Enediyne Dimerization vs Bergman Cyclization

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Ⓢ *Supporting Information*

ABSTRACT: High-level quantum chemical calculations reveal that the dimerization of enediynes to 1,3-butadiene-1,4-diyl diradicals is energetically more favored than the corresponding Bergman cyclization of enediynes. Moreover, the activation barrier of both reactions can be drastically reduced by the introduction of electron-withdrawing substituents like fluoro groups at the reacting carbon centers of the triple bonds.
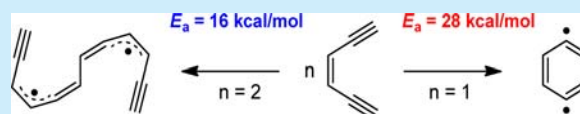
The Bergman cyclization[1] of enediynes is a very attractive method to generate highly reactive diradical intermediates en route to new aromatic rings. The parent cyclization of (Z)-hex-3-ene-1,5-diyne to 1,4-didehydrobenzene occurs at temperatures over 473 K (Scheme 1a). This temperature is necessary to overcome the electron repulsion of the filled in-plane alkyne π orbitals.[2] The resulting 1,4-didehydrobenzene represents a reactive 1,4-diradical intermediate and can, for example, irreversibly abstract hydrogen atoms from an appropriate donor to produce benzene.[3] Interest in the Bergman cyclization increased rapidly due to the discovery of the enediyne family of natural antitumor agents, such as calicheamicin and esperamicin.[4] These antibiotics employ Bergman cyclization to abstract hydrogen atoms from DNA, leading to double-strand cleavage.[5]

Scheme 1. Bergman Cyclization (a) and Transannular Ring Closure of Cyclic Diynes (b)
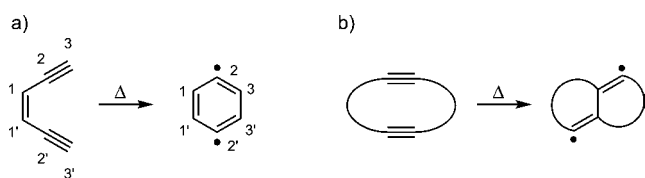
Nicolaou et al. found a relation between the critical internuclear distance of the carbon–carbon bond (C3–C3′ in Scheme 1) and the cyclization barrier.[6] Therefore, most strategies to decrease the activation barrier have tried to bring the ends of the triple bonds close enough to react.[7] This distance can be influenced, for example, by ring size if the acetylene units are connected through a larger cycle. Besides the use of steric strain, some effort has also been invested in activating the Bergman cyclization by electronic contributions.[8] Interestingly, in most of these studies, the influence of substituents, which were not directly bound to the reacting centers of the enediyne units (C3 and C3′ in Scheme 1), has been investigated.[9]

