2584 *J. Phys. Chem. A* **1998,** *102,* 2584−2593

Density Functional Study of Bergman Cyclization of Enediynes

Wei-Chen Chen, Nai-yuan Chang, and Chin-hui Yu*

Department of Chemistry, National Tsing Hua University, Hsinchu 300, Taiwan

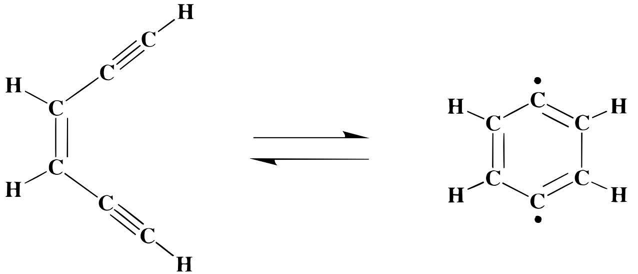
Received: October 7, 1997; In Final Form: January 28, 1998

Bergman cyclization of the enediynes (*Z*)-3-hexene-1,5-diyne (**1**), (*Z*)-3-heptene-1,5-diyne (**2**), (*Z*)-4-octene-2,6-diyne (**3**), (*Z*)-1-cyclononene-3,8-diyne (**4**), (*Z*)-1-cyclodecene-3,9-diyne (**5**), and (*Z*)-1-cycloundecene-3,10-diyne (**6**) has been studied by density functional methods. The reaction of **1** was first studied using the BP86, BLYP, BPW91, and B3LYP functionals with the 6-311G** basis set and the large ANO basis set for the latter two functionals. The BPW91/6-311G** calculations yielded results comparing well with those of high-level ab initio computations. Thus, BPW91/6-311G** was employed to study the reactions of **2**−**6**. Geometry optimizations and harmonic frequency calculations were applied for every reactant, transition structure, and product; frequency calculations were also carried out for other optimized stationary points. The optimized structure of the conformer of **6** with the lowest energy agrees excellently with the X-ray diffraction crystallographic structure. IRC (intrinsic reaction coordinate) calculations were carried out for the transition structures of **4**, **5**, and **6** to establish the reaction path. The zero-point energy corrected reaction barriers for **1**−**6** are 25.16, 27.93, 32.25, 12.09, 20.87, and 26.42 kcal/mol, respectively. Thermodynamic data, ΔH, ΔS, ΔG, ΔH_a, ΔS_a, and ΔG_a, have been evaluated at several temperatures. The temperature effect on the free energy is insignificant. The critical distance, which is the distance between the two carbon atoms forming a new bond, in the transition states of all six reactions is approximately 2.0 Å. The IRC analysis shows that the reaction coordinate is close to the critical distance, and the reactant with a larger critical distance is relatively more stable and has a higher barrier. Therefore, a smaller ring, possessing a larger strain energy and a shorter critical distance, has a lower barrier.

Introduction

The incorporated enediyne rings play a central role in the activity of a class of efficacious antitumor agents which can commonly include nine-membered rings,[1−4] such as kedarcidin chromophore, neocarzinostatin chromophore, and C-1027 chromophore, and 10-membered rings,[1,5−12] such as calicheamicin γ_1^I, esperamicin A$_1$, and dynemicin A. The Bergman cyclization[13] of the nine- or 10-membered ring of enediyne to form a 1,4-didehydrobenzene biradical[14] has been proposed as the key step in the antitumor bioactivity.[1−3,5−8,15,16] The bioactivity is attributed to the speculative mechanism that the highly reactive biradical abstracts certain hydrogens of DNA, leading to the breakdown of the cancer chromosome.[2,5−7,9,15] The research on the chemistry of these compounds has been vividly performed in many aspects, for example, the synthesis of the natural products,[10] the interaction of the antibiotics and DNA,[2,5−7,9,11,15] and theoretical simulations.[7,11,17] Two categories of theoretical modeling by means of molecular mechanics have been carried out to obtain a deeper understanding the chemistry related to the bioactivity of these antibiotics. One is to simulate both the interaction and the structure of the complexes of the enediyne compound and DNA;[11] the other is to investigate the relationship between the reactivity and the structure of the enediyne moiety.[7,17] The latter yielded useful information for chemists to synthesize simpler compounds having bioactivity similar to natural products.[5,9] The central concept is that the activation energy for the Bergman cyclization is somewhat proportional to the distance between the two atoms that form the additional bond during cyclization, hereafter named the critical distance. The ring size, the substitution, and the conformational structure are important factors that affect this critical distance.

SCHEME 1. Reaction 1: Bergman Reaction of (*Z*)-3-Hexene-1,5-diyne (1)



1

1-P

Several groups have performed high-level ab initio studies of Bergman cyclization of (*Z*)-3-hexene-1,5-diyne (**1**), reaction 1 as shown in Scheme 1, in order to establish the mechanism with accurate reaction barrier. Kraka and Cremer[18] used CCSD(T)/6-31G** to optimize the geometry of the reactant, transition state, and product of reaction 1 and also obtained the energetics along the reaction path. They found the reaction energy of 5.5 kcal/mol and reaction barrier of 29.5 kcal/mol. When the critical distance was reduced from 4.411 Å, which is the optimized value of **1**, to 3.0 Å, the energy increased by 9.2 kcal/mol; thus, the barrier decreased to 20.3 kcal/mol. They also noted that the inclusion of triple excitation in studying this reaction system yielded more reliable energetics. Lindh et al.[19,20] used the CASSCF(12,12) method to conduct the geometry optimization of reaction species in reaction 1 followed by energy calculations

---

* To whom correspondence should be addressed. Fax and phone +886-3-5721534. E-mail: chyu@hydrogen.chem.nthu.edu.tw.

S1089-5639(97)03261-1 CCC: $15.00

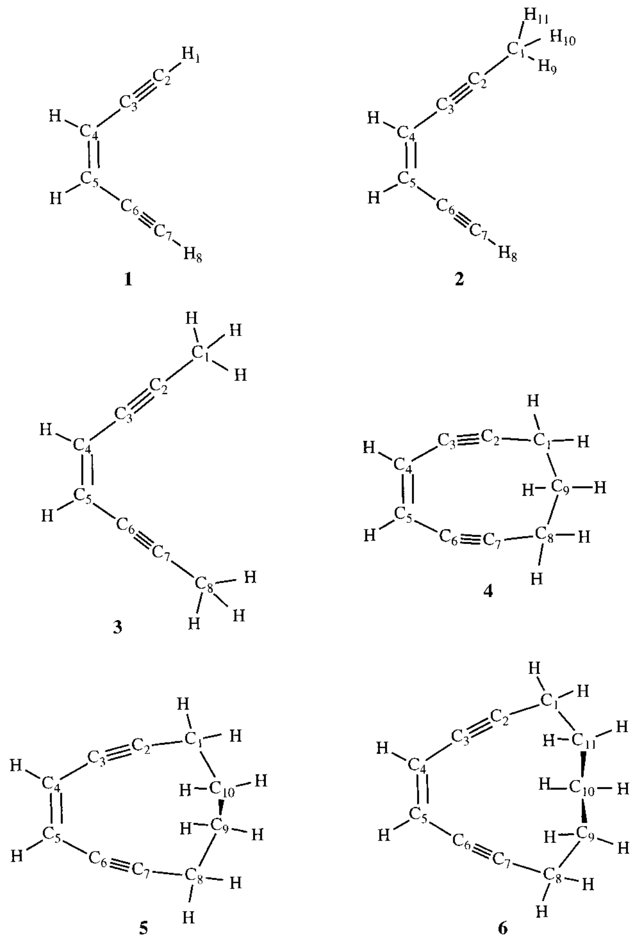


Figure 1. The six enediynes studied in this report. The labeling of atoms is for the convenience of comparison and does not follow conventional nomenclature.

by the CASPT2 method with several basis sets: DZP, TZ2P, and ANO. The calculated values with the average ANO basis set, C(5s4p2d) and H(3s2p), for the reaction energy and energy barrier were 27.70 and 43.64 kcal/mol at CASSCF(12,12) and 3.84 and 23.87 kcal/mol at CASPT2[g1], respectively. The CCSD(T)/ANO single-point energy calculation at the CASSCF(12,12)/ANO geometry provided a reaction energy and barrier of 10.81 and 29.65 kcal/mol, respectively. The CCSD(T) results agreed reasonably well with the experimentally determined heat of reaction and activation enthalpy, 8.4 ± 3.0 and 28.2 ± 0.5 kcal/mol,[20,21] respectively. The aforementioned reports studied the simplest enediyne **1** of an attainable size to carry out ab initio calculations with sufficient correlation effects included. These extensive studies on reaction 1 by high-level ab initio methods serve as a good foundation for further research on the reaction mechanism of larger enediyne rings involved in natural antibiotics.

