Proximity effect in Bergman cyclization: A semiempirical AM1 investigation

A Pramanik* & Sandip Kumar Kundu
Department of Chemistry, Calcutta University, 92 A.P.C. Road, Kolkata 700 009, India
E-mail: animesh@cucr.ernet.in
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Semiempirical quantum chemical methodology (AM1) with limited configuration interactions has been employed to explore the proximity effect in Bergman cyclization process. The energy profiles of the acyclic enediyne (Z)-hexa-1,5-diyne-3-ene 1 and a series of monocyclic enediynes have been determined considering the newly formed C-C bond distance as the reaction coordinate. The theory adequately reproduces the experimentally observed π-bond proximity effect on activation barrier in Bergman cyclization reaction.

The reported antitumor antibiotics, such as Esperamycin1, Calicheamicin2, Dynemicin3 are found to be naturally occurring DNA cleaving agents. It is known that these molecules possess a central enediyne moiety, typically in a cyclic framework. The mechanism of action has been postulated to involve binding of the molecule via its oligosaccharide unit to the minor groove of DNA,4 followed by a suitable activated triggering device (e.g., a nucleophilic attack) which initiates a cascade of reactions that leads to the generation of a highly reactive species5. The critical step is the cyclization of the enediyne moiety to form the 1,4-dehydrobenzene biradical. The biradical is capable of abstracting hydrogen atoms from the sugar unit of DNA, generating a new radical, which undergoes oxygenation under aerobic condition leading to cleavage. It is evident that the DNA cleaving ability of this class of antitumor antibiotics is crucially controlled by the ease of formation of the 1,4-biradical in these systems.

The key cyclization process mentioned above has been known in organic substrates for over two decades. Bergman et al.5,7 have reported that (Z)-hexa-1,5-diyne-3-ene 1 undergoes a thermal degenerate rearrangement (Scheme I) via a cyclic biradical intermediate 2 with a new C₂ symmetry axis. Typically, the cyclization of an enediyne system requires substantial activation energy. For example, Bergman found that the degenerate rearrangement of the parent enediyne molecule, (Z)-hexa-1, 5-diyne-3-ene 1 takes place at 200°C in a sealed tube. The activation barrier has been evaluated to be 32 kcal/mol.6 It is therefore remarkable that a similar cyclization in the naturally occurring cyclic enediyne compounds is found to be efficient at body temperature indicating an activation enthalpy as low as around 20 kcal/mol. A major challenge to the understanding of the activity of the natural antitumor antibiotics as also for the design of new classes of molecules which cleave DNA by a similar mechanism is the determination of factors which control the activation barrier for the Bergman cyclization process.

On the basis of studies of Bergman cyclization in various simple monocyclic conjugated enediyne systems, Nicolaou et al.7,8 have concluded that the ease of the reaction critically depends on the distance between the two terminal carbon atoms of the reacting π-bonds. By the combined use of MM2 and PRDDO-GVB-CI methods in conjunction with experimental studies on model systems, Magnus and Synder8,10 have proposed that the differential molecular strain in the ground state and the transition state is the determining factor for the rate of cyclization. A smaller increase in strain would lead to a reduced overall activation barrier. Some more theoretical studies have been carried out with ab initio11 and semiempirical12 (MINDO/3 and MNDO) methodologies for the parent system 1. A hybrid molecular mechanics/semi-
Empirical methodology and Density functional theory (DFT) have been employed for some monocyclic enediyne systems. However, the use of most popular and reliable semiempirical methodology AM1 remains unexploited.

**Systems examined**

Here we have carried out MO calculations using AM1 methodology focussing on the geometric and energetic changes along the reaction profile for various monocyclic enediyne systems along with the parent cyclic system 1. The monocyclic enediyne 3 to 6 (Scheme II) have been studied in which the distance (Rgs) between the cyclizing centers are varied by connecting the two triple bond of 1 with an appropriate saturated -(CH2)n-bridge. We have also made a comparative study about the performance of AM1 methodology with respect to other reported geometric and activation parameters.

**Computational Details**

The use of AM1 method offers several advantages for examining a large series of substrates, especially when biradicaloid structures are involved. We have chosen to do full geometry optimization on the potential energy surface and characterize their Hessian indices at the AM1/RHF level. In order to obtain more realistic energetics estimates, subsequent single point calculations have been carried out using the singles and pair excitation configuration interaction (PECI=8) scheme. Since the reaction involves the conversion of two in-plane \( \pi \)-bonds to a \( \sigma \)-bond (Figure 1) and another doubly filled MO (HOMO of the biradicaloid), configuration interaction among the corresponding four bonding and antibonding MO's need to be taken into account, for a minimal level of accuracy. We have included four additional MO's in the CI calculations because the out of plane \( \pi \) and \( \pi^* \) orbitals have energies close to the orbitals of interest. The corresponding results are denoted as PECI=8 data.

The determination of potential energy surface at the RHF level was carried out in the usual way by considering the newly formed bond distance between the two reacting \( \pi \)-bonds as the reaction coordinate. In view of the importance of the proximity criterion in determining the activation barrier, the variation in the distance between the reactive sites of the diynes in the reactant, transition state and the product are provided in the Table I. The heats of formation of the key stationary points computed at the RHF as well as PECI=8 levels are given in Table II. These data have been used to obtain the activation enthalpies and heats of reactions summarized in Table III.