Sondheimer[10] and Gleiter[11] have shown that conjugated and nonconjugated cyclic diynes undergo a transannular ring closure if the two parallel oriented alkyne units are located in close proximity (Scheme 1b). The intermediately formed 1,3-butadiene-1,4-diyl unit irreversibly abstracts hydrogen atoms from an appropriate donor leading to a bicyclic compound. Recently, we were able to demonstrate that electron-withdrawing groups attached to the triple bond reduce the activation energy of alkyne dimerization reactions considerably and stabilize the corresponding 1,3-butadiene-1,4-diyl intermediates.[12]
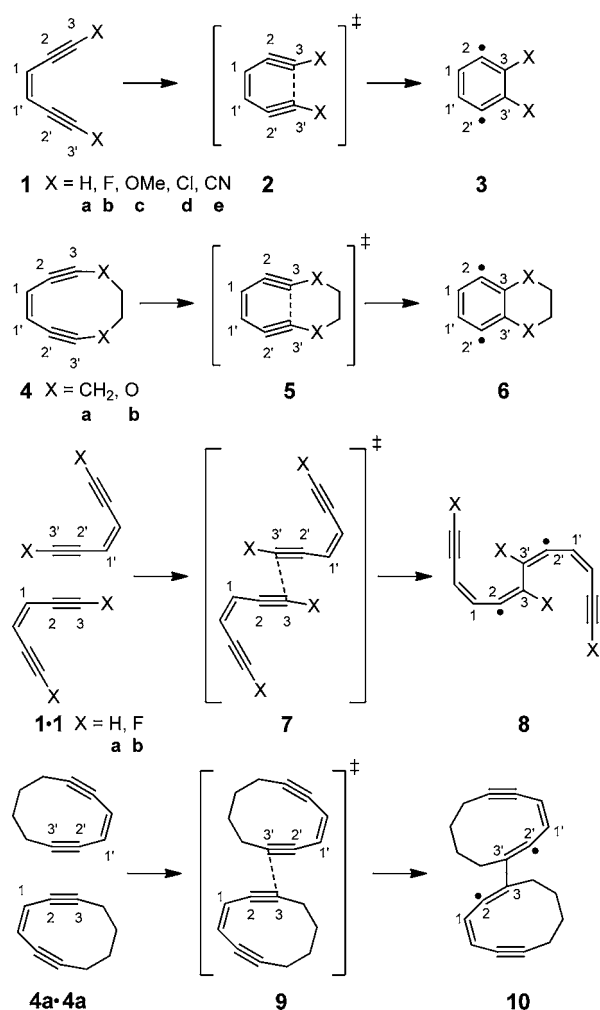
This encouraged us to investigate the dimerization of enediynes in order to compare it with the Bergman reaction (Scheme 2). To determine the dependency of both reactions on substituents, enediynes having electronegative substituents such as fluoro, chloro, methoxy, and nitrile groups attached to the triple bonds were investigated. The Bergman reaction has already been investigated by various authors using a variety of quantum-chemical methods ranging from MRDCI, CCSD(T), and UDFT to CASSCF or CASPT2 calculations.[13] Recently, we used the double-hybrid method B2PLYPD by Grimme[14] for the thermal cyclization of 1,6-cyclodecadiyne to its corresponding diradical.[12a] As the values obtained by this method show a very high consistency to experimental data,[15] we employed this approximation to optimize the stationary points for the Bergman reaction and the dimerization of the enediynes 1 and 4 (Table 1 and Figure 1). The 6-31G* basis set has been used.

The thermodynamic parameters of the Bergman cyclization of (Z)-hex-3-ene-1,5-diyne (1a) have been investigated experimentally in kinetic studies by Roth et al.[16] The activation enthalpy ($\Delta H^{\ddagger}$) was determined to be 28.2 ± 0.5 kcal/mol in gas phase at 470 K. For the reaction enthalpy, a value of 8.5 ± 1.0 kcal/mol was obtained.[16] A comparison of these experimentally determined values with the data calculated by means of B2PLYPD/6-31G* ($\Delta E^{\ddagger} = 28.0$ kcal/mol and $\Delta E = 9.2$ kcal/mol, Table 1) reveals a good agreement.

A comparison of the activation and reaction energies for the Bergman reaction of the enediynes 1 and 4 shows that the substituents bound to the carbon atoms of the triple bonds have a big influence on the reaction parameters (Table 1 and Figure 1). If the terminal hydrogen atoms of the alkynes are replaced by CN

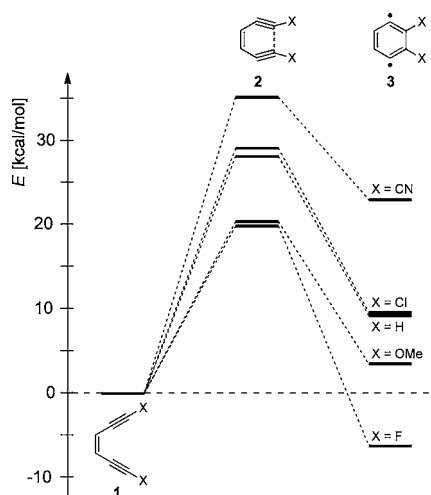## Scheme 2. Bergman Cyclization and Dimerization of the Enediynes 1 and 4

