Ab Initio Study of the Bergman Reaction: The Autoaromatization of Hex-3-ene-1,5-diyne

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Abstract: The Bergman reaction of the hex-3-ene-1,5-diyne molecule (enediyne) to form the singlet biradical *p*-benzyne structure under ring closure has been studied by ab initio methods. The complete active space (CAS) SCF method was used for geometry optimizations at five points along the reaction path of the Bergman reaction. Subsequent calculations using the multireference second-order perturbation theory based on a CASSCF reference (CASPT2) established the energetics along the reaction path, especially for the reactant, transition state, and product. The energetics were further corrected for zero point vibrational energy at the CASSCF level of theory. The study incorporated four different basis sets: a double-ζ plus polarization (DZP), a triple-ζ plus double polarization (TZ2P), and two different *average* atomic natural orbital (ANO) basis sets. The study predicts the energy barrier to ring closure to be 25.0 ± 3.1 kcal/mol and the enthalpy of reaction to be 4.9 ± 3.2 kcal/mol. The latter value deviates significantly from the value estimated on the basis of group additivity and the Born–Haber cycle. The enediyne moiety is the main functional group of a new class of anticancer agents. The activation of the Bergman reaction in these drugs has been argued to be due to a small structural change in the terminal–terminal carbon distance of about −0.5 Å originating from an epoxide conversion in the rest of the drug. The present study indicates that such a structural change is not sufficient for the Bergman autoaromatization to proceed at an appreciable rate. A new reaction path involving no biradical formation, resulting in the same products, is suggested.

Introduction

A newly discovered series of anticancer compounds, based on the autoaromatization of so-called enediynes (hex-3-ene-1,5-diyne related structures), has recently received considerable attention in the literature.[1,2] The reports included documentation of an exceptional selectivity toward cancer cells[1] for these new anticancer substances and the first total synthesis[2] of calicheamicin $\gamma_1{}^I$, a complex molecule with these selective properties.

The common functionality of the new class of anticancer agents, according to the hypothesis suggested in the literature, is the enediyne moiety, which will undergo an autoaromatization to form a biradical—the so-called Bergman reaction (see Figure 1).[3] In a subsequent step the formed biradical is believed to attack and damage the DNA of the host cell. The enediyne structure is attached to a molecular template, usually a mono- or bicyclic structure. The Bergman reaction is believed to be triggered by a structural change of the template. Additional substituents to these templates can also function as initiators, deactivators, and functional groups which can control the distribution of the drug in the human body. An intriguing fact about the five reported naturally occurring molecules is that they demonstrate that three quite different templates can successfully serve as a host to the enediyne moiety. Especially the attachment of the enediyne structure to the template varies significantly.

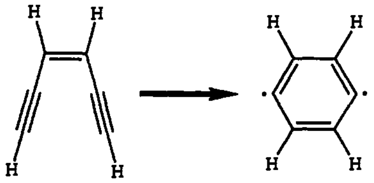

Figure 1. Bergman reaction in which hex-3-ene-1,5-diyne undergoes autoaromatization and forms the singlet *p*-benzyne biradical.

For the monocyclic template of neocarzinostatin (Figure 2a),[4] the terminal carbons of the enediyne moiety are separated by three bonds over the template structure. In the monocyclic template of kedarcidin (Figure 2b),[5] the terminal carbons of the enediyne moiety are separated by four bonds over the template structure. For the monocyclic templates of calicheamicin $\gamma_1{}^I$ (Figure 2c)[6] and esperamicin A_1 (Figure 2d),[7] the terminal carbons of the enediyne moiety are separated by five bonds over the template structure. Finally, in the bicyclic template of dynemicin A (Figure 2e),[8] the terminal carbons of the enediyne moiety are

