

CCSD(T) Investigation of the Bergman Cyclization of Eneidyne. Relative Stability of *o*-, *m*-, and *p*-Didehydrobenzene

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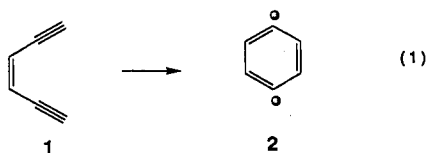
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Abstract: The energetics of the Bergman cyclization of (*Z*)-hexa-1,5-diyne-3-ene (**1**) to 1,4-didehydrobenzene (**2**) have been investigated at the CCSD(T)/6-31G(d,p) level of theory, optimizing various structures along the reaction path. The calculated reaction energy and classical barrier are 5.5 and 29.5 kcal/mol, respectively. Vibrational and temperature corrections lead to a reaction enthalpy, $\Delta_R H(298)$, of 8.0 kcal/mol and an activation enthalpy, $\Delta H^\ddagger(298)$, of 28.5 kcal/mol, indicating that previous determinations of these energies are seriously in error. Although the transition state of the reaction is located in the exit channel, it shows no biradical character, which suggests that the electronic structure of **1** is retained as long as possible. Energy changes in the entrance channel of the reaction are influenced by changes in strain caused by trans bending of the two triple bonds of **1**. If the terminal C atoms are pulled together to a distance of 3.0 Å, the reaction becomes spontaneous ($\Delta H^\ddagger(298) = 19.3$ kcal/mol) and slightly exothermic ($\Delta_R H(298) = -0.8$ kcal/mol) due to an increase of bending strain by 8.8 kcal/mol. For 1,2-didehydrobenzene (**11**), 1,3-didehydrobenzene (**12**), and 1,4-didehydrobenzene (**2**), relative energies are calculated to be 0, 13.6, and 25.4 kcal/mol, respectively, while the corresponding $\Delta H_f^\circ(298)$ values are 108.7, 122.8, and 134.4 kcal/mol, respectively, at the CCSD(T)/6-31G(d,p) level of theory.

1. Introduction

More than a decade ago, Bergman and co-workers demonstrated that enediynes cycloaromatize to give transient 1,4-diyli biradicals.¹ For example, the Bergman cyclization (**1**) of (*Z*)-hexa-1,5-diyne-3-ene (**1**) to 1,4-didehydrobenzene (**2**) occurs at 200 °C with an estimated activation energy of about 32 kcal/mol.¹



While the Bergman cyclization of enediynes was for a long time just a convenient way to generate 1,4-dehydroaromatics and their parent aromatic compounds, enediyne chemistry and the Bergman cyclization have recently experienced a surprising renaissance. A new class of antibiotics containing the enediyne unit has been discovered,² and it has been demonstrated that these natural enediynes belong to the most potent antitumor agents

ever investigated.³ Their fascinating biological activity results from the fact that, when properly triggered, the enediynes can undergo Bergman cyclization to benzenoid biradicals, which then are capable of abstracting H atoms from the sugar phosphate backbone of DNA. This leads to a double-stranded DNA cleavage and to cell death.³

In view of the antitumor activity of enediynes, numerous experimental studies have been carried out (a) to design simple monocyclic enediynes and to define the ring size necessary for spontaneous Bergman cyclization, (b) to develop viable synthetic routes to these compounds, (c) to study the fundamental chemistry of these simple ring systems, and (d) to test their biological activity.⁴ Since a mechanistic understanding of the Bergman cyclization is a necessary prerequisite of this research, both force field, semiempirical, and high-level ab initio investigations have been carried out to assess energetics, electronic changes, and steric factors of the Bergman cyclization.⁵⁻⁸ For example, Snyder⁷ described the transition state (TS) of the cycloaromatization of various enediynes by the semiempirical PRDDO method in connection with a GVB-CI approach in order to adequately assess the electronic nature of the TS. However, the rearranging enediyne was described at the PRDDO-SCF rather than the PRDDO-GVB-CI level of theory thus leading to an artificial lowering of the TS energy and an unbalanced description of the Bergman cyclization.

Koga and Morokuma⁸ have investigated reaction **1** at CASS-CF/DZ and MR-SDCI/DZ levels of theory. In the case of the

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(4) A review written in 1991^{3a} already lists 146 references, while a literature search for just 1992 leads to 60 publications in connection with enediynes and their antitumor activity.

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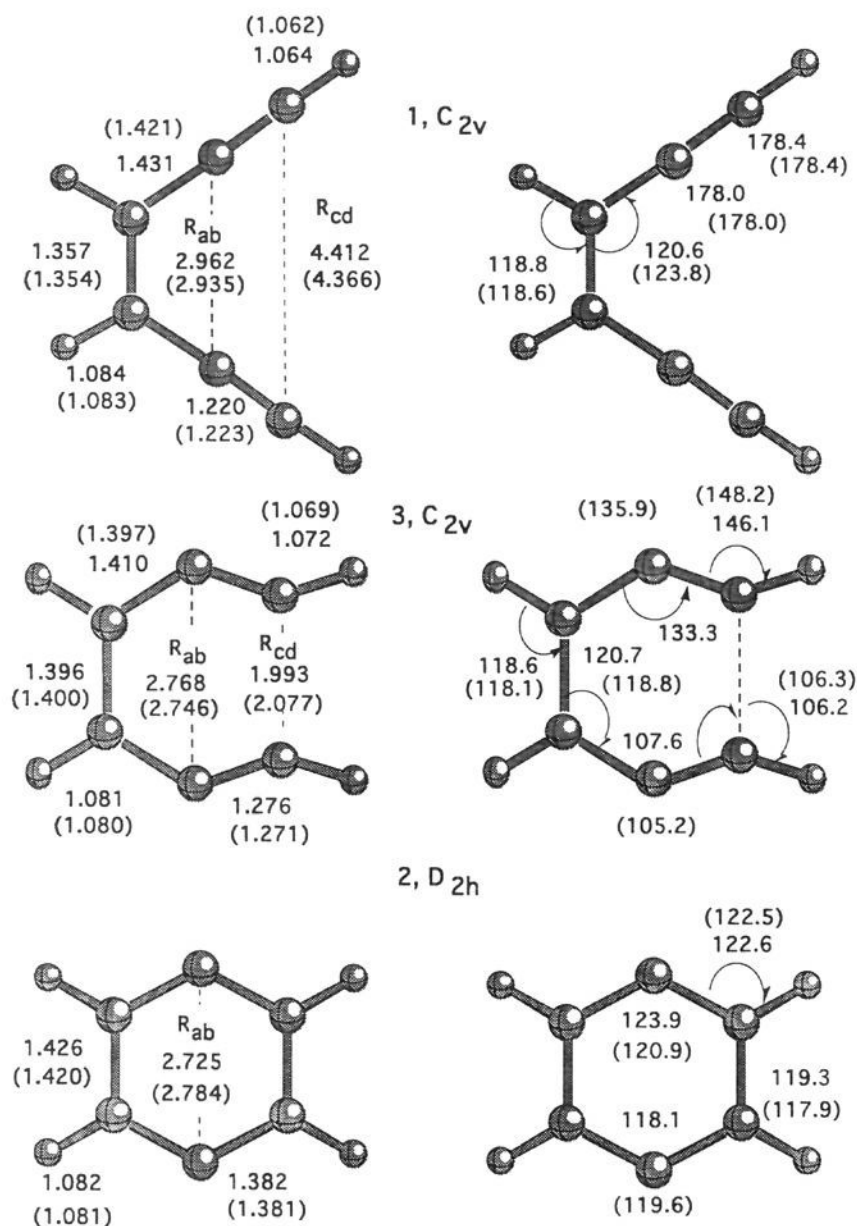


Figure 1. CCSD(T)/6-31G(d,p) geometries of (*Z*)-hexa-1,5-diyne-3-ene (**1**), 1,4-didehydrobenzene (**2**), and the transition state (TS) (**3**) of the Bergman cyclization reaction 1. Bond lengths are given in angstroms, angles in degrees. The distance between the terminal C atoms is denoted by R_{cd} , and the distance between the central C atoms by R_{ab} . MBPT(2)/6-31G(d,p) geometries are given in parentheses.

