Quantum Mechanical Analysis of the Effects of Aromaticity on the Rate of Bergman Cyclization of Enediynes

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Enediynes are naturally occurring anticancer agents that are being used as drugs to treat cancer patients; however the relationship between structure and reactivity needs to be more fully understood in order to develop better drugs with improved cell selectivity. This study investigated the role of aromaticity in the Bergman cyclization using three molecules shown below; a benzene-substituted simple enediyne, an anthracene-substituted simple enediyne, and a napthalene-substituted ten-membered enediyne. The energy of the reactants, products, reactive intermediates and transition states associated with the Bergman cyclization were determined using the Jaguar and Gaussian 98 quantum mechanical software packages with the BPW91 functional and a cc-pVDZ basis set. This information will shed light on the role that aromaticity plays in the rate of Bergman cyclization in simple and ten-membered enediynes.

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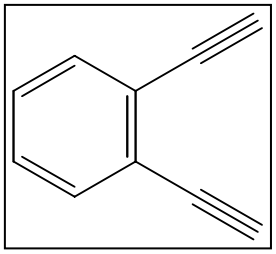

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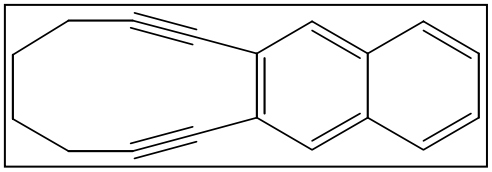

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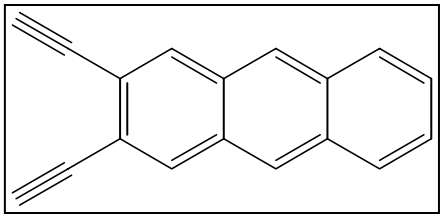

Quantum Mechanical Studies of Enediyne Anticancer Warhead Drugs to Determine the Influence of Tautomerization on Thermal Bergman Cyclization

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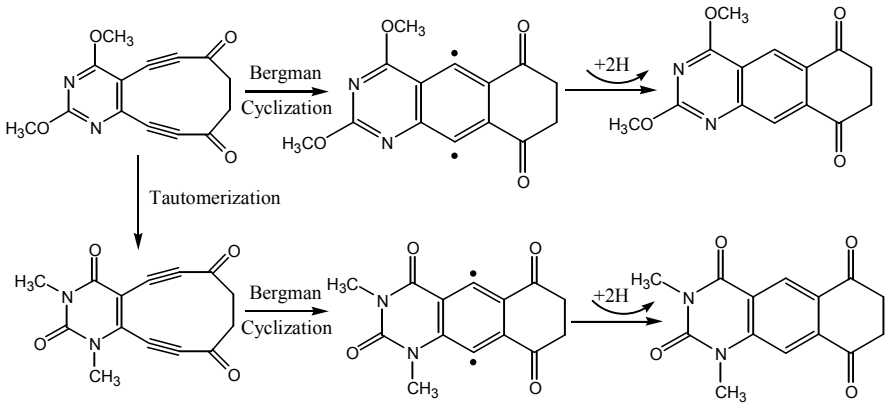
Naturally synthesized anticancer agents, such as Esperamicin A and Dynemicin A are composed of electron rich enediyne groups. This reactive group undergoes a thermal Bergman cyclization, forming a benzyne diradical intermediate that is capable of abstracting hydrogen from nearby DNA. The hydrogen atoms are removed from cancer cell DNA leading to a consequential cytotoxic effect (cell death).

It is essential to understand how various reaction conditions influence the rate of thermal Bergman cyclization. This study focuses on exploring the role of hydroxyl and o-methoxyl keto-enol tautomerization in the Bergman cyclization of simple and ten-membered enediynes using model systems as shown below. The Jaguar and Gaussian 98 quantum chemical software packages will be used to explore the potential energy surfaces of singlet and triplet state enediyne reactants, reactant intermediates and products.



Quantum Mechanical Studies of Enediyne Tautomers

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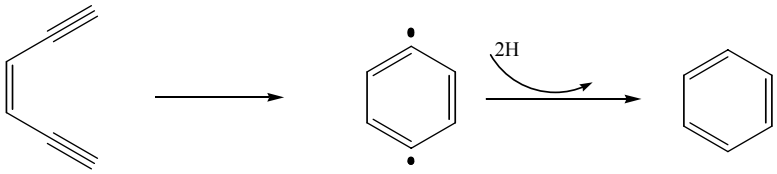
Calicheamicin, dynemicin A, and esperamicin A are naturally occurring anti-cancer warhead drugs. The structure of these molecules is diverse; however, they all contain an electron rich enediyne region that undergoes Bergman cyclization. This electrocyclic rearrangement generates a diradical intermediate that can abstract hydrogen atoms from cancer-cell DNA, resulting in cell death.

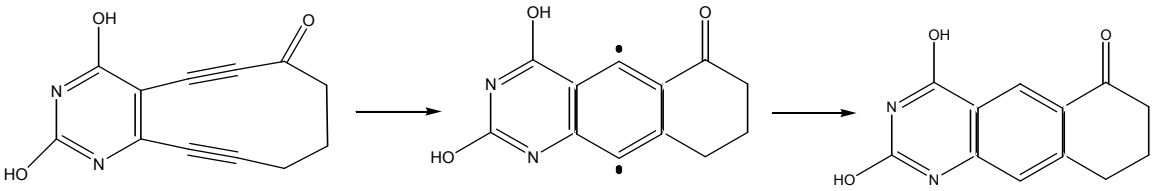
In this work, the effect of tautomerization on the Bergman cyclization of simple and ten-membered enediynes was investigated. *Ab initio* calculations using Jaguar and Gaussian 98 will be presented for the enol and carbonyl tautomeric forms of various nitrogen containing ten – membered rings. The calculations were run with the BPW91 DFT functional and the cc-pVDZ basis set. The energies of the reactant, reactive intermediates at both the singlet and triplet states, and product of each tautomer will be presented. These results will be used to identify the effects of tautomerization and the system with the lowest activation energy for Bergman cyclization.