Figure 1. Energy profiles for the Bergman cyclization of **1** calculated using B2PLYPD/6-31G*.

electronegative elements.[17] Accordingly, fluoroalkynes are among the most unstable functionalities due to their unfavorable hybridization in the C−F bond.[9c,17,18] A rehybridization facilitates the Bergman cyclization of **1b**.[9c] With activation barriers of about 20 kcal/mol the cycloaromatization reaction of **1b** and **1c** should proceed spontaneously at ambient temperature. Analogous to the noncyclic enediynes, the activation energy of the dioxacyclic enediyne **4b** (16.7 kcal/mol) is lower by ca. 8 kcal/mol than that calculated for the carbocyclic enediyne **4a** (24.4 kcal/mol). Here again a spontaneous cyclization would occur even at ambient temperature.

If we now compare the B2PLYPD/6-31G* values for the two competing reactions, it is found that the activation energies for the dimerization are by 12 to 15 kcal/mol lower than those for the Bergman cyclization. For example, the E_a value for the cyclization of **1a** amounts to 28.0 kcal/mol (Table 1 and Figure 2). For the corresponding dimerization the activation energy was calculated to be only 15.7 kcal/mol. The same holds for the reaction energies. The dimeric butadienyl diradicals are always more stable than the corresponding didehydrobenzenes. The observed range of variation is considerably high. While the

Table 1. Relative Energies (ΔE in kcal/mol) of the Transition States and Diradicals

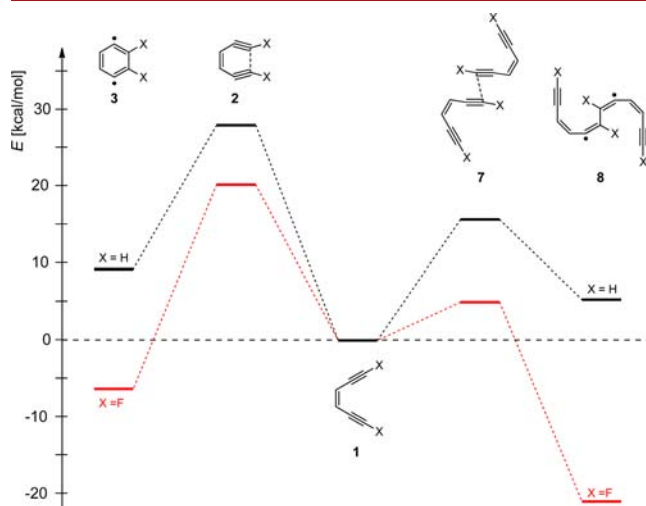|		transition state		diradical	
diyne		ΔE^a	ΔE^b	ΔE^a	ΔE^b
1a	H	28.0	29.9	9.2	14.3
1b	F	20.3	22.9	−6.2	−2.1
1c	OMe	19.8	24.0	3.4	8.1
1d	Cl	29.0	30.8	9.2	12.7
1e	CN	34.9	37.1	22.9	26.5
4a	CH₂	24.4	26.8	9.9	14.1
4b	O	16.7	19.6	−2.7	2.2
1a·1a	H	15.7	17.8	5.2	9.9
1b·1b	F	4.9	6.6	−21.2	−18.7
4a·4a	CH₂	9.3	11.1	0.9	3.9

^{a}B2PLYPD/6-31G*. ^{b}B2PLYPD/def2-TZVP//B2PLYPD/6-31G*.

groups (**1e**), both the activation barrier and the reaction energy are increased compared to the parent compound **1a**. The introduction of chlorine does not lead to any distinct changes of the energies. The introduction of fluoro and methoxy groups leads to a decrease of the activation barriers and reaction energies which was already found by BLYP/6-31G* calculations.[9c] This behavior can be explained by the Bent's rule which states that atoms direct hybrid orbitals with more p-character toward more

Figure 2. Energy (ΔE) for the Bergman cyclization (left) and the dimerization (right) of **1a,b** calculated using B2PLYPD/6-31G*.

