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Competing Pathways in the [2 + 2] Cycloadditions of Cyclopentyne and Benzyne. A DFT and ab Initio Study

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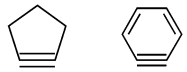
The [2 + 2] cycloadditions of cyclopentyne and benzyne to ethylene are explored at the B3LYP and CASSCF levels, supplemented by CCSD(T) and CAS-MP2 calculations at the stationary points. The biradical path in the benzyne system is computed to be about 4.1 kcal/mol lower than the concerted path, consistent with the experimentally observed loss of original stereochemistry in this cycloaddition. However, computations fail to confirm the 99% stereoretention in the corresponding reaction of cyclopentyne. The concerted and biradical paths in the latter reaction are found to involve nearly isoenergetic barriers, thus predicting only about 75% stereoretention. More sophisticated theoretical methods seem to be needed to resolve the issue in the cyclopentyne system.

Introduction

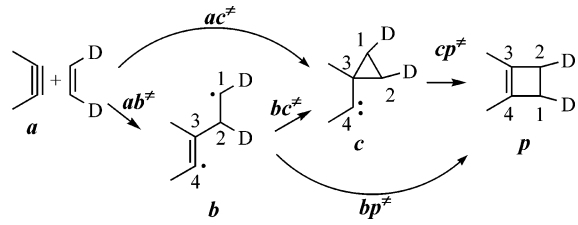
Cyclopentyne (**1*a***), the smallest cycloalkyne known to exist, gives [2 + 2] cycloadducts when generated in the presence of monoenes.[1] Notably, there is complete retention of the stereochemistry of the alkene in the adduct, the usual indicative of a concerted process. The concerted path, however, is forbidden by the Woodward–Hoffmann rules.[2,3] Recently, Laird and Gilbert[4] proposed a multistep mechanism whereby the cycloaddition reaction proceeds by the formation of a carbene intermediate (***c***) followed by ring expansion (Scheme 1).[5]



1*a* **2*a***

They provided computational support[4b] of their proposal at the RB3LYP[6] level. These calculations assumed

SCHEME 1



concerted paths for both stages of the reaction; the possibility of a nonconcerted formation of ***c*** via the biradical ***b***, or the direct rearrangement of ***b*** into the cycloadduct ***p*** was not explored. In an early study, Olivella et al.[7] suggested the biradical pathway as a viable explanation of the cycloaddition reaction. Using MNDO CI methodology, they reported that ***b*** and ***p*** are directly connected by a single transition structure (TS), without any mention of the carbene intermediate ***c***. Preliminary calculations in our laboratory indicated that the [2 + 2] cycloaddition pathways of many alkynes involve the species depicted in Scheme 1.[8] The conversion of ***c*** into ***p***, as well as that between ***b*** and ***p*** (through the TS $\boldsymbol{bp}^{\ddagger}$) are concerted processes having, in general, relatively low activation barriers. The rate determining step of the cycloaddition reaction is, therefore, either the formation of ***c*** (via $\boldsymbol{ac}^{\ddagger}$) or that of ***b*** (via $\boldsymbol{ab}^{\ddagger}$) from the reactants. Which path is actually followed depends on the nature of the alkyne. The observed stereochemical preservation in the [2 + 2] cycloadditions of cyclopentyne points to the preference of the concerted path. On the

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(1) (a) Fitjer, L.; Modaressi, S. *Tetrahedron Lett.* **1983**, *24*, 5495. (b) Gilbert, J. C.; Baze, M. E. *J. Am. Chem. Soc.* **1984**, *106*, 1885.

(2) (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395. (b) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 2046.

(3) A transition structure of C_2 symmetry was claimed for the [2_s + 2_a] cycloaddition of acetylene and ethylene (Hess, B. A.; Schaad, L. J.; Reinhoudt, D. N. *Int. J. Quantum Chem.* **1986**, *29*, 345). We repeated their calculations and found that the stationary point reported by these authors is actually a second order saddle point. The concerted path for [2 + 2] cycloadditions probably does not exist at all. See also: Bernardi, F.; Bottoni, A.; Olivucci, M.; Robb, M. A.; Schlegel, H. B.; Tonachini, G. *J. Am. Chem. Soc.* **1988**, *110*, 5993.

