN DFT/BP86	96,9 98,2	33,6	12,1	9,6	23,9	79,2



Mol A Mol B

Fig 1

Hydrogen Storage in Bundles of (5,5) Carbon Nanotubes

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Carbon nanotubes, CNTs, with their inner hollow were reported to be suitable candidates for the storage of molecular hydrogen [1]. However, the measured values of hydrogen storage in CNTs differ from 0.01% to 10% [2], depending on the purity and types of the nanotubes, applied pressure and temperature, etc. Therefore, the question: "Is the adsorption and/or absorption of hydrogen in CNTs sufficient for commercial applications?" still requires investigations. To answer this question, quantum calculations, QC, [3, 4] have been used in studies of hydrogen absorption by CNTs leading to the formation of CH bonds (chemisorption) while molecular mechanics, MM, [5], molecular dynamics, MD, [5, 6] and Monte Carlo dynamics simulations [7, 8] have been applied to investigate physisorption. However, in almost all MM and MD studies hydrogen molecules were treated as spheres [7, 8] and the type of nanotubes under study was not specified [7, 8].

Our earlier [5] MM [9] and MD [10] modeling of physisorption carried out for single (5,5), (9,0), and (7,3) CNTs composed of 220 carbon atoms with varying amount of hydrogen molecules and to a bundle of seven CNTs with 655 hydrogen molecules showed that (a) only few hydrogen molecules reside inside the nanotubes and their quantity practically does not depend on the CNTs type. (b) According to MM calculations corresponding to 0 K, concentric rings of hydrogen molecules are formed around the (5,5)nanotube. (c) MD modelling showed that for the single nanotube these rings are stable only to approximately 10 K whereas for the bundle they remain stable up to 100 K.

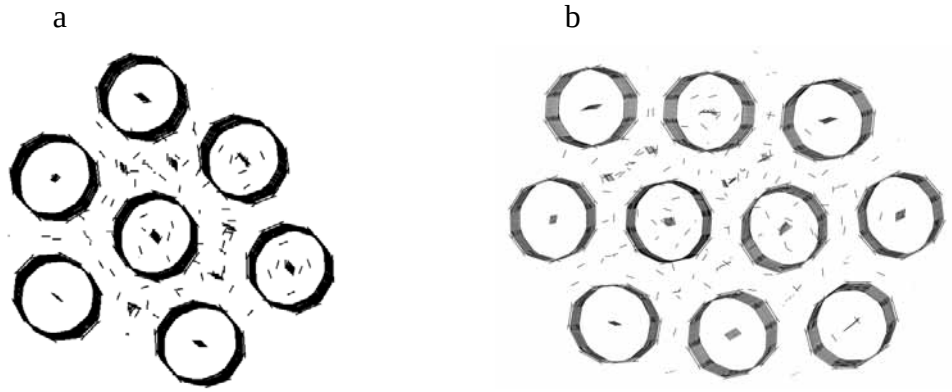

Figure 1. The minimized structure of a) nanotube bundle of seven armchair (5,5) carbon nanotubes with 231 H_2 molecules, b) nanotube bundle of ten armchair (5,5) carbon nanotubes with 340 H_2 molecules. In the present work, MD simulations were carried out for two CNT bundles consisting of seven (Fig. 1a) and ten CNTs (Fig. 1b) with 231 and 340 hydrogen molecules, respectively. As shown in Fig. 2 for the former bundle, the parallel arrangement of the CNTs in the bundles was destroyed during 400 ps at 200 K. Then the calculations were repeated for the bundles with fixed distance of 3.5 Å (corresponding to the van der Waals minimum for C..H interactions) between the tubes at one or both ends to prevent distortion of the bundles. It should be stressed that the system with the distance constraints imposed on one CNTs

end mimicked aligned brush-like CNTs reported by Li *et al* [11]. Preliminary results show that the amount of hydrogen stored in the bundle of ten carbon nanotubes is higher than that in the bundle of seven CNTs at all temperatures under study. In addition, for both bundles the temperature at which hydrogen molecules remain inside it (in and among the nanotubes) is higher than 125 K whereas for the ordinary armchair (5,5) CNT the H_2 molecules remain between the nanotubes only up to 50 K. The gravimetric volume density of hydrogen in bundles under study was found to be 1.6 %wt at 125 K and 1.0 %wt at 200 K (in ordinary nanotube 0.8 and 0.6 % wt, respectively). Although the absolute value of hydrogen storage in 10-CNT bundle is greater than in that of seven CNTs, the gravimetric density is much lower than the DOE requirements [12] (6.2wt%) that should be met for commercial application.

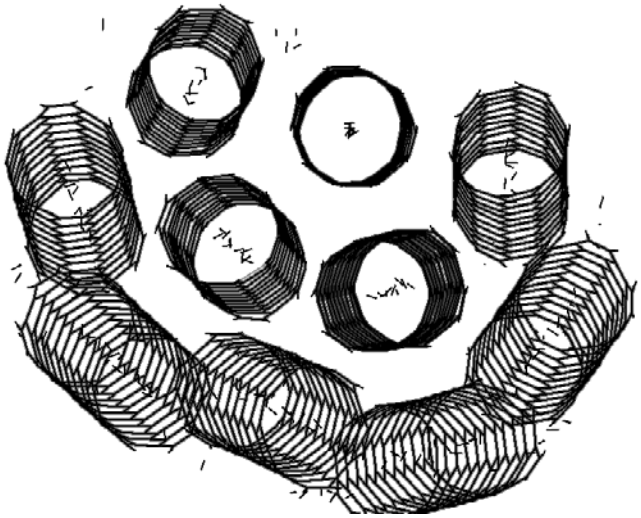

Figure 2. The structure of the bundle (consisting of ten (5,5)carbon nanotubes and 340 H_2 molecules) destroyed after 400 ps at 200 K.

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The Studies of Metal Isotope and Deuteration Effects in Vibrational Spectra of Palladium(II) Complex with Histamine

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Vibrational spectra of the palladium(II) complex with histamine were studied within the density functional theory (DFT) formalism. The spectra of N-deuterated molecule were measured and calculated. Additionally, the frequency shifts due to the isotopic replacement (Pd-104 on Pd-110) were determined theoretically. All spectra were supplemented by the potential energy distribution analysis. The theoretical results were applied to the complete band assignment of newly and previously measured spectra.

Solvation Studies on Steroid-Nucleoside Conjugates

Jesse Edwards*[1], Genzo Tanaka[3], April Anderson[1], Claudia Eybl[2], Henry Joung Lee[2], Zhengqing You[2]

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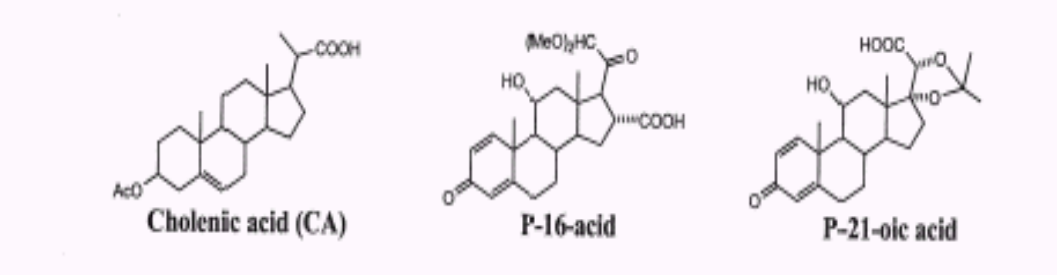
In an attempt to develop potent anti-HIV agents devoid of serious toxic effects, H. J. Lee *et. al.* developed these three novel compounds along the antedrug[6-9] scheme; AZT conjugated to Cholenic Acid (Conjugate 1), P-16 acid (Conjugate 2) (where P is an abbreviation for Prednisolone), and P-21-oic acid (Conjugate 3). These compounds make a unique class of drugs; which have been formed through ester bonds (conjugates) between AZT and the steroid and non-steroid carboxylic acids. Cholenic acid, P-16 acid, and P-21-oic acid will also be referred to as Acid 1, 2, and 3, respectively. Through H9 cell line tests it was determined that the only Conjugate 1 possessed anti-tumor behavior. In an earlier work the structural characteristics of the active compound were compared to those of the inactive compounds and their constituent components; several differences were determined. That work was done in vacuum, while this work will attempt to make similar comparisons after solvating the molecules. Particular focus will be on the position of various functional groups at the ends of the compounds. The work will be conducted using a Tripos forcefield and conformational searches while varying the dielectric constants of the model solvent system between 1 and 10. This is to mimic an aqueous up to a proteinacious environment.



Relationships between Impact Sensitivity and Molecular Properties in Nitramine Molecules

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[1]Department of Chemistry/AHPRC, [2]College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, Florida, USA, [3]Network Computing Services, Inc./AHPCRC, Minneapolis, Minnesota, USA, and [4]US Army Research Laboratory, Aberdeen Proving Ground, Maryland, USA

An objective of this work is to establish relationships between impact sensitivity for energetic materials and molecular and thermodynamic properties. We choose as our materials the nitramine group, which have been known to be the most sensitive of the energetic materials. A quantum mechanical method is applied to searching for the weakest bond of each molecule and calculating their bond dissociation energies, heats of formation and detonation. Relationships of those quantities with impact sensitivity of the nitramine group are examined.

Bond Dissociation Energies for NO_2 in Some Nitroheterocyclic Explosives

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Energetic Material storage, synthesis, and application is significantly impacted by the fundamental property of sensitivity. The method of storage and handling is effected by sensitive nature of the explosive. Possessing the ability to predict the sensitivity of energetic material candidates before expensive synthesis is begun would be an asset. Also, predicting the applications of various energetic compounds before synthesis and testing, can be made possible with the aid of sensitivity predictions. A quantum mechanical method is applied to searching for the weakest bond of a set of nitroheterocyclic explosives and calculating their bond dissociation energies. Correlation between bond dissociation and impact sensitivity will be examined.

Conformational Analysis of Various Organophosphate Acetylcholinesterase Inhibitors to Provide Structure Activity Relationships

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Quite often pharmacophores are developed in order to make predictions on the activity of various pharmaceuticals. The relative positions of various functional groups of active compounds are studied to determine common features in these compounds. The mechanism of action of nerve agents as they attak aceytlcholinesterase is an area of extreme interest. We will attempt to provide preliminary information on the points of activity of these groups of organophosphate acetylcholinesterase inhibitors and a pharmacophore may be developed. Nerve agents with similar structures will be divided into groups and aligned through a fitting routine and certain functional groups of several conformations of the inhibitors will tracked and compared to determine relationships between the relative positions of the functional groups.

Reactivities of Nerve Agents in the Gorge of Acetylcholinesterase

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In order to understand reaction mechanisms of nerve agents in the gorge of acetylcholinesterase (AChE), computational modeling methods are used. For five organophosphorous compounds, sarin, soman, tabun, gf, and vx , bond dissociation energies around phosphorous, heats of reaction, transition states for binding of these agents to SER 200 in AChE, their ageing reactions and eventual decomposition reactions recovering AChE are determined by using semi-empirical quantum mechanical codes (Gaussian 98). From those results, we will attempt to answer practical questions like differences in the ageing between soman and sarin, and oximes' ineffectiveness against aged soman.