In this article, we move one step further and study the size and strain effects by first principle calculations on larger systems: (*Z*)-3-heptene-1,5-diyne (**2**), (*Z*)-4-octene-2,6-diyne (**3**), (*Z*)-1-cyclononene-3,8-diyne (**4**), (*Z*)-1-cyclodecene-3,9-diyne (**5**), and (*Z*)-1-cycloundecene-3,10-diyne (**6**), as well as (*Z*)-3-hexene-1,5-diyne (**1**), shown in Figure 1. This study probes the effect of substitution by comparison of the mono- and dimethyl-substituted **2** and **3** to the basic enediyne moiety **1** and directly investigates the energy barrier for the rings **4**−**6**. The 10- and 11-membered ring compounds, **5** and **6**, have been synthesized.[7] The X-ray crystallographic structure of **6** is available for comparison.[7] High-level ab initio calculations including substantial electron correlation are not feasible for these ring enediynes. However, the density functional theory (DFT) has recently been applied to study many reactions, such as the vinylidene−acetylene rearrangement,[22] the Cope and Claisen rearrangement,[23] conformational behavior of glycine,[24] and various organic compounds and reactions.[25] These studies indicate that with cautious usage DFT can provide the reaction energy and barrier possessing errors similar to high-level correlated molecular orbital theories. Thus, DFT is an ideal alternative to investigate the Bergman reaction. In this article, we report the geometries and frequencies at each optimized structure of **1**−**6** and IRC calculations of the Bergman reaction for **4**−**6** carried out with density functional methods; energetics and thermodynamic data deduced from the calculations are also displayed.

Computational Details

The prototype of the Bergman reaction, the cyclization of **1** to form the singlet *p*-benzyne, reaction 1, was studied with several density functionals, which are generally believed to perform well in calculations of reaction energetics,[22−25] BP86,[26,27] BLYP,[26,28] BPW91,[26,29] and the hybrid B3LYP.[28,30] The basis set was the split-valence triple-ζ plus polarization 6-311G** set to ensure the quality of calculations, as it was noted that triple-ζ basis sets are of vital importance to obtain accurate relative energy in studying chemical reactions.[22−24] A large ANO basis set[31] was used with the BPW91 and B3LYP density functionals to ensure the completeness of the basis set and to avoid errors due to improper basis set. Geometry optimizations without any constraints were carried out for the reactant, product, and the transition-state structure. Additional details of the energetics along the reaction path were established by constraint optimization at a fixed distance between the terminal carbons, C_2 and C_7 (as labeled in Figure 1). Two such points, with the C_2C_7 distance being 3.175 and 3.0 Å, were optimized. The optimized structural parameters and energetics provided by the aforementioned density functional methods were then compared with the high-level ab initio data and experimental measurements. It turned out (details to be given in the Discussion section) that the combination of the Becke 88 exchange[26] and Perdew−Wang 91 correlation functionals,[29] BPW91, was the optimal choice for reaction 1. Thus, BPW91 was used for the systematic study of the Bergman cyclization of enediynes **2**−**6** in this work.

Harmonic vibrational frequencies were calculated at each stationary point for all compounds. The local minimum was characterized by all real frequencies, and the transition structure by one imaginary frequency. The vibrational normal modes were examined closely to confirm the reaction path. For ring enediynes **4**−**6** the intrinsic reaction coordinate (IRC) calculation,[32] which is the full intrinsic reaction path calculation as an option in the Gaussian 94 program,[33] was carried out starting at the plausible transition structure. Thermodynamic data, ΔH, ΔS, ΔG, ΔH_a, ΔS_a, and ΔG_a, were calculated using the canonical ensemble sampling of the vibrational and rotational modes at several temperatures.[34] The DFT calculations were performed with the Gaussian 94 program[33] using IBM RS6000/390 and SGI PowerChallenge R8000 workstations and Fujitsu VPP300 computers.

Results

Geometry. The optimized geometries of enediynes **1**−**6**, their transition structures for the Bergman cyclization, and the corresponding biradical products are listed in Tables 1−6, where

TABLE 1: Energies, Optimized Structures, and the Imaginary Frequency of Compounds Found in Studying the Bergman Reaction of (*Z*)-3-Hexene-1,5-diyne (1) with BPW91/6-311G Calculations**[a]

	1	**1-TS**	**1-P**
energy	−230.911 55	25.50	11.64
H_1C_2	1.069	1.077	1.089
C_2C_3	1.217	1.264	1.350
C_2C_7	4.512	2.064	1.481
C_3C_4	1.412	1.395	1.350
C_4C_5	1.368	1.407	1.481
C_5C_6	1.412	1.395	1.350
C_6C_7	1.217	1.264	1.350
C_7C_8	1.069	1.077	1.089
$\angle H_1C_2C_3$	178.90	150.26	127.39
$\angle C_2C_3C_4$	177.51	135.86	124.84
$\angle C_3C_2C_7$	51.94	105.56	117.58
$\angle C_3C_4C_5$	125.63	118.59	117.58
$\angle C_4C_5C_6$	125.49	118.57	117.58
$\angle C_5C_6C_7$	177.51	135.89	124.84
$\angle C_6C_7C_2$	51.90	105.54	117.58
$\angle C_6C_7C_8$	178.90	150.26	127.39
ϕ $H_1C_2C_3C_4$	180.0	180.0	180.0
ϕ $C_3C_4C_5C_6$	0.0	0.0	0.0
ϕ $H_8C_7C_6C_5$	180.0	180.0	180.0
imag. freq.		451i	

[a] Total energies (hartree) for the reactant, **1**, and energies (kcal/mol) relative to the reactant for others. Frequencies are in cm^{-1}.

TABLE 2: Energies, Optimized Structures, and the Imaginary Frequencies of Compounds Found in Studying the Bergman Reaction of (*Z*)-3-Heptene-1,5-diyne (2) with BPW91/6-311G Calculations**[a]

	2	**2-TS**	**2-P**	**2-A**	**2-B**
energy	−270.240 06	28.34	17.19	0.00	17.63
C_1C_2	1.454	1.479	1.511	1.454	1.514
C_2C_3	1.220	1.274	1.357	1.220	1.355
C_2C_7	4.522	2.017	1.489	4.519	1.491
C_3C_4	1.411	1.392	1.348	1.411	1.351
C_4C_5	1.365	1.408	1.481	1.363	1.477
C_5C_6	1.413	1.395	1.350	1.413	1.353
C_6C_7	1.217	1.270	1.349	1.217	1.347
C_7C_8	1.069	1.078	1.091	1.069	1.091
$\angle C_1C_2C_3$	179.00	147.76	127.34	178.95	128.41
$\angle C_2C_3C_4$	177.61	136.25	126.13	177.59	126.05
$\angle C_3C_2C_7$	51.75	104.13	115.02	51.76	114.98
$\angle C_3C_4C_5$	125.95	119.28	118.08	125.96	118.19
$\angle C_4C_5C_6$	125.56	117.93	116.76	125.52	116.77
$\angle C_5C_6C_7$	177.55	133.37	124.73	177.53	124.65
$\angle C_6C_7C_2$	51.84	109.05	119.30	51.85	119.38
$\angle C_6C_7C_8$	179.11	147.32	126.74	179.11	126.73
ϕ $C_1C_2C_3C_4$	−175.2	180.0	180.0	180.0	180.0
ϕ $C_3C_4C_5C_6$	0.0	0.0	0.0	0.0	0.0
ϕ $H_8C_7C_6C_5$	180.0	180.0	180.0	180.0	180.0
ϕ $H_9C_1C_2C_3$	−25.8	119.8	180.0	0.0	−120.1
ϕ $H_{10}C_1C_2C_3$	94.1	−119.1	−59.4	−120.2	120.1
ϕ $H_{11}C_1C_2C_3$	−146.2	0.3	59.4	120.2	0.0
imag. freq.		457i		19i	88i

[a] Total energies (hartree) for the reactant, **2**, and energies (kcal/mol) relative to the reactant for others. Frequencies are in cm^{-1}.

TABLE 3: Energies, Optimized Structures, and the Imaginary Frequency of Compounds Found in Studying the Bergman Reaction of (*Z*)-4-Octene-2,6-diyne (3) with BPW91/6-311G Calculations**[a]

	3	**3-TS**	**3-P**
energy	−309.567 96	32.42	24.68
C_1C_2	1.454	1.483	1.514
C_2C_3	1.220	1.284	1.354
C_2C_7	4.541	1.971	1.510
C_3C_4	1.412	1.387	1.350
C_4C_5	1.366	1.414	1.475
C_5C_6	1.412	1.387	1.350
C_6C_7	1.220	1.284	1.354
C_7C_8	1.454	1.483	1.514
$\angle C_1C_2C_3$	179.00	142.27	126.31
$\angle C_2C_3C_4$	177.47	133.99	126.35
$\angle C_3C_2C_7$	51.53	107.44	116.36
$\angle C_3C_4C_5$	125.92	118.58	117.30
$\angle C_4C_5C_6$	125.92	118.59	117.28
$\angle C_5C_6C_7$	177.45	133.98	126.34
$\angle C_6C_7C_2$	51.51	107.44	116.38
$\angle C_6C_7C_8$	178.95	142.25	126.31
ϕ $C_1C_2C_3C_4$	−176.1	180.0	180.0
ϕ $C_3C_4C_5C_6$	0.0	0.0	0.0
ϕ $C_8C_7C_6C_5$	−177.3	180.0	180.0
imag. freq.		460i	

[a] Total energies (hartree) for the reactant, **3**, and energies (kcal/mol) relative to the reactant for others. Frequencies are in cm^{-1}.

