The Cyclization and Conformational Variations of Kedarcidin and Neocarzinstatin

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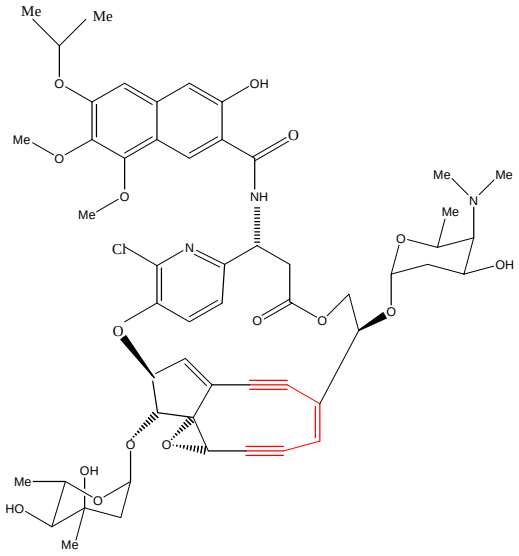
Enediynes are naturally occurring molecules that are often looked to as a solution for combating cancer. Enediyne natural products are found in nature surrounded by strands of peptides or sugars. Once in the presence of DNA, enediynes live up to their warhead nature, readily forming a diradical intermediate by Bergman cyclization. This diradical can then remove two hydrogens from DNA in order to achieve the stable benzene structure, therefore becoming cytotoxic. Since mass production of enediyne drugs is impossible from only naturally occurring enediyne molecules, organic chemists have worked on the total synthesis of a enediynes in order to keep from depleting their natural existence.

Figure 1. The structure of the enediyne natural product, kedarcidin, whose conformational variations and flexibility were studied.



In this work, the flexibility of enediyne molecules has been studied in order to better understand the possible orientations of the molecule as it attempts to insert into DNA. Molecular flexibility was determined by performing Monte Carlo: Low Mode conformational searches on the OPLS2005 force field with the GB/SA continuum solvent model for water used to simulate an aqueous environment.