Bonding and Bond Energies of Various Nerve Agents Bound to Acetylcholinesterase

Jesse Edwards[1], Genzo Tanaka[3], Makini Cobourne[2]

[1]Department of Chemistry/AHPCRC, [2]College of Pharmacy and Pharmaceutical Sciences/AHPCRC, Florida A&M University Tallahassee, Florida, USA and [3] Network Computing Services, Inc./AHPCRC, Minneapolis, Minnesota, USA

The mechanism of action of nerve agents with the active site of aceytlcholinesterase is a research topic of extreme interest. With the development of newer computational software and the advancement of computational power it is now possible to study such complex systems. Crystal structures of the enzyme with nerve agents bound to the active site also provide impetus for our study. We propose to examine the bonding and bond energies of various nerve agents in the active site of several types of aceytlcholinesterase using an assortment of Molecular Mechanics force fields, semi-empirical Hamiltonians, and MM/QM hybrid methods. We will compare the results using the different force fields and between the different methods.

Interaction of Psoralens with DNA-Bases. An *ab initio* DFT Study

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The energetics and structures of psoralen and xanthotoxine with different DNA bases have been investigated using quantum chemical methods. Adducts of psorlanes with adenine, cytosine, thymine and guanine as well as pairs of AT and GC have been studied using HF and DFT levels of computation. Long range of basis sets starting from the minimal STO-3G to cc-pVDZ were used with both methods. The two computational methods have been compared and the effect of the basis set was explored. Two minima have been located on the potential energy surface of the adducts. Effect of the psoralen probe structure on the interaction with different DNA-bases was discussed. Base-pair selectivity was investigated and compared the reported experimental results.

Ab initio Study of the Conformational Preferences of Tyrosine

Lisa C. Fedoroff, Brian W. Hopkins, and Gregory S. Tschumper

Department of Chemistry and Biochemistry, University of Mississippi

Tyrosine is an important building block of protein structure. Its conformational preferences are therefore of great interest both as an individual molecule and as part of a polypeptide structure. In this study, the potential energy surface of the neutral molecule of tyrosine was analyzed with respect to the five torsional angles shown in Figure 1. A series of one-dimensional and two-dimensional torsional angle scans were used to locate the possible minima. The scans identified 64 possible minima. These structures were further refined and characterized using the RHF and B3LYP methods and the [6-31++ G(*d*,*p*)] basis set.

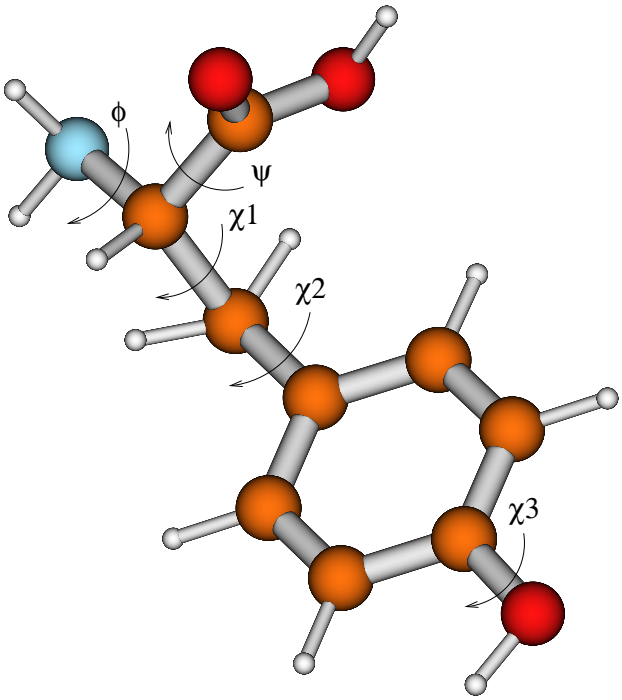

Figure 1: Torsional Angles of Tyrosine considered in this work.

Theoretical Study of the $CH_3CH_2O_2$ Self-Reaction

L. Feria* and M. Castro

Departamento de Física y Química Teórica, DEPg, Facultad de Química, Ciudad Universitaria, Universidad Nacional Autónoma de México, D.F. México. C.P. 04510.

Structure electronic calculations were carried out with the second order Møller-Plesset perturbation theory (MP2), the Hartree-Fock method (HF) and the hybrid method B3LYP which include a mixture of HF exchange with Density Functional Theory exchange-correlation on the ethyl peroxy self-reaction. There were studied four possibles pathways suggested as the mechanisms for the interaction between two $CH_3CH_2O_2$ radicals: $2CH_3CH_2O_2 \rightarrow 2CH_3CH_2O + O_2$ **(I)**, $2CH_3CH_2O_2 \rightarrow CH_3CH_2OH + CH_3CHO + O_2$ **(II)**, $2CH_3CH_2O_2 \rightarrow CH_3CH_2O_2CH_2CH_3 + O_2$ **(III)** and $2CH_3CH_2O_2 \rightarrow CH_3CH_2OH + H_2O_2$ **(IV)**.

Fully optimized geometries, harmonic vibrational frequencies, and zero-point energy corrections (ZPE) of the species $CH_3CH_2O_2$, CH_3CH_2O, CH_3CH_2OH, CH_3CHO, $CH_3CH_2O_2CH_2CH_3$, H_2O_2, O_2 and $CH_3CH_2O_4CH_2CH_3$ were calculated with MP2, HF and B3LYP using the 6-311G(2d,2p) basis set as implemented in the Gaussian 98 package.

The heats of reactions, $\Delta H_0(i)$, calculated for the ethyl peroxy self-reaction are in agreement with the experimental results. There were optimized four $CH_3CH_2O_4CH_2CH_3$ tetra-oxide species as local minima in agreement with the experimental proposal that the peroxy self-reaction proceed through the formation of a tetra-oxide intermediate.

We acknowledge financial support from CONACyT, DGEPg and DGAPA under Project IN-101901, and access to the supercomputer SG Origin 2000/32 at DGSCA-UNAM is also appreciated.

A Random-Move and Geometric-Optimization Procedure for Building Water Molecules into Protein Clefts for Molecular Structure Calculations

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Departments of Chemistry,[*] Mathematical Sciences,[#] and Computer Science,[&]
University of Illinois at Springfield, Springfield, Illinois 62703-5407

Because of the numerically intensive nature of quantum chemical calculations of the electronic properties of even relatively small molecules, it is often important to make the best predictions possible from more empirical methods of the most likely conformations of molecular species. Typical approaches to this pre-optimization of the molecular structure employ molecular mechanics to identify electrostatic forces and hydrophobic interactions, among other local affinities, which will affect the optimal interaction geometries, those possessing the lowest free energies of formation. This problem of pre-optimization is compounded when the subject molecule is a ligand, such as a pharmaceutical compound, bound to a protein, because of the strong effect exerted by the protein environment on the electronic properties of the ligand. Furthermore, the ligand often does not occupy the binding site on the protein alone – it is accompanied by one or more mobile or fixed water molecules, and functions as a ternary complex of the protein, ligand, and water molecules. Water molecules present additional problems, which arise from their substantial polarity and bonding characteristics.

The present study approaches the problem of identifying ideal locations of water molecules in protein clefts, such as the active sites of enzymes or the binding sites for receptor ligands. The program created, WATERFILL, identifies the physical extents of the binding site under examination, locates polar atoms capable of forming hydrogen bonds to water molecules, and places the water molecules in theoretically likely hydrogen-bonding positions within the binding site. Each water molecule in turn is placed according to ideal hydrogen-bonding geometry with respect to one or more of the polar atoms in the protein cleft, using the ice-I_h/ice-II transition model of liquid water. Optimization of the geometry is carried out by conducting the building procedure iteratively, choosing at random the polar loci on which to build the next water molecule, and employing an evaluation function which assigns a score to each water-filled cleft generated according to the density of the water within. Because the iterative calculations are carried out by a single processor from beginning to end for each construction of the water-filled cleft, the calculations are easily distributed among a number of processors, and require no message-passing interface between processing units.

The WATERFILL algorithm is not rigorous with respect to calculation of the free energies of formation of the protein-cleft/water complexes, as it bypasses the numerically intensive calculation of those energies in favor of a greater number of iterations, and evaluates the acceptability of the complex structure based entirely on the geometric conditions imposed in the building procedure. The value of the method for subsequent, detailed structural computations lies in its selection of a number of candidate complex structures using as many processors as are available, such that those candidate structures can be additionally refined by molecular mechanics or some other empirical evaluation scheme, before they are subjected to the rigorous, quantum-level analysis.

Theoretical *ab initio* Study of the Effects of Methylation of Guanine (G), Cytosine (C) on GC Base Pair

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and Jerzy Leszczynski

Computational Center for Molecular Structure and Interactions
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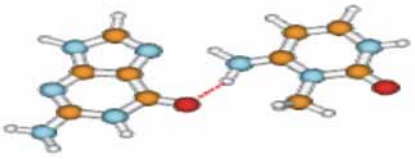
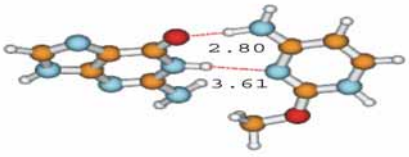
Methylation of DNA occurs most readily at N3, N7, and O6 of purine bases. The most common N-alkyl purines are 3-methyladenine (m3A), 7-methylguanine (m7G), and 3-methylguanine (m3G). These simple methylated bases are being continuously formed by the nonenzymatic alkylation of DNA by endogenous methyl donors like S-adenosylmethionine. In addition, humans are exposed to a significant amount of nitrosamines, primarily through the diet, which results in alkylation of DNA. Other sources of N-alkylation damage are simple monofunctional methylating agents like dimethyl sulfate (DMS) and some chemotherapy agents such as 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). m3A has long been thought to be the most biologically significant lesion generated from these methylated agents.

The primary aim of our study is to characterize the nature of changes in interaction energy and molecular structures of interacting species as result of methylation. For this purposes we have analyzed the results of ab intio calculations which are performed at the DFT and MP2 level of ab initio theory using standard 6-31G(d,p) basis set.

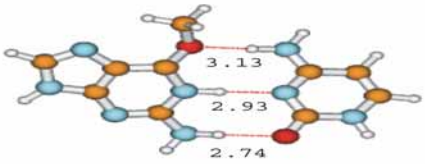
The following results have been obtained.

1. We have found significant influence of methyl group on the geometry of methylated guanine-cytosine base pair (see Figure).
2. We have obtained the order of relative stability of methylated Guanine-Cytosine base pairs as a function of the CH_3-group position.
3. Using the variation-perturbation energy decomposition scheme we have found the most important contribution to the binding energy of methylated Guanine-Cytosine base pair.