CASSCF calculations, these authors chose a 4-electron, 4-orbital and a 10-electron, 10-orbital active space, respectively, for **1** and **2** and the TS (**3**) of reaction 1 to guarantee an adequate description of the energetics of the reaction. In their best calculation, an energy barrier of 37.6 kcal/mol and a reaction energy of 22.0 kcal/mol were obtained,⁸ where the latter value implies a heat of formation ΔH_f° for **2** of about 148 kcal/mol. Wenthold, Paulino, and Squires have determined $\Delta H_f^\circ(298)(\mathbf{2})$ to be 128 ± 3 kcal/mol on the basis of energy-resolved collision-induced dissociation (CID) measurements.⁹ This suggests either an error of 20 kcal/mol in the reaction energy obtained by Koga and Morokuma or a serious error in the experimental $\Delta H_f^\circ(298)(\mathbf{2})$ value.

In view of the importance of the Bergman cyclization in connection with the new antitumor agents and because of the obvious errors in investigations of the energetics of reaction 1, an improved ab initio description of the Bergman cyclization is highly desirable. We report here for the first time coupled cluster (CC) calculations for reaction 1 including all single (S) and double (D) excitations (CCSD) together with a perturbative treatment of triple (T) excitations (CCSD(T)).¹⁰ On the basis of our CCSD(T) calculations, we are able (a) to determine correctly the energetics of reaction 1, (b) to assess the degree of alleged biradical character for TS **3**, (c) to describe the influence of steric and strain factors on the reaction mechanism, and (d) to make predictions with

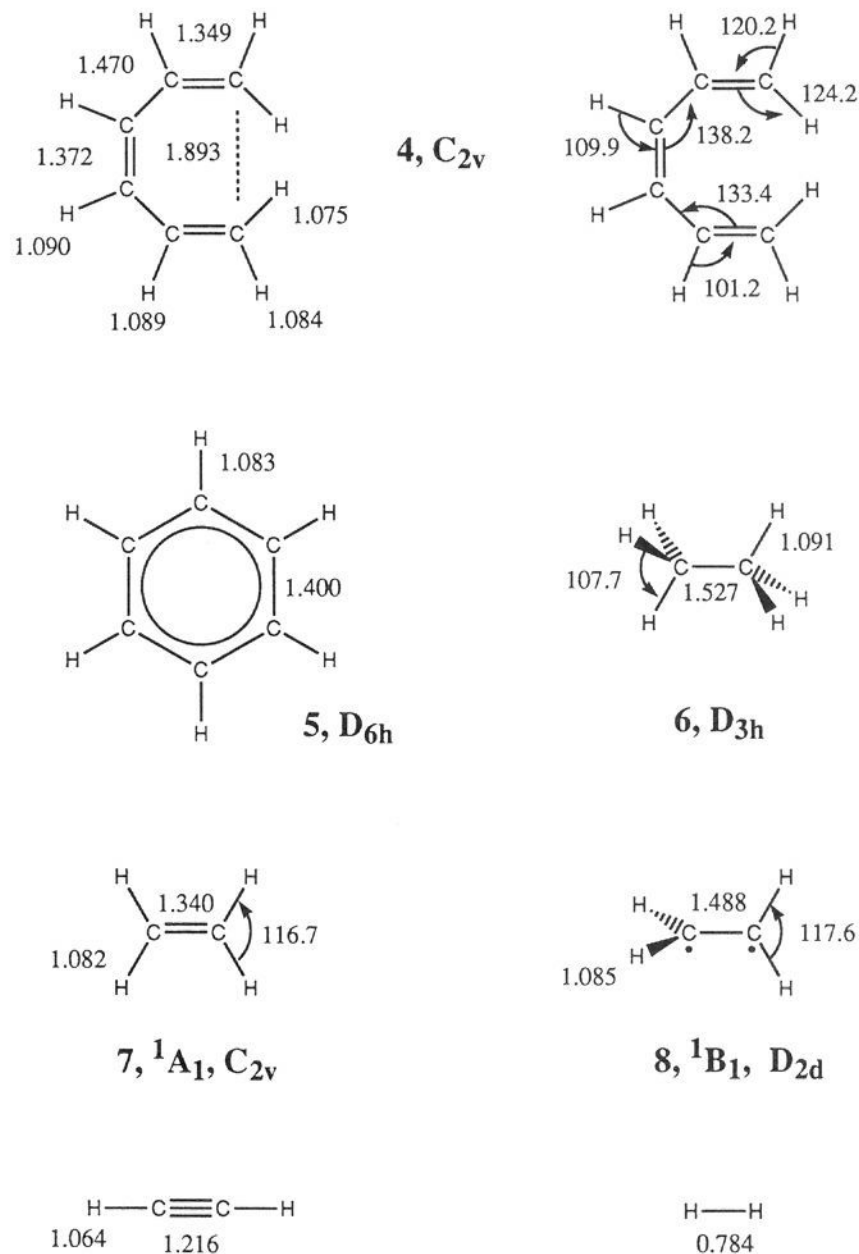


Figure 2. CCSD(T)/6-31G(d,p) geometries of reference compounds: *cis*-1,3,5-hexatriene (**4**), benzene (**5**), ethane (**6**), ¹A₁ ethylene (**7**), ¹B₁ twisted ethylene (**8**), acetylene (**9**), and hydrogen (**10**). Bond lengths are given in angstroms, angles in degrees.

regard to the spontaneity of the Bergman cycloaromatization. Apart from this, we will review the relative stability of the three didehydrobenzene isomers, which because of the involvement of **2** in the Bergman cyclization have been recently investigated experimentally.⁹ We will show that some of the published heats of formation are probably in error by as much as 8 kcal/mol.

2. Results and Discussion

CCSD(T) geometry optimizations for **1**, **2**, and **3** have been carried out with the 6-31G(d,p) basis set,¹¹ which is of DZ quality and contains, contrary to the basis set used by Koga and Morokuma, polarization functions for all atoms. In order to get starting geometries for the CC optimizations, many body perturbation theory calculations at second-order (MBPT(2))¹² have been performed. MBPT(2)/6-31G(d,p) calculations have also been used to characterize calculated stationary points with the help of second derivatives. Form **3** was found to possess one imaginary frequency and, therefore, to represent a first-order TS. GVB-PP¹³ has been employed to analyze CCSD(T) results and to compare them with the results of CASSCF and MR-SDCI investigations. Calculations have been carried out with

