An Ab Initio Investigation of Molecular Orbital Effects in DNA Intercalation

Elizabeth Andrew and Kendall Byler, Department of Chemistry

Overview
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 camptothecin1, which forms a ternary complex with the DNA strand into which it is intercalated and with 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 such as stauranthine and similar structures2 that also exhibit cytotoxicity are thought to function by the same mechanism.

Figure 1: Benzanthrone intercalated into DNA

Hydrogen bonding or other strong non-covalent interactions are essential for function and are central to ligand design for this type of inhibitor; but perhaps equally important is the electronic environment of the DNA-intercalator complex3. Do frontier molecular orbitals participate in attractive interactions that extend throughout the base pair system or do electrostatics and weak van der Waals interactions dominate? We sought to investigate this question using Symmetry-Adapted Perturbation Theory4 (SAPT), which splits the heterocycle / base pair complex into two basis systems to calculate the interaction energies between intercalator and base pair. Interactions computed by this method are decomposed into contributions from electrostatic, exchange-repulsion, induction/polarization, and London dispersion forces.

Methods
Our model system involved sliding the planar heterocycle stauranthine across the surface of the GC base pair in a grid, taking counterpoise-corrected M06-2X/6-31+G* and SAPT(0) energy calculations at each point in the grid to generate potential energy surfaces for each contributor to the overall energy of the system.

For the majority of points on the electrostatic and induction maps, the GC-GC interaction energies are lower (more attractive) than that of the stauranthine-GC complex. The exception is the region surrounding (0.00,1.00). In the case of dispersion, all points are lower in energy than stauranthine, with the minimum being centered around (0.00,1.00). Conversely, all points on the exchange map are higher in energy for the GC-GC pair, with the minimum appearing at (2.25,0.50).

Figure 2: Component potential energy surfaces from SAPT calculations

The low energy regions on both total potential energy surfaces are both local to the region around (0.50,0.50), which corresponds to a complex with significant orbital overlap.

Figure 3: Total energy surfaces

Conclusions
Neglecting orbital interactions, these molecules should reach an energetic minimum where the static and induced electric charges cancel, i.e. where the electrostatic and inductive interactions are greatest. While the GC-GC stack functions primarily as a charge transfer complex, the lowest energy complex formed by the stauranthine-GC complex involved substantial overlap of frontier orbitals and a concomitant minimization of exchange energy. The total interaction energy calculated using SAPT appears to capture the different components involved in the noncovalent binding of intercalating heterocycles in such a way as to isolate the exchange term (which has no precise physical interpretation) as descriptive of the degree of orbital interaction. Thus, SAPT interaction energies can be used in the design of DNA-intercalating drugs.

Figure 4: Frontier orbital interactions in the stauranthine-GC dimer

References

Acknowledgements
Special thanks to Dr. Bernhard Vogler and David Cook, the RCEU administrators, Dr. William Setzer and Dr. Joaquin Barroso for their support of this project. Gratitude also goes to the UAH Office of the Provost, the UAH Office of the Vice President for Research and Economic Development, and to Dr. David Young at the Alabama Supercomputer Center for his assistance and the use of the dense memory cluster for our calculations.