BERGMAN CYCLIZATION OF MALEIMIDE-BASED ENEDIYNES

Travis Greene and Carol Parish*

Department of Chemistry, Gottwald Center for the Sciences, University of Richmond, Richmond, VA 23173

Maleimide-based enediynes have shown pH dependent anti-tumor potential. Typically, cancer cells are more acidic than healthy cells. Wu and coworkers have produced enediynes that display higher function in acidic conditions than in neutral environments. To better understand the pH dependence of enediyne structural changes, we studied the barriers of activation and overall reaction energy of the Bergman cyclization of 26 enediynes. Geometry optimizations of the reactants, transition states, and products were performed with broken symmetry DFT using B3LYP/6-31G*, using the unrestricted functional for diradical systems in the singlet state. Frequency analysis confirmed that all reactants and products were minima on the potential energy surface and that transition states had one imaginary frequency along the mode that connects the reactants to the products. HOMO-LUMO analysis was used to assess through-bond coupling in the products. We find that the energetic profiles explain well the experimental findings on the maleimide enediynes. We also find that that the enediyne moiety is unresponsive to pH-dependent structural changes, however changes to the alkynyl terminal attachments or fused to the ene moiety may provide an avenue for tuning the overall reaction energies and thermodynamics.