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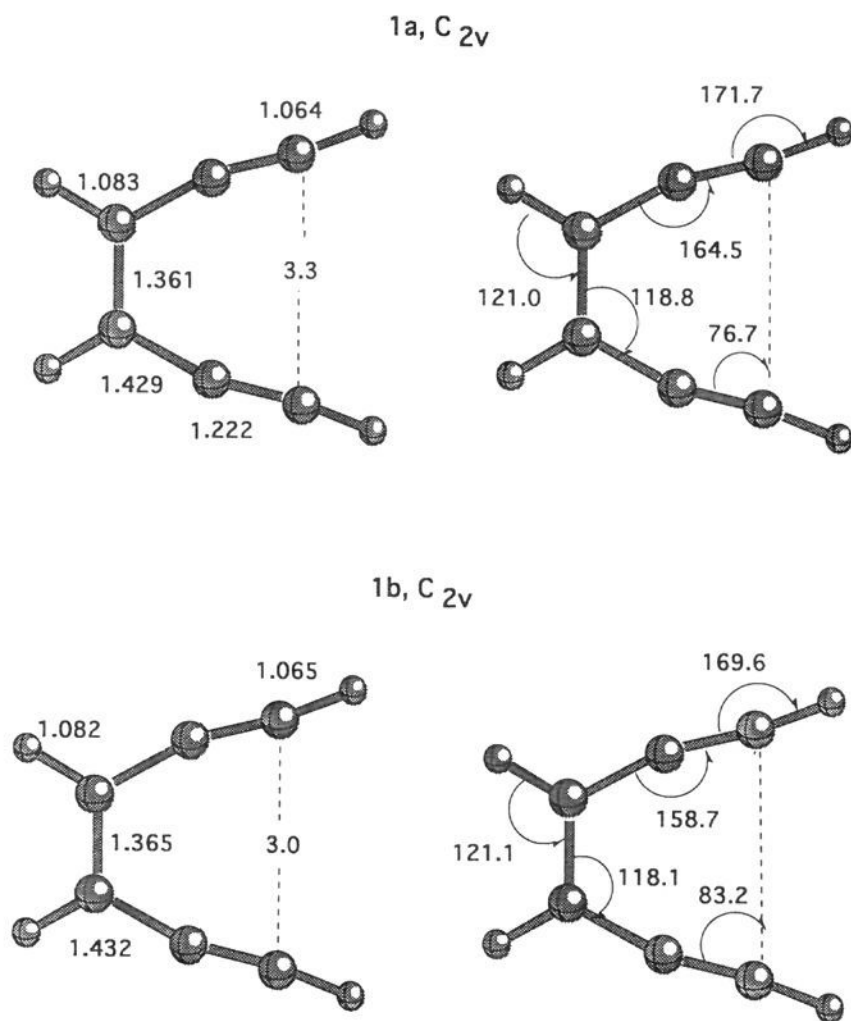


Figure 3. CCSD(T)/6-31G(d,p) geometries of intermediate structures with $R_{cd} = 3.3$ (1a) and 3.0 Å (1b). Bond lengths are given in angstroms, angles in degrees.

the ACES II program,¹⁴ which has been especially designed for large-scale correlated energy and energy gradient calculations using CC and MBPT methods.

CCSD(T)/6-31G(d,p)-optimized geometries of **1**, **2**, and the TS **3** are shown in Figure 1, with the corresponding MBPT(2)/6-31G(d,p) values given in parentheses. In Figure 2, the CCSD(T)/6-31G(d,p) geometries of reference molecules **4** (*cis*-1,3,5-hexatriene), **5** (benzene), **6** (ethane), **7** (ethylene), **8** (90° twisted ethylene (1B_1)), **9** (acetylene), and **10** (hydrogen) are shown, while Figure 3 gives the geometries of two transient points **1a** and **1b** along the reaction path of (1). Calculated energy data for the Bergman cyclization (1) as well as for some reference reactions are summarized in Tables 1 and 2.

Eneidyne **1** is a C_{2v} -symmetrical planar molecule with a conjugated π -system. Its multiple bonds are slightly longer than those in **7** or **9** (Figures 1 and 2), while the formal single bond (1.43 Å, Figure 1) is typical of a C(sp)-C(sp²) bond.¹⁵ Figures 1 and 2 reveal that π -conjugation in **1** is comparable to that in **4**, which because of significant steric repulsion represents a rotational TS with rather long CC bonds and relatively large CCC bond angles (C1C2, 1.35; C2C3, 1.47; and C3C4, 1.37 Å; C1C2C3, 124° ; C2C3C4, 133° ; C3C4C5, 138° , Figure 2). The absence of strong steric repulsion in **1** explains why this form is located at an energy minimum, which is just slightly (0.5 kcal/mol at MBPT(2)/6-31G(d,p)) above the corresponding trans form. The *cis* form **1** also benefits from stabilizing through-bond interactions, which involve the in-plane π -orbitals and the $\sigma^*(C3C4)$ orbital (see also discussion below).^{16,17}

When **5** is changed into **2**, symmetry is lowered from D_{6h} to D_{2h} , and distinct distortions of the hexagonal geometry of **5** occur,

as can be seen from the CCSD(T) geometry of **2** (Figure 1). The radical centers C1 and C4 rehybridize so that the bonding orbitals obtain more s-character, while the singly occupied orbitals get more p-character. This leads to stabilization of **2** because bonds to neighboring C atoms become stronger and stabilizing through-space (1,4) interactions increase. CC(H) distances (1.382 Å, CCSD(T), Figure 1) are almost 0.02 Å shorter than the CC bonds in **5** (1.400 Å, Figure 2). Another consequence of rehybridization at C1 and C4 is a widening of the C(H)CC(H) angles from 120° to 124° and a slight reduction of the CC(H)C(H) angles to 118° (Figure 1). While rehybridization and through-space interactions are stabilizing, through-bond interactions between singly occupied orbitals and bonding C(H)C(H) orbitals are destabilizing because they involve four electrons.¹⁶ As a consequence of these orbital interactions, the C(H)C(H) bonds are lengthened and **2** becomes less stable than 1,3-didehydrobenzene.^{9,16}

TS **3** is planar and possesses C_{2v} symmetry. The interaction distance R_{cd} is 2 Å (Figure 1), which is typical of interatomic distances between C atoms to be (dis)connected in TSs of electrocyclic reactions¹⁸ or homoaromatic CC interaction distances.¹⁹ Bending at the two triple bonds is already accomplished by 80% (CCC, 133° , Figure 1), while the C \equiv C(H) bond lengths (1.276 Å, Figure 1) have increased by just 34% of the total C \equiv C(H) lengthening accompanying the rearrangement of **1** into **2**. Obviously, geometrical parameters do not change simultaneously in reaction 1. The "stiffer" parameters (bond lengths) change slower than the "softer" parameters (bond angles). However, if the distance R_{cd} is taken as the parameter dominating the reaction coordinate, then the TS is clearly located in the exit channel (late TS) of the reaction rather than in the entrance channel (early TS) as claimed by Koga and Morokuma.⁸ Applying the Hammond postulate, a late TS should be indicative of a reaction with a small endothermic reaction energy, $\Delta_R E$.

MBPT(2)/6-31G(d,p) geometries of **1**, **2**, and **3** are similar to CCSD(T)/6-31G(d,p) geometries (Figure 1), indicating that geometries are not strongly method and/or basis set dependent. This is in line with the fact that the CASSCF4/DZ geometries of **1** and **2** calculated by Koga and Morokuma⁸ are also similar to the CCSD(T) results. The same holds for **3**, except for the CASSCF value of the R_{cd} distance (1.94 Å), which suggests that CASSCF4/DZ places the TS somewhat further out in the exit channel.

The CCSD(T)/6-31G(d,p) reaction energy $\Delta_R E$ of (1) is 5.5 kcal/mol, and the classical barrier ΔE_c is 29.5 kcal/mol (Table 1). These values differ considerably from previous estimates of the reaction energies as well as from the results obtained from other methods. For example, MBPT(2) suggests an exothermic reaction ($\Delta_R E = -12.3$ kcal/mol, Table 1) with a relatively low ΔE_c of 23.3 kcal/mol, while CCSD predicts $\Delta_R E = 27.2$ and $\Delta E_c = 37.7$ kcal/mol. The CCSD values come close to the MR-SDCI/DZ ($\Delta_R E = 22.0$, $\Delta E_c = 37.6$ kcal/mol) and the 10-electron CASSCF/DZ results ($\Delta_R E = 28.3$, $\Delta E_c = 44.7$ kcal/mol) of Koga and Morokuma.⁸ However, neither MBPT(2), CCSD, CASSCF, nor MR-SDCI results can be trusted. MBPT(2) exaggerates the stability of biradicals²⁰ and, therefore, leads to an unbalanced description of **1**, **2**, and **3**: the value of $\Delta_R E$ becomes too negative and ΔE_c too low. CCSD corrects some of the deficiencies of MBPT(2) but also overestimates pair

(17) Although the *cis* form **1** is not more stable than the corresponding trans form, **1** is a typical example of the *cis* effect found for molecules such as 1,2-difluoroethylene. See, e.g.: Cremer, D. *Chem. Phys. Lett.* **1981**, *81*, 481 and references cited therein.