TABLE 4: Energies, Optimized Structures, and the Imaginary Frequencies of Compounds Found in Studying the Bergman Reaction of (*Z*)-1-Cyclononene-3,8-diyne (4) with BPW91/6-311G Calculations**[a]

	4	**4-TS**	**4-P**	**2-A**
energy	−347.656 10	12.93	5.85	9.29
C_1C_2	1.459	1.484	1.519	1.454
C_1C_9	1.557	1.541	1.541	1.584
C_2C_3	1.223	1.276	1.343	1.225
C_2C_7	2.913	1.958	1.508	2.786
C_3C_4	1.415	1.392	1.355	1.410
C_4C_5	1.378	1.413	1.473	1.396
C_5C_6	1.415	1.392	1.355	1.410
C_6C_7	1.223	1.276	1.343	1.225
C_7C_8	1.459	1.484	1.519	1.454
C_8C_9	1.557	1.541	1.541	1.584
$\angle C_1C_2C_3$	169.93	151.77	134.82	178.02
$\angle C_1C_9C_8$	116.27	106.90	104.79	123.86
$\angle C_2C_3C_4$	156.76	133.09	125.07	154.81
$\angle C_2C_1C_9$	112.36	108.15	104.60	117.90
$\angle C_3C_2C_7$	85.21	108.15	117.19	87.81
$\angle C_3C_4C_5$	118.05	118.77	117.76	117.39
$\angle C_4C_5C_6$	118.04	118.76	117.76	117.34
$\angle C_5C_6C_7$	156.76	133.12	125.06	154.86
$\angle C_6C_7C_2$	85.20	108.12	117.19	87.81
$\angle C_6C_7C_8$	169.92	151.78	134.81	178.02
$\angle C_7C_8C_9$	112.35	108.13	104.59	117.91
ϕ $C_1C_2C_3C_4$	0.9	176.7	175.6	0.4
ϕ $C_3C_4C_5C_6$	0.0	0.0	0.0	0.0
ϕ $C_8C_7C_6C_5$	0.9	−176.7	−175.6	−0.4
ϕ $C_9C_1C_2C_3$	−29.1	159.7	165.0	−0.2
ϕ $C_9C_8C_7C_6$	29.1	−159.8	−165.0	0.2
imag. freq.		446i		256i

[a] Total energies (hartree) for the reactant, **4**, and energies (kcal/mol) relative to the reactant for others. Frequencies are in cm^{-1}.

the labeling of atoms for each compound is given in Figure 1. The optimized bond lengths have the desired symmetrical properties; for example, $R_{C_2C_3}$ equals $R_{C_6C_7}$. Nevertheless, some pairs of bond angles deviate by less than 0.2° probably because the convergence criteria are not sufficiently tight. The critical distance $R_{C_2C_7}$ is ~2.0 Å for all six transition structures; they are 2.064, 2.017, 1.971, 1.958, 1.984, and 1.995 Å for **1**−**6**, respectively. The length of the new bond, $R_{C_2C_7}$, is 0.03 Å shorter in **1-P** than in **3-P** due to the steric effect of the two methyl groups. This bond length in **2-P** lies between that of **1-P** and **3-P**. For the ring products **4-P**, **5-P**, and **6-P**, $R_{C_2C_7}$ is ~1.5 Å, which is the length of a single CC bond. The changes of the C_2C_3, C_3C_4, and C_4C_5 bond lengths from the reactant to the transition structure are larger than those from the transition

TABLE 5: Energies, Optimized Structures, and the Imaginary Frequency of Compounds Found in Studying the Bergman Reaction of (*Z*)-1-Cyclodecene-3,9-diyne (5) with BPW91/6-311G Calculations**[a]

	5	5-TS	5-P
energy	−386.978 97	21.60	12.72
C_1C_2	1.458	1.494	1.527
C_1C_{10}	1.556	1.534	1.531
C_2C_3	1.222	1.284	1.357
C_2C_7	3.393	1.984	1.500
C_3C_4	1.414	1.386	1.346
C_4C_5	1.372	1.414	1.481
C_5C_6	1.414	1.386	1.346
C_6C_7	1.222	1.284	1.357
C_7C_8	1.458	1.494	1.527
C_8C_9	1.557	1.534	1.530
C_9O_{10}	1.553	1.531	1.531
$\angle C_1C_2C_3$	171.34	140.17	124.26
$\angle C_1C_{10}C_9$	115.46	111.94	110. 33
$\angle C_2C_3C_4$	165.86	134.81	126.60
$\angle C_2C_1C_{10}$	112.01	116.81	115.20
$\angle C_3C_2C_7$	74.82	106.86	116.35
$\angle C_3C_4C_5$	119.22	118.32	117.05
$\angle C_4C_5C_6$	119.23	118.33	117.06
$\angle C_5C_6C_7$	165.86	134.81	126.60
$\angle C_6C_7C_2$	74.81	106.88	116.35
$\angle C_6C_7C_8$	171.35	140.19	124.27
$\angle C_7C_8C_9$	112.00	116.78	114.97
$\angle C_8C_9C_{10}$	115.47	111.91	110.13
$\phi\ C_1C_2C_3C_4$	−16.5	175.2	179.4
$\phi\ C_1C_{10}C_9C_8$	−118.3	−71.2	−63.7
$\phi\ C_3C_4C_5C_6$	−1.7	−0.5	0.0
$\phi\ C_8C_7C_6C_5$	−16.0	175.1	179.4
$\phi\ C_9C_8C_7C_6$	8.4	162.4	163.3
$\phi\ C_9C_{10}C_1C_2$	68.2	54.2	47.5
$\phi\ C_{10}C_1C_2C_3$	8.5	162.5	164.6
$\phi\ C_{10}C_9C_8C_7$	68.2	54.4	48.8
imag. freq.		450i	

[a] Total energies (hartree) for the reactant, **5**, and energies (kcal/mol) relative to the reactant for others. Frequencies are in cm^{-1}.

structure to the product; thus, they all are late transition states.[35] All transition structures are characterized by one and only one imaginary frequency, which is 451i, 457i, 460i, 446i, 450i, and 453i cm^{-1} for **1**−**6**, respectively. Normal mode analysis clearly indicates that the imaginary frequency mode corresponding to the reaction coordinate is the C−C stretching between the two carbon atoms forming the new bond. Several stationary points that are neither the reactant, the product, nor the transition structure of the Bergman reaction for compounds **1**−**6** are found in geometry optimization calculations. For **2**, there is one structure, **2-A**, deviating from the reactant, and the other, **2-B**, deviating from the product only by the orientation of the methyl group. The vibrational frequency analysis indicates that each one has a normal mode with a weak imaginary frequency, 19i and 88i cm^{-1} for **2-A** and **2-B**, respectively, corresponding to the rotation of methyl hydrogens; therefore, they are the transition structures of the torsional rotation of the methyl group. For the enediyne-type compounds, the two torsional conformers, **2** and **2-A**, have the same energy and the rotation about the C−C bond is nearly free. For the biradical compounds, **2-P** and **2-B**, the C−C bond rotational barrier is 0.44 kcal/mol. The transition structure between the enantiomers of **4** possesses an imaginary frequency of 256i cm^{-1}, corresponding to a flip of the tip carbon C_9 (where the labeling is the same as in Figure 1) as shown in Figure 2a. For the 11-membered ring enediyne, there are two local minima, **6** and **6-A**, as shown in Figure 2b; with energies differing by 0.58 kcal/mol. Three *p*-benzyne biradical compounds corresponding to **6** are found. The one with the lowest energy, **6-P**, is the product of the Bergman reaction of **6**. The other two, **6-B** and **6-C**, are 4.56 and 1.69 kcal/mol higher in energy, respectively. The transition structure, **6-D**, between **6-B** and **6-C** has also been identified to have the proper imaginary mode, as illustrated in Figure 2c.

Energetics. The reaction energies without the zero-point energy (ZPE) correction are 11.64, 17.19, 24.68, 5.85, 12.72, and 18.29 kcal/mol for **1**−**6**, respectively, whereas the classical barriers are 25.50, 28.34, 32.42, 12.93, 21.60, and 27.17 kcal/mol, respectively. The ZPE changes the relative energy by less than 1 kcal/mol, as summarized in Table 7. The Gibbs free enegies, ΔG, of the Bergman reaction of **1**−**6** are 14.51, 21.14, 28.73, 6.06, 13.42, and 19.39 kcal/mol, respectively, at 298 K, and the corresponding Gibbs free energies of activation, ΔG_a, are 26.35, 29.65, 35.83, 12.56, 21.57, and 27.29 kcal/mol, respectively. The substitution by methyl groups enlarges the barrier significantly. On the contrary, the strain energy of the ring lowers the barrier substantially.

