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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 ongoing or new projects related to 1.) aggregation in model asphaltenes, 2.) diradical isomers of furan, 3.) conformational analysis of the JIP1 protein and 4.) diradical isomers of pyridine.

**Diastereoselective Synthesis and Cytotoxic Evaluation of New Isoxazoles and Pyrazoles with Monoterpenic Skeleton.** New series of chiral isoxazoles and pyrazoles with monoterpenic skeleton, have been efficiently synthesized from naturally occurring (R)-Carvone, using 1,3-dipolar cycloaddition reaction with acrylonitrile oxides and diarylnitrilimines. The reaction showed high peri-, and regioselectivity. In the case of diarylnitrilimines, the reaction revealed to be highly diastereoselective. The structure of the newly synthesized adducts were fully established via spectroscopic analysis and X-ray crystallography. A succinct theoretical study was used to explain the diastereoselectivity experimentally observed. All the newly synthesized monoterpenic isoxazole and pyrazole derivatives were evaluated for their cytotoxic activity against human HT1080, MCF-7 and A-549 cancer cells

**A Molecular Dynamics investigation of the Thermostability of Cold Sensitive I707L KlenTaq1 DNA Polymerase and its Wild-Type Counterpart.** *Article featured in the Journal of Chemical Information and Modeling, Women in Computational Chemistry, Special Issue, 2019* DNA polymerase I from *Thermus aquaticus* (Taq DNA polymerase) is useful for polymerase chain reactions because of its exceptional thermostability; however, its activity at low temperatures can cause amplification of unintended products. Mutation of isoleucine 707 to leucine (I707L) slows Taq DNA polymerase at low temperatures, which decreases unwanted amplification due to mispriming. In this work, unrestrained molecular dynamics (MD) simulations were performed on I707L and wild-type (WT) Taq DNA polymerase at 341 and 298 K to determine how the mutation affects the dynamic nature of the protein. The results suggest that I707L Taq DNA polymerase remains relatively immobile at room temperature and becomes more flexible at the higher temperature, while the WT Taq DNA polymerase demonstrates less substantial differences in dynamics at high and low temperatures. These results are in agreement with previous experimental results on the I707L mutant Taq DNA polymerase that show dynamic differences at high and low temperatures. The decreased mobility of the mutant at low temperature suggests that the mutant remains longer in the blocked conformation, and this may lead to reduced activity relative to the WT at 298 K. Principal component analysis revealed that the mutation results in decoupled movements of the Q helix and fingers domain. This decoupled nature of the mutant gives way to an increasingly flexible N-terminal end of the Q helix at 341 K, a characteristic not seen for WT Taq DNA polymerase.

**Diradical Isomers of Pyrazine.** *Article featured in Hanna Riesler Festschrift Virtual Special Issue, Journal of Physical Chemistry A, 2019* Three diradical pyrazine isomers were characterized using highly correlated, multireference methods. The lowest lying singlet and triplet state geometries of 2,3-didehydropyrazine (ortho), 2,5-didehydropyrazine (para), and 2,6-didehydropyrazine (meta) were determined. Two active reference spaces were utilized. The complete active space (CAS) (8,8) includes the  $\sigma$  and  $\sigma^*$  orbitals on the dehydrocarbon atoms as well as the valence  $\pi$  and  $\pi^*$  orbitals. The CAS (12,10) reference space includes two additional orbitals corresponding to the in-phase and out-of-phase nitrogen lone pair orbitals. Adiabatic and vertical gaps between the lowest lying singlet and triplet states, optimized geometries, canonicalized orbital energies, unpaired

electron densities, and spin polarization effects were compared. We find that the singlet states of each diradical isomer contain two significantly weighted configurations, and the larger active space is necessary for the proper physical characterization of both the singlet and triplet states. The singlet–triplet splitting is very small for the 2,3-didehydropyrazine (ortho) and 2,6- didehydropyrazine (meta) isomers (+1.8 and –1.4 kcal/mol, respectively) and significant for the 2,5-didehydropyrazine (para) isomer (+28.2 kcal/mol). Singlet geometries show through-space interactions between the dehydrocarbon atoms in the 2,3-didehydropyrazine (ortho) and 2,6-didehydropyrazine (meta) isomers. An analysis of the effectively unpaired electrons suggests that the 2,5-didehydropyrazine (para) isomer also displays through-bond coupling between the diradical electrons.

**Halogen Bonding Interactions for Aromatic and Non-Aromatic Explosives Detection.** Improved sensing strategies are needed for facile, accurate, and rapid detection of aromatic and nonaromatic explosives. Density functional theory was used to evaluate the relative binding interaction energies between halogen-containing sensor model molecules and nitro-containing explosives. Interaction energies ranged from –18 to –14 kJ/mol and highly directional halogen bonding interactions were observed with bond distances ranging between 3.0 and 3.4 Å. In all geometry optimized structures, the sigma-hole of electropositive potential on the halogen aligned with a lone pair of electrons on the nitro-moiety of the explosive. The computational results predict that the strongest interactions will occur with iodine-based sensors as, of all the halogens studied, iodine is the largest, most polarizable halogen with the smallest electronegativity. Based on these promising proof-of-concept results, synthetically accessible sensors were designed using 1,4-dihalobenzene (X = Cl, Br, and I) with and without tetra-fluoro electron withdrawing groups attached to the benzene ring. These sensing molecules were embedded onto single walled carbon nanotubes that were mechanically abraded onto interdigitated array electrodes, and these were used to measure the responses to explosive model compounds cyclohexanone and dimethyl-dinitrobenzene in nitrogen gas. Amperometric current–time curves for selectors and control molecules, including concentration correlated signal enhancement, as well as response and recovery times, indicate selector responsiveness to these model compounds, with the largest response observed for iodo-substituted sensors

Fifteen undergraduate students worked on these and other projects full-time in this reporting period. Six undergraduates were supported directly on the ACS-PRF grant. This past year, students from the Parish laboratory were responsible for 12 presentations at national scientific meetings. Six of our seniors have graduated; 1 student is pursuing the Ph.D. in computational biophysics; 3 students are doing research as post-baccalaureate fellows, 1 student is working as a laboratory assistant and 1 student is working at a bank in Kenya while applying to PhD programs in mathematics. PI Parish presented the award address for the ACS Research at Undergraduate Institutions 2019 award at the ACS Orlando meeting.