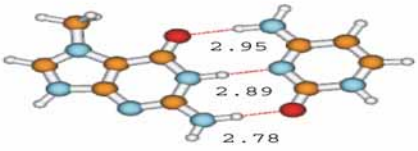

Cytosine N3 methylation = CN3:G



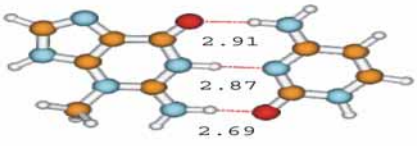
Cytosine O2 methylation = CO2:G



Guanine O6 methylation = GO6:C



Guanine N7 methylation = GN7:C



Guanine N3 methylation = GN3:C

Ab initio Study of the Physical Nature of Interactions between Neutral and Protonated Cytosine Transition States Structures and Enzyme Inhibitors with Cytosine-5-methyltransferase Active Site Constituents

Gareth Forde,[1] Pawel Kedzierski,[2] Andrzej Sokalski,[2] Robert Gora,[2] Jolanta Grembecka,[3] Glake Hill,[1] and Jerzy Leszczynski[1]

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[2] *Institute of Physical and Theoretical Chemistry, Wroclaw University of Technology, Wroclaw, Poland*

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DNA methylation is a critical step in a number of processes such as regulation of gene expression, immune protection, and embryonic development in varies types of organisms. Methylation of cytosine at C-5 is catalyzed by cytosine-5-methyltransferase. The amino acids Arg 165, Arg 163, Asn 304 Glu 119, and Cys 81, are key residues in enzyme catalysis. In this investigation, we constructed a model of both neutral and protonated transition state complexes in the active site of HhaI cytosine-5-methyltransferase. From this model the nature of interaction energies between each active site residue and transition state complexes were evaluated. First, the transition states for cytosine-5-methyltransferase-catalyzed cytosine methylation were calculated for both protonated and neutral transition states at HF/3-21G level of theory using Gaussian 98 program. The transition state structures were verified by second derivative calculations (obtaining one negative eigenvalue). Each transition state structure was superimposed on 5,6-Dihydro-5-Azacytosine bound to the active site of HhaI Methyltransferase which was obtained from Brookhaven Protein Data Bank. The SCF interaction energy between each transition state and active site constituent was decomposed using a hybrid variation-perturbation decomposition procedure, which gives the first-order electrostatic, first-order exchange, and higher order delocalization components calculated in the dimer centered basis set. Additional calculations were performed on several nucleotide analogs to probe the catalytic and structural characteristics of HhaI cytosine-5-methyltransferase inhibition. Specifically, we used the thio-derivatives and accessed the nature of there interactions with key active site constituents using the aforementioned methods.

Theoretical *ab initio* Study of Tautomeric Properties in Methylated Nucleic Acid Bases

Angela Fortner[1], Gareth Forde[1], Aviane Flood[1], Alejandro Nazario[1,2], Adrian Ford[1,3], Glake Hill[1], and Jerzy Leszczynski[1]

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Tautomerization is a phenomenon that occurs when a proton migrates across an aromatic ring in response to the displacement of a double bond. The resulting constituents are called tautomers. In DNA bases, tautomerization can lead to altered base pairing configurations or mispairing due to changes in hydrogen bonding capabilities. Such alterations are likely to be important in causing mutations. This may be promoted in part by another phenomenon termed DNA methylation. In DNA methylation small "tags" called methyl groups are covalently bonded to the bases that make up the DNA code. In humans and other mammals methyl groups play an important role in the functioning and maintenance of DNA. We have used ab initio techniques to study the ability of DNA methlyation to stabilize the tautomers of thymine, uracil, cytosine, adenine, and guanine. All calculations were performed with Gaussian 98 software. Equilibrium geometries were obtained using DFT and MP2 level of theory with the 6-31G(d,p) basis set. Vibrational frequencies were obtained to verify local minima. We evaluated the changes in relative energies and geometrical parameters of tautomeric species following methylation. Our results provide insight for future investigations aimed at understanding the mechanisms behind methylation-induced mutagenesis.

Theoretical *ab initio* Study of the Effects of Methylation on the Nature of Hydrogen Bonding in AT Base Pair

Aviane Flood*[1], Gareth Forde[1], Glake Hill[1], Leonid Gorb[1] and Jerzy Leszczynski[1]

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Cancer is one of the most prevalent diseases in the world. As a result, there is an obvious urgency in understanding cancer's mechanism and putting forth the solutions to this global epidemic. Cancer is caused by the added effects of over a dozen factors. Some of which are unavoidable, while others can be avoided through healthy lifestyle choices. One such choice is the minimization of exposures to tobacco smoke. The incomplete combustion of tobacco produces a reactive metabolite called methanediazonium ion. This cation is very reactive with the many nucleophilic centers native to DNA. The main constituents of these centers are nitrogen and oxygen atoms. Henceforth, the reactive centers in adenine are N^3 and N^7, and in thymine are O^2 and O^4.

Our primary aim of this investigation is to characterize the nature of hydrogen bonding energies and molecular structures of interacting species as result of methylation. To reach this aim we have used the standard MP2 and DFT approximations that are implemented in GAUSSIAN-98 package of programs. In addition we used the variation-perturbation energy decomposition scheme implemented in GAMESS software packages to investigate the nature of the binding between methylated bases.

Computational Portals for Chemistry

Ken Flurchick[1] and Jan Labanowski[2]

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[2]Ohio Supercomputer Center, 1224 Kinnear Rd, Columbus, OH 43212

Portal is a new catchy term of the Internet. Portals represent integrated, Web browser based, interfaces to resources and information. They started to be popular for the Web based business services, but soon showed up in research computing.

The researcher of today must use a multitude of software packages running on many different platforms. In addition, frequent updates and extensions for these software packages make it very difficult to keep up with the volume of details on how to effectively use these packages on different computers for different problems. The model of a software package being tied to a particular computer cannot keep up with the way computing is done today.

Computational Portals, multi-tiered web based problem solving environments integrated with software packages across different platforms, can facilitate access to computer resources, information, databases, documentation, and provide for archiving, journaling, plus pre and post-processing. These portals can greatly improve productivity and will become increasingly important in the era of distributed computing. There are many proprietary GUI's (Graphical User Interfaces) for many codes, however, these GUI's are often tied to a specific work station and can be used only on a local console. Web browsers (or equivalently, Java based GUI's) can provide a portable and robust environment, which can be used on any work station, or laptop.

With the advent of computational grids, the need for portable interfaces is paramount. The diversity of architectures, batch and scheduling managers, and differences in installation of software packages on various computers are factors, which make portals very attractive. The authors present their own experience with the SciPortal project.

SciPortal project was originally started as a part of the DoD High Performance Computing Modernization Program. The initial participants were: Armen Ezekielian (OSC), Geoffrey Fox (Syracuse University, now at Indiana University), Tom Haupt (Syracuse University, now at Mississippi State University), and the authors of this poster.

- The design goals were to:
- Specify problems in science language, not in shell instructions. Provide Advanced Track (extended control) and User Track (take defaults from the black box).
- Create hierarchy of contexts: User -> Problem -> Session -> Application:
- Problem -- scientific requirements for some calculations
- Session -- particular run
- Application -- computational component (applications could be chained to create multi-step computation scenario. Glue needed to connect different software packages).
- Transform scientific requirements to specific software and hardware requests
- Pay attention to the security, authentication, and accounting (DoD)
- Assumption that jobs submission and resource discovery will be done eventually by computational grid, so rather than devise some sophisticated authentication schemes we were using a simple model for testing (ssh) knowing that it will be eventually replaced with some generally accepted service (e.g., GIS of Globus).

- Provide hooks for collaborative environments, searching, journaling, indexing. Users have profiles (in XML) and hierarchical directory tree with XML files describing actions and results.
- If you want people to use this thing, it needs to offer advantages to working/login directly with shell.
- Make it extensible, so adding new pre- and post-processing tools, and analysis modules is easy. Use Object Oriented approach (Java) and use XML files (and corresponding DTDs or Schemas/XSD) to describe actions, results, necessary parameters, available resources, etc. This would allow using commodity components, and allow describing functionality and requirements of software packages.
- Eventually reach the community level participation, and have a standard way to describe and annotate the computational tasks.

We started to experiment with various approaches to Code Information Server (a piece which provides the information about codes capabilities and requirements) and actually collected a substantial database of methods and made some preliminary attempts to standardize on methods names and XML tags to be used in describing software functionality. We also made a first pass on deciding which functionality should be placed in servlets, provided as JSP Tag Libraries, and which should be put into utility classes or JavaBeans, so the software follows the Model-View-Controller pattern. This model was applied to the OHMMS software package (by John Wilkins Group: http://www.physics.ohio-state.edu/~wilkins) and we will eventually use this software to make easier interfaces to standard chemistry packages at the Ohio Supercomputer Center.

Some Problems to be Solved Under Subsequent Study of the Nature and Mechanisms for the Formation of Potential Mutations

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The modern theory of a UV - mutagenesis is based on hypothesis [1]. Bresler proposed a mechanism for the formation of base replacement mutations under the synthesis of DNA containing pyrimidine dimers [1]. He has assumed that the mutations occur because the DNA-polymerase sometimes builds-in uncomplementar nucleotides opposite the dimers. In other words, it is believed, that from the point of view of mutagenesis, all the dimers are identical and the only reason is in the imperfect operation of DNA-polymerases. At present, such point of view is conventional [2, 3].

However, the hypothesis of [1] is not capable of explaining some peculiarities of UV-mutagenesis: the untargeted mutagenesis (when mutations occur in close vicinity of the dimer); the reparation mutagenesis, in particular, the reason because of which the mutations occur under the excision reparation; the nature of complex mutations (when a DNA site is substituted with another one of different length and other nucleotide composition); replicating instabilities (when mutations occur past tens of replication cycles after the action of a mutagene); hot and cold spots of mutagenesis; why the cytosine dimers much often result in mutations than the thymine ones; as well as of solving another problems [4]. There is a number of experimental facts that contradict the conventional hypothesis.

The most productive way out of the formed situation - further development of Watson and Crick's hypothesis [5] that the mutagenesis is based on the ability of the bases to change the tautomeric state. The participation of the rare tautomeric forms in mutagenesis was discussed repeatedly [6]. The review of the experimental and theoretical data testifies that the rare tautomeric forms of the nucleotide bases, including double - proton phototautomerism is a trusty established fact [6].

Therefore, an alternative model of ultraviolet mutagenesis is being developed. The hypothesis [5] is developed. It is planned to show that the model can solve the above problems. We suppose that not all the dimers (cyclobutane or (6-4)-adducts) result in mutations, but only those with one or both bases in rare tautomeric forms. Moreover, such tautomeric forms that may influence the character of base pairing. The dimers in which the base has changed its orientation relative to the sugar-phosphate stroma (the same as in cis-anti or trans-anti dimers) may be another source of mutations. And the third source of mutations may be the pair of bases that have changed their tautomeric state and which are not dimer components. Also, it is assumed that only those canonical bases are built-in under DNA synthesis, which can form hydrogen bonds with bases of the template DNA.

