Hydride Shuffle: Ab Initio Investigations of the Hydride Transfer Mechanism in Enediyne Keto-Enol Tautomers

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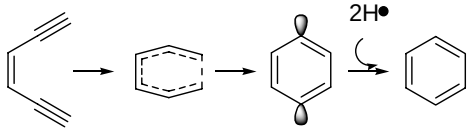
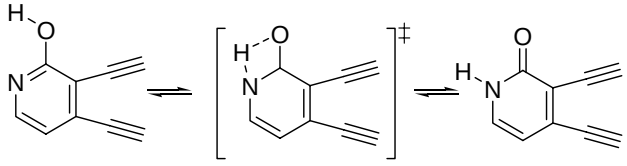
The Bergman cyclization of enediynes has become noted for its potential ability as an anti-cancer agent (Figure 1). This reaction can be synthetically induced by heat or light, but new triggering mechanisms are necessary to create cancer pro-drugs from enediyne analogs.

Figure 1. Bergman Cyclization of an enediyne.



Tautomerization, an essential reaction in many biological processes, is currently being considered as such a trigger. This study focuses on understanding the mechanism of interconversion between the enol- and keto- forms in both 3,4-diethynylpyridin-2-ol and 5,6-diethynyl-pyrimidine-2,4-diol (Figures 2 and 3). Utilizing DFT methods BPW91/cc-pVDZ and BLYP/6-31G*, each prototypic isomerization was calculated in both the gas phase and, using the PCM model, in the presence of DMSO.

Figure 2. Hydride transfer mechanism for 3,4-diethynylpyridin-2-ol.



In addition, 5,6-diethynylpyrimidine-2,4-diol (Figure 3) has two positions in which a hydride transfer will occur. This mechanistic study examines which hydride transfer will first occur.

Figure 3. 5,6-diethynylpyrimidine-2,4-diol. The two hydrogen atoms capable of tautomerizing are in red.