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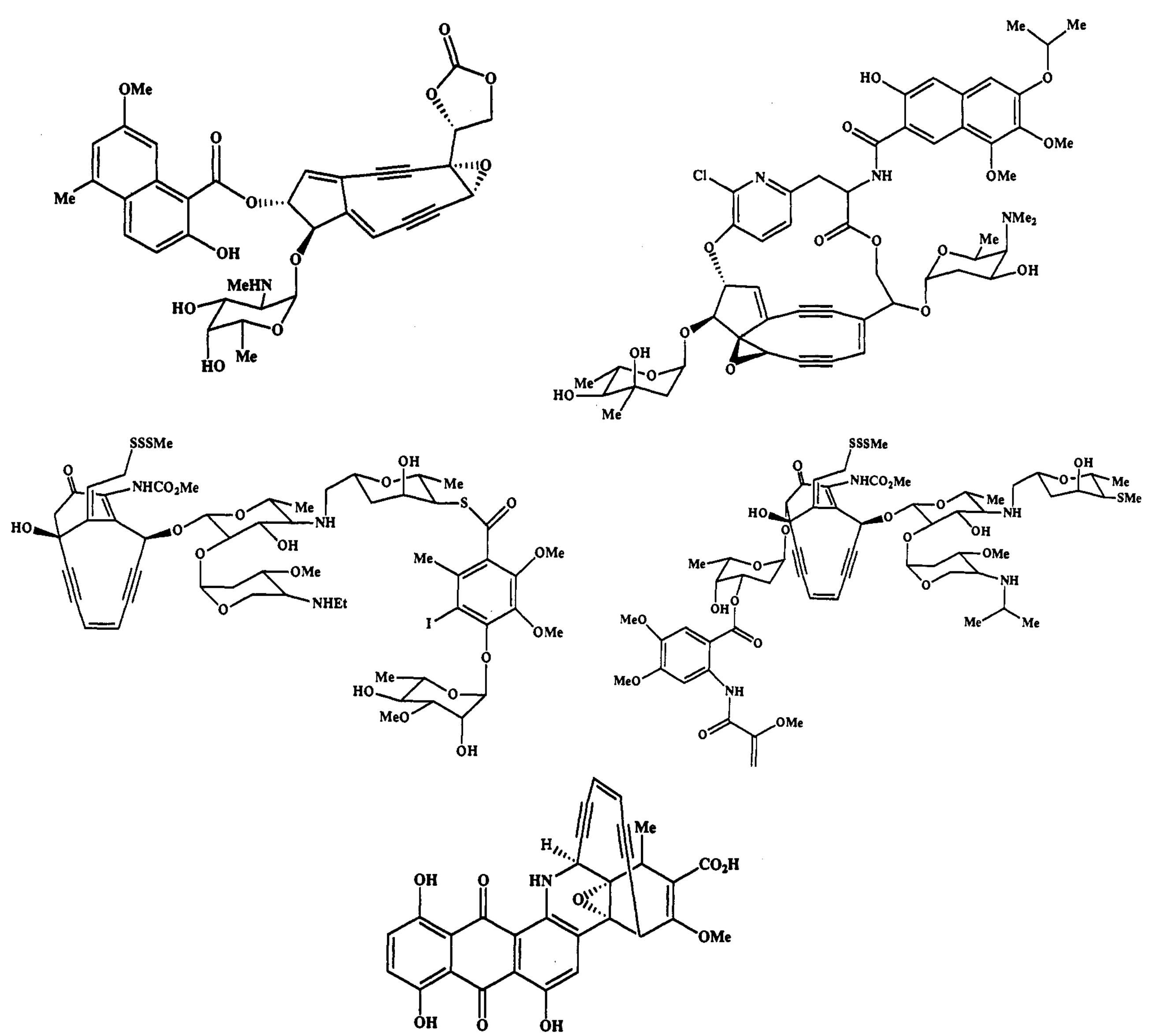

Figure 2. Structures of naturally occurring enediyne anticancer substances: (top left) the neocarzinostatin chromophore, (top right) the kedarcidin chromophore, (center left) calicheamicin $\gamma_1{}^I$, (center right) esperamicin A_1, and (bottom) dynemicin A.

again separated by five bonds over the template structure. This indicate that, in the molecular design of a new anticancer substance based on the enediyne functionality, one is relatively free to choose a template as one wishes as long as the new structure meets some general requests. The new template must function as a host for substituents and display structural changes of the templates on initiation. This structural dynamic first inhibits and then later in the cancer cell activates or promotes the Bergman reaction. To understand this in more detail it is essential to have a refined knowledge of the Bergman reaction for the model compound hex-3-ene-1,5-diyne.

A careful ab initio study of the Bergman reaction puts high demands on the level of theory. Especially the end product, the single *p*-benzyne biradical, forces us to use a multiconfigurational approach. In addition to this, studies of multiple bonds and formation of bonds are usually too complicated to be successfully modeled by a single reference approach. Furthermore, in the Bergman reaction in which two single, one double, and two triple bonds transform into six benzene bonds, we must be very careful not to be biased toward one or the other structure due to limitations in the methods which are employed. Hence, a study of the Bergman reaction not only requires a proper treatment of near degeneracy effects, which is a well-known problem in modeling multiple bonds and bond formation, but also must include an adequate description of dynamic electron correlation effects. In this paper we will employ such methods in the study of the Bergman reaction. The function of the enediyne moiety and the action or role of the molecular template will be discussed on the basis of the findings presented in this work.

Methods

The present study of the Bergman reaction is based on geometry optimizations at the complete active space SCF (CASSCF) level of theory.[9] A GVB study of *p*-benzyne (the product) by Noell and Newton[10] suggested that a bicyclic structure may correspond to a local minimum, but with an energy far above the open equilibrium structure. On the basis of this result, we confined our study of the ring closure process to reaction paths within C_{2v} symmetry. In the CASSCF calculations (placing the C_6H_4 molecule in the *xy*-plane) the active space included all out-of-plane $2p_z$ orbitals, *i.e.* the π orbitals. Furthermore, from the σ space (in-plane), we included symmetry related orbitals in an equivalent way to account for the higher symmetry (D_{2h}) of the product, orbitals to account for the

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Figure 3. In-plane 2p orbitals of (left) hex-3-ene-1,5-diyne and (right) the singlet *p*-benzyne biradical, which were chosen to be active in the CASSCF calculation of this study.