In [4], it was shown how the base replacement mutations can be formed under the post-replication SOS-reparation of the DNA containing thymine dimers. One of the mechanisms of untargeted mutagenesis is proposed in [7]. In [8] it is shown that under the formation of dimers, the tautomeric state of the constituent bases may be changed. New probable tautomeric states have been obtained under the formation of cytosine dimers (Fig.1). In [9], basing on the hypothesis of [8] it was shown how they can induce the base replacement mutations under the SOS-replication of the DNA.

Moreover, it has been shown, that the tautomeric changes can occur at non-radiative deexcitation of the DNA, which has absorbed the UV - quantum from triplet levels of energy owing to strong forced oscillations. Such oscillations result in changes of lengths of hydrogen bonds. Thus, two types of damages are initiated. First, there can be a double - proton phototautomerism affecting atoms of hydrogen of the first and second H-bonds in pairs of guanine – cytosine and adenine – thymine [8, 10]. Such state appears to be inconvertible [11] and results in an untargeted mutagenesis [7]. Secondly, the change of a tautomeric state can take place at formation of dimers, which are the basic type of photodamages, in front of which the mutations are most often formed [12]. Proceeding from the model of spontaneous semi-open states of the DNA [13], possible tautomeric states for Watson – Crick's pair of adenine-thymine influencing the character of connection of DNA chains have been obtained. As at formation of dimers the

hydrogen bonds between the chains are broken [14], all new rare tautomeric forms appear inconvertible. Fig 1 shows possible tautomeric states of bases of the G-C pair which could result from the processes described in [13].

The obtained results are of qualitative character, they may be a basis for quantum-mechanical calculations. An experimental verification is needed. Problems to be solved for testing and further investigation of the nature and mechanisms of the formation of potential mutations are enumerated in brief.

A comparison of probabilities for the formation of various potential mutations

It is known that for guanine and cytosine the probability of changes in the tautomeric state is much higher than for thymine and adenine [15]. This may be one of the reasons, because of which transitions G-C→A-T are much more frequent than the A-T→G-C ones [4]. On the other hand, it has been shown experimentally that the probability of formation of semi-open states at DNA sites of increased content of A-T pairs is much higher than at the sites of increased content of G-C pairs [16]. This fact may be the reason of a more frequent formation of thymine dimers [4]. It is easy to see that potential mutations of various types may occur with different probabilities. First one and the same rare tautomeric states (Fig. 1) may be formed from different number of virtual states.

Thus, pair G_1^*-C_1^* (Fig. 1) may be formed from four metastable states. Pairs G_1^*-C_1^*, G_2^*-C_2^*, G_3^*-C_3^*, G_4^*-C_4^*, and G_5^*-C_5^* may be formed from three states. Pairs G_6^*-C_6^* and G_7^*-C_7^* may be formed from two virtual states.

Second, it must be taken into account that the virtual states themselves are formed with different probability. thus, in [13] it is shown that the most efficient, from energy viewpoint, is a virtual conservative state with trans-orientation of the equivalent amino-protons of guanine amino-group relative to bond C_2N_3. A virtual conservative state with cis-orientation of the equivalent amino-protons of guanine amino-group relative to bond C_2N_3 is also energy-efficient. And a virtual semi-open state with trans-orientation of the equivalent cytosine amino-protons relative to bond C_4N_4 corresponds to the global maximum.

And, third, different rare tautomeric forms may be formed from one and the same virtual state with different probability. The analysis of potential surfaces obtained for G-C pair [11], enables us to make some assumptions. It would be interesting to check these conclusions by means of corresponding quantum-mechanical calculations.

As a result, it can be assumed that G_1^*-C_1^* pairs will occur more often. G_2^*-C_2^*, G_3^*-C_3^* and G_4^*-C_4^* will be more seldom. And a bit more seldom will be G_5^*-C_5^* pairs. The most seldom are pairs G_6^*-C_6^* and G_7^*-C_7^*. In Fig. 1, the pairs of bases, which are in rare tautomeric forms, are enumerated in the order corresponding to the lowering of possible probabilities of their formation.

It is clear that this consideration is only qualitative. It would be interesting to study the problem in detail and to estimate the contribution of the above-described processes. For this purpose, the probabilities of realization of different metastable states should be known. Then it would be possible to estimate their contribution to relative probabilities of the formation of various potential mutations.

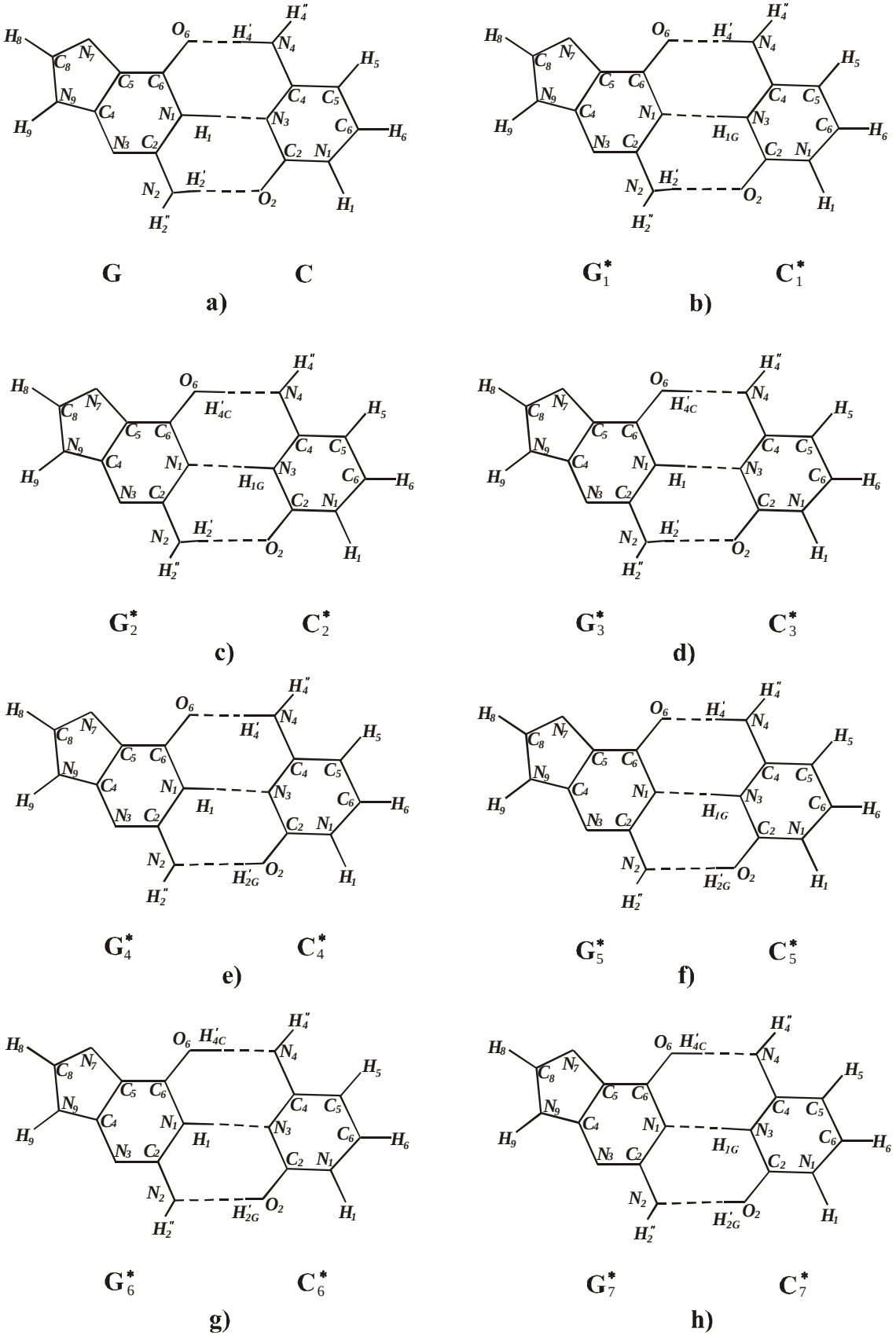

Fig. 1. The Watson-Crick's guanine (G) – cytosine (C) pair; b) – h) possible new tautomeric states of guanine and cytosine resulting from the formation of cytosine dimers.

Short list of problems to be solved under subsequent study of the nature and mechanisms for the formation of potential mutations.

The proposed model of the formation of potential mutations under DNA UV-irradiation needs experimental verification and a more thorough study. In fact, it has been indeed found that DNA bases may be in rare tautomeric forms, their tautomeric state may be changed under ultraviolet light.

Therefore, first, further experimental investigation of the formation of rare tautomeric forms in nucleotide bases, that are the components of two-chained DNA under UV-irradiation is necessary.

Second, it is necessary to study whether the tautomeric state of DNA bases may be changed under the formation of pyrimidine dimers; to find out, what rare tautomeric forms initiate; and to determine the probabilities of formation of different rare tautomeric states.

Third, further study of DNA deformation under the formation of defects is needed. In particular, under the formation of various pyrimidine dimers and (6-4)-adducts. One has to find out, whether the hydrogen bonds between the bases in different chains are broken under DNA deformation. To determine distances from different defects, at which this phenomenon still occurs. To find out, whether different tautomeric states of DNA bases may be stabilized due to DNA deformation.

Fourth, a check of the model [13] of spontaneous semi-open states of the DNA should be done. In particular, it is necessary to study, whether a metastable semi-open state is realized, because it increases the probability of transversion formation very much [4]. One needs to study both the semi-open DNA states and changes in tautomeric state of DNA bases by different methods and to compare the probability of those processes in A-T and G-C pairs, since their role in mutagenesis may be exceptionally high.

In the paper [8, 10, 12], we propose and substantiate a scheme of the mechanism of a change in the tautomeric state of bases, when UV-quantum of energy is absorbed by DNA molecule. Quantum-mechanical calculations should be done and probabilities of the formation of different tautomeric states should be found. It would be interesting to compare the probabilities of the processes taking place under deexcitation of the triplet and singlet energy levels.

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Importance of the Bifurcated H-Bonding in the Formation of Iso-Guanine Tetrads

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Iso-guanine (2-oxo-6-amino-guanine, Fig. 1) occurs naturally and may be considered an elementary nucleobase. Thus, iso-guanine may have contributed to early biopolymer evolution during ribosomal translation in vitro. Similar to guanine tetrads, the higher-order self-pairing of iso-guanine has also been recognized.[1, 2]

1H-iso-guanine 3H-iso-guanine

Figure 1. 2-oxo-6-amino-guanine

Unlike guanine tetrad, which takes either Hoogsteen bases-pair motif [3] or the bifurcated hydrogen-bonding form, [4] several different conformers have been suggested for the iso-guanine tetrads.[5]

In our present efforts to understand the roles of the H-bonding in the formation of base tetrads, the bifurcated H-bonding pattern has been found to be very important for stabilizing the iso-guanine tetrads. Quantum chemistry calculations using the density functional theory (B3LYP/6-311G(d,p) level) on the stability of iso-guanine tetrads reveal that there are at least five different forms for iso-guanine tetrad (Fig. 2), in which four conformers contain the bifurcated H-bonds. The most stable conformer **1** of iso-guanine tetrad is held together through four pairs of normal and four pairs of bifurcated H-bond. Conformer **2** with S_4 symmetry is totally stabilized by the bifurcated H-bonds. Due to the small base-pairing sector angle between the hydrogen donor and receptor faces in iso-guanine (67˚), we are unable to locate the structure for iso-guanine tetrad with Hoogsteen bases-pair motif. Only placement of a cation into the central area of the tetrad leads to a new bowl-shaped structure. Conformer **3** suggested earlier by Golas *et al* [6] has been predicted to be less stable than **1**, though they are similar in structure as can be seen from Fig. 2.

