The electronic factor in Bergman cyclization

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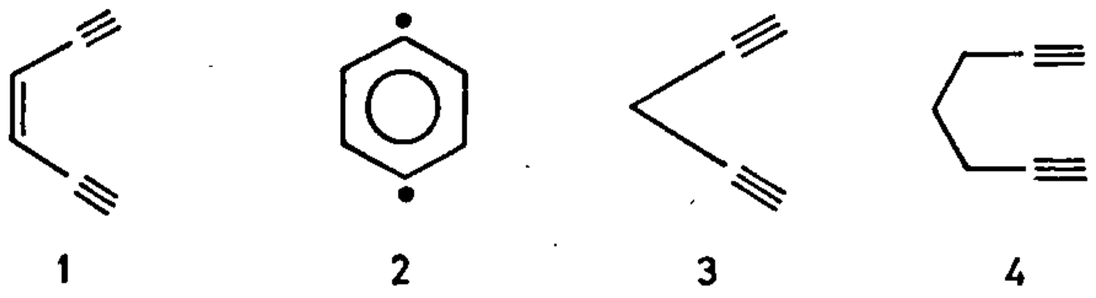
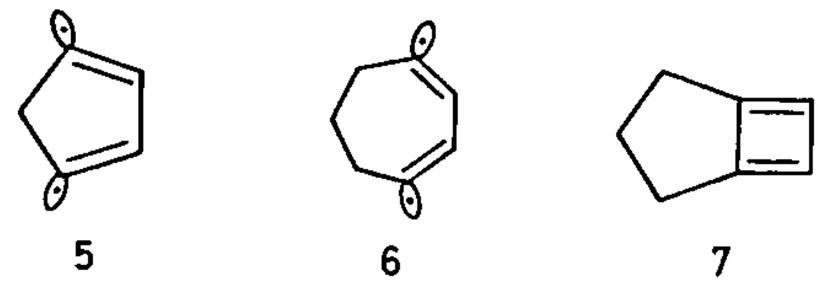
Through-bond interactions in 1,4-dehydrobenzene preferentially stabilize the out-of-phase combination of the radical hydrids. The resultant splitting between the frontier orbitals is crucial in making Bergman cyclization a symmetry-allowed process. Orbital symmetry also inhibits the radical centers from forming a C–C bond, enabling the biradical to survive as a local minimum capable of intermolecular hydrogen abstraction. Both these factors, which are important in the design of DNA cleaving molecules, are confirmed through calculations on biradicals formed from diynes in which through-bond interactions stabilize the in-phase combination of hybrids at the radical centers.

BERGMAN cyclization[1–4] has been implicated as a key process determining the activity of enediyne class of antitumour antibiotics. Cycloaromatization of the enediyne and hydrogen abstraction by the resultant biradical have been suggested to be responsible for the DNA cleaving capability of these compounds[5]. In the design of analogues, considerable effort has been expended in determining and controlling the factors contributing to the ease of the cyclization step. Reducing the distance between the terminal carbon atoms of the diyne and build-up of strain in the reactant are two strategies which have been successfully employed[6]. Based on MO calculations, we now propose that an electronic factor also plays a crucial role in Bergman cyclization (**1** → **2**) and in related processes involving **3** and **4**.

With aromaticity providing a favorable thermodynamic driving force, the formation of a biradical may appear to be a trivial transformation requiring no orbital symmetry control. However, an analysis of the symmetries of the MOs that are involved in the electronic reorganization is revealing (Scheme 1). The in-plane π MOs of the diyne, **1**, form a pair of symmetric and antisymmetric combinations. Since the newly formed C–C bond is symmetric with respect to the mirror plane conserved in the cyclization process, it is essential that the HOMO of the biradical, **2**, be an antisymmetric combination of the hybrid orbitals ($n_1 - n_2$) at the formal radical centres for the reaction to be electronically allowed[7]. While symmetry arguments are usually not valid for biradicals in view of the near degeneracy of frontier orbitals, species such as 1,4-dehydrobenzene are exceptional. As proposed earlier in related systems[8–10], strong through-bond interactions with ring C–C σ and σ^* orbitals result in substantial splitting between the symmetric and antisymmetric combinations in favour of the latter. The filled orbital interaction destabilizes the $n_1 + n_2$ MO while participation of the C–C σ^* orbitals reinforces the separation by stabilizing the antisymmetric combination. *Ab initio* calculations confirm the relatively large energy separation between the frontier orbitals. Even after making allowance for the fact that virtual orbital energies are overestimated at the Hartree–Fock level, the separation of 6.7 eV computed at the HF/6-31G* level is quite large for a biradical. Consistently, the configuration in which the $n_1 - n_2$ MO is doubly filled makes the dominant contribution in the CASSCF wave function (square of the coefficient $|c|^2$ is 0.63 and not 0.50 expected for a perfect biradical)[7,11–13]. Thus, through-bond interactions are crucial for making

