Doctoral in Chemistry
Dissertation Defense

Presents a Defense Titled:

"Density Functional Theory Modeling of π-Stacking and Electrophilic Donor-Acceptor Interactions with Application to Therapeutic Targeting of Zinc-Finger Proteins"

Presented By

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Several viruses contain conserved zinc finger (ZF) proteins that are essential for viral reproduction, making them attractive drug targets. Oxidation of the Cys thiolates release Zn^{2+}, and the ZF can no longer bind DNA or RNA. Understanding the interaction of reducible sulfur and selenium compounds (r-S/Se) with ZF proteins is valuable for explaining the beneficial viruscidal activity of these compounds and can guide the production of new anti-viral agents. DFT was used to investigate the interaction of small r-S/Se compounds with models of three classes of ZF proteins. A high correlation was found between the LUMO energy of the r-S/Se compound and an increase in interaction energy, suggesting that the LUMO energy of a potential drug could be used to test its ability to oxidize a ZF protein.

The nucleocapsid protein (NCp7) from the HIV-1 virus is an attractive drug target. Because W37, of NCp7 π-stacks to Gua in the NCp7-DNA binding site, compounds that binds with a higher affinity will be able to inhibit NCp7 binding to DNA. Methylation or metalation is proposed to increase stacking interaction between the positively charged base and W37, by lowering the LUMO of the base, bringing it closer in energy to the HOMO of W. Small models of methylated and metalated Gua π-stacked to W were investigated with DFT. The interaction energies correlated with experimental Kπ values, and with the LUMO energy of the modified MeGua, suggesting that LUMO energies could give a quick estimation of π-stacking energy.

For a more complete understanding of π-stacking interactions, a DFT study of dimers of small aromatic compounds, was undertaken. Although dispersion and electrostatics are known to stabilize π-stacking interactions, the preference for parallel displaced (PD) and or twisted (TW) over sandwich (S) geometry in these dimers is not well understood. Orbital analysis showed that PD or TW structures convert one or more π-type dimer MO with out-of-phase or antibonding inter-ring character at the S to in-phase or binding at the PD/TW structure. The change in dimer MO character was described with stacked bond order (SBO), a term introduced as an analogy to the bond order in molecular orbital theory. The SBO of a S structure is zero, parallel displacement or twisting result in a non-zero SBO and overall bonding character.

Thursday, May 1, 2014 at 10:00 a.m. in DRAGAS 2120