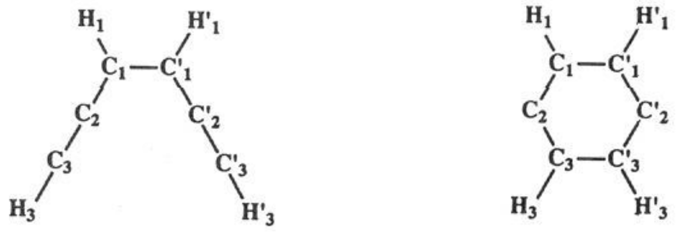

Figure 4. Structural labeling of hex-3-ene-1,5-diyne and the singlet *p*-benzyne biradical molecule as used in this work.

bond formation, and the second π orbital in the triple bond. Hence, for hex-3-ene-1,5-diyne (see Figure 3a), the active σ orbitals are the in-plane 2p orbitals which are involved in the in-plane π bond of the triple bonds and the p_σ orbital of the double bond. The corresponding orbitals in the singlet *p*-benzyne biradical (see Figure 3b) are the in-plane 2p orbitals which are the radical orbitals and the $2p_\sigma$ orbitals of the formed carbon bond and the symmetry related partner. The CASSCF calculations thus included 12 active electrons in 12 active orbitals and were all performed for the singlet totally symmetric ground state.

The reaction path was characterized by first optimizing the reactant and the product without any geometrical constraints. Additional points (two) along the reaction path were established by a geometry optimization in which the distance between the terminal carbons (the C_3–C'_3 distance, see Figure 4) of hex-3-ene-1,5-diyne was fixed. Finally, the transition state was established in a geometry optimization with no constraints other than the approximate molecular Hessian having one negative eigenvalue. At the optimized start and end structures, the zero point vibrational energy correction was computed with the CASSCF method and dynamic electron correlation was included for all structures by means of second-order multiconfigurational perturbation theory based on a CASSCF reference function (CASPT2).[11] The full Hartree–Fock matrix is used in the construction of the zeroth-order Hamiltonian (PT2F).[11b] In the CASPT2 calculations all orbitals were correlated except for the carbon 1s core orbitals. To study trends as the one-particle space is saturated, several basis sets were employed: the double-ζ plus polarization (DZP),[12] the triple-ζ plus double polarization (TZP),[13] and the *averaged* atomic natural orbital (ANO) C[14s9p4d]/(5s4p2d),H[8s4p]/(3s2p) basis set.[14] Some bond distances were reoptimized numerically at the CASPT2 level of theory. In these calculations the remaining internal coordinates were fixed at the CASSCF optimized values. Some additional energy calculations were performed with the *averaged* ANO C[14s9p4d3f]/(5s4p2d1f),H[8s4p]/(3s2p) basis set. This basis set was included in particular to improve the description of the triple bonds in the open structure. The harmonic frequencies were computed with the DZP basis set. The quenching of some of the vibrations as a consequence of the molecule being attached to a large molecular template was modeled by substituting the masses of the terminal hydrogens with infinite masses. In all instances except for the harmonic frequency calculations, real spherical harmonic Gaussians were employed.

All calculation were performed with the MOLCAS version 2 quantum chemistry program package[15] augmented with the ALASKA gradient program[16] and SLAPAF relaxation program[17] on a IBM RISC System/6000 580, except for the harmonic frequency calculations, which were performed with the SIRIUS-ABACUS package.[18]

Table 1. CASSCF and PT2F Relative Energies and CASSCF Structural Parameters for Five Structures along the Reaction Path of the Bergman Reaction as Computed with a DZP One-Particle Basis Set[a]

	structure				
	1	2^{b}	3^{b}	4^{c}	5^{d}
E_{CASSCF}	0.00^{e}	7.43	35.98	40.40	22.39
E_{PT2F}	0.00^{f}	5.39	23.10	20.63	−4.22
$R_{C_1H_1}$	1.077	1.076	1.075	1.075	1.076
$R_{C_1C'_1}$	1.371	1.357	1.396	1.409	1.449
$R_{C_1C_2}$	1.441	1.441	1.430	1.419	1.380
$R_{C_2C_3}$	1.216	1.221	1.255	1.286	1.380
$R_{C_3C'_3}$	4.476	3.175	2.117	1.923	1.448
$R_{C_3H_3}$	1.058	1.060	1.065	1.069	1.080
$\phi_{H_1C_1C'_1}$	118.4	121.0	119.8	118.9	119.1
$\phi_{H_1C_1C_2}$	116.8	119.8	121.8	122.0	123.1
$\phi_{C_1C_2C_3}$	182.0	160.5	136.8	131.2	124.4
$\phi_{H_3C_3C_2}$	181.2	171.5	151.5	141.1	123.1
$\phi_{H_3C_3C'_3}$	125.6	108.2	103.7	109.3	119.1

[a] Structure 1 is the hex-3-ene-1,4-diyne molecule, and structure 5 is the singlet *p*-benzyne biradical molecule. Energies are in kcal/mol, bond distances in Å, and angles in deg. [b] Optimized with fixed $R_{C_3C'_3}$. [c] Transition-state optimized with no geometrical constraints. [d] Although the energy is converged with seven significant figures after the decimal point, the structure does not fully have the higher symmetry. [e] Total energy, −229.608 224 hartrees. [f] Total energy, −230.162 291 hartrees.