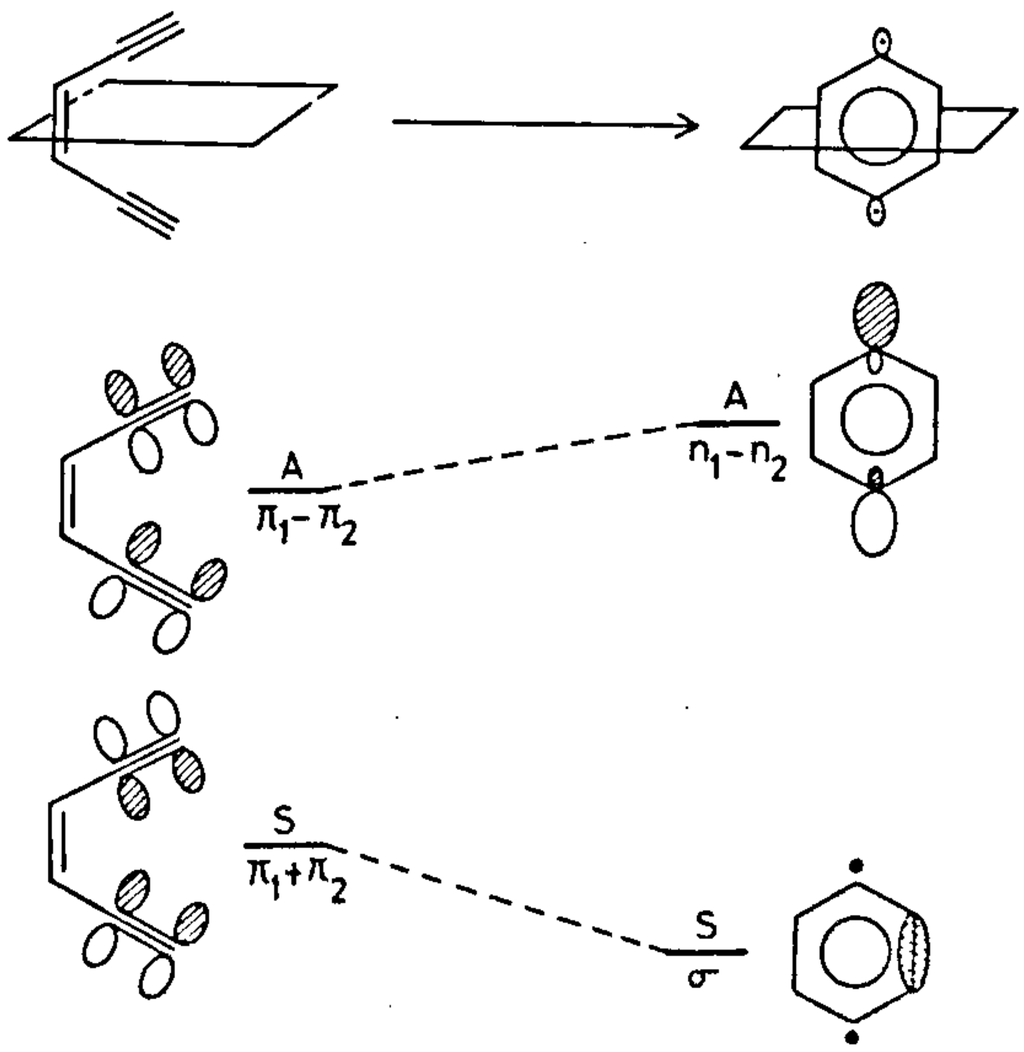


1 **2** **3** **4**



5 **6** **7**

Scheme 1



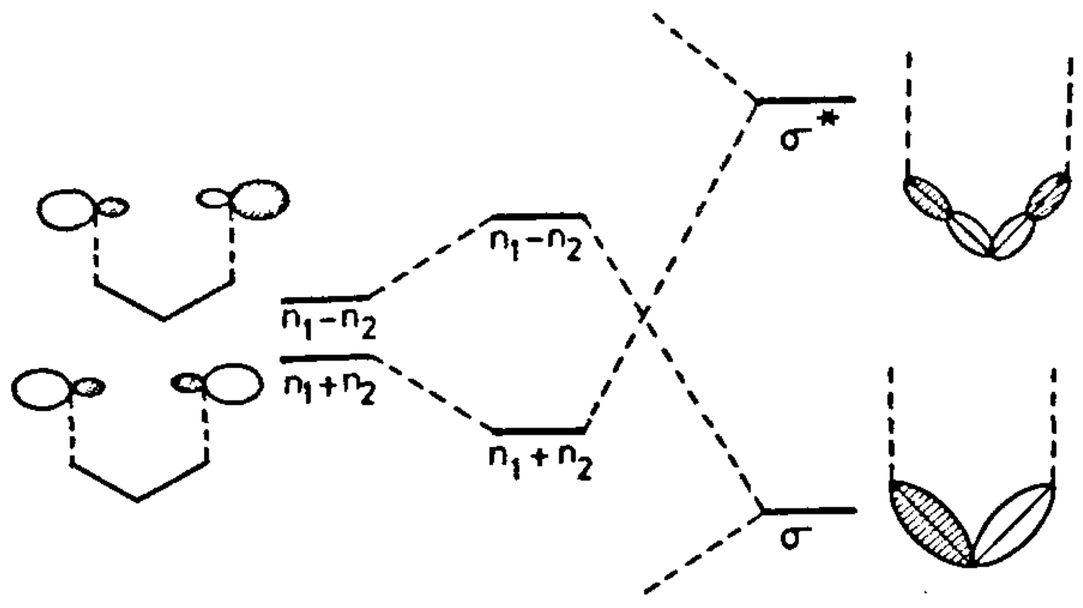


Figure 1. Frontier orbital splitting in a biradical induced by through-bond interactions involving a propano bridge.

Bergman cyclization an electronically allowed process. The antisymmetric nature of the HOMO also ensures that the biradicaloid does not readily form a new C–C bond. The species survives as a bond stretch isomeric minimum[14] and hence is capable of abstracting hydrogen atoms. Thus, both features of critical importance in the DNA cleaving capability of enediyne antibiotics are ensured by through-bond interactions.

Confirmation of the role of through-bond interactions was sought by examining the potential energy surfaces in Bergman-like cyclizations in model diynes, **3** and **4**, in which the number of intervening σ bonds is altered. Photoelectron studies on non-conjugated dienes[15–17] have established that odd number of intervening σ bonds lead to opposing through-space and through-bond effects. In contrast, even number of σ bonds lead to orbital splitting which reinforce each other in favour of the symmetric combination of π MO's. The same trend may persist in biradicaloids. For example, a propano bridge may be expected to stabilize the symmetric combination $n_1 + n_2$ as a result of both through-space and through-bond interactions (Figure 1).