Discussion

Comparison of DFT Data and Previous High-Level ab Initio Results for Reaction 1. The energetics of reaction 1 calculated by four density functional methods, BP86, BLYP, BPW91, and B3LYP, with the 6-311G** basis set, and by BPW91 and B3LYP with the ANO basis set, the same as the one used in the cited ab initio calculations, are listed in Table 8 together with high-level ab initio results and experimental data. Both the reaction energy and activation energy at CASSCF are significantly higher than the experimental measurements, although the basis set convergence is superb. The CCSD method obtains both values too high. The inclusion of triple excitations in CC methods gives data that better fit the experimental values.[20] The CCSD(T)/ANO calculation provides a ΔE_a of 29.65, best agreeing with the experimental data,[20,21] 28.23 ± 0.5 (473 K), among all available high-level ab initio calculations. The ΔE of CCSD(T)/ANO is 10.81 kcal/mol, lying in the upper region of the experimentally observed 8.4 ± 3.0 (298 K) kcal/mol. The CASPT2[g1] method yields both values lower, where the barrier is considerably lower than the experimentally observed value and the energy of reaction is in the lower region of the experimental data.

A density functional method is to be chosen for studying the Bergman reaction of **2**−**6**. The criterion is reliable geometry and energetics with more emphasis on the barrier for studying the reaction mechanism. For the density functional calculations with the 6-311G** basis set, B3LYP yields too high reaction barrier and reaction energy, 34.35 and 25.67 kcal/mol, respectively; BLYP overestimates the reaction energy by ∼9 kcal/mol. For ΔE_a and ΔE, BP86 provides 24.62 and 11.01 kcal/mol, respectively; BPW91 provides 25.50 and 11.64 kcal/mol, respectively. With the large ANO basis set, which is exactly the same as that used in the aforementioned ab initio calculations, ΔE_a and ΔE with B3LYP are 32.81 and 23.77 kcal/mol, while they are 24.40 and 10.08 kcal/mol with BPW91. The deviations between the 6-311G** and ANO basis sets are far less than those between the functionals. Since the ANO basis set is too large to be applied to larger systems, 6-311G** is an optimal choice for the basis set. All four functionals overestimate the energy of *p*-benzyne, thus giving too high reaction energy. Among them, BP86 and BPW91 better agree with the experimental and ab initio values. All but B3LYP yield reasonable barrier. Hence, the possible choice of the density functional to study the Bergman reaction is either BP86 or BPW91 with the 6-311G** basis set. We use BPW91 for other

TABLE 6: Energies, Optimized Structures, and the Imaginary Frequencies of Compounds Found in Studying the Bergman Reaction of (*Z*)-1-Cycloundecene-3,10-diyne (6) with BPW91/6-311G Calculations**[a]

	6	**6-TS**	**6-P**	**6-A**	**6-B**	**6-C**	**6-D**
energy	−426.298 70	27.17	18.29	−0.58	22.85	19.98	25.08
C_1C_2	1.461	1.488	1.524	1.459	1.535	1.520	1.531
C_1C_{11}	1.556	1.551	1.546	1.560	1.538	1.555	1.539
C_2C_3	1.222	1.282	1.354	1.222	1.359	1.351	1.359
C_2C_7	3.976	1.995	1.504	3.766	1.502	1.517	1.500
C_3C_4	1.413	1.389	1.350	1.414	1.346	1.352	1.346
C_4C_5	1.370	1.411	1.475	1.371	1.481	1.472	1.482
C_5C_6	1.413	1.389	1.350	1.413	1.346	1.352	1.345
C_6C_7	1.222	1.282	1.354	1.222	1.359	1.351	1.360
C_7C_8	1.461	1.488	1.524	1.460	1.535	1.520	1.536
C_8C_9	1.556	1.551	1.546	1.556	1.538	1.555	1.535
C_9C_{10}	1.547	1.536	1.536	1.541	1.538	1.538	1.535
$C_{10}C_{11}$	1.547	1.536	1.536	1.539	1.538	1.538	1.556
$\angle C_1C_2C_3$	170.92	142.19	125.36	172.37	121.57	127.47	122.52
$\angle C_1C_{11}C_{10}$	112.92	115.08	114.60	115.37	113.54	114.99	115.33
$\angle C_2C_3C_4$	174.19	134.62	126.40	172.02	127.09	126.28	127.05
$\angle C_2C_1C_{11}$	110.93	115.70	114.72	113.78	116.95	114.05	115.38
$\angle C_3C_2C_7$	63.45	106.85	116.42	66.89	116.06	116.35	116.27
$\angle C_3C_4C_5$	122.38	118.53	117.19	121.40	116.86	117.38	116.71
$\angle C_4C_5C_6$	122.39	118.54	117.20	120.93	116.85	117.38	116.92
$\angle C_5C_6C_7$	174.19	134.62	126.39	170.52	127.09	126.28	127.11
$\angle C_6C_7C_2$	63.45	106.84	116.41	68.22	116.06	116.35	115.95
$\angle C_6C_7C_8$	170.95	142.20	125.37	169.36	121.57	127.46	120.01
$\angle C_7C_8C_9$	110.90	115.70	114.72	110.13	116.95	114.05	121.57
$\angle C_8C_9C_{10}$	112.93	115.08	114.60	112.60	113.54	114.99	114.89
$\angle C_9C_{10}C_{11}$	114.97	116.65	115.67	116.22	112.81	116.03	114.97
$\phi\ C_1C_2C_3C_4$	−3.6	−179.7	179.0	0.8	−179.6	−179.0	178.7
$\phi\ C_1C_{11}C_{10}C_9$	−142.5	−62.8	−60.1	−61.3	−44.0	54.6	−0.3
$\phi\ C_2C_1C_{11}C_{10}$	58.6	90.1	82.6	−42.5	85.5	33.0	73.6
$\phi\ C_3C_4C_5C_6$	0.0	0.0	0.0	−0.2	0.0	0.0	0.2
$\phi\ C_8C_7C_6C_5$	−3.5	179.7	−179.0	−2.2	−179.6	179.0	179.7
$\phi\ C_8C_9C_{10}C_{11}$	142.5	62.8	60.1	156.9	−44.0	−54.6	−72.3
$\phi\ C_9C_8C_7C_6$	18.4	−110.4	−113.4	6.0	144.9	−107.3	178.6
$\phi\ C_7C_8C_9C_{10}$	−58.6	−90.1	−82.6	−64.0	85.5	−33.0	60.7
$\phi\ C_{11}C_1C_2C_3$	−18.4	110.4	113.4	54.4	144.9	107.3	120.0
imag. freq.		453i					91i

[a] Total energies (hartree) for the reactant, **6**, and energies (kcal/mol) relative to the reactant for others. Frequencies are in cm^{-1}.

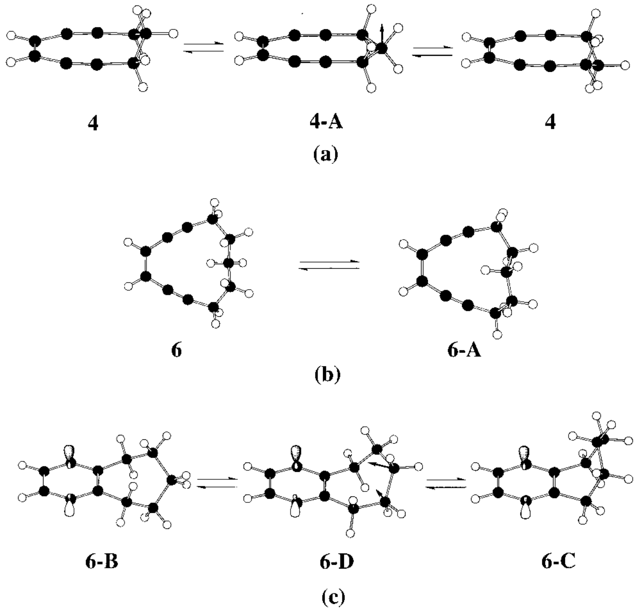


Figure 2. (a) Ring inversion of the enantiomers of **4**, where **4-A** is the transition structure; (b) conformational conversion between **6** and **6-A**; (c) conformational conversion between **6-B** and **6-C** with the transition structure **6-D**.

enediynes in this work. Although B3LYP performs well for many chemical systems,[23,25] it has been known in the literature that in several reaction systems some nonhybrid types of density functionals provide better energetics.[22,24,25] From the above analysis, we suggest that when radical or biradical characters evolve during the reaction course, the standard Becke three-parameter fit of the hybrid functional is not optimized.