Table 2. CASSCF and PT2F Relative Energies and CASSCF Structural Parameters for Five Structures along the Reaction Path of the Bergman Reaction as Computed with a TZ2P One-Particle Basis Set[a]

	structure				
	1	2^{b}	3^{b}	4^{c}	5
E_{CASSCF}	0.00^{d}	7.37	37.89	43.64	27.64
E_{PT2F}	0.00^{e}	5.11	23.51	21.55	0.42
$R_{C_1H_1}$	1.072	1.071	1.070	1.070	1.071
$R_{C_1C'_1}$	1.361	1.365	1.386	1.402	1.442
$R_{C_1C_2}$	1.432	1.431	1.422	1.409	1.370
$R_{C_2C_3}$	1.204	1.208	1.241	1.277	1.370
$R_{C_3C'_3}$	4.433	3.175	2.117	1.896	1.442
$R_{C_3H_3}$	1.053	1.053	1.058	1.063	1.071
$\phi_{H_1C_1C'_1}$	118.3	120.8	119.9	118.8	119.1
$\phi_{H_1C_1C_2}$	116.8	120.1	121.9	122.2	123.2
$\phi_{C_1C_2C_3}$	180.7	160.9	137.5	131.1	124.6
$\phi_{H_3C_3C_2}$	179.0	172.3	153.3	141.0	123.2
$\phi_{H_3C_3C'_3}$	125.5	107.6	102.4	109.1	119.1

[a] Structure 1 is the hex-3-ene-1,4-diyne molecule, and structure 5 is the singlet *p*-benzyne biradical molecule. Energies are in kcal/mol, bond distances in Å, and angles in deg. [b] Optimized with fixed $R_{C_3C'_3}$. [c] Transition-state optimized with no geometrical constraints. [d] Total energy, −229.651 251 hartrees. [e] Total energy, −230.317 776 hartrees.

Results and Discussion

Structure. The CASSCF optimized structures and the CASSCF and PT2F energies for the DZP, TZ2P, and ANO basis sets are presented in Tables 1–3. Some additional energetics for the larger ANO basis set are presented in Table 4. All calculations involve the molecule in the singlet totally symmetric state. The structural labels used throughout this paper are defined in Figure 4. A brief overview of the overall structures for the geometries at which we performed the optimizations is presented in Figure 5.

Let us first discuss what consequences our choice of methods carries. The selection of the active space in the CASSCF will as presented guarantee that the C_3–C'_3 bond, which is formed under the Bergman reaction, is treated on equal footing with the

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(18) SIRIUS is an MCSCF program written by H. J. Jensen, H. Ågren, and J. Olsen. ABACUS is an MCSCF energy derivative program written by T. Helgaker, H. J. Jensen, P. Jørgensen, J. Olsen, and P. R. Taylor.

Table 3. CASSCF and PT2F Relative Energies and CASSCF Structural Parameters for Five Structures along the Reaction Path of the Bergman Reaction as Computed with an *Average* ANO C(5s4p2d),H(3s2p) One-Particle Basis Set[a]

	structures				
	1	2^b	3^b	4^c	5
E_{CASSCF}	0.00^d	7.37	37.84	43.64	27.70
E_{PT2F}	0.00^e	5.62	25.01	23.20	2.34
$R_{\mathrm{C_1H_1}}$	1.072	1.071	1.070	1.071	1.071
$R_{\mathrm{C_1C'_1}}$	1.362 [1.356]^f (1.327^g)	1.367	1.388	1.403 (1.360^g)	1.443 [1.438]^f (1.399,^{g} 1.439^h)
$R_{\mathrm{C_1C_2}}$	1.431 (1.426^g)	1.431	1.422	1.410 (1.411^g)	1,371 (1.370,^{g} 1.373^h)
$R_{\mathrm{C_2C_3}}$	1.206 (1.203^g)	1.209	1.242	1.278 (1.267^g)	1.371 (1.363,^{g} 1.373^h)
$R_{\mathrm{C_3C'_3}}$	4.440	3.175	2.117	1.895 (1.947^g)	1.443 [1.438]^f (1.422,^{g} 1.439^h)
$R_{\mathrm{C_3H_3}}$	1.052	1.052	1.057	1.063	1.071
$\phi_{\mathrm{H_1C_1C'_1}}$	118.3	120.8	119.9	118.8	119.1
$\phi_{\mathrm{H_1C_1C_2}}$	116.8	120.1	122.0	122.2	123.2
$\phi_{\mathrm{C_1C_2C_3}}$	181.7	160.9	137.5	131.0	124.6
$\phi_{\mathrm{H_3C_3C_2}}$	179.1	172.5	153.5	141.1 (132.5^g)	123.2 (124.8,^{g} 125.3^h)
$\phi_{\mathrm{H_3C_3C'_3}}$	125.7	107.4	102.2	109.0	119.1

[a] Structure 1 is the hex-3-ene-1,4-diyne molecule, and structure 5 is the singlet *p*-benzyne biradical molecule. Values within parentheses are from other theoretical studies. Energies are in kcal/mol, bond distances in Å, and angles in deg. [b] Optimized with fixed $R_{\mathrm{C_3C'_3}}$. [c] Transition-state optimized with no geometrical constraints. [d] Total energy, −229.656 658 hartrees. [e] Total energy, −230.307 183 hartrees. [f] Reoptimized at the PT2F level. [g] CASSCF4/MIDI1 optimized structure, see ref 19. [h] GVB/4-31G optimized structure, see ref 10.