(4) (a) Laird, D. W.; Gilbert, J. C. *J. Am. Chem. Soc.* **2001**, *123*, 6704. (b) Bachrach, S. M.; Gilbert, J. C.; Laird, D. W. *J. Am. Chem. Soc.* **2001**, *123*, 6706. (c) Gilbert, J. C.; Hou, D. *J. Org. Chem.* **2003**, *68*, 10067.

(5) The following mnemonics are used throughout this paper. ***a***: alkyne, ***b***: biradical, ***c***: carbene, ***p***: product. Transition structures are labeled by combining the letter codes of the associated PES minima.

(6) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev B* **1988**, *37*, 785.

(7) Olivella, S.; Pericas, M. A.; Riera, A.; Sole, A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 613.

(8) Concerned with the highly strained nature of the two cycloalkynes reported herein, we have explored Scheme 1 for the simplest open-chain alkyne system; namely, cycloaddition of acetylene with ethylene. All species of Scheme 1 are also present in the latter system. The free energy profiles of the species in the acetylene system are presented in Figure S1 of the Supporting Information.

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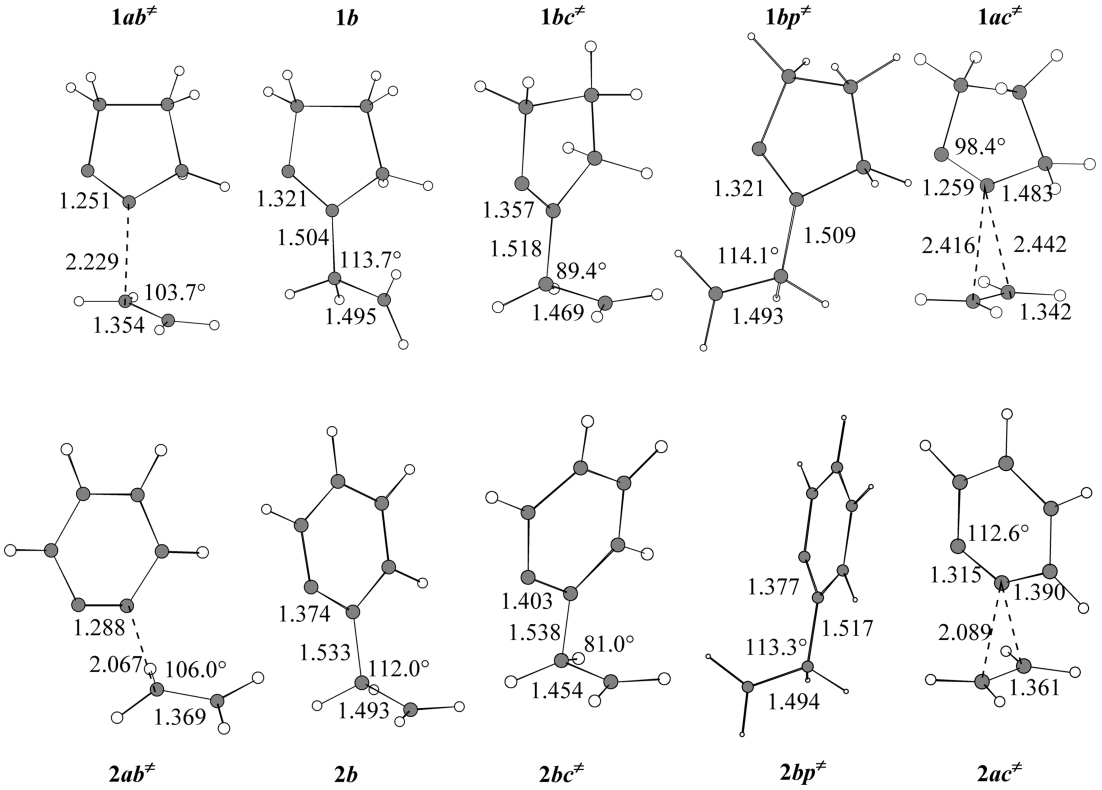