Reaction 1 has been studied thoroughly with high-level ab initio methods,[18−20] and the electronic structure, particularly the biradical character of the wave function, has been analyzed with quantitative estimates. It is accepted that the biradical character appears rather late in the reaction; thus, the transition structure does not possess strong biradical character. However, the *p*-benzyne product is conventionally believed to be a biradical and its biradical character is estimated to be 65%.[18] The single-reference methods, such as CCSD(T) and properly selected DFT, can provide an accurate reaction barrier since these methods are able to recover the partial biradical nature of the transition state; nevertheless, these methods are in principle deficient to study biradicals. Multireference methods are required for studying biradicals. The reaction energy directly involves the energy of the biradical product, and CCSD(T) and DFT methods are not generally expected to deduce accurate reaction energy. The energy of reaction at 298 K calculated with CCSD(T)/ANO is reported to be inferior to the multireference CASPT2[g1]/ANO results.[20] The DFT results for reaction 1 are fairly close to the CCSD(T) data. Thus, it is advised to be cautious regarding the energetics of biradical products. For compounds **2**−**6**, the errors of BPW91/6-311G** calculations due to the

TABLE 7: Energy of Reaction (ΔE) and Energy Barrier (ΔE_a) without and with the ZPE Correction; Enthalpy, Entropy, and Free Energy of Reaction (ΔH, ΔS, and ΔG); and the Activation Enthalpy, Activation entropy, and Activation Free Energy (ΔH_a, ΔS_a, and ΔG_a) of the Bergman Reaction of Enediynes 1−6 (Energies in kcal/mol and Entropies in cal K^{-1} mol^{-1})

	1	**2**	**3**	**4**	**5**	**6**
Relative Energy without the ZPE Correction						
ΔE	11.64	17.19	24.68	5.85	12.72	18.29
ΔE_a	25.50	28.34	32.42	12.93	21.60	27.17
Relative Energy with the ZPE Correction						
ΔE	12.67	17.90	25.14	5.54	12.59	18.28
ΔE_a	25.16	27.93	32.25	12.09	20.87	26.42
273.15 K						
ΔH	11.73	16.85	23.94	5.05	11.96	17.55
ΔS	−9.28	−14.36	−16.05	−3.38	−4.87	−6.16
ΔG	14.27	20.77	28.33	5.97	13.29	19.23
ΔH_a	24.42	27.15	31.08	11.62	20.28	25.79
ΔS_a	−6.48	−8.37	−15.95	−3.12	−4.29	−5.02
ΔG_a	26.18	29.43	35.43	12.48	21.45	27.16
298.15 K						
ΔH	11.62	16.76	23.87	5.00	11.90	17.49
ΔS	−9.67	−14.68	−16.30	−3.57	−5.08	−6.38
ΔG	14.51	21.14	28.73	6.06	13.42	19.39
ΔH_a	24.33	27.07	30.99	11.56	20.21	25.72
ΔS_a	−6.77	−8.65	−16.24	−3.34	−4.53	−5.26
ΔG_a	26.35	29.65	35.83	12.56	21.57	27.29
310.65 K						
ΔH	11.57	16.72	23.84	4.97	11.88	17.46
ΔS	−9.84	−14.82	−16.41	−3.65	−5.17	−6.48
ΔG	14.63	21.32	28.94	6.11	13.48	19.47
ΔH_a	24.29	27.03	30.95	11.53	20.18	25.69
ΔS_a	−6.91	−8.78	−16.37	−3.44	−4.65	−5.37
ΔG_a	26.44	29.76	36.04	12.60	21.62	27.36
373.15 K						
ΔH	11.33	16.54	23.71	4.87	11.76	17.34
ΔS	−10.54	−15.36	−16.78	−3.94	−5.50	−6.83
ΔG	15.27	22.27	29.97	6.35	13.82	19.89
ΔH_a	24.09	26.84	30.77	11.38	20.01	25.53
ΔS_a	−7.49	−9.33	−16.90	−3.87	−5.13	−5.85
ΔG_a	26.89	30.32	37.08	12.83	21.93	27.71
423.15 K						
ΔH	11.18	16.42	23.65	4.82	11.70	17.27
ΔS	−10.93	−15.64	−16.95	−4.07	−5.65	−7.00
ΔG	15.80	23.04	30.82	6.55	14.09	20.23
ΔH_a	23.95	26.71	30.65	11.28	19.89	25.41
ΔS_a	−7.85	−9.66	−17.21	−4.15	−5.43	−6.14
ΔG_a	27.27	30.80	37.93	13.03	22.19	28.01
473.15 K						
ΔH	11.05	16.34	23.61	4.79	11.66	17.23
ΔS	−11.22	−15.82	−17.04	−4.14	−5.75	−7.09
ΔG	16.36	23.83	31.67	6.75	14.38	20.59
ΔH_a	23.82	26.59	30.54	11.18	19.78	25.30
ΔS_a	−8.14	−9.93	−17.46	−4.37	−5.68	−6.38
ΔG_a	27.67	31.29	38.80	13.24	22.47	28.32
500.00 K						
ΔH	10.99	16.31	23.59	4.79	11.65	17.22
ΔS	−11.33	−15.90	−17.06	−4.15	−5.78	−7.13
ΔG	16.66	24.25	32.13	6.87	14.53	20.78
ΔH_a	23.75	26.53	30.49	11.12	19.73	25.25
ΔS_a	−8.28	−10.05	−17.57	−4.47	−5.80	−6.49
ΔG_a	27.89	31.56	39.27	13.36	22.63	28.49

single-reference nature of DFT are expected to be similar to those for reaction 1 since the structure of the biradical part is similar for the species involved in the Bergman reaction of all six compounds.

The best estimate of structural parameters of compounds involved in reaction 1 to date is the CASSCF(12,12)/ANO data. The geometry obtained by DFT with 6-311G** and the ANO basis sets is essentially the same. All following data refer to the computations with the 6-311G** basis set. The DFT bond lengths are slightly longer by ~0.02 Å for CH bonds and shorter by 0.01 Å for both C−C single and C−C triple bonds compared with the best CASSCF data. The transition structures from the DFT and the CCSD(T)/ANO[20] calculations are more distinct; for instance, a 0.04 Å longer HC−CH bond was obtained. The optimized length of the double bond $R_{C_4C_5}$ in **1** is 1.362, 1.353, 1.362, 1.368, and 1.371 Å with CASSCF(12,12),[19] B3LYP, BP86, BPW91, and BLYP, respectively. The calculated bond length is longer than the double CC bond of ethene, 1.339 Å. The deviations for other bond lengths between those calculated by BPW91 and ab initio methods are notably smaller. In summary, the DFT structures are quite reliable.

Structures of Compounds Involved in the Bergman Reaction. Neglecting the methyl hydrogen atoms, the cyclization of the open-ended enediynes **1**, **2**, and **3** is confined to the planar symmetry. The ring structure of **4**−**6** breaks the linearity of C−C triple bonds; the $\angle C_5C_6C_7$ and $\angle C_6C_7C_8$ are 156.76° and 169.92° for **4**, 165.86° and 171.35° for **5**, and 174.19° and 170.95° for **6**, respectively. The larger 11-membered ring **6** distorts by less than 10°, whereas the smaller nine-membered ring **4** distorts by as much as 23°. The distortion of the 10-membered ring **5** lies in between. This distortion increases the energy of the enediyne, and therefore a lower reaction barrier is encountered. The smallest ring compound **4** displays the most significant effect.

The transition structure of the six Bergman reactions is characterized by the imaginary normal mode corresponding to the CC stretching of the two carbons forming the new bond with a frequency near 450i cm^{-1}. For ring compounds **4**−**6**, the transition structure is further identified with the IRC calculation[32] depicting the reaction path starting from the TS to the reactant in one direction and to the product in the other. Plotted in Figure 3 are the relative energies of each optimized structure from IRC calculations for **4**−**6** against $R_{C_2C_7}$, which is not exactly the reaction coordinate but only something very close. The curves are quite smooth, which indicates that $R_{C_2C_7}$ can represent the reaction coordinate. The $R_{C_2C_7}$ distance of all six transition structures is approximately 2.0 Å. Therefore, the transition structure of all six enediynes is located at a similar position on each potential energy surface.

The product consists of a *p*-benzyne moiety. The BPW91 optimized $R_{H_1C_2}$, $R_{C_2C_3}$, and $R_{C_2C_7}$ for **1** are 1.089, 1.350, and 1.481 Å, which differ from the CASSCF(12,12) data[20] by 0.08, 0.03, and 0.04 Å, respectively. The bond angle $\angle C_2C_3C_4$ deviates from the ab initio value only by 0.4°. In fact, the *p*-benzyne parts among all six products are quite similar to one another, with the largest deviation of 0.08 Å for the new CC bond and ~1° in the angles. The lengths of the single bond connecting the *p*-benzyne moiety are similar among **2**−**6** as well.

