Scientific Report from a STMS visit
Cost Action P9, *Radiation Damage in Biological Systems*
Working Group 4, *Theoretical Developments for Radiation Damage*

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COST STSM Reference Number: COST-STSM-P9-02841 (16/04/2007 - 14/05/2007)
Research Proposal Title: *Application of chemoinformatics techniques in the characterization of the most stable tautomers of ionic nucleic acid bases identified by the hybrid combinatorial-quantum mechanical method for identification of the most stable tautomers.*

The purpose of the STSM visit was to perform the characterization of the most stable anionic tautomers of nucleic acid bases (NABs) identified with a hybrid quantum mechanical-combinatorial method developed by the applicant. The recently discovered tautomers might be important for the understanding of radiation damage of DNA as it is speculated that the anionic states localized on the NABs are involved in the DNA strand break process induced by the low energy electrons.

The performed characterization of the new tautomers of guanine, adenine and cytosine involved an application of the advanced chemoinformatics techniques: 1) excess electron density analysis of adiabatically bound anions of guanine was performed using the orbital hologram technique, 2) identification of important substructure features of anionic cytosine and adenine was done using substructure analysis approach and clustering.

The substructure analysis technique used to identify 2D substructure features unique to the most stable anionic tautomers of adenine and cytosine required coding 2D substructure features into Boolean arrays called fingerprints. By comparing representative fingerprints generated for groups of the most stable and less stable tautomers, we were able to demonstrate that the feature of the most stable anions of adeninie is the presence of at least one hydrogen atom at each of C2, C8 and N4 (Fig. 1 A). Using the clustering techniques, we were able to demonstrate that the most stable anions of adenine, differently than guanine, form several distinct clusters. In one cluster, the major features are additional hydogens at C4,C5 or C6. In the remaining clusters, aditional hydorgen atoms are at C2 or C8. In case of the most stable anions of cytosine, the substructure analysis suggested that the distinct 2D substructural features are: 1) at least one hydogen atom at N4, C5 and C6 (Fig. 1 B) and 2) the presence of a carbonyl rather than a hydroxyl group. The clustering of cytosine tautomers suggested that majority of the most stable tautomers are very similar as they form one cluster (an “island” in the tautomeric space).

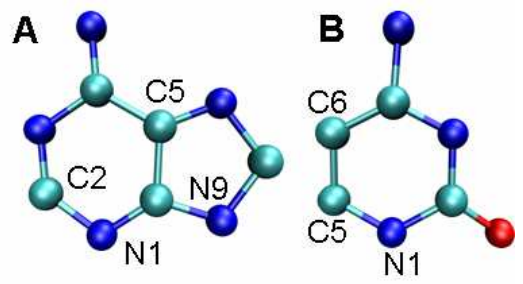

Fig. 1. Adenine (A) and cytosine (B)

The analysis of excess electron distribution in the adiabatically bound anions of guanine led to a conclusion that the singly-occupied molecular orbitals (SOMO) in these species have much less distinct antibonding character than in the case of anions of most stable neutral tautomers. This conclusion is supported by almost planar geometries of guanine rings in the former group. To measure the difference of SOMO orbitals of adiabatically bound anions and anions based on the most stable neutral species, we used not only field-based similarity techniques but also developed a novel method based on orbital density

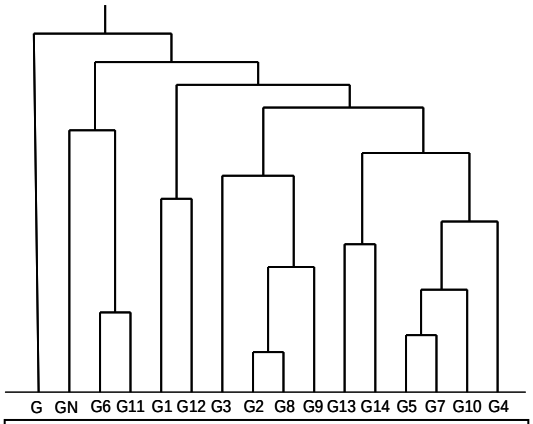

Fig. 2. Dendrogram representing clustering of orbital density holograms

holograms. The “holograms” were constructed based on the results of Bader’s analysis of the excess electron charge density. The orbital density holograms similarity was calculated using the Euclidean distance. This definition of similarity measure allowed us to perform clustering of 16 orbitals (14 most stable anionic (G1-G14) and 2 anions of the most stable neutrals (G,GN)). The dendrogram presented in Fig 2. clearly supports the conclusion that the anions of the most stable neutrals are different from adiabatically bound anions.

The results obtained during the visit will be presented at two conferences: 1) Electron Induced Processes At the Molecular Level, 25th - 29th of May 2007, Hveragerði, Iceland and 2) 4th Joint Sheffield Conference on Chemoinformatics, 18th-20th June, 2007, Sheffield, UK. We also plan to submit a standard journal article on methods we developed and applied to characterize the anionic states of guanine.