Other two tetrad conformers (**4** and **5**) consisting of both 1H-iso-guanine and 3H-iso-guanine have also been located at the B3LYP/6-311G(d,p) level of theory.

Among these five conformers, **1**, **3**, and **4** have been confirmed to have the planar structure. The conformer with S_4 symmetry has been found more twisted than the tetrad formed by guanine. However, the energy difference between the C_{4h} constrained structure is small (only 0.67 kcal/mol), the stacking interaction with other layers in the four strand structure of DNA will overrule the energy preference of the S_4 symmetry.

In conclusion, this study confirms that the bifurcated H-bonding is of vital importance in the formation of the stable structure of iso-guanine tetrads.

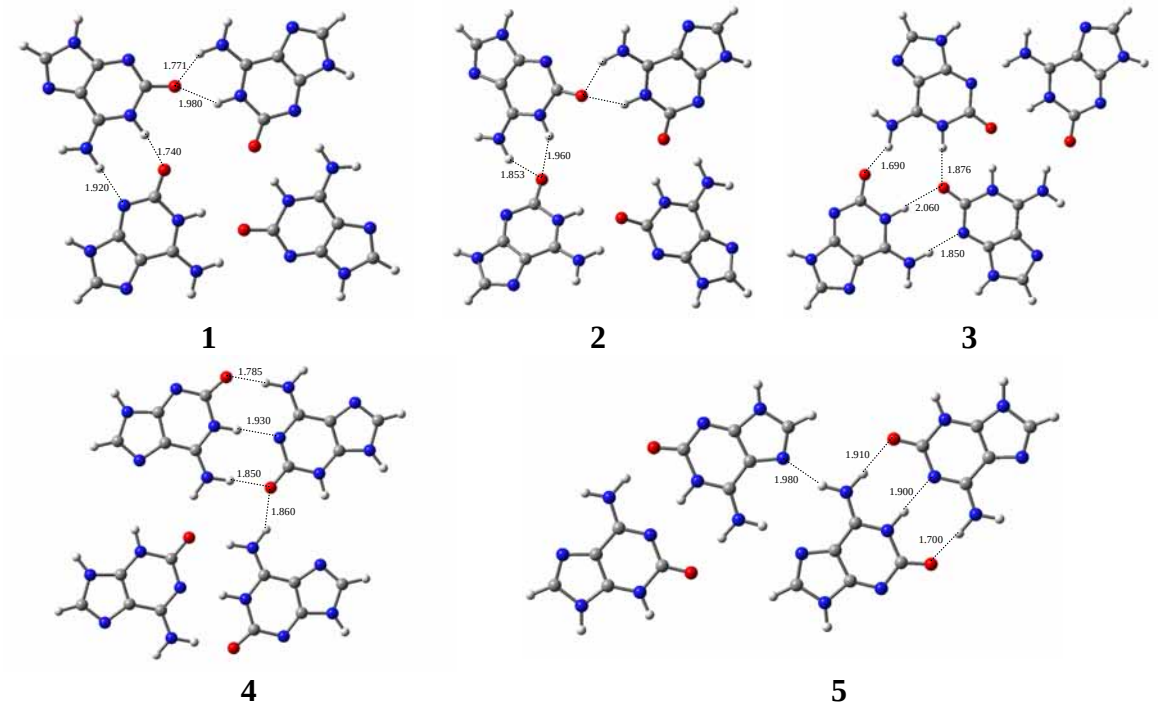

Figure 2. Five different local minima on the potential energy surface located at the B3LYP/6-311G(d,p) level of theory.

Acknowledgement

This research project in the PRC was supported by the "Knowledge Innovation Program" and the "Introducing Outstanding Overseas Scientists Project," Chinese Academy of Sciences. In the USA the project was supported by the NIH Grant No. G1 2RR13459-21 and NSF Grant No. 9805465.

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Electron-Transfer in Nitration and Nitrosation

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Despite the very similar electrophilic properties of the nitronium ion (NO_2^+) and the nitrosonium ion (NO^+), the rates of aromatic nitration and nitrosation differ by some fourteen orders of magnitude. In order to study these reactions, we performed a series of CCSD(T)/6-31G** calculations on the addition of NO^+ and NO_2^+ to benzene.

Based on these calculations, we present a novel interpretation of the mechanism of electrophilic aromatic addition based on a Marcus-Hush charge-transfer model. Both NO^+ and NO_2^+ spontaneously form (without a barrier) an intermolecular [1:1] π-complex with an arene donor. In nitration the π-complex rapidly converts to a σ-complex, which subsequently forms the final nitro-arene product. On the other hand, in nitrosation the σ-complex represents a high-energy transition state. This effectively traps the π-complex and prevents the formation of the nitrosation product. In practice, it is quite easy experimentally to isolate the NO^+-arene π-complex.

The explanation for this difference in behavior comes from Marcus-Hush theory for inner-sphere charge-transfer reactions. The two key quantities in Marcus-Hush theory, as further developed by Sutin, are the reorganization energy (λ) and the intermolecular electronic coupling element (H_{DA}). As noted earlier, NO^+ and NO_2^+ are very similar as electrophiles. This is manifest as almost identical values for H_{DA}. However, because of the large difference in the geometry between NO_2 and NO_2^+, the reorganization energy for the nitronium ion is substantially higher than that of the nitrosonium ion. This difference in λ leads to a double-well potential in the case of NO_2^+/arene complexes and to a single-well potential for NO^+/arene complexes.

The Decay of Metastable Ne_2^+: Experiment and Theory

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In a recent series of electron impact experiments involving a high resolution two sector field mass spectrometer, mass-analyzed ion kinetic energy (MIKE) peaks for metastable (spontaneous) decay reactions of the form $(Rg_2^+)^*$ -> Rg^+ + Rg have been measured (Rg = rare gas atom = Ne, Ar, Kr, Xe). Average kinetic energy release (KER) data were derived from the peak shapes and the time dependence of the metastable ion population fractions, yielding information on the fragmentation mechanisms operative in the metastable decay of $(Rg^{2+})^*$. In this way, it has been possible to demonstrate that the reaction $(Ar_2^+)^*$ -> Ar^+ + Ar proceeds through radiation induced dissociation. Specifically, a sizeable fraction of Ar_2^+ ions occupy the II(1/2)u state (i.e. the second state with a total spin of ½ and ungerade symmetry) as a result of electron impact and undergo an electric dipole transition to the lower I(1/2)g state. Since in the Franck-Condon region of this transition the I(1/2)g potential energy curve is repulsive, the Ar_2^+ molecule disintegrates.

We present CASSCF computations of the Ne_2^+ ground state and the five lowest excited states. The potential energy curves corresponding to these six states are strongly determined by spin-orbit coupling. We discuss two models for the incorporation of spin-orbit interaction: (A) An 'atomic' approximation that uses the known energy difference between $^{1/2}Ne^+$ and $^{3/2}Ne^+$ as the only parameter in the evaluation of the spin-orbit splitting in Ne_2^+ and (B) a more precise 'molecular' treatment that employs a convenient rearrangement of the computationally cumbersome $\mathbf{L}\cdot\mathbf{S}$ formalism[1]. Both approaches turn out to be well compatible. Further, different possible decay modes of the metastable II(1/2)u state of Ne_2^+ are compared. Two KER distributions peaked at 2 meV and 10 meV, respectively, are seen to be associated with radiative transitions from the II(1/2)u into the I(1/2)g state while another KER peak at about 90 meV is attributed to radiationless transitions from II(1/2)u into the continua of the lower Ne_2^+ states. We identify predissociation as the elementary mechanism of the latter process. Time constants are calculated for the alternative decay modes and compared with the experimental findings.

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Conversations with Prominent Women Scientists

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Women's participation in science is on the rise, but their recognition is not on a par with their accomplishments. The seminar will be based on personal experiences; conversations with famous women scientists. It will feature women who excelled in their particular scientific field, sometimes against all odds, and many of them also successfully managed to hold high administrative positions. The intriguing topic of missing recognition, especially when it is the question of the Nobel Prize, will be touched upon. Some statistics about the participation of women at different levels of academia will be shown and examples from all over the world will illustrate women's accomplishments in different areas of the sciences. They include the three living Nobel laureate women, the first woman professor of Tokyo University, and other luminaries, such as a real Rothschild and the Royal Princess of Thailand.

An *ab initio* Investigation of Alkylations of Cytosine

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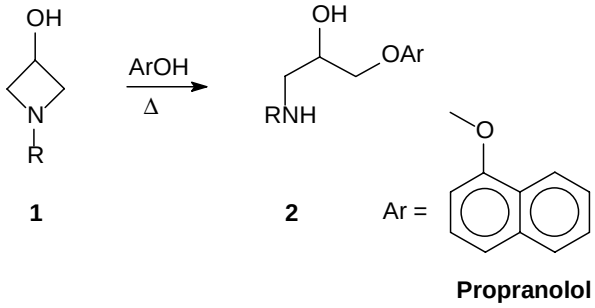
This investigation is an outgrowth of our studies involving ring opening of protonated azetidinols by phenols as a means of preparing *beta*-adrenolytic compounds structurally related to propranolol (Scheme 1). These reactions involve nucleophilic attack at **C2** (or **C4**) of the azetidine ring with cleavage of the **N-C2** (or **N-C4**) bond. With respect to the phenols, these reactions involve attachment of a *gamma*-amino alkyl substituent. Since the azetidinol must be protonated for the reaction to occur with weak and mild nucleophiles and since many malignant cells are more acidic (by about one pH unit) that the corresponding normal cells, it occurred to us that protonated azetidinols provide a potential method of selectively alkylating nucleic acid bases in malignant cells.

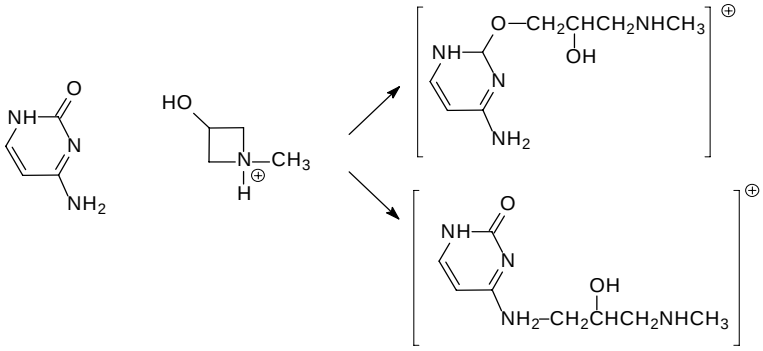


1 **2** **Propranolol**

Since cytosine is the simplest of these bases, it was chosen as the starting point for our investigation. The number of possibilities for alkylation is very large when one considers all of the possible tautomeric structures. In addition, the relative stabilities of the products cannot be discounted, since the reactions may reversible such that the thermodynamically controlled product rather than the kinetically controlled one results. Consequently, a complete post-Hartree-Foch *ab initio* investigation of the reaction of cytosine with azetidinols has the potential to be nearly monumental. We are only at the beginnings of this investigation.