Other Optimized Structures. Several structures, including enediynes, biradicals, and transition states that are not directly related to the Bergman reaction, are found in the geometry optimization of compounds **2**, **4**, and **6**. Two transition structures corresponding to the torsional rotation of the substituent methyl group of **2** are found, labeled as **2-A** and **2-B** in Table 2. The structure of **2-A** is very similar to that of **2**, bond angles being consistent within 0.4° and bond lengths within 0.03 Å, except the methyl group rotates by ~25°. The energy difference is negligible at the BPW91/6-311G** level, and the vibrational mode corresponding to the torsional rotation is 19i cm^{-1}, demonstrating the very loose confinement of the motion. The transition structure for the torsional rotation of the product

TABLE 8: Energetics of the Bergman Reaction of (*Z*)-3-Hexene-1,5-diyne (1) by Different Computational Methods; Total Energy for 1 with Fully Optimized Structure in Hartrees and Relative Energy in kcal/mol for Others

method	**1**(opt)[a]	**1** with $R_{C_2C_7}$[b]		**1-TS**	**1-P**
		3.175 Å	3.0 Å		
BP86/6-311G**	−230.935 98	7.46	9.82	24.62	11.01
BLYP/6-311G**	−230.860 80	8.23	10.78	28.60	17.75
BPW91/6-311G**	−230.911 55	7.73	10.16	25.50	11.64
BPW91/ANO	−230.934 09			24.40	10.08
B3LYP/6-311G**	−230.947 50	8.17	10.90	34.35	25.67
B3LYP/ANO	−230.970 11			32.81	23.77
CASSCF(12,12)/TZ2P[c]	−229.651 25	7.37		43.64	27.64
CASSCF(12,12)/ANO[c]	−229.656 66	7.37		43.64	27.70
CASPT2[0]/TZ2P[c]	−230.317 78	5.11		21.55	0.42
CASPT2[0]/ANO[c]	−230.307 18	5.62		23.20	2.34
CASPT2[g1]/ANO[d]	−230.306 33	5.66		23.87	3.84
CCSD/ANO[d]	−230.333 11	7.12		40.03	31.10
CCSD(T)/ANO[d]	−230.381 18	6.29		29.65	10.81
CCSD(T)/6-31G**[e]	−230.258 39		9.2	29.5	5.5
experiment[f]				28.23 ± 0.5	8.4 ± 3.0

[a] Fully optimized structure. [b] Constraint optimized with $R_{C_2C_7}$ fixed at the given value. [c] Ref 19. [d] Ref 20. [e] Ref 18. [f] Refs 20, 21.

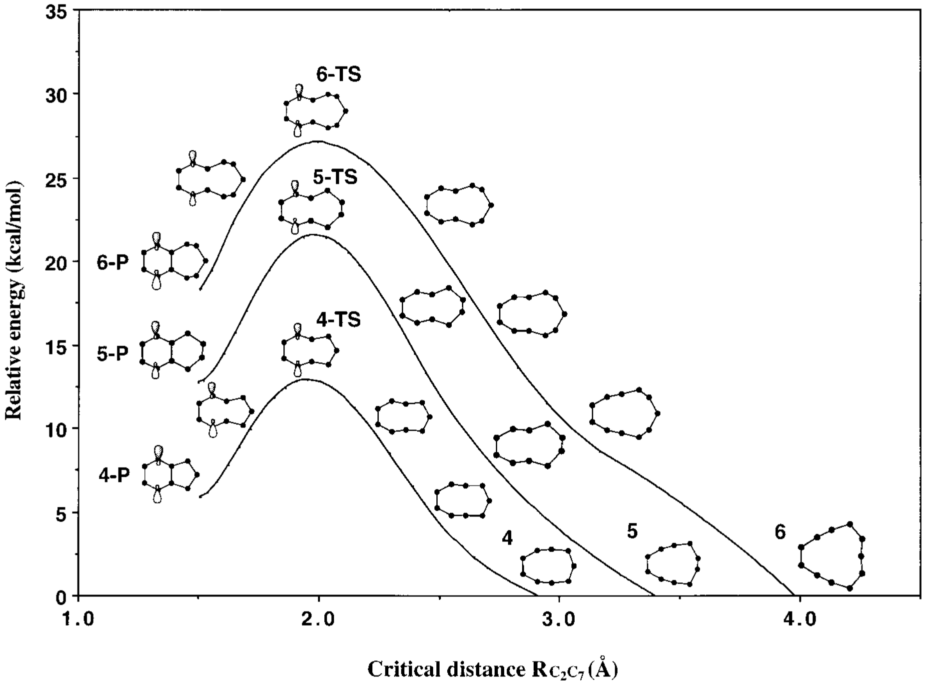


Figure 3. Energetic profile of the Bergman reaction of **4**, **5**, and **6** obtained via IRC calculations tracing the reaction path of the Bergman reaction of each compound.

2-P is also optimized, labeled as **2-B**, with the methyl group rotating by ~60° and an energy 0.44 kcal/mol higher. Similarly, other structural differences between **2-P** and **2-B** are negligible. The imaginary frequency mode in **2-B** is the torsional rotation, with a frequency of 88i cm^{-1}, which is slightly higher than that in the open-ended **2-A** due to the more restricted *p*-benzyne structure and the induced electrostatic effect. For the nine-membered ring **4**, the optimization provides a C_2 symmetrical conformer, **4-A**, of the enediyne, in addition to the C_s symmetrical global minimum, **4**. Vibrational analysis of **4-A** shows that it is a saddle point possessing an imaginary frequency for the out-of-plane motion of C_9 (as labeled in Figure 1); thus, **4-A** is the transition structure of the ring inversion between the two enantiomers of **4**, with a barrier of 9.29 kcal/mol, as shown in Figure 2a. Several conformers of enediynes or biradical products are found for **6**; thus, IRC calculations are necessary to elucidate the reaction path. Although various conformers are found only for **6**, IRC calculations have been carried out for all three ring enediynes, **4**, **5**, and **6**, in order to avoid ambiguity. Two conformers, **6** and **6-A**, Figure 2b, of the 11-membered-ring enediyne were obtained from the geometry optimization. Structures of **6** and **6-A** differ notably only in the sp^3-C ring skeleton, as tabulated in Table 6. **6-A** is lower in energy by 0.58 kcal/mol. The bond lengths in the two conformers differ by less than 0.08 Å, while the deviations of bond angles are 1−3°. The crystal structure reported by Nicolaou et al.[7] corresponds to **6-A**. The BPW91/6-311G** calculation excellently reproduces the crystallographic structure, with the bond lengths within 0.05 Å, the critical distance $R_{C_2C_7}$ within 0.1 Å, and the bond angles within 1°. The IRC analysis, Figure 3, shows that isomer **6**, rather than the slightly more stable **6-A**, is directly involved in the Bergman cyclization of the 11-membered-ring enediyne. There are three different isomers of the *p*-benzyne moiety, labeled **6-P**, **6-B**, and **6-C**, with energies 18.29, 22.85, and 19.98 kcal/mol higher than **6**, respectively. The only noticeable difference between the isomers is the orientation of the saturated carbons. The product of the Bergman cyclization of **6** is identified by IRC calculation to be the one with the lowest energy, **6-P**. The transition structure for the interconversion between the other two conformers, **6-B** and **6-C**, is identified as **6-D**, shown in Figure 2c, with an energy 5.10 kcal/mol higher than **6-C**.

The Energetics of the Bergman Reaction. The thermodynamic data of the Bergman reactions of **1**−**6**, computed on the basis of the BPW91/6-311G** calculations, are listed in Table 7. The ΔG_a of **1** at 473 K is 27.67 kcal/mol, which is fairly close to the experimental value of 28.23 ± 0.5 kcal/mol.[21] The E_a without the ZPE correction is 25.50 kcal/mol, comparing well with the high-level ab initio results of CASPT2[g1]/ANO (25.5 kcal/mol)[20] and CCSD(T) (29.8 kcal/mol).[18] The heat of reaction ΔH at 298 K is 11.62 kcal/mol, slightly higher than the other reported values. Since the basis set superposition error (BSSE) is expected to underestimate the heat of reaction[20] and the DFT method is affected by the BSSE less than ab initio methods, the results are quite reasonable. The heat of activation is 24.33 kcal/mol at 298 K, lying at the lower end of the high-level ab initio results. The entropy of reaction at 298 K is −9.67 cal K^{-1} mol^{-1}, which is lower than the CASPT2[g2] value of −12.42 cal K^{-1} mol^{-1} and the experimental value of −13.27 ± 1.84 cal K^{-1} mol^{-1}.[20] The zero-point energy corrected reaction energies are 12.67, 17.90, 25.14, 5.54, 12.59, and 18.28 kcal/mol for **1**−**6**, respectively, and the Gibbs free energies of the reaction at 298 K are 14.51, 21.14, 28.73, 6.06, 13.42, and 19.39 kcal/mol for **1**−**6**, respectively. The dimethyl-substituted **3** falls to an unstable biradical product due to both the steric repulsion and the induced electrostatic effect between the unoccupied p orbitals of the radical carbon atoms and the methyl groups. The monomethyl-substituted **2-P** has a relative free energy in between those of **1-P** and **3-P**; hence, it quantitatively supports the above argument. For the ring compounds, the free energies of reaction at 298 K are 6.06, 13.42, and 19.39 kcal/mol for **4**−**6**, respectively. The smaller the saturated ring being attached to the *p*-benzyne moiety, the lower the energy relative to its corresponding enediyne. The difference between the free energy of the transition structure and the biradical products, ΔG_a(Rev), can be evaluated by $\Delta G_a - \Delta G$ for each reaction. All except **1** have a ΔG_a(Rev) between 6 and 9 kcal/mol. The reverse barrier of **1** is higher, 11.84 kcal/mol. Thus, substituted *p*-benzynes are relatively higher in energy.