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Table 1. Energetics of the Bergman Cyclization^a

method	1	1a	1b	2	3
MBPT2//MBPT2	-230.187 343	-230.171 923	-230.174 597	-230.206 965	-230.150 157
CCSD//CCSD(T)	-230.219 473	-230.210 146	-230.203 688	-230.176 111	-230.159 412
CCSD(T)//CCSD(T)	-230.258 393	-230.250 014	-230.244 310	-230.249 567	-230.211 349
ZPE(MBPT(2)) ^b	40.7	(41)	(41)	44.6	41.4

CCSD(T)//CCSD(T) Method						
reaction ^c	$\Delta_R E(0)$	$\Delta_R H(0)$	$\Delta_R H(298)$	$\Delta_c E$	$\Delta H^*(0)$	$\Delta H^*(298)$
1b	-3.3	0.6	-0.8	20.3	21.0	19.3
1a	0.3	4.2	2.8	23.5	24.2	22.5
1	5.5	9.4	8.0	29.5	30.2	28.5

^a Absolute energies in hartrees, relative energies in kcal/mol. The notation "method 1//method 2" denotes the level of theory used for the final calculation (method 1) and the level of theory used for the geometry optimization (method 2). $\Delta_R E(0)$, $\Delta_R H(0)$, $\Delta_R H(298)$, $\Delta_c E$, $\Delta H^*(0)$, and $\Delta H^*(298)$ denote reaction energy at 0 K, reaction enthalpy at 0 K, reaction enthalpy at 298 K, classical reaction barrier, activation enthalpy at 0 K, and activation enthalpy at 298 K, respectively. All calculations have been performed with the 6-31G(d,p) basis set. ^b Zero-point energy (ZPE) corrections have been obtained from calculated MBPT(2)/6-31G(d,p) harmonic frequencies scaled with 0.93. Numbers in parentheses have been estimated from calculated values. ^c Reactions 1a, 1b, and 1 start from enediyne forms 1a, 1b, and 1, respectively.

correlation effects in relation to the electron pair, single electron correlation effects, which can be described only if T excitations are included in the CC method. CCSD is well suited to describe closed-shell systems but fails to handle biradical and closed-shell structures on an equal footing.²¹

The CASSCF and MR calculations of Koga and Morokuma⁸ suffer from the fact that a DZ basis without polarization functions is insufficient to adequately describe distorted multiple bonds or distorted ring geometries. Apart from this, 4-electron (10-electron) CASSCF descriptions will always prefer the enediyne site of (1) with two (five) bonding electron pairs as compared to the one (four) bonding electron pairs of 2. This error can be compensated only by adding a considerable amount of dynamic correlation to the CASSCF method. This is confirmed by the fact that MR-SDCI results are much better than the CASSCF results of Koga and Morokuma.⁸ But like CCSD, MR-SDCI suffers from an unbalanced description of electron pair, single electron correlation effects as opposed to electron pair correlation effects. Therefore, it is not astonishing that CCSD and MR-SDCI values show similar deficiencies as compared to CCSD(T) results.

An appropriate description of reaction 1 can be given only if T excitations are added that cover correlation effects including a single electron and an electron pair at the same time. Therefore, a CCSD(T) description of reaction 1 is superior to MBPT(2), CCSD, CASSCF, and MR-SDCI. Of course, in view of the single determinant basis of CCSD(T), one may doubt whether important multireference effects of the present problem are covered. To investigate this aspect, we will compare CCSD(T) results with available thermochemical data.

Thermochemical Data. The heat of formation of compound 1 is not experimentally known but can be estimated to be 125.8 kcal/mol using group increments.²² When this value is combined with Squires's value for $\Delta H_f^\circ(298)$ of 2 (128 ± 3 kcal/mol),⁹ a reaction enthalpy $\Delta_R H(298) = 2.2 \pm 3$ kcal/mol results, in reasonable agreement with the CCSD(T) value of $\Delta_R E = 5.5$ kcal/mol (Table 1). The CCSD(T) classical barrier $\Delta_c E = 29.5$ kcal/mol also compares well with a thermochemical estimate of $\Delta H^*(500) = 32$ kcal/mol, given by Bergman.¹

However, it can be very misleading to compare ab initio energies at 0 K with experimental heats of formation at 298 K.²³ Therefore, we have also calculated vibrational frequencies at the MBPT(2)/6-31G(d,p) level of theory and have used them to determine zero-point energies (ZPEs), and we have used vibrational and temperature corrections at 298 K to obtain reaction and activation enthalpies ($\Delta_R H(T)$ and $\Delta H^*(T)$) that can directly be compared with experimental enthalpies. The corresponding data are 8.0

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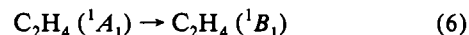
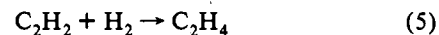
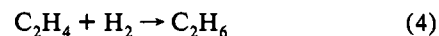
Table 2. Comparison of CCSD(T) and Experimental Reaction Enthalpies $\Delta_R H$ for Some Reference Reactions^a

reaction	method	$\Delta_R E(0)$	$\Delta_R H(0)$	$\Delta_R H(298)$	deviation	ref
2	CCSD(T)	-117.6	-103.2	-106.8	-0.8	this work
	expt	-116.8	-102.4	-106.0		9, 25
3	CCSD(T)	-123.1	-112.5	-114.6	-6.4	this work
	expt	116.9	-106.3	-108.2		22, 25
4	CCSD(T)	-40.6	-32.0	-33.7	-1.0	this work
	expt	-39.6	30.9	-32.7		25, 24
5	CCSD(T)	-51.1	-42.4	-44.3	-2.4	this work
	expt	-48.7	-40.0	-41.9		24, 25
6	CCSD(T)	66.7	64.6	64.5	0.5	this work
	expt			65		27a
1	CCSD(T)	5.5	9.4	8.0		this work
	suggested value			9-10		this work

^a All values in kcal/mol. For the notation of energy values, see Table 1. For the definition of reactions 1-6, see text.

and 28.5 kcal/mol (Table 1), which suggests that there is actually a larger discrepancy between ab initio data and experimental estimates, namely 6 kcal/mol for $\Delta_R H(298)$ and 3.5 kcal/mol for $\Delta H^*(298)$. Since the experimental $\Delta H_f^\circ(298)$ of 2 has an uncertainty of 3 kcal/mol and thermochemical estimates of highly unsaturated hydrocarbons may also have considerable uncertainties, it is useful to find out whether discrepancies result from measured, estimated, or perhaps calculated energy data.

To clarify this question, we have calculated $\Delta_R E$ and $\Delta_R H$ values of various reference reactions, namely the hydrogenation of 1 (reaction 2), 2 (reaction 3), ethylene (reaction 4), and acetylene (reaction 5). In addition, we have investigated the 90° rotation of ethylene to yield the singlet biradical state ¹B₁ (reaction 6).



