

**Electronic and Steric Characterization of the 5-Endo-Dig Radical Cyclization Reactions:
Engineering a more Reactive Synthesis of Potential Anticancer Eneidyne Compounds**

Jeff Schriber, Alexander Hahn, Diomedes Saldana-Greco, Carol A. Parish
Department of Chemistry, University of Richmond, VA

The 5-endo-dig radical cyclization reactions have been suggested to be involved in key reactions that are significant in synthesizing heterocyclic molecules in synthetic organic chemistry as well as their grave significance in the reaction cascade towards polymerizing enediynes.¹ Eneidyne are extremely potent molecules which, through the well-known Bergman cyclization, can form uni- or multi-radical products involved in the degradation of DNA of cancer cells.

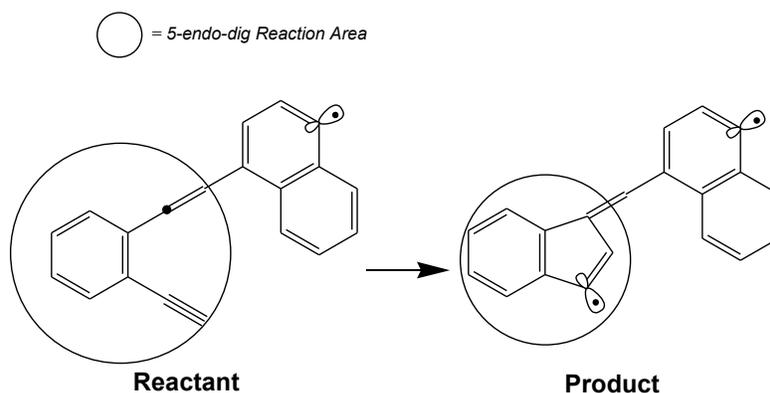


Figure 1. One potential polymerization reaction of a benzannulated enediyne involving the 5-endo-dig reaction.

Since this reaction is favorable toward several enediyne cyclization reactions, such as one depicted in Figure 1, and for other potential uses, this project seeks to engineer the basic 5-endo dig cyclization, utilizing steric effects and concepts of aromaticity, such that the reaction is more energetically favorable towards 5-endo-dig radical cyclization.²

Using DFT calculations with the unrestricted B3LYP functional theory and the 6-31G** basis set, calculations were performed on benzannulated 5-endo-dig reactions (with substitutions to one terminal carbon) to test aromaticity effects on the activation energy barrier and the energy of the reaction. In addition, we applied para-substituted benzannulation to the 5-endo-dig reactions (with substitutions to the same terminal carbon) in order to test steric effects on forcing transition-state-like geometries on the initial reactants.

The aromatic effects play a big role in both lowering activation and reaction energies. In general, an increase in aromaticity in the 5-endo-dig ring increases stability of the product, leading to lower reaction energies. The lowering of the activation energies is due to increased stability of the transition states.

References

- [1] Alabugin, I.V. et al. *Org. Lett.* 2002, 4, 1119
- [2] Wang, *Computational Study of the Energetic Profiles of 5-Endo-Dig Radical Cyclizations.* 2010