FIGURE 1. Selected geometric parameters for species ***ab***‡, ***b***, ***bp***‡, ***bc***‡, and ***ac***‡ of Scheme 1 for the cycloaddition of cyclopentyne (**1**) and benzyne (**2**) at the UB3LYP/6-311G(d,p) level. All distances are in angstroms, and all angles are in degrees.

other hand, benzyne (**2*a***) undergoes a similar cycloaddition reaction with *cis*- and *trans*-dichloroethylenes to produce dichlorobenzocyclobutenes, but with a significant loss of the original stereochemistry.[9] The latter fact indicates that in benzyne the biradical path should be operative since rotation around the C1−C2 bond of ***b*** (Scheme 1) would scramble the diastereomers. The stereorandomization is not complete, however, and this may be due to (i) a competition between cyclization and rotation in ***b*** as proposed by Jones and Levin[9] or (ii) a possible involvement of the concerted path.

The objective of the present work is (i) to characterize the structure and nature of the stationary points along the concerted and the nonconcerted paths at comparable levels of computational accuracy and (ii) to ascertain the qualitatively different mechanisms in the [2 + 2] cycloadditions of cyclopentyne and benzyne and explain the observed stereochemical outcomes in the two cases.

Computational Methods

The potential energy surfaces (PES) for the cycloaddition reactions of **1*a*** and **2*a*** with ethylene (Scheme 1) were probed using the (U)B3LYP/6-311G(d,p) and (6e, 6o) CASSCF/6-31G(d) theoretical models. The B3LYP functional has been popular as an effective and economical means for comparing the structures and energetics in both concerted and biradical systems.[10] Spin contamination in DFT methods is generally not considered to be a serious problem even when $\langle S^2 \rangle \approx 1$ as is the case with singlet biradicals.[10b] Nevertheless, we wanted to double-check the structures of the biradicaloid species, and employed CASSCF for this purpose.[11] The differences in B3LYP barrier heights for the rate determining steps in the concerted versus nonconcerted paths were within a few kcal/mol in both reactions (vide infra). To further check the energetics, we performed single-point CCSD(T) at (U)B3LYP optimized geometries, and multireference MP2[12] (CAS-MP2) calculations to include dynamic correlation in the CASSCF results. The DFT, coupled-clusters, and MP2 calculations were performed with Gaussian 98,[13] and GAMESS[14] was employed for some of the CASSCF calculations. The connectivities of the stationary points were verified by IRC[15] runs.

(9) Jones, M.; Levin, R. H. *J. Am. Chem. Soc.* **1969**, *91*, 6411.

(10) (a) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036. (b) Houk, K. N.; Beno, B. R.; Nendel, M.; Black, K.; Yoo, H. Y.; Wilsey, S.; Lee, J. K.*THEOCHEM* **1997**, *398*−*399*, 169. (c) Hrovat, D. A.; Beno, B. R.; Lange, H.; Yoo, H. Y.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 7456.

(11) The active orbitals were the in-plane and out-of-plane (π, π^*) orbitals of the triple bond in the alkyne plus (π, π^*) orbitals of the alkene. They correlate with the (π, π^*), and (σ,σ^*) orbitals of the C2−C3 and C1−C4 bonds of ***p*** (see Scheme 1 for the numbering).

(12) McDouall, J. J.; Peasley, K.; Robb, M. A. *Chem. Phys. Lett.* **1988**, *148*, 183.

(13) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98 (Rev. A.9), Gaussian, Inc., Pittsburgh, PA, 1998.

(14) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

(15) (a) Ishida, K.; Morokuma, K.; Komornicki, A. *J. Chem. Phys.* **1977**, *66*, 2153. (b) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363.