Table 4. CASSCF and PT2F Relative Energy for Five Structures along the Reaction Path of the Bergman Reaction as Computed with an *Average* ANO C(5s4p2d1f),H(3s2p) One-Particle Basis Set[a]

	structures				
	1	2^b	3^b	4^c	5
E_{CASSCF}	0.00^d	7.49	38.28	44.12	28.11
E_{PT2F}	0.00^e	4.63	23.65	20.39	−1.77

[a] The structure was optimized at the CASSCF level with the *average* ANO C(5s4p2d),H(3s2p) basis set. Structure 1 is the hex-3-ene-1,4-diyne molecule, and structure 5 is the singlet *p*-benzyne biradical molecule. Energies are in kcal/mol, bond distances in Å, and angles in deg. [b] Optimized with fixed $R_{\mathrm{C_3C'_3}}$. [c] Transition-state optimized with no geometrical constraints. [d] Total energy, −229.665 312 hartrees. [e] Total energy, −230.391 421 hartrees.

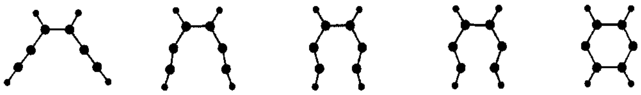

Figure 5. Structures along the reaction path of the Bergman reaction. Starting on the left is the hex-3-ene-1,5-diyne molecule, and finally on the right, we find the singlet *p*-benzyne biradical. The second structure from the right is the structure of the transition state.

C_1–C'_1 bond in the *p*-benzyne molecule. This is in contrast to the CASSCF/MRCI work by Koga and Morokuma,[19] which only used the orbitals of the C_3–C'_3 bond in the active space. Hence, in the subsequent MRCI calculations, the reference functions, based on the CASSCF, will only contain excitations among the orbitals of one-half of the molecule. The effect on the MRCI energetics for the *p*-benzyne structure due to this bias in the selection of the reference functions can be significant. Furthermore, the general observations that the SCF treatment of the inactive space will tend to underestimate bond distances, since only bonding configurations dominate this part of the wave function, and that the full CI in the active space will overestimate the bond distances, since antibonding configurations are given too much weight in the wave functions, have to be carefully considered. These effects will normally cancel each other for conjugated systems. One would expect the CASSCF geometries in these cases to agree with experimental findings. Here, however, we should anticipate the lengths of the C_1–C'_1 bond in the hex-3-ene-1,5-diyne molecule and the C_1–C'_1 and C_3–C'_3 bonds in *p*-benzyne to be overestimated, since both the π and σ orbitals of these bonds are included in the active space of the CASSCF wave function. To remedy this problem, we reoptimized these bonds at the PT2F level of theory for the smaller ANO basis set, keeping all other geometrical parameters fixed at the CASSCF optimized values (see Table 3). As expected the reoptimized distances were shorter. The different basis sets used in this study show that the DZP basis set will give errors in the bond distances in the magnitude of 0.01 Å. The difference between the TZ2P and the ANO structures is small and indicates that reliable structures can be obtained with the smaller basis set.

In hex-3-ene-1,5-diyne the ethylenic carbon–carbon bond has a computed length of 1.356 Å, which is longer than the 1.339 Å of the double bond in ethylene.[20] This is expected since the presence of a conjugated system will increase the bond length of the involved double bonds. Koga and Morokuma on the other hand found that the ethylenic bond was 1.327 Å. This is clearly too short and is due to the treatment of all electrons in the double bond in hex-3-ene-1,5-diyne as inactive. For the single and triple bonds of the hex-3-ene-1,5-diyne molecule the results of this study and that of Koga and Morokuma are more similar and close to what could be expected. The CASSCF wave function with the smaller ANO basis set is dominated by the HF configuration which contributes 85% of the weight. No other configuration exceeds 2% in weight.

For the *p*-benzyne structure we again note that the presented studh will produce a symmetric form, as opposed to the finding by Koga and Morokuma. The results presented here also agree very well with the earlier GVB study by Noell and Newton.[10] The computed length of the aromatic carbon–carbon bond next to the unpaired electrons is 1.371 Å, and the two other bonds are 1.438 Å. These results embrace the 1.397 Å value of the aromatic carbon–carbon bond distance in benzene.[21] For the singlet biradical two configurations dominate the CASSCF wave function. A configuration corresponding to a double occupation in an orbital formed by the symmetric combination of the radical orbitals has a weight of 28%. The corresponding antisymmetric combination has a weight of 57%. By rotating these configurations to pure paired and unpaired configurations, we find that biradical configurations in *p*-benzyne contribute more than 82% of the

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weight of the wave function. A different measure of the biradical character is to compare the occupation numbers of the irreducible representation in which the σ active orbitals fall. In the hex-3-ene-1,5-diyne structure the occupations are 3.984 and 2.017 electrons for the symmetric and antisymmetric representations, respectively. Here both electrons of the in-plane π orbitals are confined to the antisymmetric combination. However, in the *p*-benzyne structure, the occupation numbers have changed to 4.634 and 1.365 electrons, respectively. Thus, there is a difference in the occupation in the symmetric irreducible representation of 0.650 electrons. This excess occupation can be viewed as a measure of the biradical character, where a pure biradical structure would have an excess occupation of 1 electron.