In the calculations, CCSD(T) geometries shown in Figure 2 were used. Vibrational and temperature corrections were

(23) (a) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976. (b) Refined group increments for polyacetylenes have been published: Benson, S. W.; Garland, L. J. *J. Phys. Chem.* 1991, 95, 4915. They would lead to $\Delta H_f^\circ = 124.4$ kcal/mol for 1. However, we have refrained from using the new group increments since (1) they underestimate ΔH_f° for compounds closely related to 1 by 0.5 kcal/mol and (2) they are based on a cis increment of 0.6 kcal/mol, which is not confirmed by the ab initio calculations that suggest -0.5 kcal/mol.

determined with the help of MBPT(2)/6-31G(d,p) or experimental frequencies taken from the literature.²⁴

For reactions 2, 4, and 5, CCSD(T) reaction enthalpies agree with experimental values²⁵ within 1–2.5 kcal/mol. For example, $\Delta_R H(298)$ of reaction 2 (–106.8 kcal/mol) is within 0.8 kcal/mol of the value based on the thermochemical estimate of **1**.²² If we assume that the thermochemical estimate of ΔH_f° for **1** is correct, then CCSD(T) will underestimate the stability of **1** by 0.8 kcal/mol.²⁶ Actually, the error in calculating CC triple bonds may be as large as 2.4 kcal/mol at the CCSD(T)/6-31G(d,p) level of theory, as is revealed by the enthalpies for reaction 5 (Table 2), but error cancellation seems to reduce this discrepancy in the hydrogenation reaction of **1**. We conclude that CCSD(T)/6-31G(d,p) underestimates the stability of **1** by 2 kcal/mol.

The calculated data for reaction 6 suggest that CCSD(T) has no problems in reproducing the relative energy of a biradical. Since the error between experimental and calculated values for the barrier of rotation of ethylene (65 kcal/mol^{27a}) is just 0.5 kcal/mol, we also expect a reasonably accurate CCSD(T) description for the biradical **2**. This, of course, implies that the large deviation (–6.4 kcal/mol, Table 2) found for $\Delta_R H(298)$ of reaction 3 results from an error in the experimental $\Delta H_f^\circ(298)$ of **2** (128 ± 3 kcal/mol⁹) rather than in the CCSD(T) energies. From our calculations, we predict $\Delta H_f^\circ(298)$ of **2** to be 134–136 kcal/mol, where the upper limit is given in view of a 2 kcal/mol underestimation of $\Delta_R H(298)$ of reaction 1. We conclude that the reaction enthalpy of the Bergman cyclization is 8–10 kcal/mol and that thermochemical estimates of this value based on the experimental $\Delta H_f^\circ(298)$ of **2** are too low by 6–8 kcal/mol (see last section for revised experimental data). If entropy changes ($\Delta_R S(298) = -10.2$ eu) are added to the CCSD(T) value of $\Delta_R H(298)$, a final reaction free enthalpy $\Delta_R G(298)$ of 11 kcal/mol with an upper bound of 13 kcal/mol is obtained.

CCSD(T) theory clearly suggests that the Bergman cyclization is close to being thermoneutral, contrary to the results of previous ab initio investigations, in which the values are too large by at least 10 kcal/mol.⁸

Relative Stabilities of 1,2-Didehydrobenzene (11), 1,3-Didehydrobenzene (12), and 1,4-Didehydrobenzene (2). In view of the results discussed in the previous section, it is logical to reconsider the relative stabilities of the three isomeric benzynes 1,2-didehydrobenzene (**11**), 1,3-didehydrobenzene (**12**), and 1,4-didehydrobenzene (**2**). In Figure 4, CCSD(T)/6-31G(d,p) geometries of **11** and **12** are given, while calculated relative energies and heats of formation of **2**, **11**, and **12** are listed in Table 3.

Compound **11** has been investigated by various authors,^{28,29} but we consider here just the most recent work by Scheiner and

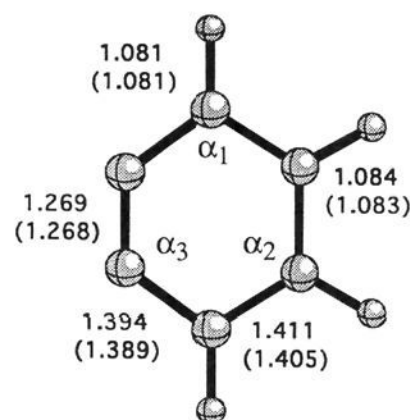
(24) Vibrational frequencies are cited as follow. (a) Benzene: Pulay, P.; Fogarasi, G.; Boggs, J. E. *J. Chem. Phys.* **1981**, *74*, 3999. (b) Ethane and acetylene: Shimanouchi, T. *Tables of Molecular Vibrational Frequencies, Vol. 1*; NSRDS-NBS-39; National Bureau of Standards, U.S. Government Printing Office: Washington, DC, 1972; *J. Phys. Chem. Ref. Data* **1977**, *6*, 993. (c) ¹A₁ ethylene: MBPT(2)/6-31G(d,p) harmonic frequencies, this work. (d) ¹B₁ ethylene: MBPT(2)/6-31G(d,p) harmonic frequencies this work. (e) H₂: Herzberg, G.; Huber, K. P. *Molecular Spectra and Molecular Structure 4: Constants of Diatomic Molecules*; Van Nostrand: Princeton, NJ, 1979.

(25) $\Delta H_f^\circ(298)$ values are reported as follow. (a) Eneidyne: from standard group increments taken from ref 22. (b) 1,2-Didehydrobenzene, 1,3-didehydrobenzene, 1,4-didehydrobenzene: ref 9. (c) Benzene, ethane, ethylene, and acetylene: Chase, M. W.; Curnett, J. L.; Downey, J. R.; MacDonald, R. A.; Valenzuela, E. A. JANAF Thermochemical Tables 1982 Supplement. *J. Phys. Chem. Ref. Data* **1982**, *11*. Chase, M. W.; Davies, C. A.; Downey, J. R.; Frurip, J. D.; McDonald, R. A.; Syverud, A. N. JANAF Thermochemical Tables, 3rd ed. *J. Phys. Chem. Ref. Data* **1985**, *14*(Suppl. 1), 1.

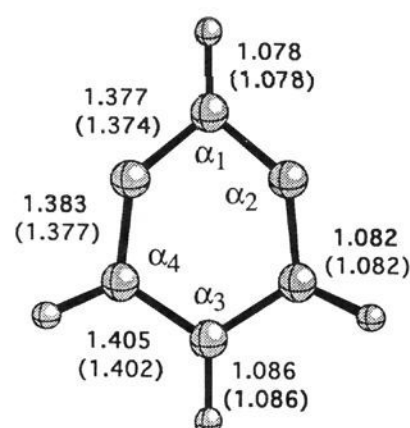
(26) Absolute errors can be larger, but because of error cancellation the residual error becomes relatively small.

(27) For experimental work, see: (a) Kalinowski, H.-O.; Kessler, H. *Topics Stereochem.* **1973**, *7*, 295. For theoretical work, see: (b) Hiroshi, I.; Yukiko, E.; Atsushi, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3619. (c) Buenker, R. J.; Peyerimhoff, S. D. *Chem. Phys.* **1976**, *9*, 75. (d) Brooks, B. R.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1979**, *101*, 307.

(28) (a) Scheiner, A. C.; Schaefer, H. F., III. *Chem. Phys. Lett.* **1991**, *177*, 471. (b) Scheiner, A. C.; Schaefer, H. F., III; Liu, B. *J. Am. Chem. Soc.* **1989**, *111*, 3118.