Comparing the data for **1**, **2**, and **3**, one finds that the first methyl substituent increases the reaction barrier by ∼3−4 kcal/mol and the free energy barrier by ∼4−6 kcal/mol. Thus, the steric effect plays an important role during the cyclization. The reaction barrier for **6**, 26.42 kcal/mol, is slightly higher than that for **1**, 25.16 kcal/mol. The smaller rings have lower reaction barriers, 12.09 and 20.87 kcal/mol for **4** and **5**, respectively. This trend is parallel to the trend of the ring strain energy, which is 14.80, 11.40, and 8.96 kcal/mol from MM2 calculations for **4**, **5**, and **6**, respectively.[7] Nevertheless, the difference in strain energy accounts for only about 40% of the difference in the reaction barrier; hence, the energy of small ring enediynes is raised not solely due to the ring strain energy. The trend of the free energy of **1**−**6** is similar to that of the energy. The ΔG_a as well as ΔG of **1** and the ring compounds **4**, **5**, and **6** vary slightly with the temperature; the free energies deviate less than 2.7 kcal/mol in the range of 0 and 500 K. On the contrary, the methyl-substituted **2** and **3** exhibit a stronger temperature effect, with a deviation of nearly 7 kcal/mol. For all six Bergman reactions, the free energy of reaction and the free energy of activation increase with temperature; the heat of reaction and the heat of activation decrease when temperature decreases; the entropy of reaction and the entropy of activation decrease as temperature increases.

The IRC results of **4**−**6** are plotted in Figure 3, showing the energy versus $R_{C_2C_7}$, where the energy belongs to the optimized geometry of the full IRC calculation whose $R_{C_2C_7}$ is given in the plot. As discussed above, the reaction coordinate can be approximately represented by $R_{C_2C_7}$. The transition structures are located at similar points on the reaction coordinate in accord with the fact that $R_{C_2C_7}$ is ∼2.0 Å for all transition structures; so are the three products. In the biradical products, the critical distance $R_{C_2C_7}$ is the length of the longer CC bond in the *p*-benzyne moiety, approximately 1.5 Å. On the contrary, the reactants are located at different positions. The reactant lies further away from the transition structure as the ring size increases since $R_{C_2C_7}$ increases according to the ring size. The free energy of activation is roughly proportional to $R_{C_2C_7}$ in the reactant. This fact agrees with the Hammond postulate[35] that a late transition structure has a higher activation energy. The ring size affects the barrier significantly. The nine-membered-ring enediyne **4** has the lowest barrier. The 10-membered ring **5** has a barrier of a few kilocalories per mole lower than that of the prototype **1**, while the 11-membered ring **6** has a barrier higher than **5** and slightly lower than **1**. The 11-membered-ring enediyne possesses the highest reaction barrier; hence, it is not a naturally preferred structure. Larger enediyne rings are likely to be more difficult to convert to their corresponding biradicals.

The calculated trend for the reaction barrier is parallel to the experimentally observed reactivity of natural enediyne antibiotics and synthesized ring enediynes. The nine-membered-ring enediyne **4** cannot be isolated, and only its biradical derivatives are found, but ring enediynes with 10 or more carbons are readily prepared in laboratory.[7] In the natural products, the chromophorial body actually stabilizes the enediyne ring; thus, a number of natural products consist of nine-membered-ring enediynes. The DNA cleavage reaction of all natural enediyne antibiotics requires a trigger except C-1027,[1,2] which has a nine-membered-ring enediyne core structure in its cytotoxic chromophore in addition to its apoprotein. This is perhaps not accidential since the nine-membered-ring enediyne has the lowest barrier. The current study reveals that substituent and ring size significantly affect the barrier of the Bergman cyclization. On the enediyne rings, all natural antibiotics possess functional substituents, such as epoxide, hydroxyl, methoxyl, and alkenyl groups. These substituted functional groups play important roles in the activity of these antibiotics. Further study to probe their specific effects is under way in this laboratory.

Summary

The Bergman cyclization of **1** has been studied by density functional theory with four functionals, BP86, BLYP, BPW91, and B3LYP, using a triple-ζ basis set 6-311G**, and with the latter two functionals using an ANO basis set. The BP86 and BPW91 functionals with both basis sets provide results that compare well with those of high-level ab initio calculations, such as CASSCF(12,12)/ANO[20] and CCSD(T)/6-31G**,[18] and BPW91 performs slightly better. The bond lengths from BPW91 and the aforementioned ab initio calculations are within 0.02, 0.07, and 0.04 Å for **1**, **1-TS**, and **1-P**, respectively; the deviations for the bond angles are less than 3°. The classical barrier of the Bergman reaction of **1** is 25.50 kcal/mol by BPW91/6-311G** and 24.40 kcal/mol by BPW91/ANO, comparing well with the values of 29.5 and 29.65 kcal/mol by CCSD(T)/6-31G**[18] and CCSD(T)/ANO,[20] respectively. The

energy of reaction is 11.64, 9.10−10.81, and 10.11 kcal/mol with BPW91/6-311G**, with CCSD(T) using several ANO basis sets, and with CCSD(T)/cc-pVTZ,[20] respectively. Thermodynamic data, such as ΔH, ΔS, ΔG, ΔH_a, ΔS_a, and ΔG_a, are evaluated at various temperatures considering vibrational and rotational frequencies. At 473 K, ΔS is -11.22 cal K^{-1} mol^{-1} and ΔG_a is 27.67 kcal/mol, comparing well with the experimental values of -13.27 ± 1.84 cal K^{-1} mol^{-1} and 28.23 $\pm$ 0.5 kcal/mol, respectively.[20,21]

The Bergman reaction of **2**−**6** has been studied by BPW91/6-311G**. Several other stationary points have been found in the geometry optimization, in addition to the reactant, product, and transition structure of the Bergman reaction. The calculated structure of the conformer of **6** with the minimal energy, **6-A**, excellently fits the X-ray crystallographic structure. The ring enediynes feature longer carbon−carbon bonds than the open-ended ones, by ~0.03 Å for single bonds, by ~0.05 Å for double bonds, and by 0.06−0.12 Å for triple bonds. The benzyne part of **4-P**, which is the biradical product of **4**, deviates from **1-P** more than others because of the small ring size. The transition structure of the Bergman reaction has been examined by the normal mode analysis and has been confirmed to have one and only one imaginary frequency. The critical distances of the transition structure are approximately 2.0 Å for all six reactions. The reaction paths of the ring enediynes, **4**−**6**, have been substantiated by IRC calculations. The imaginary frequencies corresponding to the reaction coordinate of the transition structure of the Bergman cyclization are in the range 446i−460i cm^{-1}, whereas the imaginary frequencies of the transition structure corresponding to the conformational change of the enediynes or biradical products are significantly smaller. The enthalpy of activation decreases slightly when temperature increases; for example, for reaction 1, it changes from 25.16 kcal/mol to 23.75 kcal/mol when temperature increases from 0 to 500 K. The free energy of activation increases with the temperature due to the entropy contribution. At 311 K, ΔG_a values of the Bergman reaction of **1**−**6** are 26.44, 29.76, 36.04, 12.60, 21.62, and 27.36 kcal/mol, respectively. The nine- and 10-membered rings **4** and **5** possess lower reaction barriers; thus, antibiotics with these two sizes of enediyne are the only ones abundant naturally.

Acknowledgment. The preliminary work on this project by Mr. Tzeng-Guang Tsai[36] is acknowledged. This work was supported by the National Science Council of the Republic of China under Grants NSC 83-0208-M-007-082, NSC 86-2113-M-007-018, and NSC 87-2113-M-007-003. We thank the Computer Center of National Tsing Hua University and the National Center for High-performance Computing for support of computing facility. N.Y.C. and W.C.C. acknowledge the undergraduate research fellowship from NSC, Grant NSC 84-0115-C007-01-073M and NSC 86-2815-C007-018M, respectively.

References and Notes

(1) Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 2103.