For the transition state it is observed that the structure more resembles the *p*-benzyne structure than the hex-3-ene-1,5-diyne structure (see Figure 5). However, although the C_3–C'_3 bond distance or the transition state is closer to that of the final product, the other bond distances have values which falls between the values found for the reactant and the product. An analysis of the wave function also indicates that the singlet biradical character is developed already for the transition state. In this structure the excess occupation in the symmetric representation is 0.201 electrons. The excess occupation for the structure right before the transition state is computed to be 0.060 electrons. Hence, in the Bergman reaction, the buildup of the biradical character takes place in a region close to the transition state.

A comparison with experimental structures is not possible at the present time. For the structurally associated cycloundec-1-ene-3,10-diyne molecule, which is an enediyne closed over the terminal carbons by a five-membered saturated hydrocarbon chain, some X-ray crystallography results,[22] however, are available. Here the C_1–C'_1, C_2–C'_2, and C_3–C'_3 bond distances were measured to 1.327, 2.778, and 3.661 Å, respectively. The ethylenic bond distance is unexpectedly much shorter than the 1.339 Å of the unperturbed double bond in ethylene.[20] One would have anticipated the bond to be longer due to the presence of the conjugation in the cycloundec-1-ene-3,10-diyne molecule. However, X-ray crystallography is known to underestimate the double bonds in conjugated systems with as much as 0.02 Å.[23] For the other bond distances we observe that the closure of the enediyne moiety over the terminal positions has increased the C_3–C'_3 bond distance by about 0.8 Å compared to the value found in the parent structure. Furthermore, the single bond (C_1–C_2) was found to be 1.410 Å, compared to the 1.431 Å in the open structure. The X-ray data contained no explicit numbers for the acetylenic bond distance. However, from the data presented in the paper by Nicolaou *et al.*,[22] we derive the X-ray result to be 1.189 Å, which is again significantly shorter than the 1.203 Å experimental value of the acetylenic bond distance in acetylene[24] and the 1.204 Å computed for the same bond in the hex-3-ene-1,5-diyne structure. This is clearly another manifestation of the problem with using X-ray techniques to accurately measure bond distances in conjugated systems.

Energetics. The CASSCF and PT2F energetics for the five different structures are presented in Tables 1–4 and are summarized graphically in Figure 6. These results clearly exhibit the decisive effects of inclusion of dynamic correlation. It is observed that the *p*-benzyne carries an excess contribution on the order of 25 kcal/mol compared to hex-3-ene-1,5-diyne. The PT2F method of Andersson *et al.*, however, is known to systematically overestimate the dynamic correlation contribution to the binding energy by 3.9–4.8 kcal/mol per number of produced unpaired electrons.[25] In our case the error would amount to an overestimate of the correction due to dynamic correlation by 2.5–3.1 kcal/mol (0.65 unpaired electrons in *p*-benzyne). Furthermore, the PT2F method is documented to have an error bar of 2.5 kcal/mol for the evaluation of the enthalpy of reaction.[25] Thus, the final enthalpy of reaction is, after correction of the PT2F errors, compiled to 5.1 ± 2.8 and 1.0 ± 2.8 kcal/mol for the smaller and the larger ANO basis sets, respectively. The inclusion of dynamic correlation has a similar effect on the size of the activation energy. For the transition state we estimate the PT2F systematic errors to be 0.8–1.0 kcal/mol (0.21 unpaired electrons in the transition-state wave function). Thus, the activation energies corrected for the systematic PT2F errors are computed to be 24.1 ± 2.6 and 24.5 ± 2.6 kcal/mol for the smaller and the larger ANO basis sets, respectively. From Figure 6 it is noted that the TZ2P and the ANO basis sets give similar energetics. The DZP basis set is also noted to be biased toward the closed structure. Furthermore, it is noted that the inclusion of *f*-functions in the ANO basis set on the carbons was more important for the description of the ring system rather than, as we expected, of the triple bonds in the open structure. Finally, the basis set superposition effects (BSSE) present in the system if anything favor the *p*-benzyne structure. On the basis of earlier experience with the ANO type of basis set, we anticipate this effect to be smaller than 0.5 kcal/mol.[14] The final electronic estimates, based on the larger ANO basis set including BSSE correction, of the enthalpy of reaction and the activation energy are calculated to be 1.5 ± 3.2 and 25.0 ± 3.1 kcal/mol, respectively. It is also noted that the position of the transition state is pushed toward a more open structure when the corrections for the dynamic electron correlations are added.

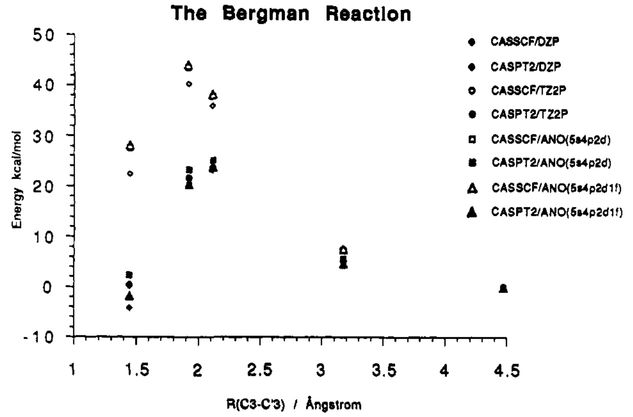

Figure 6. CASSCF and PT2F energetics for the Bergman reaction as a function of the $R_{C_3C'_3}$ distance computed with the DZP, TZ2P, and the two ANO basis sets.