11, C_{2v}

α_1 : 111.2 (110.8)
 α_2 : 122.4 (122.6)
 α_3 : 126.4 (126.6)

12, C_{2v}

α_1 : 99.8 (101.1)
 α_2 : 135.5 (122.6)
 α_3 : 114.6 (114.3)
 α_4 : 117.4 (117.9)

Figure 4. CCSD(T)/6-31G(d,p) geometries of 1,2-didehydrobenzene (**11**) and 1,3-didehydrobenzene (**12**). Bond lengths are given in angstroms, angles in degrees. MBPT(2)/6-31G(d,p) geometries are shown in parentheses.

Table 3. Relative Stabilities of 1,2-Didehydrobenzene (**11**), 1,3-Didehydrobenzene (**12**), and 1,4-Didehydrobenzene (**2**)^a

method	11	12	2
MBPT(2)//MBPT(2)	0	7.5	10.3
CCSD//CCSD(T)	0	18.0	42.5
CCSD(T)//CCSD(T)	0	13.7	25.3
ZPE(MBPT(2)) ^b	44.2	44.6	44.6
$\Delta H_f^\circ(298) - \text{CCSD(T)}^c$	108.7	122.8	134.4
$\Delta H_f^\circ(298) - \text{exptl}^d$	106 ± 3	116 ± 3	128 ± 3
estimated error of exptl $\Delta H_f^\circ(298)$	3	6	6

^a All values in kcal/mol. The notation "method 1//method 2" denotes the level of theory used for the final calculation (method 1) and the level of theory used for the geometry optimization (method 2). All calculations have been performed with the 6-31G(d,p) basis set. ^b Calculated with MBPT2/6-31G(d,p) frequencies. ^c Calculated from hydrogenation reactions using the experimental $\Delta H_f^\circ(298)$ value for benzene.²⁵ See text. ^d Reference 9.

co-workers,²⁸ which was carried out at the TCSCF/DZ+P and MBPT(2)/TZ+P levels of theory. The CCSD(T)/6-31G(d,p) geometry of **11** (Figure 3) is similar to both the MBPT(2)/6-31G(d,p) geometry and the TCSCF/DZ+P geometry published by Scheiner and co-workers.²⁸ At all levels of theory, the CC bond length (1.269 Å, Figure 4) is close to the average of the CC triple bond length of acetylene (1.216 Å, Figure 2) and the CC double bond length of ethylene (1.340 Å, Figure 2), thus indicating that the two single electrons of **11** are paired to a large extent, thus leading to a CC bond with partial triple bond character.

(29) (a) Radziszewski, J. G.; Hess, B. A., Jr.; Zahradnik, R. *J. Am. Chem. Soc.* **1992**, *114*, 52. (b) Liu, R.; Zhou, X.; Pulay, P. *J. Phys. Chem.* **1992**, *96*, 8336. (c) Sutter, H. U.; Ha, T. K. *Chem. Phys. Lett.* **1992**, *198*, 259. (d) Rigby, K.; Hillier, I.; Vincent, M. A. *J. Chem. Soc., Perkin Trans. 2* **1987**, 117. (e) Hillier, I.; Vincent, M. A.; Guest, F. M.; von Niessen, W. *Chem. Phys. Lett.* **1987**, *134*, 403. (f) Radom, L.; Nobes, R. H.; Underwood, D. J.; Li, W.-K. *Pure Appl. Chem.* **1986**, *58*, 75.

Despite the short CC bond, distortion of the benzene ring is moderate (Figure 4), as is reflected by the CC(H) and C(H)C(H) bond lengths of 1.394, 1.411, and 1.413 Å all being close to the corresponding benzene value of 1.400 Å (Figure 2). The formation of a partial CC triple bond and the moderate distortion of the benzene ring explain the relatively small biradical character (see discussion in the next section) and the relatively large stability calculated for **11** at the CCSD(T) level of theory.

When **5** is changed into **12**, the hexagonal geometry of **5** is distorted much stronger, as in the case of **11** (Figure 4). Caused by rehybridization at atoms C1 and C3, the CC(H) bonds become shorter (1.377 and 1.383 Å, Figure 4), while the C(H)CC(H) angles widen from 120° in **5** to 135.5° in **12**. As a consequence, both the C(H)CC(H) angle (99.8°) and the C1C3 distance (2.106 Å) decrease, thus supporting stabilizing through-space interactions between the single-electron orbitals at centers C1 and C3. Stabilizing through-space orbital interactions are supported by stabilizing through-bond interactions, as has been discussed in the literature,¹⁶ however, both effects together are clearly weaker than the (partially) bonding 1,2-orbital interactions in isomer **11**. Therefore, **12** is less stable than **11** by 13.7 kcal/mol according to CCSD(T) calculations (Table 3). MBPT(2) and CCSD lead to lower or higher values because of the deficiencies of these methods discussed above.

Didehydrobenzene **2** is the least stable of the three isomers, which is a result of less efficient through-space orbital interactions (distance C1C4 is 2.725 Å, Figure 1) and destabilizing through-bond interactions (see above). At the CCSD(T) level of theory, the relative energy of **2** is 25.3 kcal/mol, while considerably different values are obtained at lower levels of theory (Table 3). With semiempirical MNDO/CI calculations, Dewar and co-workers predicted **2** to have a stability similar to that of **12**, both being just 5–6 kcal/mol less stable than **11**,³⁰ which is clearly erroneous in view of our CCSD(T) investigation and the experimental $\Delta H_f^\circ(298)$ values of Wenthold, Paulino, and Squires.⁹ On the other hand, the GVB(1)/4-31G calculations of Noell and Newton³¹ come close to our CCSD(T) values, which underlines the necessity of correctly describing the two unpaired electrons.

The relative stabilities of **11**, **12**, and **2** do not change significantly when zero-point energies or other vibrational corrections are considered. With the MBPT(2)/6-31G(d,p) zero-point energies of Table 3, the energy increase in the series **11**, **12**, **2** is 0, 14, and 26 kcal/mol, respectively, which differs from the relative energies reported by Wenthold, Paulino, and Squires (0, 10, and 22 kcal/mol,⁹ see last section for revised experimental data) insofar as both **12** and **2** are predicted to be less stable by 4 kcal/mol than suggested by the experimental $\Delta H_f^\circ(298)$ values. We have determined CCSD(T) heats of formation by calculating hydrogenation energies for all three isomers as described in the previous section. The CCSD(T) values of $\Delta H_f^\circ(298)$ obtained in this way are 108.7, 122.8, and 134.4 kcal/mol for **11**, **12**, and **2** (Table 3), where the first value is within the uncertainty range (± 3 kcal/mol⁹) of the experimental $\Delta H_f^\circ(298)$ and the two other values are about 7 kcal/mol larger than the experimental $\Delta H_f^\circ(298)$. In view of the reliability of CCSD(T) energies and the considerable difficulties in determining heats of formation for dehydrobenzenes, we consider CCSD(T) energies and $\Delta H_f^\circ(298)$ values as a useful basis for a refinement of experimental results (see below).

Biradical Character of the TS of the Bergman Cyclization. According to its structural formula (see reaction 1), **2** should possess two single electrons and, therefore, 100% biradical character. With a GVB wave function, one can determine the biradical character χ of a molecule from the occupation number of the natural orbitals representing an electron pair: $\chi = 1 -$

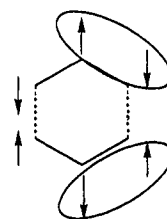
Table 4. Analysis of Natural Orbitals η_i for CCSD(T)/6-31G(d,p) Wave Functions

molecule	estimated biradical character, % ^a	$a(\text{LUMO})^b$	Y^c	biradical character ($Y - Y_{\text{ref}}$), % ^d
1	0	0.116	0.79	0
1a	0	0.115	0.80	0
1b	0	0.116	0.81	0
3	<i>e</i>	0.101	0.69	0
2	100	0.683	1.38	65
5	0	0.093	0.73	0
7	0	0.086	0.28	0
8	100	0.785	0.98	70
9	0	0.072	0.28	0
10	0	0.020	0.03	0
11	50	0.166	0.84	11
12	100	0.242	0.92	20

^a Estimated biradical character is based on simple structural formulas. In the case of **11**, we assume that the biradical structure and the closed-shell structure with a triple bond have equal weight. ^b Occupation number of natural orbital $\eta + 1$ for a $2n$ -electron system. ^c For a system with $2n$ electrons, Y is defined as the sum over all occupation numbers for η_i with $i > n$. ^d Reference values Y_{ref} have been taken from **5** and **7** for **2**, **11**, **12**, and **8**, respectively. ^e Unknown.

