

## Bergman Cycloaromatization

### Introduction

The Bergman cycloaromatization is named for Professor Robert G. Bergman who, though not the first to report arene formation from (*Z*)-enediynes, first proposed and proved the existence of the 1,4-aryldiradical intermediate in 1972.<sup>1</sup> After initial mechanistic characterization, the reaction was largely ignored until the discovery of the enediyne class of anticancer antibiotics in the 1980s. In order to design mimics of the natural products, enediyne reactivity needed to be understood.

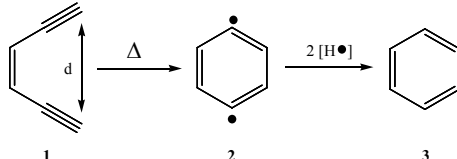


Figure 1 – Bergman cycloaromatization reaction

The cycloaromatization (Figure 1) occurs when a (*Z*)-enediyne is pyrolyzed. A 1,4-benzenediyl (2) is formed and in the presence of a hydrogen donor (usually 1,4-cyclohexadiene) forms an aromatic ring. The diradical is capable of abstracting chlorines from  $\text{CCl}_4$  to produce *p*-dichlorobenzene and, in certain cases, reacting with dissolved  $\text{O}_2(\text{g})$  to form quinones<sup>2</sup>.

Spontaneous cyclization at room temperature is observed when the alkyne termini separation distance (*d*) is 3.4 – 2.9 Å.<sup>3</sup> However, the predictive value of *d* is limited by the lack of a linear relationship between *d* and the activation barrier. Electronics and molecular strain have strong effects on the cycloaromatization.

### Reaction Control

Computational studies of alkynyl substituents were recently conducted by Prall and coworkers<sup>4</sup>. Their work demonstrated that enediynes monosubstituted with  $\sigma$ -accepting or  $\pi$ -donating functionalities have lower cyclization barriers due to interactions with  $\sigma$ -antibonding and  $\pi$ -bonding orbitals in the transition states. Monosubstituted compounds were found to be more thermally reactive than unsubstituted enediynes. In disubstituted systems, the barriers were dependent on the steric hindrance to substituents in the transition states.

Olefinic substituents also affect the Bergman reaction.  $\sigma$ -Donating groups decrease the cyclization barrier while strongly electron-withdrawing groups increase the barrier.  $\pi$ -Conjugation has little effect and most annulations raise or lower the barrier slightly.<sup>5</sup> Benzannulation of the olefinic position also shifts the kinetically important step from cyclization to hydrogen abstraction.<sup>6</sup>

Heteroatoms can be incorporated into the enediyne as well. Protonated aza-enediynes react similarly to all-carbon analogs due to a smaller singlet-triplet energy gap than unprotonated aza-enediynes.<sup>7</sup>

The prevalence of cyclic enediynes in enediyne antibiotics makes them the focus of intense study. The cyclic structures impart strain energy to the system which affects the cycloaromatizations. The half-life for the disappearance of 9-membered ring starting material

upon thermolysis is too short to be measured. However, addition of a methylene to the ring increases the thermal stability enough that the half-life becomes measurable. The thermal stability of 11-membered rings is increased even further.<sup>5</sup>

Incorporation of metal chelating moieties into the structure of an enediyne to form a ligand promotes cyclization at lower temperatures upon metal binding by decreasing the alkyne termini separation distance. Recently, Rawat and Zaleski<sup>8</sup> synthesized a (Z)-N,N'-bis[1-pyridin-2-yl-meth-(E)-ylidene]oct-4-ene-2,6-diyne-1,8-diamine ligand with four sites for coordination by biologically “innocuous” Mg<sup>2+</sup> metal, allowing the reaction to proceed at room temperature.