BERGMAN CYCLIZATION OF A SIMPLE ENEDIYNE



REACTANT REACTIVE INTERMEDIATE PRODUCT

BERGMAN CYCLIZATION OF AN ENOL DINITROGEN TEN – MEMBERED ENEDIYNE



REACTANT REACTIVE INTERMEDIATE PRODUCT

Role of Tautomeric Effects in the Bergman Cyclization of Ten-Membered Endiynes

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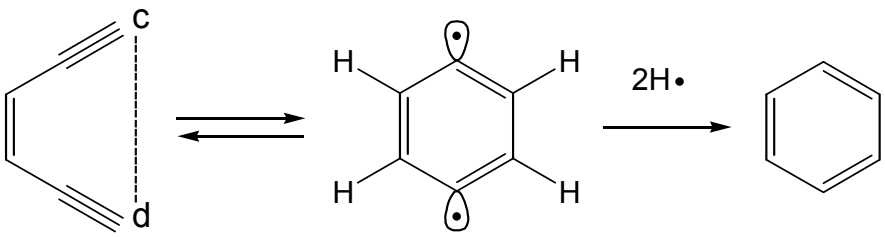
Naturally occurring enediyne antibiotics have been shown to have cytotoxic effects when the enediyne undergoes the Bergman cyclization (Figure 1). The p-benzene diradical intermediate abstracts hydrogens to form a benzene ring. Enediyne molecules with a c-d distance of less than 3.3 Å cyclize at reasonable rates at 37°C; c-d distances of 3.6 Å or greater are stable and do not cyclize. Nine- and ten-membered rings (as seen in naturally occurring enediynes) have c-d distances in the range needed to become active at body temperature. High level a*b initio* calculations were performed using Gaussian98 and Jaguar software on o-methoxy keto and enol tautomers in simple and 10-membered enediynes to investigate structure, stability, cyclization barriers, thermochemistry, and singlet-triplet energy differences in enediynes.



Quantum Mechanical Study of Heteroaromatic Enediynes

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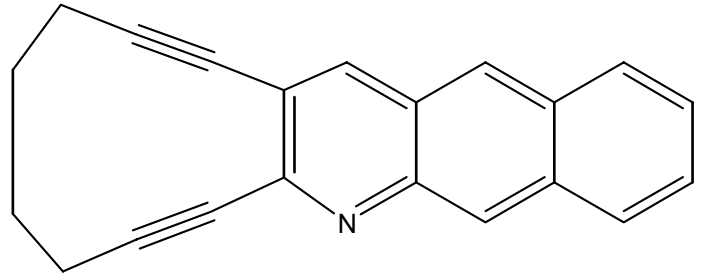
Naturally occurring antitumor drugs such as dynemicin and esperamicin contain an enediyne, which under the correct conditions will undergo a Bergman cyclization. Because of their ability to cyclize and abstract hydrogen from their environment, they have been found to be very effective antitumor prodrugs. This work used the tools of molecular modeling and design to study the kinetics and thermodynamics of the Bergman cyclization of ten-membered hetero-aromatic enediynes. In particular, we used quantum mechanical methods to study the energies and structures of ten-membered heteroaromatic enediynes that are part of larger heteroaromatic systems. These enediynes were subjected to quantum mechanical study using the Gaussian 98 and Jaguar electronic structure software. We calculated and compared the energies of the enediyne reactants (1) , the p-benzyne biradical reactive intermediates (2) and the cyclized products (3).

1



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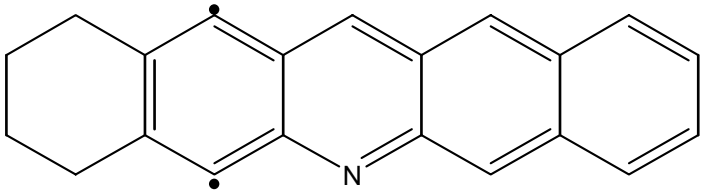

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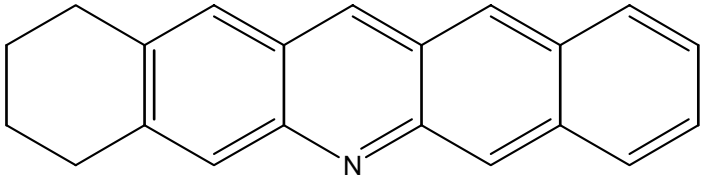

Quantum Mechanical Studies of Heteroaromatic Substitution Effects in Enediynes

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Naturally occurring anticancer agents, such as Dynemicin A, contain reactive, electron rich enediyne moieties. Under the proper conditions, the enediyne group undergoes a Bergman cyclization that results in a p-benzyne diradical that can abstract hydrogen atoms from DNA resulting in cancer cell death. In order to design anticancer agents or other endiynes of biological interest it is important to understand the factors that affect the rate of Bergman cyclization. This study will use quantum mechanical methods to understand how the rate of Bergman cyclization in ten-membered enediynes is influenced by heteroaromatic substitution at the double bond as illustrated in the examples below. Energetics for the reactant, product and reactive intermediate for the corresponding Bergman cyclization will be presented.