$2S/(1+S^2)$ with S being the overlap between the two pair orbitals. In the case of **2**, one gets 82% at the GVB(1)/6-31G(d,p) level of theory.

When a restricted CCSD(T) wave function is used for a $2n$ -electron system, the occupation numbers a_i of the natural orbitals η_i ($i = n + 1, n + 2, \dots$) give some information on both dynamic correlation effects and the multireference character of the system in question. As shown in Table 4, dynamic correlation effects are considerable for molecules with multiple bonds but increase even more in the case of conjugated double or triple bonds. For **1**, the sum Y of the occupation numbers of orbitals η_i with $i > n$ is almost 3 times as large as for acetylene or ethylene. The same is true for benzene, which can be used as a reference to assess the biradical character of **2** as described by a CCSD(T) wave function. The difference $Y(\mathbf{2}) - Y(\mathbf{5})$ suggests 65% biradical character, comparable to the value calculated for the 1B_1 state of twisted ethylene (0.70, Table 4), indicating in both cases about 30% of pairing of the two single electrons with other electrons. This pairing can occur with the σ -electrons of the C(H)C(H) bonds in **2** via a through-bond interaction mechanism.



For the ortho isomer **11**, the CCSD(T) biradical character is just 11% (Table 4), which suggests strong pairing of the two single electrons and the formation of a triple bond (see above). When **11** is changed into the meta isomer **12**, the biradical character slightly increases to 20% (Table 4), which indicates that despite the separation of the two single electrons, through-bond interactions between them lead to considerable pairing of the electrons.

With GVB(2)/6-31G(d,p) calculations, the biradical character χ is found to be 6 and 8% for enediyne **1** and TS **3**, while it is essentially zero in both cases at the CCSD(T)/6-31G(d,p) level of theory. Contrary to previous GVB-PRDDO calculations,⁷ which predict 35% biradical character for the TS of Bergman cyclizations of cyclic enediynes, the more reliable CCSD(T) calculations suggest that the biradical character is developed rather late along the reaction coordinate, which is in line with the

(30) Dewar, M. J. S.; Ford, G. P.; Reynolds, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 3162 and references cited therein.

(31) Noell, J. O.; Newton, M. D. *J. Am. Chem. Soc.* **1979**, *101*, 51.

fact that TS 3 is characterized by through-space/through-bond interactions between the two terminal C atoms of 1 ($R_{cd} = 2 \text{ \AA}$, Figure 1) and a trans distortion of the triple bonds rather than the formation of a new CC bond. This indicates that 1 tries to retain its electronic structure as long as possible and that the energy of the TS is dominated by an increase of the strain energy rather than a reorganization of electron pairing.³² Hence, both 1 and 3 should be described by the same method to obtain reasonable activation energies. The procedure used by Snyder, namely to calculate the TS of the Bergman cyclization by GVB but the rearranging enediyne by SCF,⁷ definitely leads to an underestimation of the activation energy. Another consequence of the electronic similarity of the enediyne and the TS is that the entrance channel of the Bergman cyclization can very well be investigated by methods that cover just changes in the strain energy, as has been done by various groups.⁵⁻⁷ We will investigate in the next section ways in which the energetics of the Bergman cyclization can be changed via a change of the strain energy of 1.

Influence of Strain on Reaction Energetics. As reported by Bergman, reaction 1 occurs at 200 °C.¹ However, the necessary condition for an enediyne to show anticancer and antibiotic activities is that it undergoes cycloaromatization at body temperature. In natural products, the enediyne moiety is embedded in a strained ring (mostly a 10-membered ring), and, as has been shown in several studies,⁵⁻⁷ strained monocyclic enediynes with short distance R_{cd} are characterized by reduced energy barriers to Bergman cyclization where an increase of the energy of the ground state of the enediyne seems to be the reason for the greater reactivity. On the basis of force field calculations, it has been predicted that the reaction will occur at body temperature if $R_{cd} \leq 3.2 \text{ \AA}$, while enediynes with $R_{cd} \geq 3.35 \text{ \AA}$ are expected to be thermally stable.⁶ Using this prediction as guidance for new synthetic design, Nicolaou and co-workers⁶ have synthesized 6-cyclodecene-4,8-diyne-1,2-dimethanol as the first water-soluble DNA-cleaving enediyne, with a R_{cd} distance of about 3.2 Å.

We have tested predictions based on force field calculations by freezing the R_{cd} distance in 1 at 3.3 (1a) and 3.0 Å (1b), reoptimizing all other geometrical parameters at CCSD(T)/6-31G(d,p) (see Figure 3). Although in 1a the R_{cd} distance is shortened by only 25%, one can already recognize the final ring structure. From the shapes of 1a and 1b it seems that the ring closure is achieved by putting a string around the terminal C(H) atoms and pulling them together while the neighboring C and H atoms attempt to keep their original positions. Structure 1a is 5.2 kcal/mol (Table 1, Figure 5) less stable than 1, which means that the reaction starting from 1a is almost thermoneutral, with $\Delta_R E = 0.3 \text{ kcal/mol}$ and $\Delta E_c = 23.5 \text{ kcal/mol}$. For comparison, the activation energy for 6-cyclodecene-4,8-diyne-1,2-dimethanol at body temperature has been determined to be 24.8 kcal/mol.⁶ Starting from 1b, which is 8.8 kcal/mol less stable than 1 (Table 1, Figure 5), the reaction becomes exothermic by 3.3 kcal/mol and the barrier decreases to 20 kcal/mol. From the corresponding activation enthalpies, we can predict that $\Delta H^\ddagger(298) = 19.3 \text{ kcal/mol}$, which may be considered the starting point for spontaneous reaction being reached at an R_{cd} distance of 3.0 Å. This is in line with the observation that cyclic conjugated enediynes with an R_{cd} distance of about 3 Å spontaneously undergo Bergman cycloaromatization at ambient temperature.³³

(32) Of course, increase in strain is accompanied by or the result of electronic structure changes. We simplify the description by distinguishing between increase of biradical character as a pure electronic factor and increase in strain as a mechanical factor.

(33) (a) Darby, N.; Kim, C. U.; Salaün, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *Chem. Commun.* 1971, 1516. (b) Wong, H. N.; Sondheimer, F. *J. Am. Chem. Soc.* 1966, 88, 602.

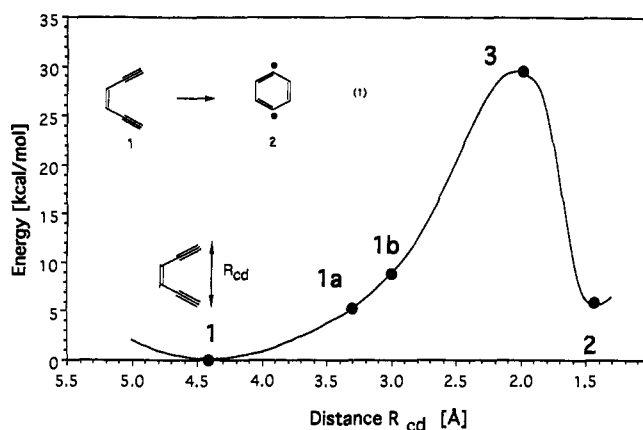


Figure 5. Reaction profile of the Bergman cyclization reaction 1 with R_{cd} as the reaction coordinate. Relative energies of (*Z*)-hexa-1,5-diyne-3-ene (1), 1,4-didehydrobenzene (2), the transition state (TS) (3), and the two intermediate structures 1a and 1b are denoted by solid dots.

