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Project Title: An Atomistic Inquiry into the Driving Forces for Nano-Aggregation and Cluster Formation in Asphaltenes

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Parish Narrative report

In the past year, the Parish laboratory has completed 4 projects, described below. We have also initiated work on 4 new projects related to 1.) aggregation in model asphaltenes, 2.) diradical isomers of pyrazine, 3.) conformational analysis of the JIP1 protein and 4.) diradical isomers of pyridine.

Analysis of MEMO1 Binding Specificity for ErbB2 using Fluorescence Polarization and Molecular Dynamics Simulations. ErbB2 signaling pathways are linked to breast cancer formation, growth, and aggression; therefore, understanding the behavior of proteins associated with these pathways as well as regulatory factors that influence ErbB2 function is essential. MEMO1 is a redox active protein that is shown to associate with phosphorylated ErbB2 and mediate cell motility. We have developed a fluorescence polarization assay to probe the interaction between MEMO1 and an ErbB2-derived peptide containing a phosphorylated tyrosine residue. This interaction is shown to be pH dependent and stronger with longer peptides as would be expected for protein-protein interactions. We have quantitatively mapped the binding interface of MEMO1 to the peptide using the fluorescence polarization assay and molecular dynamics simulations. We have confirmed that phosphorylation of the peptide is essential for binding and through mutagenesis have identified residues that contribute to favorable interactions. Our results highlight the importance of the protein-protein interactions of MEMO1 that complement the oxidase activity. In the future, these studies will provide a method for screening for selective modulators of MEMO1, which will allow for additional biological investigations.

An Extended Multireference Study of the Singlet and Triplet States of the 9,10-didehydroanthracene Diradical. The 9,10-didehydroanthracene is an aromatic diradical produced by the Bergman cyclization of a benzannulated 10-membered enediyne. It is a 1,4 diradical, similar to *para*-benzyne. Here we study the spin state occupancy of the ground state of 9,10-didehydroanthracene by employing multireference methods (MR-CISD and MR-AQCC) with different basis sets (cc-pVDZ and cc-pVTZ) and active space sizes (CAS (2,2) through CAS (8,8)). At the CAS (8,8) MR-AQCC/cc-pVDZ level of theory, we find a two-configurational singlet ground state with an adiabatic ΔE_{ST} of 6.13 kcal/mol. Unpaired electron density populations and dominant electronic configuration interactions were used to analyze the features of the 9,10-didehydroanthracene diradical.

A Computational Study of the Reactivity of 3,5-(oxo/thioxo) Derivatives of 2,7-Dimethyl-1,2,4-Triazepines. Keto-Enol Tautomerization and Potential for Hydrogen Storage. The G4-level of theory has been used to evaluate the acidity of a series of triazepines, i.e. 3-thioxo-5-oxo-, 5-thioxo-3-oxo-, 3,5-dioxo-, and 3,5-dithioxo- derivatives of 2,7-dimethyl-[1,2,4]-triazepine. The ability of their available nitrogen lone pair to form a dative bond with BH_3 has also been studied to highlight the resulting changes in acidity and to understand the behavior of the complexes formed. The effect of the substitution of sulfur by oxygen on the stability of the complex and the activation barrier of dehydrogenation has also been evaluated. The formation of these triazepine: BH_3 complexes, accompanied by the loss of H_2 molecular hydrogen, is a strongly exothermic process. With one triazepine the pathway for H_2 elimination from [triazepine]- BH_3 is characterized by a small energy barrier ranging from 11 to 23 kJ/mol. The second H_2 elimination is relatively more energetic than the first one (approximately 27 kJ/mol). Because of the steric hindrance associated with the addition of two molecules of triazepine (triazepine) $_2$ - BH_2 , the third dehydrogenation step is relatively less favorable than the

two preceding steps particularly in the case of the 3,5-dithio-derivative. The potential energy surface associated with the dehydrogenation reaction of all triazepine derivatives has been explored. The thermodynamic favorability reported in this study could allow triazepine-borane to be used as a material for H₂ storage applications.

An *Ab Initio* Exploration of the Bergman Cyclization. The Bergman cyclization is an important reaction in which an enediyne cyclizes to produce a highly reactive diradical species, *p*-benzyne. Enediyne motifs are found in natural antitumor antibiotic compounds, such as calicheamicin and dynemicin. Understanding the energetics of cyclization is required in order to better control the initiation of the cyclization, which induces cell death. We computed the singlet and triplet potential energy surfaces for the Bergman cyclization of (Z)-hex-3-ene-1,5-diyne using the CCSD and EOM-SF-CCSD methods. The triplet enediyne and transition state were found to have C₂ symmetry, which contrasts with the singlet reactant and transition state that possess C_{2v} symmetry. We analyzed the frontier orbitals of both cyclization pathways to explain the large energetic barrier of the triplet cyclization. Reaction energies were calculated using CCSD(T)/cc-pVTZ single point calculations on structures optimized with CCSD/cc-pVDZ. The singlet reaction was found to be slightly endothermic ($\Delta H_{\text{rxn}} = 13.76$ kcal/mol) and the triplet reaction was found to be highly exothermic ($\Delta H_{\text{rxn}} = -33.29$ kcal/mol). The adiabatic singlet-triplet gap of *p*-benzyne, computed with EOM-SF-CCSD/cc-pVTZ, was found to be 3.56 kcal/mol, indicating a singlet ground state.

Eighteen undergraduate students worked on these and other projects full-time this past summer. Five undergraduates were supported directly on the ACS-PRF grant. This past year, students from the Parish laboratory were responsible for 7 presentations at regional, national and international meetings. Seven of our seniors have graduated; 4 students are pursuing the Ph.D. in chemistry degree; 1 student is working as a laboratory assistant. 1 student is working in public policy and 1 student is pursuing the D.D.S. degree. PI Parish presented 2 invited talks and received the ACS award for Research at Undergraduate Institutions as well as the 2018 State Council of Higher Education for Virginia (SCHEV), Outstanding Faculty Award.