1-1-2016

An Initio Investigation of Molecular Orbital Effects in DNA Intercalation

Kendall G. Byler
University of Alabama in Huntsville

Ab Initio Investigation of Molecular Orbital Effects in DNA Intercalation

A Proposal for the Research & Creative Experiences for Undergraduates Program, Summer 2016

Faculty Research Mentor

Kendall G Byler, Department of Chemistry, MSB C223. Phone: 256-479-1150 Email: kgb0011@uah.edu

Project Summary

The overall goal of this research is to examine the magnitude of the effect of molecular orbital overlap in DNA base stacking and in the intercalation of planar aromatic heterocycles, such as quinolone alkaloids, known to be cytotoxic to tumor cells. Many quinolone alkaloids are known to have cytotoxic activity against cancer cells, as in the case of camptothecin[1], which forms a ternary complex with the DNA strand into which it is intercalated and topoisomerase I. The formation of this complex prevents DNA re-ligation by the conversion of single-strand breaks into double-strand breaks. Other quinolone alkaloids and similar structures[2] that also exhibit cytotoxicity are thought to function by the same mechanism. Structural moieties that can engage in hydrogen bonding or other strong non-covalent interactions with both the DNA strand and topoisomerase are essential for function and central to ligand design for this type of inhibitor. Perhaps equally important is the electronic environment of the portion of the heterocycle that actually intercalates in between the stack of base pairs to deliver it to the DNA-enzyme complex. Is it necessary for molecular orbitals in this part of the molecule to participate in orbital overlap that extends throughout the base pair system or do attractive van der Waals forces and electrostatics dominate?

Quantum mechanical methods have been used recently to examine the energetic basis for base stacking in DNA[3,4] and the individual energetic components that contribute to these interactions. One such method is Symmetry-Adapted Perturbation Theory (SAPT), which uses density functional theory to calculate the interaction energies for non-covalently-bound systems. Interactions computed by this method are decomposed into contributions from electrostatic, exchange-repulsion, induction/polarization, and London dispersion forces (attractive van der Waals terms). The relative importance of interactions between electrons in the highest lying orbitals and the lowest lying virtual orbitals has yet to be addressed and this research seeks to determine this. I have substantial experience with density functional examinations of interacting molecular systems[5].

All calculations will be submitted as jobs to be performed on the Dense Memory Cluster (DMC) at the Alabama Supercomputing Center (ASC). The student will be supervised by Dr. Byler every day during the period of research and will be available for discussion during regular hours and *via* email in the evening. The student's work will fit directly into the current research effort to quantify the effect of orbital interactions between DNA base pairs and intercalating heterocycles.

Student Duties

DNA Intercalators

The student will be given an account on the ASC and will be introduced to basic shell scripting and procedures for preparing and submitting computational jobs to the queuing system for processing. The chemical structures will be constructed using SPARTAN software in our computer lab for a series of quinolone alkaloids intercalated into fragments of double-stranded B-DNA. This set of quinolone heterocycles was previously reported to exhibit cytotoxicity and to intercalate well *in silico* between the base pair stacks in a molecular docking study[6]. These structures will be uploaded to the student's directory at the ASC.

Molecular Orbital Calculations

The molecular geometries of the intercalated "sandwiches" will be optimized using the M06-2X density functional in Gaussian '09 using implicit solvation on the Dense Memory Cluster at the ASC. Following this, SAPT2012 will be used to determine the interaction energies and their individual energetic components between intercalator and base pairs. Force field calculations will also be performed using an appropriate force field such as CHARMM27 in order to compare the relative degree of partial charge stabilization for both the orbital-based and non-orbital-based methods.

Non-Covalent Interactions

The results of both the force field calculations and the MO calculations will be used to extrapolate the magnitude of charge effects and frontier energetics in the intercalated "sandwiches". This will then be compared with the relative magnitudes of non-covalent interaction components calculated by SAPT. In addition, natural atomic orbital analysis will be used to assess the degree of localization/delocalization of densities in frontier molecular orbitals on the intercalators and the DNA base pairs.

Manuscript Preparation

The student is encouraged to assemble the results of this work in the form of a scientific journal article for publication. Dr. Byler will assist the student in this effort and may include the results of previous and concurrent studies into the final manuscript.

Expected Results

A comparison of the potential energy surfaces calculated by both methods (SAPT and full DFT) will be made to determine if the two calculated interaction energies are linearly related and if there are discontinuous regions that may be attributed to the effects of frontier molecular orbital interactions. Establishing a link between non-covalent interaction energy and orbital overlap will indicate the need to take heterocycle structure into account in ligand design for the purposes of targeting topoisomerases in tumor cells and will highlight certain molecular frameworks as likely intercalators.

Mentor Supervision & Interaction

Dr. Byler will introduce key concepts in computational chemistry relevant to this research and familiarize the student with the software and hardware requirements associated with high level molecular orbital calculations on chemical systems. Dr. Byler is an expert in computational methods and routinely uses *ab initio* code in the study of chemical systems. Regular meetings will be held weekly with Dr. Byler.

References

1) Li QY, Zu YG, Shi RZ, Yao LP (**2006**) Camptothecin: current perspectives. *Curr Med Chem* 13:2021–2039
2) Dias N, Vezin H, Lansiaux A, Bailly C (**2005**) Topoisomerase Inhibitors of Marine Origin and Their Potential Use as Anticancer Agents. *Top Curr Chem* 253:89–108
3) Parker T, Hohenstein E, Parrish R, Hud N, Sherrill C. (**2013**) Quantum-Mechanical Analysis of the Energetic Contributions to π Stacking in Nucleic Acids versus Rise, Twist, and Slide. *JACS* 135:1306−131
4) Hunter R, Mourik T (**2012**) DNA Base Stacking: The Stacked Uracil/Uracil and Thymine/Thymine Minima. *J Comp Chem* 33:2161-2172
5) Byler K, Li Y, Houghten R, Martinez-Mayorga K (**2013**) The Role of Imidazole in Peptide Cyclization by Transesterification: Parallels to the Catalytic Triads of Serine Proteases. *Org Biomol Chem* 11: 2979-2987
6) Byler K, Wang C, Setzer W (**2009**) Quinoline alkaloids as intercalative topoisomerase inhibitors. *J Mol Model* 15:1417–1426