(2) Takahashi, T.; Tanaka, H.; Yamada, H.; Matsumoto, T.; Sugiura, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1835.

(3) (a) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212. (b) Hensens, O. D.; Giner, J. L.; Goldberg, I. H. *J. Am. Chem. Soc.* **1989**, *111*, 3295. (c) Leet, J. E.; Schroeder, D. R.; Hofstead, S. J.; Golik, J.; Colson, K. L.; Huang, S.; Klohr, S. E.; Doyle, T. W.; Matson, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 7946.

(4) Eckhardt, M.; Brückner, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35,* 1093.

(5) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106.

(6) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. (c) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198. (d) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247. (e) Nicolaou, K. C.; Dai, W.-M.; Wendeborn, S. V.; Smith, A. L.; Torisawa, Y.; Maligres, P.; Hwang, C.-K. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1032. (f) Drak, J.; Iwasawa, N.; Danishefsky, S.; Crothers, D. M. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 7464. (g) Aiyar, J.; Danishefsky, S. J.; Crothers, D. M. *J. Am. Chem. Soc.* **1992**, *114*, 7552. (h) Nicolaou, K. C.; Tsay, S.-C.; Suzuki, T.; Joyce, G. F. *J. Am. Chem. Soc.* **1992**, *114*, 7555. (i) Walker, S.; Landovitz, R.; Ding, W. D.; Ellestad, G. A.; Kahne, D. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 4608. (j) Li, H.; Zeng, Z.; Estevez, V. A.; Baldenius, K. U.; Nicolaou, K. C.; Joyce, G. F. *J. Am. Chem. Soc.* **1994**, *116*, 3709. (k) Aiyar, J.; Hitchcock, S. A.; Denhart, D.; Liu, K. K. C.; Danishefsky, S. J.; Crothers, D. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 855. (l) Shair, M. D.; Yoon, T.; Chou, T. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2477. (m) Ho, S. N.; Boyer, S. H.; Schreiber, S. L.; Danishefsky, S. J.; Crabtree, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 9203. (n) Nicolaou, K. C.; Smith, B. M.; Ajito, K.; Komatsu, H.; Gomez-Paloma, L.; Tor, Y. *J. Am. Chem. Soc.* **1996**, *118*, 2303. (o) Depew, K. M.; Zeman, S. M.; Boyer, S. H.; Denhart, D. J.; Ikemoto, N.; Danishefsky, S. J.; Crothers, D. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2797. (p) Liu, C.; Smith, B. M.; Ajito, K.; Komatsu, H.; Gomez-Paloma, L.; Li, T.; Theodorakis, E. A.; Nicolaou, K. C.; Vogt, P. K. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 940.

(7) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.***1988**, *110*, 4866.

(8) (a) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626. (b) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. (c) Doi, T.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 3465.

(9) Nicolou, K. C.; Li, T.; Nakada, M.; Hummel, C. W.; Hiatt, A.; Wrasidlo, W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 183.

(10) (a) Clark, D. A.; Riccardis, F. D.; Nicolaou, K. C. *Tetrahedron* **1994**, *50*, 11391. (b) Hitchcock, S. A.; Chu-Moyer, M. Y.; Boyer, S. H.; Olson, S. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5750. (c) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509. (d) Danishefsky, S. J.; Shair, M. D. *J. Org. Chem.***1996**, *61*, 16.

(11) (a) Walker, S.; Gange, D.; Gupta, V.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 3197. (b) Paloma, L. G.; Smith, J. A.; Chazin, W. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1994**, *116*, 3697. (c) Ikemoto, N.; Kumar, R. A.; Dedon, P. C.; Danishefsky, S. J.; Patel, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 9387. (d) Ikemoto, N.; Kumar, R. A.; Ling, T. T.; Ellestad, G. A.; Danishefsky, S. J.; Patel, D. J. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 10506. (e) Bifulco, G.; Galeone, A.; Gomez-Paloma, L.; Nicolaou, K. C.; Chazin, W. J. *J. Am. Chem. Soc.* **1996**, *118*, 8817.

(12) (a) Haseltine, J. N.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2576. (b) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* ***1992***, *114*, 2544. (c) Magnus, P.; Lewis, R.; Bennett, F. *J. Am. Chem. Soc.* **1992**, *114*, 2560. (d) Kim, S. H.; Augeri, D.; Yang, D.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 1766. (e) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755. (f) Yoon, T.; Shair, M. D.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 6259. (g) Halcomb, R. L.; Boyer, S. H.; Wittman, M. D.; Olson, S. H.; Denhart, D. J.; Liu, K. K. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5720.

(13) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (c) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. (d) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091. (e) Gleiter, R.; Kratz, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 842. (f) Turro, N. J.; Evenzahav, A.; Nicolaou, K. C. *Tetrahedron Lett.* **1994**, *35*, 8089. (g) Kuwatani, Y.; Ueda, I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1892.

(14) (a) Noell, J. O.; Newton, M. D. *J. Am. Chem. Soc.* **1979**, *101*, 51. (b) Nicolaides, A.; Borden, W. T. *J. Am. Chem. Soc.* **1993**, *115*, 11951. (c) Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 11958. (d) Borden, W. T.; Davidson, E. R. *Acc. Chem. Res.* **1996**, *29*, 67.

(15) (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172. (c) Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25* 497. (d) Nicolaou, K. C.; Liu, A.; Zeng, Z.; McComb, S. *J. Am. Chem. Soc.* **1992**, *114*, 9279.

(16) (a) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369. (b) Myers, A. G.; Finney, N. S. *J. Am. Chem. Soc.* **1992**, *114*, 10986. (c) Hoffmann, R. *Am. Sci.* **1993**, *81*, 324. (d) Bunnage, M. E.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1110. (e) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207.

(17) (a) Snyder, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 7630. (b) Snyder, J. P.; Tipsword, G. E. *J. Am. Chem. Soc.* **1990**, *112*, 4040. (c) Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 5367.

(18) Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **1994**, *116*, 4929.

(19) Lindh, R.; Persson, B. J. *J. Am. Chem. Soc.* **1994**, *116*, 4963.

(20) Lindh, R.; Lee, T. J.; Bernhardsson, A.; Persson, B. J.; Karlström, G. *J. Am. Chem. Soc.* **1995**, *117*, 7186.

(21) Roth, W. R.; Hopf, H.; Horn, C. *Chem. Ber.* **1994**, *127*, 1765.

(22) Chen, W. C.; Yu, C.-h. *Chem. Phys. Lett.* **1997**, *277*, 245.

(23) Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 10336.

(24) Barone, V.; Adamo, C.; Lelj, F. *J. Chem. Phys.* **1995**, *102*, 364.

(25) (a) Baker, J.; Muir, M.; Andzelm, J. *J. Chem. Phys.* **1995**, *102*, 2063. (b) Brinck, T.; Haeberlein, M.; Jonsson, M. *J. Am. Chem. Soc.* **1997**, *119*, 4239. (c) Wright, J. S.; Carpenter, D. J.; McKay, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1997**, *119*, 4245. (d) Jiao, H.; Nagelkerke, R.; Kurtz, H. A.; Williams, R. V.; Borden, W. T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 5921. (e) Borrmann, A.; Montanari, B.; Jones, R. O. *J. Chem. Phys.* **1997**, *106*, 8545. (f) Ignatyev, I. S.; Xie, Y.; Allen, W. D.; Schaefer, H. F., III. *J. Chem. Phys.* **1997**, *107*, 141. (g) Chapman, D. M.; Hester, R. E. *J. Phys. Chem. A* **1997**, *101*, 3382. (h) Ono, S.; Okazaki, K.; Sakurai, M.; Inoue, Y. *J. Phys. Chem. A* **1997**, *101*, 3769. (i) Basch, H.; Hoz, S. *J. Phys. Chem. A* **1997**, *101*, 4416. (j) Chung, G.; Kwon, O.; Kwon, Y. *J. Phys. Chem. A* **1997**, *101*, 4628.

(26) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098.

(27) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822.

(28) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(29) Perdew, J. P.; Wang, Y. *Phys. Rev. B* **1992**, *45*, 13244.

(30) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(31) (a) Widmark, P.-O.; Malmqvist, P.-A.; Roos, B. O. *Theor. Chim. Acta* **1990**, *77*, 291. (b) Widmark, P.-O.; Persson, B. J.; Roos, B. O. *Theor. Chim. Acta* **1991**, *79*, 419.

(32) (a) Fukui, K. *Acc. Chem. Res.* **1980**, *14*, 363. (b) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (c) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523. (d) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1991**, *94*, 5853. (e) Baboul, A. G.; Schlegel, H. B. *J. Chem. Phys.* **1997**, *107*, 9413.

(33) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cisolowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gompertws, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94* (Revision D.2); Gaussian, Inc.: Pittsburgh, PA, 1995.

(34) McQuarrie, D. A. *Statistical Mechanics*; Harper Collins: New York, 1976.

(35) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

(36) Tsai, T. G. Master Thesis, Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, 1993.