Alkylation of Cytosine by Azetidinols

Our efforts toward modeling the reaction of cytosine and azetidinols have thus far been restricted to the most stable tautomer of cytosine and protonated 1-methyl-3-azetidinol. Even with the protonated azetidinols without substituents at the 2-position, the number of possible transition states to model doubles since the N-methyl and 3-hydroxy substituents may be either *syn* or *anti*. Thus far, both Hartree-Foch and MP2 6-31G**optimizations and Hartree-Fock frequency calculations have been or are being performed for **O-2** and **N-4** attacks (Scheme 2) by the 1-H-cytosine tautomer on the *syn* and *anti* azetidinols for a single conformer of the reactants, initially-formed products, and transition states (see Scheme2)--the transitions state calculations for **O-2** and **N-4** alkylation by the *anti* isomers are not yet complete. In the absence of a complete conformational search for the global minimum for the reactants and products, at this time the only valid comparison which can be made is with the transition state energies for **O2** and **N4**



openings of the *syn*-azetidinium ions. MP2/6-31G** calculations indicate that **O2**-opening is 0.024164 Hartree (15.16 kcal/mole) lower in energy than is **N4**-opening.

There are at least three factors which may affect the relative stabilities of transition states for the alkylation of cytosine: steric and intramolecular hydrogen bonding effects operative in the transition states, the relative stabilities of the initially formed products, and solvent effects (primarily intermolecular hydrogen bonding). It is felt by the authors that the first two of these effects are most easily investigated; consequently, no work has yet begun on assessing the importance of solvent effects.

Methylation of Cytosine

In an effort to gain some knowledge about how much conformational and hydrogen-bonding effects are affecting the activation energies, parallel investigations of the reactions of cytosine with alkylating agents not capable of intramolecular hydrogen bonding (methyl chloride and methyl diazonium ion) are being conducted. These calculations are also incomplete. Thus far, only HF/6-31G** transition states for methylation of 1-H-cytosine and 3-H-cytosine tautomers are being modeled. These calculations for the reaction of cytosine with methyl chloride are nearly complete; while those for the reaction with methyl diazonium ion are not. Several of the latter are unique and seem to involve non-classical cations and will not be discussed since these studies are too incomplete.

Transition states have been calculated for **O2** (methyl *anti* to **N4** only) and **N3** attack on methyl chloride by 1-H-cytosine (efforts to obtain a true transition state, *i.e.*, possessing a single negative vibrational mode along the reaction coordinate, for **N4** attack have so far proven futile); those for **O2** (again, methyl *anti* to **N4** only) and **N1** attack by 3-H-cytosine are complete. As expected, the 1-H tautomer provides the most stable transition state (at least, so far!). Surprisingly however, transition states involving attack by the ring nitrogen atoms not bearing a proton (*i.e.*, **N3**-attack and **N1**-attack for the 1-H and 3-H tautomers, respectively) are calculated to be more stable than are those involving **O2**-attack irrespective of the tautomer; suggesting that ring *N*-methylation should *occur faster* than *O*-methylation. This is not particularly surprising since the lone pairs on the ring nitrogen atoms are not directly involved in the aromatic nature of these cytosines and should be more available (more basic) than those on either **O2** or **N4**. In addition, the immediate products of ring *N*-methylation are *more stabile*, at least than those of *O*-methylation. This increased stability is easily interpreted on the basis that **O2**, and presumably also **N4**, methylation decreases the amount of conjugation in the products and therefore their stability.

Upon completion of transition state calculations for **O2** and **N4** attack on the trans-azetidinol, the emphasis will shift to calculation of the product and transition state energies for **N3**attack on the azetidinols, followed by **N1**, **N4** and **O2** attacks by the 3-H-cytosine tautomer.

Acknowledgement

The guidance and patience of my mentors, Drs. Leonid Gorb and Manoj Shukla, and the untiring efforts to make my visitations to Jackson State University by Tracye Lewis and Shonda Allen are gratefully acknowledged. Special thanks are due to Dr. Jerzy Leszczynski for selecting me as a participant in this program and for providing a first-class facility for the training of future African-American computational chemists.

Greater Insight into the Stacking Properties of Nucleic Acids

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One of the most study problems today involve the study of DNA. With the increase research, however, the complete characterization of nucleic acids remains a mystery. Computational Studies provide great potential in understanding in these properties. One of the most elusive properties is the interaction of Nucleic Acids bases with each other in a stacked arrangement. Only higher correlated theories have been proven effective in describing this stacking effect. Due to this fact, the number of included bases has been limited. In our present research, we decompose the 10 combinations of stacked bases to determine how important these stacking interaction are. We also will present observations about the interactions as bases are changed. Finally, we will present a statistical proposition as to predict future stacking. We will show that MP2 corrections may be predictable using smaller and less expensive terms.

"Free" Boranes and Heteroboranes in the Czech Republic

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Chemical shift calculations have made significant contributions to the structural characterization of boranes, borane anions, and heteroboranes. For a number of such compounds synthesized at Řež or elsewhere, the *ab initio*/IGLO (or GIAO)/NMR method has been used to verify the correctness of the computed or experimental geometries.

Concerning the computed geometries, it has been shown that ^{11}B chemical shifts can be computed to an accuracy of ca. 2-3 ppm when *ab initio* geometries optimized at an electron-correlated level (e.g. MP2) are employed. Most experimental geometries have performed considerably worse in this respect. In particular with diffraction-based methods, i.e. X-ray or gas-phase electron diffraction (GED), the positions of the light, strongly vibrating hydrogen atoms are difficult to determine. Large deviations between theoretical and experimental chemical shifts are indicative of shortcomings in the underlying geometry.

A considerable progress in the molecular structure determinations of free boranes and heteroboranes has been recently achieved by applying joint *ab initio*/GED approach in which chemical shift computations serve as an additional condition when refining electron-diffraction data and the computed differences between the closely-spaced distances (very common feature in the family of boranes and heteroboranes) are either fixed or so-called flexibly restrained during these refinements. Experimental structures that are too high in energy with respect to the computed ones are suspicious! In sum, the structural complexity of such systems would have rendered a meaningful application of the classical, unaided GED technique very difficult. A number of examples of the molecular structures determined either by the *ab initio*/IGLO (or GIAO)/NMR approach (e.g. newly prepared carbaboranes, phosphaboranes) or by the joint *ab initio*/GED technique (e.g. *closo*-$NB_{11}H_{12}$, *nido*-$SC_2B_8H_{10}$) will be demonstrated.

Supported by the Ministry of Education of the Czech Republic (Project LN00A028).

Extending the ONIOM Integrated MO/MO Approach to Hydrogen Bonding in Biological Systems: The Serine-Water and Threonine-Water Dimers

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A series of two-layer ONIOM(QM:QM) methods have been systematically applied to two biologically important hydrogen bonded dimers. A single configuration of the serine-water and threonine-water dimmers was optimized with MP2 theory and a DZP++ basis set. The dissociation energies of the dimers were then computed with RHF, B3LYP, MP2, and CCSD(T) electronic structure techniques with 3-21G, 6-31+G(d), and DZP++ basis sets as well as every possible two-layer ONIOM permutation using either CCSD(T)/DZP++ or MP2/DZP++ as the high-level method. The QM and QM:QM dissociation energies were compared to the target level of accuracy (CCSD(T)/DZP++). MP2 theory reproduces the target CCSD(T) data extremely well. ONIOM schemes that employ a model system that including the side chain and the α-carbon perform very well, introducing error of less than 0.21 kcal mol^{-1}. We observe that MP2:RHF approaches that use this large model system require almost the same CPU time as a B3LYP computation on the entire system but are far more accurate. Guidelines are presented for the application of two-layer ONIOM methods to hydrogen bonding between similar functional groups in large biological systems are presented.

Ab initio Studies of Tamoxifen and Related Compounds

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An extensive theoretical study of tamoxifen and related compounds has been performed at the *ab initio* HF/6-31 G** and B3LYP/6-31 G** levels. The optimized structures are in good agreement with X-ray data. Theoretical calculations indicate that the ground state energies of cis-tamoxifen and trans-tamoxifen, as well as the energies of the 4-hydroxytamoxifen isomeric pair, are very close, which confirms experimental and AM1 results and suggests nearly equivalent populations of the two isomers under equilibrium conditions. The effects of solvation were calculated with the Onsager model with full geometry optimization. The results indicate that solvation has very little effect on the total energies.

Organophosphorus Compounds, Cyanides, and Other Chemicals to Avoid

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We seek to devise improved methods for defense against and therapy for exposure to CWAs (chemical warfare agents) and TICs (Toxic Industrial Chemicals) for protection of military and civilian personnel.

While much information has been obtained on the function of organophosphorus (OP) compounds and one of their primary targets, the enzyme acetylcholinesterase (AChE), substantial questions remain on the mechanism of their interaction, as well as the mechanism of related compounds used for therapy and prophylaxis. Experimental studies on these systems are by their very nature dangerous and expensive, making this an ideal target for theoretical investigation. In this study, we attempt to understand the key molecular features leading to reversible and irreversible binding in the active site of AChE, and related reactions. QM, QM/QM and QM/MM methods are used to analyze structural effects and mechanistic details of the interactions of OP compounds, oximes, and carbamates with the enzyme active site and other key residues.

Other chemical systems are also of interest. Here we focus on the issue of collective and individual protection from cyanide and other compounds by adsorption and filtration. QM techniques are used to probe proposed reactions of CWAs and TICs with the components of filtration media to understand issues which may lead to design of advanced adsorbents with improved efficacy, increased lifetime, and decreased dependence on environmental factors.