Oxidation state-induced geometry can be used to alter the d value of an enediyne system, reflected by changes in the cyclization temperature. The Cu(I) complex [Cu(bpod)(py)<sub>2</sub>][PF<sub>6</sub>] adopts a tetrahedral form that allows cyclization at 194°C. Addition of two extra ligands to give the tetragonal octahedral complex [Cu(bpod)(py)<sub>2</sub>](NO<sub>3</sub>)<sub>2</sub> lowers the cyclization temperature to 116°C. Replacement of the pyridyl ligands in the Cu(II) complex with chlorines to give Cu(bpod)Cl<sub>2</sub> leads to dihedral angle distortion and an increase in the temperature to an intermediate 152°C.<sup>9</sup>

Both of the previously described coordination methods require incorporation of heteroatoms into the enediyne system for metal chelation. O'Connor and coworkers<sup>10</sup> have reported the use of a “super-arenophile” Ru complex [(η<sup>5</sup>-C<sub>5</sub>Me<sub>5</sub>)Ru(η<sup>6</sup>-3,4-benzocyclodec-3-ene-1,5-diyne)][OTf] (Figure 2) as both a cyclization accelerator and inhibitor. The Ru is able to complex with the arene ring of benzannelated cyclic enediynes and prevent cyclization, possibly by withdrawing electron density from the conjugated system. Certain substituents on the arene ring appear to block the Ru coordination, allowing the cyclization reaction to proceed at lower temperatures.

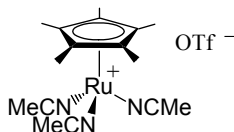


Figure 2 – [(η<sup>5</sup>-C<sub>5</sub>Me<sub>5</sub>)Ru(η<sup>6</sup>-3,4-benzocyclodec-3-ene-1,5-diyne)][OTf]

Methods of triggering a stable enediyne to undergo Bergman cycloaromatization are being developed primarily to aid in the design of mimics of natural products. Anthroquinone tautomers of molecules containing enediynes are known to cyclize faster than their dihydroanthroquinone forms.<sup>11</sup> Use of this redox trigger utilizing biological molecule-enediyne conjugates has been effected.<sup>12</sup>

Photo-induction of a Bergman cyclization was first accomplished accidentally in 1968.<sup>13</sup> The mechanism was not elucidated until 1998 when Evenzahav and Turro<sup>14</sup> proposed that the singlet diradical results in the expected aromatic product while intersystem crossing from the singlet to the triplet state could lead to photoreduction products.

Other triggering strategies, including the release of ring strain,<sup>3b</sup> acid and base-induction<sup>15</sup> and enzymatic protecting group cleavage<sup>16</sup> have also been demonstrated.

## Applications in Synthesis, Materials Science and Biology

Synthetic utility of the Bergman reaction has been severely limited by a lack of understanding about the reactivity of enediyne systems. It has been shown that the aromatization can be linked to a second radical reaction to produce polycyclic systems. Tandem ring annulation has been shown to be a viable one-pot method to produce fused aromatic and saturated rings<sup>17</sup> while Bergman has demonstrated that a double aromatization is possible, albeit in low yield, to form naphthalene.<sup>18</sup> Radical cascades can be induced by cyclization of one enediyne with

cascade initiation in a neighboring enediyne by the diradical intermediate.<sup>19</sup> Also, Bergman cycloaromatization has been used to significantly extend the  $\pi$ -systems of porphyrin rings via appended piceno groups.<sup>20</sup>

Now that synthetic possibilities are being explored, researchers are beginning to consider the Bergman cyclization for their synthetic designs. Butora and coworkers<sup>21</sup> envisioned a synthetic route to the morphine skeleton, but were unsuccessful when a model of the silicon-tethered enediyne they proposed proved thermally stable.