Results and Discussion

Figure 1 presents some of the geometric parameters that are directly related to the reacting centers in the cycloadditions of the two alkynes, for a subset of the species that are most relevant to the following discussion.[16] Along the synchronous path between the reactants and ***c***, the two molecules approach each other with their planes perpendicular to one another such that the plane of the alkyne bisects the ethylenic double bond (**1*ac*‡** and **2*ac*‡** in Figure 1). This concerted path (**2*ac*‡**) has C_s symmetry for benzyne. The corresponding path (**1*ac*‡**) for cyclopentyne would have been also symmetric if **1*a*** were planar.[17] The nature of the stationary point ***ac*‡** (**1*ac*‡** or **2*ac*‡**) depends on the level of theory employed. It is a closed-shell species. For cyclopentyne, the B3LYP functional predicts **1*ac*‡** as a TS independent of the basis set size. However, we were unable to verify this TS using either the MPW1PW91[18]/6-31G* or BPW91[19]/6-31G* functionals. The Hartree−Fock method locates it as a TS, but CASSCF moves it to **1*ab*‡** on the biradical path. Single-reference MP2/6-31G* optimization characterizes it as a TS at a similar geometry as that predicted by the B3LYP/6-311G(d,p) method. Clearly, the PES is very flat around **1*ac*‡**. The C1−C3 ≈ C2−C3 distance in the TS is 2.4 Å at the B3LYP/6-311G(d,p) level, a rather long distance for an organic TS. Due to the observed stereospecificity in the [2 + 2] cycloadditons of cyclopentyne, we tend to agree with Bachrach et al.[4b] in believing that this TS is real.

The case with benzyne is similar. CASSCF/6-31G* characterizes **2*ac*‡** as a second-order saddle point which is confirmed by the B3LYP functional when the standard 6-31G* basis is used. However, B3LYP/6-311G(d,p) and also MP2/6-31G* optimizations predict it as a genuine TS. We feel that the synchronous path to **2*c*** also exists for the cycloaddition reaction of benzyne. The C1−C3 = C2−C3 distance in **2*ac*‡** is a very reasonable 2.1 Å.

No uncertainties arose regarding the existence of the biradical paths in both reactions. UB3LYP and CASSCF methods agreed on the properties of all three species ***ab*‡**, ***b***, and ***bc*‡** along the path leading to ***c*** in Scheme 1 (as well as ***bp*‡**). The geometries of the former open-shell species may be crudely obtained by shifting the alkyne fragment in the ***ac*‡** structure toward one of the ethylenic carbons (Figure 1). They differ mainly by the C1−C2−C3 angle, and the C2−C3 distance in the case of the capture TS, ***ab*‡**. At the UB3LYP/6-311G(d,p) level, the latter distance is 2.2 and 2.1 Å in the reactions of cyclopentyne and benzyne, respectively. The biradical character in ***ab*‡**, ***b***, and ***bc*‡** are 41% (40%), 91% (88%), and 35% (25%) for cyclopentyne (benzyne), respectively.[20,21] The alkyne fragments in intermediates **1*b*** and **2*b*** have nearly attained their final geometries (in the corresponding cycloadducts **1*p*** and **2*p***). Ethylenic portions undergo further structural changes between ***b*** and ***p***, where the C1−C2 bond lengthens by an additonal 0.09 Å. Formation of the reactive TS, ***bp*‡**, basically involves a partial rotation about the C2−C3 single bond in ***b***.