The results presented in this study differ from the CASSCF/MRCI results of Koga and Morokuma, who found that the dynamic correlation correction lowered the enthalpy of reaction by only about 8 kcal/mol and the activation energy by about 6 kcal/mol. The reported enthalpy of reaction of 1.5 ± 3.2 kcal/mol is different from the 22.0 kcal/mol computed by Koga and Morokuma and the 14 kcal/mol reported by Jones and Bergman,[3] both of which are more endothermically pronounced. For the CASSCF/MRCI study we attribute the discrepancy to the inadequate selection of the active orbitals. The enthalpy of reaction reported by Jones and Bergman is computed from the group equivalent techniques[26] in estimating the heat of formation of the hexa-1,5-dien-3-yne structure and the heat of formation of the *p*-benzyne structure compiled as $\Delta H_f(C_6H_6) + 2D_e(C_6H_5$–$H) + D_e(H$–$H)$. The latter compilation in particular is not adequate due to the large structural differences between the *p*-benzyne structure and the benzyne and phenyl structures. This scheme would also require the two hydrogen abstractions to be

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Table 5. CASSCF Harmonic Frequencies of Hex-3-ene-1,5-diyne Molecule Computed with the DZP Basis Set[a]

mode	freq	quenched freq	symm
1	3624	2380	a_1
2	3377	3377	a_1
3	2225	1654	a_1
4	1643	1311	a_1
5	1296	1062	a_1
6	895	485	a_1
7	552	221	a_1
8	385	341	a_1
9	97	8	a_1
10	3624	2387	b_1
11	3360	3360	b_1
12	2232	1502	b_1
13	1494	1181	b_1
14	1060	804	b_1
15	721	416	b_1
16	549	279	b_1
17	207	109	b_1
18	779	778	b_2
19	537	331	b_2
20	309	181	b_2
21	997	997	a_2
22	554	538	a_2
23	522	281	a_2
24	208	113	a_2

[a] The unperturbed and quenched frequencies are ordered so that they correspond to the same set of eigenvectors. Frequencies are in cm^{-1}.

Table 6. CASSCF Harmonic Frequencies of the Singlet *p*-Benzyne Biradical Molecule Computed with the DZP Basis Set[a]

mode	freq	quenched freq	symm
1	3393	3392	a_1
2	3392	1474	a_1
3	1422	1401	a_1
4	1395	1237	a_1
5	1240	1185	a_1
6	1189	1011	a_1
7	1005	704	a_1
8	993	388	a_1
9	646	42	a_1
10	3378	3378	b_1
11	3378	1731	b_1
12	1708	1510	b_1
13	1534	1272	b_1
14	1351	1105	b_1
15	1095	769	b_1
16	999	413	b_1
17	602	166	b_1
18	772	758	b_2
19	742	517	b_2
20	429	247	b_2
21	951	935	a_2
22	918	672	a_2
23	637	510	a_2
24	465	153	a_2

[a] The unperturbed and quenched frequencies are ordered so that they correspond to the same set of eigenvectors. Frequencies are in cm^{-1}.

similar. The reported activation barrier of 25.0 ± 3.1 kcal/mol should be compared with the 37.6 kcal/mol estimate by Koga and Morokuma and the experimentally measured activation energy of 32 kcal/mol. In comparison with the CASSCF/MRCI result the prediction in this paper is expected to be better, due to the more rigorous selection of the active orbitals. The experimental value, based on half-life times for isotopic rearrangements of hexa-1,5-dien-3-yne deuterated either at the ethylenic or the acetylenic position in a gas-phase pyrolysis experiment at 200 °C, is somewhat closer to our finding. In the derivation of the enthalpy of reaction, Jones and Bergman estimated the differential free energy from the time it took to "approximately half-equilibrate" the isotopic mixture. This value was then stated to be identical with the enthalpy of reaction under the assumption that the entropy of reaction is zero. Although the experimental value is closer to the CASSCF/MRCI result, we believe that both of these findings are associated with uncertainties and that the value presented here is more reliable.

The structures of the reactant and the product are different in many ways, with one system having a ring structure and the other being open. We also observe that the bonds significantly change their character (single, double, and triple to aromatic) in the ring closure process. This could manifest itself in that the magnitude of the zero point vibrational energy is significantly different for the two structures. To investigate this, the harmonic frequencies for the reactant and the product at the CASSCF/DZP level of theory were compiled (see Tables 5 and 6).

Since we have no interest in the individual values of the harmonic frequencies, but rather the overall correction, this level of theory is more than appropriate. From Tables 5 and 6, it is seen that the zero point correction to the total energy is 44.7 and 48.1 kcal/mol, respectively, for the reactant and the product. This will correct our computed enthalpy of reaction to 4.9 ± 3.2 kcal/mol. Some of the vibrations of the molecule under study would of course be quenched if the structure was attached to a template as described in the introduction. To mimic this effect on the zero point correction, the masses of the terminal hydrogens (H_3 and H'_3) were substituted with large masses in the harmonic frequency analysis. These results are also presented in Tables 5 and 6. The zero point vibrational corrections now become 34.4 and 35.7 kcal/mol, respectively, for hex-3-ene-1,5-diyne and the *p*-benzyne structure. Hence, the attachment of the molecule to a template will reduce the enthalpy of reaction by about 2 kcal/mol compared to that of the free species.