The Bergman cycloaromatization has found uses in materials science. It has been found that cyclic polyynes, driven by the stability of the final product, will undergo repeated Bergman cyclization to form fullerenes.<sup>22</sup> Also, aromatic polymeric materials are under investigation as new resist materials for thin-film lithography where the Bergman cyclization is used to cure the polymer, making it less susceptible to strand-scission under oxygen plasma resist removal conditions.<sup>23</sup>

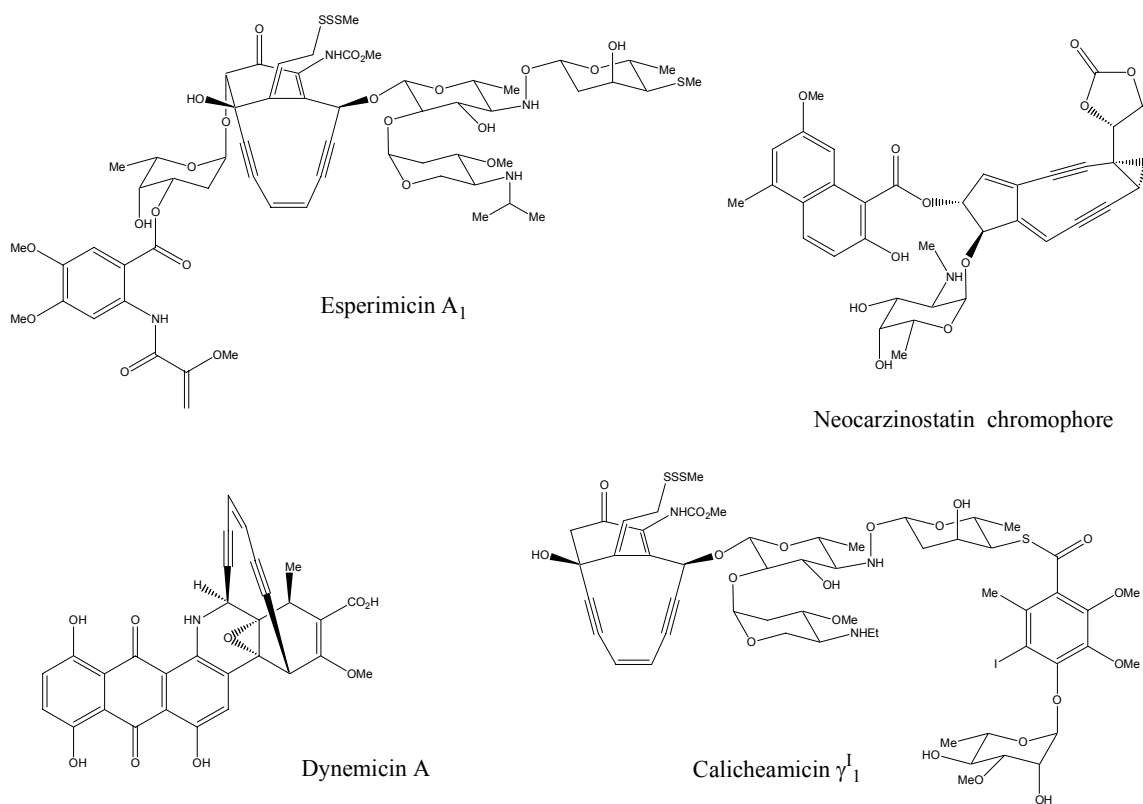
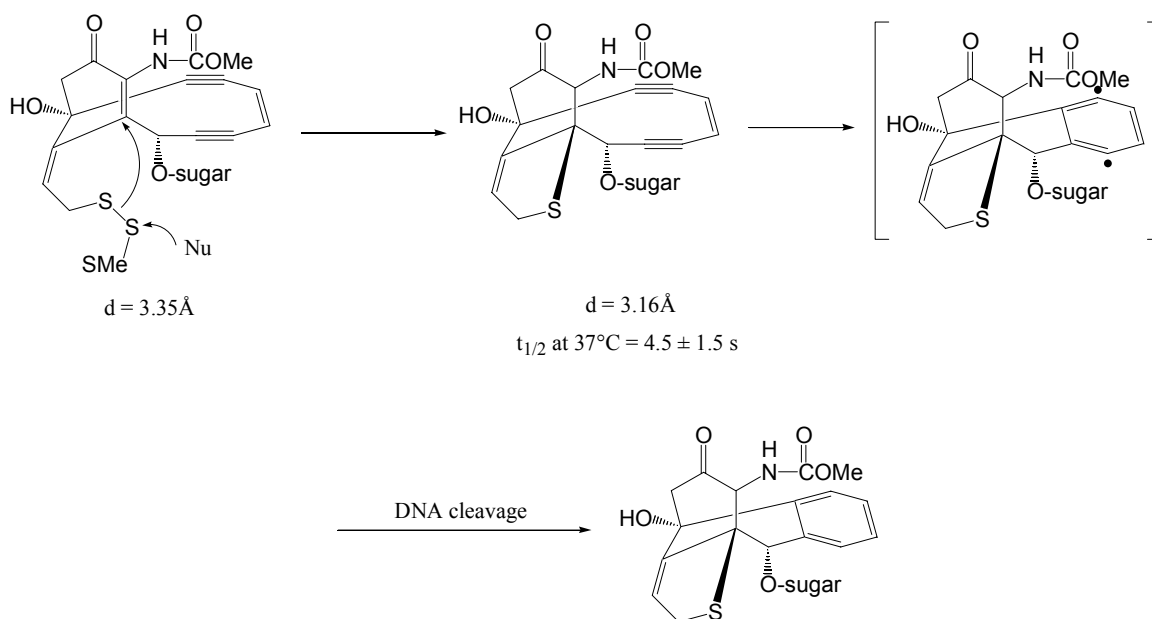