Revised Thermochemical Data

After this work was completed, we learned from Prof. Squires that improved collision-induced dissociation (CID) experiments of *o*-, *m*-, and *p*-chlorophenyl anions in a flowing afterglow triple quadrupole apparatus have led to more reliable heats of formation for the three benzyne, namely 107 ± 3 (11), 123 ± 3 (12), and $137 \pm 3 \text{ kcal/mol}$ (2).³⁴ While the first value agrees within 1 kcal/mol with the previously reported heat for formation for the ortho isomer,⁹ the latter values are 7 and 9 kcal/mol, respectively, higher than the heats of formation reported by Wenthold, Paulino, and Squires.⁹ Squires and co-workers convincingly show in their work that "CID threshold measurements for the elimination reactions investigated can be extremely sensitive to small amounts of isomeric impurities in the reactant ion beam if this contaminant yields the same CID fragment ion with a greater efficiency and lower threshold energy than the main component."³⁴ In this connection, it is particular interesting that the authors became aware of these errors by independently carrying out MCSCF and correlation-consistent CI (CCCI) calculations on the three benzyne, which led to heats of formation of 107–116 (11), 124–131 (12), and 138–140 kcal/mol (2) depending on the method and basis set used.^{35a} The best values obtained are 107, 125, and 138 kcal/mol.

In Figure 6, CCSD(T)-based heats of formation are compared with the new experimental values. Theoretical and experimental ΔH_f° values now agree within the experimental error bars, i.e., deviations are 1.7 (11), 0.2 (12), and 2.6 kcal/mol (2). CCCI calculations of Squires and co-workers^{35a} seem to be in even better agreement with the revised experimental heats of formation, but it is difficult to say whether experimental or CCCI-based ΔH_f° values are really more accurate than the corresponding CCSD(T) values obtained in this work. The CCCI calculations cover relatively small parts of nondynamic and dynamic correlation effects. They are not size-extensive and do not contain the important T excitation effects. This can lead to an underestimation of the stability of the meta and para isomers. Also problematic is that the CCCI calculations were based on MCSCF(8,8)/3-21G and MCSCF(2,2)/6-31G(d) or /6-311G(d,p) geometries, which (similar to GVB or HF) underestimate bond lengths slightly.^{35a}

CCSD(T), on the other hand, has the advantages of being size-extensive and of covering a large part of dynamic correlation effects, in particular the important T effects (*vide infra*). In addition, it includes nondynamic correlation effects, but these

(34) Wenthold, P. G.; Squires, R. R. *J. Am. Chem. Soc.*, to be published.

(35) (a) Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* 1993, 115, 11958. See also: (b) Nicolaides, A. T.; Borden, W. T. *J. Am. Chem. Soc.* 1993, 115, 11951.

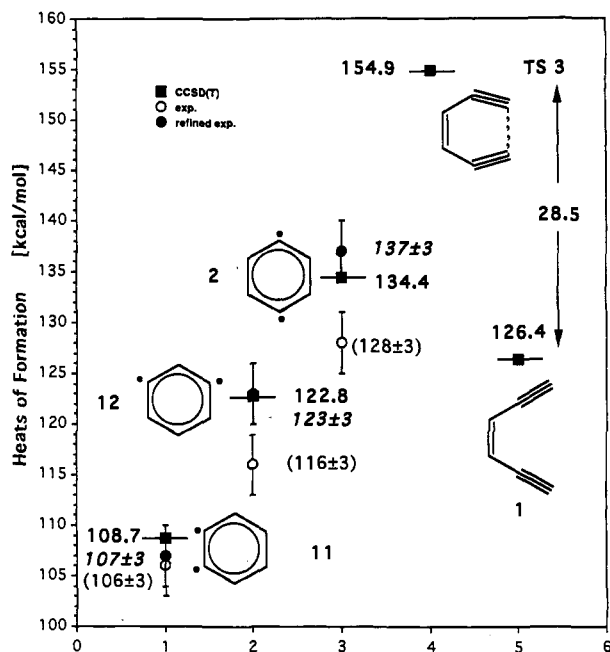


Figure 6. Comparison of CCSD(T)-based and experimental heats of formation, $\Delta H_f^\circ(298)$, of **1**, **2**, **3**, **11**, and **12** (for experimental values, see refs 9 and 34).

may not all be covered when starting from a single determinant reference function. In this way, **11** may be predicted to be somewhat too unstable and **2** somewhat too stable. Accordingly, the true heats of formation of the three benzyne may lay between the CCSD(T) and CCI values.

Conclusions

The following conclusions can be drawn from the investigation described in this work.

(1) CCSD(T)/DZ+P theory is an appropriate tool for adequately describing cyclization reactions that include biradicals, insofar as it is superior to CASSCF and MR-SDCI calculations with a constrained active space and a basis set lacking polarization functions.

(2) Analysis of the CCSD(T) natural orbitals shows that TS **3** does not possess significant biradical character. Although the geometry of **3** already resembles that of **2**, its electron distribution is still close to that of **1**. That implies that the actual formation

of the biradical must occur far out in the exit channel. As a consequence, reaction barriers evaluated as $E(3, \text{GVB}) - E(1, \text{SCF})$ must be erroneous.

(3) Reliable energy and enthalpy data to be comparable with experimental data can be obtained only if ZPE and other vibrational corrections are considered. Our final $\Delta_R H(298)$ value for the Bergman cyclization of **1** is 8.0 (corrected 10) kcal/mol, and the corresponding $\Delta H^\ddagger(298)$ is 28.5 kcal/mol.

(4) The slow energy increase in the entrance channel of the Bergman cyclization can be influenced by changes in the strain energy of an enediyne, where the distance R_{cd} is the controlling parameter for the energy change. We calculate that for a decrease of R_{cd} to 3.0 Å, the cycloaromatization reaction becomes spontaneous ($\Delta H^\ddagger(298) = 19.3$ kcal/mol). This can be used for the synthetic design of anticancer drugs in enediyene research using force field calculations.⁵⁻⁷

(5) CCSD(T)/6-31G(d,p) calculations suggest $\Delta H_f^\circ(298)$ values of 109, 123, and 134 kcal/mol for benzyne isomers **11**, **12**, and **2**, respectively. Accordingly, the meta and para isomers **12** and **2** are 14 and 25 kcal/mol less stable than the ortho isomer **11**. The originally published experimental $\Delta H_f^\circ(298)$ values⁹ for **12** and **2** are too low. This has recently been confirmed by Wenthold and Squires, who with refined measurements found $\Delta H_f^\circ = 107 \pm 3$ (**11**), 123 ± 3 (**12**), and 137 ± 3 kcal/mol (**2**).³⁴

Work is in progress to extend investigations to the Bergman cyclization of (*Z*)-1,2,4-heptatrien-6-yne, an enyne-allene system that produces a biradical at lower temperatures.³³

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Note added in proof: W. R. Roth, H. Hopf, and C. Horn (*Chem. Ber.*, in press) recently measured the energetics of the Bergman cyclization. They obtained for the ΔH_f° value of **2** 138.0 ± 1.0 kcal/mol, the enthalpy of reaction **1** 8.5 ± 1.0 kcal/mol, the entropy of **1** -7.2 ± 1.8 eu, and the activation enthalpy of **1** 28.2 ± 0.5 kcal/mol; these values are in good agreement with our CCSD(T) results.