Some MM2 calculations by Nicolaou *et al.*[22] on a dynemicin A like structure (see Figure 2e) indicate that a change of the C_3–C'_3 bond distance from around 3.6 to about 3.2 Å would allow for the Bergman reaction to spontaneously proceed to ring closure. This would in energetics (see Figure 6) correspond to an energy input of about 5 kcal/mol. This structural change seems, in light of the findings presented here, to be too moderate to explain the activation of the Bergman reaction. The structure is at this point about 1 Å away from the transition state, the new aromatic bond is far from formation, and the system would need an additional input of 15 kcal/mol of energy in order to pass the transition state. Transition-state theory predicts an activation energy of 15 kcal/mol at 300 K to correspond to a half-life time of around 74 s. This is not a low enough half-life time to explain the function of the drug. It can only be concluded from the data presented here that a geometry change as suggested by Nicolaou *et al.*[22] is not enough to promote the action of the drug as suggested via a Bergman reaction and the formation of the singlet biradical.

Alternative explanations of the mechanism of the drug have to be considered. In addition to the high remaining activation barrier of the Bergman reaction, it is difficult to explain why the drug in the highly reactive biradical structure would not react with the hydrogens available in the cytosole before reacting with the DNA molecule. This suggests that, in order for the hydrogen extraction to be from DNA rather than from the cytosole, the agent has to be vary close to DNA prior to activation. Furthermore, it is known from studies of the metabolism of cells that radical chemistry is rather an exception than a rule and when it occurs it is under very controlled situations, such that the highly reactive radical structure will not react with the wrong target molecule (the radical structure is many times kept protected in some deep trench of an enzyme). This indicates that an alternative reaction mechanism would have its merits if it required some sort of a coupling between the ring closing mechanism in the enediyne structure of the drug and the hydrogen or hydroxide abstraction from the DNA molecule and if the chemistry was not of the radical type. It has been observed at this laboratory that the addition of a hydrogen atom to the reactant, at the position of the orbitals of the unpaired electrons in the product, reduces the activation barrier for the ring closure process.[27] The addition of a second hydrogen atom to the other position will completely remove the enefgy barrier to ring closure. A mechanism in which two hydrogen atoms (or one hydrogen atom and one hydroxide or two hydroxides) are abstracted from a molecular fragment simultaneously with the ring closure in the enediyne moiety would change the reaction barrier from that of a formation of two radical orbitals to that of a hydrogen atom abstraction. We are currently in this laborabory investigating the ring closure mechanism of the doublet benzene radical, the process of a simultaneous ring closure in enediyne, and the abstraction of two hydrogen atoms from the hexa-2,4-diene molecule resulting in the formation of benzene and hexa-1,3,5-triene. The latter mechanism is a closed shell mechanism, a Woodward–Hoffman allowed reaction, and a mechanism which requires the drug to be close to the structure from which the hydrogen abstraction will occur. It is believed that this mechanism has the potential of shedding some new light on the aspect of the function of the enediyne based drugs.

Summary

The autoaromatization of hex-3-ene-1,5-diyne to a singlet biradical *p*-benzyne structure, the Bergman reaction, has been studied by means of ab initio calculations. The computations involved geometry optimizations for five structures along the reaction path of the Bergman reaction by the means of the CASSCF method. The study used the DZP, TZ2P, and two ANO basis sets. The energetics were then computed at the PT2F level of theory. The PT2F energies were computed at the CASSCF optimized structures and at structures in which the C_1–C_1' bond distance was reoptimized. Zero point vibrational energy correction was added for the reactant and product at the CASSCF/DZP level of theory.

The computed enthalpy of reaction of 4.9 ± 3.2 kcal/mol is about one-third of the value estimated from experiment, 14 kcal/mol. Here we argue that the ground on which the experimental value is deduced (the group additivity assumption, *etc.*) is not well founded. The activation barrier, 25.0 ± 3.1 kcal/mol, is more closely related to the direct measurement of this property in a gas-phase pyrolysis experiment, 32 kcal/mol. However, the difference is larger than the error limits of the theoretical values, which renders some uncertainty to the experimental measurements.

A study of the quenching of the vibrations in the molecule as it is attached to a molecular template indicates that the enthalpy of reaction for the ring closure is reduced by about 2 kcal/mol.

Finally, whether the function of the template is to inhibit, activate, or promote the Bergman reaction is not clearly documented by this study. The promotion due to the structural change as suggested by earlier studies is not, according to this study, large enough for the Bergman reaction to proceed at an appreciable rate. However, it the action of the drug is *not* via the formation of a biradical, as suggested here, it seems more likely that the most important function of the template relative to the enediyne moiety is to inhibit the reactivity. Studies of these effects are under way at this laboratory.

Here we also want to mention the very recent work by Langley *et al.* in which the DNA–esperamicin A_1 complex is simulated by molecular dynamics simulation.[28] This study shows that the enediyne fragment pokes down in one of the growes of the DNA helix. This positions hydrogens in the very vicinity of the C_2 and C'_2 carbons. This again supports the possibility that the ring closure is simultaneous with the hydrogen abstraction.

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