Figure 3 – Enediyne class of anticancer antibiotics

The enediyne class of anticancer antibiotics including calicheamicins, esperamicins, dynamicins, the neocarzinostatin chromophore and several other members (Figure 3) was discovered in the 1980s<sup>24</sup> and was the impetus for renewed interest in the Bergman cyclization. The antibiotics show potent cytotoxicity due to their ability to cleave DNA. The antibiotics share three major components: 1) a structure that targets them to DNA, 2) an enediyne “warhead” that introduces double strand breaks via hydrogen abstraction from the backbone by the diradical formed upon cyclization, and 3) a triggering device that keeps the enediyne stable until it reaches the DNA target. The mechanism for generation of the calicheamicin  $\gamma_1^I$  diradical is shown in scheme 1.<sup>15</sup>



Scheme 1 – Mechanism of calicheamicin  $\gamma_1^1$  activity

Mylotarg<sup>TM25</sup> is an “antibody-targeted chemotherapy” drug designed by Wyeth-Ayerst for the treatment of Acute Myeloid Leukemia. The compound consists of a humanized TgG<sub>4</sub>, kappa antibody conjugated to a calicheamicin derivative. The antibody is used to selectively target calicheamicin to the CD33 antigen (a sialic acid-dependent adhesion protein) on the surface of leukemic myeloblasts and immature normal cells of myelomonocytic lineage, but not healthy hematopoietic stem cells.

Enediynes have been used to damage proteins as well as DNA.<sup>26</sup> Recently, an estrogen-cyclic enediyne conjugate has been used in targeting and selective cleavage of the estrogen receptor.<sup>27</sup>

Jones and coworkers<sup>2</sup> created catalytic antibodies for enediyne cyclization by inoculating mice with a transition state hapten analog. The antibody was shown to produce an unexpected quinone resulting from oxygen reaction with the diradical. Equally unexpected was the finding that the same product was formed in solution with yields proportional to the amount of dissolved oxygen in the buffer. The exact mechanism remains to be elucidated.

Vasella and coworkers<sup>28</sup> attempted to probe the interactions between two saccharide molecules by appending them to the alkynyl positions of a benzannelated enediyne. They hoped that cyclization would bring the two sugars into close proximity. However, upon cyclization, the diradical abstracted hydrogen from the benzylic positions on the protecting groups, resulting in a 10-membered ring via diastereoselective combination of the benzyl radicals.

## Conclusions

The utility of the Bergman cycloaromatization reaction was recognized when the enediyne class of antitumor antibiotics was discovered. Other uses of the reaction were not probed until the reactivity of enediynes was better understood. Now however, applications are seen in synthesis, materials science and biology.

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