difference between **3a** and **8a** amounts to 4.0 kcal/mol, a value of 14.9 kcal/mol is found for the difference between **3b** and **8b**. The fluoro-substituted diradical **8b** is much more stable than the corresponding starting material **1b·1b**. This means that, if only the energetic aspect of the competing reaction is taken into account, the dimerization is by far more preferred than the Bergman cyclization. The higher activation barriers for the Bergman reaction are due to the fact that syn-arrangement of the interacting orbitals suffers from additional four-electron destabilization.[9d] The p-benzynes **3** are aromatic, whereas the radical centers in the dimers **8** can enjoy allylic stabilization. Similar effects were found when comparing the Bergman reaction with the cyclizations of enyne−allenes.[9d,19]

The consideration of the entropy leads to a different picture (Table 2): The Gibbs free energies $\Delta G^{\ddagger}$ (T = 298.15 K, p = 1.000

Table 2. Distances R of C3−C3′, Relative Energies (ΔE), Gibbs Free Energies (ΔG), and Occupation Numbers for the Linear Combinations of the Nonbonding Orbitals n_1 and n_2 of 2a, 3a, 7a, and 8a

	2a	3a	7a	8a
R(C3−C3′)[a] (Å)	2.01	1.45	1.90	1.48
R(C3−C3′)[b] (Å)	1.92	1.41	1.84	1.48
ΔE^{a} (kcal/mol)	28.0	9.2	15.7	5.2
ΔE^{c} (kcal/mol)	29.9	14.3	17.8	9.9
ΔE^{d} (kcal/mol)	30.0	10.6	21.3	10.3
ΔE^{e} (kcal/mol)	45.0	30.8	32.6	13.1
ΔE^{f} (kcal/mol)	23.0	1.7	10.8	1.0
$\Delta G_{289}{}^{a}$ (kcal/mol)	29.1	13.8	28.7	19.4
$n_1{}^{e}$	1.729	1.224	1.670	1.106
$n_2{}^{e}$	0.276	0.776	0.336	0.895

[a]B2PLYPD/6-31G*. [b](10/10)CASSCF/6-31G*. [c]B2PLYPD/def2-TZVP//B2PLYPD/6-31G*. [d]CCSD(T)/def2-TZVP//B2PLYPD/6-31G*. [e](10/10)CASSCF/cc-pVTZ//(10/10)CASSCF/6-31G*. [f](10/10)CASPT2/cc-pVTZ//(10/10)CASSCF/6-31G*.

atm) for the dimerization of **1a** and the Bergman reaction of **1a** have almost the same value. ΔG of the dimerization of **1a** is now higher than the ΔG of the Bergman reaction. In other words, enediynes react via Bergman cyclization only under conditions which favor the entropic factor.

For a more accurate comparison of the competing reactions of **1a**, single-point calculations were performed on the B2PLYPD/6-31G*-optimized structures by means of CCSD(T)/def2-TZVP. The CCSD(T)[20] approximation delivers the most reliable results on energetics of the Bergman reaction.[13a] Furthermore, the stationary points of both competing reactions were optimized using (10,10)CASSCF/6-31G*, and single-point calculations were performed on these structures by means of (10,10)CASSCF/cc-pVTZ and (10,10)CASPT2/cc-pVTZ. While B2PLYPD and CCSD(T) are based on a single reference configuration, the CASSCF[21] and CASPT2[22] approximations can also describe degenerated correlation effects. This is extremely important for diradical states. Furthermore, the CASPT2 method considers dynamic correlation effects.

The energies obtained from CASSCF calculations are predictably too high, as no dynamic correlation is taken into account in this approximation (Table 2). The energies from B2PLYPD and CCSD(T) calculations coincide within a range of a few kcal/mol. The CASPT2 energies for the transition states and diradicals are ca. 4−11 kcal/mol lower than the energies obtained by B2PLYPD. A comparison of the CASPT2-calculated

values for **2a** (ΔE = 23.0 kcal/mol) and **3a** (ΔE = 1.7 kcal/mol) with the experimentally determined ones for **2a** (28.2 ± 0.5 kcal/mol) and **3a** (8.5 ± 1.0 kcal/mol) shows that CASPT2 tends to overestimate the stabilization energies for diradical species.