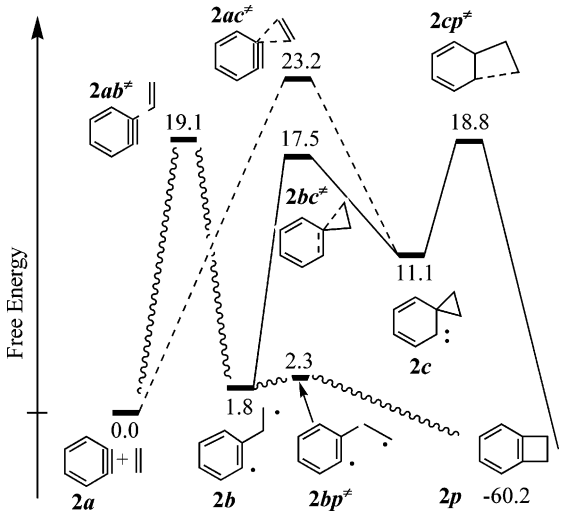
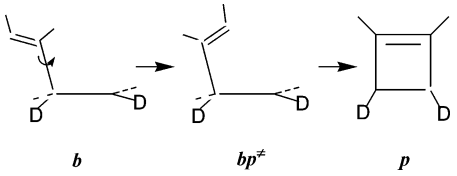
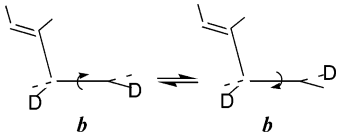


FIGURE 2. Free energy profiles of the concerted (dashed lines) and biradical paths in the cycloaddition of benzyne and ethylene.[16] The minimum energy path is indicated by the wavy lines. UB3LYP/6-311G(d,p) free energies (kcal/mol, 298 K) are given.



The barrier between ***b*** and ***bp*‡** is of similar magnitude (vide infra) as that in the isomerization of ***b*** through rotation about the C1−C2 bond.



The relative free energies of the stationary points corresponding to all species in Scheme 1 on the energy surfaces are given in Figures 2 and 3 for the cycloaddi-

(16) Ball and stick models with selected geometric parameters of all stationary structures in this work are available in the Supporting Information.

(17) Note that geometry of approach of an alkyne to ethylene differs from the corresponding approach of a planar carbene. The latter path also has C_s symmetry, but the symmetry plane contains the ethylenic double bond instead of being perpendicular to it. Further, bond formation is concerted but asynchronous. See, for example: (a) Apeloig, Y.; Karni, M.; Stang, P. J.; Fox, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 4781. (b) Zurawski, B.; Kutzelnigg, W. *J. Am. Chem. Soc.* **1978**, *100*, 2654.

(18) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664.

(19) (a) Perdew, J. P.; Chevary, J. A.; Vosko, S. H.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. *Phys. Rev. B* **1992**, *46*, 6671. (b) Perdew, J. P.; Burke, K.; Wang, Y. *Phys. Rev. B* **1996**, *54*, 16533.

(20) Occupation number of the CASSCF natural orbital corresponding to the LUMO is used here as a measure of biradical character. For a discussion of biradical character in open-shell singlets, see, for example: Ozkan, I.; Kinal A.; Balci, M. *J. Phys. Chem. A* **2004**, *108*, 507 and references therein.

(21) Biradical character in cyclopentyne itself (**1*a***) is 26.1% (vs 17.6% in benzyne). Multideterminantal wave functions always introduce some biradical character even to species regarded as closed-shell systems; e.g. ethylene and benzene have 10% biradical character according to our measure. Thus we consider benzyne as a normal closed-shell species whereas cyclopentyne has a partial biradical character. In DFT calculations the biradical character is reflected in RDFT-UDFT instability and spin contamination; the RB3LYP/6-311G(d,p) determinant is stable in benzyne whereas slightly unstable in cyclopentyne (UB3LYP energy is lower by 1.0 kcal/mol, and $\langle S^2 \rangle = 0.3$).