Modeling of 2-Methyl-4-Nitroaniline (MNA) Adsorption on the Si (100) Surface

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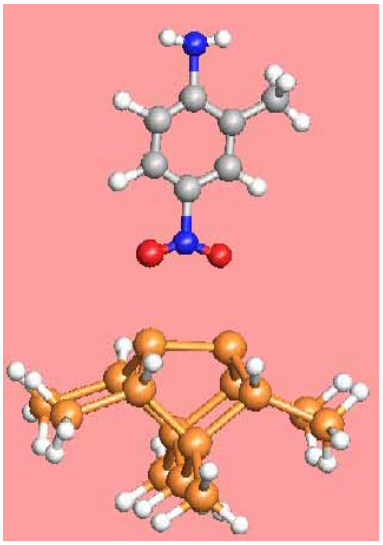
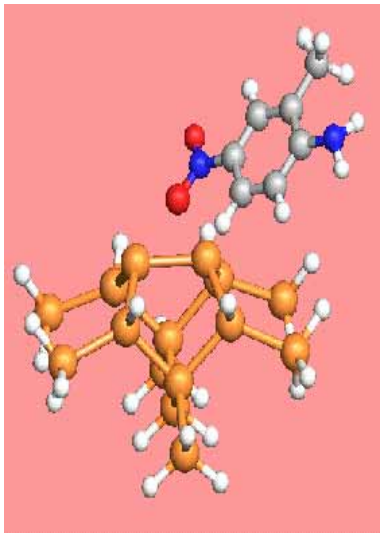
The Si (100) surface is one of the best-examined semiconductor surfaces due to its major technological importance for semiconductor devices. This work initiates a full study of a model system to describe the Si (100) surface for localized adsorption studies with the molecule, 2-methyl-4-nitroaniline (MNA). The long term goal is to determine the least expensive theoretical method and model system to describe the localized adsorption of molecular compounds on the Si (100) 2x1 surface. Several cluster models for the hydrogen-terminated Si (100) 2x1 surface have been developed in our group for adsorption studies. The clusters present a limited number of Silicon atoms from the infinite crystal and have their dangling bonds terminated with hydrogen atoms. This study expands the adsorption studies to the naked, more reactive surface of Si (100), for which experimental results are available. An expanded minimal cluster, containing a single Si surface dimer, and double undersurface layers, $Si_{15}H_{24}$, and a single MNA molecule aligned according to experimental data were submitted to a 6-31G** unrestricted Hartree-Fock unconstrained geometry optimization. The final geometry challenges expected results, but encourages further investigation using correlated methods. The reasons for the discrepancies between theory and experiment will be discussed.



Most probable orientation according to experimental results



Hartree-Fock optimized orientation

Multidimension Vibration Hamiltonian of Methylamine

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The two large-amplitude motions - NH_2 wagging and CH_3 internal rotation take place in methylamine, CH_3NH_2. The complete set of potential and kinematic coupling constants, characterizing the Hamiltonian of a non-rigid molecule CH_3NH_2 with two large-amplitude coordinates is derived from standard quantum chemical data for the equilibrium geometries, normal frequencies and eigenvectors in the ground and transition states. The reconstruction of the Hamiltonian is made *via* the following steps: classification of the generalized coordinates according to the irreducible representations of the group of the semi-rigid molecular model (SRMM); linear transformation of the ground state normal coordinates into the frame of the transition state taking into account the Eckart conditions; perturbative solution of the inverse vibrational problem.

Vibrations of CH_3NH_2 are characterized by 15 normal modes. In the ground and transition states CH_3NH_2 molecular belongs to the C_S (σ_{xy}) and C_S (σ_{yz}) symmetry point groups respectively. The vibrational Hamiltonian is constructed in the reactive coordinates [1-3]. The large-amplitude coordinate X characterizes NH_2 group inversion. That belongs to the A' and A'' irreducible representation in C_S (σ_{xy}) and C_S (σ_{yz}) respectively. The large-amplitude coordinate ϕ characterizes internal rotation of the CH_3 group and that belongs to the A'' irreducible representation in both C_S (σ_{xy}) and C_S (σ_{yz}). These coordinates are coupled with 13 small-amplitude, transverse vibrations $\{Y_k\}$, k = 3 ÷ 15. The SRMM is a basis for describing the nuclear motion in non-rigid molecules [4]. Its symmetry group is isomorphic C_{6V} point group [5]. The irreducible representations of the point groups of the stationary points are related via SRMM group by the correlation diagram. The NH_2CH_3 molecular belongs to the point group symmetry C_S at stationary points of the PES. The transfer modes belong to A', A" and are coupled with tunneling coordinate ϕ to yield potential interactions terms of the forms $F_{1k}(\phi)\cdot\{Y_k\}$, $F_{2k}(\phi)\cdot\{Y_k^2\}$. The coupling functions $F_{1k}(\phi)$, $F_{2k}(\phi)$ must be so that interaction terms in the Hamiltonian will be totally symmetric. The following types of couplings between, ϕ, and transverse vibrations, Y, exist: $HL: A' \cos 3\phi$; $HG: A' \sin 3\phi$; $As: (A'')^2 \cos 6\phi$, where HL – half-linear, HG – half-gated, As – angular squeezed [3].

The type of coupling $X\cdot\{Y_k\}$ is chosen from following conditions: if the irreducible representations X and Y_k are the same in both symmetry groups the C_S (σ_{xy}) and C_S (σ_{yz}), than linear (L) $X\cdot Y_k$ coupling exist; if coordinate is totally symmetric in both groups, coupling is (G) gated $(1 - X^2)\, Y_k$; in other cases coupling is squeezed (Sq) $X^2\, Y^2$. The squeezed couplings exist for L and G vibrations too. The G and HG couplings lower the barrier and thus enhance tunneling. The L and HL couplings prolong the tunneling path and consequently decrease tunneling. The As and Sq couplings change transverse frequencies along tunneling path [1].

The equilibrium geometries and the normal mode eigenvectors and eigenfrequencies at stationary points of PES was calculated by ab initio quantum chemical method within Gaussian program by CI/6-311g** method.

As shown in [3] reactive coordinates can be chosen so that: (I) the kinematic matrix, $\mathbf{G}^{\#}$, is the unit matrix for all types of transverse vibration in the saddle-inversion transition state; (II) the force matrix, $\mathbf{F}^{\#}$, is a block-diagonal supermatrix, different blocks of $\mathbf{F}^{\#}$ correspond to vibrations of different symmetry; the non-diagonal elements of $\mathbf{F}^{\#}$ are determined by coupling

coefficients. Near the stationary points the potential function and the classic kinetic energy, are reduced to quadratic forms of the displacements, $X\text{-}X^{\#}$,$\phi\text{-}\phi^{\#}$,$\{Y\text{-}Y^{\#}\}$ and $X\text{-}X^{0}$,$\phi\text{-}\phi^{0}$,$\{Y\text{-}Y^{0}\}$, and conjugate momenta, $p_{\phi}^{\#}$,$\{p_{Y}^{\#}\}$ and p_{ϕ}^{0},$\{p_{Y}^{0}\}$. These coordinates transform into normal modes *via* (3N-6)×(3N-6) matrices:

$$Q^{\#} = P^{\#}\left(X - X^{\#}, \phi - \phi^{\#}, \{Y - Y^{\#}\}\right), \qquad Q^{0} = P^{0}\left(X - X^{0}, \phi - \phi^{0}, \{Y - Y^{0}\}\right) \qquad (1)$$

To define variations of transverse coordinates with respect to that in transition state of saddle-inversion, initial state is 'projected' to the latter [3] so that Eckard conditions will be truth. The potential energy is expended in a power series of reactive coordinates $X,\{Y_k\}$ and Fourier series of ϕ:

$$V = V_o\left\{\begin{array}{l} V_{2D} + \sum\limits_{k=3,5,7,9-15} \frac{\omega_k^2}{2} Y_k^2 + \sum\limits_{k=3,5,7,9-10}^{G} C_k\left(1 - X^2\right)Y_k + \sum\limits_{k=3,5,7,9-10} C_k^{(3)} X Y_k \cos 3\phi + \\ + \sum\limits_{k=3-15}^{As} \alpha_{kk}^{\phi} Y_k^2 \cos 6\phi + \sum\limits_{k=3-15}^{Sq} \alpha_{kk}^{X} X^2 Y_k^2 + \sum\limits_{k=4,6,8}^{L} \frac{\omega_k^2}{2}\left(Y_k - \frac{C_k^2}{\omega_k^2} X\right)^2 + \\ + \sum\limits_{k=4,6,8}^{HL} C_k Y_k \cos 3\phi + \sum\limits_{3.5.7.9-10}^{Br} C_k\left(1 - \cos 6\phi\right)Y_k + \sum\limits_{k=11-15}^{HG} C_k Y_k \sin 3\phi + \end{array}\right\} \qquad (2)$$

ω_k – dimensionless frequencies, V_o – normalization factor, C_k – constants of HL-, HG-, L- and G- couplings, α_{kk} – constants of As-, Sq – couplings. The two dimension 2D potential is presented as:

$$V_{2D}(X, \phi) = \frac{1}{4}\left(1 - X^2\right)^2 + \alpha X \cos 3\phi + V_1 \cos 6\phi \qquad (3)$$

α = 0.055 - coupling constant of inversion vibration with rotation one. The parameters of 2D potential were determined by iterative procedure from the height of adiabatic potential at transitions states and ratio of tunneling frequencies at stationary points. The eigenfrequency of 2D potential is defined by expression: $\Omega_x^2 = 2V_0/(m_x X_0)$. The equation (2) of PPE is presented at dimensionless form. The potential energy is measured in units of $\gamma\hbar\Omega_x$, $\gamma = m_x\Omega_x X_o^2/2\hbar$, m_x and Ω_x are the reduced mass and the eigenfrequency of X-vibration in the minimum of the 2Dpotential. The dimensionless transfer frequencies ω_k are defined as: $\omega = \sqrt{2}\nu_y/\Omega_x$. The set of coupling constants are taken from values of transfer coordinates at stationary points. The X and ϕ depended Y_kY_k - constants are determined from frequencies variations in stationary points [1]. The estimation of $\alpha_{kk'}$was shown that the contribution of nondiagonal elements was small and only Sq-, As- couplings must be taken into account. The kinetic energy is represented in the following form:

$$\begin{array}{l} \hat{T} = 0.5\left(1 + g_{xx}X^2\right)p_x^2 + 0.5\left(1 + g_{\phi\phi}\cos^2 3\phi\right)p_\phi^2 + \\ + \sum\limits_{k=3,5,7,9-10}^{g}\left\{0.5\left(1 + g_{kk}X^2\right)p_k^2 + g_{xk}Xp_xp_k\right\} + \sum\limits_{k=4,6,8}^{L}\left\{0.5\left(1 + g_{kk}X^2\right)p_k^2 + g_{xk}X^2p_xp_k\right\} + \\ + \sum\limits_{k=4,6,8}^{HL}\left\{0.5\left(1 + g_{kk}\cos^2 3\phi\right)p_k^2\right\} + \sum\limits_{k=3,5,7,9-10}^{HG}\left\{0.5\left(1 + g_{kk}\cos^2 3\phi\right)p_k^2 + g_{k\phi}\cos 3\phi p_k p_\phi\right\} + \\ + \sum\limits_{k=3,5,7,9-10}^{Br}\left\{0.5\left(1 + g_{kk}\cos^2 3\phi\right)p_k^2 + g_{k\phi}\sin 6\phi p_k p_\phi\right\} \end{array} \qquad (4)$$

g_{kk} – dimensionless kinematic coupling. The coefficients of kinematic couplings are evaluated from the secular equations for the stationary points in which the kinematic matrices have the following form: $\mathbf{G}^0 = (\mathbf{S}^0)^T\,\mathbf{S}^0$. The $\mathbf{S}^0$ is the matrix which transform the normal coordinates of the ground state into those of saddle-inversion state $\mathbf{Q}^{\#} = \mathbf{S}^0\,\mathbf{Q}^0$. $(\mathbf{S}^0)^T$ is transposed to $\mathbf{S}^0$. The

matrix $\mathbf{S}^0$ is uniquely related to the **s-** matrix, which transform the Cartesian displacements in the corresponding stationary point into generalized normal coordinates [3]. The results are summarized in table.