An analysis of the CASSCF wave function allows the determination of the diradical character of the transition states and products. As a measure of the diradical character, the occupation numbers of the frontier orbitals n_1 (antibonding linear combination) and n_2 (bonding linear combination) can be used (Figure 3 and Table 2).[23] In a perfect diradical both frontier
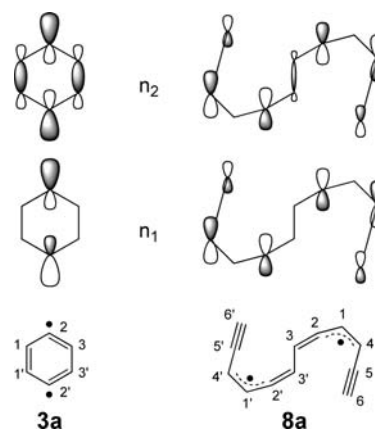

Figure 3. Schematic representation of the linear combinations of the nonbonding orbitals of the diradicals **3a** and **8a**. The orbital n_1 represents the antibonding linear combination, whereas the orbital n_2 is the bonding linear combination.

orbitals would be equally populated. The transition states **2a** and **7a** exhibit only a small diradical character. In the case of the products the diradical character of the butadienyl **8a** is more pronounced than for the didehydrobenzene **3a**. While **3a** is far from being "perfect", this is not the case for **8a**. This difference can be explained by the through-bond interactions[24] between the orbitals of the centers C2 and C2′. Whereas in **3a** a strong through-bond interaction takes place via two σ bonds (C1−C1′ and C3−C3′), in **8a** only a small through-bond interaction via one σ bond (C3−C3′) is found. In addition, the distribution of the unpaired electrons among the carbon centers differs significantly. Diradical **3a** has two sp²-hybridized radical centers (C2 and C2′) interacting with each other through the σ skeleton (Figure 3). In the case of **8a**, the carbon centers C2 and C2′ are almost sp-hybridized. Besides the centers C2 and C2′, electron density in the linear combinations of the nonbonding orbitals is also found for the atoms C4, C4′, C6, and C6′. The coefficients at C4 and C4′ are even higher than those at C2 and C2′. Depending on the perspective, **8a** can be considered as a combination of two allyl radicals (without taking the orbitals of the triple bonds C5−C6 and C5′-C6′ into consideration) or of two pentadienyl radicals (taking the orbitals of the triple bonds C5−C6 and C5′-C6′ into consideration) which weakly interact through the C3−C3′ σ bond.

To summarize, we showed that the dimerization of enediynes is energetically more favored than the corresponding Bergman cyclization. The calculated dimerization barrier for (Z)-hex-3-ene-1,5-diyne was more than 10 kcal/mol lower than that found for the Bergman cyclization. For the fluoro-substituted systems, the differences were even higher. In view of these calculations, the question arises why the dimerization reaction of enediynes is, as far as we know, not described in the literature. A detailed

literature search reveals that most reactions of enediynes were performed at high temperatures and/or high dilution. These factors favor the unimolecular Bergman cyclization over the bimolecular dimerization due to entropic reasons. However, there are hints for the occurrence of dimerization reactions. For example, in 1972, Bergman et al.[1b] stated that hex-3-ene-1,5-diyne "polymerizes at moderately high concentrations in solution even at 25 °C. When kept sufficiently dilute, however (<0.01 m), the material can be heated to 200 °C without extensive decomposition".[1b] Based on our calculations, we believe this polymerization is not triggered by a radicalic impurity but by butadienyl diradicals formed during a dimerization reaction. An extremely appealing aim would be trapping this diradical by adequate reagents. This would not only confirm the proposed mechanism but also deliver a new C–C bond formation reaction that proceeds at low temperatures, without the help of catalysts and starting from simple enediynes as starting materials.

■ ASSOCIATED CONTENT

ⓈSupporting Information

Computational details, absolute energies, and Cartesian coordinates for all calculated compounds This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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