The electronic structures of the cyclized biradicaloids derived from **3** and **4** computed using AM1 (ref. 18) and *ab initio* procedures with the 6-31G* basis set[19] confirm the above analysis. In contrast to **2**, the biradicaloids **5** and **6** have a symmetric HOMO (frontier orbital gap of 9.0 and 8.6 eV at the HF/6-31G* level). The corresponding doubly-filled configuration makes the dominant contribution to the MCSCF wave function ($|c|^2 = 0.77$ and 0.59 in **5** and **6**, respectively). Hence, cyclization of diynes **3** and **4** to the biradicals **5** and **6**, respectively, are electronically forbidden. As a direct consequence, the potential energy surfaces connecting **3** and **4** to the corresponding biradicals, with the distance between the terminal carbon atoms as the assumed reaction coordinate, are calculated to have sharp discontinuities at the RHF level. Examination of the PE surface near the product region led to a transition state only 2.3 kcal mol^{-1} (AM1) higher in energy. Interestingly, this structure corresponds to the transition state leading to the formation of the bicyclic diene, **7** and not of **4**. The preference of the biradical **6** to form a new C–C bond is again a result of the symmetric nature of the HOMO. Thus, orbital symmetry fundamentally alters the nature of the PE surfaces in these systems.

In summary, Bergman cyclization is to be viewed as an important addition to the list of biradicaloid processes in which orbital symmetry plays a key role[20]. Through-bond interactions and orbital symmetry should not be overlooked while designing synthetic analogues of enediyne type DNA cleaving molecules.

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