TABLE 1. Relative Energies[a] (kcal/mol) of Various Species in the Cycloaddition Reactions of Cyclopentyne and Benzyne with Ethylene at Different Levels of Theory

	***ab*‡**	***b***	***bp*‡**	***bc*‡**	***ac*‡**	***c***	***cp*‡**	***p***
cyclopentyne (**1*a***) + C_2H_4								
UB3LYP/6-311G(d,p)	3.33	−24.25	−22.78	−15.07	1.68	−36.43	−30.75	−84.68
CCSD(T)[b]	4.58	NA	NA	−8.61	6.71	−36.26	−30.43	−86.91
CAS-MP2[c]	12.79	−15.73	−13.45	−0.30	13.19[d]	−27.58	−18.53	−74.50
benzyne (**2*a***) + C_2H_4								
UB3LYP/6-311G(d,p)	9.24	−9.42	−9.40	5.21	12.08	−2.64	5.03	−76.79
CCSD(T)[b]	8.51	NA	NA	8.48	16.05	−3.66	3.69	−80.86
CAS-MP2[c]	15.49	−6.03	−7.51	18.08	20.71	8.27	16.36	−78.10

[a] Electronic energies without ZPVE relative to the reactants. [b] Single-point CCSD(T)/6-31G* at UB3LYP/6-311G(d,p) optimized geometries. [c] Single-point multireference MP2/6-31G* at (6e, 6o) CASSCF/6-31G*-optimized geometries except for ***ac*‡** for which B3LYP/6-311G(d,p) geometries were employed. [d] CAS-MP2/6-31G* value at RMP2/6-31G*-optimized geometry is 11.99 kcal/mol.

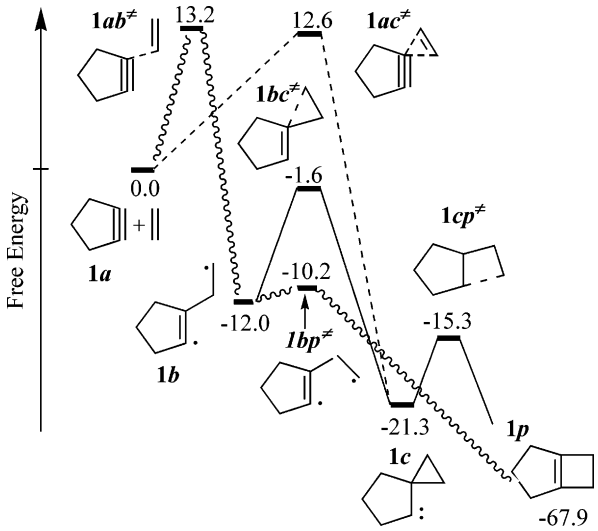


FIGURE 3. Free energy profiles of the concerted (dashed lines) and biradical paths in the cycloaddition of cyclopentyne and ethylene.[16] UB3LYP/6-311G(d,p) free energies (kcal/mol, 298 K) are given.

tions of **2*a*** and **1*a***, respectively.[22] Cycloaddition of benzyne is considered first (Figure 2). The biradical TS, **2*ab*‡**, for the initial capture of ethylene by benzyne is 4.1 kcal/mol lower than the concerted TS, **2*ac*‡**. We investigated the relative energies further by single-point CCSD(T) and CAS-MP2 calculations. The electronic energies are presented in Table 1. CCSD(T) and CAS-MP2 favor **2*ab*‡** even more than B3LYP. It appears that the concerted path is ruled out for benzyne and that the cycloaddition proceeds by the biradical path. The biradical **2*b*** then directly rearranges into the adduct **2*p*** via **2*bp*‡** which lies above the biradical minimum by only 0.5 kcal/mol. The isomerization barrier in **2*b*** is also very low[23] so that isomerization and cyclization can compete, resulting in incomplete loss of stereoretention. Our numerical results for benzyne are in accord with the arguments of Jones and Levin.[9]

The situation is less certain for the reaction of cyclopentyne (Figure 3). The concerted TS, **1*ac*‡**, for the initial capture of ethylene by cyclopentyne is lower than the biradical TS, **1*ab*‡**, by 0.6 kcal/mol at UB3LYP level. However, CCSD(T) reverses the relative order of **1*ab*‡** and **1*ac*‡** while CAS-MP2 is sensitive to the geometry employed for **1*ac*‡** (Table 1). It appears that the two species are nearly isoenergetic, and therefore, both pathways should be operative in the cycloaddition of