Reconstructed form of PES can be applied for calculation of tunneling splitting in the ground and first exited states of all vibrations using the perturbation instanton approach (PIA). The PIA method developed in [1-3] enables a description of multidimensional tunneling without arbitrarily reducing the number of the degrees of freedom. The PIA method will be converged if the coupling constants obey the condition $C_k/\omega_k < 0.7$. In our case this condition is true as follows from table. The largest constants are G-coupling of X-coordinate with N-C stretch (C/w = -0,323) and with NH_2 symmetric bend (C/w = 0,392). Those give basic contribution into spectral densities of G-vibrations, which determine decrease adiabatic barrier with respect to 2D one. Such couplings (C/w ~ 0.4) are able to change tunneling splitting by 1-2 orders of magnitude [1]. The consideration of interactions large-amplitude vibrations with transfers ones significantly affects the parameters of 2D potential. The height of renormalized 2D potential is twice that in adiabatic potential, which is equal to 6.39 κcal/Mole.

Table. Type of coupling and potential coupling constants

Vibrations	number	Type of coupling $\{Y_k\}$ ϕ	C/ω	α^{ϕ}/ω^2	Type of coupling $\{Y_k\}$ X	C/ω	α^{X}/ω^2	C/ω YXcos 3ϕ	g_{kk}
$\gamma(CH_3)$, torsion	ν_1	T(ϕ)	-						
γNH_2, wagging	ν_2	HL			T(X)				
ν(NC) stretch	ν_3	Br	0.005	-0.003	G	-0.323	-0.043	0.003	0.037
δ (CH_3)bend	ν_4	HL	0.030	0.025	L	-0.120	0.012	-	0.136
δ(CH_3) bend	ν_5	Br	0.002	-0.004	G	-0.014	0.003	0.019	0.010
δ(CH_3) bend sym	ν_6	HL	-0.043	0.007	L	-0.020	-	-	-0.369
ν(CH) stretch	ν_7	Br	-	-0.001	G	-0.026	0.003	0.005	-0.104
ν(CH) stretch sym	ν_8	HL	0.062	0.006	L	0.033	0.009	-	0.204
δ(NH_2) bend sym	ν_9	Br	-0.004	-	G	0.392	0.012	-0.031	0.028
ν(NH) stretch sym	ν_{10}	Br	0.002	-	G	-0.075	-0.045	0.003	0.259
δ$(CH_3$-$NH_2)$ bend	ν_{11}	HG	-0.033	-	Sq	-0.033	0.068	-	0.060
δ(CH_3) bend asym	ν_{12}	HG	0.073	-0.002	Sq	0.073	-0.007	-	-0.267
ν(CH) stretch asym	ν_{13}	HG	-0.025	-0.002	Sq	-0.025	0.007	-	0.141
δ(NH_2) bend asym	ν_{14}	HG	-0.012	-	Sq	-0.012	0.052	-	-0.025
ν(NH) stretch asym	ν_{15}	HG	-0.021	-	Sq	-0.021	-0.055	-	0.040

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One-Electron Reduction of Nitrobenzene by Iron (II) Compounds. A DFT Investigation

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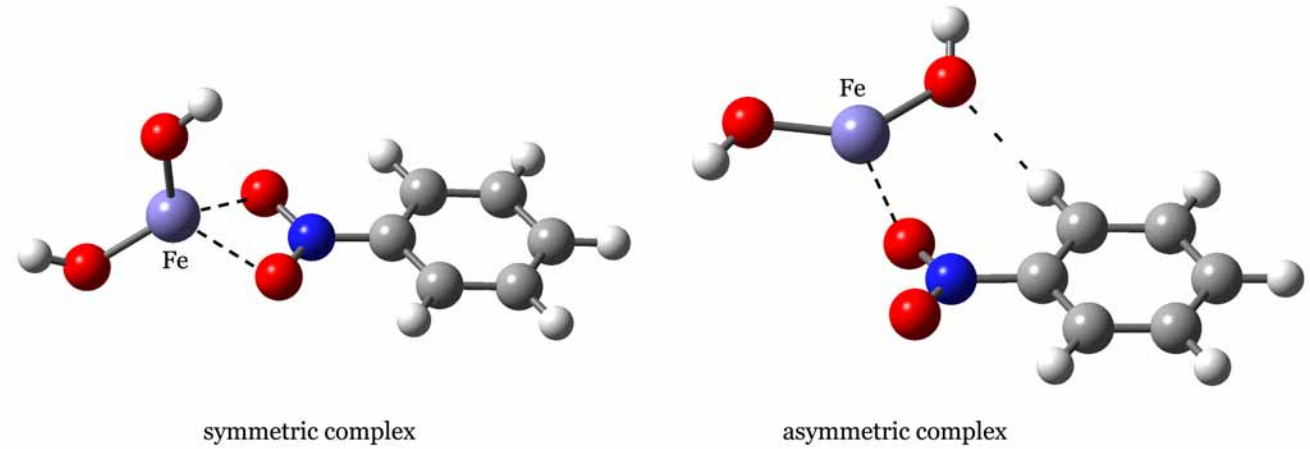
The development of cleanup technologies for a disposal of explosives is a challenge for environmental science. Such development involves the coordination of experimental and theoretical investigations to integrate both technological and fundamental aspects of key process. Although the major processes affecting the natural and engineering treatment of explosives have been investigated qualitatively, many issues remain unsolved regarding a reaction mechanism.

We choose different complexes between nitrobenzene and iron(II) containing species as a simplest models for these kind of reactions. We have applied the DFT level of ab initio theory with conjunction with BLYP and B3LYP exchange and correlation functionals. The standard 6-311++G(d) basis set has been used. All geometry minima have been verified by the absence of imaginary frequencies. The analysis on the internal instability of DFT solution has been also performed.

The following most important results are obtained.

1. We have performed an estimation for thermodynamical probability of Red-Ox reactions between nitrobenzene and iron (II) compounds such as Fe^{+2}, $[FeOH]^{+}$, $Fe(OH)_2$, $[Fe(OH)_3]^{-}$.
2. We have found that reaction of direct elimination of oxygen from nitro-group is more thermodynamically preferable than the reaction of direct elimination.
3. We have revealed that the electronic structure of symmetric (see Figure) complex between nitrobenzene and $Fe(OH)_2$ could be described as the result of intramolecular electron transfer. This finding suggest the non-barrier process for the transfer of the first electron from $Fe(OH)_2$ to nitrobenzene molecule.



symmetric complex asymmetric complex

Atom-centered Density Matrix Propagation (ADMP): A New Approach to *ab initio* Molecular Dynamics

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A new method to perform Ab Initio Molecular Dynamics will be described. This method is similar to the Car-Parrinello (CP) approach, but differs by using the single-particle density matrix, represented in Gaussian basis sets. The density matrix elements are propagated along with the classical nuclear degrees of freedom using an extended Lagrangian approach.[1,2] Some of the major advantages of the method include asymptotic O(N) scaling with system size, better adiabatic control and the flexibility to use accurate and effective exchange-correlation density functionals (including gradient-corrected and hybrid functionals). Interesting results from a recent study of protonated water clusters using this method will be presented. If time permits, proton transport along a water chain, and ro-vibrational spectra of medium sized chloride-water clusters will also be discussed.

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Average Local Ionization Energy as a Measure of Local Polarizability

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The average local ionization energy, $\bar{I}(\mathbf{r})$, is defined as the summation over all occupied molecular orbitals of the product of the electronic density and the absolute value of the orbital energy of the ith molecular orbital, divided by the total electronic density. $\bar{I}(\mathbf{r})$ can be interpreted as the average energy needed to remove an electron at any particular point in the space of the molecule. It has been demonstrated that there is a good inverse relationship between the polarizabilities of atoms and their first ionization energies. We have also showed that there is a good inverse correlation between polarizability and $\bar{I}(r_s)$ for the atoms He through Kr, where r_S is the radial distance corresponding to a spherical shell containing 98% of the electronic charge. In this poster, we are investigating the idea that the average local ionization energy can serve as a measure of local polarizability.

Structures and Properties of Sarin and Soman

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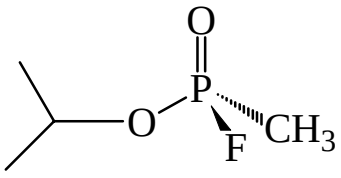
Sarin (GB, isopropyl methylphosphonoflouridate) and soman (GD, pinacolyl methylphosphonofluoridate) are the lethal warfare agents which act for the nerve system inhibiting the enzyme acetylcholinesterase by phosphonylation of serine (Ser200).

The most stable conformers of sarin and soman are determined in high-level-correlated calculations with extended Gaussian basis sets. The two molecules are found to have three low-energy conformers each. For both molecules two of the lowest-energy conformers are almost of the same stability with a very small barrier separating the corresponding minima. The third conformer of sarin is found to lie about 1 kcal/mole above the lowest—energy form. For soman the corresponding value is equal to about 4 kcal/mole. These data have an impact on the mechanism of the toxic action of sarin and soman. According to our investigations sarin and soman are structurally and electronically highly similar and differences in their features arise mostly from the size and spatial arrangement of the alkoxy substituent at phosphorus. These may hinder the access to the phosphorus during the phosphonylation of serine.

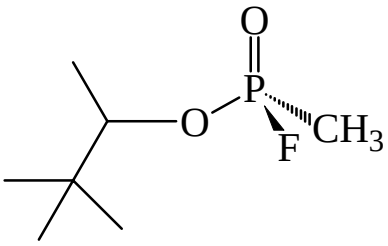
The influence of solvents on the conformations and solvation energies of sarin and soman was also investigated.

Acknowledgements

AHPCRC coop. agreement # DAAHO4-95-2-0003/ contract # DAAHO4-95-C-0008.



Isopropyl methylphosphonofluoridate
(sarin, GB)



Pinacolyl methyl phosphonofluoridate
(soman, GD)

Post-Haretree–Fock Study of Guanine and Methylguanine

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Because of their biological importance nucleic acid bases are subject of numerous experimental and theoretical investigations. Their rare tautomers are suggested to be responsible for the spontaneous point mutations in DNA strings.

Our study is devoted to the determination of the geometry parameters and energies for selected tautomers and transition states of guanine and methylguanine at the high level of theory. Extended Gaussian basis sets were used to assure the convergence of the results at the MP2 level. The single point calculations were carried out at the MP4(SDTQ) and CCSD(T) levels for the reference optimized geometries. The energy minima were veryfied by the calculation of the harmonic vibrational frequencies.

The relative stability of tautomers does not depend on basis set used. One obtains the following energy sequence:

7H_keto<9H_keto<9H_enol<7H_enol.

Enol forms with rotated hydroxyl group were also investigated. Their energy is slightly higher than standard enol forms.

Acknowledgements

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