**Results and Discussion**

Energy profile for (Z)-hexa-1,5-diyne-3-ene 1. The energy profile of Bergman cyclization for the unsubstituted enediyne molecule 1 computed at the AM1/RHF level corresponds to the previous
semiempirical\textsuperscript{12} and \textit{ab initio}\textsuperscript{11} studies. The transition state smoothly connects the reactant 1 and the 1,4-dehydrobenzene(D\textsubscript{2h}) have the expected Hessian index of 1 and 0, respectively. The separation between the terminal carbon atoms of the diyne is very large in the reactant, 4.40 Å (Table I). This distance is brought down quite substantially in transition state. In fact the newly formed C–C bond distance, R\textsubscript{gs} (1.74 Å), in the transition state is close to that in the product (1.47 Å). The product like geometry of the transition state is consistent with the endothermicity of the reaction and Hammond postulate\textsuperscript{18}.

The AMI/RHF computed heat of formation of the transition state is 172.0 kcal/mol (Table II), which reduces to 152.0 kcal/mol on inclusion of configuration interaction at the AMI/PECI=8 level. This variation indicates that the transition state is a biradical species. The product also shows a similar energy pattern (Table II), consistent with its expected biradical character.

At the AMI/RHF level, the AMI procedure significantly overestimates the enthalpy of activation of Bergman cyclization of 1 (Table III). However, the AMI/PECI=8 calculated value of 38.4 kcal/mol is reasonably close to the experimental value of 32.0 kcal/mol. The AMI/PECI=8 calculated heat of reaction, 19.7 kcal/mol (Table III), is also slightly higher than the experimental value of 14 kcal/mol. Interestingly, the performance of AMI/PECI=8 methodology is superior to that of other semiempirical procedures\textsuperscript{12} and in fact is as good as that of the highest level \textit{ab initio} calculation carried out so far\textsuperscript{11}. The procedure is indicated to be well suited for studying the energetics of Bergman cyclization.

Analysis of the MO’s of the transition state and the biradicaloid intermediate shows that both have an antisymmetric (A) HOMO and a symmetric (S) LUMO, consistent with the qualitative description (Figure 1). The orbital energies of antisymmetric HOMO and symmetric LUMO of the biradical intermediate, 1,4-dehydrobenzene 2, were found to be -8.4 and -1.7 eV, respectively, at the AMI level. Even allowing for the usual underestimation of the energies of unfilled orbitals by SCF procedures, the calculated energy separation is fairly large. The system is best termed as a biradicaloid rather than that as a biradical.

Energy profiles for monocyclic enediynes 3–6. The nature of energy profiles computed at AMI/RHF level, for Bergman cyclizations of the enediynes, 3 to 6, are similar to that of 1. All the reactions are one-step process and the transition states are found to be uniformly product like. Although the R\textsubscript{gs} values vary over a wide range, from 4.40 to 2.78 Å, the new C–C bond in the transition state is formed to nearly the same extent, 1.72–1.68 Å. The R\textsubscript{gs} values are quite close to the corresponding lengths in the 1,4-biradical products, 1.47–1.53 Å (Table I). In view of the negligible variation in the key distance in the transition state structures, the activation enthalpy is likely to be determined by the large differences in the terminal atom distances in the reactants. A large separation implies a great degree of geometric distortion to attain
the transition structure and hence a large activation barrier. The above expectation is fully borne out by the computed energetics. Using the more reliable AM1/PECI=8 heats of formation of the transition states (Table II) for the enediynes, 3 to 6, a dramatic reduction in the activation enthalpies is found as the separation between the carbon atoms forming the new C–C bond becomes smaller (Table III).

On going from the acyclic enediyne, 1 to the monocyclic derivative 5, enclose in a 11-membered ring, the reactive carbon atoms are brought together from 4.40 to 3.59 Å. However, the separation is apparently still large, as 5 is computed to have an enthalpy of activation of 38.9 kcal/mol at the AM1/PECI=8 level of cyclization similar to the value obtained for 1. The result is consistent with the experimentally observed stability of 5 at 25°C. The previously reported values of enthalpy of activation for Bergman cyclization of 5 is 35.9 kcal/mol at MM2/PRDDO level. When the carbon atoms forming the new C–C bond are held at a shorter distance of 3.24 Å, as in 4 the computed enthalpy of activation is significantly reduced by 6 kcal/mol to 32.9 kcal/mol at the AM1/PECI=8 level (Table III). Experimentally, the reduction in Bergman cyclization barrier on going from 1 to 4 is about 8 kcal/mol. Consistent with this trend, the activation enthalpy is computed to be reduced further for 6. However, no experimental study has been carried out for this substrate. Further along this series, the monocyclic enediyne 3 with a remarkably short Rgs (2.78 Å at the AM1 level) is calculated to have the least barrier for cyclization, 22.1 kcal/mol (Table III). This molecule has been experimentally found to undergo spontaneous Bergman cyclization at 25°C.

The above comparisons suggest that the AM1/PECI=8 computed activation for Bergman cyclization for various enediynes are generally reasonable. It is evident that the theory adequately reproduces the experimentally observed π -bond proximity effect on activation barrier in Bergman cyclization reaction. Therefore, this methodology can be used predictively to analyse the energy profiles for related cyclisation of new designed enediyne systems.

It is interesting to point out that the symmetry of the AM1/RHF computed MO’s of the transition state and 1,4-biradicaloid intermediates involve in the Bergman cyclization of the monocyclic enediynes confirm to the pattern obtained for the acyclic system. The HOMO is antisymmetric in the case of the enediynes 4 and 5, while it is pseudo-antisymmetric in the case of the enediynes 3 and 6.

Conclusions

AM1 calculations with limited CI (PECI=8) have been used to obtain reliable activation parameter for Bergman cyclization of acyclic 1 and cyclic enediyne systems 3–6. The results confirm the important role of the proximity effect. As the two in plane π – bonds are brought closer by enclosing the enediyne moiety in a ring, the strong four electrons destabilization is significantly in the ground state of the reactant geometry itself. As a result, the activation barrier for Bergman cyclization decreases remarkably, as in the case of 3 (Table III).

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References


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