TABLE 2. Triple-Bond Strain vs Activation Free Energy (kcal/mol) in the Cycloaddition of Several Representative Alkynes with Ethylene

alkyne	strain energy[a]	$\Delta G^{\ddagger}$ [b]
cyclopentyne (**1*a***)	70	13
benzyne (**2*a***)	50	19
cyclohexyne	41	25[c]
acetylene	0	49[c]

[a] Reference 26. [b] UB3LYP/6-311(d,p) at 298 K. [c] See the Supporting Information.

cyclopentyne (**1*a***). Assuming equal barrier heights for the two paths, we would predict about 75% stereoretention in cyclopentyne;[24] decisively larger than that in benzyne, but considerably less than the experimental 99% stereospecificity.[1] Further work using more expensive methods (e.g., MRCI) is clearly needed to resolve the issue in the cyclopentyne system. Unfortunately, we are unable to carry out this task with our current facilities. Incidentally, we expect a similar problem in the cycloaddition of related molecules such as norbornyne[4] and bicyclo[2.2.1]hept-2-en-5-yne.[25]

We next inquire about the possibility of generalizing the results presented above to the [2 + 2] cycloadditions of other alkynes. For this purpose we consider a series of cyclomonoynes with increasing ring size, or more specifically, in decreasing triple-bond strain. Cyclopentyne is the smallest member of this series with benzyne and cyclohexyne following it. We model a large cycloalkyne with acetylene. The concerted TS (***ac*‡**) in the acetylene system lies about 12 kcal/mol above the biradical path at the UB3LYP/6-311G(d,p) level.[8] The concerted

(22) Due to the biradical species, proximity of the triplet surface and, therefore, the possibility of intersystem crossing is a concern. We optimized the triplet states of both systems at UB3LYP/6-311G(d,p) level. The triplet minimum is nearly isoenergetic with the singlet biradical ***b*** in both systems (geometries are also similar; see the Supporting Information). Single point CAS(6,6)/6-31G* calculations support the DFT results suggesting that DFT singlet and triplet energies of the biradicals are trustworthy. This minimum is most likely the global one in the region of the triplet surface covering the species involved in Scheme 1. Further, the triplet surface is higher than the singlet elsewhere in Scheme 1. We believe intersystem crossing is not operative in the cycloaddition.

(23) Due to the flat nature of PES in the region of biradical species it is not easy to discern the isomerization TS from ***bp*‡**. This was less of a problem with CASSCF than it was with DFT. The barriers involved are definitely small (0−2 kcal/mol), but their precise magnitudes cannot be predicted by the present methods.

(24) There seems to be less competition between rotation and cyclization in **1*b*** since the barriers are 0.5 and 1.8 kcal/mol, respectively.

(25) Kitamura, T.; Kotani, M.; Yokoyama, T.; Fujiwara, Y. *J. Org. Chem.* **1999**, *64*, 680.

path in the cyclohexyne system does not seem to exist. Despite many attempts, we could only locate a second-order saddle point which was about 4 kcal/mol above the biradical TS. We believe that if ***ac***‡ in the cyclohexyne system existed at all it would be above the biradical TS by about this amount (which is similar to the value in benzyne). Table 2 compares the strain estimates of Johnson and Daoust[26] with activation free energies in the cycloaddition of several representative alkynes. Quite expectedly, activation free energies decrease as bond strain increases (or vice versa). One would expect that all cycloalkynes larger than cyclopentyne would behave similarly in their cycloadditions, with the biradical path preferred. It seems that stereospecifity in the [2 + 2] cycloadditon is peculiar to cyclopentyne apparently due to the large strain present in this molecule and should not be expected in higher membered cycloalkynes.

Supporting Information Available: Optimized geometries and energies for all structures at B3LYP/6-311G(d,p) and CASSCF(6,6)/6-31G*; free energy profiles of the species in the cycloaddition of acetylene; data for the cyclohexyne system. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Johnson, R. P.; Daoust, K. J. *J. Am. Chem. Soc.* **1995**, *117*, 362.